Tuesday, 6 September 2005

CAROTID STENTING

2547 Prevention of disabling and fatal strokes – acute outcome and long-term follow-up of carotid stenting in patients with asymptomatic carotid stenosis: a comparison of two different age groups

J. Sugita[1], K. Rabe[1], E. Schluessmann[1], H. Goedel[1], A. Roemer[1], K. Lang[1], P. Schneider[2], H. Sievert[3]. *[1]CardioVascular Center, Frankfurt, Germany; [2]Sankt Katharinen Hospital, Neurolog. Dept., Frankfurt, Germany; [3]Cardiovascular Center Frankfurt, Adult Cardiologist (Medical Office), Frankfurt, Germany*

Background: The 5-year-results of the ACST Trial have shown a significant benifit of immediate carotid endarterectomy (CEA) for patients with asymptomatic carotid stenoses aged <75, but not for those >75 years of age. We compared the acute and long-term results of carotid stenting of asymptomatic stenoses in these two age groups.
Patients: Results of carotid stenting of 233 asymptomatic stenoses in 223 patients younger than 75 years were compared to the results of 107 asymptomatic lesions in 104 patients older than 75 years. There were no other significant differences regarding baseline characteristics.
Methods: We used embolic protection devices in 85.0% and 87.9% respectively. 99.1% and 98.1% of the patients were treated with stent implantation. Follow-up investigations included a neurological examination before discharge, after 1 month and thereafter whenever an event occurred. A carotid duplex scan was performed after 1 and 6 months. Thereafter, a questionnaire was sent every year.
Results: Concerning the patients younger than 75, the procedure was technically successful in all lesions. During or within 30 days after the intervention 2 patients developed a minor stroke and 1 patient died due to non-cerebral cause. Thus, the stroke/death rate at 30 days was 1.3%. Follow-up ranged from 1 month to 11 years (mean 1.1 ± 2.2 years, 433 patient years). During follow-up the following events occurred: Ipsilateral major stroke in 2, ipsilateral minor stroke in 1, non-cerebrovascular death in 11 patients. The annual rate of ipsilateral stroke and cerebrovascular death was 0.7%. In patients older than 74 years the procedure was technically successful in 102/104. During or within 30 days of the procedure the following complications occurred: Minor stroke in 1 patient, major stroke in 3 patients and 2 non-cerebral deaths. The death/stroke rate at 30 day was 5.9%. Follow-up ranged from 1 month to 7.5 years (mean 1.2 ± 1.7 years, 172 patient years). During follow-up the following events occurred: Cerebrovascular death in 1, ipsilateral major stroke in 2, ipsilateral minor stroke in 1, non-cerebrovascular death in 13 patients. The annual rate of ipsilateral stroke and cerebrovascular death was 2.3%. The differences between both groups were not significant.
Conclusion: Carotid stenting is a successful technique to prevent stroke and can be performed in patients older than 74. The peri-procedural risk seems to be higher in the elderly although the difference was not significant. This has to be weighed up with the higher risk of surgery and natural course of the disease.

2548 Assessment of the Willis circle flow changes after successful and complicated stenting for severe internal carotid stenosis (ICAS)

A. Kablak-Ziembicka[1], T. Przewlocki[2], P. Pieniazek[2], P. Musialek[2], R. Rudko[2], R. Motyl[3], W. Tracz[2]. *[1]Institute of Cardiology, Collegium Medicum, Dept. of Cardiac and Vascular Diseases, Krakow, Poland; [2]Institute of Cardiology, CM UJ, Dept of Cardiac and Vascular Diseases, Krakow, Poland; [3]Institute of Neurology, Krakow, Poland*

Immediate flow changes in the Willis circle due to carotid stenting (CS) have not been widely studied so far. Study aimed to assess impact of successful and complicated by periprocedural stroke CS on the Willis circle flow in pts with ICAS.
Methods: We included 66 pts with ICAS: Group I - 50 pts (32M, aged 63.0±8.6y) with unilateral ICAS (QA: 86.6±8.8%); Group II – 16 pts (14M, aged 63.3±8 y) with bilateral ICAS (stenosis on CS site: 84.6±11.6%, opposite 99.7±11.3%). Control group included 33 pts (25M, aged 61.2±9.2y) without lesions in extra- and intracranial arteries. All pts underwent transcranial color-coded doppler ultrasound prior and during 24 hours after CS, with assessment of systolic velocities in ipsilateral to CS site – middle (iMCA) and anterior (iACA) cerebral arteries, as well as contralateral middle (cMCA) and anterior (cACA) cerebral arteries.
Results: The CS was uncomplicated in 62(94%) pts. Hyperperfusion syndrome (HS) occurred in 2(3%) pts with bilateral ICAS; TIA - in 2(3%) pts (1 pts-bilateral ICAS), thus in Group I complications rate was 2% vs. 18% in Group II ($p<0.05$). Prior CS, pts in Group I and II had decreased iMCA velocities by mean 23% and 21%, as compared to Controls ($p<0.001$ and $p=0.016$). Group II pts but not I, had also lower cMCA velocities, compared to Controls ($p<0.001$). The collateral pathway via anterior communicating artery (ACoA) was found in 84% Group I pts and all Group II pts. The CS caused rapid closure of collateral flow via ACoA in Group I, resulting in sudden change of flow direction in iACA and flow increase in iMCA exceeding by 49% velocities found in Controls ($p<0.001$). In Group II, we found iMCA velocity increase exceeding by 50% these in Controls ($p=0.009$), and enlargement of collateral flow via ACoA ($p=0.002$), resulting in significant increase in cMCA velocity ($p<0.001$), equal as in Controls ($p=0.817$). In 2 HS pts, iMCA and cMCA velocities after CS were 2.4-4.9-fold and 7.2-7.4-fold higher compared to values before CS (both $p<0.000$), resulting in significant flow increase in iMCA and cMCA by 210% vs. Controls. Pts with HS had very low initial cMCA velocities compared to others in Group II ($p=0.018$). On the contrary, in TIA pts velocity in iACA was decreased by 72% after CS, compared to Controls.
Conclusions: Uncomplicated CS is followed by rapid velocity increase in cerebral arteries exceeding by half values encountered in healthy subjects. Whereas, clinically manifested hyperperfusion syndrome was related to over 2-folded increase of MCA velocities over normal ones. Complications more often occur in pts with bilateral ICAS.

2549 One-stage coronary and peripheral intervention (OCAPI) in patients with high risk of cardiovascular events: short and long-term results

P. Buszman[1], M. Debinski[2], K. Milewski[2], A. Gruszka[2], L. Kinasz[3], B. Gorycki[3], M. Mandecki[3], S. Kiesz[4]. *[1]Upper-Silesian Heart Center, Coronary Care Unit, Katowice, Poland; [2]Upper-Silesian Heart Center, Coronary Care Unit, Katowice, Poland; [3]American Heart of Poland, Department of Vascular Diseases, Ustron, Poland; [4]University of Texas School of Medicine, San Antonio, TX, United States of America*

There is a high coincidence of peripheral and coronary artery disease which ranges between 30 and 50%. Complex diagnosis and treatment of the patients with diffuse atherosclerosis by means of One-stage Coronary and Peripheral Percutaneous Transluminal Intervention (OCAPI) provides the opportunity to use similar equipment, technique and pharmacology as one procedure to prevent cardiovascular events (CVE). The aim of the study is assess wether OCAPI is feasibile and comparable to multivessel coronary intervention (MPCI).
Methods and results: the OCAPI registry consisted of 75 patients (56 males; mean age 62,6±9,3 years) presenting critical narrowings of coronary and peripheral arteries. 184 coronary and peripheral arteries (2.5±0,6 per patient) were treated, including 57 carotid or vertebral, 28 iliac or femoral and 21 renal arteries. The MPCI group consisted of 80 patients (53 males, mean age 62,9±10.9) who had 2.5±0.6 coronary arteries dilated at one stage. There was no significant difference between the groups in respect to demographic data and mean number of dilated vessels. Pharmacological protocol (double anti-platelet treatment, heparinization and serial ACT evaluation) and an arterial sheath removal regimen were similar in both groups. The OCAPI procedures lasted longer than MPCI (103,9±35,0 vs 87,7±38,9 min., p=0.007) and required more fluoroscopy (28.3±13,6 vs 24,8±5.5 min., p=0.035). However, the total volume of injected non-ionic contrast was similar for both procedure (315±109 vs 306±93, p=0,572). The serum creatine level did not significanlty change and there was no acute renal failure after OCAPI. One TIA and one episode of non-fatal subarachnoidal hemorrhage occurred following OCAPI, but there were no deaths or other major complications. In contrary there was one episode of acute renal failure, three - with exaggeration of chronic renal failre and two episodes of hemorrhage required blood transfusion in MPCI group. There was no MI or death after MPCI. At 15,6±3,7 months follow-up reintervention was required in 12 patients (16%) in OCAPI group and in 20 (25%) in MPCI group. There was one death in every group.
Economic analysis in OCAPI group showed significant cost reduction in comparison with projected costs for staged percutaneous or surgical treatment.
Conclusions: We suggest that OCAPI is a safe and cost-effective procedure that is associated with an acceptable rate of serious CVE and which might replace multiple high risk surgical interventions. OCAPI is a comparable procedure to MPCI.

2550 Carotid angioplasty in octogenarian patients

O. Mendiz[1], L. Valdivieso[2], G. Lev[2], C. Fava[2], R. Costantini[2], L. Villagra[2]. *[1]Buenos Aires, Argentina; [2]Fundacion Favaloro, Cardiologia Intervencionista, Buenos Aires, Argentina*

Background: octogenarian patients (Ptes.) had worse outcomes in previous reported carotid angioplasty (CA) series.
Objective: to compare in-hospital and one year follow-up (FU) evolution of =80 years old Ptes. who underwent CA (Group A; n=33) with younger Ptes. (Group B; n=321).
Methods: Between November/1995 and May/2004, 354 consecutive CA were performed. The first Ptes of the series had been done without Protection Devices (PD) were also included in the analysis. Ptes. characteristics were; mean age 82,0±1,6 vs. 66,6±8,1 years; male 75,8% vs. 71,3% (p=ns); Diabetes 6,1% vs. 23,9% (p=0.01); Hypertension 72,7% vs. 88,0% (p=0.02); Asymptomatic 48,5% vs. 56,0% (p=0.02). PD were used in 76,8% vs. 71,6% (p=ns).
Angiographic success (AS) was considered as residual stenosis <30%; and clinical success (CS) as AS without 30-days major complications (death, major stroke [NIH scale >4], urgent surgery or AMI).
Results: As was achieved in 96.9% vs. 99.7% (one catheterization failure and one failure to cross a total occlusion with the guidewire). CS was 93,9% vs. 97.8% (p=ns); major stroke 0% vs. 1,24%; minor stroke 0% vs. 1,86%; TIA 3,0% vs. 2,8%; related death 0% in both groups and non-related death 3,0% vs. 0,6% (3 deaths after emergent CABG or valve surgery, without neurological complications); any stroke or related death 0% vs. 3,1%.
All eligible Ptes. of Group A (n=32) and 90% of Group B were followed. One year FU was reached by 23 and 260 of each group. Events at FU in Group A

were; one non-related death (after a year), no stroke or restenosis (echo-Doppler evaluation).
Conclusion: In this series, octogenarians who received CA had similar in-hospital and one-year evolution of younger Ptes.

2551 Is routine cerebral protection during carotid artery stenting in octogenarians feasible and safe? Results of a multicenter registry

I. Iakovou[1], B. Reimers[2], G.M. Sangiorgi[3], J. Schofer[4], M. Schlueter[4], M. Montorfano[5], F. Airoldi[5], A. Colombo[3]. [1]*Centro Cuore Columbus, EMO, Milano, Italy;* [2]*Mirano Hospital, Cardiology Department, Mirano, Italy;* [3]*EMO Centro Cuore Columbus, Milan, Italy;* [4]*Center for Cardiology and Vascular Ins, Hamburg, Germany;* [5]*San Raffaele Hospital, Interventional Cardiology, Milan, Italy*

Purpose: Carotid artery stenting is being used as an alternative treatment to surgical endarterectomy. The availability of cerebral protection systems has expanded the area of application of this procedure. To evaluate the short-term outcome of patients =80 years who underwent carotid stenting with the routine use of cerebral protection devices.
Methods: In 4 centers, 68 patients aged more than 80 years (72% men; mean [±SD] age, 83±3 years)were treated with carotid stent implantation on 73 arteries. Cerebral protection was used in all patients and involved filter devices (n=59), occlusive distal balloons (n=12), or proximal balloon protection (n=2).
Results: The protection device was positioned successfully in 99% of the 73 attempted vessels. Neurologic complications occurred within 30 days after 4 procedures (5.4%), including 1 major stroke, 1 minor stroke, and 2 transient ischemic attacks. There was 1 death (following a major stroke). The post-hospital 30-day incidence of major stroke and death was 1.4%(1/73) vs. 1.8%(9/488) in patients <80 years (p=0.7). Two patients (2.7%) had non occlusive dissections related to usage of protection devices without neurologic complications.
Conclusion: Carotid stenting with routine cerebral protection in cotogenarians appears feasible and safe, with a low occurrence of major complications. The incidence of major neurologic complications in this study was lower than in previous reports of carotid artery stenting without cerebral protection.

2552 Treatment of asymptomatic carotid artery stenosis by carotid artery stenting in daily routine patients

B. Mark[1], R. Zahn[2], T. Ischinger[3], E. Roth[4], K. Hauptmann[5] on behalf of ALKK CAS-Registry. [1]*Herzzentrum Ludwigshafen, Kardiologie, Ludwigshafen, Germany;* [2]*Herzzentrum Ludwigshafen, Kardiologie, Ludwigshafen, Germany;* [3]*Städtisches Klinikum, Kardiologie, München-Bogenhausen, Germany;* [4]*Stadtkrankenhaus, Kardiologie, Worms, Germany;* [5]*Krankenhaus der Barmherzigen Brüder, Kardiologie, Trier, Germany*

Background: An increasing number of patients (pts.) with carotid artery stenosis is treated by carotid artery stenting (CAS). While the treatment of syptomatic stenosis is well-accepted, CAS of asymptomatic stenosis is still discussed controversally.
Methods: We analysed the data of the prospective CAS-Registry of the ALKK (Arbeitsgemeinschaft der Leitenden Krankenhaus-Kardiologen).
Results: From 1996 to 2004, 1954 consecutive pts. were included. 910 (46.6%) of pts. had asymptomatic stenosis (mean value between hospitals: 48.1±15.6%; range: 16-83%). There was an increase in frequency from 20% in 1996 to 54% in 2004 (p for trend <0.001). The pts.' clinical characteristics and outcome until discharge is shown in the TABE.
In the logistic regression analysis, symptomatic stenosis showed a trend to a higher rate of hospital death or stroke (odds ratio 1.59; 95% confidence interval 0.96-2.63; p=0.07).

Table

	Asymptomatic n=910 (100%)	Symptomatic n=1044 (100%)	p-value
Age (years)	70 (64-75)	71 (65-77)	<0.001
Male gender (%)	73	71	0.17
CAD (%)	75	59	<0.001
Stenosis pre-CAS (%)	90 (80-95)	90 (80-95)	0.45
Stenosis post-CAS (%)	5 (1-20)	5 (1-10)	0.13
Max. balloon diameter (mm)	5 (5-6)	5 (5-6)	0.59
Duration of CAS (min)	40 (30-60)	40 (30-60)	0.60
Ipsilateral stroke (%)	2.4	3.8	0.05
Death or stroke (%)	3.0	4.8	0.04

Clinical characteristics and outcome until discharge in asymptomatic vs. symptomatic patients

Conclusion: Almost half of the pts. form the ALKK CAS-Registry were treated for an asymptomatic carotid artery stenosis, with increasing frequency over the time. The hospital event rate (death or stroke) of asymptomatic pts. was lower compared to pts. with symptomatic stenosis (3.0% vs. 4.8%; p=0.04).

STROKE

2553 Prognostic implications of right-sided insular damage, cardiac autonomic derangement and arrhythmias after acute ischaemic stroke

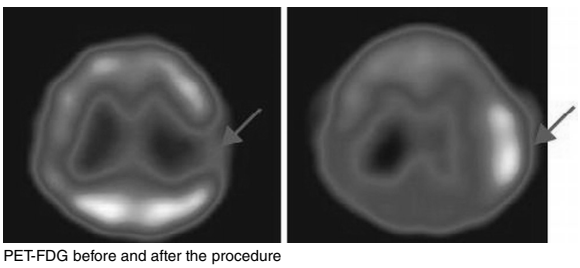
F. Colivicchi[1], A. Bassi[2], M. Santini[3], C. Caltagirone[2]. [1]*Rome, Italy;* [2]*IRCCS S. Lucia, Neurology, Rome, Italy;* [3]*S. Filippo Neri, Cardiology Dept., Rome, Italy*

Recent studies have consistently shown that acute ischemic stroke is associated with impairment of cardiac autonomic balance and increased incidence of cardiac arrhythmias. Moreover, abnormalities of cardiovascular autonomic control have also been reported to retain prognostic relevance after ischemic stroke. Besides, stroke-related autonomic abnormalities appear as more relevant in patients with a right-sided hemispheric infarctions, while concurrent involvement of the right insular cortex may even imply further derangement of cardiovascular function.
This prospective study was designed and undertaken to asses the impact of right-sided insular damage, cardiac autonomic derangement and cardiac arrhythmias on clinical outcome, as expressed by total mortality, after acute ischemic stroke.
The study populatioin included 208 consecutive patients (116 men and 92 women; mean age 69.5±7.8 years) with acute first-ever ischemic stroke and without major concurrent comorbidity. Stroke severity on admission was assessed by the NIH Stroke Scale. No patient received thrombolytic therapy. Neuroimaging studies (CT or MRI) were performed on admission and repeated by the end of the first week to confirm brain infarct size and localization. The presence of right-sided insular involvement was assessed on the basis of brain imaging. All patients underwent 24-hour Holter monitoring (HM) within 72 hours from admission.
During a 12-month follow-up period, 48 patients died (overall one-year probability of death was 0.23; 95% CI, 0.17-0.30). Multivariate analysis (Cox model) demonstrated that age, stroke severity on admission, presence of right-sided insular damage, as well as SDNN<100ms and presence of non-sustained ventricular tachycardia on HM, were independent predictors of 12-month all-cause mortality. We conclude that among patients with ischemic stroke, the recognition of right insular involvement and the analysis of autonomic and arrhythmic markers may constitute an improved strategy that more accurately identifies patients at high risk for total mortality. Integration of traditional risk stratifiers, such as age and stroke severity, with autonomic and arrhythmic markers, as well as the careful search for right-sided insular involvement, may represent a more powerful approach for effective identifications of stroke patients at risk for early mortality.

2554 Initial experience with stem cells therapy in acute ischaemic stroke

M.L.F. Mendonca[1], G.R. Freitas[2], C.H.E. Falcao[1], C. Gonzales[3], A. Manfrim[3], S.A. Silva[1], R. Borojevic[2], H.F. Dohmann[4]. [1]*Pró-Cardíaco Hospital, Rio de Janeiro, Brazil;* [2]*Federal University of Rio de Janeiro, Rio de Janeiro, Brazil;* [3]*Pró-Cardíaco Hospital, Rio de Janeiro, Brazil;* [4]*Pro-Cardiaco Hospital, Interventional Lab, Rio de Janeiro, Brazil*

Hypothesis: clinically, several techniques have been tested to optimise the penumbra zone after an acute ischemic stroke (AIS), without good results. Our data showed the ability of autologous bone marrow mononuclear cells (ABMNC) to pass through the hemato-encephalic barrier acutely after an AIS. Some models have been published showing ABMNC's angiogenic and anti-apoptotic abilities. We'd like to test these abilities to optimize the penumbra zone recovery, improving patient's (Pt) functional recovery.
Methods: we submitted a safety protocol to the National Ethical Committee, approved after 7 months analysis. An open label trial of 15 Pt with AIS due to middle cerebral artery occlusion, spontaneously recanalised. Pts are divided in: A) Pts receiving 30 million ABMNC between the third and the fifth day after AIS by related artery catheterisation (n=10); B)control group (n=5). As a safety study, delivery procedure(DP) are monitored by transcranial Doppler and EEG. At follow-up, brain perfusion with 99mTc-ECD SPECT; DWI-MRI and brain PET-FDG are done.
Results: we report our first case (enrollment should be completed until ESC meeting), a 54 y/old female with NIHSS of 17 and functional impairment well related to a severe left parietal hypoperfusion-hypometabolism images. DP showed no adverse effects, with no blood flow or epileptogenic disturbances. Pt improved well showing a NIHSS of 7, after two months. Interestingly, one week after DP, PET-FDG showed a marked increase in treated area's glucose metabolism (Figure).



PET-FDG before and after the procedure

Conclusion: this very first case of ABMNC after AIS suggested DP's safety that must be confirmed by other cases. PET-FDG images strongly suggest the ability of ABMNC in pass through the hemato-encephalic barrier and reach the penumbra zone.

2555 Natriuretic peptides and the risk of stroke

S. Kurl[1], J.A. Laukkanen[2], J. Sivenius[3], H. Ruskoaho[4], K. Nyyssonen[2], O. Vuolteenaho[5], J.T. Salonen[2]. [1]*Kuopio, Finland;* [2]*University of Kuopio, Research Institute of Public Health, Kuopio, Finland;* [3]*Kuopio University Hopsital, Department of Neurology, Kuopio, Finland;* [4]*University of Oulu, Department of Pharmacology and Toxicol, Oulu, Finland;* [5]*University of Oulu, Department of Physiology, Oulu, Finland*

Purpose: Subclinical risk markers may enhance risk stratification for the development of various cardiovascular diseases. Natriuretic peptides are associated with the increased risk of heart failure. However, very little is known about the prognostic significance of both N-terminal fragments of proA-type and proB-type natriuretic peptides with respect to the risk of stroke.
Methods: Plasma N-terminal fragments of proANP and proBNP were measured in a representative population-based sample of 951 men (age 46-65) from Eastern Finland. There were a total of 41 strokes and 31 were Ischemic strokes during an average follow-up period of 10 years. Men with a history of stroke at baseline were excluded.
Results: The multivariate adjusted risk was 1.27-fold (95% confidence intervals 1.09 to 1.50, p =0.003) for any stroke and 1.35-fold (95% confidence intervals 1.13 to 1.61, p =0.001) for ischemic stroke for each SD (160.8 pmol/L) increment in N-terminal fragment of proBNP after adjustment for age, body mass index, systolic blood pressure, alcohol, smoking, serum LDL-cholesterol and HDL-cholesterol, family history of coronary heart disease, c-reactive protein and use of anti-hypertensive medications. The respective risks were 1.22-fold (95% confidence intervals 1.03 to 1.46, p =0.025) and 1.26-fold (95% confidence intervals 1.04 to 1.54, p =0.027) increment in N-terminal fragment of proANP.
Conclusions: Our finding shows that N-terminal fragments of proB- and proA-type natriuretic peptides are strong predictors for any stroke. N-terminal fragments of proANP and proBNP add to the prognostic value of risk factors that provides a non-invasive marker for identifying men at high risk for stroke in a population based sample of men.

2556 Stroke in diabetic and non-diabetic patients: course and prognostic value of admission serum glucose

C. Stoellberger[1], I. Exner[2], J. Finsterer[3], J. Slany[3], C. Steger[3]. [1]*Wien, Austria;* [2]*Kaiser-Franz-Josef-Spital, 1st Medical Department, Wien, Austria;* [3]*KA Rudolfstiftung, Wien, Austria*

Background, Aims: Whether diabetes mellitus affects the prognosis of stroke patients, and whether admission hyperglycemia influences prognosis similarily in diabetic as non-diabetic patients is assessed controversially. Aim of the study was to 1) compare the course of diabetic and non-diabetic acute stroke patients and 2) assess the influence of admission serum glucose levels on mortality.
Methods: In 57 Austrian medical departments the hospital course of consecutive stroke patients was documented prospectively between June 1999-October 2000.
Results: Two-hundred-ninety-six(30%) of 992 patients had a history of diabetes mellitus. Intracerebral hemorrhage was more frequent in non-diabetic patients than diabetic(13 versus 5%, p=0.0001). Coronary heart disease was more frequent in diabetic than in non-diabetic patients(25 versus 24%, p=0.0003). The mortality was 18% among non-diabetic and 16% among diabetic patients(p=0.3559). Among patients who were discharged alive, the Barthel Index increased from 50 to 90 in non-diabetic and from 45 to 75 in diabetic patients(p=0.0403). In non-diabetic patients, admission serum glucose $>$9.2 mmol/L was associated with a more than 4-fold increased mortality, compared with patients with serum glucose $<$5.7 mmol/L($p<0.0001$).
Conclusions: Diabetic stroke patients need special care since they tend to have a poorer recovery than non-diabetic patients. Admission hyperglycemia in non-diabetic acute stroke patients predicts a poor prognosis.

2557 Effects of clopidogrel and aspirin in combination versus aspirin alone on platelets in patients after recent ischaemic stroke. For the PLavix Use for Treatment Of Stroke (PLUTO-Stroke) trial

V.L. Serebruany[1], A. Malinin[2], W. Ziai[3], A. Pokov[1], D.L. Bhatt[4], M.J. Alberts[5], D. Hanley[3]. [1]*HeartDrug, Towson, United States of America;* [2]*Barnaul, Russian Federation;* [3]*Johns Hopkins University, Baltimore, United States of America;* [4]*Cleveland Clinic, Cleveland, United States of America;* [5]*Northwestern University, Chicago, United States of America*

Background: persistent platelet activation may contribute to secondary vascular events in patients with ischaemic stroke. Clopidogrel is widely used in patients after recent ischaemic stroke; however, the ability of this thienopyridine to yield additional antiplatelet protection on top of aspirin has never been explored in a controlled study with the comprehensive assessment of platelet activity. We determined antiplatelet properties of clopidogrel with aspirin (C+ASA) versus aspirin alone (ASA) in patients after ischemic stroke in the frame of the PLUTO-Stroke trial.
Methods: seventy patients with documented ischemic stroke between 1 and 3 months earlier were randomly assigned to C+ASA, or ASA groups. All patients received ASA 81 mg for at least a month prior to screening. Other antithrombotic agents were not allowed. Platelet studies included ADP-, collagen- and arachidonic acid-induced conventional plasma aggregometry; shear-induced activation by PFA-100 analyser, and platelet reactivity by PFA-100 and Ultegra analyzers; expression of PECAM-1, P-selectin, GP IIb/IIIa (antigen and activity), vitronectin receptor, and formation of platelet-leukocyte microparticles by flow cytometry. Platelet tests were performed at baseline and after 30 days after randomisation.
Results: there were no deaths, hospitalizations, or serious adverse events. There were no differences in the baseline platelet characteristics between C+ASA and ASA groups, or significant changes in platelet parameters in the ASA group, except mild reduction of collagen-induced aggregation (p=0.001), however, there was a trend towards diminished platelet activity at 30 days. In contrast, therapy with C+ASA resulted in a significant inhibition of platelet activity assessed by ADP- (p=0.00001), and collagen-induced (p=0.02) aggregation; closure time prolongation (p=0.03), and reduction of platelet activation units with Ultegra (p=0.00001); expression of PECAM-1 (p=0.01), and GP IIb/IIIa activity with PAC-1 (p=0.02) when compared with ASA group. Therapy with C+ASA also resulted in the reduced formation of platelet-leukocyte microparticles (p=0.02). Arachidonic acid-induced aggregation, expression of GP IIb/IIIa antigen, P-selectin, and vitronectin receptor did not differ between groups.
Conclusion: treatment with C+ASA for one month provides significantly greater inhibition of platelet activity than ASA alone in patients after recent ischaemic stroke in the frame of the small randomised trial.

2558 Components of the metabolic syndrome and risk for first-ever acute ischaemic non-embolic stroke in elderly subjects

K. Kalantzi[1], H. Milionis[2], E. Rizos[2], K. Seferiadis[3], D. Mikhailidis[4], M. Elisaf[2], J. Goudevenos[1]. [1]*University Hospital of Ioannina, Dept of Cardiology, Ioannina, Greece;* [2]*University Hospital of Ioannina, Dept of Internal Medicine, Ioannina, Greece;* [3]*University Hospital of Ioannina, Laboratory of Biochemistry, Ioannina, Greece;* [4]*Royal Free Hospital, Dept of Clinical Biochemistry, London, United Kingdom*

Purpose: Metabolic syndrome (MetSyn) represents a constellation of lipid and non-lipid risk factors for cardiovascular disease and is recognized as a target for increased behavioural therapy. The aim of our study was to determine the association between acute ischaemic/non-embolic stroke and the MetSyn in elderly individuals was assessed in a population-based case-control study in the prefecture of Ioannina, Greece.
Methods: A total of 163 patients aged older than 70 years admitted with a first-ever acute ischaemic/non-embolic stroke and 166 healthy controls were included.
Results: The prevalence of MetSyn (defined according to NCEP/ATP III criteria) was high in stroke patients (46.0% vs. 15.7%, $p<0.001$). Compared to controls, patients with MetSyn showed higher concentrations of triglycerides, lipoprotein(a), uric acid and fibrinogen, and lower high-density-lipoprotein cholesterol (HDL-C) and apolipoprotein A-I levels. In logistic regression analysis, crude and adjusted odd ratios (OR) for MetSyn were 5.33 [95% Confidence Interval (CI), 2.91-9.79; $p<0.0001$] and 2.59 (95%CI, 1.24-5.42; p=0.012), respectively. The analysis of interaction between MetSyn and its individual components revealed significant associations with abdominal obesity [adjusted OR, 2.74, 95%CI, (1.15-6.50); p=0.02], hypertension (2.03 (0.91-4.49); p=0.08), high fasting glucose levels [2.95 (1.19-7.35); p=0.02], high triglyceride [5.55 (2.71-11.37); $p<0.0001$], and low HDL-C [5.42 (2.85-10.30); $p<0.0001$]. Notably, in stroke patients with the MetSyn the inverse relationship between HDL-C levels and ischaemic stroke was negated [OR, 1.04 (1.02-1.05); $p<0.0001$].
Conclusions: MetSyn is associated with an increased risk for acute ischaemic/non-embolic stroke in elderly subjects with significant contributions from its individual components. In the presence of MetSyn, HDL-C loses its protective role against ischaemic stroke.

DRUG-ELUTING STENTS FOR LEFT MAIN STENOSIS: CURRENT STATUS

2609 Percutaneous treatment of left main coronary artery disease with taxus paclitaxel-eluting stent. An analysis of the TRUE study

D. Antoniucci[1], A. Migliorini[1], G. Sangiorgi[2], G. Parodi[1], P. Agostoni[3], C. Di Mario[4], E. Grube[5], A. Colombo[3] on behalf of Taxus Real-life Usage Evaluation (TRUE) Study. [1]*University of Florence, Cardiology Department, Florence, Italy;* [2]*EMO Centro Cuore Columbus, Interventional Cardiology Unit, Milan, Italy;* [3]*St. Raffaele Hospital, Interventional Cadiology Unit, Milan, Italy;* [4]*Royal Brompton Hospital, Cardiology Department, London, United Kingdom;* [5]*Siegburg HeartCenter, Cardiology Department, Siegburg, Germany*

Purpose: The percutaneous treatment of unprotected left main coronary artery

(LMCA) disease is progressively gaining acceptance in light of the first results form drug-eluting stent registries. The Taxus™ paclitaxel-eluting stent (PES) has been proved effective in selected lesions of patients undergoing percutaneous coronary intervention (PCI), but data in more complex settings, such as LMCA, are lacking. We thus assessed early and mid-term results of patients treated for unprotected LMCA disease in the TRUE Study.
Methods: Consecutive high-risk patients undergoing Taxus stenting were enrolled at 7 European centers. Unprotected LMCA disease was one of the inclusion criteria along with small vessel (<2.75 mm) disease, long (> 28 mm) lesions, chronic total occlusions, bi/trifurcations and diabetes. Major adverse cardiac events (MACE), including death, myocardial infarction (MI), target lesion (TLR) and target vessel revascularization (TVR), were adjudicated at 1 and 7 months. Acute, sub-acute and late stent thrombosis were also evaluated.
Results: Across the 1050 included subjects, 113 (10.8%) were treated for unprotected LMCA disease. Mean left ventricular ejection fraction (LVEF) was 52% ± 11, with 16% patients with EF <40% and 15% patients in NYHA class III-IV. Multi-lesion intervention was done in 65% of the patients. In 66% of cases the distal LMCA was the target lesion. The 1-month MACE rate was 8.6%. Specifically, death rate was 2.9%, MI rate 3.9%, TVR rate 3.9% with 2% TLR (none of them by means of bypass surgery). No acute or sub-acute stent thrombosis occurred. At 7-months, in the 88 eligible patients, MACE rate was 26.1%, with 5.7% deaths, 4.9% MI and 18.1% TVR (with 13.1% TLR). Bypass surgery was the revascularization strategy in 3.7% of the patients. Only one (1.1%) late thrombosis occurred. Interestingly, the 7-months MACE rate was 14.7% in non-bifurcational LMCA, while in LMCA disease involving the bifurcation it was 33.3% (p=0.053).
Conclusions: Percutaneous treatment of unprotected LMCA disease with PES in high risk patients is feasible, leading to an acceptable mid-term mortality rate (which compares favourably with historical surgical registries of high risk subjects). The rate of repeated revascularizations is still significant mainly when the bifurcation is involved (22% vs. 12% in non-bifurcational LMCA), but lower than that from bare-metal stent registries. Of interest, in the majority of the cases the repeat revascularization was accomplished by means of percutaneous intervention, with a very low (<4%) rate of bypass surgery at 7 months.

2610 One year clinical and angiographic outcomes following drug-eluting stent implantation in left main bifurcation lesions

L. Ge[1], J. Cosgrave[2], I. Iakovou[2], P. Agostoni[2], G.M. Sangiorgi[2], F. Airoldi[2], N. Corvaja[2], A. Colombo[2]. [1]*Zhonghshan Hospital, Fudan University, Cardiology Department, Shanghai, China;* [2]*EMO Centro Cuore Columbus, Milan, Italy*

Purpose: To evaluate the long-term outcome following implantation of drug-eluting stents (DES) in unprotected left main (LM) bifurcation lesions.
Methods: We identified 70 consecutive patients who were treated with DES in unprotected LM bifurcation lesions from April 2002 to January 2004. Of these 42 patients were treated with sirolimus-eluting stent (SES) and 28 patients were treated with paclitaxel-eluting stent (PES).
Results: Stents to the left anterior descending and to the circumflex were implanted in 62 patients. During 1 year clinical follow-up, 3 (4.3%) patients died of cardiac causes. One of them had myocardial infarction and adjudicated as possibly due to stent thrombosis. Angiographic follow-up was available in 80% of patients. The per lesion restenosis rate was 13.4% in the entire cohort of which 10.7% occurred in lesions treated with SES and 16.1% in those treated with PES (p=0.58). All restenosis were focal and occurred in the lesions treated with a stent sized to post-procedural reference vessel diameter ratio <1.0 (17.6% vs.0%, p=0.04). The restenosis rate in lesions treated with ≤ 3.0 mm stents was 20.0% (12/60) and 6.5% (3/46) in the ones treated with >3.0 mm stents (p=0.06), with target lesion revascularization rate (TLR) of 29.4% (10/34) and 5.6% (2/36), respectively (p=0.01). The per patient TLR rate at 1 year was 17.1%. One year survival free from major adverse cardiac events was 77.1%.
Conclusions: Treatment of LM bifurcation lesions using DES is safe and feasible with low 1 year mortality. The need for revascularization in 17% of patients demands for improvement. A more liberal use of IVUS guidance could possibly improve some results.

2611 Immediate results and 6-month angiographic follow-up of the treatment of left main stenosis with drug eluting stent

M.E. Di Salvo[1], N. Garro[1], A. Petralia[1], F. Scardaci[1], G. Ussia[1], A.R. Galassi[1], S. Moshiri[1], C. Tamburino[2]. [1]*Ferrarotto Hospital, Interventional Cardiology, Catania, Italy;* [2]*Ospedale Ferrarotto, Istituto di Cardiologia, Catania, Italy*

Background: Unprotected left main (ULM) bare metal stenting (BMS) has become widely used, but restenosis rate remains high (20-to-40%).
Recently drug eluting stents (DES) have been introduced in clinical practice, but only few data concerning safety and reduction of restenosis in unprotected LM disease are available at the moment.
Methods: We report our series of 94 patients (pts) with ULM stenosis who underwent PCI with Sirolimus (34.1%) or Paclitaxel (65.9%) eluting stents from June 2002 to January 2005. Seven pts (7.4%) were affected by in-stent restenosis after a previous bare metal stenting. Mean pt age was 65 ± 9 y, the ejection fraction was 51 ± 12; 30 pts (33%) were diabetic, and 48 (52%) had unstable angina. Bifurcation was treated in 56% of pts. Stenosis in other vessels was in 89% of pts. The follow-up was at 1, 3 (clinical and stress test) and at 6 months (angiography).
Results: Procedural success was obtained in 98,7%. In-hospital MACCE were 3 (3.2%) deaths (1 acute thrombosis, 1 sub-acute thrombosis, 1 cardiac failure not related to stenting) and 1 CABG for ostial recoil. Non-Q wave AMI occurred in 1 pt (1,1%).
At 1-month clinical follow-up (86 pts) there was no recurrence of symptoms, 1 patient died for cardiac failure. At 6-month clinical follow-up 1 patient died for non-cardiac disease, 3 patients (4.2%) had TLR (2 re-PTCA and 1 CABG). Six-month angiography achieved in 70 pts showed restenosis in 5 pts (7.1%).
No different outcome was observed between Sirolimus and Paclitaxel stents.
Conclusion: Our preliminary data are encouraging; immediate results and mid-term outcome confirm the safety of DES implantation in ULM stenosis with a low rate of untoward events.

2612 Percutaneous treatment of unprotected left main coronary stenoses with paclitaxel-eluting stents. Mid-term results of a multicenter study

J.A. Baz[1], M. Valdes-Recarey[1], J.M. Hernandez[2], I. Lozano[3], J.M. De La Torre[4], V. Mainar[5], M. Sanmartin Fernandez[6]. [1]*Hospital Meixoeiro, Unidad de Cardiología Intervencionista, Vigo, Spain;* [2]*Hospital Clinico de Malaga, Unidad de Hemodinamica, Malaga, Spain;* [3]*Hospital Central de Asturias, Unidad de Hemodinamica, Oviedo, Spain;* [4]*Hospital Marques de Valdecilla, Servicio de Hemodinamica, Santander, Spain;* [5]*Hospital General de Alicante, Unidad de Hemodinamica, Alicante, Spain;* [6]*Vigo, Spain*

Although surgery remains the standard treatment for left main stenoses, preliminary experience with drug-eluting stents appears promising. In this regard, the majority of data comes from single center studies, mostly with sirolimus-eluting stents.
Aim: to evaluate the early and mid-term clinical results of a paclitaxel-eluting stent for the percutaneous treatment of unprotected left main lesions.
Methods: beginning on march/2003, a total of 91 patients with unprotected left main stenoses treated with Taxus® stents were included in a multicenter prospective study. There were no exclusion criteria, except patient or referral physician refusal. Technical issues, such as IVUS guidance, use of glycoprotein IIbIIIa inhibitors or predilatation method were left to operators' discretion. Combined aspirin and clopidogrel was maintained through a minimum of 6 months. Six-month angiographic follow-up was recommended.
Results: Mean age was 67.7 ± 11.4 years-old (88-39), female patients represent 20% and diabetics 33%. The indication for coronary revascularization was an acute coronary syndrome in 58% of the cases, including 9 patients with ST elevation MI (10%). Thirty-nine patients (43%) were considered poor surgical candidates (Euroscore > 6). Forty-four lesions (48%) were located at the bifurcation, including 15 cases (16%) with both LAD and CX ostia affected. An intra-aortic balloon pump was used prophylactically in 14% and glycoprotein IIbIIIa inhibitors in 44%. Transradial approach was used in 27% of the cases. Direct stenting was applied in 35%. Only 13% of the procedures were performed under IVUS guidance. One-month adverse events included: myocardial infarction in 5.5% and death in 4.4% (only one intraprocedural in a ST elevation MI case). At 6 months, total mortality was 9.9% (cardiac death in 5.5%). Among elective cases (n = 76), total mortality at 6 months was 4% (cardiac death in 1.4%). Target vessel revascularization was required in only 3.3%
Conclusions: in this high-risk population, percutaneous treatment of left main coronary artery disease with Taxus® stents is associated with low rates of target vessel repeated revascularization and cardiac death at 6-months follow-up.

2613 Percutaneous treatment of unprotected left main disease in the era of drug eluting stents

J. Pinto, E.J. Garcia Fernandez, M. Abeytua, L. Garcia Nielsen, G. Bocuzzi, E. Garcia, P. Avanzas, C. Cortina. *Hospital Universitario Gregorio Maranon, Department of Interventional Cardiology, Madrid, Spain*

Introduction: and Objectives: Left main disease is observed in 3-5% of the patients undergoing coronary angiography because of chest pain, congestive heart failure or cardiogenic shock. Coronary artery bypass graft has been thought to be the treatment of choice due to the procedural risk and longterm restenosis in distal lesions involving the bifurcation. We have analysed 2 years of experience in our centre with percutaneous treatement of unprotected left main disease using metallic or drug eluting stents according to the operator discretion.
Methods and Results: Since January 2003, 83 consecutive patients with significant stenosis of unprotected left main were electively treated with percutaneous interventional procedures in our centre. All the procedures had at least one stent implanted in 63 (73%) drug eluting stents were used) Criteria for stent selection were size and lesion complexity (big sizes > 4.0 mm and non bifurcation lesions were treated with metallic stents). Mean age was 68±11 years and 64 (77%) were male. In 69 patiens (83%) the stenosis was located distally in the left main and in 46 (54%) there was a significant involvement of at least one of the branches. Left ventricular ejection fraction was 48.7±11.8. Mean calculated EuroSCORE

was 5.6±2.8 and 70 patients (84%) had multivessel disease. The procedure was angiographically successful in 83 (100%) patients. One patient (1.2%) died before discharge and one had a non Q myocardial infarction. During the 30 days post procedure one more patient died. At 6 month follow up there was one more death for an accumulated death of 3.6% Six patients (7%) underwent target lesion revascularization (4 PCI and 2 CABG; 2 metallic (10%) and 4 DES (6%). With a mean follow up of 9.8 months, 72 (89%) patients were free of major cardiac events (death, myocardial infarction and target lesion revascularization).
Conclusion: Percutaneous treatment of unprotected left main disease is associated with a high rate of immediate and midterm success. In the era of drug eluting stents, adequate selection of stent type can lead to very good results independently of type of stent used. Availavility of bigger sizes drug eluting stents will probably generalize the use of DES in the percutaneous treatment of left main disease.

2614 Preliminary results of the left main TAXUS pilot study

T. Lefevre[1], O. Darremont[2], M. Silvestri[3], M.C. Morice[4], Y. Louvard[4], J.L. Leymarie[2], P. Garot[5], T. Unterseeh[5]. *[1]I.C.V. Paris-Sud, Cardiologie Interventionnelle,ANGIO/ICPS, Massy, France; [2]Clinique Saint Augustin, Bordeaux, France; [3]UCV, Marseille, France; [4]Institut Hospitalier Jacques Cartier, Institut Cardiovasculaire Paris Sud, Massy, France; [5]Hôpital Claude Galien, Institut Cardiovasculaire Paris Sud, Quincy, France*

Background: CABG is the gold standard treatment of unprotected left main (LM) stenosis. However, PCI using bare metal stents has emerged as an alternative to cardiac surgery with favorable 12-month outcome despite increased re-intervention rates. We aimed to investigate the feasibility, safety and efficacy of DES in the treatment of unprotected LM lesions.
Methods: A pilot study using the paclitaxel-eluting TAXUS stent was conducted in 3 French centers with a large experience in LM stenting. Pts with de novo LM stenosis were prospectively and consecutively included after informed consent. For distal LM stenosis, the strategy consisted in stenting of the main branch followed by provisional T stenting of the side branch. All Pts received clopidogrel and aspirin before and after the procedure (at least 6 months). A clinical follow-up was scheduled at 1, 6 and 12 months after the indexed procedure. Angiographic follow-up was recommended at 4 to 6 months after the procedure.
Results: Between March 2003 and January 2005, 205 Pts were included, mean age 69+11 years, 75% male, 36% unstable angina, 29% diabetics, 30% 3-vessel disease. The mean Euroscore was 4.8+3.4 (estimated mortality rate after surgery 8.0±17.3%). The mean LM reference diameter was 3.7±0.5 mm. LM lesion was ostial-proximal in 27%, mid shaft 10% and distal 78% (non exclusive). All Pts were successfully treated on the LM (stent length 18±6mm). In Pts with distal LM stenosis, a second stent was used in 37% (stent length 13±5mm) and a final kissing balloon inflation was performed in 96%. Apart from the LM stenosis, a total of 1.2±0.9 lesions were treated during the hospitalisation (total stent length 46±17 mm). At hospital discharge (5±4 days), the MACCE rate was 3.4%. Two Pts died (1%), thrombotic occlusion during the procedure (N=1) and suddenly at day 2 (N=1). One Pt had subacute thrombosis of LAD stent at day-5 and was treated successfully by re-PCI and 4 Pts had asymptomatic non-Q-wave MI. One pt had sudden death after discharge at day 8. The death rate at 1-month follow-up was 1.5%. A total of 102 Pts have reached 6-month follow-up and 76 of them had a repeat coronary angiogram. There was 2 additional deaths (non-cardiac) but no late stent thrombosis or MI. The restenosis rate was 6.6% of the pts (N=5), due to geographical miss in 4 of them and due to diffuse in-stent restenosis in one.
Conclusion: LM PCI using the TAXUS stent is feasible and safe. Preliminary results showed favourable 6 month follow-up. Final results will be presented at the meeting.

CLINICAL TRIALS: PERCUTANEOUS CORONARY INTERVENTIONS VERSUS SURGERY

2615 Two-year follow-up of coronary stenting, bypass graft (CABG) and medical therapy (MED) for left-anterior-descending artery(LAD) lesions; a quantitative coronary angiography(QCA) matched comparison

Y. Wakita[1], Y. Ozaki[2], T. Yasukawa[3], H. Shinjoh[3], Y. Kuroda[3], K. Asai[3], H. Takashima[3], T. Itoh[3]. *[1]Aichi Medical University, Department of Cardiology, Nagakute, Japan; [2]Fujita Health University, Division of Cardiology, Toyoake, Japan; [3]Aichi Medical University, Department of Cardiology, Nagakute, Japan*

While coronary stenting and bypass graft(CABG) are well-accepted treatments for LAD lesions, log-term outcome has not yet fully understood as compared to medical therapy(MED). One-thousand-forty-nine patients with LAD lesions were assigned to one of three treatments(PCI,MED,CABG). Of the 1049 patients baseline angiographic features were matched between stenting(n=115), CABG(n=115) and MED(n=115) by QCA using reference-diameter(RD) less than 2SD of the QCA-reproducibility(=0.10mm) and minimal-lumen-diameter(MLD) less than 3SD. Major-adverse cardiac-events(MACE) were defined as cardiac death, Q-wave myocardial infarction(MI) and CABG. Minor Inconvenient cardiac-event(MICE) was restenosis after stenting. All cardiac events were examined during an average 22 month-follow-up.

table 1

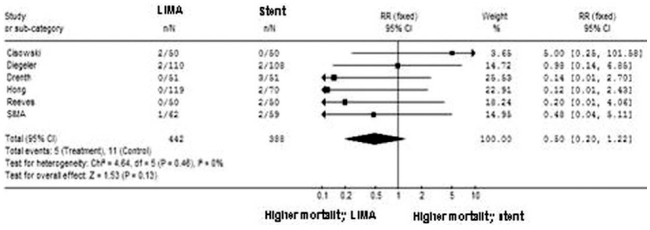
	Stent	CABG	MED	p(ANOVA)
RD pre(mm)	2.27±0.31	2.24±0.61	2.22±0.38	n.s.
MLD pre(mm)	0.89±0.24	0.92±0.23	0.91±0.25	n.s.
MACE(%)	8	2	12	<0.05
Overall cardiac events(%)	38	2	12	<0.01

Conclusions: Two-year MACE were significantly lower in CABG than PCI and MED in this matched population with small vessels. Whilst drug-eluting-stent(DES) may eliminate the restenosis(MICE), CABG to the LAD could have an advantage in some patients.

2616 Mortality rate after left internal mammary artery versus coronary stenting for isolated disease of proximal left anterior descending coronary artery: a meta-analysis from six randomised trials

R. Moreno Gomez[1], G. Guardado[2], C. Fernandez[2], F. Alfonso[2], R.A. Hernandez[2], E. Rodriguez[2], C. Macaya[2]. *[1]Madrid, Spain; [2]Hospital Clinico San Carlos, Cardiology Dept., Madrid, Spain*

The results of randomized trials comparing left internal mammary artery (LIMA) versus coronary stenting (CS) for isolated proximal left anterior descending coronary artery disease (IPLAD) have considered CS only as an alternative to LIMA, CS being associated with no advantages over LIMA, and even with a higher incidence of events secondarily to higher need for subsequent revascularization procedures. The aim of this study was to compare mortality rates after LIMA and CS for IPLAD.
Methods: Six randomised studies comparing LIMA and CS for IPLAD were identified. Overall, 830 patients were included (388 allocated to LIMA, and 442 to CS). Follow-up in these studies ranged from 6 months to 4 years. Mortality rates during follow-up, as well odds ratio for mortality comparing patients allocated to LIMA and CS were calculated. Out of the 6 trials, bare metal stents were used in 5, and sirolimus-eluting stents in 1.
Results: Mortality rate was 2.8% in patients allocated to LIMA (11/388), in comparison with 1.1% in those allocated to CS (5/442) (Odds Ratio 2.51; 95% Confidence Interval: 0.88 – 7.15; p=0.075). See figure:



Figure

Conclusion: in patients with isolated proximal LAD disease, there is a trend to higher mortality in patients allocated to LIMA in comparison with those allocated to CS.

2617 Clinical judgment and treatment options in stable multivessel coronary artery disease: results from the 1-year follow-up of the MASS II Study

A. Pereira[1], N.H.M. Lopes[2], P.R. Soares[2], J.E. Krieger[2], S.A. Oliveira[2], L.A.M. Cesar[2], J.F. Ramires[2], W. Hueb[2]. *[1]Heart Institute Sao Paulo, Cardiology, São Paulo, Brazil; [2]Heart Institute Sao Paulo, Cardiology, São Paulo, Brazil*

There is still no consensus on the best treatment for patients with stable multivessel CAD and preserved LV function. Here, we examine the predictive power of clinical judgment in the incidence of cardiovascular events in a group of individuals with multi-vessel CAD prospectively followed-up in the MASS II Study, a clinical trial designed to compare medical treatment (MT), angioplasty/stent (PCI) and surgical myocardial revascularization (CABG).
Methods: Preferred treatment allocation was recorded for each of the 611 randomized patients in the MASS II Study prior to randomization. We have divided our sample according to physician-guided decision and randomization result. Patients were subsequently randomized and treated according to randomization status. The incidence of the composite end-point of death, myocardial infarction and refractory angina was compared between patients concordant and discordant regarding physician-decision and randomization-decision.
Results: The number of concordant individuals (physician-guided x randomization) was 292 (48.2%), being not statistically different between the three studied treatments (p = 0.11). Overall, there was a significant difference (p = 0.02) in the incidence of combined events, due to a higher incidence of events in the group of discordant patients as compared to concordants. In a Cox proportional hazard model adjusted for age, sex, treatment allocation, hypertension, diabetes, smok-

ing status and total cholesterol, clinical judgment was still a powerful predictor of outcome (p = 0.01). The main subgroup explaining this difference was due to a worse outcome in the subgroup of discordant patients submitted to PCI (p = 0.003). Angiographic variables were more used in the clinical decision regarding PCI than clinical variables and the only independent predictor of concordance status in the PCI group was the number of diseased vessels (p = 0.01). Interestingly, PCI was as good as an option for treating multi-vessel CAD as medical or surgical treatment in the subgroup of patients where PCI would be clinically chosen (p=0.42).
In conclusion, our data suggest that the best treatment option for individuals with multi-vessel CAD and preserved left ventricular function defined by the physician is a predictor of the incidence of cardiovascular events. Angiographic variables appear to be more commonly used in the decision-making process regarding PCI. Clinical decision-making appears to be able to define a particular subgroup of patients where PCI treatment is as good as CABG or MT for this patient population.

2618 Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularisation: LE MANS case controlled study

P. Buszman[1], E. Peszek-Przybyla[1], B. Bialkowska[2], M. Wilczynski[3], M. Debinski[1], K. Milewski[1], A. Bochenek[3], M. Tendera[4]. *[1]Upper-Silesian Heart Center, Coronary Care Unit, Katowice, Poland; [2]Upper-Silesian Heart Center, Coronary Care Unit, Katowice, Poland; [3]Upper-Silesian Heart Center, Department of Cardiac Surgery, Katowice, Poland; [4]Upper-Silesian Heart Center, 3rd Department of Cardiology, Katowice, Poland*

Background: The advent of coronary stenting provided more predictable acute and long term results making percutaneous intervention (PCI) a potentially viable alternative to coronary bypass surgery (CABG) in selected pts with left main (LM) disease.
Methods: 289 consecutive pts with >50% LM stenosis were screened for eligibility for intent-to-stent PCI or CABG from March 2002 to August 2004. 122 pts deemed suitable for both PCI and CABG were enrolled in this case matched study. PCI pts (n=61) had planned angiography within 4-6 months. LV function was evaluated by 2-D echo before and 12 months after index procedure. F-up visit including treadmill stress test was scheduled after one year.
Results: PCI vs CABG cohorts compared for age (60.8±10.8 vs 61.0±8.4, p=0.91), gender (79 vs 74% male, p=0.67), nr of additional diseased vessels (2.04 vs 2.3, p=0.12), CCS functional class (3.1±0.9 vs 3.0±0.9, p=0.67), EF(52.1±14.4 vs 53.9±7.5%, p=0.35), presence of diabetes (17.3 vs 16.3%, p=0.99), Euroscore (3.1±2.5 vs 3.4±2.7, p=0.52) and distal LM involvement (54.1 vs 45.9%, p=0.137). LIMA was used in 66% of CABG pts and drug eluting stents in 15% of PCI pts. During the index hospitalization there were no deaths with PCI and 3 deaths with CABG (p=0.08). PCI was also associated with less major adverse events (MAE, defined as myocardial infarct, heart failure, repeat revascularisation, stroke, serious bleeding or infection, 1.6 vs 29.5%, p< 0.001) and hospital days (7.04±5 vs 11.0±4.2 days, p< 0.001). After 17.9±6.7 month f-up there was 1 death with PCI, no death with CABG and higher MAE with PCI (13.1 vs 32.7%, p= 0.018). Repeat revascularization was higher with PCI (20% vs 8%, p= 0.12) but functional CCS class after 12 month improved equally after PCI and CABG (1.3±0.9 vs 1.0±1.2, 2-way ANOVA p=0.12). LM in-stent restenosis occurred in 9 pts (14.7%) and was treated with repeat PCI. EF improved slightly with PCI to 55.1±14.2%, (p=0.09), while after CABG remain unchaged (53.9±8,6, p=0.93). One year after the procedure pts after PCI perfomed better on tredmill stress test (workload 9.6±2.7 vs 7.5±3.9 METs, p=0.001). Kaplan-Meier analysis did not show any significant differences in survive rate and MAE free survival between the groups (F Cox test, p=0.33). A randomized experience is ongoing and 6 month f-up of 80 pts will be presented at the meeting.
Conclusion: Stent supported PCI can be performed with favorable acute and late outcomes in comparison to CABG in selected pts with LM disease. Similar acute results with improved late outcomes would be expected with routine use of DES.

2619 Multiple vessel stenting in drug eluting stent era: one year follow up of the ERACI III study

A. Rodriguez[1], L. Grindfeld[2], C. Fernandez-Pereira[3], J. Mieres[3], D. Berrocal[2], C.F. Vigo[3], W. O'Neill[4], I. Palacios[5] on behalf of ERACI III Investigators. *[1]Otamendi Hospital, Interventional Cardiology Dept., Buenos Aires, Argentina; [2]Italian Hospital, Interventional Cardiology, Buenos Aires, Argentina; [3]Otamendi Hospital, Interventional Cardiology, Buenos Aires, Argentina; [4]William Beaumont Hospital, Cardiology Dept., Royal Oak MI, United States of America; [5]Massachusetts General Hospital, Cardiac Unit, Boston, United States of America*

Background: Previous randomized data (ERACI II) between Coronary Bypass Surgery (CABG) vs bare stent therapy(PCI) in patients(pts) with multiple vessel disease demonstrated a significantly lower incidence of repeat revascularization procedures (TVR) in those pts allocated in CABG group.The role of Drug Eluting Stent (DES) therapy in similar cohort of pts are not well stablished.
Methods: Pts with multiple vessel disease meeting clinical an angiographic criteria of the previous ERACI II trial, were included prospectively and consecutively in five centers in Buenos Aires,during June 2002 to September 2004 all treated with DES (ERACI III).At least one DES was implanted. Primary end point was to compare incidence of repeat revascularization procedures (TVR) and MACCE (death,myocardial infarction, stroke and TVR) between ERACI III pts (225) vs ERACI II pts, PCI (225) and CABG (225) arm. Late stent thrombosis was suspected under the presence of cardiac death or Q myocardial infarction in the target vessel and confirmed by a repeat angiogram. Clopidogrel 75mg per day during six months were indicated. A mean clinical follow up at 12.8 months was obtained.
Results: Comparing ERACI II, ERACI III pts had similar baseline clinical and angiographic characteristics. Unstable Angina 78%,Diabetics 21% and Three vessel disease 47%.Stent/pt in ERACI III was higher compared to ERACI II PCI arm p=0.08. In ERACI III,all the six pts with late stent trhombosis was associated with antiplatelet therapy discontinuation.
*p=0.034 **p=0.014 # p=ns ## 0.044

	ERACI III	ERACI II stent arm	ERACI II CABG arm
TVR	8.8% * #	17% *	5.3%#
MACCE	14.2% **	26.2% **	20%
Late stent thrombosis	2.6% ##	0 ##	

Conclusions: ERACI III pts compared to ERACI II, PCI arm, showed a significant lower incidence of TVR and MACCE. Compared with CABG arm there were a trend to lower MACCE in ERACI III pts.

2620 Arterial revascularitation therapies study, part II. Sirolimus-eluting stents for the treatment of patients with multivessel de novo coronary artery lesions

C. Macaya on behalf of all the ARTSII investigators. *Hospital Clinico San Carlos, Servicio de Cardiologia, Madrid, Spain*

Background: Arterial Revascularization Therapies Study (ARTS1) was a randomized multicenter trial of 1205 patients with multivessel disease (MVD), comparing surgery (ARTS1-CABG, n=605) against bare metal stenting (ARTS1-BMS, n=600) on clinical outcome, costs and cost-effectiveness. At 1 year, survival free from major adverse cardiac and cerebrovascular events (MACCE) was 87.8% in the ARTS1-CABG versus 73.8% in ARTS1-BMS, driven by a 17.2% difference in repeat revascularization favoring CABG. As the sirolimus stent(SES) has reduced restenosis compared to BMS, further evaluation of MVD stenting with SES versus the CABG and stent arms of ARTS I are warranted.
Methods: ARTS II is a multicenter (n=45), non-randomized, open-label, stratified trial with 607 patients treated with SES (ARTS2). The primary aim is the effectiveness of SES versus ARTS1-CABG measured as survival free of MACCE at 1 year. Secondary objectives include MACCE at all follow-up visits (1 & 6 months, 1, 3 & 5 years), quality of life and cost effectiveness.
Results: In ARTS2 there were 2.5 ± 0.5 diseased vessels vs. 2.3 ± 0.5 in ARTS1-CABG and 2.2 ± 0.5 in ARTS1-BMS. The number of treated lesions were 3.2 ± 1.1 (ARTS2) vs. 2.6 ± 1.0 anastomosed segments (ARTS1-CABG) and 2.5 ± 1.0 treated lesions (ARTS1-BMS). Postprocedural CK-MB release > 5 times upper limit of normal was observed in 1.5% in ARTS2 patients vs. 12.7% in ARTS1-CABG and 6.2% in ARTS1-BMS. ARTS2 patients received 3.7 ± 1.5 stents with average total stented length of 73 ± 32 mm vs. 2.8 ±1.3 and 48 ± 22 mm in ARTS1-BMS. At 1 month, stent thrombosis occurred in 5 (0.8%) in ARTS2 vs. 17 patients (2.8%) in ARTS1-BMS.
At 6 months, survival free of MACCE was 93.6% in SES vs. 91.0% in ARTS1-CABG and 80.0% in ARTS I-BMS. Revascularization free survival was 97.3% in ARTS2 vs 94.5% in ARTS1-CABG and 84.7% in ARTS1-BMS.
Conclusions: Despite more extensive disease and treatment, the overall MACCE rate at 6 months in ARTS II is systemically lower than in ARTS I for both CABG and stent arms. Lower repeat revascularization appears to be the main driver for an overall lower MACCE rate in ARTS II compared to the ARTS1-BMS group. The primary endpoint of survival free of MACCE at one year and a subanalysis on stable versus unstable angina and the use of reopro will be presented at the meeting.

NOVEL THERAPEUTIC STRATEGIES IN CHRONIC HEART FAILURE

2625 Effects of aldosterone blockade in patients with mild-moderately severe heart failure treated with a beta-blocker

N. Murphy[1], C. Berry[2], C. Fisher[1], A. Seed[1], G. DeVito[3], S. Galoway[4], P. Vallance[4], J.J.V. McMurray[1]. *[1]University of Glasgow, Department of Cardiology, Glasgow, United Kingdom; [2]Western Infirmary, Department of Cardiology, Glasgow, United Kingdom; [3]University of Strathclyde, Department of Physiology, Glasgow, United Kingdom; [4]University College Hospital, Department of Medicine, London, United Kingdom*

Background: Spironolactone improves prognosis in severe heart failure (HF), however, the effects of this drug in patients with mild-moderate HF treated with a beta-blocker are uncertain.
Methods: We conducted a randomised, double-blind, placebo placebo controlled

study of spironolactone (25 mg daily) in patients with optimally treated HF due to left ventricular systolic dysfunction. Blood was collected at baseline and after 12 weeks for measurement of arginine vasopressin (AVP), b-type natriuretic peptide (BNP), a marker of collagen turnover (procollagen type III N-terminal amino peptide [PIIINP]), and endogenous inhibitors of nitric oxide synthase (asymmetric dimethylarginine [ADMA]). Heart rate variability and cardiopulmonary function at rest or in response to exercise were also quantified. Compliance with study treatment was confirmed by pill-counts. Comparisons of mean (standard deviation [SD]) change in variables between placebo and spironolactone -treated groups were performed using ANOVA with correction for baseline differences.
Results: 40 patients with NYHA class I (20%); II (70%) or III (10%) HF were randomised. Spironolactone-treated patients were older (mean (SD) age 65(7.4) yrs v 59(9.5) yrs, but the groups were well matched otherwise. Two placebo-treated patients did not complete the study. No changes were observed in any of the study tests in the placebo-treated patients. In spironolactone-treated patients, an increase from baseline was observed in serum potassium concentration: 4.4(0.4) mmo/L to 4.7(0.5) mmol/L, P=0.05. Decreases from baseline in the spironolactone group were found in the plasma concentrations of PIIINP: 3.5(1.0) mmolL to 2.9(0.6) mmolL, P=0.04; BNP: 116(140) pg/ml to 53(64) pg/ml, P=0.09 and ADMA: 0.7(0.2) mmolL to 0.5(0.05) mmolL; P=0.008. Creatinine clearance decreased by - 39.1(39.8) mL/min in spironolactone-treated patients. No other differences were observed.
Conclusions: Aldosterone receptor blockade resulted in potentially beneficial changes in potassium and some biomarkers. Although renal function declined, spironolactone was well tolerated.

2626 Elevated plasma asymetric dimethylarginine (ADMA) in CHF patients: effect of allopurinol treatment on ADMA and on free oxygen radical load

W. Doehner[1], S.M. Bode-Boeger[2], J. Martens-Lobenhoffer[2], S. von Haehling[3], M. Cicoira[3], M. Rauchhaus[1], D.O. Okonko[3], S.D. Anker[1]. *[1]Charite, Virchow Klinikum, Dept. of Cardiology, Berlin, Germany; [2]Otto-von-Guericke University, Clinical Pharmacology, Magdeburg, Germany; [3]National Heart and Lung Institute, Cardiac Medicine, London, United Kingdom*

Background: asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase (NOS), affects regulation of vasodilator capacity via reduction of NO synthesis and increased generation of oxygen free radicals (OFR). Endothelial dysfunction and increased OFR are characteristic findings in chronic heart failure (CHF). Elevated ADMA levels may contribute to these abnormalities in CHF. Allopurinol treatment has been shown to decrease OFR load and improve vasodilator capacity. We studied ADMA in patients with stable CHF and aimed to test whether allopurinol reduces plasma ADMA levels in these patients.
Methods: CHF patients (n=16, mean age 68±2y, NYHA 2.4±0.6, peak VO2 14.3±3.5 mL/kg/min, serum uric acid 562 ±81 μmol/L, range 455–743 μmol/L) were in random order allocated to allopurinol 300 mg per day or placebo for one week in a single center study in a double-blinded, cross-over study design. Patients were hyperuricemic but free of gout and had no history of allopurinol or uricosuric treatment. At baseline and after each treatment phase plasma levels of ADMA, symmetric dimethylarginine (SDMA), arginine and allantoin, (a marker of OFR exposure) were measured.
Results: ADMA was elevated in CHF patients at baseline compared to reference control values from our laboratory (0.523±0.11 vs 0.330±0.06 μmol/L, $p<0.01$). ADMA remained elevated after placebo (0.533±0.078 μmol/L). Allopurinol therapy decreased ADMA to 0.505±0.079 μmol/L (vs placebo: $p<0.03$). SDMA was also elevated at baseline compared to controls (0.883±0.274 vs 0.442±0.09 μmol/L, $p<0.05$), but did not change after allopurinol ($p>0.5$). Arginine did not change during the study (allopurinol vs placebo: 75.6±23.1 vs 75.9±21.1 μmol/L, $p>0.5$). Allantoin was elevated in CHF compared to reference control values from our laboratory (25.6±3.80 vs 14.9±7.9 μmol/L). After allopurinol treatment, allantoin levels were reduced by 19% (21.4±3.87 μmol/L $p<0.02$ vs baseline).
Conclusion: ADMA plasma levels are increased in CHF patients. Allopurinol treatment results in a significant reduction of ADMA potentially via improved activity of the ADMA degrading enzyme dimethylarginine dimethylaminohydrolase. This is paralleled by a reduction of allantoin, indicating decreased free radical load. Allopurinol may represent a new antioxidative strategy to reduce ADMA in CHF.

2627 Use of insulin sensitizing agents in outpatients with congestive heart failure appears safe, and may have important clinical benefits when compared with sulfonylureas and insulin

R.A. Krasuski[1], B. Smith[2], S. Carey[1], A.D. Galbreath[3], K.C. Stajduhar[4], M.D. Kwan[4], R. Ellis[1], G.L. Freeman[3]. *[1]Wilford Hall Medical Center, Cardiology, Lackland AFB, United States of America; [2]Univ. of Texas Disease Managment Ctr., San Antonio, United States of America; [3]University of Texas Health Science Ctr, Cardiology, San Antonio, United States of America; [4]Brooke Medical Center, Cardiology, San Antonio, United States of America*

Purpose: Many standard therapies in diabetes are contraindicated in patients with congestive heart failure (CHF) due to renal dysfunction and fluid issues. Recent population studies have focused on hospitalized patients and show conflicting results. This study was designed to examine impact of antiglycemic therapy on clinical outcomes in CHF outpatients.
Methods: We examined a cohort of 1063 community-based patients with CHF randomized into a prospective, controlled clinical trial of CHF disease management. CHF was defined by symptoms and systolic or diastolic dysfunction by echo. Medication profiles were collected at enrollment and follow-up was over 18 months. Medications were grouped into 2 classes: insulin secretors (sulfonylureas and exogenous insulin) and insulin sensitizers (glitazones and metformin); patients receiving only one of these classes were compared.
Results: The 299 diabetic patients (28% of the cohort) were older, had a higher prevalence of coronary disease (76% vs. 57%, $p<0.001$), and were more likely treated with an ACE inhibitor. Despite no observed mortality difference, hospitalization for CHF was significantly more frequent in diabetics ($p<0.001$). More than twice as many patients were treated with secretors than with sensitizers (~30% of each group were NYHA Class III or IV). No difference was seen in hospitalization for CHF, but a trend toward lower mortality was present with sensitizers (see below). Results remained consistent after adjustment for baseline differences.

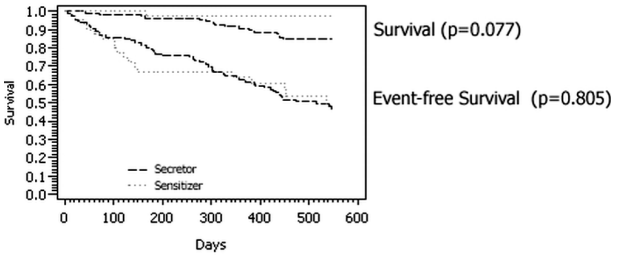


Figure 1

Conclusion: Diabetes has an important impact on heart failure hospitalization in outpatients with CHF. The use of insulin sensitizers in these patients appears safe, and may have important clinical benefits compared to sulfonylureas and insulin.

2628 Acute and chronic effects of subcutaneous insulin-like growth factor-1 (IGF-1) on haemodynamics in chronic heart failure

H.P. Brunner La Rocca[1], R. Schindler[2], W. Kiowski[3], D. Ramsay[3], A. Linka[2], J. Zapf[4], M.Y. Donath[4]. *[1]Kantonsspital Basel, Kardiologie Dept., Basel, Switzerland; [2]University Hospital, Cardiology, Basel, Switzerland; [3]University Hospital, Cardiology, Zurich, Switzerland; [4]University Hospital, Endocrinology, Zurich, Switzerland*

Insulin-like growth factor-1 (IGF-1) enhances myofibrillar development in cardiomyocytes of rats in culture and in vivo. Furthermore, cardioprotective effects were found in various rat models of heart failure. In human, IGF-I has vasodilatory effects and improves cardiac function in healthy volunteers. Acutely, it also has positive effects on haemodynamics in patients with heart failure. However, chronic effects on cardiac function in human are not known. We, therefore, compared the acute and chronic effects of IGF-1 sc. in patients with chronic heart failure (CHF).
Methods: Fifteen patients (13 male, age 52±13 years) with CHF (left ventricular ejection fraction <40%) under stable condition were randomly assigned to IGF-1 sc 60 μg/kg body weight/day (n=7) or placebo (n=8) for 3 months. Right-heart catheterisation using a Swan-Ganz catheter and thermodilution was performed at baseline and after 3 months of therapy. Additionally, haemodynamic measurements were repeated 3 hours after injection. In addition, ergospirometry was performed on separate days before and after 3-month therapy and a third time after another 3 months.
Results: IFG-1 increased cardiac output 3 hours after injection (4.5±0.9 to 5.1±0.5 vs placebo 4.4±0.8 to 3.8±0.6 l/min, p<.05) and decreased pulmonary (173±76 to 138±61 vs placebo 160±45 to 210±82 dyne s cm^{-5}) and systemic vascular resistance (SVR: 1218±196 to 1130±108 vs placebo 1295±272 to 1596±333 dyne s cm^{-5}, all $p<0.05$). Also, filling pressures tended to decrease, but the difference between the 2 groups did not reach statistical significance (pulmonary wedge pressure 12±9 to 9±6 vs placebo 12±7 vs 10±7mmHg). In contrast, no haemodynamic changes were seen after 3 months therapy in either group (e.g. cardiac output 4.7±0.5 to 4.7±1.0 vs placebo 4.1±0.8 vs 4.2±0.8 l/min; SVR 1173±129 to 1190±205 vs placebo 1390±230 to 1433±439 dyne s cm^{-5}, all $p>0.1$). In addition, spiroergometry did not change significantly in either group (VO2max 1770±424 to 1803±447 and 1817±493 3 months later vs placebo 1633±690 to 1581±441 and 1744±446 ml/min 3 months later, $p>0.1$).
Conclusion: Whereas IGF-1 has positive haemodynamic effects acutely in patients with congestive heart failure, no long-term benefits could be found after 3-month therapy.

2629 Ultra-low doses of antibodies to c-ending fragment of the angiotensin II type 1 receptor in patients with congestive heart failure: first clinical experience

V.V. Ivanenko[1], N.A. Davidova[2], S.A. Sergeeva[3], O.I. Epshtein[3], V.I. Petrov[4], Y. Lopatin[5]. *[1]Volgograd Cardiology Centre, Coronary Artery Disease, Volgograd, Russian Federation; [2]Medical University, Cardiology, Volgograd, Russian Federation; [3]Materia Medica Holding, Moscow, Russian Federation; [4]Volgograd Medical University, Clinical Pharmacology, Volgograd, Russian Federation; [5]Volvograd Cardiology Centre, Coronary Artery Disease Dept., Volgograd, Russian Federation*

Background: Ultra-low doses of antibodies to C-ending (intracellular) fragment of the angiotensin II type 1 receptor (anti-AT1) are a principally new class of neurohumoral modulators. The aim of our study was to investigate the efficacy and safety of anti-AT1 in pts with congestive heart failure (CHF).
Methods: 58 pts (mean age 56.1±0.9 years) with CHF (NYHA class II-IV, mean 2.8±01, mean ejection fraction 27±0.7%) were included into the randomized, single-blind, placebo-controlled study. Baseline therapy (ACE inhibitor, b-blocker, diuretics and digoxin) wasn't changed during the study. Pts with CHF were randomly assigned to anti-AT1 3 tabs/day (group I, n=30) or placebo (group II, n=28). 2D Echo, tredmill-test (Naughton), 6-min walking test and analysis of heart rate variability (HRV) were performed before and after three months of therapy.
Results: After 3 months of therapy with anti-AT1 NYHA class reduced to 17% (p=0,008), in placebo group to 7.1% (n.s.). Significant increase of left ventricular ejection fraction was noted in both groups: group I +22.1% (p<0.0001), group II +12.9% (p=0.02). However, significant changes of stroke volume (+15%, p=0.04), end diastolic volume (-7%, p=0.04), end systolic volume (-14.2%, p=0.002) were observed in group I, while in placebo group these changes were not significant. Significant increase both exercise time (+13.3%, p=0.04) during tredmill-test and distance during 6-min walking test (+11.2%, p=0.001) was noted only in the group I. Analysis of HRV changes showed the increase of SDNN in group I (+20.6%, p=0.07). In placebo group SDNN decreased to 6.6% (n.s.). Adverse events related with anti-AT1 were not observed.
Conclusions: The adding of ultra-low doses of antibodies to C-ending fragment of the angiotensin II type 1 receptor to standard therapy is a promising way for treatment pts with CHF. Large clinical trials are indicated.

ARTERIAL REMODELLING. FOCUS ON THE VASCULAR SMOOTH MUSCLE CELL

2631 Smooth muscle cells in human atherosclerotic plaque secrete HMGB1, and proliferate in response to it

A. Porto[1], R. Palumbo[1], M. Pieroni[2], G. Aprigliano[3], R. Chiesa[3], A. Maseri[3], M. Bianchi[1]. *[1]Vita-Salute University S. Raffaele, Dept Biological-Technological Research, Milan, Italy; [2]Catholic University, Cardiology Department, Rome, Italy; [3]San Raffaele Hospital, Cardio-Thoracic-Vascular Department, Milan, Italy*

Background: High Mobility Group Protein 1 (HMGB1) is a chromatin protein leaked out by necrotic cells and secreted by activated myeloid cells. The extracellular protein is a potent mediator of inflammation. We tested whether cells within human atherosclerotic plaques could secrete HMGB1and respond to it.
Methods and Results: We put into culture human carotid endoarterectomy specimens (n=25), obtained from patients with >70% carotid stenosis, and normal internal mammary arteries specimens from patients (n=10) undergoing coronary artery by-pass surgery. By western blot we found a large amount (40 pg/mg of tissue) of HMGB1 in the supernatant of atherosclerotic but not of normal arteries. The absence in the supernatants of lactate dehydrogenase, a marker of necrosis, indicated an active secretion of HMGB1. Extracellular HMGB1 in atherosclerotic plaque originates not only from endothelial and neointimal foam cells, but also from smooth muscle cells (SMCs). SMCs from plaques contained HMGB1 in the cytosol whereas SMCs of normal arteries contained HMGB1 only in the nuclei; a cytoplasmic localization is an indication of active secretion. Significantly, after cholesterol loading HMGB1 was secreted by cultured SMCs isolated from normal and atherosclerotic arteries (Fig. 1). In turn, human aorta SMCs proliferate and migrate in response to HMGB1. Thus, SMCs both secrete and respond to HMGB1.

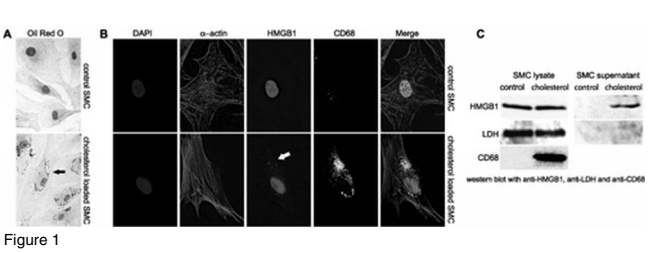


Figure 1

Conclusions: HMGB1 is expressed and secreted by cells within the human atherosclerotic plaque and promotes SMC migration and proliferation. Human SMCs can secrete HMGB1 when challenged with cholesterol. HMGB1 appears as a key player in neointimal hyperplasia of atherosclerotic plaques and restenosis after angioplasty.

2632 Induction of heart and smooth muscle-specific genes in human mesenchymal stem cells and epicardium-derived cells after forced myocardin expression

J. van Tuyn[1], S. Knaan-Shanzer[2], M.J.M. van de Watering[2], A.C. Gittenberger-de Groot[3], M.J. Schalij[4], E.E. van der Wall[4], A.A.F. de Vries[2], D.E. Atsma[4]. *[1]LUMC, Cardiology, Leiden, Netherlands; [2]Leiden University Medical Center, Molecular Cell Biology, Leiden, Netherlands; [3]Leiden University Medical Center, Anatomy, Leiden, Netherlands; [4]Leiden University Medical Center, Cardiology, Leiden, Netherlands*

We studied the potential of the transcription factor myocardin to induce cardiac and smooth muscle gene expression in bone marrow-derived mesenchymal stem cells (MSCs) and epicardium-derived cells (EPDCs) from human adults, in order to enhance their differentiation into cardiomyocytes for transplantation purposes.
Results: In vitro expanded EPDCs resemble MSCs in morphology and surface marker expression. However, unlike MSCs, EPDCs could not be differentiated into osteoblasts or adipocytes in vitro using standard differentiation procedures. RT-PCR analysis demonstrated that MSCs and EPDCs naturally express the connexin 43, dHand and mef2C genes. EPDCs but not MSCs also express the cardiac marker genes GATA4 and cardiac troponin T (cTnT). Forced myocardin expression using an adenovirus vector led to the activation of the atrial and ventricular myosin light chain 2, alpha-myosin heavy chain (alpha-MHC), atrial natriuretic factor, SERCA2a and eHand genes in both cell types, and of GATA4 and cTnT in MSCs. In addition to the activation of heart muscle-specific genes, myocardin also induced expression of the smooth muscle-specific myosin heavy chain (smMHC) gene in MSCs and EPDCs. Neither cell type expressed cardiac troponin I or Nkx2.5 before or after stimulation with myocardin. Interestingly, immunofluorescence microscopy revealed that in the presence of exogenous myocardin only 10% of the MSCs, but virtually 100% of the EPDCs stained positive for cardiac myosin and actinin, SERCA2a and the smooth muscle protein smMHC.
Conclusions: Our findings demonstrate that myocardin activates a wide range of heart muscle genes and the highly specific smooth muscle marker gene smMHC in both cell types, underscoring that myocardin plays an important role in both smooth and cardiac muscle development. The difference in myocardin responsiveness between EPDC and MSC cultures may indicate that additional regulatory factors, present in all EPDCs but only in a subfraction of MSCs, are required for heart and/or smooth muscle gene activation.

2633 Factors governing adaptive arterial remodelling under smooth muscle cell cycle reentry

J.R. Sindermann[1], C. Kobbert[2], J. Ebbing[2], R. Voss[3], G. Breithardt[2], K.L. March[4], G. Plenz[5]. *[1]University of Muenster, Department of Cardiology and Angiology, Muenster, Germany; [2]University of Münster, Cardiology/Arteriosclerosis Research, Münster, Germany; [3]Institute f. Arteriosclerosis Research, University of Münster, Münster, Germany; [4]Krannert Institute of Cardiology, Department of Medicine, Indianapolis, United States of America; [5]Arterioscler. Res./Cardiovasc. Surg., University of Münster, Münster, Germany*

Purpose: We have previously shown that genetically induced smooth muscle cell (SMC) cycle reentry by expression of T antigen (TAg) in transgenic mice resulted in spontaneous neointima formation and adaptive arterial remodeling. The herein presented study was designed to investigate the influence of TAg-induced SM cell cycle reentry on the expression of matrix metalloproteinases (MMPs) and collagens as potential key players in vascular remodeling.
Methods: SMC were obtained from the transgenic mouse model of adaptive arterial remodeling expressing a temperature sensitive TAg under control of the smooth muscle-myosin heavy chain (SM-MHC) promoter. These SMC allowed inducible transgene (TAg) expression at the permissive temperature of 33°C in comparison to the absence of TAg at the restrictive temperature of 39.5°C. SMC with constitutively expressed TAg under control of the same SM-MHC promoter were obtained from a second mouse model and were used as controls to distinguish a transgene effect from the temperature effect. Array technology, Northern blotting and RT-PCR were employed to unravel the patterns of collagen and MMP expression.
Results: Transgenic mice presented enhanced SMC proliferation resulting in increased vessel wall area and spontaneous neointima formation in the presence of perfect adaptive arterial remodeling. In vitro studies revealed that SM-cell cycle modulation resulted in fundamental changes in collagen and MMP expression. SM-cell cycle reentry resulted in significantly increased RNA levels of collagen type IV alpha 2, collagen type V alpha 2 and collagen type XI alpha 1. In contrast, other members of the collagen system known to play a pivotal role in the vessel wall such as collagen type III and type VIII were found to be down-regulated under cell cycle reentry. Studies on MMP expression revealed a significant down-regulation for MMP-3, whereas other members such as MMP-2, -9 and –11 were not affected by SM-cell cycle reentry.
Conclusions: These results provide evidence that adaptive arterial remodeling is made possible by complex changes in the extracellular matrix involving both

the collagen anabolism and catabolism in the presence of SMC proliferation. This insight into vascular remodeling will help to improve the understanding of vascular geometry during atherosclerosis and following vessel trauma. Our results may also pave the way to the development of new therapeutic paradigms based on the directional rather than absolute control of SMC proliferation and vascular remodeling in vascular diseases.

2634 Vascular smooth muscle cells from stable and unstable atherosclerotic plaques show epigenetic commitment even after 25 plating passages

M.L. Rossi[1], N. Marziliano[2], P.A. Merlini[3], E. Bramucci[4], E. Arbustini[2], P. Presbitero[5], D. Zavalloni[5], D. Ardissino[6]. *[1]Milan, Italy; [2]IRCCS Policlinico San Matteo, Laboratory of Medical Genetics, Pavia, Italy; [3]Niguarda Hospital, IV Division of Cardiology, Milan, Italy; [4]IRCCS, Policlinco S Matteo, 4 Division of Cardiology, Pavia, Italy; [5]Istituto Clinico Humanitas, Unità Operativa di Emodinamica, Rozzano, Italy; [6]Maggiore Hospital, 6Division of Cardiology, Parma, Italy*

Background: Unstable angina and myocardial infarction are the clinical manifestations of the abrupt thrombotic occlusion of an epicardial coronary artery as a result of spontaneous atherosclerotic plaque rupture or fissuring, and the exposure of highly thrombotic material. Proliferation of vascular smooth muscle cell (VSMC) and differential expression of inflammatory and apoptotic markers have been demonstrated to be among one of the most important mechanisms in the atherosclerosis progression. It has been proposed that the combined overexpression of inflammatory and pro-apoptotic genes from the VSMC may be the initial triggering for both plaque rupture and thrombotic response. Our aim was to collect those VSMC from atherosclerotic plaques and establish stabile, long term primary cell cultures as model for biochemical and molecular genetics studies.
Methods and Results: We have isolated VSMC from 15 patients with stable angina (SA) and 15 with acute coronary syndromes without ST elevation (ACS) after dissection under light microscopy. VSMC grown out from the explants after 10-15 days in Ham's F12 supplemented with 10% FCS, were confirmed to be smooth muscle cells by their typical "hill and valley" morphology and by alpha-actin immunofluorescent staining: they confirmed the above pattern up to 25 plating passages before undergoing cellular senescence. We also profiled gene expression at each plating passage via microarray analysis. In order to clarify weather different cellular commitment were present in the ACS and SA VSMC, we applied small interfering RNA (siRNA) to revert the ACS pattern into SA and viceversa. The different gene expression profiling for all the biological functions in VSMC cultured cells from ACS and SA plaques was kept in in vitro conditions up to 25 passages. Furthermore the phenotypic reversibility of ACS and SA VSMC was possible up the 15 passage, while only SA to ACS transitions were allowed after this time-point.
Conclusions: We have demonstrated through molecular and cellular studies that the cell differentiation between SA and ACS VSMC is kept in primary cell cultures up to 25 plating passages thus letting to speculate that epigenetic mechanisms might underlie this differentiation. Furthermore, the results of this study suggest a new cell system model for studies on the pathophysiology of unstable angina and myocardial infarction.

2635 Proteomic approach to identify changes in protein expression modified by 17 beta-estradiol in bovine vascular smooth muscle cells

L. Molero, A. Garcia-Mendez, S. Alonso-Orgaz, C. Carrasco, P.J. Mateos-Caceres, C. Macaya, A.J. Lopez-Farre. *Hospital Clinico San Carlos, Cardiovascular Research Unit, Madrid, Spain*

The proteomic approach may facilitate to find unknown cellular mechanism stimulated by pathological and pharmacological situations.
Aim: To use proteomics to analyze modifications in the level of expression of different proteins in bovine vascular smooth muscle cells (BVSMC) incubated in the presence and in the absence of 17beta-estradiol (10^{-7} mol/l).
Methods and results: In two dimensional electrophoresis using a pH range of 4 to 7 we identified several areas which the level of expression of contains proteins was different between control and 24 hours 17beta-estradiol-incubated BVSMC. Two isoforms of alpha-enolase were observed in BVSMC. The expression of alpha-enolase isoform 1 was enhanced after 17beta-estradiol incubation (20.76 $\pm$ 1.51 vs 12.74 $\pm$ 4.63; arbitrary units, $p< 0.05$). Three isoforms of heat shock protein 60 (HSP60) were observed in BVSMC. The expression of HSP60 isoform 3 was reduced by 17beta-estradiol (12.85 $\pm$ 2.77 vs 28.24 $\pm$ 4.22; arbitrary units, $p< 0.05$). Three isoforms of the protein vimentin were also detected. The expression of vimentin isoforms 2 and 3 was reduced by 17beta-estradiol (27.90 $\pm$ 1.75 vs 34.45 $\pm$ 2.83 and 28.39 $\pm$ 4.28 vs 47.32 $\pm$ 5.33 respectively; arbitrary units, $p< 0.05$). The expression of caldesmon, a protein associated with the contractile processes was also reduced by 17beta-estradiol (13.68 $\pm$ 2.77 vs 20.20 $\pm$ 5.72 in controls; arbitrary units, $p< 0.05$). Finally three disulfude isomerase isoforms were detected in BVSMC. The expression of disulfide isomerase isoform 3 was reduced by 17beta-estradiol (36.00 $\pm$ 6.9 vs 21.6 $\pm$ 4.00 in controls; arbitrary units, $p< 0.05$).
Conclusion: 17beta-estradiol modified the expression of several proteins isoforms associated with SMC proliferation (alpha-enolase, vimentin, HSP-60), cell contraction (vimentin, caldesmon) and cell redox modulation (protein disulfide isomerase). These findings confirm that 17beta-estradiol may modulates a wide range of signalling pathways in BVSMC.

2636 Signalling pathway after mechanical injury aorta smooth muscle cells is transduced through elastin binding protein

M. Szperl[1], A. Hinek[2]. *[1]Institute of Cardiology, Molecular Biology, Warsaw, Poland; [2]Hospital for Sick Children, Cardiovascular Research Program, Toronto, Canada*

Physical disruption of atherosclerotic lesion by balloon angioplasty results in increased luminal diametry and immediate symptomatic relief in most cases, although this initial success is often complicated by restenosis. Among other components insoluble elastin and elastin-derived peptides seems to play a crucial role in the proper function and remodeling of arterial walls. Elastin degradation products were reported to regulate Vascular Smooth Muscle Cells proliferation through a signaling cascade involving Elastin Binding Protein (EBP). The purpose of the present study was to determine whether EBP could function as a mechanotransducer in Aorta Sooth Muscle Cells (AoSNC. Porcine AoSMC were isolated by enzymatic digestion and cultured in alpha-MEM, and mechanical injury was created by rubber policeman at presence or absence of 0.1 M Lactose (which cause shedding of EBP), 10 mg/ml Doxycycline (MMPs inhibitor), or 50mg/ml k-Elastin (Elastin degradation product). After injury cells were incubated for another 15 min, 30 min, 1h, or 24h. The mitogenic effect was determined by the incorporation of [3H]Thymidyne. We performed Western Blotting with antibodies to: phosphorylated tyrosine (p-tyr), phosphorylated src (p-src), phosphorylated ERK1/2 phosphorylated cyclin-dependent kinase c2 (p-Cdc2), cyclin dependent kinase c2 (Cdc2), and cyclin B1.
Results: Western Blot analysis with anti-p-tyr antibody indicated that mechanical injury AoSMC leads to early (15 min) phosphorylation some proteins. Further analysis revealed that transition from G2 to M phase (expression p-Cdc2, Cdc2, and cyclin B1) and cellular proliferation was activated after mechanical injury. Above mentioned effects were abolished by galactosugar, which cause shedding of EBP from the cell surface, and enhanced by k-Elastin, which is a ligand of EBP.
Conclusion: We found that mechanical disruption transduced activation of c-Src depends on the presence of EBP, and than ERK1/2 phosphorylation cascade. This causes increase in expression cyclin and cyclin-dependent kinase, and than increase in cellular proliferation. Our results indicate, that mechanical injury of AoSMC transduces pro-mitogenic signals and these effects are due to generation of intracellular signals transduced through the Elastin Binding Protein.

NOVEL ASPECT OF CALCUIM-HANDLING IN HEART FAILURE

2637 Reduced sorcin expression induces decreased cardiac contractility and dilated cardiomyopathy

K.F. Frank[1], B. Bolck[2], A. Malik[2], Z. Ding[3], K. Brixius[2], J. Schrader[3], R.J. Roger[4], R.H.G. Schwinger[2]. *[1]University of Cologne, Department III of Internal Medicine, Cologne, Germany; [2]University of Cologne, Department III of Internal Medicine, Cologne, Germany; [3]Heinrich-Heine-Universität, Physiology, Düsseldorf, Germany; [4]Harvard Medical School, Boston, United States of America*

Sorcin (SOR), an EF-hand Ca^{2+}-binding protein, interacts with the sarcoplasmic reticulum Ca^{2+}-release channel (ryanodine-receptor, RYR). This binding may alter intracellular Ca^{2+}-handling and cardiac contractility. We aimed to investigate the influence of adenoviral-mediated downregulation of SOR expression on cardiac contractility and in vivo cardiac function.
An adenovirus encoding SOR anti-sense DNA with a separate cassette for GFP (green fluorescent protein) both driven by the CMV-promoter to induce reduced expression of SOR (Ad.asSOR.GFP) was generated. A reporter virus encoding for both beta-galactosidase and GFP served as control (Ad.GFP). The adenoviruses were injected into coronary arteries of rat hearts (n=6 in each group) via a catheter-based technique. To assess cardiac function, echocardiography was performed at pre-injection as well as 7 and 12 days post-injection. In parallel, cardiomyocytes were isolated and transfected for 48 hrs to examine cell shortening, Ca^{2+}-transients and force frequency relationship.
Utilizing immunhistochemistry, a significant decrease (- 80%) in SOR expression was found in Ad.asSOR.GFP-infected vs. Ad.GFP-infected cardiomyocytes. Twelve days after adenoviral exposure, rat hearts displayed a similar degree in fractional shorting, however, hearts infected with Ad.asSOR.GFP were dilated with significantly increased end-diastolic diameters (1.6$\pm$0.12 mm vs. 2.2$\pm$0.08, $p<0.05$). Heart rate was reduced in Ad.asSOR.GFP (179$\pm$13.9 bpm) vs. Ad.GFP (217$\pm$3.5 bpm). After 14 days of adenoviral exposure, the animals were sacrificed; dilated cardiomyopathy was confirmed as judged by increased heart weight (1.07$\pm$0.1 vs.1.34$\pm$0.1 g). Body and liver weight remained unchanged. Cell-contracting experiments (frequency: 0.5 Hz) exhibited reduced cell shortening in Ad.asSOR.GFP, which was even more pronounced upon increasing stimulation frequencies up to 5 Hz. Ca^{2+} transients showed decreased peak systolic Ca^{2+} development.

Reduced SOR expression using adenoviral anti-sense gene transfer results in dilated cardiomyopathy and diminished force transients. This suggests an essential role of SOR in regulation of intracellular Ca^{2+}-handling, cardiac contractility and cell differentiation.

2638 FKBP12.6 overexpression in rabbit cardiomyocytes isolated from failing heart restores contractile function

D. Zibrova, T. Seidler, N. Teucher, W. Schillinger, C. Christians, S. Sosalla, H. Kogler, G. Hasenfuss. *Georg-August University Goettingen, Dept. Cardiology and Pneumology, Göttingen, Germany*

In heart failure, Ca^{2+} release from the sarcoplasmic reticulum (SR) is disturbed. FK506-binding protein (FKBP) FKBP12.6 is tightly associated with cardiac SR Ca^{2+}-release channel (RyR2) and coordinates its function. Recently, it has been shown that in heart failure, the abnormal Ca^{2+} leak through the Ca^{2+}-relase channel is caused by a partial loss of RyR-bound FKBP12.6 and a consequent conformational change in RyR. To investigate whether FKBP12.6 may represent a new molecular target to improve the contractile function, we overexpressed FKBP12.6 by adenovirus (Ad)-mediated gene transfer in rabbit myocytes isolated from failing hearts.

In the animal model, heart failure was induced by 4-5 weeks of rapid ventricular pacing at a rate of 400 bpm with an externally programmable pacemaker. Sham-operated animals with switched off implanted pacemakers served as a control. Development of heart failure was assessed by echocardiography at baseline, 2, 3, and 4 weeks. To assess the molecular interaction of FKBP12.6 with RyR2 in rabbit failing heart, co-immunoprecipitation was performed. The levels of RyR-associated FKBP12.6 were in fact decreased in failing hearts compared to sham control. Overexpression of the transgene was verified at the protein level using immunoblotting. The contractility of isolated rabbit cardiomyocytes was measured by video-edge detection 24 hours post transfection with Ad-FKBP12.6 and Ad-LacZ (beta-galactosidase control) at a multiplicity of infection of 100. In Ad-LacZ cell population, fractional shortening of failing cardiomyocytes was significantly reduced compared to cardiomyocytes isolated from the hearts of sham-operated animals (1.77±0.1%, n=84 vs. 2.35±0.1%, n=101, respectively; $p<0.001$). In the failing-heart group, cardiomyocytes overexpressing FKBP12.6 showed a significant increase in fractional shortening in comparison with Ad-LacZ transfected cells (1.96±0.1%, n=102 vs. 1.77±0.1%, n=84, respectively; $p<0.05$), indicating the partial restoration of cardiomyocyte contractility. In the sham-operated group, a similar increase in contractility in cardiomyocytes overexpressing FKBP12.6 was observed (2.64±0.1, n=109 vs. 2.35±0.1, n=101 of LacZ control; $p<0.05$), which is consistent with our previously obtained data demonstrating a positive inotropic effect of FKBP12.6 overexpression in non-failing rabbit cardiomyocytes. This suggests that adenoviral FKBP12.6 overexpression restores, in part, fractional shortening of rabbit failing cardiomyocytes and is a strategy to improve contractile function in heart failure.

2639 Alterations of SERCA 2a-activity and phospholamban phosphorylation in mice with beta-adrenoceptor deficiency

K. Brixius[1], S. Lee[1], S. Grafweg[1], R.J. Wiesner[2], J.-P. Giacobino[3], W. Bloch[4], R.H.G. Schwinger[1]. *[1]Clinic III of Internal Medicine,Cologne Univ., Lab. of Muscle Res. & Mol. Cardiology, Cologne (Koln), Germany; [2]Institute of Vegetative Physiology, University of Cologne, Cologne, Germany; [3]University of Genéve, Dept. of Medical Physiology, Genéve, Switzerland; [4]German Sport University, Dept. of Cell & Mol Sport Medicine, Cologne, Germany*

beta-adrenergic stimulation is one of the main mechanisms modulating cardiac function under physiological conditions, whereas a chronical increased beta-adreneric stimulation may worsen cardiac function under pathophysiological situations, e.g. heart failure. The present study investigated cardiac function in hearts of female mice with total deficiency of the β1-, β2- and beta3–adrenoceptors (To-β-KNO, n=8) in comparison to wildtype mice (WT, n=8).

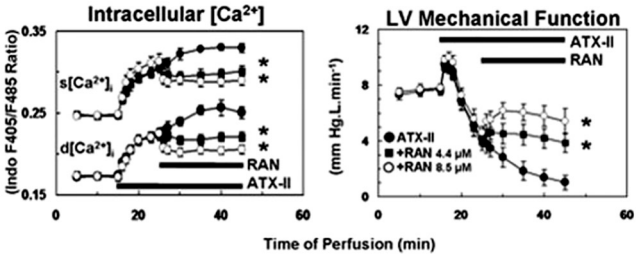
Heart weight (To-β-KNO vs. WT: 80.1±7.7 mg vs. 116.6±8.9 mg) and heart-to-body weight ratio (To-β-KNO vs. WT: 3.24±0.29*10-3 vs. 5.04±0.12*10-3) were significantly smaller in To-β-KNO as compared to WT. This was accompanied by a decrease in the size of the cardiomyocytes in To-β-KNO (86% of WT). Protein expression of SERCA 2a, the ryanodine receptor and the Na^+/Ca^{2+}-exchanger were similar in To-β-KNO and WT mice, but phospholamban protein expression was increased. PKA-dependent phosphorylation of phospholamban at serin 16 was absent in To-β-KNO and Ca/CAM-kinase dependent phosphorylation at threonin 17 was decreased in To-β-KNO. All alterations were paralleled by a decrease in SERCA 2a activity. A similar maximal calcium-dependent tension but an increased myofibrillar calcium-sensitivity was measured in To-β-KNO as compared to WT. No alterations were observed for the protein expression of β-tubulin and mitochondrial cytochrome C oxidase subunit, indicating that the mitochondria may be incorporated into functional complexes with sarcomeres and sarcoplasmic reticulum.

Conclusions: In the absence of β-agonistic stimulation, SERCA 2a – activity is mainly regulated by alterations of phospholamban expression and phosphorylation. The decreased SERCA 2a activity following β-adrenoceptor deficiency may be partly compensated by an increased myofibrillar calcium-sensitivity.

2640 Inhibition of late INa by ranolazine reduces Ca^{2+} overload and LV mechanical dysfunction in ejecting rat hearts

H. Fraser[1], L. Belardinelli[1], L. Wang[2], J.J. McVeigh[1], A.S. Clanachan[2]. *[1]CV Therapeutics, Inc, Pharmacological Sciences, Palo Alto, United States of America; [2]University of Alberta, Pharmacology, Edmonton, Canada*

Ranolazine (RAN) is a compound under development as a drug for the treatment of angina. Studies on the effects of RAN on cardiac ion currents indicate that it preferentially inhibits late Na^+ channel current (INa), relative to peak INa, with an IC50 of 6μM. Augmented late INa may contribute to ischemia-induced Na^+ and Ca^{2+} overload that causes left ventricular (LV) dysfunction. Hence, we tested the hypothesis that inhibition of late INa by RAN reduces Ca^{2+} overload and thereby improves LV mechanical function. Working hearts from male SD rats were perfused with Krebs solution and paced at 5 Hz. Indo-1 ratios, indicative of LV intracellular Ca^{2+} concentrations ($[Ca^{2+}]_i$), were acquired at 500 Hz to determine diastolic ($d[Ca^{2+}]_i$) and systolic ($s[Ca^{2+}]_i$) Ca^{2+} concentrations simultaneously with LV work. Sea Anemone Toxin (ATX-II, 12nM), known to enhance late INa, increased both $d[Ca^{2+}]_i$ and $s[Ca^{2+}]_i$. This was associated with an initial and transient increase in LV work that was followed by a decline to 14±8% (n=11) of baseline. RAN (8.5μM), added after 10 min of ATX-II exposure, prevented further increases in $d[Ca^{2+}]_i$ ($P<0.001$) and $s[Ca^{2+}]_i$ ($P<0.001$) and reduced values relative to ATX-II alone. RAN (8.5μM) prevented deterioration in LV function and enhanced LV work from 14±8% to 68±11% (n=9) of baseline ($P<0.001$). Similarly, a lower concentration of RAN (4.4μM, n=9) also prevented further increases in $d[Ca^{2+}]_i$ ($P<0.05$) and $s[Ca^{2+}]_i$ ($P<0.05$) and also enhanced LV work from 14±8% (n=11) to 50±11% (n=9) of baseline ($P<0.05$).

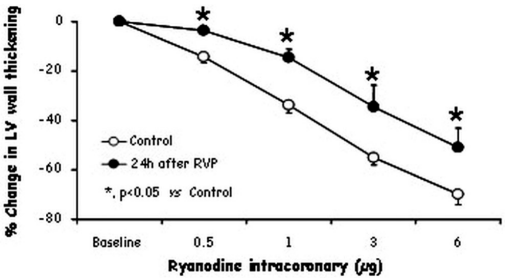


Thus, simultaneous measurements of $[Ca^{2+}]_i$ and LV work indicate that late INa activation by ATX-II increases both $d[Ca^{2+}]_i$ and $s[Ca^{2+}]_i$ and impairs LV function, and by inhibiting late INa, RAN reverses the Ca^{2+} overload and LV dysfunction caused by ATX-II.

2641 Inotropic and ryanodine receptor adaptations during late preconditioning secondary to rapid ventricular pacing in conscious dogs

L. Lucats[1], B. Ghaleb[2], V. Chalvignac[1], A. Bize[1], J.B. Su[1], L. Hittinger[1], A. Berdeaux[1]. *[1]ENVA, INSERM U660, Maisons-Alfort, France; [2]Faculté de Médecine Paris Sud, Dept Pharmacologie, Le Kremlin Bicetre, France*

The ryanodine (RYA) receptor is a key element in calcium handling and excitation-contraction coupling, both being altered during myocardial stunning. Accordingly, we investigated whether late preconditioning (LPC) by rapid ventricular pacing (RVP) against myocardial stunning could modify the myocardial contractile pattern and the RYA receptor. Six conscious dogs instrumented to measure left ventricular wall thickening (LVWT) underwent one week apart i) a "control" sequence with a 10-min coronary artery occlusion (CAO) followed by reperfusion and ii) a "pacing" sequence with a 10-min CAO preceded 24h earlier by RVP (240 beats/min, 40min). Four additional dogs received intracoronary RYA (0.5-6μg) before and 24h after RVP. In the control sequence, CAO induced a fall in LVWT (-95% from 3±0.3mm) and subsequent myocardial stunning along with depressed dWT/dtmax (maximal rate of LVWT). With "pacing", myocardial stunning was significantly reduced, demonstrating LPC. At baseline 24h after RVP, LVWT was similar vs "control" but dWT/dtmax was significantly increased by 8% from 25±3mm/s vs control. This parameter was also increased throughout subsequent stunning.



In the second group, RYA dose-dependently decreased LVWT in control state (e.g., -55±2% from baseline at 3μg) (Figure). Interestingly 24h after RVP, this dose-response curve was significantly rightward shifted with LPC (e.g., -33±6% from baseline at 3μg). In conclusion, the LPC heart secondary to RVP is characterized by a phenotype adaptation, i.e., an increase in the velocity of myocardial thickening and a concomitant change in the response to RYA blockade. Thus we speculate that LPC against myocardial stunning by RVP results from adaptations in contractility and/or excitation-contraction coupling through RYA receptor.

2642 Targeted proteolysis activates calcineurin

O. Ritter[1], K. Schuh[2], L. Neyses[3]. *[1]University of Wuerzburg, Cardiology Dept., Wurzburg, Germany; [2]University of Wuerzburg, Depatrment of Clinical Biochemistry, Wuerzburg, Germany; [3]Manchester Heart Center, Universitiy Department of Medicine, Manchester, United Kingdom*

Background: Calcineurin (CnA) is important in the regulation of myocardial hypertrophy. We demonstrated that targeted proteolysis of the CnA autoinhibitory domain under pathological myocardial workload leads to increased calcineurin activity in human myocardium. Here we investigated the proteolytic mechanism leading to activation of calcineurin.
Methods and Results: In patients with diseased myocardium we found strong nuclear translocation of calcineurin. In contrast, in normal human myocardium there was a cytosolic distribution of calcineurin. Stimulation of rat cardiomyocytes with angiotensin II increased calpain activity significantly (433%±11; $p<0.01$, n=6) and caused proteolysis of the autoinhibitory domain of calcineurin. Inhibition of calpain by a membrane permeable calpain inhibitor prevented proteolysis. We identified the cleavage site of calpain in the human calcineurin sequence at amino acid 424. Calcineurin activity was increased after angiotensin II stimulation (310%±29; $p<0.01$, n=6) and remained high after removal of angiotensin II (214%±21; $p<0.01$, n=6). Addition of a calpain inhibitor to the medium decreased calcineurin activity (110%±19; p=n.s., n=6) after removal of angiotensin II. Ang II stimulation of cardiomyocytes also translocated calcineurin into the nucleus as demonstrated by immunohistochemical stainings and transfection assays with GFP-tagged calcineurin. Calpain inhibition and therefore suppression of calpain-mediated proteolysis of calcineurin enabled calcineurin exit from the nucleus.
Conclusion: 1) Angiotensin II stimulation of cardiomyocytes increased calpain activity, leading to 2) proteolysis of the autoinhibitory domain of calcineurin. 3) This causes an increase in calcineurin activity and results in nuclear translocation of calcineurin. 4) Loss of the autoinhibitory domain renders calcineurin constitutively nuclear and active, even after removal of the hypertrophic stimulus.

TREATMENT OF IN-STENT RESTENOSIS

2643 The RIBS II (Restenosis Intra-stent: Balloon angioplasty versus rapamycin-eluting Stenting) randomised study

F. Alfonso Manterola[1], A. Bethencourt[2], J.R. Lopez-Minguez[3], R. Mantilla[4], J. Angel[5], M.J. Perez-Vizcayno[6], C. Macaya[6] on behalf of The RIBS II Investigators. *[1]Madrid, Spain; [2]H Son Dureta, Cardiology, Palma de Mallorca, Spain; [3]H Infanta Cristina, Cardiology, Badajoz, Spain; [4]H Meixoeiro, Cardiology, Vigo, Spain; [5]H Valle de Hebrón, Cardiology, Barcelona, Spain; [6]Hospital Clinico San Carlos, Interventional Cardiology, Madrid, Spain*

Purpose: drug-eluting stents (DES) are considered an attractive strategy in patients (P) with in-stent restenosis (ISR) but currently there is only limited information on the value of DES in these P.
Methods: the RIBS II (Restenosis Intra-stent: Balloon angioplasty [BA] vs elective rapamycin-eluting Stenting) is a multicenter, randomised, study designed to determine the efficacy of DES in P with ISR. Main inclusion criteria included ISR producing symptoms/ischaemia, first ISR, anatomy suitable to both therapeutic strategies, reference vessel diameter >2.5 mm and ISR length <33 mm. From February 2003 to April 2004, 150 P with ISR were enrolled (central randomisation) at 7 University Hospitals in Spain, 74 allocated to BA and 76 to DES. All P were treated with dual antiplatelet therapy and repeat angiography was scheduled at 9 moths. Primary end-point was recurrent restenosis rate by QCA. A composite of major adverse events (death, myocardial infarction and target vessel revascularisation [TVR]) constituted a secondary end-point.
Results: mean age was 64±11 years and 25% of P were female. Baseline clinical characteristics (unstable angina 45%, diabetes 35%, median time to ISR 6.6 months) and angiographic findings (diffuse ISR 60%, LAD location 52%), were similar in both groups. All P have completed the 9 month clinical follow-up and the scheduled angiography was available in 142 P (96% of eligible). At late angiography the DES arm showed a significantly larger minimal lumen diameter (2.40±0.7 vs 1.52±0.7 mm, $p<0.001$) and a lower rate of recurrent restenosis (11% vs 39%, $p<0.001$). At last clinical follow-up (mean follow-up 11.7±1 months) the event-free survival was 89% in the DES arm vs 67% in the BA arm (Log rank p=0.002). Freedom from TVR was 91% and 70% (Log rank p=0.002) in the DES and BA arms respectively. The complete 1 year clinical follow-up will be presented.
Conclusion: this randomised study demonstrated that DES are superior, both clinically and angiographically, to conventional BA in P with ISR.

2644 A randomised, multicenter, European comparison of a polymer-free paclitaxel-eluting stent with two different doses and a standard control arm for the treatment of in-stent-restenosis (ELUTES II)

J. Rodermann[1], E. Camenzind[2], I. De Scheerder[3] on behalf of the ELUTES II Investigators. *[1]University Essen, Cardiology dept., Essen, Germany; [2]University Hospital of Geneva, Division de Cardiology, Geneva, Switzerland; [3]University Hospital Gasthuisberg, Department of Cardiology, Leuven, Belgium*

Background: drug-eluting stents (DES) have been demonstrated to reduce angiographic and clinical recurrence significantly after treatment of de novo coronary artery stenosis. Many centres have already begun using DES to treat patients with in-stent-restenosis (ISR) despite the absence of evidence to support their efficacy, compared to vascular brachytherapy (VBT), in this population. We performed the ELUTES II trial to evaluate a polymer-free paclitaxel eluting stent for the treatment of ISR.
Methods and results: based on the promising results of the ELUTES I trial for the treatment of de novo stenosis this three-arm, multicentre, randomised, double-blinded trial (n=116) investigated the safety and efficacy of polymer-free V-Flex-Plus coronary stents (Cook Inc.) coated with two doses of paclitaxel (0.9 and 2.7 $\mu g/mm^2$ stent surface area) applied directly to the abluminal surface of the stent compared to a control arm (PTCA or PTCA + bare metal stent at the physicians discretion) in in-stent-restenosis in bare metal stents without prior VBT. Inclusion criterias were in-stent-restenosis >60%, reference vessel diameter 2,75-3,5mm and lesion length <25mm. The primary efficacy endpoint was angiographic percent diameter stenosis at 9 month. At angiographic follow up, percent diameter stenosis was 59.7 ± 24.8 in controls (n=30) and 39.6 ± 32.7 in the high dose paclitaxel-arm (n=33; p=0.007). Binary restenosis rate (>50% at follow up) decreased from 60% to 33% (p=0.045). Freedom from major adverse cardiac events (MACE) was the primary safety endpoint. In the high dose arm it was 82% and in the control arm 57% ($p<0.05$). The low-dose arm showed no significant difference in the described endpoints compared to control arm.
Conclusions: paclitaxel applied directly to the abluminal surface of a bare metal coronary stent is considered safe and significantly improves angiographic outcome (2.7 $\mu g/mm^2$) for treatment of in-stent-restenosis with results comparable to vascular brachytherapy.

2645 Randomised trial for the treatment of in-stent restenosis by a paclitaxel coated balloon catheter – PACCOCATH ISR

B. Scheller[1], C. Hehrlein[2], W. Bocksch[3], W. Rutsch[4], D. Haghi[5], U. Dietz[6], M. Boehm[1], U. Speck[7]. *[1]Universitaetsklinikum des Saarlandes, Innere Medizin III, Homburg/Saar, Germany; [2]Innere Medizin III, Medizinische Universitätsklinik, Freiburg i.Br., Germany; [3]Kardiologie, Campus Virchow-Klinikum, Charite, Berlin, Germany; [4]Kardiologie, Campus Mitte, Charite, Berlin, Germany; [5]I. Medizinische Klinik, Universitätsklinikum, Mannheim, Germany; [6]Kardiologie, Deutsche Klinik für Diagnostik, Wiesbaden, Germany; [7]Radiologie, Charite, Berlin Mitte, Berlin, Germany*

Background: drug-eluting stents have shown promising anti-restenotic effects in clinical trials. However, the stent-in-stent concept in the treatment of in-stent restenosis (ISR) seems to be questionable. In prior animal trials, we demonstrated a highly significant reduction of neointimal formation by drug eluting balloon catheters (DEB). The aim of the PACCOCATH ISR study is to investigate the treatment of ISR by the novel DEB.
Methods and results: the PACCOCATH ISR study is a randomised, double blinded German multicenter trial on efficacy and tolerance of the DEB in the setting of coronary ISR. Since January 2004, 104 patients were randomized to rePTCA of ISR either using the coated PTCA balloon (3 μg paclitaxel/mm^2 balloon surface) or a non-coated balloon of the same type. Balloon inflation time was 60 seconds each. Major inclusion criteria were an ISR in a native coronary artery with a diameter stenosis of at least 70%, < 25 mm length, and a vessel diameter of 2.5 to 3.5 mm. The primary endpoint is late lumen loss after 6 months (independent angiographic core lab; U.D.). Secondary endpoints are binary restenosis rate and major adverse cardiac events. The study design includes the separate analysis of the first 52 patients. So far, no adverse events attributable to the investigational device occurred.
Conclusions: treatment of coronary ISR with paclitaxel coated balloon catheters is safe. Complete angiographic and clinical follow-up of 52 patients will be presented at the meeting.

2646 Sirolimus-eluting stent implantation for in-stent restenosis is associated with favourable long-term results despite suboptimal stent expansion

T.M. Schiele[1], T. Meissler[2], J. Rieber[2], A. Koenig[2], I. Erhard[2], K. Theisen[2], U. Siebert[3], V. Klauss[2]. *[1]Munchen, Germany; [2]Ludwig-Maximilians-University, Cardiology Dept., Munich, Germany; [3]Harvard School of Public Health, Harvard Center for Risk Analysis, Boston, United States of America*

Background: The implantation of sirolimus-eluting stents (SES) is a promising new option for the treatment of in-stent restenosis (ISR). Data on the respective

mechanistic effects responsible for treatment success of SES for ISR has been reported only scarce. Thus the aim of our study was to describe the acute and chronic effects of SES on vessel morphology using quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS).
Methods: In 50 consecutive patients (PT) who received SES for ISR, clinical, procedural, QCA- (CAAS II, Pie Medical, Leiden, The Netherlands) and IVUS (Jomed, Uppsala, Sweden) data were collected prospectively at baseline before (PRE) and after (POST) intervention and at 6-months follow-up (FU).
Results: The population analysed revealed a high prevalence of cardiovascular risk factors. Approximately 50% of PT had three-vessel coronary artery disease. Only diffuse ISR (lesion length 15.3±4.6mm) of symptomatic PT were treated with SES (mean stent length 18.7±6.5mm), the mean balloon inflation pressure was 13.2±2.2atm. By QCA the minimum lumen diameter (MLD) PRE was 0.8±0.6mm (POST 2.8±0.9mm, acute gain 2.0±1.0mm). All stent implantation procedures led to an sufficient angiographical appearance. At FU MLD measured 2.5±0.9mm resulting in a very low late lumen loss (0.3±0.8mm). Percent diameter stenosis PRE was 75±18% (POST 9±12%, FU 21±13%). IVUS revealed a lumen cross-sectional area (CSA) PRE of 1.6±1.1mm^2. By an acute gain of 5.2±1.4mm^2, the resulting lumen CSA POST was 6.8±2.0mm^2, thereby meeting only 81% of the mean stent CSA of the originally implanted stent (8.4±1.4mm^2). Only due to a very low intima hyperplasia CSA (0.3±0.6mm^2) the lumen CSA at FU showed very favourable results (6.5±1.9mm^2). Neither the external elastic membrane CSA nor the reference segments revealed any significant changes throughout the entire observation period.
Conclusions: Implantation of SES for ISR is, despite a favourable angiographic appearance, characterised by insufficient stent expansion. Due to a very effective suppression of neointima formation, comparable with data following de-novo SES implantation, the long-term results were nevertheless very promising. Relevant vessel remodelling or edge effect, as has been observed with vascular brachythrapy, do not seem to play a role after SES implantation for ISR.

2647 Sirolimus eluting stents for the treatment of recurrent and diffuse in-stent restenosis: immediate and med term clinical and angiographic outcome

I. Sheiban[1], A. Chiribiri[2], C. Moretti[2], P. Lombardo[2], S. Beninati[2], S. Colangelo[2], W. Grossomarra[1], G.P. Trevi[1]. [1]*University of Turin, Division of Cardiology, Interv. Card., Turin, Italy;* [2]*Depart. Internal Medicine, Divison of Cardiology - Cath Lab, Torino, Italy*

Background: The use of drug eluting stents coated with anti-proliferative drugs might represnt an effective treatment for in-stent restenosis (ISR). In this study we report our experience in the use of sirolimus-elunting stent (Cypher) for the treatment of recurrent and diffuse ISR.
Methods: 136 consecutive patients (pts) (age 65±10 years; 69% male) with diffuse and recurrent ISR in native coronary vessels were treated with Cypher intrastent implantation. Among coronary risk factors diabetes was present in 37%. 34 pts (41%) had a previous myocardial infarction and 18% had a previous coronary artery surgery. A total number of 174 DES (1,3 stent/patient) were implanted. Mean lesion lenght was 18±7 mm (from 13 to 33 mm). Double antiaggregation therapy was continued for at least 3 months following the procedure. Follow up visits were planned at 1, 3, 6 and 9 months all pts. The following events were evaluated: death, recurrence of angina,new myocardial infarction, SAT, target vessel revascularization (TVR) or target lesion revascularization (TLR). An elective 9-month angiographic follow up was planned in all pts
Results: Procedural success was 100%.No procedural MACE were observed. One in-Cypher SAT occurred (0.7%) and was successfully treated 2 days after DES implantation. Mean follow-up period was 240±115 days. 85 pts were followed for at least 6 months 51 for at least 12 months. No deaths, no stroke no q-AMI occurred during this period. 18 pts underwent clinical-driven angiographic control: 2 (1.5%) because of non-Q AMI, 8 pts (5.9%) for recurrent angina, 8 pts (5.9%) for positive ischemia test. Angiopraphic control revealed in-Cypher restenosis only in 6. The remaining 12 pts had disease progression on native vessels. Thus TVR/TLR occurred in only 6 pts (4.4%). 73 pts (54%) completed elective 9-month angiographic follow-up All were free of symptoms. Only 2 patients had in Cypher restenosis. Thus total angiographic control was performed in 91 patients: angiographic restenosis was 8.8%. Total MACE during follow up was 14.7%.
Conclusions: The treatment recuurrent and diffuse ISR with Cypher stent is safe and effective; very few events occurred at short and med-term follow-up. These results, if confirmed in larger studies, indicate that sirolimus-elutintg stent can represent the first choice option for the treatment of ISR.

2648 Repeat percutaneous intervention for in-stent restenosis after sirolimus-eluting stent implantation in de novo coronary artery lesions

G. Melzi[1], J. Cosgrave[2], E. Tsagalou[1], F. Airoldi[1], I. Michev[1], M. Montorfano[1], M.G. Sangiorgi[2], A. Colombo[1]. [1]*San Raffaele Hospital, Milano, Italy;* [2]*Centro Cuore Columbus, Milano, Italy*

Drug-eluting stents (DES) have been reported to reduce the need for repeat revascularization.
Aim of the Study: To evaluate the clinical outcome of patients treated with repeat percutaneous intervention (re-PCI) for in-sirolimus eluting stent (SES) restenosis.
Methods: Our study population comprised all consecutive patients who underwent re-PCI for SES-restenosis between September 2002 and June 2004. In-hospital events and 6 month major cardiac adverse events (MACE) were recorded for all pts.
Results: Eighty-five patients (116 lesions) were included: 26 (30.5%) were diabetics, 12 (14.1%) had unstable angina. Mean age was 62±9 years and ejection fraction 52±10%. Ninety lesions (77.5%) were focal (<10mm), 19 (16.5%) were diffuse and 7 (6%) were occlusive. Average lesion length was 9.6±7.1 mm. Twenty-seven (23.2%) lesions were treated with SES, 26 (22.4%) with paclitaxel eluting stents, 39 (33.6%) with balloon angioplasty, 18 (15.5%) with cutting balloon. Only 1 patient was treated with bare metal stent implantation. No patient died during hospitalization; 1 patient had an in-hospital non-Q wave myocardial infarction. Mean follow-up was 9.4±4.5 months. Hierarchical MACE rate was 10%, 4 (4.7%) patients died. Three patients experienced sudden death (two of them with EF<30%), one, with history of severe aortic and mitral regurgitation, died due to pulmonary oedema. During follow-up there were no cases of myocardial infarction and 5 (5.8%) pts underwent target lesion revascularization (TLR); none of the TLR occurred in restenotic lesions treated with repeat DES implantation.
Conclusions: The treatment of DES restenosis is associated with favourable early and mid-term results. Furthermore, treatment of in-DES restenosis with placement of an additional DES seems to be associated with a low rate of re-PCI.

NEW STENT TECHNOLOGY

2649 The quantitative angiographic results of Rapamycin and Paclitaxel coated stents on inflammatory coronary lesions in pigs

X. Zhou[1], G.Q. Gang[2], D.Y. Zeng[3], B. Zhang[1], B. Liang[1], S.P. Wang[1], X.Z. He[2], F.T. Han[2] on behalf of DES anti-inflammation research group. [1]*No.1 Aff. Hospital of Dalian Medical Univ., Dalian, China;* [2]*Center Hosp of Dalian, Cardiology, Dalian, China;* [3]*1ST Hosp Chinese Medical University, Heart Center, Shenyang, China*

Rapamycin and Paclitaxel coated stents are commonly used in PCI to prevent restenosis now, but the anti-inflammation effects are rarely mentioned.
Aim: To investigate the anti-inflammation effects of Rapamycin and Paclitaxel coated stents on interleukin-1βinduced coronary stenosis in pigs.
Methods: 14 male domestic mini pigs (2 to 3 months old and weighing 25 to 30 kg) were operated with thoracotomy. The mid LAD and LCx were undermined 10 mm segment respectively and aseptically wrapped with cotton mesh soaked with IL-1β 50 ug. Two weeks after the operation, quantitative coronary arteriography (QCA) was performed and results showed severe stenosis at IL-1β treated LAD and LCx sites (Table 1). All the stenosis sites were randomized into Rapamycin coated stents group (FirebirdTM, n=7), Paclitaxel coated stents group (TAXUSTM, n=9) and bare-metal stents (BMSs) group (YINYITM, n=8). Four weeks after the PCI, follow-up QCA was performed. The results showed as follows (Table 1).

Table 1. QCA Results

	Rapamycin stents (n=7)	Paclitaxel stents (n=9)	BMSs (n=8)
Before PCI			
Lesion length (mm)	10.4 ± 0.05	9.6±0.11	10.2±0.07
Reference dimeter (mm)	3.22 ± 0.03	3.13±0.06	3.11±0.02
MLD (mm)	0.93 ± 0.01	0.91±0.05	0.91±0.04
Diameter stenosis (%)	70.6 ± 0.07	71.3±0.02	70.8±0.03
After PCI			
Stent size, mm	3.32±0.07	3.33±0.01	3.31±0.05
Stent-artery ratio	1.09±0.04	1.12±0.02	1.11±0.06
MLD (mm)	3.11±0.02	3.13±0.01	3.14±0.02
Follow-up angiography			
In-lesion MLD (mm)	2.97±0.04	2.82±0.05	1.45±0.04†
Late lumen lose (mm)	0.14±0.02	0.31±0.03*	1.69±0.02†
Diameter stenosis (%)	4.5±1.1	9.9±1.4	57.5±1.3†
In-stent MLD (mm)	2.96±0.03	2.80±0.02	1.32±0.05†
Late lumen lose (mm)	0.15±0.06	0.33±0.01*	1.82±0.06†
Diameter stenosis (%)	4.8±1.3	10.5±1.1	57.9±1.1†

*p<0.05 vs Rapamycin coated stents group, †p<0.001 vs Rapamycin coated stents group and Paclitaxel coated stents group.

Conclusion: Compared with BMSs, both Rapamycin and Paclitaxel coated stents reduced 1 month angiographic late lumen loss within the stent and the lesion. Rapamycin coated stents seems better than Paclitaxel in reducing 1 month angiographic late lumen loss with inflammation lesions in pigs.

2650 A novel polymer metal stent coated with an integrin-binding cRGD peptide inhibits neointimal hyperplasia by recruitment of endothelial progenitor cells

R. Blindt[1], I. Astafieva[2], C. Fach[3], N. Krott[4], J. Bernhagen[5], R. Hoffmann[6], C. Weber[3], F. Vogt[6]. [1]*University Hospital RWTH Aachen, Medical Clinic I, Aachen, Germany;* [2]*Guidant Corporation, Santa Clara, United States of America;* [3]*Molecular Cardiovascular Research, Molecular Cardiovascular Research, Aachen, Germany;* [4]*"Biomat", Interd. Center of Clinical Research, Aachen, Germany;* [5]*Institute of Biochemistry, University Aachen, Aachen, Germany;* [6]*University Hospital RWTH Aachen, Medical Clinic 1, Aachen, Germany*

The goal of this study was to evaluate a novel stent coating containing the integrin-binding cyclic RGD (cRGD) peptide for its potential to reduce neointimal hyperplasia and accelerate stent re-endothelialisation by attracting endothelial progenitor cells (EPCs). Effects of cRGD on EPC recruitment were analyzed by cell seeding, flow and Boyden chamber experiments in vitro. Coating with cRGD significantly increased the outgrowth of EPCs and supported their recruitment under flow conditions. The invasive potential of EPCs but not of smooth muscle cells was highly stimulated by cRGD. Quantitative detection of the peptide was established by high performance liquid chromatography (HPLC) and mass spectroscopy (MS). For in vivo studies, a non-resorbable polymer-coating with the capacity to incorporate sufficient amounts of the hydrophilic peptide (67 μg/stent) was developed for Guidant TetraTM stents, and cRGD was continuously released over more than 72 hours without burst effect. Twelve loaded and 12 unloaded polymer stents, and 12 bare metal stents were deployed in porcine coronary arteries (n=36) and coronary stenosis was analyzed after 4 and 12 weeks (n=6 each). Stenosis rates were 36±5%, 36±3%, and 40±6% after 4 weeks ($p>0.05$) and 37±7%, 60±7%, and 54±3% after 12 weeks (p=0.016), respectively. HPLC and MS confirmed adequate tissue levels of cRGD. Immunostaining for CD34 revealed a nearly complete stent endothelialization of cRGD-loaded (83±3%), but not unloaded polymer stents (35±2%, P=0.020) or bare metal stents (36±3%, P=0.021) after 4 weeks, while endothelialization was complete in all groups (95±6%, 87±8% and 93±3%, P=0.585) after 12 weeks. Due to its potential to attract EPCs, coating with cRGD may accelerate stent re-endothelialization and reduce in-stent restenosis.

2651 Cobalt-chromium stents in porcine coronary arteries: angiographic and ultrasonographic outcomes

P. Buszman[1], A. Zurakowski[2], K. Milewski[2]. [1]*American Heart of Poland, Department of Vascular Diseases, Ustron, Poland;* [2]*Upper-Silesian Heart Center, Coronary Care Unit, Katowice, Poland*

To prove that Co-Cr stent is safe and at least as effective as stainless steel stent (SS) and so, it can serve as an ideal platform for DES.

Methods: Six domestic pigs weighing from 35 to 40 kg were included in the study. Three days prior to the procedure we administered 500mg of Ticlopidine and 150mg of Aspirin and continued this therapy for 28 days. During the procedure each animal received 100mg/kg of heparin and NTG i.c. Under intravenous anesthesia we punctured one of the femoral arteries and inserted a standard 6F introducer sheath. Then we used JR4 and Amplatz R-L guiding catheters. Six Co-Cr and 7 SS stents (3x15mm), were deployed into two different coronary segments under QCA control. Each stent was implanted under such pressure so that the proportion of a dilated stent to the vessel equaled 1,15:1,0. On the 28th day after procedure a control coronarography was performed and then all animals were sacrified to isolate the stents with arteries for further ex vivo IVUS and histopathological analysis.

Results: All vessels were patent after the implantation and after 4 weeks. No acute or late thrombosis was observed. Based on QCA performed in f-up, we observed much lower MLD in Co-Cr group (2,39 ±0,21 for BMS vs 1,99 ±0,28 for Co-Cr; p=0,01) and statistically significant difference in mean LL (0,47 ±0,13 for BMS vs 0,94 ±0,29 for Co-Cr; p=0,003). However, further IVUS examination didn't confirmed these results (p=NS). Analysis of IVUS image at 5 parts of stents, revealed a non-uniform growth of neointima in the Co-Cr stents ($p<0,05$) and uniform growth in SS stents.

Conclusion: Co-Cr stents proved to be safe but their worse efficacy in comparison to BMS (based on QCA) need to be explained. Histopathological results at 28 day will be presented at the meeting.

2652 In vivo biocompatibility of resorbable stents made of poly (lactic acid) stereocopolymers in rabbit iliac arteries

D. Miteva[1], T. Sharkawi[2], E. Durand[1], C. Brasselet[1], M. Vert[2], A. Lafont[1]. [1]*INSERM EMI0016, Faculte de Medecine Paris 5, Paris, France;* [2]*UMR CNRS 5473 Faculte de Pharmacie, Montpellier, France*

Background and Objective: To overcome several problems of conventional metallic stents, there have been many attempts to manufacture stents made of bioresorbable materials. Polylactic acid (PLA) is a hydrolytically degradable material with non-toxic metabolic end products (carbon dioxide and water) that is used in many therapeutic applications. The information and conclusions on the influence of in vivo biocompatibility and degradation of biodegradable PLA as stents in the arteries have not been reported yet. This study was designed to compare the influence of the D/L isomer ratio on the arterial biocompatibility and degradation of PLA stents in rabbit iliac arteries.

Methods and Results: Three types of PLA (PLA L/D=1, PLA L/D=2.08 and PLA L/D=3) tubular stents were implanted in the iliac arteries of three groups of male New Zealand white rabbits (n=15). Angiography was performed before, immediately after stenting and at the time of sacrifice (4 and 10 weeks). Stented arteries segments were then processed for immunohistological and chemical analysis. Endothelialization was generally completed within 4 weeks for the three stereocopolymers. The percentage of collagen content in the intima remained unchanged between week 4 and week 10 (from 49% to 52%) for the three ratios. The immunohistological analyses demonstrated that 4 weeks after stent implantation a greater proportion of L-units in polymer chains was associated with a significant increase in the inflammatory and proliferative response of the artery (from 5.62±2.18%, PLA L/D=3, to 1.07±0.9%, PLA L/D=2.08, $P<0.01$ and 2.18±0.15%, PLA L/D=1, $P<0.04$; and from 4.59±1.72%, PLA L/D=3, to 1.85±0.67%, PLA L/D=2.08, $P<0.06$ and 1.36±0.7%, PLA L/D=1, $P<0.03$). Interestingly, 10 weeks after implantation the percentage of the inflammatory and proliferative cells decreased significantly in the arteries stented with the highest L/D=3 ratio and remained stable for the other two ratios. The structure of the PLA stents, was maintained for up to 10 weeks. The degradation profile for the L/D=2.08 ratio was slightly slower than the others, loosing 33% of its initial molecular weight at D70 compared to 60% and 54% for PLA L/D=1 and PLA L/D=3, respectively.

Conclusion: Neointimal proliferation and inflammatory rates suggest sufficient biocompatibility of PLA stents with low L-isomer forms implanted in rabbit iliac arteries within 10 weeks.

2653 Effect of bioabsorbable magnesium alloy stent on neointimal formation in a porcine coronary model

R. Waksman[1], R. Pakala[1], D. Hellinga[1], R. Baffour[1], P. Kuchulakanti[1], R. Seabron[1], F. Tio[2]. [1]*Washington Hospital Center, Cardiology Research Foundation, Washington, United States of America;* [2]*Biomedical Research Foundation, Pathology, San Antonio, TX, United States of America*

Background: Bioabsorbable Magnesium alloy stent carry the potential to overcome limitations of permanent metallic stents such as chronic inflammation, late stent thrombosis, the need for prolonged antiplatelet therapy and artifacts when imaged by Multi Slice Computed Tomography or Magnetic Resonance Imaging. This study aimed to test the safety and efficacy of the absorbable magnesium alloy stents in porcine coronary arteries.

Methods and results: fifteen magnesium alloy stents and 9 stainless steel stents were randomly deployed in the coronary arteries of 9 juvenile domestic pigs. Twenty-eight days later after performing angiogram and intravascular ultra sound animals were sacrificed, vessels harvested and analyzed by Histomorphometry. At 28 days magnesium alloy stents showed signs of degradation without evidence of stent particles embolization or excess of inflammation, and without thrombosis or fibrin deposition. Neointimal thickness (382.9 ± 154.18 mm) and neointimal area (2.44 ± 0.88 mm^2) were significantly less in the stented segments of magnesium alloy stents as compared with the neointimal thickness (636.49 ± 227.34 mm) and neointimal area (5.03 ± 1.5 mm^2) in the stented segments of the control metallic stented vessels ($p<0.05$ and $p<0.001$ respectively). However, IVUS and histomorphometry analysis detected smaller vessel and stent area in the magnesium alloyed stents when compared to control.

Conclusion: deployment of Magnesium alloy stents in coronary arteries were feasible and safe and was associated with less neoinitma formation when compared to control. Special care should be applied to stent expansion and the potential of recoil of the magnesium alloy bioabsorbable stents.

2654 Influence of stent surface topography on the outcomes of patients undergoing coronary stenting: a randomised, double-blind, controlled trial

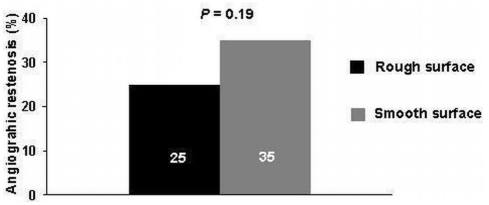
A. Dibra[1], A. Kastrati[2], J. Mehilli[2], J. Pache[2], R. von Oepen[3], J. Dirschinger[4], A. Schoemig[2]. [1]*Deutsches Herzzentrum, Adult Cardiology, Munich, Germany;* [2]*Deutsches Herzzentrum, Adult Cardiology, Munich, Germany;* [3]*Abbott Inc., Redwood City, United States of America;* [4]*1. Medizinische Klinik rechts der Isar, Cariology, Munich, Germany*

Objective: To study the relationship between stent surface topography and outcome in patients undergoing implantation of stents with rough and smooth surfaces.

Background: Surface topography is considered an important determinant of the bare stent performance. Specifically designed rough surface may increase the drug storing capacity of stents but its direct impact on the risk of restenosis is not known.

Methods: A total of 200 patients with significant stenosis in native coronary vessels were randomly assigned in a double blind way to receive either a rough (minimum and maximum root mean square roughness values 0.09 μm and 0.21 μm, respectively) or a smooth surface stent. The primary end point of the study was late lumen loss. Secondary end points included angiographic restenosis and clinical outcomes. The study was designed to test the non-inferiority of rough sur-

face stents to smooth surfaces stents with respect to late lumen loss, based on a non-inferiority margin of 0.20 mm.
Results: Follow-up angiography was performed in 77% of the patients. Late lumen loss was 1.0 ± 0.7 mm in the rough surface stent group and 1.2 ± 0.7 mm in the smooth stent surface group with a mean difference of -0.20 mm [95% CI, -0.43 to 0.02] between the two stents
(P < 0.001 from test for equivalence and P = 0.08 from test for superiority). Angiographic restenosis rates were 25% with rough surface stents and 35% with smooth surface stents, P = 0.19 (see figure).



Stent-Surface-Restenosis

Conclusion: These results show that a rough stent surface does not increase restenosis as compared to a conventional smooth stent surface after coronary stent implantation.

LESSONS FROM THE HEART FAILURE SURVEYS

2664 Management and 1-year outcome of elderly patients hospitalised with heart failure: a nationwide heart failure survey in Israel – HFSIS 2003

S. Gottlieb[1], A. Shotan[2], B.S. Lewis[3], J. Leor[4], S. Stern[1], A. Sandach[4], A. Caspi[5], M. Garty[6] on behalf of HFSIS 2003 Steering Committee and Investigators. *[1]Bikur Cholim Hospital, Heart Institute, Jerusalem, Israel; [2]Helel Yaffe, Cardiology, Haderah, Israel; [3]Carmel Hospital, Cardiology, Haifa, Israel; [4]Sheba Medical center, Neufeld Cardiac research Institute, Tel-Hashomer, Israel; [5]Kaplan Medical Center, Heart Institute, Rehovot, Israel; [6]Rabin Medical center, Recanati Institute, Petach-Tikva, Israel*

Background: the prevalence of HF is increases with advancing age. We investigated the effect of age on etiology, precipitating factors, management and 1-yr mortality of pts hospitalised with HF.
Methods: a prospective 2-month nationwide survey of consecutive HF pts admitted to all 25 public hospitals in Israel in 2003, included 4102 pts (median age 75) who were divided into 2 age subgroups: <75 and ≥75 yrs (53%).
After adjustment for covariates and medications at discharge, variables associated with worse 1-yr outcome in elderly pts were: age, systolic BP<115 mmHg, NYHA class III-IV, renal failure, anemia, use of digoxin and spironolactone, while favorable outcome was associated with the use of ACE-I/ARB and b-blockers.

	Age<75 yrs (N=1933)	Age ≥75 yrs (2169)	P
Age, yrs (m±SD)	63±9	81±6	0.0001
Women	34%	51%	<0.0001
Hypertension	71%	80%	<0.0001
Diabetes	58%	43%	<0.0001
NYHA III-IV	36%	45%	<0.0001
Atrial fibrillation	25%	42%	<0.0001
Anemia (Hb<12Gr%)	44%	45%	<0.0001
Renal failure	36%	45%	<0.0001
Diuretics	70%	81%	<0.0001
Spironolactone	23%	18%	<0.0001
ACE-inhibitors	61%	57%	<0.01
ARB	10%	8%	<0.01
Beta-blockers	64%	52%	<0.0001
Digoxin	14%	15%	ns
In-hospital Mortality	3.1%	6.2%	<0.0001
1-yr Mortality	21.0%	34.5%	<0.0001

Conclusions: this observational nationwide HF survey suggests that elderly pts with HF are hospitalised with a worse presentation, undergo less often evaluation for HF, and are treated less often with evidence-based medications. Better evaluation of HF and greater adherence to guidelines should be advocated in elderly pts with HF to improve their unacceptably high mortality.

2665 Clinical features and mid-term outcome of hospitalisation for heart failure. A systematic community real life study

L. Fauchier[1], C. Rea[2], A. De Labriolle[3], R. Charlon[2], C. Monpere[4], P. Gabach[2], B. Charbonnier[3]. *[1]Centre Hospitalier Universitaire, Cardiologie, Tours, France; [2]CNAMTS, Service Médical Région Centre, Orleans, France; [3]CHU Trousseau, Cardiologie, Tours, France; [4]Centre de Bois Gibert, Readaptation cardiovasculaire, Ballan Mire, France*

Hospitalisation for congestive heart failure (HCHF) is frequent, severe and costly, yet few population-based data are available that take into account modern advances in diagnosis and therapy in the real life. The aim of the study was to describe the clinical features and outcomes of HCHF of all cause in unselected patients.
Methods: The study was based on a systematic retrospective analysis of patients with HCHF (defined as main diagnosis after hospital discharge on national registers) during month october 2003. These patients were seen in 27 institutions in the community of the Center region in France (n = 2440329 in 1999). Information for readmission to hospital and mortality was obtained after 8 months of follow-up for each patient.
Results: From systematic analysis of all hospitalisation in the community, 525 were registered as HCHF for 509 patients. This represents an incidence rate of 250/100000 habitants per year. Median age was 82 (18-102), 53% were male, 53% had coronary heart disease, 24% had normal systolic function (LVEF > 50%) and 198 (38%) already had HCHF in the previous year. Mean duration of hospital stay was 11.3 days and was longer for older patients: 9.8 days when age <75 vs 11.8 when age >75. In hospital mortality was 10%. On discharge, 59% were using ACE inhibitors, 13% had angiotensin II receptor antagonist, 24% had beta blockers and 89% had diuretics. At follow-up, percentage of use of medical treatment was similar. Functional class was NYHA I for 14%, II for 36%, III for 34% and IV for 16%. Male and patients < 80 were more likely to have new HCHF. Eight month mortality rate was dramatically high (57% including the in hospital mortality).
Conclusion: Mortality and hospitalization rate after HCHF remain very high in the community despite improvements in medical treatment that are far to be systematically used. Therapeutic and managed-care research is therefore still required.

2666 Advice on non-pharmacological measures to patients after hospitalisation for heart failure is insufficient: experience from the EuroHeart Failure Survey

M. Lainscak[1], M. Komajda[2], I. Keber[3], M.J. Lenzen[4], F. Follath[5], K. Swedberg[6], J.G.F. Cleland[7]. *[1]Murska Sobota, Slovenia; [2]Hôpital Pitié Salpétriere, Department of Cardiology, Paris, France; [3]Clinical Centre Ljubljana, Department of vascular disease, Ljubljana, Slovenia; [4]Erasmus Medical Center, Thoraxcenter, Department of Cardiology, Rotterdam, Netherlands; [5]University Hospital Zürich, Department of Medicine, Zürich, Switzerland; [6]Sahlgrenska University Hospital/Östra, Department of Medicine, Göteborg, Sweden; [7]University of Hull, Department of Cardiology, Kingston upon Hull, United Kingdom*

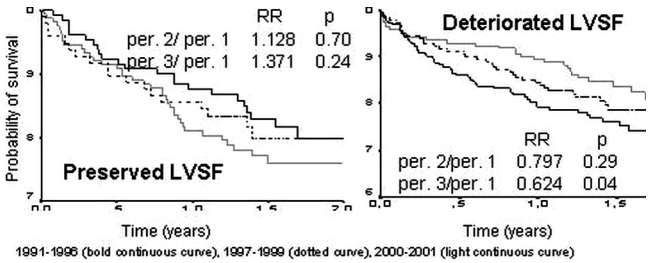
Background: Advice on lifestyle, diet, vaccination and therapy are part of the standard management of heart failure. However, there is little information on whether patients with heart failure recall receiving such recommendations and whether they admit to following them. We aimed to obtain information on the patients perception about being given non-pharmacological measures advice, and whether they follow the advice they remember.
Methods: The EuroHeart Failure Survey screened unselected consecutive deaths and discharges from 115 hospitals in 24 countries belonging to the ESC during 2000-2001. This report focuses on 2331 patients who had a clinical diagnosis of heart failure during the index admission who were interviewed 12 weeks after discharge. Clinical characteristics and pharmacological treatment were retrieved from medical documents, while information on non-pharmacological advice was obtained at interview.
Results: The mean age of the included patients was 67 (12) years and 38% were women. Evidence of acute myocardial infarction (40%), arterial hypertension (55%), atrial fibrillation (41%), diabetes mellitus (28%), and renal dysfunction (15%) as well as rates of treatment with ACE inhibitors (66%), beta blockers (44%), and spironolactone (23%) were mainly consistent with the total survey cohort. Overall, patients recalled receiving 4.1 (2.7) items of advice with higher rates in Central Europe and Mediterranean. In most cases (range 54% - dietary calorie intake to 84% - alcohol consumption) patients reported they completely followed the advice. General dietary advice (cholesterol or fat – 63%, salt – 60%) was more likely to be followed than heart failure-specific advice (avoidance of NSAID – 17%). Thirty-six percent of patients reported receiving influenza vaccination. There was no uniform pattern of lifestyle advice across the European regions or within the country. Patients, who recalled more than 4 items of advice were younger and more often received ACE inhibitors (71% vs. 62%), beta blockers (51% vs. 38%), and spironolactone (25% vs. 21%).
Conclusions: Recall and patient-implementation of dietary and lifestyle advice after hospitalization for heart failure is insufficient. Younger age and prescription of appropriate pharmacological treatment are associated with higher rates of recall and implementation.

2667 Evolution of the prognosis of hospitalised heart failure patients with deteriorated and preserved systolic function

L. Grigorian, A. Varela-Roman, M.A. Bandin Dieguez, C. Pena Gil, J.R. Gonzalez-Juanatey. *Santiago de Compostela, Spain*

Aims: to investigate whether the evolution of the prognosis of patients hospitalised with congestive heart failure (CHF) affects in the same way to those with preserved or deteriorated left ventricular systolic function (LVSF).

Method and Results: 1482 patients who had been admitted to a Cardiology Service in the last 10 years with CHF were evaluated. The prevalence of preserved LVSF rose from 37% to 47% during the study period.
The 1-year survival rate remained unchanged in the whole group of patients. Although, the prognosis of patients with deteriorated LVSF was improved significantly (1-year survival rates of 76%, 77% and 84% in periods 1 (1991-1996), 2 (1997-1999) and 3 (2000-2001), respectively); the risk of death tended to rise (not statistically significant) within the preserved LVSF group (1-year survival rates in periods 1, 2 and 3 of 88%, 86% and 81%, respectively).



1991-1996 (bold continuous curve), 1997-1999 (dotted curve), 2000-2001 (light continuous curve)
Kaplan-Meier survival curves.

Conclusion: although the death rate among hospitalized CHF patients with deteriorated LVSF decreased over the past 10 years, in our centre application of current clinical guidelines has led to no such fall for patients with preserved LVSF. This situation points to a need to reconsider the diagnostic and therapeutic strategy to be employed with this latter group of patients.

2668 Management of octogenarians enrolled in Euro Heart Failure Survey I does not follow ESC guidelines

M. Komajda[1], M. Hochadel[2], O. Hanon[3], F. Follath[4], K. Swedberg[5], A. Gitt[6], J.G.F. Cleland[7]. *[1]Pitie Salpetriere Hospital, Departement de Cardiologie, Paris Cedex 13, France; [2]Institut für Herzinfarktforschung, Ludwigshafen, Germany; [3]Broca Hospital, Department of Geriatrics, Paris, France; [4]University Hospital, Zurich, Switzerland; [5]Sahlgrenska University Hospital Ostra, Department of Medicine, Goteborg, Sweden; [6]Institut für Herzinfarktforschung, Oberarzt Kardiologie, Ludwigshafen, Germany; [7]University of Hull, Department of Cardiology, East Yorkshire, United Kingdom*

Background: Chronic Heart failure is common in elderly patients. Available data suggest that treatment of heart failure in these patients does not follow international recommendations.
Objectives: We therefore compared the treatment received by in 2780 octogenarians (GR1, median age = 85y) and 7912 younger patients (GR2, median age = 69y)enrolled in 116 hospitals across 24 ESC countries participating in Euro Heart Failure Survey I. Legend (*) = $p<0.0001$.
Results: The use of ACE inhibitors (50% vs 66%), betablockers (24% vs 42%), Spironolactone (15% vs 23%) and IV inotropic agents (5% vs 8%) was significantly reduced in GR1 (all =*) whereas loop diuretics (86% vs 78%), nitrates (49% vs 46%) and digoxin (34% vs 30%) were more commonly prescribed (all $p<0.01$) in GR1 vs GR2. Oral anticoagulant therapy (15% vs 26%) and lipid lowering drugs (7% vs 25%) were less frequently used in GR1. Drugs for neurological/psychological disorders (35% vs 28%), antibiotics (36% vs 28%), bronchodilators (23% vs 19%) and pain relieving drugs (26% vs 17%) were more common in GR1 (all=*). 39% older patients and 51% younger patients had EF<45% or moderate/severe LV systolic dysfunction (LVSD).Only 19% of GR1 patients with LVSD were prescribed, ACE inhibitors + betablockers vs 41% in GR2 (*). Finally, 19% of patients with LVSD who were octogenarians were treated by spironolactone vs 32% in GR2 (*). No gender difference was observed in the rate of prescription of CV medications in GR1 except for digitalis compounds [40% female patients (F) vs 36% male patients (M)], antithrombotic drugs (72%F vs 79%M) and IV inotropes (4%F vs 6%M), (all $p<0.04$).
Conclusion: In hospital, octogenarians with heart failure are less likely to receive recommended drugs and more likely to receive drugs to relieve symptoms than younger HF patients. Medications for treatment of comorbid factors are also more commonly prescribed in these elderly patients. Underprescription of recommended HF drugs is observed both in the overall elderly population and in the subgroup of patients with depressed systolic function.

2669 Vitamin E and heart failure development in the GISSI prevenzione trial

G. Levantesi[1], A. Macchia[1], L. Tavazzi[2], G. Tognoni[1], F. Valagussa[3], R. Marchioli[1] on behalf of GISSI Prevenzione Investigators. *[1]Consorzio Mario Negri Sud, Clinical Pharmacology and Epidemiology, Santa Maria Imbaro, Italy; [2]IRCCS Policlinico San Matteo, Department of Cardiology, Pavia, Italy; [3]Ospedale San Gerardo, Department of Cardiology, Monza, Italy*

Recent evidence suggests that vitamin E (VE) treatment increase mortality in a dose dependent fashion, although the mechanisms for such increment are unknown. The HOPE Trial suggested an increase of heart failure (CHF) in patients treated with VE. However, the relationship between left ventricular function and the effect of VE treatment has not been measured so far.
GISSI-Prevention was a multicenter, open-label, randomized trial that tested the efficacy of n-3 polyunsaturated fatty acids (n-3 PUFA) 1 g/d, vitamin E 300 mg/d, both, or neither in 11,323 patients with recent (<3 months) myocardial infarction. Mean follow-up duration was 3.5 years. This analysis was carried on in 8,415 patients with ejection fraction (EF) measured and no CHF at baseline. Heart failure development during follow-up was defined in the study protocol as hospitalization for the management of CHF. Cox regression models adjusted for relevant prognostic indicators were fitted.
The main characteristics of patients were well balanced in the 4,213 and 4,202 patients allocated to vitamin E and control group, respectively. During follow up, 192 patients (2.3%) were hospitalized for CHF. Patients allocated vitamin E treatment had a non-significantly 21% (95%CI 0.91 to 1.61, P=0.18) increased risk of CHF. However, as compared to patients with preserved left ventricular function, those with mild to moderate ventricle dysfunction (EF < 50%)had a significant 57% increase (95%CI 1.05 to 2.34, P=0.028) of CHF during follow up.
VE does not have a role in cardiovascular prevention. The available evidence on the harmful effect on ventricular function in patients with left ventricular dysfunction should discourage the use of vitamin E in patients with or at risk of CHF.

RENAL DYSFUNCTION; COMMON RISK FACTOR IN HEART FAILURE

2670 Renal insufficiency is a major predictor of mortality in hospitalised patients with both systolic and diastolic heart failure

Y. Amsalem, M. Garty, A. Sandach, A. Caspi, D. Ezra, S. Behar, J. Leor on behalf of HFSIS group. *Chaim Sheba Medical Center, Neufeld Cardiac Research Institute, Tel Hashomer, Israel*

Background: studies which tested the prognostic value of renal insufficiency (RI) in heart failure included selected patients enrolled in clinical trials. We sought to explore the prognostic impact of renal insufficiency in a large, unselected population of heart failure patients.
Methods: we analysed data from a cohort of 3,771 hospitalised patients with heart failure. The patients were stratified into four groups based on their estimated glomerular filtration rate (GFR). Multivariate logistic regression models were used to evaluate the association between RI (estimated GFR<60 ml/min/1.73m^2) and all-cause mortality in the entire cohort and in systolic (ejection fraction<50%) and diastolic (ejection fraction $\geq$ 50%) dysfunction groups separately.
Results: the prevalence of RI was 57%: 572 (15%) had severe RI - estimated GFR<30 ml/min/1.73m^2 (creatinine 3.3±1.6 mg/dL) and 1580 (42%) had moderate RI - estimated GFR of 30-59 ml/min/1.73m^2 (creatinine 1.5±0.3 mg/dL). Patients with RI were less likely to be prescribed angiotensin-converting enzyme (ACE) inhibitors or aspirin (both $p < 0.01$). Decreasing renal function significantly predicted higher one year mortality (log rank test, p=0.0001). Every 10 ml/min/1.73m^2 decline in GFR was associated with a 6% increase in 1-year mortality. After adjustment for all prognostic variables, severe RI and moderate RI remained strong predictors of one year mortality (OR-2.20, 95% confidence interval [CI] 1.54-3.17 and OR 1.30, 95% CI 0.94-1.80; respectively). Mild RI (estimated GFR of 60-89 ml/min/1.73m^2) was not associated with increased mortality. There was no correlation between systolic vs. diastolic dysfunction and the mortality risk attributed to renal insufficiency.
Conclusion: renal insufficiency is frequent in patients with HF. These patients are less likely to be prescribed evidence-based therapies. Our study extends the data about the strong association between renal insufficiency and poor outcome to a broad population of unselected, "real life", hospitalized heart failure patients. These patients require improved surveillance and therapy.

2671 Clinical and prognostic significance of renal dysfunction in stable patients with chronic heart failure

E.A. Jankowska[1], T. Witkowski[2], L. Tomkiewicz-Pajak[3], P. Podolec[3], W. Banasiak[2], P. Ponikowski[2]. *[1]Polish Academy of Sciences, Institute of Anthropology, Wroclaw, Poland; [2]Military Hospital, Cardiology Department, Wroclaw, Poland; [3]Institute of Cardiology, Jagiellonian Univ, Collegium Medicum, Krakow, Poland*

Background: Renal failure constitutes a major risk factor for cardiovascular morbidity and mortality, and as a coexisting disease deteriorates outcome in most cardiovascular conditions. Its clinical and prognostic significance in stable patients with chronic heart failure (CHF) remains unclear.
Methods: We prospectively examined 256 patients with stable systolic CHF (men: 85%, age: 59±1 years, NYHA class I/II/III/IV: 31/132/77/16, ischaemic aetiology: 66%, left ventricular ejection fraction [LVEF]: 31±1%, peak oxygen consumption [peak VO2]: 15.0±0.3 mL/min/kg). Impaired renal function was defined as glomerular filtration rate GFR<45 mL/min/1.73m^2 (estimated from the Cockroft-Gault formula).
Results: In all patients with CHF, the mean GFR was 60±1 mL/min/1.73m^2 (range: 24-110). GFR<45 mL/min/1.73m^2 and GFR<60 mL/min/1.73m^2 were found in 44 (17%) and 132 (52%) patients with CHF, respectively. Subjects with

GFR<45 mL/min/1.73m^2 (as compared to those with GFR≥45 mL/min/1.73m^2) were older (66±2 vs. 57±1 years, p<0.001), thinner (body mass index: 25±1 vs. 27±1 kg/m^2, p<0.01), had slightly more advanced CHF as expressed by NYHA class (2.5±0.1 vs. 2.2±0.1, p=0.06), and the etiology of CHF was more often ischaemic (89% vs. 61%, p<0.01). Reduced GFR was related to impaired exercise tolerance expressed as diminished peak VO2 (r=0.19, p<0.01) and augmented ventilatory response to exercise (VE-VCO2 slope) (r=-0.14, p<0.05). During the follow-up (mean: 30±1 months, >18 months in all who survived), 65 (25%) patients died. Impaired renal function, as assessed by reduced estimated GRF, was related to increased mortality in univariate (GFR as a continuous variable [mL/min/1.73m^2]: HR=0.97, 95%CI: 0.96–0.99, p=0.002; GFR dichotomized [< vs. ≥45 mL/min/1.73m^2]: HR=3.29, 95%CI: 1.94-5.60, p<0.0001) and multivariate analyses (adjusted for age, NYHA class, CHF aetiology, LVEF, and peak VO2; in all models p<0.01 for GFR). The 30-month survival rate for patients with CHF with GFR<45 mL/min/1.73m^2 was 33% (95%CI: 24-42%) vs. 76% (95%CI: 69-83%) in those with GFR≥45 mL/min/1.73m^2 (p<0.0001).

Conclusions: Patients with stable CHF demonstrate a high prevalence of renal impairment, which is associated with severity of the disease and exercise intolerance. Reduced GFR strongly predicts increased mortality in this group of patients, independently of conventional prognostic factors.

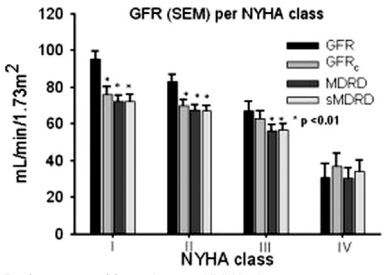
2672 Severity of heart failure influences the performance of formulas estimating renal function

T.D.J. Smilde[1], H.L. Hillege[1], G. Navis[2], A.A. Voors[1], D.J. Van Veldhuisen[1]. [1]*University Medical Center Groningen, Cardiology, Groningen, Netherlands;* [2]*University Medical Center Groningen, Nephrology, Groningen, Netherlands*

Background: Renal function is an important risk marker in patients with chronic heart failure (CHF). In clinical practice glomerular filtration rate (GFR) is used to determine the renal function. As it is not feasible to perform direct measurements of renal function in large scale studies investigators mostly rely on serum creatinine derived estimates of renal function. However, none of these formulas have been validated in CHF patients. Therefore, we validated in CHF patients three commonly used formulas estimating GFR and evaluated whether the severity of CHF influences their performance.

Methods: In 80 CHF patients; age 59±10 years, LVEF 0.28±0.10 and NYHA I/IV. GFR was measured with the gold standard 125I-iothalamate clearance (GFR). Body weight, plasma creatinine and albumin were determined to calculate GFR using Cockcroft-Gault (GFRc) and Modification of Diet in Renal Disease (MDRD) formulas. GFR and GFRc were corrected for body surface area (BSA). To compare these formulas with the true GFR we used the Bland-Altman method.

Results: The mean GFR was 75±27 mL/min/1.73m^2, and the mean GFRc, MDRD and the simplified MDRD were 67±21, 62±19, and 63±18 mL/min/1.73m^2, respectively. All formulas differed significantly of the true GFR. Furthermore, there was a substantial underestimation of all formulas in patients with NYHA I-III, and GFRc and simplified MDRD overestimated the GFR in NYHA IV (Figure).



Performance of formulas per NYHA class

Conclusions: In CHF, serum creatinine derived formulas estimating GFR underestimate the true GFR. The performance of the formulas appear to be better in patients with NYHA III and IV.

2673 Even mild increase of serum creatinine in patients with heart failure is predictive of increased total mortality in elderly patients

G. Kamensky[1], J. Murin[2], J. Fabian[3], E. Goncalvesova[3], I. Riecansky[4] on behalf of PROMIS. [1]*Ruzinov Faculty Hospital, Noninvasive CV Diagnostics, Bratislava, Slovakia;* [2]*Ruzinov Faculty Hospital, 1st Internal Clinic, Bratislava, Slovakia;* [3]*Slovak Inst. of Cardiovascular Disease, Department of heart transplantation, Bratislava, Slovakia;* [4]*Slovak Inst. of Cardiovascular Disease, Cardiologic Clinic, Bratislava, Slovakia*

Background: Impaired renal function is associated with poor outcomes among chronic heart failure (HF) patients.

Objectives: The goal of the study was to determine the prevalence of worsening renal function (WRF), it's clinical predictors and outcomes associated with WRF in patients with HF intolerant to ACE-I treated by valsartan in addition to standard HF therapy.

Methods: In prospective multicenter study (69 outpatients cardiologists and internists) 1114 patients with documented heart failure (mean age 66.57+9.9 ys, 512 men, 570 women) were followed for a mean 713.6±161.3 days. WRF was defined as a rise in serum creatinine of 26.5 umol/l (> 0.3 mg/dl).

Results: Among the 1114 HF patients studied (mean EF 40.7+10.3, mean serum creatinine 102,9±34,6 umol/l, NYHA class II. 35%, NYHA III. 51%) WRF developed in 9.2%. In multiple logistic regression analysis diabetes mellitus (OR 2.02 [95% CI 1.31 to 3.11]), gender (OR 1.95 [95% CI 1.24 to 3.07]), hemoglobin (OR 0.961 [95% CI 0.947 to 0.975]) and serum creatinine over 132 umol/l (>1.5 mg/dl) (OR 0.50 [95% CI 0.32 to 0.77]) were independently associated with higher risk of WRF after undjustment for all other prognostic factors. During follow-up 111 patients died (10.2%). In the group of patients with WRF 16.9% died compared to patients without WRF (9.6%, log rank = 6.21, p = 0.0127). In Cox regression analysis, age (OR 1.034 [95% CI 1.013 to 1.055]), gender (OR 1.90 [95% CI 1.30 to 2.76]), NYHA class (OR 3.49 [95% CI 2.05 to 5.20]) and serum creatinine over 132 umol/l (OR 2.50 [95% CI 1.65 to 3.81 respectively]) were independent predictors of total mortality.

In conclusion, our study found not only that patients with HF and mildly elevated serum creatinine (lower than 132 umol/l) are predictive of increased morbidity and mortality, but also that those patients had significantly higher WRF compared to those with higher serum creatinine during 2-years follow up. This finding is consistent with previous observations that even mild renal insufficiency in patients with HF may have a substantial attributable risk for CVD and mortality in the elderly population.

2674 Is a possible relation between NTproBNP and anaemia parameters dependent on kidney function in patients with chronic heart failure?

P.W.F. Bruggink-Andre de la Porte[1], P. van der Meer[2], D.J.A. Lok[3], J. van Wijngaarden[3], J.H. Cornel[4], D.J. van Veldhuisen[2], A.W. Hoes[5]. [1]*Deventer Hospital, Cardiology, Deventer, Netherlands;* [2]*University Hospital, Groningen, Cardiology, Groningen, Netherlands;* [3]*Deventer Hospital, Cardiology, Deventer, Netherlands;* [4]*Medical Center Alkmaar, Cardiology, Alkmaar, Netherlands;* [5]*University Medical Center Utrecht, Julius Center, Utrecht, Netherlands*

Background: The origin of anemia in chronic heart failure (CHF) is complex and not quite clear. In this study we assessed the relation between brain natriuretic peptide (NTproBNP)as a parameter of the seriousness of CHF, and different anemia parameters in CHF patients with a normal or an impaired renal function.

Methods: In the DEAL-HF study in 240 patients with CHF NYHA III and IV with a mean LVEF of 31%, NTproBNP, hemoglobine (HB), erythropoietin (EPO), vitB12, folate, iron and ferritin, and renal function were determined at baseline. Anemia was defined as HB < 12.5 g/dl. Chronic Renal Failure (CRF) was defined as creatinin >160μmol/L.

Different effects for all (anemic and non-anemic) patients of these parameters were assessed using interaction (effectmodification) in lineair regression. If interaction is significant, subgroup analysis is shown.

Results: Anemia was seen in 40 patients (17%), CRF in 32 patients (14%). Different effects of anemia parameters (interaction) were only found for EPO (table 1).We did not find a significant relation between NTproBNP and vitB12, folate and ferritin.

Table 1

Chronic Renal Failure (CRF)	Variable CHF parameter	Dependent variable Anemia parameter	Standardized regression coeff. beta	Significance
NoCRF	NTproBNP	EPO	0.447	0.000
CRF	NTProBNP	EPO	0.314	0.080
	CRF*NTproBNP	EPO	-0.412	0.000
	NTproBNP	Hemoglobin	-0.304	0.000
	CRF*NTproBNP	Hemoglobin	0.005	0.963
	NTproBNP	Iron	-0.217	0.001
	CRF*NTproBNP	Iron	0.011	0.000

NTproBNP N=237; EPO N=234; HB N=239; Iron N=227; noCRF N=202; CRF N=32. CRF*NTproBNP: effectmodification by renal function.

Conclusion: We found a significant relation between NTproBNP and EPO, HB and iron, but only with EPO this relation differed significantly for patients with or without CRF. In patients with a normal renal function we saw a significant relation of EPO and NTproBNP, in patient with CRF we did not see this significant relationship. Most likely a decrease of EPO production in CRF will be the cause of this poor relationship.

2675 Prognostic value of CystatinC in patients admitted with acute heart failure

J.P.E. Lassus[1], V.-P. Harjola[2], K. Siirila-Waris[2], J. Melin[3], K. Pulkki[4], K. Peuhkurinen[5], M.S. Nieminen[2] on behalf of The FINN-AKVA study group. *[1]Helsinki University Central Hospital, Division of Cardiology, Helsinki, Finland; [2]Helsinki University Central Hospital, Division of cardiology, Helsinki, Finland; [3]Central Finland Central Hospital, Department of Medicine, Jyväskylä, Finland; [4]Helsinki University, Department of Clinical Chemistry, Helsinki, Finland; [5]Kuopio University Hospital, Department of Cardiology, Kuopio, Finland*

Background: Acute heart failure is associated with poor prognosis. CystatinC (cysC) is a novel, sensitive marker of renal function and has recently been implicated to have an independent prognostic value in cardiovascular disease.
Objective: To investigate the prognostic value of cysC in patients hospitalised for acute heart failure, and compare it to other, established, markers.
Method: FINN-AKVA is a prospective multicenter study of 622 patients hospitalized for acute heart failure. CysC (Dako) and creatinine were evaluated in 160 patients, and BNP (Abbott), NT-proBNP and troponinT (Roche Diagnostics) in 227 patients, approximately 48h from admission. Cockcroft-Gault formula was used to calculate an estimated GFR. All-cause mortality at 6 months was assessed after categorizing patients in tertiles of each biomarker.
Results: The patients were 74.7 ± 10.6 (range 40-98) years old, 48.4% female and 50.4% had a previous history of CHF. All-cause mortality at 6 months was 14.4%. Mortality increased from the lowest to the highest tertile of each biomarker, with an inverse relationship for GFR (figure). The highest mortality was observed in the third tertile of cysC, 7-fold higher than in the first tertile ($p<0.01$). For creatinine, BNP and NT-proBNP the trend was similar (NS). 6-month mortality in troponinT positive (>0.03 ug/l) patients was 17.2%, 1.3-fold that of TnT negative patients.

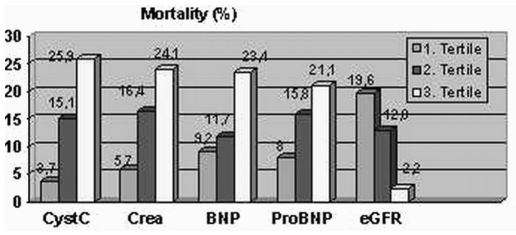


Figure 1

Conclusion: The highest 6-month mortality was observed in the highest tertile of cystatinC, and was significantly higher than the mortality in the lowest tertile. The trends were similar in the established risk markers, but not statistically significant. Thus, cystatinC seems to be a promising new risk marker in patients admitted with acute heart failure.

PUZZLING ANGIOGRAPHIC FINDINGS IN ACS

2676 Prognosis and risk stratification of non-obstructive CAD in acute coronary syndrome: observations in TIMI 11B, OPUS-TIMI 16 and PROVE-IT-TIMI 22

R. Bugiardini[1], O. Manfrini[1], S.A. Murphy[2], G. De Ferrari[3], E. Braunwald[2], C.P. Cannon[2] on behalf of TIMI 22 investigators. *[1]University of Bologna, Dip. Med. Interna, Cardioangiologia, Bologna, Italy; [2]Brigham and Women's Hospital, Boston, United States of America; [3]Policlinico S Matteo, Pavia, Italy*

Background: Prognosis of patients with non-obstructive coronary artery disease (CAD) is assumed to be benign. Accordingly there are not critical pathways specifically developed to assess risk and management of these patients.
Methods: We explored the outcome of patients with non-obstructive CAD (<50% lumen stenosis) in the setting of acute coronary syndrome, and the prognostic value of the TIMI risk score in the study populations of 3 TIMI trials (TIMI 11B, OPUS-TIMI 16 and PROVE-IT-TIMI 22). The primary end-point of this analysis was the composite of death, myocardial infarction, unstable angina requiring rehospitalization, revascularization, and stroke at 1-year follow-up.
Results: Angiographic data were available in 10838 patients. Of these patients 910 (8.3%) had non-obstructive CAD: 443 patients (48.7%) had normal coronary arteries (0% stenosis) and 467 patients (51.3%) had mild–CAD (>0 to <50% stenosis). A primary end point event occurred in 102 patients (11.2%): 39 patients (8.8%) with normal coronary arteries and 63 patients (13.5%) with mild–CAD. Noteworthy, non-obstructive CAD had 2% of death and myocardial infarction at 1-year follow-up. Risk in mild–CAD was not significantly greater than in normal angiography (2.8% versus 1.3%). Patients with and without a primary end point event matched well with regard to treatment, gender and baseline characteristics. There was a higher (P=0.049) incidence of the primary end point in patients with unstable angina as the index event. Event rates of patients with non-obstructive CAD increased significantly as the TIMI risk score increased: 10.9% for a score of 0-2; 15.5% for a score 3-4; and 30.3% for a score ≥5 (P=0.0054 by chi-2 for trend).
Conclusion: Patients with acute coronary syndrome and non-obstructive CAD have a relatively poor prognosis at 1-year follow-up. The TIMI risk score could be used in clinical practice to predict the likelihood of non-obstructive CAD patients to develop future coronary events.

2677 One year outcome in non-ST elevation acute coronary syndrome patients with normal coronary arteriograms or mild disease: a report from the RITA 3 trial

T.R.D. Shaw[1], R.A. Henderson[2], C.T. Clayton[3], S.J. Pocock[3], D.J. Wheatley[4], P.A. Poole-Wilson[3], K.A.A. Fox[1]. *[1]Edinburgh, United Kingdom; [2]Nottingham, United Kingdom; [3]London, United Kingdom; [4]Glasgow, United Kingdom*

The RITA3 Trial enrolled 1810 patients with unstable angina or non-ST elevation infarct in a randomised comparison of early conservative versus interventional care (arteriography and revascularisation). 895 patients were randomised to the early intervention arm and the intended arteriogram was carried out in 865 (97%) at a median of 2 days after randomisation: complete angiographic reports were available in 861. We have reviewed the 1 year outcome of those patients in the intervention arm who were found to have normal coronary arteriograms or mild coronary disease.
Normal coronary arteriograms were reported in 103 (12%) patients: 77% were female. None had intervention as an immediate treatment. By 1 year follow-up no patient required angioplasty (PCI) or coronary bypass surgery (CABG). No patient died or had myocardial infarction within this period. However, 40% still reported chest discomfort. Antianginal drug therapy was still used by 60%, aspirin by 53%, ACE therapy by 11% and a statin by 40%. In this group 16 had a normal ECG throughout and 6 had bundle branch block: in the 81 others with ST/T abnormalities there was a dynamic ECG change in 48% during admission and in 73% between admission and follow-up.
69 patients (8%) had mild coronary disease (stenosis <50% luminal diameter). 1 patient had early PCI. None had CABG. No patient died or had infarction by 1 year but 39% continued to have chest pain, 78% were on antianginal drugs, 80% on aspirin, 34% on ACE inhibitor and 63% on a statin.
Patients with suspected non-STEMI acute coronary syndrome who are found to have normal coronary arteriograms or mild disease have a good outcome to 1 year but are an acute and chronic management problem as optimal drug therapy is uncertain and many of these patients continue to complain of chest pain.

2678 Characteristics of patients with suspected acute coronary syndrome and elevated troponin-I without significant coronary artery stenosis

C. Tron, H. Eltchaninoff, L. Sebagh, F. Vochelet, B. Baala, A. Cribier. *C.H.U. Charles Nicolle, Service de Cardiologie, Rouen cédex, France*

Extensive literature has shown that in the setting of acute coronary syndromes (ACS), troponin elevation identify a high-risk subgroup of patients for whom an early invasive approach is recommended. However, a subset of patients with suspected ACS and troponin elevation do not exhibit significant coronary artery disease on coronary arteriography (CA). We sought to assess the characteristics of these patients.
Methods: Consecutive patients with elevated Troponin-I (> or = 1 μg/l) who underwent CA for suspected ACS without ST-segment elevation were included in the study if they had normal coronary arteries or mild coronary disease (< 50% diameter stenosis and absence of dissection or visible thrombus). The Immulite assay was used for Troponin-I measurement.
Results: Since January 2002, 1299 patients (Pts) with ACS and elevated Troponin-I underwent CA in our institution. Among them, only 31 Pts (2.4%), with a mean age of 63 ± 13 years (55% male) were found to have no ST segment elevation and no significant coronary lesion, and represent our study group. Three (9.7%) patients had prior coronary angioplasty. Risk factors for coronary disease were: hypercholesterolemia (65%), smoking (45%), hypertension (58%), diabetes (13%). ECG showed: ST-segment depression (13%), inverted T-wave (30%), left bundle-branch block (7%), no or non specific ECG changes (50%). No patient received IIb/IIIa inhibitors. Mean ejection fraction was 60 ± 14%. Peak Troponin-I was 15 ± 16 μg/l, ranging from 1.0 to 57.2 μg/l. No patient died during hospital stay. Myocardial infarction without significant coronary stenosis was the final diagnosis at discharge in 19 Pts (61%), whereas a non ischemic cause was found in 12 Pts (39%): myocarditis (n=3), myxoma (n=1), nodal tachycardia (n=1), aortic stenosis (n=1), left ventricular hypertrophy (n=1), Takotsubo cardiomyopathy (n=1), non ischemic cardiomyopathy (n=1). In 3 Pts, no cardiac disease was shown.
Conclusion: Among patients undergoing CA for ACS with elevated Troponin-I, the incidence of patients with no significant coronary artery stenosis is very low. In 39% of these patients, Troponin-I elevation is not of ischemic origin. Efforts should be directed to non-invasively identify this subset of patients who do not benefit from an invasive strategy.

2679 Angiographic findings in a series of patients with Troponin-negative acute coronary syndrome

A.G. Rebeiz[1], M.Y. Khoury[2], W.S. Gharzuddine[2], M.S.A. Arnaout[2], J.I. Sawaya[2], A.G. Abchee[2], H.A. Dakik[2], A.T. Nasrallah[2]. [1]*Duke University Medical Center, Cardiology Division, Durham NC, United States of America;* [2]*American University of Beirut, Cardiology, Beirut, Lebanon*

Background: Acute coronary syndrome is the clinical surrogate of coronary atherothrombosis. The triage and risk stratification of patients with unstable angina remains an important clinical challenge in view of the substantial short and long-term morbidity. Several studies have correlated the angiographic and prognostic profile of acute coronary syndrome (ACS) with a few indicators, most importantly troponin T or I release. In this study, we assess the prevalence of angiographic disease in a cohort of 100 consecutive patients admitted with unstable angina who had negative troponin T levels.
Methods: Consecutive patients admitted with unstable angina who had no evidence of troponin T release underwent routine coronary angiography within 48 hours. The findings were analyzed for the presence and complexity of coronary lesions. Their clinical outcome was evaluated.
Results: One hundred patients were included in the study. Mean age (±SD) was 58.9 ± 10.8 years and 81 (81%) were men. Thirty-four percent had prior history of coronary artery disease (CAD), 27% were diabetics and 36% had ST or T changes on electrocardiogram. All patients were treated with aspirin, heparin and beta-blockers. Coronary angiography revealed the presence of significant CAD (>75% diameter stenosis) in 78% of the patients. Thrombus formation was detected in 15.3% of the culprit lesions. Mean culprit lesion stenosis was 83%. Sixty-six percent of the culprit lesions had severe complexity, characterized by the presence of high-grade stenosis and/or thrombus formation. There was no significant difference between lesions complexity when analyzed according to the presence of prior history of CAD (P value= 0.180). Revascularization was recommended for 55% of the patients.
Conclusion: Patients with unstable angina and negative troponin T, manifest significant anatomic, mildly thrombotic disease by angiography, frequently warranting revascularization. Novel diagnostic modalities and markers are needed in order to better identify patients at risk.

2680 Do coronary angiographic data improve the accuracy of risk assessment in-patients with non ST-segment elevation acute coronary syndromes?

W. Wasek[1], P. Maciejewski[2], A. Torun[1], M. Niewada[3], B. Kaminski[4], B. Klosiewicz-Wasek[1], B. Bednarz[1], A. Budaj[1]. [1]*Postgraduate Medical School, Dpt. of Cardiol. Grochowski Hospital, Warsaw, Poland;* [2]*Warsaw, Poland;* [3]*Warsaw Medical University, Dpt. of Clin. and Experiment. Pharm., Warsaw, Poland;* [4]*School of Economics, Dpt. of Division of Decision Analysis, Warsaw, Poland*

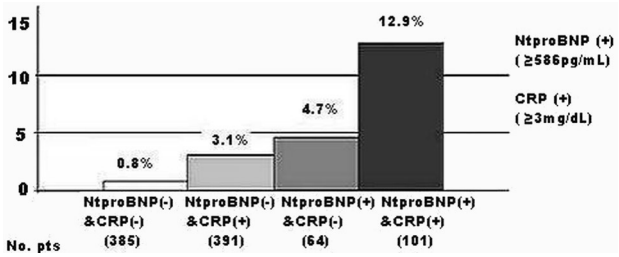
Background: In-patients (pts) with NSTE ACS the long-term risk of death and MI is estimated by scores based on noninvasive variables. Much less is known about the relation between the degree of atherosclerotic burden in coronary tree and long-term risk of pts with NSTE ACS. It might be suggested that the predictive accuracy of noninvasive scores could be strengthened if clinical data were combined with findings derived from coronary angiogram.
Methods: The study group consisted of 112 consecutive pts (age 62±10; 76 men) treated invasively for NSTE ACS. 27 pts (24%) had a history of diabetes mellitus (DM) and 37 pts (33%) a history myocardial infarction (MI). The coronary angiograms prior to intervention were evaluated blindly for the four angiographic scores: (1) Stenosis score was derived from the assessment of the degree of stenosis in 15 segments of coronary tree. (2) Vessel score showing number of main vessels stenosed > 70%. (3) Extensity score assessed the proportion of lumen length irregularity in 15 segments. (4) Complexity score described the number of complex plaques. The angiographic analysis also focused on the flow and the presence of thrombus (according to TIMI) and the size of the culprit lesion vessel. The intervention was successful in 95% of cases. All pts were followed-up for 6 to 24 months for the occurrence of death or MI.
Results: In the follow-up period the composite end point of death or MI occurred in 20 pts (17%). In order to indicate the risk predictors from the group of clinical and angiographic variables (age, sex, history of DM or MI, four angiographic scores and culprit lesion vessel characterization) the forwarded logistic regression analysis was performed. The independent predictors of composite end point were stenosis score (OR 1.12; 95%CI 1.06-1.18; p<0.001) and size of the vessel (OR 0.5; 95%CI 0.26-0.95; p=0.03)
Conclusion: Our preliminary data show that an attempt to add angiographic variables in the risk assessment scoring systems in order to strengthen their predictive accuracy is justified.

THE IMPORTANCE OF BIOMARKERS IN ACUTE CARDIAC CARE

2682 Clinical significance to elevated NT-proBNP and hs-CRP in troponin-negative patients with acute coronary syndromes

O. Bazzino[1], J.J. Fuselli[2], R. Ahuad[3], S. Salzberg[4], M. Russo[5], J. Gant Lopez[6], D. Perez de Arenaza[1], R. Nordaby[7] on behalf of PACS investigators. [1]*Hospital Italiano De Buenos Aires, Cardiology Dept, Buenos Aires, Argentina;* [2]*CEMIC, Cardiology, Buenos Aires, Argentina;* [3]*Hospital Privado Antártida, Cardiology, Buenos Aires, Argentina;* [4]*Hospital Fernandez, Cardiologia, Buenos Aires, Argentina;* [5]*Instituto Cardiologia Hospital Español, Cardiology, Buenos Aires, Argentina;* [6]*Hospital Alemán, Cardiology, Buenos Aires, Argentina;* [7]*Hospital Francés, Cardiology, Buenos Aires, Argentina*

Background: Patients with non-ST segment elevation acute coronary syndromes(NSTE-ACS) and negative troponin levels are a low risk group in whom new prognostic markers could improve the prognostication scheme. The purpose of this study is to determine whether the elevation of NT-proBNP and hs-CRP have a prognostic significance in this specific subset of patients.
Methods: We studied 941 consecutive patients with NSTE-ACS and baseline troponin T (TnT) values below 0.03 ng/mL. Centralized measurements of NT-proBNP, TnT, and hs-CRP, were performed 3 h (median) after admission. Upon admission, patients were classified into low(LR, score 0-2), moderate(MR, score 5,6)) and high(HR, score 5-7) TIMI risk groups
Results: Age (mean ± SD) was 66 ± 12 years. Ischemic ST segment depression was observed in 12%. NT-proBNP levels over 586 pg/mL, and hs-CRP values over 3mg/dL, were measured in 18% and 52% of all patients respectively. LR, MR, and HR TIMI categories, represented 65%, 33% and 2% of all patients respectively. Overall mortality rate at six months was 3.3%. After logistic regression analysis for the prediction of 6-month death, the following independent variables emerged: NT-proBNP (OR 3.99, 95% CI 1.88-8.94), hs-CRP (OR 3.44, 95% CI 1.38-8.55) and TIMI risk score (OR 1.42, 95% CI 1.03-1.94). The rates of death at 6 months according to biomarkers levels are shown in the figure.



Conclusions: Patients with NSTE-ACS and negative TnT levels are an heterogeneous group. In these patients, elevated NT-proBNP and hs-CRP add strong prognostic information to that provided by the traditional risk predictors.

2683 Relationship between plasma N-terminal pro-B-type natriuretic peptide and heart rate variability in patients with acute myocardial Infarction. Data from the RICO survey

M. Zeller[1], D. Moreau[1], G. Dentan[2], Y. Laurent[3], A. Oudot[1], L. Janin-Magnificat[4], L. Rochette[5], Y. Cottin[1] on behalf of RICO survey working group. [1]*CHU Le Bocage, Cardiology, Dijon, France;* [2]*Clinique de Fontaine, Cardiology, Fontaine les Dijon, France;* [3]*CH, Cardiology, Semur en Auxois, France;* [4]*CH, Cardiology, Beaune, France;* [5]*Faculty of Medicine, LPPCE-IFR n°100, Dijon, France*

Background: We aimed to investigate the relationships between the autonomic nervous system, as assessed by heart rate variability (HRV) and levels of N-terminal Pro-B-type Natriuretic Peptide (Nt-proBNP), in the setting of acute myocardial infarction (MI).
Patients and method: Plasma Nt-proBNP (Elecsys, Roche) was measured on admission in consecutive non-selected patients admitted < 24h for acute MI. Patients with chronic atrial fibrillation or pace maker were excluded from the study. The mean of standard deviation of RR intervals (SDNN), percentage of RR intervals with >50ms variation (pNN50), square root of mean squared differences of successive RR intervals (rMSSD), and frequency domain parameters (total power (TP), high frequency and low frequency power ratio (LF/HF)) were assessed by 24h holter ECG monitoring at 5 ± 2 days after MI onset.
Results: Among the 461 patients included in the study, median (interquartile range) Nt-proBNP value was 104(29-322) pmole/L. Multiple regression analysis on log transformed values showed that plasma propeptide level was negatively associated with LF/HF (p=0.013), pNN50 (p=0.035), SDNN (p=0.005) and TP (p=0.004) even after adjustment for age and sex. Patients with highest quartile of Nt-proBNP were older (74 vs 59 y, p<0.0001), were more likely to be women (47 vs 23%, p<0.0001), hypertensive (64 vs 44%, p<0.0001), had higher admission heart rate (81 vs 75 b/min, p<0.0001), but were less likely to be smokers (19

vs 46%, p<0.0001). LVEF as assessed by echocardiography was significantly lower in this group (47 vs 58%, p<0.0001). Moreover, highest Nt-proBNP quartile group had lower median levels of SDNN, LF/HF and total power (76.1 vs 87.6 ms, p=0.002; 1.9 vs 3.3, p=0.0001 and 1461 vs 2165 ms^2, p<0.0001, respectively), but similar median pNN50 and rMSSD levels. Logistic regression analysis showed that highest quartile of propeptide was independently associated with LF/HF, even after adjustment for clinical covariates that could potentially affect autonomic function (age, sex, BMI, heart rate, hypertension, beta blocker medication, and smoking) (p=0.035).
Conclusions: Our population-based study shows for the first time the importance of the determination of Nt-proBNP levels in predicting decreased HRV after acute MI. Moreover, our results suggest that high Nt-proBNP levels are associated with a decrease in the effects of the sympathetic system.

2684 BNP-guided treatment can predict the medium-term risk in patients with acute heart failure

N. Aspromonte[1], E. Carbonieri[2], V. Ceci[3], A. Chiera[3], P. Giovinazzo[4], L. Milani[4], A.B. Scardovi[3], R. Valle[4]. *[1]Rome, Italy; [2]Department of Cardiology, Heart Failure Unit, San Bonifacio, Italy; [3]S.Spirito Hospital, Cardiology, Rome, Italy; [4]Heart Failure Unit, Department of Cardiology, San Dona'Di Piave (VE), Italy*

Objectives: the aim of the study was to evaluate if plasma levels of B-type natriuretic peptide (BNP) would provide an index to guide in-hospital drug treatment and to predict medium-term prognosis in heart failure (HF) patients (pts) after hospital discharge.
Background: neurohormonal activation characterizes the disease and recently, measurement of plasma brain natriuretic peptide (BNP), indicates the severity of left ventricular dysfunction and relates to outcome.
Methods: we evaluated 200 consecutive pts (age 77±10 (35–96) years, 49% males) hospitalized for HF (DRG 127). Using a cut-off of 250 pg/ml and/or changes in plasma BNP (days 2-3 after admission), 2 groups were identified: the low BNP group (responders) (n= 68, BNP <250 pg/ml and/or > 30% reduction) and the high BNP group (non responders) (n = 132, BNP > 250 pg/ml and < 30% reduction).
Results: during a mean follow-up period of 6 months, there were 8 readmissions and 6 deaths among responders (n=68) compared with 36 readmissions in 25 deaths in the non-responders (p < 0.01). The ability of the BNP value on discharge to discriminate between patients with events and event-free indicates good discriminating power (ROC analysis; AUC value of 0.79 (confidence interval: 0.72 - 0.85). Kaplan-Meier curves of predischarge BNP values showed that the risk of events increases across increasing pre-discharge BNP cut-off values: < 250 pg/ml = 16%, 251 – 499 pg/ml = 44%, >500 pg/ml = 78% (p < 0.001).
Conclusions: after initial treatment HF pts need to be risk stratified by means of the BNP test to guide further management and to identify subjects with poor prognosis. An aggressive therapeutic and follow-up strategy may be justified for pts with high BNP levels and/or no changes after hospital admission for worsening HF.

2685 Serial measurements of NT-proBNP can predict fatal outcome in APE

M. Kostrubiec, A. Kaczynska, A. Bochowicz, M. Szulc, A. Kuch-Wocial, A. Kuczynska, H. Berent, P. Pruszczyk. *Medical University of Warsaw, Department of Internal Medicine and Hypertension, Warsaw, Poland*

Objective: Plasma brain natriuretic peptides were proven to predict outcome in acute pulmonary embolism (APE). Moreover low NT-proBNP or BNP levels characterized patients with benign hospital course. Plasma levels BNP/NTproBNP are elevated in chronic precapillary pulmonary hypertension and further biomarkers increase during follow up is a potent predictor of poor survival. However there are limited data on evolution of BNP/NTproBNP levels in APE. Therefore, we tried to assess the prognostic significance of serial measurements of serum NT-proBNP in APE.
Material and Methods: We evaluated 118 patients (43M, 75F, aged 63±17 years) with APE proven by high probability lung scintigraphy or spiral CT. On admission, 12hrs and 24hrs after admission blood samples were collected for NT-proBNP (Roche, ECLIA).
Results: Ninety one % of pts were anticoagulated, while 9% pts received also thrombolysis. There was 11 APE related deaths during 40-days observation. Two patients died during first 24h after the admission. Serum NT-proBNP concentration was higher in non-survivors than in survivors on admission (n=11, median 2052 pg/ml (range: 16-33340) vs. 15862 pg/ml (951-60958), p=0,001), after 12h (n=10, 1790 pg/ml (15-46336) vs. 13428 pg/ml (885-42758), p=0,001) and after 24h (n=9, 1007 pg/ml (9-33243) vs. 10829 pg/ml (35-70018), p=0,005). Moreover, in the group of survivors NT-proBNP decreased during first 24hrs of the treatment (p<0,0001), while in the non-survivors NT-proBNP remained at the same high level. Interestingly, rapid decrease of NT-proBNP occurred in all trombolysed pts during 24hrs, while in anticoaguleted pts the changes were less pronounced, moreover in 21 pts even increase was noticed (delta%NT-proBNP median –78%(min –90%, max –14%) vs. –39%(min –98%, max 783%), respectively, p=0,03).
Conclusion: . Normal or near normal NT-proBNP values or their rapid decrease within first 24 hrs of the treatment indicate good prognosis, while persistent elevated NT-proBNP during treatment suggests high risk patients.

2686 Nt-pro brain natriuretic peptide and albuminuria, but not high sensitivity C-reactive protein predict cardiovascular death in the general population after adjustment for traditional risk factors

M.H. Olsen[1], T.W. Hansen[2], M.K. Christensen[3], F. Gustafsson[4], K. Wachtell[5], K. Borch-Johnsen[6], T. Joergensen[2], P. Hildebrandt[4]. *[1]Niva, Denmark; [2]Glostrup University Hospital, Research Center for Prevent and Health, Copenhagen, Denmark; [3]Glostrup University Hospital, Clinical Physiol. and Nuclear Medicine, Glostrup, Denmark; [4]Frederiksberg University Hospital, Department of Internal Medicine, Copenhagen, Denmark; [5]Department of Cardiology, Rigshospitalet, University of Copenhagen, Denmark; [6]Gentofte University Hospital, Steno Diabetes Center, Copenhagen, Denmark*

Background: We wanted to investigate whether N-terminal pro brain natriuretic peptide (Nt-proBNP), urine albumin/creatinine ratio (UACR), and high sensitivity C-reactive protein (hsCRP) predicted cardiovascular (CV) death in the general population after correction for traditional CV risk factors.
Methods: In a population based sample of 2656 people, aged 41, 51, 61 or 71 years, we measured in 1993 traditional CV risk factors, left ventricular (LV) mass and ejection fraction by echocardiography, pulse wave velocity, Nt-proBNP (n=2522), UACR (n=2655) and hsCRP (n=2510). CV death was assessed after 9.5 years.
Results: Both in subjects with and without prior stroke or myocardial infarction, log(Nt-proBNP) (HR=1.7*** and HR=2.4***), logUACR (HR=1.7* and HR=2.6***) and log(hsCRP) (HR=1.5* and HR=1.6***) predicted CV death. In Cox regression analyses, baseline log(Nt-proBNP) (hazard ratio (HR)=1.5***), logUACR (HR=1.8***) and log(hsCRP) (HR=1.2*) predicted CV death independently of smoking status (HR=1.7, P=0.06), prior stroke or myocardial infarction (HR=1.8***), age (HR=2.0***) (10 years older) and male gender (HR=3.6***) (?2=446***). However, serum hsCRP did not enter the model when all CV risk factors was included: Log(Nt-proBNP) (HR=1.6***), logUACR (HR=1.5**), heart rate (HR=1.04***), LV relative wall thickness (HR=23**), exercise (HR=0.07**), log(plasma glucose) (HR=4,6, P=0.08), log(serum insulin) (HR=1.8, P=0.06), smoking status (HR=2.1*), prior stroke or myocardial infarction (HR=2.0**), age (HR=2.4***) (10 years older) and male gender (HR=4.4***) (?2=480***). The predictive value of these two models exceeded that of a model based on all traditional CV risk factors, echocardiographic data and pulse wave velocity. *P<0.05, **P<0.01, ***P<0.001.
Conclusion: Nt-proBNP and UACR, but not hsCRP carried independent prognostic information over and above that of traditional CV risk factors indicating that Nt-proBNP and UACR were markers of subclinical CV hypertrophy and microvascular damage, respectively. Whereas the inflammation assessed by hsCRP was reflected in the traditional CV risk factors. All three risk markers predicted CV death even in people with known CV disease, indicating that they perhaps were markers of unstable subclinical CV disease.

2687 Prognostication by serial in-hospital measurements of N-terminal proBrain Natriuretic Peptide in acute coronary syndromes: what and when to measure?

B. Noergaard[1], C.J. Terkelsen[1], K. Thygesen[1], L. Grip[2], L. Heickendorff[3]. *[1]Aarhus University Hospital, Dept. of Medicine & Cardiology, Aarhus C, Denmark; [2]Sahlgrenska University Hospital, Department of Cardiology, Gothenburg, Sweden; [3]Aarhus University Hospital, Clinical Biochemistry, Aarhus, Denmark*

Background: A gradient of risk for adverse clinical events in Acute Coronary Syndrome (ACS) with increasing levels of N-terminal proBrain Natriuretic Peptide (NT-proBNP) has been demonstrated, but the optimum cut-off level and timing of NT-proBNP measurements for prognostication is yet unsettled.
Methods: This study was part of the TRIM (Thrombin Inhibition in Myocardial Infarction) study including 452 patients with ACS (latest episode of chest pain <24 hours from study inclusion). NT-proBNP (Elecsys 2010, Roche Dignostics) was measured on blood samples drawn at admission, 6, 12, 24, 36, 48, 72, and 96 hours. Thirty-five patients died during a median follow-up time of 28 months.
Results: Based on ROC analyses we evaluated the NT-proBNP measurements at the cut-off limits of 600,1000 and 1400 ng/L, and every chosen cut-off levels revealed significant prognostic value independent of sampling time. However, a cut-off of 1000 ng/L showed the highest predictive accuracy regarding death. 39% of the study population developed NT-proBNP values >1000 ng/L during the in-hospital course.
Relative risk (CI) of death for patients with NT-proBNP >1000 ng/L at admission was 4.4(2.2-8.8). All samples (except for the 36-hour result)added significantly to the predictive value of the admission NT-proBNP measurement; however, the 24-hour result conveyed the most additional information (chi2=10.63; P=0.007). More than one late NT-proBNP sample provided no additional prognostic information to the admission result.In multivariate analyses including conventional risk variables, a history of previous AMI (RR= 3.7; CI=1.8-8.1), admission NT-proBNP >1000 ng/L (RR=3.3; CI=1.5-6.8), admission troponin T > 0.06 mg/L (RR=2.3;

CI=1.0-5.3) revealed independent predictive value. The information of the 24-hour NT-proBNP result added significantly to the final multivariate model (chi2=4.84, P=0.03).
Conclusion: A NT-proBNP cut-off limit of 1000 ng/L determined on admission and after 24 hours conveys strong, independent predictive information of long-term outcome in ACS.

OUTCOME OF STABLE ANGINA

2688 Prognosis of angina in 121,020 primary care patients: mortality comparisons with randomised trials and general population

H. Hemingway[1], A. Mc Callum[2], M.J. Shipley[1], K. Manderbackka[2], P. Martikainen[3], I. Keskimaki[2]. *[1]UCL Medical School, Department of Epidemiology and Public Health, London, United Kingdom; [2]Stakes, National R&D Centre, Division of Health and Social Services, Helsinki, Finland; [3]University of Helsinki, Department of Sociology, Helsinki, Finland*

Background: Angina patients selected into recent trials (e.g. ACTION, PEACE) have low mortality, but it is not known how this differs from the large pool of unselected patients in primary care, or the general population.
Objective: To compare the mortality rates among patients with angina in primary care with the mortality of patients in recent angina trials, and the general population.
Design: National registry data with median 4 years follow up to end of 2001.
Participants: 121,020 cases of angina were defined in people aged 40-89 years, who had no previous history of myocardial infarction or coronary disease. We distinguished two angina sub-populations: patients with a nitrate prescription (nitrate) and patients who in addition had an abnormal invasive or non-invasive test result (test).
Setting: Finland.
Main Outcome Measures: Death from all causes (N=21,897) and death from coronary heart disease (N=7,978).
Results: Age standardised occurrence rate of angina per 100 population in women was 1.31 (nitrate) and 0.27 (test), and in men was 1.24 (nitrate) and 0.52 (test). Age adjusted all cause mortality rates per 100 person years in women were 3.65 (nitrate) and 3.55(test), and in men were 6.91 (nitrate) and 5.75 (test). These mortality risks are higher than those found in recent trials (e.g. ACTION (1.64%) and PEACE (1.69%)) and also higher than expected using age, sex and calendar year mortality rates from the total Finnish population (see table).

SMRs in angina patients aged <65 years

	Women		Men	
Standardised mortality ratios	Nitrate	Test	Nitrate	Test
All cause mortality	1.77 (1.6-19)	1.69 (1.4-2.0)	2.07 (2.0-2.2)	1.52 (1.4-1.6)
Coronary mortality	2.86 (2.4-3.4)	5.21 (4.1-6.6)	2.58 (2.4-2.8)	3.13 (2.8-3.5)

Values greater than 1 denote a higher risk than the general population. Figures in parentheses are 95% confidence intervals.

Conclusion: Unselected patients with angina in primary care have a higher mortality than those selected into recent randomised trials, and a higher mortality than the general population. These findings challenge the widely held assumption that the prognosis of angina is benign.

2689 Threefold increased 1-year mortality in the elderly with stable angina and first angiographic diagnosis of coronary artery disease in clinical practice – results of the STAR registry

A.K. Gitt[1], H. Wienbergen[1], R. Schiele[1], T. Heer[1], F. Towae[1], M.G. Gottwik[2], S. Schneider[1], J. Senges[1] on behalf of STAR. *[1]Herzzentrum Ludwigshafen, MI Research Institute, Cardiology, Ludwigshafen, Germany; [2]Klinikum Nuernberg Sued, Cardiology, Nuernberg, Germany*

Background: Patients (Pat) older than 75 years (>75y) have a significantly higher mortality after acute coronary syndromes. Little is known about the outcome of patients >75y with stable angina in clinical practice.
Methods: Between Sept 2001 and March 2003, a total of 2002 consecutive Pat with AP and first angiographic diagnosis of CAD were enrolled in the STAR-Registry (50 centers). We examined differences in the grade of disease, interventional and medical treatment as well as outcome between Pat>75y and Pat<75y.
Results: Pat>75y more often presented with 3-vessel CAD at the time of first angiographic diagnosis. Pat>75y more often were female and had a higher prevalence of diabetes. Pat>75y less often underwent PCI at the time of invasive diagnosis of CAD and less often were treated with statins as compared to Pat<75y. We found no difference in the frequency of CABG between Pat >75y and Pat<75y during the first year after invasive diagnosis of CAD. In clinical practice, Pat>75y with stable AP had a nearly threefold 1-year mortality than Pat<75y.
Conclusion: Pat>75y with stable AP and first angiographic diagnosis of CAD more often were female and more often had concomitant risk factors. They had a nearly threefold 1-year mortality than Pat<75y in clinical practice.

Abstract 2689 – Table 1. The elderly with AP and documented CAD

	Pat > 75y (n=310)	Pat < 75y (n=1692)	p-value
Age (years, median)	78	65	<0.01
Female	50.0%	26.3%	<0.01
Diabetes	30.0%	25.8%	=0.11
Hyperlipoproteinemia	65.8%	68.6%	0.33
Hypertension	81.0%	72.5%	<0.01
3-vessel CAD	36.1%	24.0%	<0.01
PCI at time of diagnosis	36.8%	47.6%	<0.01
CABG during 1-year-follow-up	29.6	26.2%	=0.23
ASA	88.7%	90.2%	=0.40
Betablockers	76.1%	77.4%	=0.61
ACE-Inhibitors	66.1%	58.7%	=0.01
Statins	68.1%	74.6%	=0.01
1-year-mortality	8.1%	3.1%	<0.01

2690 A simple score for non-invasive prediction of coronary artery disease

T. Wolber[1], M. Maeder[2], R. Atefy[2], W. Riesen[3], H. Rickli[2], P. Ammann[2]. *[1]Goetzis, Austria; [2]Kantonsspital St. Gallen, Kardiologie ABt., St.Gallen, Switzerland; [3]Kantonsspital, Institute for Clinical Chemistry, St. Gallen, Switzerland*

Background: Natriuretic peptides have been shown to be elevated in patients with myocardial ischemia. We sought to create a simple scoring system using clinical data, stress-testing and B-type natriuretic peptide (BNP) levels for non-invasive prediction of clinically significant coronary artery disease (CAD).
Patients and methods: Patients with stable angina pectoris and normal systolic left ventricular function were eligible for this prospective study. We excluded patients with atrial fibrillation, valvular heart disease or renal dysfunction. Serum BNP levels were obtained at rest before bicycle stress testing. Coronary angiography was performed the next day. Stenosis of 50 percent lumen diameter or more was considered to be clinically significant. A 4-point score was calculated, using one point for each of the following items: positive stress-test, BNP > 50 ng/l, three or more out of five cardiovascular risk factors (arterial hypertension, dyslipidemia, smoking, diabetes, positive family history).
Results: 71 patients (35% female, mean age 70 ± 16 years) were included in the study. 32 (45%) showed significant coronary stenosis. Calculated sensitivity, specificity, negative (NPV) and positive predictive values (PPV), negative (NLR) and positive (PLR) likelihood ratios of analysed variables are shown in the table. A serum BNP level > 50 ng/l was the best single diagnostic parameter. The negative predictive value of a score of 0 points was 0.93, the positive predictive value of a score of 3 points was 1.0. Receiver operating curve analysis of the score resulted in an area under the curve of 0.88.

Diagnostic Accuracy of the score

	Sensitivity	Specificity	PPV	NPV	NLR	PLR
> 2 Risk factors	0,66	0,74	0,68	0,73	0,46	2,56
Positive Stress Test	0,47	0,87	0,75	0,67	0,61	3,66
BNP > 50 ng/L	0,66	0,97	0,95	0,78	0,35	25,59
Score 1 point	0,94	0,67	0,70	0,93	0,09	2,81
Score 2 points	0,66	0,92	0,88	0,77	0,37	8,53
Score 3 points	0,19	1,00	1,00	0,60	0,82	18,75

Conclusion: The scoring system combining exercise stress test, patient history and resting serum BNP values improves non-invasive prediction of CAD. These findings might have significant impact on daily cardiology practice.

2691 Evaluation of comorbidity scores to predict mortality in patients with coronary artery disease

J. Chirinos[1], J.P. Zambrano[2], A. Veerani[2], G. Perez[2], A. Schob[2], A.J. Mendez[2], S. Chakko[2]. *[1]University of Miami School of Medicine, Medicine, Miami, United States of America; [2]University of Miami School of Medicine, Medicine, Miami, United States of America*

Background: Coronary artery disease (CAD) remains a leading cause of death. There is limited data on mortality risk-stratification in patients with CAD based on the presence of comorbid conditions.
Aim: We aimed to test the ability of 2 comorbidity scores: the modified Charlson index (MCI) and the newly proposed CAD-specific index (CSI) (Sachdev M et al. J Am Coll Cardiol 2004;43:576-582) to predict death in patients with established CAD.
Methods: We prospectively followed 305 males with hemodynamically significant CAD undergoing coronary angiography. We correlated the MCI and the CSI with 5-year all-cause mortality.
Results: In univariate logistic regression, the odds ratio for death increased by 31% per point increase in MCI (95% CI=17-46%; p<0.0001). The odds ratio for death increased by 16% per point increase in the CSI (95%CI=8.5-25%; p<0.0001). In logistic regression models that adjusted for age, gender, left ventricular ejection fraction, and the number of vessels involved with hemodynamically significant CAD, both the MCI and the CSI were the strongest predictors of mortality according to the chi-square value for each term. In these models, the adjusted odds ratio per point increase in MCI was 1.32 (95%CI=1.17-1.48; p<0.0001); the corresponding adjusted odds ratio per point increase in the CSI was 1.17

(95%CI=1.09-1.26; p<0.0001). The model including the MCI had a slightly higher chi-square value (45.1 vs. 39.1) and area under the receiver operator characteristic curve (0.742 vs. 0.727) than the model including the CSI.
In order to appreciate distinct risk categories derived from both scores, patients were classified by each score into 3 groups, such that each group would have approximately the same number of patients in each of the 3 categories. This approach was undertaken separately for MCI and the CSI. Survival probabilities for patients with MCI scores of 0-1, 2-3, and >3 were 85.8, 76.1, 65.6%, respectively (chi-square=13.19; p=0.001). Survival probabilities for CSI of 0-2, 3-5, and >5 were 83.8, 80 and 62.7%, respectively (chi-square=12.8; p= 0.002). The difference between these risk categories was also evident and highly significant when analyzed by the Kaplan-Meier method (log-rank p for both scores <0.0001).
Conclusions: The MCI and the newly proposed CSI are extremely powerful tools to predict all-cause mortality in patients with established CAD. Although the CSI was not superior to the MCI, its simplicity make it valuable in populations with a low prevalence of comorbidities that were not included in this score.

2692 Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease

J.C. Tardif[1], A. Diaz[2], M.G. Bourassa[2], M.C. Guertin[3]. *[1]Montreal Heart Institute, Cardiology Dept., Montreal, Canada; [2]Montreal Heart Institute, Department of Medicine, Montreal, Canada; [3]Coordinating Center, Montreal Heart Institute, Montreal, Canada*

Background: Heart rate reduction is the cornerstone of the treatment of angina. The prognostic value of heart rate in patients with stable coronary artery disease (CAD) is not known.
Methods: We assessed the relationship between resting heart rate (RHR) at baseline and cardiovascular mortality/morbidity while adjusting for risk factors. A total of 24913 patients with suspected or proven CAD from the Coronary Artery Surgery Study (CASS) registry were studied for a median follow-up of 14.7 years.
Results: All-cause and cardiovascular mortality and cardiovascular rehospitalizations were increased with increasing heart rate (P<0.0001). After adjusting for age, sex, hypertension, diabetes, smoking, number of diseased, coronary vessels, ejection fraction, recreational activity, treatment with diuretics, beta-blockers, antiplatelets and lipid-lowering drugs, patients with resting heart rate higher or equal to 83 bpm at baseline had a significantly higher risk for total mortality (hazard ratio (HR) =1.32, CI: 1.19-1.47, P<0.0001) and cardiovascular mortality (HR =1.31, CI: 1.15-1.48, P<0.0001) when compared to the reference group. When comparing patients with heart rates between 77-82 bpm and higher or equal to 83 bpm to patients with a heart rate lower or equal to 62 bpm, the HR for time to first cardiovascular rehospitalization were 1.11 and 1.14 (P<0.001 for both). The association between heart rate and total mortality held true in all analyzed subgroups: men vs women, old (>65 years) vs young, diabetics vs non-diabetics, hypertensives vs normotensives, body mass index >27 or <27, those with EF >50% or EF <50%, and patients treated with beta-blockers or without such a treatment.
Conclusion: Resting heart rate is a simple measurement with prognostic implications. High resting heart rate is predictor for total and cardiovascular mortality independent of other risk factors in patients with CAD.

2693 Asymmetric dimethylarginine as a prospective risk factor for cardiovascular events in patients with coronary artery disease

R. Schnabel[1], E. Lubos[1], K.J. Lackner[2], H.J. Rupprecht[1], C. Bickel[3], L. Tiret[4], T.F. Muenzel[1], S. Blankenberg[1] on behalf of AtheroGene. *[1]Johannes-Gutenberg-Universität, II. Med. Clinic, Mainz, Germany; [2]Johannes Gutenberg-University, Department of Clinical Chemistry, Mainz, Germany; [3]Bundeswehrzentralkrankenhaus, Department of Internal Medicine, Koblenz, Germany; [4]Faculté de Médecine Pitié-Salpêtrière, INSERM U525, Paris, France*

Background: As a competitive inhibitor of endothelial nitric oxide synthase asymmetric dimethylarginine has been related to atherosclerotic disease. Little is known about the prognostic impact of baseline asymmetric dimethylarginine determination.
Methods: In a prospective cohort of 1908 patients with coronary artery disease we assessed baseline serum concentration of asymmetric dimethylarginine in 1874 consecutive patients with coronary artery disease. 114 individuals developed the primary endpoint death from cardiovascular causes or non-fatal myocardial infarction during a mean follow-up of 2.6 ± 1.2 years.
Results: Median concentrations of asymmetric dimethylarginine levels were higher among individuals who subsequently developed the primary endpoint than among those who did not (0.70 versus 0.63 μmol/L; P<0.001). The risk of future cardiovascular event increased with increasing thirds of baseline asymmetric dimethylarginine (P for trend <0.001) such that individuals in the highest third at entry had a hazard ratio 2.47 times higher than those in the lowest third (95 percent confidence interval 1.51 to 4.03; P<0.001). This relationship remained nearly unchanged after adjustment for most potential confounders. Prediction models that simultaneously incorporated asymmetric dimethylarginine, B-type natriuretic peptide, C-reactive protein, and creatinine in addition to traditional risk factors revealed B-type natriuretic peptide (hazard ratio 1.92, 95 percent confidence interval 1.25 to 2.95; P=0.003) and asymmetric dimethylarginine (hazard ratio 1.87, 95 percent confidence interval 1.25 to 2.78; P=0.002) as the strongest risk predictors.
Conclusions: High levels of baseline asymmetric dimethylarginine independently predict future cardiovascular risk. Asymmetric dimethylarginine has prognostic value beyond traditional risk factors and novel biomarkers and might guide therapeutic strategies.

CORONARY INTERVENTION IN FACE OF RENAL DYSFUNCTION

2694 Use of intravenous dose of N-acetylcysteine for the prevention of contrast-induced nephropaty in high risk coronary patients. A randomised controlled trial

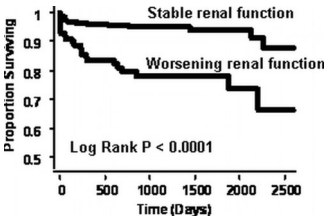
N. Carbonell[1], M.L. Blasco[1], R. Sanjuan Manez[2], J. Sanchis[3], V. Bodi[3], L. Insa[3]. *[1]Hospital Clínic i Universitari, Coronary Care Unit, Valencia, Spain; [2]Hospital Clinic i Universitari, Department of Cardiology, Coronary Care Unit., Valencia, Spain; [3]Hospital Clinic i Universitari, Cardiology, Valencia, Spain*

Current prospective studies evaluating the role of N-acetylcysteine (NAC) in patients undergoing coronary angiography have yielded inconsistent data. Furthermore, there is poor information concerning high risk coronary patients with normal renal function at baseline.
Aim: To determine laboratory and clinical benefit of intravenous (iv) dose of NAC as an adjunct to saline hydration in patients with acute coronary syndrome and baseline normal renal function.
Methods: Prospective, double-blind, placebo-controlled trial of patients with acute coronary syndrome who underwent coronary angiography. Patients were randomly assigned to receive either NAC (600 mg iv twice daily starting at least during the six hours before the administration of contrast dye) or placebo, in addition to 0,45% iv saline at a rate of 1 ml/kg of body weight per hour. Randomization was carried out with computer-generated random numbers. Hospital pharmacists provided the attending nurse with the assigned treatment. The primary end point was development of CIN, defined as an acute increase in the creatinine concentration ≥ 0.5 mg/dl and/or a >25% increase above baseline level at 48 hours after contrast dosing.
Results: Two hundred and sixteen patients were prospectively enrolled in the study (NAC=107 vs placebo=109 patients). There were no significant differences between treatment groups with regard to baseline clinical characteristics, concomitant medications, indications for coronary angiography and baseline serum creatinine. CIN overall incidence was 10% (21patients), 10.5% in the NAC group and 9.5% in the placebo group (p=NS). In addition, there were no significant changes in serum urea nitrogen concentrations 48 h after cardiac catheterization compared to baseline levels. The incidence of in-hospital adverse clinical events was low: no patient with CIN required dialysis, the median Coronary Care Unit stay was 4.5 (2-24) and 4 (2-37) days in the NAC and placebo group, and the mortality rate was 2.8% vs 4.6%, respectively (p=NS). Adjustment for age, body-mass index, diabetes mellitus, systolic blood pressure and volume of contrast dye did not influence these results.
Conclusions: The main finding of the current study is that prophylactic dose of iv NAC provides no additional benefit to one-half isotonic iv saline hydration in high risk coronary patients with normal renal function who undergo coronary angiography.

2695 Prognostic significance of worsening renal function following primary coronary angioplasty

A. Goldberg, M. Kapeliovich, L. Gruberg, S. Petcherski, H. Hammerman, W. Markiewicz, R. Beyar, D. Aronson. *Rambam Medical Center, Cardiology Department, Haifa, Israel*

Background: Recent studies have emphasized the prognostic value of baseline renal dysfunction in acute coronary syndromes. Worsening renal function (WRF) after coronary angioplasty is associated with poor outcome. However, the prognostic significance of WRF following primary angioplasty is unknown.
Methods: We used a prospective database of 370 patients (pts) who underwent primary angioplasty for ST-elevation myocardial infarction. Baseline glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease equation. WRF was defined as >25% increase in creatinine above baseline. The relationship between WRF and long-term mortality was analyzed using multivariate Cox proportional hazards models, adjusting for age, gender, diabetes, Killip class on admission, heart rate and blood pressure on admission, and anterior location of infarction.
Results: WRF occurred in 97 pts (31.6%). During a median follow up of 1040 days, 16 pts (5.9%) with stable renal function and 22 pts (22.7%) with WRF died. Kaplan-Meier survival curves are shown in the Figure. In a Cox multivariate analysis, both baseline renal dysfunction (adjusted RR 1.17 for every 10 ml/min decline in GFR; 95% CI 1.03-1.35; P = 0.02) and WRF (adjusted HR 4.2; 95% CI 2.2-8.1; P < 0.0001) were significant independent predictors of 1- year mortality.
Conclusion: WRF occurring following primary angioplasty is a powerful and inde-



Kaplan-Meier Curves

pendent predictor of long-term mortality. Small elevations of creatinine may serve as a simple marker to identify patients at a very high risk.

2696 Renal toxicity Evaluation and COmparison between Visipaque (Iodixanol) and hExabrix (Ioxaglate) in coronary angiography in Renal insufficiency-RECOVER trial

S.H. Jo, T.-J. Youn, B.-K. Koo, J.-S. Park, H.-J. Kang, B.-H. Oh, M.-M. Lee, Y.-B. Park. *Seoul National University Hospital, Internal Medicine, Cardiovascular Center, Seoul, Korea, Republic of*

Background: The use of iodinated contrast media can result in nephropathy especially in high risk patients. It is uncertain whether iodixanol is less nephrotoxic than ioxaglate in high-risk patients.
Methods: We conducted randomized, prospective, single center study comparing the nephrotoxic effects of an iso-osmolar, dimeric, non ionic, contrast medium (iodixanol), with those of a low-osmolar, ionic, dimeric contrast medium (ioxaglate). This study involved 282 patients with calculated creatinine clearance (by Cockroft-Gault formula) =60mL/min who underwent coronary angiography. Half-saline was given intravenously at a rate of 1ml per kilogram per hour at least for 8hours before and 8hours after administration of contrast agent. The primary end point was a development of contrast-induced nephropathy (CIN). CIN was defined is an increase of 25% or more in serum creatinine within 2 days after coronary angiography.
Results: There were no differences in age, sex, incidence of diabetes mellitus, baseline serum creatinine, creatinine clearance or contrast volume. CIN occurred in 10 of 164 patients (6.1%) in iodixanol group and 18 of 117 patients (15.4%) in ioxaglate group (P=0.013, odd ratio 2.99, 95% confidence interval, 1.262 to 7.127). This difference was more distinct in patients with diabetes mellitus. The occurrence of CIN within the diabetic patients were 5.8% (4/69) in iodixanol group and 21.7% (10/46) in ioxaglate group (p=0.018). And in patients with baseline serum creatinine =1.4, the CIN after coronary angiography occurred significantly higher in ioxaglate group than in iodixanol group, 25% (12/48) and 8.2% (5/61) respectively (p=0.019). In ioxaglate group, 4.3% of patients had an increase of 1.0mg per deciliter or more, but in the iodixanol group, only in 2.4% patients had. By multivariate analysis, the use of iodixanol was the only risk factor for developing CIN (odds ratio 3.1, 95% confidence interval, 1.27 to 7.53)
Conclusion: The incidence of CIN was lower in patients with iodixanol than those with ioxaglate after coronary angiography. This difference was more prominent in higher risk groups.

2697 Creatinine clearance as a long-term predictor of myocardial infarction and death in patients undergoing coronary artery bypass surgery

M. Holzmann[1], S. Ahnve[2], N. Hammar[3], K. Klerdal[4], T. Nordqvist[4], K. Pehrsson[5], T. Ivert[6]. *[1]Stockholm, Sweden; [2]Karolinska Institute, Department of Preventive Medicine, Stockholm, Sweden; [3]Karolinska Institute, Division of Epidemiology, Stockholm, Sweden; [4]Stockholm Centre of Public Health, Department of Epidemiology, Stockholm, Sweden; [5]Karolinska University Hospital, Department of Cardiology, Stockholm, Sweden; [6]Karolinska University Hospital, Department of Thoracic Surgery, Stockholm, Sweden*

Introduction: renal insufficiency is an independent predictor of early death and postoperative complications in patients undergoing coronary artery bypass grafting (CABG). The association of renal insufficiency (RI) with long-term prognosis after CABG is less clear.
Hypothesis: renal insufficiency predicts long-term risk of fatal and non-fatal myocardial infarction (MI) and all-cause mortality in patients undergoing CABG.
Methods: 6575 consecutive patients without dialysis-dependent RI undergoing a first isolated CABG who survived 30 days postoperatively were included. Creatinine clearance (Ccr) was calculated using the Cockroft-Gault formula and related to fatal and non-fatal MI, and all-cause mortality within 5 years.
Results: normal renal function (Ccr = 90 ml/min) was present in 1875 (29%) patients. Mild (Ccr 60-90 ml/min), moderate (Ccr 30-60 ml/min) and severe (Ccr <30 ml/min) RI was present in 3161 (49%), 1333 (21%) and 57 (1%) patients, respectively. There were 628 deaths and 496 fatal and non-fatal myocardial infarctions during follow-up. After adjustment for potential confounding factors in multivariate analyses mild, moderate and severe RI all predicted mortality within 5 years post-CABG; relative risk (RR) 1.2, (95% confidence interval (CI) 1.0-1.6), RR 1.7, (95% CI 1.3-2.3) and RR 5.0, (95% CI 3.0-8.3), respectively, compared to normal renal function. In patients with moderate and severe RI there was an increase in long-term risk of fatal and non-fatal MI; RR 1.5 (95% CI 1.1-2.0) and RR 2.3, (95% CI 1.2-4.5), respectively.
Conclusions: renal insufficiency is an independent predictor of all-cause mortality as well as fatal and non-fatal MI within 5 years post-CABG. This risk factor is very common and present in more than half of this patient population.

2698 Renal insufficiency in patients undergoing percutaneous coronary intervention: results of the SHAKESPEARE Registry

L. Gruberg[1], J.-P. Bassand[2], D. Hasdai[3], A. Cieslinski[4], M.G. Gottwik[5], K. Dawkins[6], A. Cieslinski[7], A.K. Gitt[8] on behalf of The Shakespeare Study Group. *[1]Rambam Medical Center, Heart Institute, Haifa, Israel; [2]Besancon, France; [3]Rabin Medical Center, Department of Cardiology, Petah Tikva, Israel; [4]Posnan, Poland; [5]Nuernberg, Germany; [6]Southampton, United Kingdom; [7]Posnan, Poland; [8]Ludwigshafen, Germany*

Cardiovascular disease is the leading cause of death in patients with chronic kidney disease (CKD). Even mild or moderate CKD is associated with increased morbidity and mortality in these patients while undergoing percutaneous coronary intervention (PCI). We evaluated the impact of CKD in a large, contemporary registry of consecutive patients undergoing elective, urgent or emergent PCI. Since 2/2002, a total of 13,100 consecutive patients undergoing PCI have been enrolled in 30 centers in 7 countries of the European Society of Cardiology to document clinical practice of coronary interventions as well as outcomes as part of the international SHAKESPEARE Registry. We examined the outcomes of CKD patients (serum creatinine >2.0 mg/dL) in this registry and compared them to patients without CKD.
Results: CKD at baseline was present in 371 patients (3%). Compared to patients without CKD, patients with CKD were older and more likely to have hypertension, diabetes, PVD, prior CABG and CVA and reduced LV function with three-vessel disease. Short-term and 12-month outcomes are shown in the Table. By multivariate analysis, CKD was an independent predictor of in-hospital mortality (OR:2.69, CI=1.70-4.27), as were age (OR:1.06, CI=1.04-1.07), heart failure (OR: 5.73, CI=3.86-8.52) and diabetes (OR:1.37, CI=1.00-1.71).

Table 1

	No CKD (n=12,729)	CKD (n=371)	p
Age (years)	64 (54-72)	70 (62-76)	<0.05
Hypertension (%)	63	75	<0.05
Diabetes mellitus (%)	23	41	<0.05
Unstable angina (%)	28	41	<0.05
EF <30% (%)	4.1	12.4	<0.05
Death In Hospital (%)	1.6	6.2	<0.05
Death (30-Days)(%)	0.6	3.2	<0.05
Death (12-Months)(%)	2.4	9.5	<0.05
MACE (%)	4.3	13.0	<0.05

Conclusions: Baseline CKD in patients undergoing PCI was associated with an increased risk in short-term and late mortality after PCI. After correction for differences in baseline characteristics and treatment, CKD was the strongest independent determinant outcome with a nearly threefold increased mortality.

2699 Predictors of contrast nephropathy in patients with ST-segment elevation myocardial infarction treated with primary angioplasty

G.I. Papaioannou[1], H. Athar[2], M.R. Dada[2], S.B. Patel[2], E.N. Deliargyris[3], W.E. Boden[2], F.J. Kiernan[2], R.G. McKay[2]. *[1]Halandri Attikis, Greece; [2]Hartford Hospital, Cardiac Catheterization Laboratory, Hartford, CT, United States of America; [3]Athens Medical Center, Cardiac Catheterization Laboratory, Marousi Attikis, Greece*

Purpose: Contrast nephropathy (CN) is associated with increased in-hospital morbidity and mortality in patients undergoing percutaneous coronary intervention (PCI). Several risk factors for CN after PCI have been suggested. However, there is paucity of data about independent predictors of CN in ST-Segment Elevation Myocardial Infarction (STEMI) patients treated with primary PCI.
Methods: A risk adjustment model for CN in STEMI patients after primary PCI was developed using a single center prospective interventional database. Standard methods were used to determine the relationship between individual variables and CN (post procedural increase of the serum creatinine level by 0.5 mg/dL). Stepwise logistic regression was subsequently performed including all significant univariate varyables to identify independent predictors of CN.
Results: A total of 864 consecutive STEMI patients with symptom onset less than 12 hours (mean age 62.7±14.7; 67.8% males), treated with primary PCI between 1/00 and 11/03 were analyzed. The incidence of CN was 4.3% (38 patients; 27 men/11 women). The study group included 59 patients (6.8%) presented with cardiogenic shock. Treatment included use of intra-coronary stents in 92.5%, and periprocedural use of glycoprotein IIb/IIIa antagonists in 85% of the population. A total of 18 univariate variables with a significant relationship to CN were identified. Multivariate logistic regression analysis identified anemia, blood transfusion during index hospitalization, and age over 65 year as independent predictors of CN (Table 1).

Table 1

Independent Predictors	Odds Ratio	95% CI	P Value
Blood Transfusion	1.49	1.9-10.3	0.001
Baseline Anemia*	1.27	1.6-8.1	0.002
Age >65 years	1.23	1.5-8.1	0.005

*Baseline Anemia = Hematocrit<39% (men), <36% (women).

Conclusions: In STEMI patients undergoing primary PCI, advanced age, anemia at presentation and need for blood transfusion, are independent predictors of contrast nephropathy.

ICD THERAPY; EXPANDING ROLE IN PRIMARY PREVENTION

2700 How many patients are candidates to an ICD on the basis of recent clinical trials? Data from the ALPHA study registry

R. Pedretti[1], P. Ferrero[2], G. Molon[3], T. Bordonali[4], E. Occhetta[5], C. Fantoni[6], F. Accardi[7], J.A. Salerno Uriarte[6]. *[1]IRCCS Fondazione Salvatore Maugeri, Cardiology Department, Tradate, Italy; [2]San G Battista Hospital, University of Torino, Torino, Italy; [3]Sacro Cuore Hospital, Negrar (VR), Italy; [4]Spedali Civili Hospital, University of Brescia, Brescia, Italy; [5]Maggiore Hospital, University of Piemonte Orientale, Novara, Italy; [6]Circolo Hospital and Macchi Foundation, University of Insubria, Varese, Italy; [7]Guidant Italia, Milan, Italy*

Recent primary prevention trials showed that ICD improves survival in post-MI patients with left ventricular dysfunction or Congestive Heart Failure (CHF) of both ischemic and non-ischemic etiology. However, in clinical practice, it is not clear how many patients may be considered candidates for ICD implantation.
Aim of the present analysis is to assess, in the large population of the ALPHA (T-wave Alternans in Patients with Heart fAilure) study registry, how many patients are eligible for an ICD on the basis of MADIT II, SCD-HeFT and COMPANION Trials inclusion criteria.
In the ALPHA study registry 3513 consecutive outpatients affected by CHF were evaluated in the heart failure clinics of 9 centers in Italy: 71% males; age 67±13 years; echo LVEF 34±10%; QRS complex duration ≥ 120 ms 47%; NYHA class I-II-III-IV patients were 9, 56, 29 and 6% respectively; 46% were affected by coronary artery disease and 26% had dilated cardiomyopathy. We estimated that of 3513 patients, 654 (19%) could be considered candidates for ICD implantation on the basis of MADIT II (coronary artery disease, NYHA class I-II-III and LVEF ≤ 30%) and 1736 (51%) on the basis of SCD-HeFT criteria (NYHA class II-III and LVEF ≤ 35%).
Of the registry population, 542 (16%) could be considered candidates for CRT+ICD implantation on the basis of the COMPANION criteria available in the registry (NYHA class III-IV, LVEF ≤ 35%, QRS ≥ 120ms).
In conclusion, in this outpatient population with heart failure a proportion of patients ranging from 16% to 51% may be considered for an ICD. Thus, candidates to ICD represent a large group of CHF patients, expecially on the basis of SCD-HeFT Trial. Effective risk stratification algorithms are needed in order to maximize the ICD benefit and its cost-effectiveness in the primary prevention of sudden cardiac death.

2701 Italian cardioverter-defibrillator registry. Trend of the main clinical data in the years 2001-2002-2003

A. Proclemer[1], M. Ghidina[2], G. Cicuttini[2], D. Gregori[2], P.M. Fioretti[1] on behalf of Associazione Italiana di Aritmologia e Cardiostimolazione A.I.A.C.. *[1]At. Ospedaliera S.M. Misericordia, U.O Cardiologia, Udine, Italy; [2]I.R.C.A.B. Foundation, Udine, Italy*

Purpose: Several trials demonstrated the efficacy of implantable cardioverter-defibrillator (ICD) therapy in particular high risk patients. To evaluate the effects in the clinical practice of these trials, we report the main epidemiological data and the most important clinical characteristics of patients enrolled in the Italian ICD Registry in the years 2001, 2002, and 2003.
Methods: The Italian ICD Registry collects 85% of the data concerning the national ICD implantation activity on the base of the European Implantable Defibrillator form (EURID). Data are validated for quality of information and uniqueness at the moment of data entry and in successive steps at the time of the annual analysis.
Results: The number of ICDs implanted in Italy continued to increase according to the general trend in European countries: 2400 in the year 2001, 3934 in the year 2002, 5318 in the year 2003. The number of ICDs per million of inhabitants was 42.1 in the year 2001 (+11.8% respect to 2000), 69.0 in the year 2002 (+63.9% respect to 2001), 93.3 in the year 2003 (+35.2% respect to 2002).
The number of implanting centres increased from 273 in the year 2001 to 304 in 2002, and 340 in 2003. The median age was 67 years in the year 2001-2002, 68 years in the year 2003. The prevalence of male patients was 79.3% in 2001, 82.3% in 2002, 81.4% in 2003. The main indication in the years 2001, 2002, and 2003, was syncope (25.5%, 29.3%, and 32.9%, respectively), followed by palpitations (17.7%, 18.5%, 16.4%) and cardiac arrest (10.0%, 13.1%, 16.5%). The use of prophylactic ICD increased from 6,4% in 2001 to 18.2% in 2003. Ventricular tachycardia was the main index arrhythmia in 50.4% to 55.0% of cases, ventricular fibrillation in 13.5% to 18.1%, both in 4.1% to 6.5%. The vast majority of patients presented at the enrolment either mildly or severe EF reduction (30 to 50%, less than 30%). Amiodarone was administered in 29.7% to 40.0% of patients. Single chamber ICDs were implanted in 45.7% and 39.2% of patients in the years 2002 and 2003, dual chamber ICDs in 34.9% and 32.4%, biventricular ICDs in 19.4% and 28.4%, respectively.
Conclusions: The ICD implantation rate in Italy increased significantly in the period 2001-2003, similarly to the trend in other western countries and following the publication of controlled studies in the field of sudden cardiac death prevention. The Italian ICD Registry showed in the last three years an important increase of prophylactic and sophisticated ICD utilization, including dual chamber pacing or cardiac resynchronisation therapy.

2702 Electrical storm in patients with implantable cardioverter defibrillators: management with selective vs non selective b-adrenergic blockade

S. Chatzidou[1], G. Vassilopoulos[1], S. Voyatzis[1], A. Skoura[1], S. Rokas[2], S. Rokas[1]. *[1]"Alexandra" General Hospital, Dpt. of Clinical Therapeutics, Athens, Greece; [2]Therapeutics Clinics, Univ. of Athens, Athens, Greece*

Introduction: Electrical Storm (ES) is a frequent event among recipients of implantable cardioverter defibrillators (ICDs). Recently, the efficacy of beta-blockers in the management of this condition has been proved. The purpose of this study is to investigate whether there are any differences in the effectiveness between selective and non-selective beta-blockers in the management of ES
Methods: This study is based on analysis of data from 30 patients with ICD, 16 men and 14 women with a mean age of 60±4 years (range 45 to 70 years). All the patients developed ES 24-48 hours before admission at the hospital. The left ventricular ejection fraction was 28±8% (range 20% to 40%). ES was defined as ventricular tachycardia or fibrillation resulting in device discharge more than two times during 24h. Patients with an acute coronary syndrome, electrolyte disturbances and hemodynamic instability were excluded from the study.
Initially in all patients amiodarone was administered intravenously. At the same time the patients were randomized in two groups: In group I (n=15), in which oral propranolol was administered, at a dose of 40 mg to 160mg/day and in group II (n=15), in which oral metoprolol was administered, at a dose of 50mg to 200mg/day. The dosage of both drugs was titrated according to the hemodynamic tolerance of the patients.
Results: The mean number of arrhythmic episodes constituting ES was 13±3 (range 5 to 24) for group I and 12±3 (range 6 to 23) for group II (p: NS). In twelve patients (80%) of group I and in seven patients of group II (46.67%) ES was terminated during the first 48 hours (p<0,01). In three patients of group II ES was terminated 72-96 hours after admission. The untreated and hemodynamic stable patients (two of group I and one of group II) underwent radiofrequency ablation 5 days later, whereas in one patient of group I and three patients of group II with hemodynamic instability and respiratory failure, mechanical ventilation was necessitated. Finally, one patient of group II died within the first two days after admission.
Conclusions: Non selective beta-blockers are more effective than selective beta-blockers in the management of ES.

2703 Storms of ventricular arrhythmias occurring in ischaemic and non-ischaemic heart failure patients implanted with a biventricular cardioverter-defibrillator for primary or secondary prevention

M. Gasparini[1], M. Lunati[2], L. Padeletti[3], A. Carboni[4], A. Vincenti[5], M. Tritto[6], A. Curnis[7], L. Allaria[8] on behalf of the InSync/InSync ICD Italian Registries Investigators. *[1]Istituto Clinico Humanitas, Cardiologia, Rozzano (MI), Italy; [2]Ospedale Niguarda Ca' Granda, Cardiologia, Milano, Italy; [3]Careggi Hospital, Florence, Italy; [4]Maggiore Hospital, Parma, Italy; [5]Ospedale S. Gerardo, Cardiologia, Monza, Italy; [6]Casa di Cura Mater Domini, Cardiologia, Castellanza, Italy; [7]Spedali Civili, Cardiologia, Brescia, Italy; [8]Medtronic, Sesto San Giovanni, Italy*

Background: Recent trials have shown benefit of implantable cardioverter defibrillators (ICD) for primary or secondary prevention. Aim of the study was to prospectively evaluate incidence of ventricular arrhythmias occurring in ischemic (I) and non-ischemic (NI) heart failure patients implanted with a biventricular cardioverter-defibrillator (CRTD) for primary (PP) or secondary prevention (SP).
Methods and Results: 421 patients (93.2% male, mean age 65±9 years, range 32-92) have been enrolled from 41 Italian cardiological centres, between January 1999 and March 2004, and implanted with a Medtronic CRTD (InSync ICD, InSync Marquis, InSync III Marquis). At baseline mean NYHA class was 2.9±0.6, left ventricular ejection fraction was 26±7%, QRS complex was 168±32 ms (left bundle branch block in 65% of patients). Electrical storms were defined as the occurrence of ≥ 3 separate VT/VF episodes within a 24-hour period, each separated by ≥5 minutes. Results are shown in the table.
Conclusions: In heart failure patients implanted with biventricular ICDs, the incidence of electrical storms was, as expected higher in SP than in PP patients,

Table 1. Results

Patient group	No. of patients	FU (patient years)	Patients with VT/VF	Patients with VT/VF storms	Patients with storms (out of all patients)	Rate of patients with with storms (per 100 patient years)
All	421	671.3	110	35	8.3%	5.2
PP	227	328.8	51	8	3.5% °	2.4 *
SP	194	342.5	59	27	13.9%	7.9
I	292	443.0	63	18	6.1%	4.1
NI	129	228.3	47	17	13.2% °°	7.4 **

° P=0.0001 vs SP; * P=0.002 vs SP; °° P=0.02 vs I; ** P=0.05 vs I

while, quite unexpectedly, the incidence of ventricular arrhythmia storms was higher in NI than in I patients.

2704 Incidence and timing of spontaneous ventricular tachyarrhythmias in patients with coronary disease and an implantable defibrillator for primary prevention of sudden cardiac death

K. Sonne[1], J.C. Geller[2], S. Reek[2], J. Mittag[2], H.U. Klein[2]. [1]*Universital Hospital Magdeburg, Division of Cardiology, Magdeburg, Germany;* [2]*University Hospital Magdeburg, Division of Cardiology, Magdeburg, Germany*

After extending the indication to primary prevention of sudden cardiac death in high risk patients, the number of implanted cardioverter-defibrillator (ICD) systems has been rising exponentionally in recent years. However, there is little information about the incidence and timing of spontaneous ventricular tachyarrhythmias after ICD implantation for primary prevention of sudden cardiac death during long term follow-up.

Methods: We retrospectively analyzed the follow-up data of 97 patients who received a prophylactic ICD at our institutionat between 1996 and 2002 using MADIT (Multicenter Automatic Defibrillator Implantation Trial) I (42 patients) or II (55 patients) criteria.

Results: During a mean (±SD) follow-up time of 40.6±10.4 (range 8.3-101.7) months, 29/97 patients (30%) experienced 180 appropriate ICD shocks for ventricular tachycardia (VT) or ventricular fibrillation (VF). The mean time (range) to the first event was 14.9±10.4 (0.5 - 38) months. Cumulative survival free of hypothetical death, defined as treated VT or VF, was 97% after one year, 90.1% after two years and 80.5% after three years (detailed information in figure 1). There were significantly more ICD discharges for ventricular arrhythmias in MADIT I versus MADIT II patients (7 vs. 22 patients, p= 0.000).

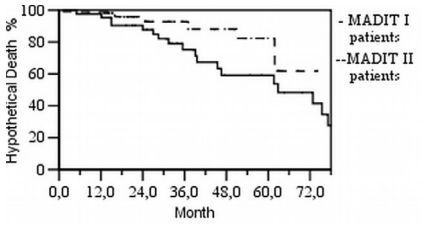


figure 1

Conclusions: Patients with a left ventricular ejection fraction (EF) < 35%, a history of myocardial infarction, non-sustained VT, and inducible VT/VF are at high risk of VT/VF after implantation, whereas patients in whom the only implantation criteria was EF <30% and a history of MI have a significantly lower risk for VT/VF. Therefore, in addition to reduced EF (<30%) and history of MI, further more specific criteria may improve patient selection for prophylactic ICD implantation.

2705 Low rate of prophylactic ICD-Implantation in real life 2 years after MADIT II – the German situation unmasked by the Prevention of Sudden Cardiac Death II Registry

H. Voeller[1], M. Block[2], H. Klein[3], W. Kamke[4], T. Fetsch[5], A. Suciu[6], K. Contzen[6]. [1]*Klinik am See, Cardiology Dpt., Rudersdorf, Germany;* [2]*Klinikum Augustinum, München, Germany;* [3]*Uniklinik Magdeburg, Madgeburg, Germany;* [4]*Spreewaldklinik, Burg, Germany;* [5]*IKKF, München, Germany;* [6]*Guidant Medizintechnik, Giessen, Germany*

Purpose: The MADIT II trial in early 2002 as well as its predecessors (MADIT I, MUSTT) have demonstrated the survival benefit from the implantable cardioverter/defibrillator (ICD) of patients after myocardial infarction (MI) with impaired left ventricular ejection fraction (LVEF) ≤ 30%, ≤ 35% or ≤ 40% respectively. The goals of the PreSCD-II registry are to collect recent data about the incidence of pts with high risk for sudden cardiac death (SCD) after MI, as well as to describe their prognosis in relation to their initial LVEF as the primary risk marker and the chosen therapy options.

Methods: Since Dec. 2002, 9798 consecutive pts after MI (> 10.000 targeted for Feb. 2005) were screened in 22 centers for cardiac rehabilitation in Germany (76% male, 62±12 yrs). 75% of the pts had the last MI 4 to 8 weeks prior to inclusion, in 90% it was their first MI. 90% of the pts had revascularization before inclusion, mainly PCI (75%) and/or CABG (24%). Additional diseases as hypertension, diabetes or renal insufficiency were documented in 73%, 25%, and 5% of the pts respectively. 3% had atrial fibrillation. Medication at discharge from rehabilitation consisted of beta-blockers (95%), ACE-inhibitors (90%), statins and antiplatelet agents in 96% of the pts. Mean LVEF: 56±11%. Pts were classified according to their LVEF at inclusion into group 1 with LVEF was ≤ 30%, group 2 with 30% < LVEF ≤ 40%, and into control group 3 with preserved LVEF > 40%. All pts are followed-up for 3 years (at 4,8,12,24 and 36 months) to document mortality, cause of death, cardiac events and interventions.

Results: 249 pts (2.5%) out of 9798 (=100%) had a LVEF ≤ 30%, 661 pts (6.7%) had 30% < LVEF ≤ 40%. Only 51 pts (20.5%) of group 1 received an ICD either early during the rehabilitation phase (25 pts,10%) or later initiated by their local practitioners (26 pts,10.5%). The reasons for 79.5% of the pts not receiving ICD implant are diverse: reduced life expectancy or physical conditions (38 pts,15%), pts too old (19 pts,7.5%), 13 pts (5%) refused ICD implant, 52 (21%) pts requested consultation with local physician first, in 68 pts (27.5%) either the rehabilitation or the implanting centre denied ICD implantation. No data exist for 8 pts (3.5%).

Conclusions: The incidence of pts after MI with significantly impaired LVEF ≤ 30% (2.5%) is smaller than expected. While the vast majority of these pts were medicated according to guidelines, only 20.5% of eligible pts received ICD therapy in line with randomized studies.

ABLATION IN SUPRAVENTRICULAR AND VENTRICULAR ARRHYTHMIAS

2706 Improved remote control ablation of accessory pathways using second generation 3-magnet vs. first generation 1-magnet mapping catheter

K.J. Chun[1], S. Enst[2], S. Matthew[2], D. Bansch[2], F. Ouyang[2], M. Antz[2], K.-H. Kuck[2]. [1]*AK. St. Georg, Kardiologie, Hamburg, Germany;* [2]*AK St. Georg, Medizinische Klinik II, Kardiologie, Hamburg, Germany*

Introduction: AV reentrytachycardia (AVRT) can be cured using radiofrequency current (RFC) ablation. The magnetic navigation system (MNS) Niobe (Stereotaxis Inc.) in conjunction with a motorunit advancer system (Cardiodrive, Stereotaxis) allows complete remote controlled navigation of a magnetic ablation catheter. First human experience showed feasibility of successful accessory pathway (AP) ablation using the first generation 1-magnet mapping catheter. This study compares the initial ablation results using the first generation 1-magnet catheter (1-M) vs. second generation 3-magnet catheter (3-M; Helios I, II, Stereotaxis Inc; both 4 mm tip).

Methods: In a total of 32 pts (23 male; age: 38 ± 15 years) electrophysiology study established the diagnosis of APs. For mapping and ablation, in the first 19 pts, the 1-M catheter was used, the remaining 13 pts were treated with the 3-M catheter using the MNS. The first left sided AP was only mapped but not ablated due to the study protocol. Right and left sided APs were ablated in a temperature controlled mode (max. 55-60°C, max. 40 W, 60–120 s).

Results: Overall successful remote controlled AP ablation was achieved in 23/31 pts (74.2%), procedural parameters amounted to a median of 5.5 RFC applications (range 1-30), fluoroscopy time of 19 ± 15 min and procedure time of 202 ± 64 min. Introduction of the 3-M catheter after 19 pts resulted in a marked decrease of all procedure parameters and increased succes rate which are summarized in Table 1. No complications or reccurrences were observed.

Table 1. MNS procedure parameters for accessory pathway ablation

	Overall (32 pts)	1 magnet ablation catheter (19 pts)	3 magnet ablation catheter (13 pts)
Procedure Duration [min]	202 ± 64	215 ± 64	183 ± 59
Fluoroscopy [min]	19 ± 15	24 ± 16	12 ± 11
RFC [Median]	5.5	7	3
Success	23/31 (74.2%) 1 pt only map	12/18 (66.7%) 1 pt only map	11/13 (84.6%)

Conclusion: The new magnetic navigation system Niobe allows remote controlled mapping and ablation of APs, if necessary via a transseptal or retrograde approach. The second generation 3-M catheter improved both ablation efficacy and procedural parameters.

2707 A prospective randomised comparison of carto, NavX and conventional X-rays for catheter ablation: the catheter location trial

S. Harris, D. Gupta, M. Alzetani, M. Earley, S. Sporton, A. Nathan, R. Schilling. *St Bartholomew's Hospital, Cardiology Department, London, United Kingdom*

Introduction: The NavX (ESI, St Paul, MN) non-fluoroscopic mapping system has the potential to reduce X-ray exposure during electrophysiological procedures. This is the first prospective randomised controlled study to compare radiation exposure, safety and cost between conventional, electroanatomical (Carto) and high frequency electrical field (NavX) mapping techniques.

Methods: All patients undergoing catheter ablation (except AV node and AF ablation) were randomised to a Carto, NavX or conventional mapping procedures. Im-

mediate procedural success was defined using standard criteria (eg bi-directional block for typical atrial flutter, non inducibilty of AVNRT/AVRT etc). All patients were seen 6 weeks following the procedure and success defined as both freedom from symptoms and no documented recurrence of any arrhythmia other than ectopy. Procedure costs included diagnostic and ablation catheters, Carto reference patch and the complete NavX kit. All costs are the published UK list prices. Statistical comparison was made against conventional procedures.
Results: One hundred and twenty patients (54% men) aged 48±17 (mean±SD) were randomised. 5 patients were withdrawn as no arrhythmia could be induced. There were no significant differences between Carto and NavX in any variable.

	Carto (n=37)	NavX (n=38)	Conventional (n=40)
Acute procedural success (%)	88	93	90
6 week success (%)	85	84	85
Procedure duration (min)	103 (50) p=0.9	106 (37) p=0.85	102 (64)
Fluroscopy time (min)	6.2 (7.0) p=0.001	5.7 (8.5) p= 0.001	18.5 (17.5)
Radiation dose (Gy cm^2)	5.6 (6.8) p=0.03	4.9 (6.1) p=0.03	29.3 (57.9)
Catheters used per case	2.4 (0.7)	3.8 (1.2)	4.4 (1.1)
Cost per case (Euros)	2185	2475	1895

Conclusion: For all catheter ablation procedures, procedure duration and outcome are similar for Carto, Navx and conventional procedures. Both Carto and NavX are associated with reduced fluoroscopy time and radiation dose compared to conventional x-rays but at an increased cost. The costs of NavX are likely to reduce as we become more comfortable using fewer catheters for EP procedures.

2708 Catheter ablation of AV nodal reentrant tachycardia using the remote navigation system Niobe: results of the first 100 patients

S. Ernst[1], K.R.J. Chun[2], B. Schmidt[2], F. Ouyang[2], P. Falk[2], D. Baensch[2], M. Antz[2], K.H. Kuck[2]. *[1]St. Georg Hospital, II. Med. Abteilung/Cardiology Dept., Hamburg, Germany; [2]St. Georg General Hospital, II. Medical Department, Hamburg, Germany*

The magnetic navigation system (MNS) Niobe (Stereotaxis Inc, USA) allows remote-controlled navigation by changing the orientation of a small magnet embedded in the tip of an ablation catheter by two outer permanent magnets (0.08 Tesla). In addition, using a motor unit (Cardiodrive, Stereotaxis) advancing and retracting of the magnetic catheter can be performed from the control room without radiation exposure for the investigator.
Methods: A total of 100 pts (71f, mean age 50 ± 16 yrs) underwent an invasive electrophysiologic study using the MNS. After positioning of conventional diagnostic catheters, the magnetic ablation catheter was advanced in the right atrium manually. The remaining procedure was then performed from within the control room. In case of failure to reach the target site or inability to achieve permanent ablation effect, switch to a conventional ablation catheter was possible.
Results: Using conventional electrophysiologic criteria, all 100 pts were successfully ablated using the MNS. Mean procedural parameters and ranges are summarized in the table (RFC, radiofrequency application). In one pt, a pneumothorax had to be treated after

	all pts	initial 20 pts	last 20 pts	
RFC	7.3 ± 5.5	8.8± 7.7	6.1 ± 3.9	n.s.
Duration (min)	142 ± 62	188 ± 77*	103 ± 32*	*p< 0.005
Fluoroscopy (min)	8.8 ± 8.9	13.6 ± 12.5*	3.6 ± 2.3*	*p< 0.005

Conclusions: Remote catheter ablation of AV nodal reentrant tachyarrhythmia using the new magnetic navigation system Niobe is feasible and safe. A significant learning curve was observed, which finally led to a decrease of procedural parameters with special emphasis on radiation exposure for both patients and investigators.

2709 Fluoro-free ablation for right sided atrio-ventricular reentrant tachycardias

D. Cavaco, P. Adragao, K. Reis-Santos, J.F. Santos, A. Pinheiro-Vieira, F. Morgado, R. Bernardo, R. Seabra-Gomes. *Hospital de Santa Cruz, Department of Cardiology, Carnaxide, Portugal*

Background: Novel mapping tools allow for tachycardia ablation with less exposure to X-Ray.
The aim of the present study was to analyze the effectiveness and safety of totally non-X-Ray catheter ablation, guided by NAVX® system, in the treatment of right sided atrio-ventricular (AV) reentrant tachycardias.
Methods: Twenty consecutive patients, mean age 37 years old (14 to 61), presenting with supraventricular tachycardia, suggestive of AV nodal reentrant tachycardia (AVNRT) or AV reentrant tachycardia involving a right sided pathway, underwent electrophysiological study guided by the NAVX® system, without the use of X-ray. In all, catheters were placed in the coronary sinus, His bundle and RV apex, guided by the NAVX® mapping system, without X ray. After confirmation of the diagnosis an ablation RF catheter (conventional, 4 mm tip) was used for mapping and ablation. Two patients were excluded because the EPS revealed tachycardia involving a left sided concealed pathway.
Results: In 15 patients the EPS showed AVNRT to be present, and in 3 patients manifest AV pathways were involved (1 anterior, and 2 postero-septal). Ablation was successfully performed in all of the 18 patients, without X-Ray,with a mean of 4±2 applications. No complications occurred. There were no recurrences at 6 months follow-up.
Conclusions: Ablation of right sided AV reentrant tachycardias guided by NAVX® system, without fluoroscopy seems to be a safe and effective technique, with success rates comparable to the conventional fluoroscopy based approach

2710 Identification of successful RF catheter ablation sites in patients with ventricular tachycardia based on electrogram characteristics during sinus rhythm

K. Zeppenfeld, P. Kies, M.C.E.F. Wijffels, M. Bootsma, L. van Erven, M.J. Schalij. *Leiden University Medical Center, Cardiology, Leiden, Netherlands*

Background: zones of slow conduction facilitate reentry, the major mechanism of ventricular tachycardia (VT) after myocardial infarction (MI). Identification of these zones during sinus rhythm (SR) is desirable for Radiofrequency Catheter Ablation (RFCA) of hemodynamically untolerated VT. Local conduction velocity appears to correlate with electrogram duration. The purposes of this study were to define normal electrogram characteristics and to evaluate the significance of low amplitude-long duration electrograms recorded during SR to identify successful RFCA sites.
Methods: electroanatomic mapping was performed during SR in 10 control patients with a normal left ventricle (LV) and in 10 patients with stable VT after MI. From the controls we derived reference values for electrogram amplitude, duration and fragmentation. In patients after MI areas with signals exceeding these values were related to successful ablation sites.
Results: 95% of normal LV electrograms were =1.0mV and =28ms (range 5-39ms) and all had =4 deflections. Based on these results cut-off values for low amplitude, fragmentation and long duration were set at 1mV, 4 deflections and 40ms respectively. In infarcted hearts 653 electrograms (44%) were <1.0mV, of these 303 were =40ms with >4 deflections and restricted to circumscribed areas. Twenty-seven of 28 VT remained non-inducible after RFCA within these areas resulting in a 96% sensitivity and 82% specificity for low amplitude-long-duration electrograms predicting successful ablation sites
Conclusion: identification of successful RF target sites during SR in patients with VT is feasible with a high sensitivity and specificity using a mapping strategy based on voltage and duration criteria.

2711 Clinical effectiveness of radiofrequency catheter ablation of ventricular arrhythmias with the origine in the left ventricular outflow tract (LVOT) in paediatric patients

M. Shkolnikova[1], S. Termosesov[2], R. Garipov[2], I. Ilich[2], V. Beresnitskaya[2]. *[1]Moscow Institute for Paediatry&Surgery, Arrhythmia Department, Moscow, Russian Federation; [2]Russian Center for Children Arrhythmia, Moscow, Russian Federation*

Radiofrequency catheter ablation (RFCA) now is one of the main methods for treatment of the drug resistant arrhythmias. The aim of this study is to evaluate the effectiveness and safety of RFCA of ventricular arrhythmias (VA) in children and adolescents without structural heart diseases with the origine in LVOT.
Patients and methods: 13 patients (5 boys and 8 girls) aged 13 to 17 (mean age 15,3) years old with symptomatic VA were studied with ECG, echocardiography, 24 hour monitoring and surface ECG mapping before and after the procedure. The follow-up period was from 3 to 12 months. RFCA of the arrhythmogenic focus in LVOT was performed in all this patients. Transaortic access was used for mapping and ablation in LVOT. Activation and pace mapping methods were used. The catheter position during the RF energy applications near the ostium of the coronary arteries (>1.2 cm) was precisely controlled by continuous fluoroscopy and coronarography.
Results: the earliest ventricular activation was found in LVOT: 2 pts (15,4%) – in the right Valsalve sinus (RVS); 10 pts (84,6%) in the left Valsalve sinus (LVS). Ectopic beat ventricular actvation was 43-89 ms earlier than ECG activation. The RFCA through the aortic valve cusp was performed with the effective temperature in the range of 50 to 55°C. Usually the elimination of ectopic activity was achieved on the first seconds of heating. The mean application and fluoroscopy time were 1.55 min and 20.1 min in the LSV patients and 7.3 and 74.3 min in the RSV patients. The common success was achieved in 100% of pts. In one child with RSV origine of arrhythmia only intermittent effect was observed (there were no ectopic activity registered in this patient in 6 month period – postpone effect). There were no arrhytmia reccurences and complications in this group of patients in 12 months of follow-up period.
Conclusion: RFCA in Valsalve sinuses in pediatric patients with VA arrhytmias without structural heart deseases is effective and safety procedure.

PREHOSPITAL DIAGNOSIS AND MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION

2712 Prehospital diagnosis and start of treatment reduces time delay and mortality in real life patients with STEMI

E. Björklund[1], U. Stenestrand[2], J. Lindback[3], L. Svensson[4], L. Wallentin[5], B. Lindahl[5] on behalf of RIKS-HIA Investigators. [1]*Dept of Cardiology, Uppsala University Hospital, Uppsala, Sweden;* [2]*Dept of Cardiology, University Hospital Linkoping, Linkoping, Sweden;* [3]*Uppsala Clinical Research Center, Uppsala University Hospital, Uppsala, Sweden;* [4]*Division of Cardiology, South Hospital, Stockholm, Sweden;* [5]*Dept of Cardiology, Uppsala University Hospital, Uppsala, Sweden*

Time to reperfusion remains a key modifiable determinant in ST-elevation myocardial infarction (STEMI). A prehospital versus hospital thrombolytic treatment strategy has been shown to reduce time to treatment and mortality in randomised trials. We therefore evaluated time from onset of symptom to thrombolysis and mortality in a large cohort of unselected STEMI patients according to prehospital or hospital thrombolysis.

Methods: Time to thrombolysis and outcome were studied in a prospective cohort of patients admitted to the coronary care units of 74 Swedish hospitals in 2000-2003. Only patients younger than age 80 years with a diagnos of acute myocardial infarction (AMI) and with thrombolytic treatment were included. All patients (n=13360) were used when evaluating symptom duration, whereas only patients with the first recorded AMI were used when evaluating 30-day (n=11263) and one-year mortality (in 2000-2002) (n=9088). Mortality data were obtained from the Swedish National Cause of death register. Time to thrombolysis (minutes) are expressed as median (with 25th-75th percentile).

Results: The prehospital treatment population was significantly younger and contained less women, diabetes mellitus, previous MI, stroke and heart failure and used less medication indicative of heart failure and ischemic heart disease. In multivariable analyses, after adjusting for a number of risk factors including the above and rescue angioplasty, a prehospital treatment strategy was associated with significantly lower one-year mortality (OR 0.71; 95% CI, 0.56-0.9).

Table 1

	n/n	Prehospital	Hospital	p-value
Time to thrombolysis	1651/9150	114 (70-200)	170 (107-295)	p<0.001
30-day mortality (%)	1749/9514	5.3%	7.6%	p=0.001
1-year mortality (%)	1251/7837	7%	11%	p<0.001

Conclusion: Prehospital diagnosis reduces time to thrombolysis by almost one hour and reduces adjusted long-term mortality in real life patients. This approach is therefore recommended as one treatment alternative in acute STEMI.

2713 Pre-hospital detection of acute myocardial infarction with ultrarapid H-FABP imunoassay

P. Ecollan[1], J.-P. Collet[2], M.L. Tanguy[3], G. Boon[1], R. Haas[1], M.F. Fievet[1], N. Bertho[1], G. Montalescot[2]. [1]*Pitié-Salpêtrière Hospital, SAMU, Paris 75013, France;* [2]*Hopital Pitie salpetriere, Institut du Coeur, Bureau 2-236, Paris Cedex 13, France;* [3]*Pitié-Salpétrière, Department of Biostatistics, Paris, France*

Aim: To assess if early detection of AMI can be improved in outpatients presenting with chest pain by immediate use of a portable whole blood immunoassay measuring soluble human fatty acid binding protein (H-FABP).

Study design: Prospective single centre study.

Methods: We enrolled 108 consecutive outpatients with acute ischemic type chest pain in whom the first medical care was delivered by a mobile intensive care unit (MICU). Pre-hospital and in hospital blood samples were drawn the first 12 hours to measure cTnI, myoglobin, CK-MB. Acute myocardial infarction (AMI) was defined by a positive cTnI on any samples over the first 12 hours. In all patients, cTnI, H-FABP, myoglobin, CK-MB were performed in the MICU. The predictive value of elevated biomarkers for evolving AMI was determined by univariate and multivariable analyses.

Results: Pre-hospital cTnI sample was normal in 85 patients (78.7%) of whom 32 (29.6%) had subsequent cTnI elevation over the next 12 hours. In patients with normal admission cTnI, ST elevation>1mm was strongly linked to evolving AMI (OR 9.4, 95%CI 3.3-26.5, p<0.0001). Of the pre-hospital biomarkers measurements, a positive H-FABP (OR=72.2, 95%CI 16.7- 312.5, p<0.0001) was strongly associated with MI as compared to myoglobin (OR 2.7, 95%CI 1.0-7.1, p=0.04) or CK-MB (OR=2.1, 95%CI 0.4-9.9, p=0.37). In multivariable analysis, pre-hospital H-FABP and ST elevation remained the only two independent predictive factors of AMI. Pre-hospital H-FABP in addition to ECG improved early sensitivity for AMI from 62,5% [95%CI 43.7%-78.9%] to 93,8% [95%CI 79.2%-99,2%] (p=0,002), and improved negative predictive value from 78,9% to 95,5% (p<0.0001).Among those with normal pre-hospital cTnI and no ST elevation (n=57), assessment based only on elevated H-FABP had 83,3% sensitivity [95%CI 51.6%-97.9%], 93,3% specificity [95%CI 81.7%-98.6%] and 95,5% negative predictive value [95%CI 84.5%-99,4%] for evolving AMI. In hospital clinical events (death or MI) were significantly higher in patients with an elevated hFABP as compared to those with a negative test (86% versus 12,7%, p<0.0001).

Conclusion: Early assessment of H-FABP in patients presenting with chest pain improves greatly the diagnosis of ongoing MI, the predictive value of which is independent of 12-lead ECG changes.

2714 Impact of pre-hospital care in patients with acute myocardial infarction (AMI) in a French general hospital

A.E. Dubart[1], O. Equine[2], D.-P. Luttenbacher[2], C. Deligne[3], S. Pouwels[2], W. El-Achkar[3], M. Wibaux[2], C. Mycinski[2]. [1]*CH Bethune, Emergency and prehospital care unit, Bethune, France;* [2]*CH Bethune, Cardiologic intensive care unit, Bethune, France;* [3]*CH Bethune, Emergency and prehospital care unit, Bethune, France*

Background: It is now admitted that applying the best strategy for prompt delivery of high quality coronary care improves outcome in patients with AMI. Regarding to the recommendations, some studies have shown some differences in the real clinical setting. This strategy must be adapted to local organization. The French emergency medical system with mobile intensive care unit (MICU), physician staffed, permit prompt reperfusion strategy with prehospital thrombolysis (PHT). The aim of our study was to compare prospectively the real impact and efficacy of a pre-hospital fibrinolytic therapy (FT) initiated by MICU, with therapy first started in-hospital.

Methods: A single centre registry of patients with AMI was started in 2000. All consecutive patients with AMI occurring within 24 hours between 01/01/2000 and 31/12/2004 were studied. The collected datas were: age, sex, delays from onset of symptoms (OS) to first medical care (FMC) and to fibrinolytic therapy, topography of AMI, type of management and in-hospital mortality.

Results: 857 patients, mean age 68 ± 10 years, range 26 to 96 years, men 66%, were collected. 584 patients (68%) had STEMI, 276(47%) had reperfusion strategy with 139(50%) PHT, 106(38%) in-hospital thrombolysis (IHT) and 31(12%) primary angioplasty (PA). Prehospital managed patients were slightly younger (60±8 y vs 64±10 y). Pre-hospital vs In-hospital managed patients had a significant reduction in mean delay times from OS to FMC: 99 vs 178 min respectively (p<0,01), and from FMC to FT, 25 vs 50 min respectively (p<0,01). In-hospital mortality was significantly lower with PHT (5,8% vs 10,4%, p<0,01). In patients with STEMI managed within 6 hours, 61% had reperfusion strategy and in-hospital mortality was greatly reduced with PHT (5,9% vs 8,7%). No death occurred in patients managed within 3 hours from OS with PHT.

Conclusions: Our registry confirms the efficacy of pre-hospital thrombolysis initiated by MICU, and demonstrates her superiority over therapy first started in-hospital.

2715 Pre-hospital thrombolysis of unselected STEMI patients in Helsinki from 1997 to 2003 – time delays an all-cause mortality

H. Luurila[1], J. Puolakka[2], P. Holmstroem[2], J. Boyd[2], M. Kuisma[2]. [1]*Helsinki University Central Hospital, Department of Clinical Pharmacology, Helsinki, Finland;* [2]*Helsinki University Central Hospital, Helsinki Emergency Medical Services, Helsinki, Finland*

Purpose: We report time delays and all cause mortality and compare the results in different age groups (<75 years and ≥75 years) and in different pain to needle time windows (<1 h, <2 h, 2-4 h and >4 h) after pre-hospital thrombolytic therapy for STEMI.

Methods: We studied all STEMI patients treated with pre-hospital thrombolysis in Helsinki from 1997 to 2003. Patients presenting with shock or pulmonary oedema and those who died before reaching the hospital were also included. The decision to initiate thrombolysis was made by an emergency physician either on the scene or after 12-lead ECG transmission. Pre-hospital data was prospectively collected into the Helsinki Pre-hospital STEMI Thrombolysis Register. The study plan was approved by the Institutional Review Board.

Results: A total of 632 patients (417/217, male/female) were included. The mean age was 65 years (61/72, male/female). There were 161 (25%) patients ≥75 years old (59/102, male/female). The median call delay was 50 minutes (24-120 min, 25%-75% percentiles). The median pain to needle time was 101 minutes (70-168 min, 25-75% percentiles) in all 632 patients and did not differ in different age groups (97 min in <75 and 105 min in ≥75 years old patients, p= 0.066). 59% of the patients received thrombolysis within 120 min of the onset of the symptoms, 40% within 90 min and 15% within 60 min respectively. Pre-hospital all-cause mortality was 2.1% (13/632) and 30 d all-cause mortality was 11.2% (71/632). The 30 d all-cause mortality was higher in ≥75 years old patients (41/161, 25%) compared to <75 year old patients (30/471, 6.3%) (p<0.001). The all-cause mortality was time delay dependent; 30 d all-cause mortality with 1 h delay was 7% (7/97), 2 h 9% (33/372), 2-4 h 14.6% (22/151), and over 4 h 12.8% (11/86).

Conclusions: The unselected study data was collected in an organised prehospital system treating high-risk medical emergencies. The all-cause mortality after fibrinolytic treatment in STEMI was dependent on pain to needle time delay and increased when the delay exceeded 2 hours. Thrombolysis was provided within 2 hours of pain onset to the majority of the patients. The all-cause mortality in over 75 years old patients was significantly higher.

2716 ST-segment recovery in patients with ST-elevation myocardial infarction reperfused by pre-hospital fibrinolysis, prehospital initiated facilitated PCI or primary PCI

H. Thiele[1], M. Scholz[2], P. Sick[2], E. Boudriot[2], J. Niebauer[2], G. Schuler[2]. *[1]Leipzig, Germany; [2]University of Leipzig - Heart Center, Internal Medicine/Cardiology, Leipzig, Germany*

Background: The ST-segment recovery at 90 min is an indirect parameter for the assessment of myocardial tissue perfusion. Complete ST-segment recovery is associated with a favourable prognosis for patients with STEMI. The optimal reperfusion strategy in patients with STEMI is still matter of debate in particular in patients presenting early after symptom onset. The ST-segment recovery for patients treated by either prehospital fibrinolysis or prehospital initiated facilitated PCI in comparison to primary PCI has not been assessed.
Methods: In the Leipzig prehospital fibrinolysis study patients with a STEMI (symptoms $<$ 6 h) were randomized to either prehospital fibrinolysis (n=82; group A) or facilitated PCI after prehospital fibrinolysis (n=82, group B). Furthermore, a control group of patients with primary PCI (n=136, group C) was prospectively assessed. ST-segment resolution at 90 min was analyzed by blinded observers as percentage resolution of the initial ECG. Categorization was performed as complete ($>$70%), incomplete (70% to 30%), or no resolution ($<$30%).
Results: The times between the initial ECG and the follow-up ECG were similar between the treatment groups (A: 126$\pm$42 min, B: 124$\pm$90 min; C: 129$\pm$46 min, p=n.s.). The ST-segment resolution at 90 min as a continuous parameter was 82.8$\pm$23.5% for group B vs. 59.1$\pm$45.3% in group A ($p<0.001$) and 62.6$\pm$34.0% in group C (p=n.s. vs. A, $p<0.001$ vs. B). The percentage of patients with complete resolution was highest in group B with 80% vs. 52% group A and 47% group C ($p<0.001$). The improved ST segment recovery was also reflected by a trend towards an improved outcome in the occurrence of the combined clinical endpoint of death, re-myocardial infarction, stroke and major bleeding for patients in group B (8% vs. 14% group C and 21% group A, p=0.16).
Conclusions: Prehospital initiated facilitated PCI results in the highest percentage of complete ST-segment recovery in comparison to prehospital fibrinolysis or primary PCI. It might therefore be the preferred reperfusion strategy for patients with STEMI.

2717 High mortality in patients with ST elevation myocardial infarction and pre-hospital resuscitation despite a high rate of early reperfusion therapy. Results of the PREMIR registry

U. Zeymer[1], L. Nibbe[2], R. Arntz[3], B. Dirks[4], K. Ellinger[5], H. Genzwuerker[6], J. Senges[7]. *[1]Klinikum Ludwigshafen, Medizinische Klinik B, Ludwigshafen, Germany; [2]Charite - Campus Rudolf Virchow Klinik, Berlin, Germany; [3]Universitätsklinikum Benjamin Franklin, Berlin, Germany; [4]Universitätsklinikum Ulm, Ulm, Germany; [5]Klinikum Ravensburg, Ravensburg, Germany; [6]Universitätsklinikum Mannheim, Mannheim, Germany; [7]Klinikum Ludwigshafen, Medizinische Klinik B, Ludwigshafen, Germany*

Background: Recent studies and registries suggest a low mortality in patients with ST elevation myocardial infarction treated with early reperfusion therapy. Little is known about the outcome of patients with STEMI and pre-hospital cardiopulmonary resuscitation (CPR).
Methods: In a nationwide prospective registry (PREMIR: PREhospital acute Myocardial Infarction Registry) data of consecutive patients with STEMI already diagnosed pre-hospital in the ambulance by emergency physicans by 12-lead ECG were collected. A total of 64 ambulance systems in Germany were in involved in PREMIR. Pre- as well as in-hospital treatments and events were recorded.
Results: So far 2242 patients with STEMI were included, of whom 280 had pre-hospital CPR. Of the latter the mean age was 64 years, 73% were men, 24% had a previos myocardial infarction, 28% were diabetics and 35% were smokers. In the pre-hospital ECG 46% had an anterior, 48% an inferior infarct and 6% left bundle branch block. Over 90% of the patients were given aspirin and heparin. 165 (60%) patients were treated with pre-hospital thrombolysis. 58 (21%) died before hospital arrival. Addional in-hospital reperfusion therapy with thrombolysis (n=23) and/or percutaneous coronary intervention (n=116) was performed, leaving only 35 (12.7%) patients without any early reperfusion therapy. The in-hospital mortality of admitted patients was 35.6%. Therefore 130 of 280 patients (46.5%) of patients with STEMI and pre-hospital CPR died.
Conclusion: Patients with STEMI already diagnosed in the ambulance by emergency physicans and pre-hospital CPR have a high mortality of nearly 50% despite an about 90% rate of early reperfusion therapy. Therefore the optimal therapy of these patients deserves further research.

OUTCOME IN NON ST-ELEVATION ACUTE CORONARY SYNDROME

2718 Prospective comparison of the five risk scores in the unselected acute coronary syndromes patients treated according to the contemporary guidelines: one-year follow-up

K.J. Filipiak[1], M. Grabowski[2], G. Karpinski[2], R. Glowczynska[2], A. Rdzanek[2], Z. Huczek[2], L. Malek[2], G. Opolski[2]. *[1]Warsaw, Poland; [2]University Hospital, Cardiology Dept., Warszawa, Poland*

Background: To date there have been conducted no detailed studies comparing recommended or widely-accepted risk scores (RS) for acute coronary syndromes (ACS) risk stratification, especially in long-term observations of unselected patient cohorts. Many different RSs have been proposed for the long-term risk estimation in ST-elevation myocardial infarction (STEMI), as well as in non-STEMI and unstable angina (NSTEMI/UA) patients (pts). Aim of this study was to prospectively compare five RSs (TIMI RS for STEMI, TIMI RS for NSTEMI/UA, SIMPLE RS, ZWOLLE RS, GRACE RS) in 931 ACS pts treated in referral, university hospital with 24-hour invasive cardiology on-site.
Methods: One-centre ACS registry prospective study (601 STEMI and 330 NSTEMI/UA pts) from 2002-2003 years with one-year follow-up. The predictive value of each RS was assessed with the evaluation of area under ROC curves. The models' goodness-of-fit was checked by Pearson or Hosmer-Lemeshow tests. Evaluated RS were applied according to the pre-defined population, respectively to: all ACS pts (SIMPLE RS, GRACE RS), STEMI pts (TIMI RS STEMI), NSTEMI/UA pts (TIMI RS NSTEMI/UA) or STEMI pts treated invasively (ZWOLLE RS). All RSs were tested for prediction of the total mortality of their pre-defined population at one-year.
Results: Mean age in 931 pts was 63 years, 27% with previous myocardial infarction, 16% diabetes, 6% NYHA III/IV class, 3% in cardiogenic shock. 88% STEMI and 81% NSTEMI/UA pts were treated invasively. In-hospital and discharge pharmacotherapy was prescribed according to the contemporary guidelines. 1-year total mortality was 14.8% and 10.9% for STEMI and NSTEMI/UA pts respectively. All evaluated RSs displayed high adequacy and reliability estimated with ROC curves, though, the TIMI RS STEMI (ROC=0.84) and GRACE RS (0.84) proved superior. Other ROC curves values were: 0.80, 0.79 and 0.63, respectively for: SIMPLE, ZWOLLE, TIMI NSTEMI/UA RSs.
Conclusions: All evaluated RSs could be used in the unselected ACS pts treated according to the contemporary guidelines to predict one-year total mortality. TIMI RS STEMI and GRACE RS proved superior.

2719 Simplifying risk stratification in non-ST-segment elevation acute coronary syndromes

P. Tricoci[1], K. Pieper[1], L.K. Newby[1], R.P. Giugliano[2], F. Van de Werf[3], P.W. Armstrong[4], R.A. Harrington[1], R.M. Califf[1]. *[1]Duke University Medical Center, Duke Clinical Research Institute, Durham, United States of America; [2]Brigham & Women's Hospital, TIMI Study Group, Boston, United States of America; [3]University Hospital Gasthuisberg, Department of Cardiology, Leuven, Belgium; [4]University of Alberta, Edmonton, Canada*

Baseline risk is strongly associated with benefit from antithrombotic drugs and an early invasive strategy in non-ST-segment elevation acute coronary syndromes (NSTE ACS). Although several risk scores exist, a simpler risk stratification method may be particularly useful and more widely adopted in clinical practice.
Aim: To explore the relationship between the presence of any of 2 of age $\geq$60 years, positive cardiac markers (CM+) and ST-segment depression $\geq$1 mm (STD) with the 30-day rate of death or myocardial infarction (D/MI).
Methods: We explored relationships between the presence, alone or in combinations, of these 3 well-understood predictors of 30-day D/MI in 17,597 patients in the combined datasets from 4 previously-completed randomized trials of NSTE ACS: PURSUIT, PARAGON A and B, and GUSTO IIb. We then tested our criteria in a subset of this population enrolled in countries using an invasive strategy in $\geq$50% of patients (n=9974). Finally, we compared the 30-day D/MI rate based on these simplified criteria with that based on a TIMI risk score $\geq$4 in a different cohort composed of the pooled data from TIMI 11b and TACTICS-TIMI 18 trials(n=5941).
Results: In the overall 4-trials population, patients with any 2 of the 3 risk features (n=9821) had a 16.4% 30-day D/MI rate vs. 9.2% if $<$2 (n=7776). A similarly high-risk population (n=5450) was identified using the presence of 2 of 3 risk factors after enriching for the use of an invasive management strategy (16.3% 30-day D/MI). In the TIMI 11b/TACTICS-TIMI 18 population patients with at least 2 of 3 risk factors (n=2549) had a 10.9% 30-day D/MI rate, almost 2-fold higher compared with isolated STD (5.8%) or CM+ (4.5%) and similar to the rate of D/MI (10.4%) among 2648 patients with TIMI risk score $\geq$4.
Conclusions: A simple approach based on the presence of at least 2 of age $\geq$60 years, CM+ and STD identifies a large NSTE ACS population at particularly high risk of 30-day D/MI. This simplified approach may be easily adopted early and at the bedside in clinical practice and used as a high-risk benchmark in designing NSTE ACS clinical trials.

2720 The simple risk score for predicting the outcome of patient with acute coronary syndrome without ST-segment elevation treated either with invasive or conservative strategy

M. Gierlotka[1], M. Gasior[2], L. Polonski[1], G. Opolski[3], Z. Kalarus[4]. *[1]Silesian Centre for Heart Disease, III Card. Dep. Silesian School of Med., Zabrze, Poland; [2]Silesian Center for Health Disease, III Cardiology Dept. Silesian School of Med., Zabrze, Poland; [3]Warsaw Medical University, Department of Cardiology, Warsaw, Poland; [4]Silesian Centre for Heart Disease, I Card. Dep. Silesian School of Med., Zabrze, Poland*

Patients (pts) with acute coronary syndromes (ACS) without ST-segment elevation (unstable angina [UA]/non-ST-segment elevation myocardial infarction [NSTEMI]) present with a wide spectrum of risk for death and they are treated either with conservative or invasive strategy. The aim of this analysis was (1) to develop the risk score, and (2) to assess the relationship between the developed risk score and 30-day mortality of UA/NSTEMI pts treated either with invasive or conservative strategy.
Methods: We used 12-month data from a prospective, population-based registry of ACS conducted in Silesia region of Poland. From 14581 pts, 9515 (65.3%) were hospitalized due to UA/NSTEMI (6425-UA; 3090-NSTEMI). The development of the risk score was based on multivariate logistic regression model including variables available at pts presentation.
Results: Of 9515 pts with UA/NSTEMI (30-day mortality 4.7%), 37.4% had early coronary angiography performed with lower 30-day mortality than conventionally treated pts (2.0% vs. 6.3%, $p<0.0001$). The logistic model performance was 0.83; 0.83 in conservative, 0.75 in invasive group [area under the receiver operating curve (AUC)]. The risk score variables were selected as follows (points): age 65-74y (1); age $\geq$75y (2); male sex (1); pulmonary oedema at admission (1); cardiogenic shock at admission (2); positive myocardial necrosis markers (1); prior MI (1); lack of history of hypertension and smoking and hyperlipidaemia (1). The performance of the risk score (AUC) was 0.83 (0.82-conservative, 0.79- invasive). The pattern of the benefit of invasive strategy is shown in the table.

Table.

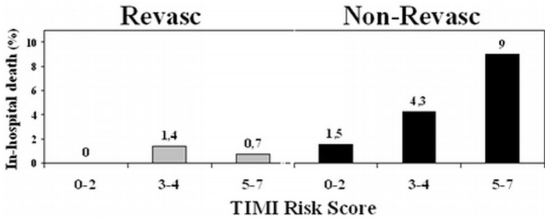
Risk score points	Conservative [N]	Conservative [30-day mortality]	Invasive [N]	Invasive [30-day mortality]	Absolute risk reduction [% (95% CI)]	Relative risk reduction [% (95% CI)]
0	1016	0.8%	878	0.5%	0.3 (-0.8 - 0.8)	42.1 (-80.0 - 81.4)
1	1793	1.8%	1432	0.8%	1.0 (0.2 - 1.6)	57.0 (16.0 - 78.0)
2	1507	3.5%	823	1.9%	1.6 (0.1 - 2.7)	44.7 (4.7 - 68.0)
3	1039	9.9%	310	6.8%	3.1 (-0.6 - 6.0)	31.7 (-6.4 - 56.5)
4	389	23.4%	68	16.2%	7.2 (-3.9 - 15.1)	30.9 (-18.1 - 61.4)
$\geq$5	166	51.2%	16	43.8%	7.5 (-17.0 - 29.5)	14.6 (-34.6 - 55.5)

Conclusion: We developed a simple "real life" risk score for predicting not only the outcome but also the absolute and relative benefit of invasive versus conservative treatment of ACS pts without ST-segment elevation.

2721 Myocardial revascularisation eliminates the risk gradient defined by the TIMI risk score in non-ST-segment elevation acute coronary syndromes

J. Ferreira Santos[1], J. Ferreira[2] on behalf of Portuguese Society Cardiology Acute Coronary Syndromes Investigators. *[1]Sao Bernardo Hospital, Cardiology, Setubal, Portugal; [2]Santa Cruz Hospital, Cardiology Department, Carnaxide, Portugal*

Background: The TIMI Risk Score is a simple and effective tool for risk stratification in patients (pts) with non-ST-segment elevation acute coronary syndromes (NSTE-ACS). Aggressive therapeutic management guided by risk stratification is increasingly used in order to improve clinical outcome.
Aim: We sought to evaluate the impact of myocardial revascularization (Revasc) on the risk gradient defined by the TIMI Risk Score in a NSTE-ACS population.
Methods: We studied 6446 pts with NSTE-ACS included in a prospective nationwide clinical registry since 2002. Pts were stratified by TIMI Risk Score in low (0 to 2), intermediate (3 and 4) and high risk (5 to 7). Clinical outcome, evaluated by in-hospital death, was assessed in pts submitted or not to Revasc during the index hospitalization and according to TIMI Risk Score stratification. TIMI Risk Score performance was tested in revascularized and non-revascularized pts.
Results: In-hospital mortality was 1,1% in low, 3,6% in intermediate and 7,1% in high risk pts stratified by the TIMI Risk Score (Qui-square trend = 62.5, $p<0.001$). Revasc was performed during hospitalization in 1693 pts (26,3%) and was associated with a significantly lower mortality (adjusted HR 0.53, 95% CI, 0.30-0.96). The risk gradient defined by the TIMI Risk Score was not observed in pts submitted to Revasc (Qui-square trend = ns) but persisted in the remaining population (Qui-square trend = 56.9, $p<0.001$) (Figure).
Conclusions: In NSTE-ACS pts, TIMI Risk Score defines a significant gradient for in-hospital mortality that is eliminated by Revasc.

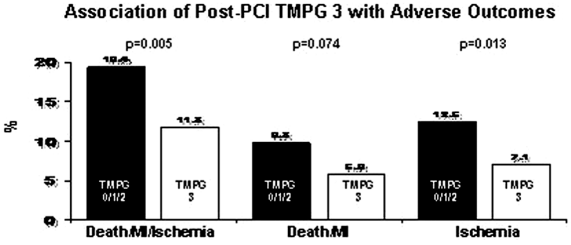


Risk gradient defined by TIMI score

2722 Associations of TIMI myocardial perfusion grade with biomarkers, Holter findings, and clinical outcomes among patients with moderate-high risk ACS

C.M. Gibson[1], A.J. Kirtane[2], S.A. Murphy[1], D.A. Morrow[1], C.H. McCabe[1], E. Braunwald[1]. *[1]Harvard Medical School, TIMI Study Group, Boston, United States of America; [2]Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, United States of America*

Background: The importance of the coronary microvasculature in acute coronary syndromes (ACS) is well-established but the relative merits of various metrics assessing it have not been established.
Methods: We sought to examine associations between angiographic measures of myocardial perfusion with biomarkers, Holter findings, and clinical outcomes in the PROTECT TIMI-30 trial of 857 patients with non-ST elevation ACS (NST ACS) undergoing PCI.
Results: The TIMI Myocardial Perfusion Grade (TMPG) was significantly associated with the baseline Troponin-I (TpI) and CK-MB as well as the peak TpI, CK-MB, and CRP and absolute rise in TpI and CRP. The post-PCI TMPG was also associated with the baseline and peak in TpI and CK-MB. The duration of ischemia was longer among patients with abnormal baseline TMPG (8.2 vs. 3.7 min, p=0.027) and abnormal post-PCI TMPG (8.7 vs. 3.2 min, p=0.047). An ischemic event by 48 hrs was more common among patients with abnormal post-PCI TMPG (12.5% vs. 7.1%, p=0.013). Abnormal post-PCI TMPG was additionally associated with death/MI/an ischemic event by 48 hrs (p=0.005). There was a trend for abnormal post-PCI TMPG to be associated with death/MI (9.3% vs. 5.9%, p=0.07). In contrast, the post-PCI coronary flow reserve (CFR) based upon the improvement in the TIMI frame count after adenosine, was not associated with the baseline, peak, or absolute rise of any biomarker, Holter findings, or clinical events.



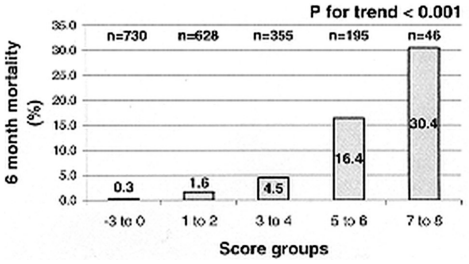
Figure

Conclusions: Abnormal myocardial perfusion assessed using the TMPG was associated with significant rises in biomarkers, the occurrence/duration of ischemic events, and clinical outcomes while the CFR was not. These data now prospectively validate prior data associating the TMPG with clinical outcomes in the NST ACS PCI setting.

2723 Prediction of all-cause mortality at 6 months in 30-day survivors of acute coronary syndrome: prospective validation of the ACSIS score

A. Sandach[1], O. DavidZadeh[2], S. Matezki[3], V. Guetta[3], H. Hod[3], S. Behar[1], M. Snyder[2], E. Schwammenthal[4]. *[1]Israel Society for Prevention of Heart attack, Ramat Gan, Israel; [2]Bar-Ilan University, Statistics, Ramat-Gan, Israel; [3]Sheba Medical Center, Tel Hashomer, The Heart Institute, Ramat Gan, Israel; [4]Sheba Medical Center, Tel Hashomer, The Cardiac Rehabilitation Istitute, Ramat Gan, Israel*

Background: In the Acute Coronary Syndrome Israeli Surveys (ACSIS 2000 and 2002) use of multiple secondary prevention drugs was associated with substantial survival benefits. The number of these drugs at discharge (from 1 to 4) was an independent predictor of 6-month all-cause mortality in 30 day survivors of acute coronary syndrome (ACS). Risk scores therefore need to take discharge medication into consideration.
Methods and Results: The bootstrap method for variable selection was used to obtain a parsimonious predictive model and a score for risk assessment of ACS survivors – the ACSIS score – was derived. Positive or negative points were assigned for each risk factor (age, diabetes, heart failure), or protective factor (coronary angiography during hospitalization, number of secondary prevention drugs at discharge), respectively, weighted proportionally to the value of the relevant β-coefficients. The accuracy of the risk score to predict 6-month all-cause mortality was then prospectively tested in 1975 discharged ACS survivors of the 2004 ACSIS cohort. The results are presented in the figure below.
Conclusion: The ACSIS score, which takes both risk factors and the protective



ACSIS Score

effect of therapeutic interventions into consideration, is a stable, convenient, and highly accurate bedside tool for risk stratification of ACS survivors.

SYNCOPE; NEW APPROCHES TO AN OLD PROBLEM?

2732 Prospective evaluation of emergency patients with syncope: value of an update two-step diagnostic strategy in clinical practice

C. Kouakam[1], P. Lestavel[2], C. Daems-Monpeurt[3], K. Ouchalal[4], P. Derambure[3], D. Lacroix[4], S. Kacet[4]. *[1]Lille University Hospital, Service de Cardiologie A, Lille Cedex, France; [2]Lille University Hospital, Emergency Department, Lille, France; [3]Lille University Hospital, Neurophysiology Department, Lille, France; [4]Lille University Hospital, Cardiology Departement, Lille, France*

Background: In spite of progresses during the past 2 decades, the management of patients with syncope (S) remains a challenge. We aimed to prospectively assess the diagnostic yield of an update two-step diagnoctic strategy in which cardiologic, neurologic and psychiatric evaluation were selectively performed.
Methods and Results: The study population consisted of 947 emergency patients (549 F/398 M, mean age 49 $\pm$ 22 years) presenting with a presyncopal (44%) or a syncopal episode (56%). All the patients were administrated a 67-item historic questionnaire and underwent a prospective multidisciplinary evaluation to determine the diagnosis. The diagnostic algorithm comprised 2 main steps: the history and physical examination which had to be performed in the emergency room (first step), and the further screening tests which had to be guided by the initial diagnostic hypothesis (second step). The cause of S was assigned according to predetermined diagnostic criteria. Among the 947 patients, 475 (50%) presented with recurrent episodes, 18 (1.9%) had a family history of sudden death, 133 (14%) had a structural heart disease, 112 (12%) had a history of cardiac arrhythmia, 160 (17%) had a history of psychiatric disorder, 77 (8%) had a history of seizure or stroke, 205 (22%) had systemic hypertension and 87 (9%) had diabetes. After initial evaluation, diagnosis was considered certain in 254 patients (27%), probable in 486 patients (51%) and unknown in 201 patients (22%). In-hospital evaluation was performed in 232 patients (24%). Final diagnosis was considered certain certain in 377 patients (40%), probable in 533 patients (56%) and unknown in 37 patients (4%). The aetiologies of S and/or preS were as follow: neurally-mediated reflex syndrome in 564 patients (60%), cardiovascular in 115 patients (12%), psychiatric in 100 patients (11%), neurologic in 76 patients (8%) and others in 55 patients (6%).
Conclusions: Our diagnostic strategy improved S diagnosis with only 4% of unexplained aetiology. These results points out the importance of a multidisciplinary approach of syncope patients.

2733 Clinical characterisitcs and diagnostic management of patients attended because of syncope in emergency department in Spain. A prospective study

A. Moya I Mitjans[1], A. Martin[2], R. Garcia-Civera[3], C. Del Arco[2], G. Baron[4], P. Laguna[2], J. Martinez-Alday[5]. *[1]Barcelona, Spain; [2]Spanish Society of Emergency Medicine, Arrhythmia Division, Madrid, Spain; [3]Hospital Clínico, Department of Cardiology, Valencia, Spain; [4]Hospital Virgen del Rocio, Department of Cardiology, Sevilla, Spain; [5]CH Donostia, Department of Cardiology, Bilbao, Spain*

Aim: To assess the clinical characteristics, the diagnostic approach and the adherence to "Guidelines on Management of Syncope" (GMS) of the European Society of Cardiology of patients (pts) attended to Emergency Department (ED) because of syncope.
Methods: Between november 14th and december 14th 2003, data from all pts with syncope attended at ED in 19 hospitals in Spain were collected. Diagnosis made at ED were posteriorly reviewed according to the criteria defined in the GMS.
Results: During this period, 1,428 pts were included. The list of the performed tests as well as its diagnostic yield is: Baseline ECG performed in 1322 (92%) pts with a diagnostc yield of 2.4%; Blood analysis in 1011 (71%) pts with a diagnostic yield of 3%; Thorax X Ray in 741 (52%) pts with a diagnostic yield of 1%; ECG monitoring in 237 (17%) pts with a diagnostic yield of 6%; Echocardiogram in 28 (2%) pts with a diagnostic yield of 18%; Orthostatic arterial blood pressure in 68 (5%) pts with a diagnostic yield of 3% and carotid sinus massage in 6 (0.4%) pts with a diagnostic yield of 17%. Table I shows the final diagnosis at ED as well as the reviewed diagnosis according to the GMS. 221 (16%) pts, were admitted at the hospital. Of the remaing 1,207 pts, 959 (79%)were not sent to further ambulatory specific evaluation.

Table I

Etiology	Clinical diagnosis: # pts (%)	Diagnosis according ESC. # pts (%)	p
Neuromediated	544 (47)	247 (23)	<0.001
Orhostatic	95 (8)	62 (6)	0.03
Arrhythmic	94 (8)	52 (5)	0.002
Cardiopulmonar	53 (5)	25 (2)	0.004
Situational	75 (7)	50 (5)	ns
Unknown	292 (25)	620 (59)	<0.001

Conclusions: In this serie there was an overuse of unespecific tests and an underuse of specific tests adressed to the etiologic diagnosis of syncope. In addition, according to the stablished diagnostic criteria defined by the GMS of the European Society of Cardiology guidelines, too many patients were diagnosed of specific etiologies of syncope according to the criteria defined in GMS. The admission rate in of this series was lower than the described by other authors.

2734 The best management of syncope. A population-based prospective systematic evaluation of patients referred urgently to general hospitals based on the guidelines of the European Society of Cardiology

M. Brignole on behalf of GIMSI. *Ospedali del Tigullio, Department of Cardiology, Lavagna, Italy*

Background: The Guidelines on Syncope of the ESC provide the best current standard for the management of the patients with syncope
Aim: Population-based systematic evaluation based on a strict adherence to those guidelines.
Methods: This prospective multicentre observational study enrolled all consecutive patients referred to the emergency departments of 11 general hospitals from October 4th 2004 to November 5th 2004 because affected by transient loss of consciousness as principal symptom. In order to maximize the application of the standards recommended by the Guidelines two main actions were taken: the use of a decision making software designed in strict accordance to the Guidelines (EGSYSâ software, version 1.0) and the designation of a trained core medical personnel – both locally in each hospital and centrally – who verified the adherence to the diagnostic pathway for all patients and eventually gave advices for its correction.
Results: There were 542 patients (median age 71, interquartile range 48-81, 53% males). Adherence to guidelines was achieved in 86% of patients. Among these, a definite diagnosis was made in 98% (unexplained in 2%): neurally-mediated syncope was found in 66%, orthostatic hypotension in 10%, primary cardiac arrhythmias in 11%, structural cardiac or cardiopulmonary disease in 5% and non-syncopal attacks in 6%. Diagnosis was made by the initial evaluation alone (consisting in history, physical examination and standard electrocardiogram) in 49% of cases. Hospitalization for the management of syncope was appropriate in 25% of cases; in further 13% of cases, hospitalization was required for other reasons. The median in-hospital stay was 5 days (interquartile range 3-9). Apart from the initial evaluation, a total of 358 appropriate tests was performed in 190 patients (41%) (mean 1.9$\pm$1.1 per patient): 1 test was necessary in 20%, 2 tests in 11% and ^{3}3 tests in 10%.
Conclusion: Guidelines can be implemented in the clinical practice provided that they are carefully and systematically applied. The results of this study define the current standard for the management of syncope

2735 Results of longitudinal GIS-study. Syncope in older patients: clinical characteristics and prognosis

A. Ungar[1], C. Mussi[2], T. Cellai[1], A. Landi[3], G. Noro[4], L. Ghirelli[5], P. Abete[6], A. Del Rosso[7]. *[1]Gerontology and Geriatric Medicine, Dept. of Critical Care Medicine, Florence, Italy; [2]University of Modena, Gerontology and Geriatric Medicine, Modena, Italy; [3]Gerontology and Geriatric Medicine, Dept. of Critical Care Medicine, Firenze, Italy; [4]Santa Chiara Hospital, Unit of Geriatric Medicine, Trento, Italy; [5]S.M. Nuova Hospital, Geriatric Unit, Reggio Emilia, Italy; [6]Federico II University, Geriatric Department, Napoli, Italy; [7]Fucecchio Hospital, Cardiology Unit, Fucecchio, Italy*

Background: In spite of growing evidence-based information guiding standardized approach to syncope, data gathered in the fastest growing segment of the population, the "older elderly" (>75 years), are substantially limited.
Aims: to test the applicability and safety of a standardized diagnostic algorithm, to define the prevalence of different types of syncope in older patients referred to geriatric departments and to evaluate impact of syncope on morbidity and mortality.
Methods: we enrolled 242 elderly patients (age 78$\pm$7 years, range 65-98 years) referred to geriatric Departments for suspected syncope. All patients were evaluated according to an algorithm for diagnostic approach to syncope previously established derived from ESC Guidelines on Syncope: first line evaluation (history,

physical examination and ECG), secondary evaluation (cardiac and neuroautonomic diagnostic tests).
Results: in 11 patients a syncope-like condition was found (5 transient ischemic attacks or strokes, 6 seizures). First line evaluation permitted to obtain certain diagnosis in 37.2% of the cases; a suspected diagnosis of cardiac, neurally-mediated or cerebrovascular syncope in 59.3% of the cases. Suspected diagnosis of cardiac causes was confirmed in 43.7%; neurally-mediated cause was confirmed in 83.5% of the cases. In absence of cardiac disease cardiac causes of syncope was extremely rare (only 4%). Neurally-mediated causes was the most common type of syncope (66.6%,).Cardiac causes represented 14.6% and unexplained syncope was only 10.4%. We found prodromic symptoms in both neurally-mediated (83%) and cardiac syncope (70%). Until now 184 patients were clinically re-evaluated: 30 patients died during follow-up (16.3%). Mortality was higher in patients with cardiac causes of syncope than in the others (24.2% vs. 13.5%, p=0.004). 43 patients (25.3%) had a new syncopal episode, particularly in patients with orthostatic hypotension. The prevalence of depression increased from 30% to 58% of the cases during follow-up, independently from recurrence of syncope.
Conclusion: A standardized diagnostic protocol is applicable in geriatric departments and reduces unexplained syncope to 10%. When cardiac disease was excluded after the initial evaluation cardiac syncope is very rare also in geriatric patients. Recurrent syncope is very frequent in this population. Older patients with syncope had high mortality, particularly when cardiac syncope is present.

2736 Placebo effect of the implantable loop recorder in patients with recurrent neurocardiogenic syncope

M.J. Antolinos[1], F.J. Lacunza[1], A. Garcia-Alberola[2], M.C. Cerdan[1], J.J. Sanchez[1], J. Martinez-Sanchez[1], M. Valdes[1]. *[1]University Hospital Virgen Arrixaca, Cardiology, El Palmar, Spain; [2]University Hospital Virgen Arrixaca, Cardiology, El Palmar, Spain*

Definitive pacemakers have been suggested to exert a placebo effect in patients with recurrent neurocardiogenic syncope. Other implantable devices could have a similar effect. The aim of the study was to assess whether the implantable loop recorder can reduce by itself the number of syncopal episodes in patients with recurrent syncope and absence of structural heart disease.
Method: A subcutaneous loop recorder device (Reveal Plus) was implanted for diagnostic purposes in 19 patients with recurrent syncope of unknown origin, absence of structural heart disease and normal ECG. To enter the study patients were required to suffer at least two syncopes during the year before the device implant, and to have completed a one-year follow-up period after the implant. One patient presenting a prolonged sinus arrest during a nocturnal syncope received a definitive pacemaker and was excluded from the analysis. The rest of the patients did not receive any specific pharmacologic or non-pharmacologic treatment upon recurrence of syncope. Follow-up visits with interrogation of the device were scheduled every 6 months and within 48 hours in case of syncope or presyncope. The number of syncopes within the year before and after the implant of the loop recorder were compared using a Wilcoxon's non-parametric statitistical test.
Results: Eighteen patients (12 men, age: 58.2 $\pm$ 17.9 y.) were analyzed. Hypertension and diabetes were present in 4 and 2 respectively. All patients underwent a head up tilt table test potentiated with nitroglycerin before implanting the recorder and 6 (33.3%) had a positive result. The median of syncopal episodes in the year before the implant (3.5, range: 2 to 12) decreased significantly during the subsequent year (median: 0, range: 0 to 20, $p<0.05$). Ten patients (55.6%) with a median of 2.5 syncopes (range: 2 to 4) in the year before the implant did not experience any recurrence after receiving the device. The absence of syncope during follow-up was not predicted by any demographic or clinical variables.
Conclusion: A significant reduction in the number of syncopal episodes is observed after the implant of an implantable loop recorder in patients with recurrent syncope of unknown origin and normal heart.

2737 A new therapeutic option for the patients with recurrent neurocardiogenic syncope: ambulatory tilt training

V. Öztürk, O. Kozan, B. Akdeniz, O. Aslan, N. Baris, D. Aytekin, O. Badak, S. Guneri. *Dokuz Eylul University, Cardiology, Izmir, Turkey*

Purpose: Tilt training is a suggested method of therapy in the syncope guidelines. In previous tilt-training studies; patients were trained after hospitalization and then advised to go on tilt training at home. These studies were time consuming for both doctors and patients. This study aimed to determinate the efficacy of ambulatory tilt training in persons with syncope.
Methods: Patients with at least three episodes of syncope, one of which was seen during last 6 months, were included the study. These patients were randomized into two groups after diagnostic tilt testing. In the fist group tilt training was performed and preventive recommendations were given. Control group had no tilt training but got only recommendations. Patients were trained in our tilting room for training without using tilt table. Patients had to stand and lean with upper back against a wall, the feet 15-30 cm away from the wall, without moving until the patient could perform the passive exercise for 30 minutes, same procedure was continued by the patient at home by the supervision of this exercise program.
Results: 29 patients (26 female 3 male) were recruited to the study. Fifteen of these patients (mean age: 43,8$\pm$12,1) were tilt trained and 14 patients were in the control group (mean age: 34,3$\pm$13,8). Majority of the patients with neurocardiogenic syncope was cardioinhibitor type IIb. Mean follow up duration was 8 months. Ambulatory tilt training significantly decreased mean number of syncope (3.8$\pm$1.78 - 0,27$\pm$0,59; p=0.0001) and presyncope 2,87$\pm$1,81-1,07$\pm$0,88; p=0.002). Whereas the mean number of presyncope was significantly elevated in the control group (1,79$\pm$0,80-2,43$\pm$1,34). Mean number of syncope was also significantly decreased in the control group (3.64$\pm$1.27 – 0.93$\pm$0.99; $p<0.01$). Comparing the tilt training and control groups; the decrease of number of syncope tended to be more prominent in tilt training group (p=0.054). Syncope developed only 3 out of 15 patients in the tilt group, two of them had not properly adjusted to training programs, whereas in the control group syncope occurred 7 of 14 patients. No complication occurred related to tilt training during the follow up period.
Conclusion: Ambulatory tilt training significantly improved the symptoms in patients with neurocardiogenic syncope. Tilt training once a day, up to 30 minutes was effective and easily accepted by the patients for the prevention of neurocardiogenic syncope

CONTROVERSIAL ISSUES ON BRUGADA SYNDROME

2738 Flecainide is more sensitive than procainamide to unmask the ECG Brugada pattern

F.J. Lacunza[1], A. Garcia-Alberola[2], M.C. Cerdan[1], J.R. Gimeno-Blanes[1], J. Martinez-Sanchez[1], J.J. Sanchez-Munoz[1], M. Valdes[1]. *[1]University Hospital Virgen Arrixaca, Cardiology, El Palmar, Spain; [2]University Hospital Virgen Arrixaca, Cardiology, El Palmar, Spain*

Sodium channel blockers are known to unmask the typical ECG pattern in patients with Brugada syndrome and concealed or border-line ECG abnormalities. It has been suggested that procainamide may have a lower sensitivity than other class I drugs in this settings. However, no data are available comparing the diagnostic value of different sodium channel blockers in the Brugada syndrome. The aim of the study was to evaluate the result of a flecainide provocation test in patients with non-diagnostic Brugada patterns and a negative procainamide test.
Methods: Flecainide (2 mg/kg IV in 20 min) was administered to 22 patients (17 men, age:34.8 $\pm$ 8.2 y) with suspected Brugada syndrome, non-diagnostic baseline ECG and a negative provocation test with procainamide. The flecainide test was performed at least 3 days after the procainamide challenge. Recently summarized criteria reported by the Second Consensus Conference on the Brugada Syndrome were strictly applied to classify the response to both provocation tests.
Results: Five subjects were relatives of patients with a typical Brugada syndrome, 3 presented with recurrent syncope and suspected Brugada pattern and the rest were asymptomatic. Out of 22 patients with negative procainamide tests 3 (13.6%) developped a diagnostic Brugada pattern after flecainide administration (Fig. 1). Two additional patients (9.1%) converted from a type 3 to a type 2 ST-segment elevation, and the rest did not show significant changes.

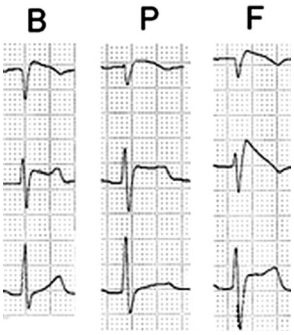


Fig. 1. Right precordial leads. B: Baseline, P: After procainamide F: After flecainide

Conclussion: A provocation test with flecainide has higher sensitivity than a procainamide test to unmask a diagnostic ECG Brugada pattern in suspected patients with non-diagnostic baseline ECG.

2739 Electrophysiologic importance of the right ventricular outflow tract: analysis of the induced ventricular tachycardia characteristics in Brugada syndrome

N.M. Nobuyuki Murakoshi[1], K.A. Kazutaka[2], Y.T. Yasuaki Tanaka[1], Y.Y. Yasuhiro Yokoyama[1], K.Y. Kentaro Yoshida[1], K.K. Keisuke Kuga[1], A.T. Atsushi Takahashi[3], I.Y. Iwao Yamaguchi[1]. *[1]University of Tsukuba Graduate School, Department of Cardiology, Tsukuba-City, Japan; [2]University of Tsukuba Graduate School, Department of Cardiology, Tsukuba-City, Japan; [3]Yokosuka Kyosai General Hospital, Cardiovascular Center, Yokosuka-city, Japan*

Background: Brugada syndrome is an arrhythmogenic disease characterized by an ECG pattern of distinct ST-segment elevation in the right precordial leads and an increased risk of sudden cardiac death as a result of ventricular fibrillation(VF).

Experimental studies proposed that the transmural dispersion of the action potential duration of the right ventricular outflow tract (RVOT) could be the underlying mechanisms of both the ST-segment elevation in the right precordial leads, and the initiation of the ventricular tachyarrhythmia (VT) due to phase 2 reentry of the RVOT that degenerated into VF in Brugada syndrome. We therefore evaluated the electrophysiologic characteristics of the induced VT in Brugada syndrome to clarify whether the RVOT could be an arrhythmogenic subatrate in comparison with non-Brugada idiopathic VF.
Methods: There were 24 patients (23 males 1 female; mean age=54 year old) with Brugada syndrome and 12 patients (11 males and 1 female; mean age=48 year old) with non-Brugada idiopathic VF, who underwent programmed ventricular stimulation (PVS). PVS was done by using up-to 3 extrastimuli during 2 drive cycle length from the two RV sites with twice the diastolic threshold. The QRS morphology and the intracardiac conduction properties of the induced VT were precisely evaluated to determine the origin of the initiating VT that degenerated into VF.
Results: PVS reproducibly induced repetitive VT with a mean cycle length of 205 ms that degenerated into VF in 21 of 24 patients (87%) with Brugada syndrome. The morphology of the repetitive VT was a left bundle branch block pattern with an inferior axis in 18 of 21 patients (86%), and the intracardiac conduction sequences during the VT revealed conduction from the RVOT to the RV apex in these patients irrespective of the stimulation sites. On the other hand, the initiation property of VF was not uniform in patients with non-Brugada idiopathic VF.
Conclusions: The majority of the patients had repetitive VT originating from the RVOT that degenerated into VF in Brugada syndrome, however, the patterns of the initiation of VF were various in idiopathic VF, suggesting that the RVOT might play an important role of VF in Brugada syndrome. From the electrophysiologic characteristics of the induction pattern of VT, RVOT contributed as an arrhythmogenic substrate in the majority of patients with Brugada syndrome.

2740 Is programmed ventricular stimulation really useful for risk stratification in patients with Brugada type 2-3 EKG? Experience issued of the COBRA (Collective Observatory of BRugadA) population

G. Quiniou[1], R. Carlioz[2], J.M. Davy[2], R. Frank[2], G. Lascault[2], A. Leenhardt[2], J.J. Blanc[2]. *[1]Brest, France; [2]COBRA committee, France*

Na channel blockade (NaCB) is widely used to unmask the typical Brugada (B) EKG in patients (pts) with type 2-3 EKG pattern. Inducible malignant ventricular arrhythmias (VA) by programmed ventricular stimulation (PVS) is used as an indication for ICD implantation in asymptomatic pts with family history (FH) of sudden death (SD). The objective of this study was to evaluate the incidence of VA induction in type 2-3 converted to type 1 B EKG after NaCB in the French registry (COBRA).
Methods: 376 pts were included in the COBRA survey. For each B pt, data regarding FH, presence of symptoms or not, basal EKG and/or after NaCB, PVS results and therapeutic options at the time of diagnosis were collected. All EKGs were reviewed by the COBRA committee, according to the European task force EKG criteria [coved back-type ST segment elevation $\geq$2mm, T wave flat or negative in V1-3]. Either Flecainide (F) or Ajmaline (A) were used for NaCB.
Results: out of 376 pts included, 153 underwent NaCB. 93 were classified as type 1, 40 as type 2 and 21 as type 3 before NaCB. From 40 pts with type 2 EKG [35 males, 43,5$\pm$11years, 18 with FH: 15 aborted SD, 7 B] 17 were symptomatic [2 SD, 6 syncope (S), 3 near syncope (NS), 6 palpitations (P)]. NaCB challenge resulted in 37/40 type 1 conversion [92,5%] (20/23 F, 17/17 A). Out 32 PVS, 15 were positive [47%] (5 VT, 10 VF). From 21 pts with type 3 EKG [16 males, 43$\pm$13 years, 11 with FH: 9 SD, 8 B], 9 were symptomatic (1 SD, 5S, 2 NS, 1 P). NaCB resulted in 20 type 1 conversion [95%] (15/16 A, 5/5 F). Out of 17 PVS, 4 were positive [23%] (2 VT, 2 VF).

Table 1: Results of PVS after positive NaCB

NaCB +	Type II with FH	Type II without FH	Type III with FH	Type III without FH
Symptomatic pts	4/5 (80%)	2/10 (20%)	1/3 (33%)	1/5 (20%)
Asymptomatic pts	6/9 (67%)	3/8 (37,5%)	1/7 (14%)	1/2 (50%)
Total	10/14 (71%)	5/18 (28%)	2/10 (20%)	2/7 (28%)

Conclusion: there is a high rate of tested type 2-3 B EKG pts displaying a type 1 after NaCB in the COBRA population. PVS had only a major interest among symptomatic or not pts with type 2 EKG displaying type 1 and FH of SD [out of 14 pts, 10 (71%) PVS were positive]. Among pts with type 3 EKG displaying type 1 (symptomatic or not, with or without FH), PVS is mostly negative.

2741 The circadian variation of temporal QT interval dispersion in right precordial leads in Brugada syndrome

T. Kanemori[1], H. Shimizu[2], Y. Furukawa[2], T. Mine[2], T. Masuyama[2], M. Ohyanagi[2]. *[1]Hyogo College of Medicine, Cardiovascular Division, Nishinomiya, Japan; [2]Hyogo college of Medicine, Cardiovascular division, Nishinomiya, Japan*

Background: In Brugada syndrome (BS), ventricular fibrillation (VF) occurs mainly during the night. However, the precious mechanism of VF occurrence in that time remains unclear. We evaluate temporal QT interval dispersion in BS using 12 leads 24-h Holter monitoring.
Methods: Eight patients with BS (B group) who showed spontaneous ST elevations at right precordial leads (V1-2) and in whom VF was induced by the programmed stimulation, and nine patients with normal heart (C group) were enrolled in this study. QT and RR interval in right precordial leads were measured by automated analysis on the basis of 256-beats records every 3 hours in both groups. Standard deviation of QT interval (QT-SD) was calculated for each patient and also the heart rate variability was analyzed as the high-frequency component (RR-HF), low frequency component (RR-LF) and the LF/HF ratio (RR-LF/HF).
Results: During the night (AM 0:00-6:00), QT-SD increased significantly in B group than in C group (4.9$\pm$1.1 vs. 6.7$\pm$1.3 ms, $p<0.01$, respectively), and RR-HF was higher in B group(806.4$\pm$438.6 vs. 1672.5$\pm$1432.4 msec2, $p<0.01$, respectively), but there was no difference in RR-LF/HF. However, during the day (AM 6:00-PM 6:00), there was no difference in QT-SD, RR-HF, and RR-LF/HF in both groups (Figure 1).

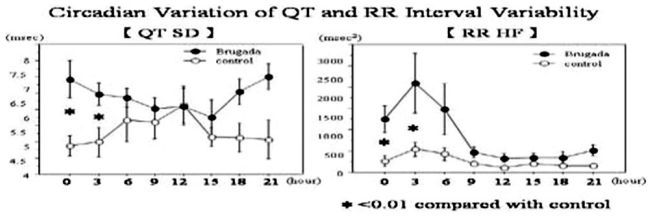


Figure 1

Conclusion: These findings suggest that the increase of the temporal dispersion of ventricular repolarization in right ventricular outflow tract along with an increase vagal tone may possibly facilitate the phase 2 reentry and the occurrence of VF during the night.

2742 Follow up data of prophylactic ICD implantation in Brugada syndrome

A. Sarkozy, J. Kourgiannides, T. Boussy, J. Chierchia, P. Geelen, M. De Zutter, P. Brugada. *OLV Hospital, Cardiovascular Center, Aalst, Belgium*

Background: The treatment of patients with Brugada syndrome without previous aborted sudden death is controversial. We report the follow up of patients with Brugada syndrome who have received an implantable cardioverter-defibrillator (ICD) and had not suffered from cardiac arrest before implantation.
Methods: We reviewed all patients who underwent prophylactic ICD implantation between 1991 and 2003. The indication was based on the family history, syncope, the presence of type I (coved ST elevation) ECG pattern and the result of the EP study. 36 patients, 26 males (72%), age: 50$\pm$14.6 years, were included. 15 (42%) patients had a positive family history of sudden death (SD) and 17 (47%) patients had suffered from syncope. 15 (41%) patients had spontaneous type I and 11 (30%) patients type II ECG pattern. An ajmaline test was performed in 31 (86%) patients and 27 (81%) had a type I response. 34 patients underwent an EP study and 29 patients (85%) had sustained inducible VT/VF.
Result: The follow up was 50 $\pm$ 32 months. 6 (17%) patients had appropriate shock during follow up. There was no statistically significant difference in any parameter between the two groups with or without appropriate therapy. Out of the 6 patients prior to the ICD implantation 4 patients had resting type I and 2 type II ECG. Both patients with initial type II ECG had strongly positive ajmaline test and later during the follow up at least one documented spontaneous type I ECG. 2 patients had a family history of SD, and 2 other had syncope. 2 patients had neither syncope nor positive family history. During the EP study all 6 patients had induced sustained VT/VF. 11 out of 36 (30%) patients had inappropriate shock during follow up.
Conclusions: Individuals with Brugada syndrome undergoing prophylactic ICD implantation have a substantial risk of (aborted) sudden death. Prophylactic implantation of an ICD based on clinical and electrophysiologic variables is justified.

2743 Safety of ajmaline challenge in patients suspicious of Brugada syndrome

C.G. Veltmann, R. Schimpf, C. Echternach, J. Kuschyk, S. Spehl, F. Streitner, M. Borggrefe, C. Wolpert. *University Hospital Mannheim, Cardiology, Mannheim, Germany*

Intravenous ajmaline challenge is a common procedure to identify patients with Brugada syndrome if the diagnostic type 1 ECG pattern is not overt in the basal ECG. The aim of this study was to evaluate the safety and side effects of intravenous ajmaline challenge in 236 consecutive patients suspicious of Brugada syndrome.
Patients and methods: In 236 patients (mean age 43 $\pm$ 23 years, 139 males) suspicious of Brugada syndrome intravenous ajmaline was infused with a maximal dose of 1mg/kg body weight within 5-10 minutes under continuous ECG monitoring following the recommendation of the Brugada consensus conference.

Criteria for termination of the test were appearance of the diagnostic type I ECG pattern of Brugada syndrome and furthermore an increase of the QRS duration of more than 30%, high degree AV-block or the development of ventricular premature beats or tachycardia. In 66% of the cases the test was performed due to a syncope of unknown origin, in 14% due to abnormal basal ECG, in 8% because of a family history of sudden cardiac death or Brugada syndrome, in 9% due to palpitations and nsVT and in 3% because of aborted sudden cardiac death.
Results: In 42 patients the ajmaline challenge was positive with development of a diagnostic type I ECG (17%). In the remaining 194 patients the test was negative. In 64% of the patients the test was stopped at the maximal ajmaline dose, in 10% prematurely due to increase of the QRS duration and in 9% due the premature ventricular extra beats. In one patient two 4 seconds lasting polymorphic VT were observed, which did not need further medical treatment.
Conclusions: Ajmaline challenge can securely be performed under close monitoring during drug application. The risk of serious side effects using this protocol is very low (0.4%). However, due to the potential risk of dangerous arrhythmias ajmaline challenge should only be performed by experienced physicians.

WHATS NEW IN CARDIAC COMPUTED TOMOGRAPHY?

2744 Improved evaluability and diagnostic accuracy of noninvasive coronary artery angiography using 64-slice spiral computed tomography with 330 ms gantry rotation

D. Ropers[1], K. Anders[2], U. Baum[2], W. Bautz[2], W.G. Daniel[3], S. Achenbach[3]. *[1]University of Erlangen-Nurnberg, Dept. of Cardiology & Internal Medicine II, Erlangen, Germany; [2]Department of Diagnostic Radiology, University of Erlangen, Erlangen, Germany; [3]Department of Internal Medicine II, University of Erlangen, Erlangen, Germany*

Noninvasive coronary angiography using multi-detector CT (MDCT) has improved rapidly during the last years. However, even with 16-slice CT and sub-millimeter collimation, a significant portion of coronary arteries have been unevaluable. A newly developed 64-slice CT system with increased gantry rotation speed offers further improvement of spatial and temporal resolution. We determined evaluability and accuracy of this 64-slice CT scanner (Sensation 64, Siemens, Germany) for the detection of coronary artery stenoses.
A total of 84 pts. (52 men, 32 women, mean weight, 83 $\pm$ 15 kg, mean age, 58 $\pm$ 10 y, range, 35 - 77 y) referred for invasive coronary angiography due to suspected coronary artery disease were studied by MDCT (64x0.6 mm collimation, 330 ms tube rotation, 550-750 mAs, 120 kV, 80 ml contrast agent). Patients with a heart rate $>$ 60 bpm received 100 mg atenolol orally 60 minutes prior to the scan and, if necessary, up to 20 mg metoprolol intravenously immediately before the investigation. Axial cross sections (slice thickness 0.75 mm in 0.5-mm intervals) were reconstructed using an ECG-gated half-scan reconstruction algorithm. All coronary artery segments with a diameter of 1.5 mm or more were assessed concerning the presence of stenoses exceeding 50% diameter reduction. Results were compared to quantitative coronary angiography on a per-artery and per-patient basis.
The mean heart rate during the scan was 58$\pm$9 bpm. β-Blockers were administered to 62 pts. (74%). The mean breathhold duration was 9.6 s. A total of 26 pts. (31%) demonstrated significant coronary artery disease in invasive angiography (1-vessel disease in 16 pts., 2-vessel-disease in 8 pts., 3-vessel disease in 2 pts.). Out of 336 coronary arteries (left main, left anterior descending, left circumflex and right coronary artery, including their respective side branches in 84 pts.), 321 (96%) could be evaluated in MDCT. In evaluable arteries, 40/44 significant lesions were detected and absence of occlusion or stenosis exceeding 50% diameter reduction was correctly identified in 258/277 arteries (sensitivity 91%, specificity 93%). The negative predictive value was 98%. Overall accuracy (including unevaluable segments) was 89% (298/336). In a per-patient analysis, 25 of 26 pts. with significant stenoses were identified (sensitivity 96%). With a specificity of 91% (53/58), diagnostic accuracy was 93%.
As compared to previous scanner generations, 64-slice MDCT with routine β-blockade permits the detection of significant coronary artery stenoses with improved evaluability and diagnostic accuracy

2745 Non-invasive coronary angiography with multislice computed tomography angiography in patients presenting with acute chest pain

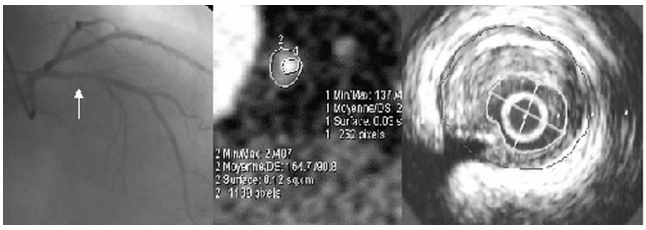
D.R. Coles[1], P. Wilde[2], C. Rogers[3], M. Oberhoff[3], K.R. Karsch[3], A. Baumbach[3]. *[1]Bristol, United Kingdom; [2]Bristol Royal Infirmary, Clinical Radiology, Bristol, United Kingdom; [3]Bristol Royal Infirmary, Bristol Heart Institute, Bristol, United Kingdom*

Background: Multislice Computed Tomography (MSCT) Coronary Angiography has shown potential to detect coronary artery stenoses in selected elective patient groups. The aim of this prospective clinical trial was to assess the accuracy and clinical relevance of MSCT coronary angiography in patients presenting with acute chest pain.
Methods: 120 consecutive patients (mean age 61.9 years, 65% male) underwent Coronary MSCT Angiography (Siemens Sensation 16) before a scheduled conventional coronary angiography (CCA). All patients were admitted to the hospital with acute chest pain. Patients with STEMI and patients requiring immediate cardiac catheterisation were excluded. Further major exclusion criteria were atrial fibrillation and renal impairment.
Coronary MSCT was acquired with a 16 slice CT, using retrospective ECG-gating, 420msec rotation and collimation: 12x1.0mm (n=57) and latterly 16x1.0mm (n=63). Blinded visual assessment of Coronary MSCT to detect coronary artery disease was performed on a 11 segment model after image quality assessment. The accuracy of Coronary MSCT was compared to CCA to detect significant stenoses ($>$50%).
Results: 113 patients underwent both investigations (8 previous CABG, 7 previous stent). The mean heart rate was 61$\pm$9bpm. Prevalence of significant coronary artery disease was 74%. 1243 native segments were assessed by MSCT, of which 22% were non-analyzable (199 non diagnostic, 74 not seen). The majority of non-analyzable segments were in distal and side branch segments (68%). The overall ability of Coronary MSCT to detect the presence of at least one significant stenosis in all native segments had a sensitivity of 92% and specificity 55%, a Positive Predicitive Value 86% and Negative Predicitive Value of 70%. Coronary calcification was a major cause of inaccuracy. In patients without coronary calcification (n=10), MSCT angiography had a Negative Predictive Value of 100%.
Conclusion: In this patient cohort with a high prevalence of coronary disease and high levels of coronary calcification, the accuracy of MSCT coronary angiography was less than in previously reported studies on elective patients. The clinical relevance of this technology to screen and risk stratify patients with acute chest pain is limited.

2746 Quantification of coronary intermediate stenosis using 64-slice computed tomography compared to intravascular ultrasound

C. Caussin[1], S. Ghostine[2], D. Pesenti-Rossi[2], M. Habis[2], C.Y. Angel[3], B. Lancelin[2], J.F. Paul[3]. *[1]C.C. Marie Lannelongue, Service de Cardiologie Interventionelle, Le Plessis Robinson, France; [2]CC Marie Lannelongue, Cardiologie interventionnelle, Le Plessis Robinson, France; [3]C.C. Marie Lannelongue, Radiologie, Le Plessis Robinson, France*

Background: Minimal lumen area (MLA) measured by sixteen slice computed tomography (CT) has shown to have an acceptable correlation with intravascular ultrasound (IVUS), but reproducibility and measurement accuracy were insufficient for clinical use. We aimed to quantify intermediate ambiguous coronary stenosis using MLA with the new 64-slice computed tomography (CT) compared to IVUS.
Methods: Thirty-one patients were prospectively enrolled in the study. Inclusion criteria was a 35 to 60% diameter stenosis on a proximal epicardial artery. All patients had QCA, ECG retrospectively gated 64 slice-CT (Siemens) with 330 ms rotation time and IVUS (40 MHz Atlantis, Galaxy 2, Boston Scientific). All data were analysed by 2 observators independently to the IVUS and QCA findings.
Results: Mean age was 64$\pm$10 y. Clinical presentation was silent ischemia (34%), stable angina (28%) and unstable angina (22%). The lesion analysed was on the LAD in 58%, the left main in 19%, the RCA in 10% and the circumflex in 10%. In 1 (3%) patient CT was not analysed because of artefacts. With IVUS mean MLA was 5.0$\pm$2.7mm^2. Correlation between IVUS MLA and CT MLA was r=0.83 ($p<0.001$). The 95% confidence interval for CT MLA measurement compared to IVUS was [-38%,+34%]. In our population with ambiguous lesion, sensitivity, specificity and accuracy for significant lesion classification using 64 slice-CT compared to IVUS was respectively 94%,81% and 90%.



Angio, 64 slice CT and IVUS comparison

Conclusion: Using MLA measurement 64-slice CT was able to quantify coronary stenosis with a good correlation in comparison to IVUS in patient with intermediate stenosis. 64-slice CT technology seems to improve MLA measurement accuracy compared to 16-slice CT.

2747 Assessment of coronary artery stents by 16-slice computed tomography

M. Gilard[1], J.C. Cornily[1], P.Y. Pennec[1], G. Le Gal[1], M. Nonent[2], J. Mansourati[1], J.J. Blanc[1], J. Boschat[1]. *[1]CHU la Cavale Blanche, Department of Cardiology, Brest Cedex, France; [2]CHU La Cavale Blanche, Radiology, Brest, France*

Purpose: To analyze coronary stents using 16-slice computed tomography (MSCT) in comparison with coronary angiography.
Materials and Methods: 310 patients referred for conventional coronary angiog-

raphy, underwent MSCT on next day (16*0.75 mm cross section; 420 ms rotation; 110 ml contrast agent IV at 4ml/s). The MSCT scan was analyzed by two independent blinded reviewers.
Results: 143 patients had a history of previous stenting (232 stents). 190 (82%) of the 232 stents were detected. Intrastent lumen was interpretable in 126 (64%) of the detected stents Lumen interpretability depended on stent diameter: for stent diameter >3 mm, 81% of lumens were interpretable, as against 51% with < or = 3 mm stent diameter ($p<0.001$). Restenosis detection likewise depended on stent diameter: with small stents (< or = 3mm), sensitivity and specificity of MSCT were 54% and 100% respectively; positive and negative predictive values 100% and 95%. For stents with >3mm diameter, values were 86%, 100%, 100% and 99% respectively.
Conclusion: 16-slice MSCT allows analysis of in-stent lumen in about one half of all stented angioplasties. It performs better when stent diameter is more than 3 mm, and might offer a non-invasive alternative to conventional coronary angiography for monitoring stented coronary arteries. Technical progresses might improve interpretability and hence increase the yield of MSCT in this application.

2748 Assessment of LV function and perfusion using MSCT; correlation with gated SPECT

J.D. Schuijf[1], H.J. Lamb[2], J.W. Jukema[3], P. Dibbets-Schneider[4], M.P.M. Stokkel[4], A. de Roos[2], E.E. van der Wall[3], J.J. Bax[3].
[1]Leiden University Medical Center, Cardiology Department, Leiden, Netherlands; [2]Leiden University Medical Center, Radiology, Leiden, Netherlands; [3]Leiden University Medical Center, Cardiology, Leiden, Netherlands; [4]Leiden University Medical Center, Nuclear Medicine, Leiden, Netherlands

Background: Multi-Slice Computed Tomography (MSCT) is currently used for non-invasive coronary angiography; however, assessment of LV function and resting perfusion is also possible.
Aim: A head-to-head comparison between SPECT perfusion imaging and MSCT was performed to assess LV function and perfusion.
Methods: Consecutive patients (n=17, 16 men, age 60±12 yrs) with previous myocardial infarction underwent both SPECT (during rest and stress) and MSCT. LV end-diastolic and end-systolic MSCT images were reconstructed in the short-axis orientation. LV ejection fraction (LVEF) was calculated (using MASS, Medis, The Netherlands) and regional wall motion abnormalities and perfusion defects were noted. Using a 17-segment model, each segment was assigned a wall motion score (1=normokinesia, 2=hypokinesia, 3=akinesia and 4=dyskinesia) and perfusion transmurality score (0=no perfusion defect, 1=transmurality 1-25% of LV wall thickness, 2=transmurality 26-50%, and 3=transmurality 51-100%). SPECT segments obtained during rest were scored using the same 17-segment model according to a 4-point scoring system: 0=normal (activity >70%), 1=mild-moderate defect (activity 50-70), 2=severe defect (activity 30-50%), 3=absent tracer activity (<30%).
Results: Average LVEF as demonstrated by SPECT and MSCT were 47±9% and 45±11% (r=0.73). Resting perfusion defects were observed on SPECT in 65 of 289 (22%) segments. MSCT demonstrated perfusion defects in 60 (92%) segments correctly, whereas the absence of perfusion defects corresponded in 220 (98%) segments without perfusion defects. The degree of transmurality paralleled the degree of tracer activity inversely; agreements for the individual scores 0-3 were 98%, 71%, 52% and 81% with a total agreement of 91% (kappa-value 0.77, $P<0.001$). In a total of 73 (25%) of segments, abnormal wall motion was present; 16% of segments demonstrated hypokinesia, 10% akinesia and only 1% dyskinesia. In the segments with perfusion defects, abnormal wall motion was demonstrated in 89% segments, whereas normal wall motion was observed in 93% of segments with no perfusion defects.
Conclusion: In patients with previous infarction, the same MSCT data set used for non-invasive angiography can be used to evaluate LV function and perfusion defects, showing excellent correlation with SPECT.

2749 Multislice computed tomography of the coronaries: intraindividual comparison of radiation dose exposure with conventional coronary angiography

A. Deetjen[1], S. Moellmann[1], G. Conradi[1], O. Ekinci[1], J. Hansel[1], A. Kluge[2], C.W. Hamm[1], T. Dill[1]. *[1]Kerckhoff Heart Centre, Cardiology Department, Bad Nauheim, Germany; [2]Kerckhoff-Heart Center, Department of Radiology, Bad Nauheim, Germany*

Background: Multislice CT of the coronaries (MSCTA) is increasingly performed. For the amount of radiation applied in comparison to conventional coronary angiography (CA) only estimations exist. The aim of this study was the intraindividual comparison of the effective radiation dose applied for both techniques MSCTA and CA.
Patients and methods: 56 patients (68 ± 8 years, 49 male, body surface 1,94 ± 0,13 m^2) underwent MSCTA and CA. For MSCTA the standard protocol consisted of pre-monitoring, monitoring, calcium scoring and CT coronary angiography using a 16-slice dedicated CT scanner (rotation time 370 ms, 120 kV, ECG-pulsing). CA was performed using 8 standard projections for LCA and RCA together (lateral, LAO, RAO, and PA) on an actual system with automatic selection of X-ray beam filtration. 50 of 56 patients underwent left ventricular angiography. To compare the radiation doses of both investigations the effective dose was chosen as parameter. Following the guidelines proposed by the European Working Group for the Guidelines on Qualitity Criteria in CT a conversion factor was used for the equation of the effective dose: E = k x DLP. In conventional angiography effective dose were estimated using dose-area product and a conversion factor according to the data published by Le Heron (Le Heron, J.C. Estimation of effetive dose to the patient during medical x-ray examinations from measurments of DAP. Phys Med Biol 1992; 37: 2117-2126) for lateral and posteroanterior exposures in the chest area.
Results: The mean effective dose for MSCTA including pre-monitoring and monitoring scans was 10,36 mSV, s.d. 2,18 mSv (n=56); if calcium scoring was added to MSCTA the dose was 12,67 mSv, s.d. 2,58 mSv (n=45). In comparison the mean effective dose of CA was 3,33 mSv, s.d. 2,42 mSv (n=56). A subgroup of patients (n=10) with bypass grafts were compared in addition. The effective dose for CTA was 12,95 mSv, s.d. 1,75 (n=10). In comparison the mean effective dose of CA was 6,27 mSv, s.d. 4,04 (n=10).
Conclusions: This intraindividual comparison demonstrates that even with new and dedicated cardiac scanners, MSCTA is still associated with a relatively high radiation dose exposure. It is approximatly 3 times more than for CA. The calcium scoring in comparison is a relatively low dose technique. This study emphasizes that indications for MSCTA have to be clearly defined.

NEW FRONTIERS IN CARDIAC POSITRON EMISSION TOMOGRAPHY

2750 Repeatability of cold pressure testing as stimulus for myocardial blood flow response

P.T. Siegrist[1], P. Koepfli[2], S.P. Fleischmann[2], T. Schepis[2], N. Comte[2], C.A. Wyss[2], P.A. Kaufmann[2]. *[1]University Hospital Zurich, Nuclear Cardiology, Zurich, Switzerland; [2]University Hospital Zurich, Nuclear Cardiology, Zurich, Switzerland*

Objectives: Positron emission tomography (PET)allows absolute measurement of myocardial blood flow (MBF; mL/min/g). MBF increase after cold pressure test (CPT) is widely used for the assessment of endothelial function, particularly in smokers. Nevertheless, no data exist on the repeatability of CPT-induced flow increase.
Methods: O15-labeled water and PET were used to measure MBF at rest in 10 young healthy controls (mean age 27±3) and 10 age-matched healthy smokers (mean age 25±3; 4 pack-years, cotinin: 1620±1923 µg/L, FCOHb 2.3±1.1%). After allowing for decay of O15-labeled water MBF was measured while immersion of the left foot into ice water during 2 minutes (CPT 1). After 40 minutes measurement was repeated with immersion of the right foot into ice water during 2 minutes (the change of extremity was chosen to avoid decreased response by habituation).
Results: The comparison of repeated CPT-induced flow reserve showed an excellent repeatability (see table 1) both in young healthy volunteers and in age-matched smokers.

Table 1

	Controls	Smokers	p
Flow increase CPT1	1.45±0.26	1.47±0.28	ns
Flow increase CPT2	1.51±0.45	1.35±0.33	ns
Mean Diference (%)	+4±26	-8±12	ns

Conclusions: CPT-induced changes in MBF as assessed by PET are repeatable in healthy volunteers and in smokers. There were no significant differences in healthy volunteers compared to smokers, probably indicating that at this young age coronary endothelial dysfunction is not yet detectable with this technique.

2751 Multifocal cardiac uptake of [18F]-FDG PET in patients with acute infarction in ischaemic and non-ischaemic heart regions, persistant at 10 weeks

C. Godino[1], C. Messa[2], D. Cianflone[3], A. Margonato[3], N. Cristell[3], V. Leccese[2], F. Fazio[2], A. Maseri[3]. *[1]University Vita-Salute San Raffaele of Milan, Cardiology Department, Milan, Italy; [2]University of Milan Bicocca, Nuclear Medicine, Milan, Italy; [3]University Vita-Salute San Raffaele, Cardiology, Milan, Italy*

Objectives: We investigated cardiac [18 F]-flurodeoxyglucose uptake by positron emission tomography ([18F]- FDG-PET) in fasting patients (pts) with their first acute myocardial infarction (FAMI) and at 3 months follow-up.
Methods: 12 pts (1 female, age 59±10) with single vessel disease, soon after successful primary PTCA and 12 pts (CSA pts, control, 3 females, age 60±8) with uncomplicated chronic stable angina and 3-vessel disease were investigated. Baseline left ventricular ejection fraction (LVEF) of FAMI and CSA pts were 52±10% and 61±3%, respectively. Myocardial [18F]-FDG-PET scan was performed in FAMI pts within 48 hrs after primary PTCA and repeated after 9.6±4.3 weeks, and in CSA pts only at baseline. Plasma levels of glucose, free fatty acid, insulin, hs-CRP, IL-6 and HOMA index were determined.
Results: [18F]- FDG uptake was below intraventricular background (Bg) in all circumferential or longitudinal ventricular slices in CSA pts (mean FDG uptake

index, FUI:0.70±0.2 of Bg). By contrast, 10 out of 12 FAMI pts had an average wall uptake, 1.3 to 3 fold higher of Bg (FUI:1.73±0.40 p<0.0001). In FAMI pts, FDG uptake was heterogeneous, being limited to the culprit area (infarct-related vascular district) in 2 pts, to the non-culprit areas in 2 pts and involving both culprit and non-culprit areas in the remaining 6 pts. On average 60% of segments had an uptake >Bg.
At follow-up, regional cardiac [18F]-FDG uptake remained unchanged in 7 pts, was reduced in 4 and became positive in multiple segments in 1 pt who was negative in the initial study. No FAMI pts developed recurrent instability, during follow-up LVEF was unchanged (55±9%).
Statistically significant differences was only found in IL-6 plasma levels, between FAMI and CSA pts(8.47±6.59 pg/mL vs 2.17±1.18 pg/mL; p<0.003), and in FAMI pts between basal and follow-up (8.47±6.59 pg/mL vs 3.24±1.83 p<0.02).
Conclusion: Massive multifocal, persistent cardiac glucose uptake was observed in the majority of FAMI pts, mostly in areas perfused by non stenosed coronary arteries and normocontractile, possibly related to increases GLUT1 glucose transporter expression and function in ischemic and nonischemic cardiac regions, as a protective response to ischemic injury, previously reported.

2752 Diagnostic value of simultaneous brachial and ankle blood pressure measurements for the extent and severity of coronary artery disease as assessed by myocardial perfusion imaging

Y. Igarashi, T. Chikamori, H. Tomiyama, Y. Usui, S. Hida, H. Tanaka, K. Harafuji, A. Yamashina. *Tokyo Medical University, Department of Internal Medicine II, Tokyo, Japan*

Background: Although simultaneous brachial and ankle blood pressure measurements are simple methods to evaluate atherosclerosis, their diagnostic value for coronary artery disease (CAD) is undetermined. The purpose of this study was to evaluate the diagnostic value of ankle-brachial pressure index (ABI) and brachial-ankle pulse wave velocity (baPWV) for the extent and severity of coronary artery disease as assessed by myocardial perfusion imaging.
Methods and Results: Three hundred thirty four consecutive patients with suspected coronary artery disease, excluding those with previous myocardial infarction or coronary intervention, were evaluated. The magnitude of myocardial ischemia was evaluated by myocardial perfusion imaging. Using a 20-segment model, percent of ischemic segments to total segments were expressed as % myocardium ischemic. In patients with ≤1, 2 and ≥3 coronary risk factors, % myocardium ischemic was 2.7±0.4, 4.0±0.5, 7.9±0.8%, respectively (p<0.0001 for trend). Applying ABI with a cutoff of 1, % myocardium ischemic was similar in patients with ≤1 or 2 risk factors. In patients with ≥3 coronary risk factors, however, those with ABI <1 showed greater % myocardium ischemic than those with ABI ≥1 (10.1±1.3, 6.6±1.0%; p=0.03). No such additional value was observed using baPWV. More importantly, among high-risk patients with ABI <1, who also underwent coronary angiography, significant CAD was found in 88% (28/32) of the patients and multi-vessel CAD in 69% (22/32).
Conclusions: The addition of simultaneous brachial and ankle blood pressure measurements to coronary risk factors help further stratify patients with multiple risk factors. Although this approach is simple, it facilitates the identification of high-risk patients who require aggressive treatment, since >10% myocardium ischemic, usually associated with multi-vessel CAD, is regarded as a scintigraphic indicator for coronary revascularization.

2753 Absolute quantification of subepicardial and subendocardial blood flow in human hibernating myocardium

M.T. Khan[1], P. Punjabi[2], Y. Bouchareb[1], H. Kindler[1], O.E. Rimoldi[1], P.G. Camici[1]. *[1]Imperial College School of Medicine, MRC Clinical Sciences Centre, Faculty of Med., London, United Kingdom; [2]Imperial College, NHLI, London, United Kingdom*

Background: Previous studies using positron emission tomography (PET) for the quantification of regional myocardial blood flow (MBF) have shown that, in the majority of patients (pts), average transmural MBF in hibernating myocardium (HM) is similar to that measured in the myocardium of healthy controls (HC). It is not known, however, if subendocardial (endo) MBF is normal or reduced in human HM. Aim of this study was to quantify subepicardial (epi) and endo-MBF in pts with coronary artery disease and HM and age matched HC.
Methods: Seven pts (aged 64±11 years) and 7 HC (aged 56±4; p=ns vs pts) were studied. HM was defined as severe dysfunction in an area subtended by a stenotic coronary artery with maintained viability demonstrated by PET with F18-fluorodeoxyglucose. In pts and HC, regional MBF was quantified (ml/min/g) using a high resolution PET scanner (ECAT EXACT3D) with oxygen-15 labelled water. MBF in HM was compared with that in a remote (REM) segment with preserved contraction in the same pt and with MBF in HC.
Results: Average transmural MBF was 0.91±0.22 ml/min/g in HB (p=ns vs REM and HC), 0.99±17 ml/min/g in REM and 0.73±0.11 in HC (p<0.05 REM vs HC). Epi-MBF was 0.77±0.17 ml/min/g in HB (p=ns vs REM and HC), 0.86±13 ml/min/g in REM and 0.61±0.15 in HC (p<0.01 REM vs HC). Endo-MBF was 1.24±0.56 ml/min/g in HB (p=ns vs REM and HC), 1.15±27 ml/min/g in REM and 1.00±0.18in HC (p=ns REM vs HC).
Conclusions: The results of the present study do not provide evidence of ongoing underperfusion at rest in human HM and confirm the findings of previous PET studies indicating that average transmural MBF in HM is similar to that measured in REM and in the myocardium of HC. The increased MBF observed in REM is consistent with previous findings showing increased work and oxygen consumption in these regions.

2754 A preliminary clinical study on hypoxia imaging of myocardium with 99m-technetium-HL91 in coronary artery diseases

Y.M. He[1], X.J. Yang[1], Y.W. Wu[2]. *[1]1st affiliated hospital of suzhou university, Cardiology Department, suzhou, China; [2]1st affiliated hospital of suzhou univ, Nuclear Medicine Department, suzhou, China*

Aim: To evaluate the concept of hypoxia imaging of myocardium using simultaneous thallium-201 (Tl-201) and 99mTc-HL91 imaging.
Methods: Twenty mCi 99mTc-HL91 was injected intravenously, and 30 minutes later, 4~5mCi Tl-201 was injected intravenously at peak exercise in anginal pectoris patients. AMI patients repeated the same procedure aforementioned except needing no exercise. All patients underwent imaging immediately, at 3ird and 24th hour, respectively, after injection of Tl-201. Use of separate energy windows allowed simultaneous imaging of 99mTc-HL91 and Tl-201. Semiquatitative/qualitative analysis was performed using a 17-segment model. Immediate and 24-hour-delayed Tl-201 myocardial perfusion images and 3-hour-99mTc-HL91 hypoxia images were analyzed.
Results: 99mTc-HL91 provided pretty discernible hypoxia imaging of myocardial tissues in CAD patients for further myocardial segment analysis. Fifteen CAD patients undergoing dual-isotope imaging had 255 segments in total. There were 109 abnormal segments on the immediate Tl-201 imaging, taking up 43%, and 160 positive segments on the 3-hour-99mTc-HL91 imaging, taking up 63%. There were 40 (partially) reversible segments (ischemic/viable segments) on 24-hour-delayed-Tl-201 imaging and 73 positive segments on 99mTc-HL91 imaging among 109 abnormal segments based on immediate Tl-201 imaging, in which the 40 (partially) reversible segments were all positive of hypoxia imaging. The Tl-201 detection rate was 37%, and the 99mTc-HL91, 67%, with the latter being significantly higher than the former (P=0.0001).

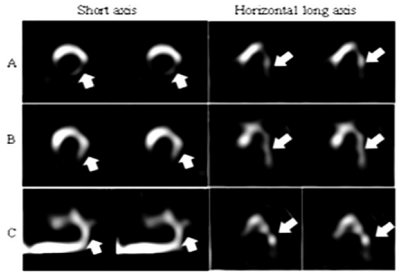


Fig1. A, immediate Tl-201 imaging; B, 24-hour-Tl-201 imaging; C, 3-hour-99mTc-HL91 hypoxia imaging. Note the decreased myocardial perfusion of inferolateral segments was reversible on the 24-hour-Tl-201 imaging, suggesting the presence of the ischemic/viable myocardium tissues, which was found positive on the hypoxia imaging (arrows).

Hypoxia imaging of myocardium tissues

Conclusions: Hypoxia imaging of myocardium may offer a new noninvasive approach for assessment of myocardial ischemia/viability. Large-scale clinical studies are warranted.

2755 Real-time 3-dimensional echocardiography and left ventricular volumes in ischaemic cardiomyopathy: a comparison to single photon emission computed tomography and cardiac magnetic resonance imaging

J. Chan[1], C. Jenkins[2], F. Khafagi[3], L. Du[2], T.H. Marwick[2] on behalf of Cardiac Imaging Group, University of Queensland. *[1]Princess Alexandra Hospital, Medicine (University of Queensland), Brisbane, Australia; [2]Princess Alexandra Hospital, Medicine (University of Queensland), Brisbane, Australia; [3]St Andrew's Hospital, Queensland Diagnostic Imaging, Brisbane, Australia*

Left ventricular (LV) volumes have important prognostic implications in patients with chronic ischemic and dilated cardiomyopathy (IC).
Purpose: We sought to examine the accuracy and reproducibility of real-time 3D echo (RT-3DE) in assessing LV volumes in IC compared to Tl-201 single photon emission computed tomography (SPECT) and cardiac magnetic resonance imaging (MRI).
Methods: Thirty patients with chronic ischemic heart disease (age 62±9 years, 23 men) underwent LV volume assessment with RT-3DE, SPECT, and cardiac MRI. A novel semi automated border detection algorithm was used by RT-3D echo to measure end diastolic volume (EDV) and end systolic volume (ESV). SPECT LV volumes were estimated using a commercial version of the Cedars-Sinai quantitative gated SPECT (QGS) software package. The results of both imaging modalities were compared to MRI as the standard of reference.
Results: RT-3DE and SPECT volumes showed excellent correlation with cardiac MRI (table 1). However, both RT-3DE and SPECT underestimated LV volumes compared to MRI (ESV, SPECT 74±58 ml vs. RT-3DE 95±48 ml vs. MRI 96±54 ml); (EDV, SPECT 121±61 ml vs. RT-3DE 169±61 ml vs. MRI 179±56 ml). The

degree of volume underestimation with RT-3DE was not significant for ESV. The results of RT-3D echo were reproducible with excellent intraobserver (ESV r=0.98, -2±6 ml; EDV, r=0.98, -1±6 ml) and interobserver (ESV r=0.97, -2±6 ml; EDV r=0.95, -3±10 ml) correlations.

Table 1. Comparison of RT-3DE and SPECT to MRI as standard of reference

		Mean Difference ± SD	r r	Regression Equation	p	Standard Error of Estimate
RT-3DE	ESV (ml)	-0.9±18.8	0.94	y=0.83x+15.2	NS	16.9
	EDV (ml)	-10.4±26.4	0.90	y=0.99x-8.5	0.04	26.9
SPECT	ESV (ml)	-22.1±18.6	0.95	y=1.02x-23.7	0.001	18.9
	EDV (ml)	-58.2±28.3	0.89	y=0.97x-53.2	0.001	28.7

Conclusion: RT-3DE is accurate and reproducible in the quantitative assessment of LV volumes in chronic ischemic and dilated cardiomyopathy. RT-3DE is more accurate than SPECT with less underestimation of LV volumes

NEWS ON INFLAMMATION IN CHRONIC HEART FAILURE

2765 Effect of neurohormones, cytokines, and collagen markers on the risk of all-cause mortality: results from the EPHESUS trial

J. Ketelslegers[1], F. Zannad[2], J. Vincent[3], R. Mukherjee[3], M. Rousseau[4] on behalf of EPHESUS Investigators. *[1]University of Louvain, Division of Cardiology, Brussels, Belgium; [2]Clinical Investigation Center INSERM-C, Dommartin-les Toul, France; [3]Pfizer, New York, United States of America; [4]Cliniques Universitaires St-Luc, Department of Internal Medicine, Brussels, Belgium*

In EPHESUS, eplerenone reduced mortality in post-AMI patients with left ventricular systolic dysfunction (LVSD) and heart failure (HF). The effect of baseline levels of biomarkers on risk of all-cause mortality was examined.
Baseline blood samples were collected from 476 patients. Biomarkers included brain natriuretic peptide (nt-proBNP), atrial natriuretic peptide (nt-proANP), endothelin-1, soluble e-selectins, tumor necrosis factor-a (TNF-a), interleukin-6 (IL-6), ultrasensitive C-reactive protein (hsCRP), osteopontin, type I procollagen (PIP), aminoterminal propeptide of type III procollagen (PIIINP), 7S domain of type IV collagen (7SIVC), tissue inhibitor of metalloproteinase (TIMP), and type I collagen (ICTP). Separate Cox's models were fit for each biomarker; for each model the relevant marker was the only explanatory variable.
The predictive strength of the baseline biomarkers for the risk of all-cause mortality is shown in the Table.

Effects of Baseline Values of Biomarkers

Variable	Hazard Ratio	95% Confidence Limit	P-value
nt-proBNP	5.75	3.56, 9.31	<0.0001
nt-proANP	3.05	2.01, 4.64	<0.0001
Endothelin-1	3.44	1.73, 6.83	0.0004
Se-selectins	0.90	0.50, 1.61	0.7
TNF-alpha	0.96	0.64, 1.43	0.8
IL-6	1.67	1.17, 2.38	0.0044
hsCRP	1.36	1.07, 1.72	0.01
Osteopontin	2.15	1.25, 3.71	0.006
PIP	0.20	0.09, 0.43	<0.0001
PIIINP	1.65	0.75, 3.64	0.2
7SIVC	3.84	1.43, 10.35	0.008
TIMP	1.54	0.58, 4.07	0.3
ICTP	3.31	1.92, 5.71	<0.0001

Biomarkers that are associated with HF, endothelial dysfunction, and cardiac remodeling significantly predict all-cause mortality in post-AMI patients with LVSD and HF. Nt-proBNP, nt-proANP, PIP, and ICTP were the strongest predictors of all-cause mortality. Endothelin-1, 7SIVC, IL-6, osteopontin, and hsCRP were also significant predictors of death.

2766 Influence of pentoxifilline in addition to conventional heart failure treatment on neurohormonal profile and immune systems in patients with chronic heart failure

A. Sytchev, S. Nasonova, A. Skvortsov, V. Mareev, Y. Belenkov. *Moscow, Russian Federation*

An important role in the current neurohormonal theory of pathogenesis of heart failure is assigned to proinflammatory cytokines (TNF-a, IL-6). Increased level of TNF-a has been reported in patients with heart failure and associated to the severity of disease. Reducing the level of TNF-a improved the clinical course of disease in experiment, which provided a theoretical basis for elaborating a new trend in therapy for heart failure.
Aim: Studying the effect of addition of pentoxifylline (P) (a drug inhibiting the production of TNF-a) to conventional therapy (CT) (digoxin, diuretics, ACE inhibitors, b- blockers) on neurohormonal status, and circulating plasma levels of TNF-a receptor (p55), and IL-6 in patients with mild-to-moderate chronic heart failure.
Methods: 40 patients with NYHA class I-III heart failure due to ischemic heart disease and idiopathic dilated cardiomyopathy (50%/50%) with ejection fraction below 40% were randomized to 2 groups: 1)CT (n=20) and 2) CT + P (400 mg TID) (n=20). In each group 10 patients with IHD and 10 pts with IDC were randomised. After randomisation two groups were compared by the aetiology, severity of disease, gender, and age. Determination of activity main neurohormons (noradrenaline, aldosterone, plasma renin activity, and brain natriuretic peptide) with soluble TNF-a receptor level (p55) (taking part in realization of biological effects of TNF-a), and IL-6 plasma level determinations were performed at baseline and then 3 months after randomisation.
Results: No statistically significant difference in neurohormonal changes (noradrenaline, aldosterone, plasma renin activity, and brain natriuretic peptide) was found between 2 groups. Significant decrease in TNF-a level from 1592 to 1496 pg/ml (p= 0.042) was revealed in group of combined therapy. The level of IL-6 was not changed in either of groups.
Conclusion: Comparing to CT long-term combined therapy with CT+P dose not have any apparent advantages over CT in terms of controling activity of renin-angiotensin and sympatho-adrenal systems in pts with mild-to-moderate CHF.

2767 Left ventricular dysfunction in Chagas disease cardiomyopathy model treated with Etanercept

V.M.C. Salemi. *University of São Paulo Medical School, Heart Institute (InCor), São Paulo, Brazil*

Background: Chagas' disease affects more than 10 million people in Latin America. It leads to an inflammatory dilated cardiomyopathy in 30% of these patients as a late consequence of infection by protozoan Trypanossoma cruzi, producing worse outcome than other dilated cardiomyopathies. Previous animal studies have shown increased plasma levels of tumor necrosis factor in patients with chronic Chagas' cardiomyopathy. The aim of this study was to evaluate the effect of Etanercept (soluble tumor necrosis factor receptor) on left ventricular (LV) function in Trypanossoma cruzi-infected Syrian hamsters.
Methods: We studied by high-resolution echocardiography 60 female Syrian hamsters, divided into 3 groups: A) 20 control, B) 20 untreated Trypanossoma cruzi-infected, and C) 20 Trypanossoma cruzi-infected treated with Etanercept (2.5 mg/kg 2x/week over 10 weeks). The infected animals were peritonealy inoculated with T cruzi Y strain blood trypomastigotes. Echocardiogram was performed before infection, 8 months after infection (pre-treatment) and 11 months after infection (post- Etanercept treatment). We analyzed LV dimensions in diastole (LVDD) and in systole (LVSD), and fractional shortening (FS).
Results: Etanercept treated group presented a greater ratio of heart weight/body weight ($p<0.05$) and a decrease in survival compared to other groups ($p<0.05$). Results are shown in Table 1.

Table 1. LV assessment before treatment (8 mo. after infection) and after treatment (11mo. after infection)

Groups	LVDD (mm)		LVSD (mm)		FS (%)	
	pre-treat	post-trear	pre-treat	post-treat	pre-treat	post-treat
Control	0.55	0.57	0.33	0.37	40	39
Infected	0.55	0.57	0.33	0.36	37	37
Infected +Etanercept	0.54	0.63*	0.35	0.50*	39	22*

Conclusions: Etanercept treatment in experimental Chagas' disease cardiomyopathy increased cardiac dilation, LV dysfunction and mortality. This drug should be used with caution in patients with Chagas' disease.

2768 Increased toll-like receptor 4 expression on blood monocytes in patients with chronic heart failure

G. Foldes, S. von Haehling, D. Okonko, E.A. Jankowska, P. Poole-Wilson, S.D. Anker. *Imperial College NHLI, Department of Clinical Cardiology, London, United Kingdom*

Innate immunity activation mediated by myocardial Toll-like receptors (TLRs) is involved in cardiovascular disease. However, the importance of TLR4 and TLR2 on peripheral white blood cells in human chronic heart failure (CHF) is not known. In this study, 20 patients with CHF due to coronary heart disease or dilated cardiomyopathy (66±3 years, NYHA class: 2.2±0.1, LVEF: 29±2, mean±SEM) and 12 healthy age-matched controls were enrolled. As assessed by flow cytometry analysis on whole blood settings, TLR4 and TLR2 expressions were detectable on CD14+ monocytes, but not on other leukocytes. We have shown that baseline monocyte TLR4 expression was significantly higher in CHF patients compared to healthy controls (mean fluorescence intensity, 7.4±1.5 vs. 4.2±1.0, $P<0.05$). Monocyte TLR4 expression was markedly higher in CHF due to coronary heart disease than to dilated cardiomyopathy (9.2±2.8 vs. 5.53±1.4, $P<0.05$), suggesting that changes in TLR4 expression may also be due to the primary disease underlying heart failure. Ex vivo administration of lipopolysaccharide (LPS, 10 ng/ml), an exogenous ligand of TLRs, caused a 3-fold ($P<0.001$) increase in TLR4 expression at 3 hours, similarly in CHF patients and healthy subjects. The increase in the number of TLR4-expressing cells by LPS tended to be higher in CHF than healthy controls (2.8-fold vs.1.8-fold, P=0.3). In contrast to TLR4, we found that monocyte TLR2 expression was decreased 2.2-fold in CHF patients (14±5 vs. 5.9±0.7, $P<0.05$) and LPS caused only a moderate increase in TLR2 expression (1.6-fold, $P<0.05$). These results are the first to show that TLR4 and TLR2 are differentially regulated in heart failure. Altered innate immune response via monocyte TLR signalling system may contribute to the pathophysiology of human CHF.

2769 High prevalence of a proinflammatory and a procoagulant state in patients with congestive heart failure

R. Marcucci[1], F. Giannotti[2], M. Baldi[2], C. Nozzoli[3], S. Del Pace[2], A. Michelucci[2], R. Abbate[2], G.F. Gensini[2]. *[1]University of Florence, Cardiology Dept., Firenze, Italy; [2]University of Florence, heart and vessels, Florence, Italy; [3]AOU Careggi, Medicina Generale, Florence, Italy*

Heart Failure (HF) is associated with a higher risk for thromboembolic complications. The pathophysiology of thromboembolism is multifactorial but increasing evidence points to the fulfillment of Virchow's triad (abnormalities of blood flow, blood constituents and vessel wall abnormalities) for thrombogenesis in HF. Scarse data are available on the possible role of hypercoagulability in conferring an increased thrombotic risk in HF. In addition, data are available on the possible role of a proinflammatory state in the pathogenesis of HF, but no study has investigated the possible association between inflammation and hypercoagulability in HF. Aim of our study was to investigate in patients with HF: 1) the clotting activation by measuring D-dimer (DD) levels and Thrombin-antithrombin complexes (TAT); 2) the inflammatory state by measuring interleukin (IL6) and C reactive protein (CRP) levels. We studied 155 patients with HF (98 M/57 F; 72.7±10.8 yrs) and 150 healthy subjects as controls, comparable for age and sex (95 M/55 F; 72.7±10.8 yrs). 42 patients were in class NYHA II, 61 were in class NYHA III and 52 in IV. DD and TAT levels were significantly higher in patients than in controls [DD:399 (126-4885) ng/mL versus 101 (62-325) ng/mL, $p<0.01$; TAT: 4.6 (0.5-103) μ/mL versus 2.5 (0.3-5.6) μ/L, $p<0.01$]. 107/169 (63.3%) patients had DD levels above the 95th percentile of controls (250 ng/mL) and 94/155 (60.6%) patients had TAT levels above the 95th percentile of controls (4.1 μg/L). DD and TAT levels were significantly higher ($p<0.05$) in the IV class NYHA with respect to the II and III. CRP and IL6 levels were significantly higher in patients than in controls [CRP:10 (0.7-21) mg/L versus 1.9 (0.8-5.4) mg/L,$p<0.01$; IL6: 8.9 (0.9-51.5) pg/mlL versus 4.6 (0.5-12) pg/mL,$p<0.01$]. pro-BNP levels were significantly higher than in controls [3249 (52-154126) pg/mL vs 214 (80-354) pg/mL]. We demonstrated a significant correlation between DD and CRP ($r=0.45$;$p<0.001$); DD and IL6 ($r=0.42$,$p<0.001$); TAT and CRP ($r=0.41$, $p<0.001$); CRP and pro-BNP ($r=0.37$,$p<0.01$); IL6 and pro-BNP ($r=0.37$; $p<0.004$); DD-pro.BNP ($r=0.56$; $p<0.001$). These results demostrate the high prevalence of hypercoagulability in HF which is associated with a proinflammatory state and prompt clinical trials addressed to evaluate the use of antithrombotic therapy in HF patients.

2770 Screening of circulating cytokines for novel biological markers in patients with congestive heart failure

T. Tamura[1], Y. Furukawa[1], K. Ono[2], T. Kita[1], T. Kimura[1]. *[1]Kyoto University, Department of Cardiovascular Medicine, Kyoto, Japan; [2]Kyoto Medical Center, Division of Translational Research, Kyoto, Japan*

Background: Chronic myocardial inflammation can lead to myocardial hypertrophy and fibrosis, which are typical pathology of human failing heart. A number of cytokines play important roles in inflammation, and thus, presumably contribute to the pathophysiology of congestive heart failure (CHF). Although increased circulating levels of some inflammatory cytokines have been indicated in CHF, many other cytokines have not been fully examined because of their extensive number.
Purpose: To determine potential circulating markers of CHF by screening serum levels of a variety of cytokines and cytokine receptors.
Methods: Serum levels of 124 cytokines and soluble cytokine receptors were screened in each of 16 subjects by antibody array or ELISA (for adiponectin and resistin). Nine of 16 subjects were CHF patients with an average LVEF of 29% and the other 7 subjects were controls with normal left ventricular function. Age, male:female ratio and body mass index were not significantly different between the groups. Proteins analyzed included inflammatory cytokines and soluble receptors such as TNF-a, sTNF-RI and sTNF-RII that have been reported to be increased in the sera from CHF patients. In antibody array assay, densitometric value of each target protein was normalized to an internal positive control and expressed as relative expression. Data were statistically analyzed by Student's-t test, if the values distributed parametrically, or by Mann-Whitney U test, if the values distributed non-parametrically.
Results: Circulating levels were significantly increased in CHF relative to control subjects for only 3 of 124 molecules: adiponectin (CHF vs. control = 11.2±1.7 vs. 5.4±1.1 mg/mL; mean+SEM, $p<0.05$) an adipocytokine that may counteract cardiac hypertrophic stimuli; eotaxin-3 (9.9±2.9 vs. 1.0±0.5, $p<0.05$) an unique chemokine that not only stimulates chemotaxis of eosinophils and Th2 lymphocytes but acts as a natural antagonist on CCR1, CCR2 and CCR5; amphiregulin (3.9±1.4 vs. 0.3±0.3, $p<0.05$) a cytokine produced by activated mast cells. No molecule indicated a significant decrease in CHF relative to controls.
Conclusion: Adiponectin, eotaxin-3 and amphiregulin were determined as potential circulating markers of CHF by screening of 124 cytokines and soluble receptors in the sera of CHF patients and control subjects. The clinical significance of these molecules as biological markers should be evaluated in a large scale prospective study. Screening of serum protein levels using antibody array may be useful for determining potential biological markers for cardiovascular diseases.

FROM METABOLIC ABNORMALITIES TO DIABETES AND CHRONIC HEART FAILURE

2771 Clinical impact of metabolic syndrome on cardiac events in survived patients with acute myocardial infarction

D. Nakatani, H. Sato, Y. Sakata, K. Kinjo, H. Mizuno, M. Shimizu, M. Hori on behalf of Osaka Acute Coronary Insufficiency Study (OACIS) Group. *Osaka University Graduate School of Medicine, Internal Medicine and Therapeutics, suita, Japan*

Background: Although several epidemiologic studies have reported that metabolic syndrome (MetS) is a higher risk of morbidity and mortality in the primary prevention setting, few data are available regarding the clinical impact of MetS after acute myocardial infarction (AMI).
Methods: To investigate the clinical impact of MetS on cardiac events after AMI, we prospectively studied 3,858 survivors after AMI registered in the Osaka Acute Coronary Insufficiency Study (OACIS). MetS was defined by modified National Cholesterol Education Program criteria.
Results: The frequency of MetS was 32.1%. The mean follow-up period in this study was 851±630 days. The long-term probability of cardiac events (composite of cardiac death and non-fatal reinfarction) was higher in patients with MetS than those without it (7.7% vs. 5.3%, P=0.002). After adjustment for baseline characteristics, MetS was an independent predictor of subsequent cardiac events after AMI (hazard ratio (HR); 1.64, 95% CI; 1.18 to 2.28, P=0.003). In addition, the adjusted HRs for cardiac events increased with the number of metabolic abnormalities: 1.0 (reference) for a metabolic abnormalities of 0; 1.00 (95% CI; 0.56 to 1.80, P=0.998) for 1; 1.30 (95% CI; 0.75 to 2.25, P=0.357) for 2; 1.76 (95% CI; 1.00 to 3.10, P=0.049) for 3; 2.03 (95% CI; 1.00 to 4.13, P=0.049) for 4/5 (P=0.001 for trend). By multivariate linear regression analysis, the number of metabolic abnormalities was independently and positively associated with log translated high sensitive C-reactive protein (hs-CRP) measured at mean 25 days after the onset of AMI (P=0.004).
Conclusions: MetS is an independent predictor of subsequent cardiac events after AMI. MetS seems to be associated with a higher risk of cardiac events in the secondary as well as in the primary prevention setting, probably in relation to the elevated CRP.

2772 Metabolic syndrome is associated with various echocardiographical markers of diastolic dysfunction

F. Raoux[1], R. Dumaine[1], F. Lamaison[2], C. Dourmap[2], F. Pousset[1], R. Isnard[1], D. Thomas[1]. *[1]Pitie Salpetriere hospital, cardiology, Paris, France; [2]Pitié-Salpêtriere, Department of endocrinology, Paris, France*

Purpose: Recent observations suggest that standard Doppler indexes of transmitral filling (E/A ratio, isovolumetric relaxation time IVRT) are altered among patients presenting with a metabolic syndrome (MS). We sought to further assess diastolic function of patients with MS using tissue Doppler imaging (TDI) of the mitral or tricuspid annulus, as well as M-mode Doppler flow propagation velocity (Vp) and compare it to diastolic patterns among control patients.
Methods: Echocardiographical characteristics were assessed among 88 patients without any cardiac disease (44 patients with MS and 44 patients without MS, matched for age and gender). The patterns of pulsed-wave transmitral flow (E wave velocity, A wave velocity and duration, IVRT), Vp, E/Vp ratio, pulmonary veins flow as well as DTI of lateral mitral (peak early diastolic E' and peak atrial systolic A' motion velocities) and tricuspid annulus (peak early diastolic E'w and peak atrial systolic A'w motion velocities) were assessed.
Results: Mean age was similar between the 2 groups (55,3 ± 8,02 vs. 50,5 ± 15,7 years, p=NS). Markers of diastolic function were all significantly different between patients with and without MS (table 1).

Table 1

	MS group (n=44)	Control group (n=44)	p
E/A ratio	0.95±0.30	1.22±0.43	0.001
IVRT (ms)	110.95±22.86	83.47±20.57	< 0.0001
E-1/2 deceleration time (ms)	244.90±64.88	146.36±54.74	< 0.0001
Mitral A wave duration (ms)	139.20±17.10	120.54±17.60	< 0.0001
Pulmonary vein A wave duration (ms)	117.74±24.17	105.51±16.70	0.01
E'/A' ratio	0.93±0.36	1.38±0.61	< 0.0001
E/E' ratio	5.10±1.62	4.40±1.33	0.02
E'w/A'w ratio	0.80±0.23	1.04±0.31	0.0001
Vp (cm/s)	52.00±12.5	63.90±17.40	0.0006
E/Vp ratio	1.36±0.43	1.14±0.42	0.03

Conclusion: Diastolic function as assessed by pulsed-wave transmitral flow as well as DTI and M-mode Doppler flow propagation velocity is altered among patients presenting with a metabolic syndrome as compared with control patients.

2773 Efficacy of long-term combined therapy with angiotensin converting enzyme inhibitor and angiotensin receptor blocker in patients with congestive heart failure and diabetes mellitus

K.G. Adamyan, L.R. Tumasyan, A.B. Nargizyan. *Institute of Cardiology, Yerevan, Armenia*

Background: It has been well established, that in patients (pts) with congestive heart failure (CHF) diabetes mellitus (DM) is associated with higher morbidity and mortality, despite advances in therapy. However, it remains controversial, whether prognosis distinguishes between CHF patients with and without left ventricular (LV) systolic dysfunction and whether combined therapy with angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) reduces morbidity and mortality in diabetic CHF pts.
The aim of study was to assess the efficacy of long-term combined therapy with perindopril (P) and eprosartan (E) in pts with preserved and deteriorated systolic function with III NYHA class CHF of ischemic origin and DM.
Methods: 48 pts (age 58.3±1.7) with type II DM and 44 non-diabetic pts (age 59.2±1.4) with an echocardiographic diagnosis of cardiomyopathy (LV end-diastolic dimension >60 mm, ejection fraction<35%) and 42 pts (age 63.8±2.2) with type II DM and 44 non-diabetic pts (age 65.6±2.1) with preserved systolic function were prospectively studied for an average 36±1.8 months. These clinically stable pts were randomly assigned to groups receiving and non-receiving E (up to 600 mg) in addition to P (up to 8 mg) and diuretics.
Results: The 3-year mortality [45.8% vs. 31.8%; relative risk (RR)=0.76, $p<0.05$] and hospitalization rate (81.3% vs. 61.4%; RR=0.84, $p<0.05$) were higher in diabetic pts with DCM compared with non-diabetic pts. Similarly, DM was significantly associated with higher 3-year mortality (38.1% vs. 22.7%; RR=0.76, $p<0.05$) and hospitalization rate (78.6% vs. 54.5%; RR=0.84, $p<0.05$) in pts with preserved LV systolic function. Combined treatment with P and E has resulted to reduction of 3-year mortality (34.8% vs. 25%; RR=0.71, $p<0.05$) and hospitalization rate (66.4% vs. 52.3%; RR =0.81, $p<0.05$) in pts with and without LV systolic dysfunction, respectively. The event-free analysis showed a lower probability of mortality (RR reduction at 23% and 28%) and hospitalization rate (RR reduction at 19% and 22%) in pts without and with systolic dysfunction, respectively, treated with P+E compared to pts not treated with E ($p<0.01$ for all), regardless the presence of LV systolic dysfunction.
Conclusion: DM worsens the prognosis of CHF pts with both preserved and deteriorated systolic function. Treatment with P+E provides similar prognostic benefit in diabetic pts with ischemic CHF, regardless of presence of LV systolic dysfunction. Therefore combined therapy with ACEI and ARB should be considered in all patients with ischemic CHF and DM.

2774 The incidence of obesity after heart transplantation and its correlation with the developement of new onset diabetes in a cohort of 307 patients over a study period of 10 years

J. Garcia-Lara[1], M.G. Crespo-Leiro[2], M.J. Paniagua-Martin[2], I.P. Garrido-Bravo[2], J. Muñiz[3], G. Aldama-Lopez[2], P. Piñon-Esteban[2], A. Castro-Beiras[2]. *[1]A Coruna, Spain; [2]Servicio de Cardiologia, Hospital Universitario Juan Canalejo, A Coruña, Spain; [3]Universidad de A Coruña, Instituto de Ciencias de la Salud, A Coruña, Spain*

New onset diabetes (NOD), a frequent complication after heart, transplantation (HT) has been shown to be related to immunosuppression (IS). The correlation of obesity with NOD, after controlling for immunosuppressive medication dose, is unknown.
Objective: Determine the incidence of obesity after HT, its relation with total steroid dose and its correlation with the development of NOD.
Patients and Methods: Retrospective analysis of 307 patients with the following characteristics: older than 18 years, >1 year survival after HT and diabetes free before HT. We estimate the presence of obesity according to the BMI: 30- 34 mild obesity (MiO), 35-40 moderate obesity (MoO), 40-45 severe obesity (SO), >45 morbid obesity (MorO). We determine the prevalence of NOD at 1, 5 and 10 years after HT.
Results: Mean age was 55 years, 84% males. Prevalence of MiO, MoO, SO and MorO at 1year after HT was 30%, 18%, 4%, 0.7% respectively. At 5 years 35%, 25%, 5% and 3% respectively. At 10 years 22%, 26%, 4% and 7% respectively. After a mean observation period of 68 months, 23% of patients developed NOD. The statistical analysis showed a correlation between the BMI and development of NOD at 5 years after adjusting for steroid cumulative dose, IS regime, sex and age (OR 1.11; CI 1.03- 1.22; p = 0.01).

Table 1: Obesity prevalence in our serie

Obesity	1 Year	5 Years	10 Years
Mild	30%	35%	22%
Moderate	18%	25%	26%
Severe	4%	5%	4%
Morbid	0.7%	3%	7%

Conclusion: In a large cohort of HT recipients, the prevalence of moderate obesity or more (BMI > 30) at 1, 5 and 10 years after HT is 23%, 33% and 37% respectively. An increased BMI is associated with NOD development at 5 years after heart transplantation.

2775 Insulin sensitivity in non-obese patients with congestive heart failure is related to concentration of interleukin 6

I. Wojtkowska[1], K. Kaminski[2], M. Zelachowska[1], B. Szepietowska[3], M. Szelachowska[3], W.J. Musial[2]. *[1]Medical University in Bia[3]ystok, Department of Cardiology, Bia[3]ystok, Poland; [2]Medical University in Bialystok, Department of Cardiology, Bialystok, Poland; [3]Medical University, Dept. of Endocrinology and Diabetology, Bialystok, Poland*

Interleukin 6 (IL6) is a pleiotropic cytokine involved in inflammatory response and insulin resistance in obese patients. Its increased concentration in patients with congestive heart failure (CHF) is a marker of poor prognosis. Recent studies have revealed increased insulin resistance in patients with CHF. It is not known, however, whether IL6 plays a role in insulin sensitivity in non-obese patients with heart failure.
Aim: We have performed a pilot study to investigate the relationship between indices of insulin sensitivity and IL6 concentrations in patients with CHF.
Material and Methods: Fifteen non-obese males with stable moderate CHF (NYHA class II and III) and 21 healthy, age and BMI matched male controls were enrolled to the study. People with known diabetes, impaired glucose tolerance, current or recent infection were excluded from the study. Patients had oral glucose tolerance test (OGTT) performed and glucose and insulin concentrations measured. Indices of insulin sensitivity: serum glucose and insulin in OGTT, sigma insulin and homeostasis model assessment (HOMA) were calculated. Fasting IL6, sIL6R and sgp130 concentrations were assessed using ELISA kits (R'n'D Poland).
Results: Patients with CHF group presented significantly higher concentration of IL6 than the control group (3.1 ± 2.2 pg/mL vs 1.8 ± 1.1 pg/mL respectively $p<0.05$). In this group of patients IL6 concentration positively correlated with HOMA and the concentration of insulin in 120th minute of OGTT ($r=0.57$ $p<0.005$ and $r=0.79$ $p<0.05$ respectively). No correlations of insulin sensitivity indices with IL6 soluble receptors were found.
Conclusion: Insulin sensitivity in non-obese patients with CHF is related to the concentration of IL6. Hence, this cytokine may be involved in the pathogenesis of insulin resistance in patients with heart failure.

2776 Glycemic control and treatment patterns of patients with heart failure

W.H.W. Tang[1], A. Jain[2], H. Miller[3], C.M. Harris[2], R.C. Starling[4], J.B. Young[4]. *[1]Gates Mills, United States of America; [2]Cleveland Clinic Foundation, Information Technology, Cleveland, United States of America; [3]Cleveland Clinic Foundation, Internal Medicine, Cleveland, United States of America; [4]Cleveland Clinic Foundation, Cardiology, Cleveland, United States of America*

Background: Glycemic control has important impact on clinical outcomes for cardiac patients. However, data regarding long-term glycemic control and treatment patterns of patients with chronic heart failure and diabetes mellitus in the contemporary era are lacking.
Methods: We reviewed 617 consecutive ambulatory patients with chronic heart failure and type 2 diabetes mellitus seen at outpatient cardiology and internal medicine clinics, with hemoglobin A1c (HbA1c) testing between 1999-2004. Patients who underwent cardiac transplantation were excluded. Clinical, demographic, laboratory and survival data were extracted from routinely-employed electronic medical records. Adequate glycemic control was defined as HbA1c <7mg/dL. Sequential HbA1c measurements were collected over a 3-year period of follow-up.
Results: In our patient cohort at baseline (mean age 64 ±12 years, 65% male), 314 patients (51%) had inadequate glycemic control, where 235 patients (38%) had HbA1c levels between 7-9.9 mg/dL, and 79 patients (13%) had HbA1c levels =10 mg/dL. Among the 552 patients who had at least one 2-year follow-up HbA1c assessment, 301 (55%) had inadequate glycemic control. The average HbA1c level was 7.6 mg/dL and remained constant during the 2 years of follow-up. On average, HbA1c testing was performed 3 times during a 2-year period. During the 3-year follow-up, 117 patients with baseline HbA1c <7 mg/dL (39%) experienced worsening glycemic control, while 100 patients with baseline HbA1c =7 mg/dL (32%) showed improvement in glycemic control. Improvement in glycemic control is associated with less hospitalization and mortality. In our cohort, 48% used insulin, 24% used sulfonylurea drugs, 12% used metformin, and 7.7% used thiazolidinediones. Over 50% of patients who showed improvement in glycemic control required conversion to insulin therapy.
Conclusions: Inadequate glycemic control is prevalent in ambulatory patients with chronic heart failure and concomitant type 2 diabetes mellitus. The clinical significance and predictors of inadequate glycemic control needs further exploration.

BETA-RECEPTORS AND BETA-BLOCKERS: ANY NEWS?

2777 How does nebivolol improve outcome in patients with diastolic heart failure? Results of the SENIORS echocardiographic substudy

S. Ghio[1], G. Magrini[1], A. Serio[1], F. Fucilli[2], A. Ronazeki[3], P. Karpati[4], P.A. Poole-Wilson[5], L. Tavazzi[1] on behalf of the SENIORS investigators. *[1]Policlinico S Matteo, Division of Cardiology, Pavia, Italy; [2]Arcispedale S.Anna, Cardiology Department, Ferrara, Italy; [3]Péterfy Hospital, Budapest, Hungary; [4]St Stepan Hospital I, Budapest, Hungary; [5]Imperial College, Cardiac Medicine, BH found.S Marks, London, United Kingdom*

Background: Although preserved ventricular function (diastolic heart failure) is present in a sizeable proportion of all heart failure patients, much uncertainty exists in the treatment of this syndrome. The SENIORS trial recently demonstrated that nebivolol reduces the composite risk of all cause mortality or cardiovascular hospital admission in elderly patients with chronic heart failure and, importantly, that ejection fraction did not influence the clinical effects of nebivolol.
Aim: The present study sought to determine whether nebivolol improves systolic and/or diastolic left ventricular (LV) function in patients with predominantly diastolic heart failure.
Methods: The echocardiographic substudy of the SENIORS trial randomised 103 patients in 29 European centers; 44 had an ejection fraction (EF) =35% and 59 had an EF >35%. LV end-diastolic volume (EDV), EF, mitral valve E/A ratio and E wave deceleration time were assessed at baseline and after 12 months. Echocardiograms were submitted to a core laboratory for quantitative analysis. Each parameter was measured - blinded to treatment - three times, and the average value was taken as a data point.
Results: in patients with systolic heart failure (EF 27.4% and EDV 218 ml at baseline) nebivolol improved EF (estimated difference 4.7%, 95%CI: 1.4-8, p=0.006) and reduced EDV (estimated difference -22.3ml, 95%CI: -39-4.3, p=0.015) but no changes were observed in E/A ratio or E deceleration time. In patients with predominantly diastolic heart failure (EF 51.4% and EDV 134 ml at baseline) no significant changes were observed in either systolic or diastolic parameters.
Conclusions: Nebivolol induces significant reverse remodelling effects in heart failure patients with advanced systolic LV dysfunction. The absence of detectable changes with standard echocardiography in the group with predominantly diastolic heart failure necessitates another hypothesis for the improvement in outcome in such patients.

2778 Comparative effects of nebivolol versus carvedilol on left ventricular function in patients with dilated cardiomyopathy – a 12 month study

A.P. Patrianakos[1], F.I. Parthenakis[1], E.A. Zacharis[1], G.F. Diakakis[1], M. Homatidis[1], D. Georgala[1], P.E. Vardas[2]. *[1]Heraklion University Hospital, Cardiology Dept., Heraklion, Crete, Greece; [2]Heraklion University Hospital, Department of Cardiology, Heraklion, Greece*

Purpose: The benefits of b-blockers in the treatment of patients with chronic heart failure (HF) has been demonstrated, but there is evidence of differential effects among them favoring the third generation non-selective b-blocker Carvedilol. Nebivolol a new, third generation, selective beta 1- blocking agent has not been adequately studied in these patients. We compared the efficacy of Nebivolol and Carvedilol on Left Ventricular (LV) function in patients with Non-Ischemic Dilated Cardiomyopathy (NIDC).
Methods: Sixty-five clinical stable patients, with angiographically proven NIDC, NYHA functional class II-III, LV Ejection Fraction(EF) <40%, on conventional HF treatment were randomized to Nebivolol or Carvedilol (target dose 5 mg once daily or 25 mg b.i.d., respectively) treatment. An echocardiographic study and exercise test with Naughton protocol were performed at baseline, 3 and 12 months after on all patients.
Results: Thirty-four pts were assigned to receive Nebivolol and 38 to receive Carvedilol.
During the 12 month follow-up 4 patients (11.7%) discontinued Nebivolol, while 3 pts (7.8%) stopped Carvedilol. We evaluated 65 pts, (58.3 ±9.9 y), with no significant baseline differences concerning age, sex, NYHA functional class or LVEF. At the 3 month follow-up. patients on Nebivolol or Carvedilol displayed significant improvement in NYHA class (2.14 ±0.29 vs2.52±0.48,p=0.02 and 2.25±0.44 vs 2.55±0.51, p=0.05), an increase in LVEF (35.9±11 vs 31.1 ±8,4%, p=0,001 and 34.5 ± 8.4 vs 27.5±7.4,p<0.001respectively) compared to baseline, without any significant further improvement during follow-up. However the inter-group analysis showed that patients in the Carvedilol group showed a greater increase in LVEF at 3 months (p=0.057) which became significant at the 12 month follow-up (35±31% vs 20±19%, p=0.03) compared to Nebivolol patients. Diastolic dysfunction began to regress to earlier stages in Carvedilol patients after 3 months of treatment (p=0.057) with a significant difference at 12 months treatment (p=0.005). In the Nebivolol group, a significant improvement in the improvement of diastolic dysfunction was found at the 1 year follow-up(p=0.02).
Conclusion: Both Nebivolol and Carvedilol treatment appears relatively safe with beneficial effects on LV systolic and diastolic function in pts with NIDC at 12 months treatment. However, Carvedilol exhibits more favorable effects on LV function than Nebivolol in NIDC patients.

2779 Increased gene expression of collagen type I and III in dilated cardiomyopathy is reduced by beta-receptor blockade

J. Shigeyama[1], Y. Yasumura[1], A. Sakamoto[2], Y. Ishida[3], T. Fukutomi[4], M. Kitakaze[1], K. Miyatake[1]. *[1]National Cardiovascular Center, Division of Cardiology, Suita, Japan; [2]National Cardiovascular Center, Division of Biotechnology, Suita, Japan; [3]National Cardiovascular Center, Division of Radiology, Suita, Japan; [4]Nagoya City University Graduate School, Department of Internal Medicine, Nagoya, Japan*

Background and Objectives: β-Blocker is now widely used for congestive heart failure including dilated cardiomyopathy (DCM). The objective of this study is to elucidate its molecular effects on DCM with special focus on collagen synthesis.
Methods: For DCM patients, carvedilol (10 mg bid, n=12) or bisoprolol (2.5 mg bid, n=5) were administered. Before and 4 months after the b-blocker therapy, cardiac catheterization was performed. Washout rate (WR) of ^{123}I-metaiodobenzylguanidine from the heart was used as an indicator of cardiac sympathetic nerve activity (SNA). From the right ventricular muscle biopsied, total RNA was extracted to synthesize cDNA mixture. By using real-time RT-PCR (ABI7700), the cDNA amounts of the following genes were normalized to that of GAPDH: collagen type I and III (Col I and Col III), transforming growth factor-β1 (TGF-β1, a collagen stimulator) and hepatocyte growth factor (HGF, a collagen inhibitor). The amount of a certain cDNA of interest was determined relative to that in the standard cDNA mixture, which was synthesized from normal heart total RNA (Invitrogen).
Results: End-diastolic volume index (153±32 vs. 113±23ml/m^2, p<0.01), left ventricular ejection fraction (21±7 vs. 35±9%, p<0.01), plasma BNP concentration (165±146 vs. 45±79pg/ml, p<0.01), and WR (53±14 vs. 42±13%, p<0.01) significantly improved 4 months after the administration of β-blockers. The mRNAs expression levels of both Col I (1.08±0.72 vs. 0.65±0.26, p<0.05) and Col III (2.06±1.81 vs. 1.05±0.74, p<0.05) were significantly reduced by β-blocker. Col I (r=0.560, p<0.05) and Col III (r=0.630, p<0.01) expressions correlated with WR before β-blocker treatment. The extents of changes in both Col I (r=0.813, p<0.01) and Col III (r=0.619, p<0.01) mRNAs expressions were positively correlated with that in TGF-β1. Moreover, the extent of changes in TGF-β1 (r=0.606, p<0.05) mRNA expression correlated with that in WR. No negative correlations were observed with HGF. In 6 out of 17 patients, we were able to extract whole homogenate protein as well as total RNA, the protein expression levels of TGF-β1 (77.1±42.8 vs. 57.2±41.5, p<0.05) were significantly reduced by β-blocker.
Conclusions: Elevated cardiac SNA is considered to induce upregulation of Col I and Col III genes, which is reduced by β-blocker, in patient with DCM. TGF-β1 is a candidate mediator for this signaling pathway. This study provides a novel rationale for β-blocker therapy for DCM.

2780 Higher mortality in patients with heart failure and Gln27Glu polymorphism of the beta-2 adrenergic receptor gene

Mansur, A.C. Pereira, R.S. Fontes, R.A. Canzi, A.C. Pereira-Barretto, F. Araujo, J.E. Krieger. *Heart Institute (incor) Hc Fmusp, Clinical Division, São Paulo, Brazil*

Previous studies suggested that polymorphisms in the beta-2 adrenergic receptor gene may be associated with prognosis in patients with heart failure. At least three functional polymorphisms in the beta-2 adrenergic receptor gene were identified: Arg16Gly, Gln27Glu, and Thr164Ile. The aim of the present study was to test the hypothesis that these functional polymorphisms may be associated with disease severity and increased mortality in a cohort of patients with heart failure of different etiologies.
Methods: We studied prospectively 503 patients with heart failure of different etiologies (idiopatic 37.3%, ischaemic 28.2%, hypertensive 20%, Chagas' disease 11.9%,alchoolic 2.6%). Arg16Gly, Glu27Gln and Thr164Ile polymorphisms were genotyped in all patients. We compared genotype frequencies of the studied polymorphisms with genotype distribution in a control population and with baseline clinical and echocardiographic variables of the patients. Kaplan-Meier survival curves were constructed comparing the different genotypes. Mortality risk was assessed with a Cox proportional hazards model adjusted for other covariates associated with increased mortality in patients with heart failure.
Results: Studied polymorphisms were in Hardy-Weinberg equilibrium. The studied polymorphisms were not more frequent in patients as compared to controls. There was no association of the studied polymorphisms with the etiologies of heart failure. Mortality was higher for patients harbouring the Glu27 allele (p=0.017). In addition, the Glu27 allele was still significantly associated with increased mortality (RR = 1.7, p=0.05) in a multivariate Cox regression analysis even after adjustment for age, gender, body mass index, etiology of heart failure, baseline ejection fraction on echocardiography, serum sodium and therapy with angiotensin converting enzyme inhibitors and with betablockers.
Conclusions: Mortality in this series of patients with heart failure was associated with beta-2 adrenergic receptor gene Gln27Glu polymorphism. Knowledge regarding the interaction of specific genetic profiles with prognosis may add to our current approach in the care of patients with heart failure.

2781 Clinical significance of beta-adrenergic receptor polymorphisms in the patients with chronic heart failure

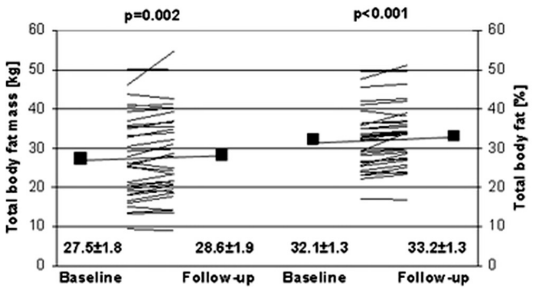
M. Metra[1], S. Nodari[1], L. Covolo[2], N. Pezzali[1], C. Zani[2], U. Gelatti[2], G. Nardi[2], L. Dei Cas[1]. *[1]Cardiology, University and Hospital, Dept. of Exp. and Appl. Medicine, Brescia, Italy; [2]Igiene, University, Dept. Exp. and Appl. Medicine, Brescia, Italy*

Background: Beta-adrenergic receptors (AR) display genetic heterogeneity which may affect the risk, pathogenesis and progression of HF. Beta-1ARArg389 polymorphism is associated with a 3-fold higher agonist-promoted activity, compared to the beta-1 Gly389 allele, in vitro. The Arg16 beta-2AR variant has less agonist-induced down-regulation than Gly16, as well as the Glu27 beta-2AR variant, compared with the Gln27. Thus, the Arg16 and Glu27 alleles may be associated with increased sensitivity to beta-2AR stimulation.
Objective: We assessed the relation between the above mentioned polymorphisms and the clinical characteristics of the patients with HF.
Methods: Genotyping was performed in 316 patients with HF due to ischemic (49%) or idiopatic (51%) dilated cardiomyopathy (NYHA class, 2.33±0.33; LVEF, 31±11%; peak VO2, 15.5±5.09 ml/kg/min). Clinical variables, including demographics, NYHA class, heart rate and blood pressure, laboratory exams, Echo-Doppler and cardiopulmonary exercise test results, were compared between the patients with different gene polymorphisms.
Results: Three-hundred-one patients (95%) were on ACE inhibitors or ARBs, 269 (85%) on beta-blockers, 260 (82%) on furosemide, 151 (48%) on antialdosteronics, 125 (40%) on digitalis. Age, sex, cause of HF and therapy were evenly distributed across all the different sub-groups. Arg389Gly polymorphism was not associated with differences in any variable. As regards beta-2AR polymorphisms, the 47 patients homozygotes for the Arg16 polymorphism had, compared with the others, a lower prevalence of concomitant COPD (15% vs 27%, p=0.03) and a lower E wave amplitude at Doppler-Echocardiography (55±20 vs 72±29 cm/sec, p=0.006). The patients homozygotes for the Glu27 beta-2AR allele (n=39) had, compared with those homozygotes for the Gln27 allele (Gln27Gln, n=150) and with all the others (Gln27Gln+Gln27Glu, n=277), a better NYHA class (2.10±0.75 vs 2.45+0.86, in the Gln27Gln, p=0.02 and 2.36+0.84 in the Gln27Gln+Gln27Glu, p=0.06), a lower prevalence of severe mitral regurgitation (8% vs 17% in the Gln27Gln, p=0.05 and 18% in the Gln27Gln+Gln27Glu, p=0.03, respectively) and a higher peak VO2 (17.9±5.8 vs 15.1±5.1 ml/kg/min in the Gln27Gln, p=0.02 and 15.2+4.9 mL/kg/min in all the others, p=0.01).
Conclusions: Beta-2AR gene polymorphisms have clinical consequences in HF. The Glu27 beta2-ARs polymorphism, associated with a higher beta-2AR density in vitro, is associated with a lower impairment of the maximal functional capacity and of the left ventricular function.

2782 Initiation of treatment with carvedilol or bisoprolol and changes in body fat mass in patients with chronic heart failure

M. Lainscak[1], I. Keber[2], S.D. Anker[3]. *[1]Murska Sobota, Slovenia; [2]Clinical Centre Ljubljana, Department of vascular disease, Ljubljana, Slovenia; [3]NHLI, Imperial College, Department of Clinical Cardiology, London, United Kingdom*

Background: Body wasting is an independent risk factor for mortality in chronic heart failure (CHF). Several studies have shown that treatment with beta blockers (BB) increases body mass in CHF. However, specific information about changes in body composition is not available.
Methods: We prospectively followed 33 non-cachectic ambulatory CHF patients (age 65±11 years, LVEF 36±5%, NYHA II-IV) who were started on carvedilol (N=21) or bisoprolol (N=12) and treated for at least 6 months (255±66 days, range 212–401 days). Body composition was measured using the bioimpedance method.
Results: All patients tolerated BB and at the end of follow-up majority of them received at least half or the full recommended dose (88% and 70%, respectively). During follow-up, the proportion of patients receiving ACE inhibitors (94% vs 97%) and spironolactone (67% vs 73%) did not change while fewer patients received furosemide (64% vs 42%). During follow-up, body weight (83.4±3.2 kg vs 83.7±3.2 kg), body mass index (29.2±1.1 vs 29.3±1.1) and total body water did not change (50.4±1.1% vs 50.1±1.1%). Total body fat mass increased in 24 of 33 patients (73%) with the median change of +0.97kg. Total body fat content increased in 29 of 33 patients (88%) and the median change was +0.9%. Baseline and follow-up values for individual patients and the mean value are depicted in the figure. New York Heart Association class and Minnesota Living with Heart Failure Questionnaire improved from 2.9±0.4 to 2.2±0.6 and 46±18 to 30±16, respectively (p<0.001 for both).
Conclusion: In patients with CHF, initiation of treatment with carvedilol or bisoprolol increases total body fat mass and body fat content. BB therapy appears to contribute to reduced lipolysis and increased body energy stores.



RISK FACTORS IN CHRONIC HEART FAILURE

2783 The prognostic value of body mass index in patients with heart failure and preserved left ventricular systolic function. Data from the IN-CHF registry

R. Lavecchia[1], D. Lucci[2], G. Castiglioni[2], A. Fontana[2], M. Gorini[2], E. Picchio[2], A.P. Potena[2], A.P. Maggioni[2] on behalf of IN-CHF Investigators. *[1]ANMCO Research Center, Florence, Italy; [2]ANMCO Research Center, Florence, Italy*

Background: Previous reports showed the reverse epidemiology of a conventional cardiovascular risk factor, such as obesity, in patients (pts) with heart failure (HF). However the role of obesity in HF pts with preserved ejection fraction (EF) is not well established. The aim of this study was to describe the impact of body mass index (BMI) in terms of outcome, in a population of outpts with HF and preserved EF.
Methods: All pts with HF and EF >40% included in a large nationwide cardiology database (IN-CHF Registry) were selected for this analysis. Pts were categorized in 4 groups of BMI, A: underweight (<22), B: healthy weight (22-24.9), C: overweight (25-29.9), and D: obese (≥30). Multivariable analyses were performed to identify the independent predictors of 1-year all cause mortality.
Results: Of the 1296 pts considered in this analysis (mean age 64 years), 38% were of female sex. A history of hypertension was progressively more frequent from underweight to obese pts (A=35%, B=49.7%, C=57.2%, D=59.8%, p=.0001) while anemia was progressively less frequent (A=26.4%, B=25.8%, C=13.7%, D=10.1%, p=.04). At univariate analysis, 1-year all cause mortality was progressively lower from underweight to obese pts (A=11.5%, B=8.8%, C=6.9%, D=4.0%, p=.03). Multivariable analysis did not confirm a significant association between obesity and the risk of death at 1 year. The only independent predictors of death were age (hazard ratio [HR], 1.02; 95% confidence interval, [CI], 1.01-1.5) and advanced NYHA class (HR 2.88; 95% CI, 1.88-4.41).
Conclusions: In our large cohort of outpatient whit HF and preserved EF, the reverse epidemiology of obesity was not confirmed, suggesting that this observation is likely limited to higher risk pts such as those with low EF. In HF with preserved EF, advanced age and NYHA class resulted as the only clinical independent predictors of death at 1 year.

2784 NT-proBNP, but not BNP, is increased in patients with severe obesity

F. Fernandes[1], F.J.A. Ramires[2], P.C. Buck[2], I. Almeida[2], R. Rabelo[3], C. Cerquato[4], A. Halpern[4], C. Mady[2]. *[1]University of Sao Paulo, Heart Institute (InCor), Sao Paulo, Brazil; [2]University of São Paulo-Medical School, Heart Institute (InCor), São Paulo, Brazil; [3]diagnostic center, Fleury, São Paulo, Brazil; [4]University of São Paulo, Endocrinology, São paulo, Brazil*

Background: left ventricular enlargement and eccentric hypertrophy are the most common cardiac morphological abnormalities in obese individuals. This cardiac remodelling depends on severity and duration of obesity.
Objective: to investigate the cardiac involvement in patients with severe obesity using NT-proBNP and BNP, correlating their levels with body mass index (BMI), duration of obesity (DO) and waist circumference (WC).
Methods: thirty-three patients with obesity (23 females, mean age 39 years) and normal systolic ventricular function were compared to 30 healthy thin individuals (IMC<25 kg/m^2, 9 females, mean age 43 years). The T test was used to assess the difference between groups, and Spearman correlation was used to analyze the relation between duration of obesity, BMI and WC.
Results: all patients had level III obesity (mean BMI of 46.39 kg/m^2), long-term obesity (mean of 15.64 years) and abnormal WC (mean 131.37cm).
There was a significant increase in LogNT-proBNP (p=0.003) in patients with obesity (mean 1.67, CI 95%: 1.50-1.83 log pg/mL)when compared to control group (mean 1.32, CI 95%: 1.17-1.47 log pg/mL). The log NT-proBNP correlated with duration of obesity in these patients (r=0.339, p < 0.004).
However, when the BNP was analyzed, there were no differences in the Log-BNP (p=0.63) in patients with obesity (mean 0.73, CI 95%: 0.46-1.00 log pg/mL)when compared to control group (mean 0.66, CI 95%:0.51-0.81 log pg/ml).
Conclusion: NT-proBNP, but not BNP, is increased in patients with severe obesity and is correlated with duration of obesity. NT-proBNP may be helpful as an early diagnostic tool for detection of cardiac burden due to obesity.

2785 Relation of NTproBNP level to body composition characteristics in cachectic and noncachectic heart failure patients

P. Rozentryt[1], J.U. Nowak[2], A. Brachowska[2], L. Polonski[2], S.D. Anker[3]. *[1]Zabrze, Poland; [2]Silesian Center for Heart Diseases, III Department of Cardiology, Zabrze, Poland; [3]National Heart & Lung Institute., Clinical Cardiology, London, United Kingdom*

Body mass has been shown as important prognostic factor in heart failure (HF). Natriuretic peptides plasma level have been accepted as powerful biochemical markers of HF severity. It is suggested that higher fatness may influence concentration of natriuretic peptides. Our aim therefore was to evaluate relation between NTproBNP level and body composition parameters in heart failure patients with verying body compositions.

We performed DEXA scannning in 166 HF patients (140M,26F, age: 56±13y, NYHA: 2,7±0,7, EF: 25±9%). 88 patients had lost more than 6% of dry body weight, their BMI had fallen below 25 kg/m^2 and were asignd cachectic. Remaining 76 were not cachectic. In all patients NTproBNP levels were measured. All parameters expresed as means±SD were compared using student-t test and data are shown in the table. We computed linear correlation coefficients between body composition parameters and NTproBNP.

BMI did not correlate with NTproBNP level in either groups. In cachectic patients fat tissue content correlated weakly with NTproBNP (r=0,26, p<0.04), what was not seen in noncachectics. Lean tissue mass signifficantly and negatively correlated with NTproBNP in both groups, but correlation was higher in cachectics than in noncachectics (r=0,32, p<0.01 and r=0,24, p<0.04 respectively). We than performed regression anlysis of clinical, biochemical and body composition parameters with NTproBNP as dependent variable. The parameters that significantly and independently of age, NYHA class predicted plasma NTproBNP were: lean body mass (p<.0003), creatinine (p<.0001), plasma cholesterol (p<.003), VO2max (p<.01) and EF (p<.03)

Body composition linical chracteristics

	Cachectic	NonCachectic	p-values
NYHA class	2,7±1	2,4±0,8	.001
BMI [kg/m^2]	21±3	28±4	.0002
NTproBNP [pg/ml]	5179±5741	2019±2223	.00000
Fat tissue [kg/m^2]	5,6±2,4	8,4±2,7	.00000
Lean tissue [kg/m^2]	15,7±2,1	18,9±2,2	.00000
Fat/lean	0,34±0.16	0,44±0,15	.0002

Conclusion: We have found little evidence to support suggestions of fat tissue influence on plasma NTproBNP. Conversely, lean body mass seems to have much more stronger association with severity of the syndrome.

2786 Symptomatic skeletal myopathy in patients with hypertrophic cardiomyopathy: incidental finding or leading clinical symptom?

F. Lieder[1], T. Lawrenz[2], M. Bartelsmeier[2], G. Beer[2], H. Kuhn[2]. *[1]Münster, Germany; [2]The Bielefeld Klinikum, Department of Cardiology, Bielefeld, Germany*

Background: Structural and functional abnormalities of skeletal muscle have been described in patients with secondary cardiomyopathy and CHF. In patients with hypertrophic cardiomyopathy (HCM) subclinical involvement of skeletal muscle has been described in a few case reports and in-vitro studies. Until now, no symptomatic, overt skeletal myopathy was demonstrated in HCM patients.

Patients and Methods: The study group consists of 12 consecutive pts (7 females, 23-71 y) with HCM (10 HOCM, 2 HNCM) with overt skeletal myopathic symptoms (e.g. hypotonia and weakness). In one pt (male, 41y.) with HNCM bilateral deafness was present. The 10 pts with HOCM were successfully treated with catheter interventional treatment (TASH) 14±10 months before. In all pts open biopsy of gastrocnemius muscle and cardiopulmonary exercise testing (CPX), in 2 pts with HNCM in addition endomyocardial biopsy (EMB) was performed.

Results: CPX revealed abnormal low oxygen consumption both at anaerobic threshold (8.5 ±2.3 ml/min/kg) and at maximal workload (9.7 ±2.3 ml/min/kg; max. workload: 50±17 watt) in all pts. Microscopy of calf muscle revealed distinct muscle fiber type disproportion with fiber type I predominance in all pts (fiber type I/type II: 3.2 ±2.1, 1.0–7.0 (normal value: 0.8)), abnormal fiber type I grouping in 8 pts, abnormal subsarcolemmal accumulation of mitochondria in 9 pts and large electron dense inclusions within abnormally swollen and deformed mitochondria in 3 pts. In 2 pts with HNCM EMB revealed abnormal mitochodrial configuration with large inclusions, in one pt. genetic analysis of mitochondrial DNA disclosed a A3243G mutation, indicating the MELAS-syndrome (Mitochondrial myopathy, Encephalopathy, Lactic Acidosis and Strokelike episodes).

Conclusions: In patients with HCM and typical symptoms of skeletal myopathy specific histologic alterations of calf muscle are frequent findings, characterised by distinct fiber type I predominance and mitochondrial abnormalities. These patients may be identified by persisting low peak oxygen uptake assessed by CPX. In HCM patients a careful examination of skeletal muscle is mandatory, because myopathic symptoms may point out to a systemic mitochondrial disorder (e.g. MELAS-syndrome) with distinct prognostic relevance.

2787 Hyperhomocysteinaemia in chronic heart failure: pathophysiological and prognostic importance

M. Naruszewicz[1], R. Zymlinski[2], H. Bukowska[1], B. Millo[1], J. Majda[2], E.A. Jankowska[3], W. Banasiak[2], P. Ponikowski[2]. *[1]Pomeranian Academy of Medicine, Department of Clinical Biochemistry, Szczecin, Poland; [2]Military Hospital, Cardiology Department, Wroclaw, Poland; [3]Polish Academy of Sciences, Institute of Anthropology, Wroclaw, Poland*

Background: Hyperhomocysteinemia (HHcy) exerts numerous adverse biological effects on the vascular bed and myocardium. Patients with chronic heart failure (CHF) may be particularly susceptible to these effects, but it has never been prospectively investigated.

Methods: In 113 consecutive patients with CHF (81 men, age: 65±11 years), plasma homocysteine (Hcy) level was elevated (13.2±7.0 μmol/L, p<0.0001 vs. reference values in our laboratory), and 41 (36%) patients had HHcy (prospectively defined as plasma Hcy level ≥14μmol/L). Only 3 clinical indices predicted HHcy after correction in the multivariate analysis: advanced NYHA class (p=0.03), impaired renal function (p=0.01), and therapy with furosemide (p=0.009). HHcy was related to impaired survival (hazard ratio: 4.0, 95%CI: 1.8–8.6, p=0.0005) also when adjusted for conventional risk predictors (all p<0.05). In patients with HHcy, the 18-month survival was 63% (95%CI: 49-78%) as compared to 88% (95%CI: 80-95%) in those with normal Hcy levels (p=0.002). In the second study, we confirmed elevated Hcy levels in 38 CHF patients when compared with 30 age- and sex-matched healthy controls (p<0.0001), and demonstrated significant correlations between plasma Hcy and pro-inflammatory cytokines (interleukin [IL] -6: r=0.25, p<0.05 and tumour necrosis factor [TNF] -alpha: r=0.43, p=0.0002) and high sensitivity C-reactive protein (hsCRP) (r=0.40, p=0.0009). In this study, 8 CHF patients received a 8-week open-label therapy with folic acid (10mg/day), vitamin B6 (150mg/day) and B12 (1mg/week), which resulted in a decrease of Hcy (15.6±3.6 vs. 8.7±1.7 μmol/L, p<0.001), TNF-alpha (2.3±0.7 vs. 1.8±0.8 pg/mL, p=0.08), IL-6 (16.7±6.3 vs. 12.6±6.7 pg/mL p=0.07) and hsCRP levels (5.1±3.4 vs. 2.4±1.3 mg/L, p=0.03; baseline vs. end, respectively).

Conclusions: HHcy commonly occurs among unselected, stable CHF patients, is related to the disease severity and impaired renal function, and may reflect the proinflammatory status. HHcy is also an independent marker of poor prognosis. In CHF patients, the supplementation of folic acid, vitamins B6 and B12 lowers Hcy levels and partially corrects proinflammatory response.

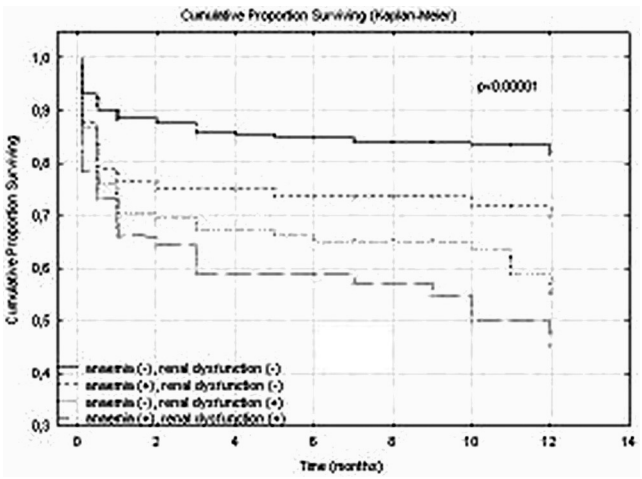
2788 Reduced kidney function and anaemia – strong risk factor of poor outcomes in patients with chronic heart failure

M. Roik, S. Stawicki, M.H. Starczewska, A. Solarska-Polchlopek, R. Rodzoch, D. Kosior, O. Warszawik, G. Opolski. *University Hopsital, 1 st Department of Cardiology, Warsaw, Poland*

Anemia (A) is widely prevalent and is often associated with worsening of renal function (WRF). Data on the mortality hazard associated with A and WRF in patients with CHF are insufficient. We therefore sought to study the impact of WRF and A on the outcome of patients hospitalized due to CHF.

Methods: This study is an analysis of relationship between survival time (1 year follow-up)and the level of kidney dysfunction and hemoglobin. We defined WRF as a cretinine level > 1.4 mg/dl and A as hemoglobin level < 12 g/dl. Baseline clinical paremeters were measured immediately after the admission. Mean age was 69±11, 316 male pts. We divided the pts into the gropus: gr. I - non-A and without WRF (n = 276); gr. II - A without WRF (n = 72); gr. III – non-A with WRF(n = 92); gr. IV – A with WRF (n = 56);

Results: The gr. did not differ in etiology of CHF, comorbidities (diabetes mellitus, Hypertension), wall motion score index and treatment used (p = NS). Pts from gr IV were older, of ischemic etiology, in NYHA IV class (p < 0.001). During 12



The Kaplan-Meier curve

month 18% death occurred in gr I, 29% in gr. II, 41% in gr. III and 62% in gr. IV ($p < 0.005$). The rehospitalisation rate was significantly higher in gr IV, respectively (78% vs. 67% vs. 60% vs. 54%, $p < 0.05$). Kaplan-Meier analysis was used to compare survival times between the 4 groups stratified by level of kidney function and by the level of haemoglobin and showed lower survival in pts with A and WRF(figure). A multivariate logistic regression had showed that both A and WRF in pts with CHF are strong predictor of mortality (OR 2.56, CI: 1.29-5.08, $p <$ 0,005).

Conclusions: WRF and A are significant independent and additive predictors of short and long-term prognosis in patients with CHF.

METABOLIC SYNDROME; IS IT AN INDEPENDENT CARDIOVASCULAR DISEASE RISK FACTOR?

2789 C-reactive protein and the risk of developing the metabolic syndrome. A population study

R. Cifkova[1], J. Frohlich[2], Z. Skodova[1], V. Lanska[3], V. Adamkova[1], E. Bojanovska[1], M. Jozifova[1], M. Galovcova[1]. *[1]IKEM, Department Preventive Cardiology, Prague 4, Czech Republic; [2]University of British Columbia, Vancouver, Canada; [3]Inst Clin Exp Medicine, Department of Biostatistics, Prague, Czech Republic*

Objectives: Recent evidence suggests that increased plasma levels of C-reactive protein (CRP) may predict the development of diabetes and hypertension. The aim of our study was to examine whether CRP, a marker of inflammation, is associated with the incidence of the metabolic syndrome (MS) in a representative sample of the Czech population.

Design and Methods: In 1997/8, a cross-sectional survey of cardiovascular risk factors was performed in 3,209 randomly selected individuals from 9 districts of the Czech Republic (a 1% population sample aged 25-64 years; mean age 45 years; respondence rate 64.4%), a subgroup of 2,632 individuals was re-examined 3 years later. CRP was determined by high-sensitivity assay (Immulite, USA; not performed in 286 individuals). At baseline, MS was found in 673 individuals, who were excluded from this analysis. A total of 1,427 probands were evaluated (39 were excluded because of a history of MI, PTCA, CABG, stroke, and/or TIA or a revascularization procedure; 57 because of a recent history of acute febrile illness; 43 because of CRP greater than or equal to 10.0 mg/L (to limit confounding) likely to be related to acute infection or diseases and; 107 because they were on medication interfering with CRP levels [ASA, statins, HRT]). The incidence of MS over 3 years was assessed by tertiles of CRP at baseline.

Results: see Table.

MS incidence by CRP tertiles at baseline

	I	II	III	p
Males, n	213	213	213	
CRP median, mg/l	0.41	0.99	2.51	
MS incidence, n (%)	13 (6.1)	18 (8.5)	46 (21.6)	< 0.001
OR* (95% CI)	1.0	1.16 (0.54-2.49)	2.41 (1.19-4.87)	< 0.01
Females, n	262	262	264	
CRP median, mg/l	0.32	0.86	2.94	
MS incidence, n (%)	13 (5.0)	24 (9.2)	35 (13.3)	< 0.01
OR* (95% CI)	1.0	0.91 (0.42-1.96)	0.86 (0.40-1.85)	n.s.

*Adj. for age, BMI, smoking.

Conclusions: Higher CRP levels are associated with future development of MS in males, but not in females (possibly because of lower incidence of MS). Our results suggest that inflammation may also be involved in the pathogenesis of MS.

2790 Metabolic syndrome, low-density lipoprotein cholesterol, and risk of cardiovascular disease: a population based study

J. Jeppesen[1], T. Hansen[2], S. Rasmussen[1], H. Ibsen[1], C. Torp-Pedersen[2]. *[1]Glostrup University Hospital, Medical Department M, Glostrup, Denmark; [2]Bispebjerg University Hospital, Department of Cardiology, Copenhagen, Denmark*

Purpose: To study the role of the metabolic syndrome as a cardiovascular risk factor in a general population compared with that of a high LDL cholesterol level.

Methods: This study was a prospective cardiovascular study and comprised of a random sample of 2493 men and women, age 41-72 years, without major cardiovascular diseases. At baseline, lipids, glucose, insulin and blood pressure as well as other traditional cardiovascular risk factors were determined. The metabolic syndrome was defined according to the National Cholesterol Education Program criteria. The study population was subdivided into four groups on the basis of presence (15%) or absence of the metabolic syndrome (85%) and presence (15%) or absence of high LDL cholesterol (85%) defined as a level > 5.02 mmol/L.

Results: After a mean period of 9.5 years, 233 had a cardiovascular endpoint, consisting of a combined endpoint of cardiovascular death, ischemic heart disease, and stroke. In multivariate proportional-hazard models, adjusting for age, sex, and smoking, and with subjects without the metabolic syndrome and LDL cholesterol < or = 5.02 mmol/L as reference (73%), the relative risk of an endpoint (95% CI) was 1.49 (1.04-2.13) in participants without the metabolic syndrome and LDL cholesterol > 5.02 mmol/L (12%), 1.80 (1.26-2.57) in subjects with the metabolic syndrome and LDL cholesterol < or = 5.02 mmol/L (12%), and 3.20 (1.99-5.15) in participants with both the metabolic syndrome and LDL cholesterol > 5.02 mmol/L (3%).

Conclusions: In a general population, the metabolic syndrome was associated with a similar or higher risk compared with high LDL cholesterol.

2791 Dramatic changes in prevalence of lipid disorders, overweight, prehypertension and hypertension among adolescents during the Russian reforms (1989-2003)

D. Denissova[1], L. Zavjalova[2]. *[1]Novosibirsk, Russian Federation; [2]Institute of Internal Medicine, Novosibirsk, Russian Federation*

High blood pressure, overweight and lipid disorders are known risk factors of coronary artery disease. Control of the factors since adolescence may reduce cardiovascular morbidity and mortality in adulthood. During the 1990s the Russian population was exposed to major political, economic and social changes accompanying by remarkable variation in health status.

Aim: Aim of the study was to assess trends in prevalence of overweight, lipid disorders, arterial prehypertension and hypertension among adolescent population in Novosibirsk during the reforms (1989-2003).

Methods: Four cross-sectional surveys of representative samples of school children aged 14-17 in 1989 (656), in 1994 (620), in 1999 (626) and in 2003 (667) were carried out. Total sample was 2569 (1214 males and 1355 females). Body mass index (BMI, kg/m^2), systolic (SBP) and diastolic blood pressure (SBP), serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were measured. Diet was estimated using 24-hour dietary recall.

Results: According to the 4th Report of the NHBPEP Working Group (2004), prevalence of arterial prehypertension during the period was high in both gender groups with decreasing from 58% to 36% ($P < 0,01$) in boys and from 31% to 23% in girls; arterial hypertension also decreased from 12% to 6% in boys ($P <$ 0,05) and from 16% to 5% in girls ($P<0,05$).

According to NCEP-peds criteria (1992), prevalence of high TC (200 mg/dl and more) during the period (1989-2003) significantly decreased from 22% to 8% ($P < 0,01$) in males and from 32% to 17% ($P < 0,05$) in females. The similar trends were found in prevalence of high LDL-C (130 mg/dl and more) and low HDL-C (<35 mg/dl).

Frequencies of overweight (BMI = 23 kg/m^2 and more) decreased from 18% to 11% in boys ($P<0,05$) and from 22% to 10% ($P<0,05$) in girls. The most decreasing of the parameter was revealed in 1999.

Trends in diet during the period of reforms showed significant decreasing of total energy intakes (from 3021 to 2340 kcal in boys and from 2300 to 1640 kcal in girls) and basic nutrient intakes (proteins, fats and carbohydrates). At the post-reform period (survey at 2003 year) the average consumption of energy and basic nutrients by adolescents slightly increased.

Conclusion: The data from Novosibirsk indicate a parallel trend to decreasing in classical CVD risk factors in adolescents following the period of socioeconomic reforms in Russia.

2792 Low serum concentrations of adiponectin are a risk factor for coronary events in apparently healthy middle-aged men. Results from the 14 year follow-up of the MONICA-Augsburg Cohort 1984-1998

W. Koenig[1], J. Baumert[2], N. Khuseyinova[1], C. Meisinger[2], H. Loewel[2]. *[1]University of Ulm Medical Center, Department of Internal Medicine II, Ulm, Germany; [2]National Research Center for Health, Institute of Epidemiology, Neuherberg, Germany*

Purpose: Adiponectin, an obesity related hormone produced by adipocytes is involved in several crucial steps in atherogenesis. Adponectin induces nitric oxide expression from endothelial cells, inhibits proliferation and migration of vascular smooth muscle cells, and interferes with the transformation from macrophages to foam cells. It is also linked to insulin resistance and has anti-inflammatory properties. Thus, it has been postulated that high serum concentrations may be protective against coronary heart disease (CHD) and type 2 diabetes.

Methods: Serum concentrations of adiponectin were determined by ELISA (R&D, Wiesbaden, Germany) in 938 apparently healthy men aged 45-64 years, sampled from the general population in 1984 and followed until 1998.

Results: During this period 98 men suffered from a coronary event (fatal and non-fatal myocardial infarction and sudden cardiac death) diagnosed according to the MONICA protocol. Median baseline levels of adiponectin were lower in subjects who experienced a future event compared to event-free subjects (5.6 μg/ml versus 6.3 μg/ml p=0.021). Adiponectin (log-transformed) was positively correlated with HDL cholesterol (Pearson correlation coefficient R=0.38, $p<0.001$), Apo A1 (R=0.34, $p<0.001$), and age (R=0.17, $p<0.001$), and negatively with non-HDL cholesterol (R=-0.15, $p<0.001$) and body mass index (R=-0.19, $p<0.001$), but not with inflammatory markers like C-reactive protein. In a Cox model, adjusted for age, the relative risk (RR) of a future coronary event, comparing the top tertile of the adiponectin distribution to the bottom tertile was 0.50, 95% confidence interval, CI, 0.29-0.84). After controlling for potential confounders, the RR slightly increased but still remained statistically significant (RR 0.52, 95% CI, 0.30-0.89).

Only after further inclusion of HDL-cholesterol in the model, the estimate for the predictive value of low adiponectin lost its statistical significance (RR 0.60; 95% CI 0.34-1.07).
Conclusions: Lower levels of adiponectin are associated with increased risk of future coronary events in apparently healthy middle-aged men. The protective effect of high serum concentrations might at least in part be explained through its strong positive correlation with HDL-cholesterol concentrations.

2793 Social gradient in the metabolic syndrome – explained by psychosocial and behavioural factors?

E. Prescott[1], M. Osler[2], N. Godtfredsen[2], P. Schnohr[2], J. Barefoot[3]. *[1]Rigshospitalet, Cardiology Department, Copenhagen, Denmark; [2]Copenhagen, Denmark; [3]North Carolina, United States of America*

Introduction: A strong social gradient in metabolic syndrome (MS) has been noted previously. We explored the association between educational level and MS and whether associations were explained by psychosocial or behavioural factors.
Methods: Cross-sectional analyses were conducted using 3318 women and 2483 men aged 20-97 examined in 2001-2003 in the Copenhagen City Heart Study. An MS index was defined from the seven components: waist-hip-ratio, HDL, triglyceride, systolic blood pressure, blood glucose, C-reactive protein and fibrinogen and related to educational level. Psychosocial factors were fatigue and depression, perceived stress, social network and cohabitation. Behavioural factors were smoking, alcohol and physical activity.
Results: There was an inverse social gradient in prevalence of the seven components of MS. The age adjusted Odds-Ratio (95%C.I.) for occupying the most disadvantaged quintile of the following variables, comparing highest with lowest educational level, were for men and women, respectively: waist-hip-ratio 0.48 (0.34-0.69) and 0.48 (0.33-0.69); HDL 0.61 (0.45-0.84) and 0.46 (0.33-0.64); triglyceride 0.71 (0.51-0.98) and 0.37 (0.25-0.53); systolic blood-pressure 0.64 (0.44-0.92) and 0.76 (0.50-1.15); blood glucose 0.57 (0.41-0.80) and 0.55 (0.38-0.78); C-reactive protein 0.53 (0.37-0.74) and 0.44(0.31-0.63), and; fibrinogen.0.50 (0.35-0.70) and 0.56 (0.38-0.82). Overall results did not differ for men and women and the pooled OR for having high MS index score was 0.39 (0.29-0.53) for highest versus lowest educational level. Although most psychosocial and behavioural factors were independently related to MS, OR's for education were not affected by multivariate adjustment.
Conclusion: There is a strong inverse social gradient in prevalence of the metabolic syndrome, which is not explained by psychosocial or behavioural factors.

2794 Metabolic syndrome is the only non-classical risk factor independently associated with mild renal insufficiency

A. Cordero Fort[1], M. Laclaustra[2], M. Leon[2], A. Grima[3], J.A. Casasnovas[4], E. Luengo[2], A. del Rio[2], E. Alegria[5] on behalf of MESYAS Registry investigators. *[1]Pamplona, Spain; [2]Hospital Clínico Universitario, Cardiology, Zaragoza, Spain; [3]Cardiovascular prevention.Ford Factory, Valencia, Spain; [4]Hospital Miguel Servet, Cardiology, Zaragoza, Spain; [5]Clínica Univeristaria de Navarra, Cardiology, Pamplona, Spain*

Background: Renal dysfunction, even mild renal insufficiency (RI), is associated with an increased prevalence of cardiovascular risk factors and coronary heart disease. Hypertension and diabetes are the most frequently related risk factors to RI. Metabolic syndrome (MS), a cluster of non-classical risk factors, has been related to RI.
Objective and methods: This MESYAS Registry substudy aims to assess MS as an independent risk factor for mild RI without creatinine elevation. Glomerular filtration rate (GFR) was assessed by the Modification of Diet in Renal Dysfunction (MDRD) equation among 11,041 active workers, included in the MESYAS Registry. The assessment of the MS was made according to the modified ATP III criteria when three of the following five were present in the same subject: body mass index (BMI) >28.8 kg/m^2; blood pressure (BP) $>130/85$; triglycerides >150 mg/dl; HDL-cholesterol <40 mg/dl (males) or <50 mg/dl (females); fasting plasma glucose >110 mg/dl.
Results: The prevalence of mild renal dysfunction (GFR $<$ 60mg/dl/1.73m^2) was 23.6%, and moderate-severe (GFR 60-90mg/dl/1.73m^2) 3.3%. The prevalence of all cardiovascular risk factors increased in both categories of renal dysfunction, except low-HDL cholesterol, hipertriglyceridemia, and overweight. Multivariant logistic regression showed that hypercholesterolemia (OR: 1.1), LDL-cholesterol $>$ 160 mg/dl (OR: 1.2), MS (OR: 1.4), hypertension (OR: 1.8), age $>$ 50 (OR: 2.6), and diabetes mellitus (OR: 3.0) were independent risk factors for any degree of renal dysfunction with normal creatinine levels. Hipertriglyceridemia, low-HDL cholesterol obesity and overweight did not confer any significant risk
Conclusion: MS is a non-traditional cardiovascular risk factor that can be considered an independent risk factor for subclinical renal dysfunction.

PROGNOSIS IN HYPERTROPHIC CARDIOMYOPATHY

2795 Spectrum of novel mutations in a European population with hypertrophic cardiomyopathy and consequences for molecular strategy; The Eurogene Heart Failure Study

S. Morner[1], P. Richard[2], L. Tavazzi[3], E. Galve[4], A. Waldenstrom[1], C. Hengstenberg[5], M. Komajda[6], R. Isnard[6] on behalf of "Eurogene Heart Failure" study group (LEDUCQ Foundation). *[1]Department of Cardiology, Heart Centre, Umea, Sweden; [2]Hôpital Pitié-Salpêtrière, UF Cardiogénétique et Myogénétique, Paris, France; [3]IRCCS Policlinico San Matteo, Division of Cardiology, Pavia, Italy; [4]Hospital Universitari Vall d'Hebron, Department of Cardiology, Barcelona, Spain; [5]University Hospital Regensburg, Clinic and Policlinic for Int Medicine, Regensburg, Germany; [6]Hopital Pitié-Salpêtrière, Service de Cardiologie, Paris, France*

Purpose: Hypertrophic cardiomyopathy (HCM) is often caused by mutations in sarcomeric protein genes and is characterised by an important genetic heterogeneity. Information about the genotype could have clinical implications for genetic counselling and for risk assessment. The aim of the study was to identify the molecular genetic defects in patients originating from seven European countries, with emphasis on the spectrum of novel mutations.
Methods: In 293 unrelated patients with familial or sporadic HCM, mutation analysis of the myosin binding protein C and beta myosin heavy chain genes was performed, followed by cardiac troponin T, cardiac troponin I and myosin regulatory light chain genes, by direct sequencing of both strands of the coding exons.
Results: A mutation was found in 158 index patients (54%). A total of 115 different mutations, including 71 novel ones (62%), were identified in the five genes studied (Table). In the cardiac myosin binding protein C gene there were 72% nonsense mutations, including insertion/deletions, splice site and termination mutations. The remaining 28% were missense mutations leading to an amino acid substitution. In the beta myosin heavy chain gene, all mutations were missense mutations and most of them (60%) were located in the globular domain of the protein. Independent of the mutated gene, mutations were found throughout the gene, except for cardiac troponin I, in which all mutations found were located in the C terminal part of the protein.

Table 1. Distribution of mutations in 158 index patients with hypertrophic cardiomyopathy

	Myosin binding protein C (MYBPC3)	Beta myosin heavy chain (MYH7)	Cardiac troponin T (TNNT2)	Cardiac troponin I (TNNI3)	Myosin regulatory light chain (MYL2)
Patients with mutation	82	63	6	6	1
Number of different mutations	57	46	5	6	1
Number of novel mutations	35 (61%)	33 (72%)	2 (40%)	0 (0%)	1 (100%)

Conclusions: In spite of the numerous mutations already described, the vast majority of mutations found in this study were novel, and most mutations were "private". This means that a strategy for genetic analysis and counselling should involve screening of entire genes, and the low rate of mutation recurrence is also a limitation in the establishment of phenotype-genotype correlations.

2796 Prognostic relevance of left atrial size in hypertrophic cardiomyopathy: the Italian HCM Registry

S. Nistri[1], I. Olivotto[2], M. Galderisi[3], M.A. Losi[3], M.G. Valsecchi[3], B. Pinamonti[3], M.R. Conte[3], F. Cecchi[4]. *[1]CMSR Veneto Medica, Altavilla Vicentina, Italy; [2]Firenze, Italy; [3]Istituto Superiore di Sanità, Lab of Epidemiology and Statistics, Rome, Italy; [4]Careggi Teaching hospital, Cardiology Department, Florence, Italy*

Background: The present study was aimed at assessing left atrial (LA) dimensions as a potential predictor of outcome in hypertrophic cardiomyopathy (HCM).
Methods: A total of 1491 patients from the nationwide Italian Registry for HCM (mean age 47$\pm$17 years, men 61%, obstructive 19%), followed for 9.4$\pm$7.4 years after the initial echocardiographic evaluation, represent the study group.
Results: Average LA size was 43+9 mm (median 42 mm; 75th percentile 48 mm). LA dimension was larger in patients with severe symptoms (NYHA class III-IV: 48+9 mm; vs. 42+9 mm in NYHA I-II; $p<0.001$), paroxysmal or chronic atrial fibrillation (47+9 mm vs. 42+8 mm in sinus rhythm, $p<0.001$), and outflow obstruction (>30 mmHg, 46+9 mm, vs. 42+9 mm <30 mmHg; $p<0.001$). At univariate analysis, each 5-mm increase in LA size was associated with a 1.2 hazard ratio (HR) for all-cause mortality ($p<0.0001$). At multivariate analysis, LA values >48 mm (75th percentile) had a HR of 1.9 for all-cause mortality (p=0.008), 2.0 for cardiovascular death (p=0.014) and 3.1 for heart failure-related death (p=0.008), but were not associated with sudden death (p=0.81). Similar results were obtained after the exclusion of patients with atrial fibrillation (HR 1.7, p=0.0078) or resting outflow obstruction (HR 1.8, p=0.0029). In an independent HCM cohort of 537 patients from the U.S., an LA size >48 mm had an HR of 1.8 for all-cause mortality (p=0.019), 2.7 for cardiovascular death (p=0.003) and 3.8 for heart failure-related death (p= 0.034).
Conclusions: In a large cohort of HCM patients from a nationwide registry, LA was very commonly enlarged, with average dimensions exceeding commonly used reference limits. Severe degrees of LA dilatation were predictive of all-cause,

cardiovascular and heart failure-related mortality, independent of coexistent atrial fibrillation or obstruction. Our findings were validated in an independent HCM cohort, and are relevant for the early identification of patients at risk of disease progression ad heart failure-related complications.

2797 Prognostic value of intra-left ventricular electromechanical asynchrony in patients with mild Hypertrophic Cardiomyopathy compared to power athletes

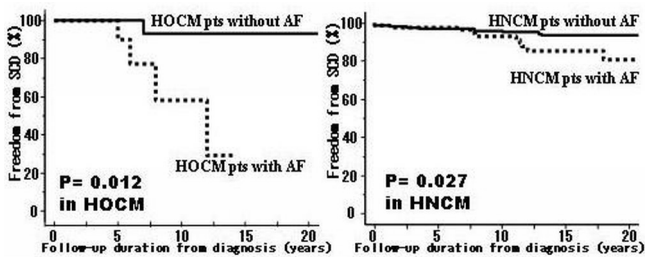
A. D'Adrea[1], P. Caso[2], F. Vigorito[3], F. Scotto di Uccio[3], F. Moscato[3], E. Pezzullo[4], R. Calabro'[5], M. Scherillo[3]. *[1]Second University, Cardiologist, Naples, Italy; [2]Monaldi Hospital, Cardiology, Naples, Italy; [3]Rummo Hospital, Cardiology, Benevento, Italy; [4]Naples, Italy; [5]Monaldi - Second University, Cardiology, Naples, Italy*

Background: the distribution and the magnitude of left ventricular (LV) hypertrophy are not uniform in patients with hypertrophic cardiomyopathy (HCM), which results in heterogeneity of regional LV systolic function.
Aims: we sought to assess the indexes of myocardial activation delay, using Doppler Myocardial Imaging (DMI), as potential predictors of cardiac events in patients with HCM compared to power athletes (ATL).
Methods: the study population included 70 young HCM patients (29.4 $\pm$ 5.9 years) with mild septal hypertrophy (15 to 18 mm), and 85 age- and sex- comparable ATL with septal hypertrophy ($>$ 13 mm), followed-up for 44.4$\pm$10.8 months. Using pulsed DMI, in 6 different basal myocardial segments were measured: myocardial peak velocities and systolic time-intervals; myocardial Intra-ventricular (IntraV-del) and Inter-ventricular (InterV-del) systolic delays.
Results: DMI analysis showed in HCM lower myocardial both systolic and early-diastolic peak velocities of all the segments. HCM showed also a significant increase of both Inter- ($p<0.01$) and Intra-V delays ($p<0.0001$), while homogeneous systolic activation of the ventricular walls was assessed in ATL. During the follow-up, 11 sudden deaths in HCM, and no cardiovascular event in ATL were observed. By Cox's proportional-hazards regression analysis, family history of sudden cardiac death (Hazard Ratio: 1.28; 95% CI: 1.09-1.32; $p<0.001$), non-sustained episodes of ventricular tachycardia (Hazard Ratio: 2.68; 95% CI: 1.2- 4.32; $p<0.0001$), and DMI Intra-V-Del (Hazard Ratio: 3.3; 95% CI: 1.3-4.4; $p<0.0001$) were the only independent predictors of sudden cardiac death. The global chi-square of this combined clinical, ECG Holter and DMI test model was 66.3 ($p<0.00001$). In particular, an IntraV-Del $>$ 30 msec well distinguished HCM from ATL (sensitivity: 90.1%; specificity: 97.5%). An IntraV-Del $>$ 45 msec identified HCM patients at higher risk of ventricular tachycardia and cardiac events (sensitivity: 89.6%; specificity: 90.5%; test accuracy: 90.6%).
Conclusions: DMI may represent a valid supporting tool for the differential diagnosis between mild forms of HCM and athlete's heart. In HCM patients, DMI indexes of Intra-V-Del may provide additional information for selecting subgroups of patients at increased risk of sudden cardiac death at follow-up. Accordingly, such patients may be more actively identified for early intensive treatment and survey.

2798 Relationship of atrial fibrillation to sudden cardiac death in patients with hypertrophic cardiomyopathy: a comparision between obstructive and non-obstructive hypertrophic cardiomyopathy

B. Yashiro[1], K. Kajimoto[2], Y. Terajima[2], N. Kawashiro[1], T. Imai[2], N. Hagiwara[2], H. Kasanuki[2]. *[1]Tokyo Women's Medical University, Cardiology, Tokyo, Japan; [2]Tokyo Women's Medical University, Cardiology, Tokyo, Japan*

Few data are available regarding relationship between atrial fibrillation (AF) and hypertrophic cardiomyopathy (HCM)-related mortality or sudden cardiac death (SCD) in patients (pts) with HCM. Therefore, in this study, we evaluated the clinical significance of AF for long-term prognosis in pts with obstructive (HOCM) and non-obstructive HCM (HNCM)
Methods: A retrospective study of 75 pts with HOCM and 350 pts with HNCM, who were diagnosed and followed-up in our hospital, was performed. HCM-related mortality (sudden death, heart failure-related death, and stroke-related death) and a probability of SCD were analyzed and compared between HOCM and HNCM. Mean follow-up duration was 12$\pm$7 years.
Results: Among 75 pts with HOCM and 350 pts with HNCM, AF was documented in 15 (20%) pts (paroxysmal AF in 14 pts) and 104 (30%) pts (paroxysmal AF in 73 pts), respectively. In both HOCM and HNCM pts, HCM-related mortality in pts with AF was significantly higher than those in pts without AF (26.7% vs. 4.0%; p=0.0007 and 13.5% vs. 6.9%; p=0.025, respectively). Similarly, in both HOCM and HNCM pts, the probability of SCD showed significant difference between pts with and without AF (p=0.012 and p=0.027, respectively; Figure). Furthermore, the probability of SCD in HOCM pts with AF was significantly higher than those in HNCM pts with AF (13% vs. 7.7%; p=0.035).
Conclusions: There was a significant relationship between AF and the probability of SCD in pts with HOCM and HNCM. Moreover, the probability of SCD in HOCM pts with AF was significantly higher than those in HNCM pts with AF. Therefore, it is suggested that AF is an important prognostic indicator of long-term cardiovascular mortality including SCD in pts with both HOCM and HNCM.



Impact of AF on SCD

2799 Utility of N-terminal pro-B-type natriuretic peptide to predict clinical outcome in patients with hypertrophic cardiomyopathy

F. Bayrak, B. Mutlu, G. Kahveci, E. Eroglu, T. Karaahmet, Y. Basaran. *Kosuyolu Heart and Research Hospital, Cardiology Dept., Istanbul, Turkey*

Background: The identification of hypertrophic cardiomyopathic patients at risk for sudden death and/or progression to heart failure remains a formidable challenge. This study was designed to assess the value of plasma N-terminal pro B-type natriuretic peptide (Nt-proBNP) level in predicting the clinical outcome of patients with hypertrophic cardiomyopathy (HCM).
Methods and Results: 80 consecutive patients who were diagnosed as HCM were prospectively included in the study. A clinical evaluation and blood sampling for Nt-proBNP were performed for each patient after the echocardiographic examination. Patients were prospectively followed for a mean of 498 days (range 30-805) for clinical endpoints which were defined as a composite of cardiovascular death, and worsening of heart failure symptoms. Of the 18 patients with clinical endpoints, 1 died of sudden death, and 17 had worsening of heart failure symptoms. Variables associated with an increased hazard of clinical endpoints in univariate analysis were log Nt-proBNP, NYHA functional class, left ventricle outflow obstruction and female gender. Nt-proBNP level (p=0.015, HR=1.6) and NYHA functional class (p=0.025, HR=3.7) were the independent variables associated with an increased risk of experiencing clinical endpoints (Table 1). Nt-proBNP plasma level =1500 pg/ml detected patients with clinical endpoints with a sensitivity and specificity of 83% and 81%, respectively. The event free survival was found to be significantly lower in patients with Nt-proBNP levels =1500 pg/ml.

Table 1

	Univariate		Multivariable	
	p	HR (95% CI)	p	HR (95% CI)
Log NT-proBNP	0.0001	2.9 (1.56-3.24)	0.015	1.6 (1.10-2.55)
NYHA class III	0.0001	8.5 (3.32-22.0)	0.025	3.7 (1.17-12.09)
LV outflow obstruction	0.006	4.2 (1.52-12.0)	–	–
Female gender	0.017	3.5 (1.25-9.89)	–	–
Maximum wall thickness	0.130	1.8 (0.83-4.11)	–	–
Age	0.141	1.02 (0.99-1.05)	–	–
Family history of sudden death	0.148	2.9 (0.68-12.9)	–	–

LV indicates left ventricle; NYHA, New York Heart Association.

Conclusions: Nt-proBNP is an independent predictor of outcome in HCM patients and may be helpful in risk stratification.

NURSES IN CARDIOVASCULAR DISEASE MANAGEMENT: MAKING THE DIFFERENCE?

2809 Caregiver burden of partners of HF patients; a description and demographic influences

M.L. Luttik[1], T. Jaarsma[1], R. Sanderman[2], D.J. van Veldhuisen[1]. *[1]University Medical Centre Groningen, Cardiology, Groningen, Netherlands; [2]University of Groningen, Health Psychology, Groningen, Netherlands*

Background: HF patients living with a partner have better prognosis compared to patients who are living alone. However caring for chronically ill elderly patients can be burdensome and stressful and may contribute to compromised mental and physiological functioning of these caregivers. Within the field of HF, the caregiver situation is still a neglected research area. Yet to preserve the supportive impact of partners on patiënt outcomes, it may be important to explore the burden of partners and its predictors.
Aim: The aim of this study is to gain insight in the caregiver burden of partners of HF patients and to investigate the influence of their age and gender.
Method: Cross sectional data were collected in 143 partners of HF patients who participated in a large multicentre Heart Failure trial in the Netherlands (COACH). HF partners were asked to complete the Caregiver Reaction Assessment Scale (CRA), which is designed to assess different aspects of the caregiver situation of caregivers of patients with various chronic conditions. Demographic data were collected by interview.

Results: In total 143 HF partners (mean age 68, 81% female) completed the CRA scale. Although most partners (95%) experience a positive impact of caregiving on their self-esteem, a considerable number of HF partners also reported a negative impact of the patiënt's disease on their lives. Seventeen percent of the HF partners indicated a disrupted daily schedule, 12% of the partners reported financial problems and 11% reported lack of family support and loss of physical strength. Younger partners (< 65 years) reported more financial problems compared to elderly partners (p=0.08). Women reported significantly more lack of family support compared to men (p=0.03) and men tended to report more financial problems than women (NS) (table 1).
Conclusion: This study is one of the first to describe the burden of partners of patients with HF. We found moderate feelings of burden, especially in the area of disrupted daily schedule. Financial problems seem to be more present in younger, male partners, while women more often experience a lack of family support. Interventions strategies aimed at improving patient outcome should also incoporate strategies that assess the burden of partners of HF patients.

2810 Persistent positive effect of a dedicated heart failure programme during a follow-up of 5 years

G.V.J. Cleuren, C.M.H.B. Lucas, C.J.J.H. Kirchhof. *Rijnland Hospital, Cardiology, Leiderdorp, Netherlands*

During the last decades the positive effect of several dedicated heart failure programs as a means to guide patients with CHF has been demonstrated as shown by both a decrease in mortality and morbidity. Dedicated nurse do have a prominent role in many programs. Sofar effect of it has been demonstrated in studies with a relatively short follow-up. Therefore we present data from a dedicated CHF-program involving 2 CHF-nurses after an extended follow-up of 5 years. Data are compared to the results from those years working without CHF-program.
Method: From 2000 until 2004 a dedicated heart failure program has been running at the Cardiology department in Leiderdorp involving 1 cardiologist and 2 dedicated heart failure nurses. Characteristics, mortality, admission and readmission rate of all patients were put into a database and compared to results before 2000.
Results: In total 861 individual patients have been admitted for CHF from 2000 until 2004. 260 of the patients died. Characteristics of the patients showed that mean age was 77, with 52% male patients. In the table the number of first and readmissions are shown with data without CHF-program pictured from 1996 until 1999. From 2000 data were collected with a CHF-program running.

	First admission	Readmission
1995	108	63
1996	125	57
1997	127	51
1998	145	30
1999	148	42
2000	175	11
2001	162	14
2002	212	23
2003	209	18
2004	191	22

Conclusion: As shown installation of a CHF-program involving dedicated nurses results in a persistent decrease in the number of readmissions compared to the years before. Also the number of patients dying each year appears to be acceptable in this elderly population compared to larger populations.

2811 Feasibility of immediate home based intra-venous diuretic therapy in NYHA class III/IV CHF-patients, a pilot study

H. Van de Wetering[1], W. Wijtenhorst[1], W.J.S. Louridtz[1], G. Hoogvliet[2], F.J.M. Bongers[3], A.W.J. van 't Hof[4]. *[1]Isala Klinieken, Cardiology, Zwolle, Netherlands; [2]Isala Klinieken, Department of Transmural Care, Zwolle, Netherlands; [3]Dalfsen, Netherlands; [4]Isala Klinieken, Cardiology, Zwolle, Netherlands*

Purpose: To investigate the feasibility and effects of immediate home-based administration of intravenous [IV] diuretics by Advanced Practice Nurses [APN] or Clinical Nurse Specialists [CNS]. The intention is to replace the traditional hospitalisation and to improve Quality Of Life [QOL] in NYHA-class III/IV, Chronic Heart Failure [CHF] patients.
Methods: In a non-randomised, single centre design, CHF-patients with known aetiology and an indication for IV-diuretic treatment were screened in the emergency room. Patients who met the in- and exclusion criteria and gave their informed consent received immediate home-based IV-therapy. In case of deterioration of the CHF-situation, after successful initial treatment, patients received repeated home-based IV-therapy until six months after inclusion. Two weeks after initial treatment and two-monthly thereafter, or more frequent when needed, the effect of the medication regime was reassessed and education and support was given to optimise the CHF-situation on the APN/CNS co-ordinated heart failure outpatient clinic. Additionally, 24/7 telephonic back-up by a senior cardiologist was available.
Results: Twenty-two patients (12 men, 8 women) were consecutively enrolled in the study. Mean age was 69 years (± 17). NYHA Class III: 73%, Class IV: 18%. Mean left ventricular ejection fraction was 25% (± 12.5). The initial home-based treatment succeeded in 12 pts (55%). Mean duration of the initial home-based treatment was 8.1 (± 3.6) days. Mean number of house calls was 9.9 (± 6.2). Eight patients had to be hospitalised; 5 due to insufficient response to the diuretic treatment and 3 for non-cardiac reasons. One patient withdrew informed consent. Two patients died; one suddenly at home, probably due to cardiac arrest and one in hospital due to cardiogenic shock. The initial poor QOL, on the Minnesota Living with Heart Failure questionnaire, with a total score of 60 (37-70) (dimensions: physical 30.5 (24-34) and emotional 10 (5-15.5)), improved at the one month follow-up by 9.5 points (total score 52 (23-57.5), dimensions: physical 27 (11.5- 34.7) and emotional 12 (3-18)).
Conclusions: Immediate home-based administration of IV-diuretics by APN/CNS in CHF-patients is a feasible, patient friendly and safe alternative to the usual in-hospital care and has a positive effect on QOL. To assess efficacy, this pilot is now followed by a trial with randomisation to either hospital admission or home-based treatment.

2812 Nurse initiated telephone follow-up after acute myocardial infarction improves health related quality of life, but not anxiety and depression. A randomised controlled trial

T.A. Hanssen[1], J.E. Nordrehaug[2], G.E. Eide[1], B.R. Hanestad[3]. *[1]Haukeland University Hospital, Centre for Clinical Research, Bergen, Norway; [2]Haukeland University Hospital, Department of Heart Disease, Bergen, Norway; [3]University of Bergen, Public Health and Primary Health Care, Bergen, Norway*

Background: In addition to optimal medical treatment it is important that patients with an acute myocardial infarction (AMI) are provided information and education. Although recommended, only a minority of patients are offered systematic psychosocial care after discharge from hospitals in several European countries.
Aim: The purpose of the present study was to evaluate the effect of a post discharge nurse initiated telephone follow-up intervention on anxiety, depression and health related quality of life (HRQOL), in a context where existing follow-up services are poorly developed.
Method: All patients with a diagnosis of AMI, admitted to the Department of Heart Disease, at Haukeland University Hospital, from September 2001 until December 2003 were potentially eligible and invited to participate in the study. Two-hundred-and-eighty-eight patients consented to participate and were randomised to an intervention group or a control group. The intervention group received nurse initiated telephone follow-up and the control group received standard post discharge follow-up.
Data is collected at baseline, six weeks after discharge, and three and six months after discharge. The Hospital Anxiety and Depression Scale was used to measure anxiety and depression, and HRQOL was measured using the Mental and Physical Component Summary Scales in the SF-36 ® Health Survey. The study was approved by the Privacy Issues Unit, at the Norwegian Social Science Data Services, and by The Regional Committee for Medical Research Ethics.
Results: Although HRQOL improved significantly over time in both groups, a statistical significant difference, in favour of the intervention group, was found on the Physical Health Component Summary Scale (PCS) (p = 0.034) but not on the Mental Health Component Summary Scale. No statistical significant differences were found between the control and the intervention groups for levels of depression and anxiety three and six months after discharge. At all time points approximately 80% in both groups scored 7 or less, a score that reflects normal levels of anxiety and depression.
Discussion: Effect of the intervention was found in the PCS reflecting improvement in the physical dimension of HRQOL. The intervention had no effect on anxiety and depression, but the potential for improvement was smaller than expected, as the mean levels and the proportion of cases with a score categorised as cases for anxiety and depression, was not higher in the study population than what is found in the Norwegian general population.

2813 Lifestyle changes following acute myocardial infarction: patients perspectives

C. Condon. *University College Cork, School of Nursing and Midwifery, Cork, Ireland*

Purpose: Acute myocardial infarction (AMI), accounts for approximately 7000 deaths in Ireland each year. The diagnosis has major implications for an individual in terms of health and social gain, quality of life and living and adapting to a chronic illness. The diagnosis requires an individual to undertake changes to lifestyle patterns such as diet, smoking habits, exercise and stress management. The purpose of this study was to explore patients' perspectives in terms of making lifestyle changes 6 weeks following AMI.
Method: A descriptive qualitative study was undertaken. Ten participants were interviewed six weeks following discharge from hospital about their experiences. Data was collected using in depth interviewing. The data was analysed using thematic analysis. Four themes were identified: lifestyle warning signs, taking responsibility for lifestyle changes, professional support and looking forward to the future.

Results: Findings offer insight into the everyday realities which patients experience regarding lifestyle changes following AMI. Patients were aware of the impact of their negative lifestyle on their health but appeared powerless to make changes prior to the myocardial infarction. The cardiac event motivated them to try to make lifestyle changes but it was more difficult than they anticipated. Particular difficulties were found in the areas of quitting cigarette smoking and stress management. In addition, participants appeared to be instigating too many changes at once. Overall, participants did not seem to have any concept of use of primary health care or the benefits of seeking or receiving continued professional advice and guidance in the community.
Conclusion: The study highlighted the need for health professionals to
Ø Develop an individualised multi disciplinary team approach based on an individual needs assessment
Ø Develop Primary Care Services to establish a support network for patients
Ø Extend Cardiac Rehabilitation Services to all cardiac patients
Ø Re evaluate public media campaigns to assess effectiveness in making behavioural changes
Ø Develop stress management courses for both patients and staff

2814 Nurses can play central role in modern cardiovascular prevention

L. Matwiejczyk[1], T. Zdrojewski[1], P. Zagozdzon[2], M. Bogowicz[1], P. Bandosz[1], M. Kazmirski[1], T. Thomsen[3], B. Wyrzykowski[1] on behalf of the working group of Sopkard and Gdynia-Kard projects.. *[1]Medical University of Gdansk, Dept. of Hypertension and Diabetology, Gdansk, Poland; [2]Medical University of Gdansk, Zaklad Higieny i Epidemiologii, Gdansk, Poland; [3]Medical University of Glostrup, The Center for Medical Prevention, Glostrup, Denmark*

Introduction: evaluation of cardiovascular risk as the part of screening procedures and prevention of cardiovascular diseases is a complex medical, organizational and economic problem. The computer program PRECARD with its 10 major risk factors analysis estimates a long-term absolute risk of myocardial infarction, stroke or death.
Aim: We decided to survey need for using PRECARD in evaluation of cardiovascular risk and making therapeutic decisions in everyday practice of general practitioners and cardiologists. We also wanted to check to what extent nurses have ability to give support in this process.
Material and methods: we invited 2 groups to take part in our survey: 42 nurses from 15 outpatient clinics and a random sample of 50 general practitioners and cardiologists from Northern Poland. 35 physicians (70%) and 42 nurses (100%) decided to participate in the survey. Given instructions about PRECARD they were asked to evaluate the risk of myocardial infarction, stroke and death during examination in 10 consecutive patients. After that, they completed standardized questionnaire which consisted of 16 questions.
Results: the average age of physicians was 41±9 and nurses 46±7. Most of doctors (96%) and nurses (98%) stated there is a need for evaluation of cardiovascular risk, using a wide range of major risk factors, in order to make accurate therapeutic and treatment decisions. 92% physicians and 90% nurses found the program helpful in estimation of cardiovascular risk. A great amount of doctors (86%) regarded PRECARD as the one that helped them make treatment decisions. The way the program works met almost all expectations of 96% of physicians and 100% of nurses. Both doctors (92%) and nurses claimed that usage of graphical methods in showing cardiovascular risk to patients can give them stronger motivation to overcome their bad habits. Finally, 62% of physicians claimed that the only disadvantage of the program is that the visit lasted longer than a traditional visit. On the other hand 78% of nurses perceived they can help physicians in shortening visit and give them essential information about cardiovascular risk by using PRECARD before a traditional examination. The accurate control of all nurses management regarding using the PRECARD program showed very good quality of their work.
Conclusions: the usage of PRECARD can help in proper estimation of cardiovascular risk before making therapeutic decisions in everyday practice. Nurses have essential skills and knowledge to support physicians in this process. Both, doctors and nurses accept this kind of cooperation.

SCIENCE HOT LINE

2815 Cyclin A2 promotes cardiac regeneration after myocardial infarction and prevents heart failure

H.W. Chaudhry, R.K. Cheng, T. Asai, H. Tang, S.L. Jakob, D.J. Wolgemuth. *Columbia University College of Physicians and Surgeons, Dept. of Medicine, New York, USA*

Mammalian myocardial infarction (MI) is typically followed by scar formation with eventual ventricular dilation and heart failure. It has not been definitively shown in previous studies that significant myogenesis can be achieved in mammalian infarcts with sustained recovery of cardiac function. Here we present a novel model system in which mice constitutively expressing cyclin A2 (cycA2) in the myocardium elicit a regenerative response after MI and exhibit significantly limited ventricular dilation and heart failure. New cardiomyocyte formation was noted in the infarcted zones as well as cell cycle re-entry of peri-infarct myocardium with an increase in DNA synthesis and mitotic indices. Transgenic (Tg) and littermate (NTg) controls were subjected to anterolateral MI. Serial MRI scans were utilized to assess volumetric ejection fraction (EF) at 3 weeks and 3 months post-MI. Infarction volume percentage was measured histologically at 3 weeks post-MI and was similar for both groups. Immunofluorescence and confocal microscopy were used to detect phospho-histone H3 (H3P), a mitosis-specific marker, in cardiomyocytes using anti-α-sarcomeric actin (αSA). Tg mice displayed markedly enhanced EF compared with NTg at 3 weeks post-MI {Tg: 37.96±3.18 (n=12), NTg: 26.96±4.01 (n=8), p=0.045} and at 3 months post-MI {Tg: 40.19±3.43 (n=12), NTg: 22.95±3.12 (n=8), p=0.002}. Confocal analysis revealed increased mitotic cardiomyocyte nuclei in the peri-infarct zone in Tg {Tg mitotic index: 0.018; NTg: 0.000; p=0.05, 3 months post-MI}. Sequential labeling with BrDU over 3 months demonstrated enhanced DNA synthesis in the Tg {Tg BrDU-positive index: 0.478; NTg: 0.001; p=0.008}. In Tg, an increased frequency of small (~5 μm diameter) cells were noted in the infarct zone that expressed H3P and αSA. The cells were characterized as "side population" (SP) cells which co-expressed αSA and ABCG2 (known marker of SP cells). αSA/ABCG2-positive cells were noted in the infarct zone of Tg and NTg at 2 and 3 weeks post-MI. Nuclear localization of cyc A2 was noted in the infarct zone cardiomyocytes of Tg only. Thus the presence of SP cells per se did not appear to confer enhanced mitotic ability to small cardiomyocytes noted in the infarct zone of NTg, whereas more mitoses were noted in these cells in Tg. These results indicate that cyc A2 Tg mice are able to repair damaged myocardium with an increase in cardiac function, either through cell cycle re-entry of peri-infarct myocardium or by augmenting endogenous regenerative mechanisms via induction of SP cells with enhanced proliferative capacity. The ability of cultured transgenic cardiomyocytes to undergo cytokinesis provides mechanistic support for the regenerative capacity of cyclin A2.

2816 Vaccination against interleukin 12 attenuates atherosclerosis in low-density lipoprotein receptor deficient mice

A.D. Hauer[1], C. Uyttenhove[2], J.C. Renauld[3], T.J.C. van Berkel[1], J. van Snick[3], J. Kuiper[1]. *[1]Division of Biopharmaceutics, Leiden University, 2333 CC, Leiden, The Netherlands; [2]Ludwig Institute for Cancer Research and Cellular Genetics Unit, Université de Louvain, Belgium; [3]Ludwig Institute for Cancer Research and Experimental Medicine Unit, Université de Louvain, Belgium*

Objectives: Interleukin 12 (IL-12) is thought to play a central role in a number of (auto)immune diseases, such as arthritis, Crohn's disease, and atherosclerosis. IL-12 is a key inducer of proinflammatory, Th1-type cytokines and the production of these cytokines is thought to enhance the development of atherosclerosis. Clinical studies show that administration of anti-IL-12 antibodies is associated with decreased production of proinflammatory, Th1-type cytokines and this may induce remission in patients with active Crohn's disease [1]. In the present study we developed a method to block endogenous IL-12 by means of vaccination and determined the effect of this vaccination on atherogenesis.
Methods and Results: Vaccination of LDL receptor deficient ($LDLr^{-/-}$) mice against IL-12 was accomplished by 5 intra-muscular injections with 2 μg of IL-12-PADRE complex in combination with the adjuvant o/w emulsion (low dose)/MPL/QS21 (a gift of GSK, Belgium) every 2 weeks. This resulted in the formation of anti-IL-12 antibodies that specifically blocked the biological action of IL-12 in an *in vitro* bio-assay. In addition we could show that IL-12 vaccination blocked the *in vivo* IFN-gamma response to IL-12 for more than 90%. Subsequently, we determined the effect of IL-12 vaccination on atherosclerosis and two weeks after the final vaccination atherogenesis was initiated in the carotid arteries by perivascular collar placement [2]. IL-12 vaccination resulted in a significant reduction (68.5%, $p<0.01$) in atherogenesis as compared to control mice. IL-12 vaccination also resulted in a significant decrease in intima/media ratio's (66.7%, $p<0.01$), and in the amount of stenosis (57.8%, $p<0.01$, which are both clinically important parameters. Besides effects on plaque size, the composition of the plaques was changed upon IL-12 vaccination, since both the α-smooth muscle cell actin and collagen content in the neointima increased 3- ($p<0.01$) and 4-fold ($p<0.01$), respectively. Vaccination against IL-12 resulted in a reduced inflammatory status of the plaque, which was reflected by the complete absence of IFN-γ positive cells within atherosclerotic plaques, whereas control plaques contained IFN-γ positive cells ($p<0.05$).
Conclusions: We conclude that the functional blockade of IL-12 by vaccination resulted in a significant reduction in atherosclerosis in $LDLr^{-/-}$ mice. Vaccination against IL-12 improved plaque stability and IL-12 vaccination may therefore be considered as a promising strategy to treat atherosclerosis.
References: [1] Mannon PJ et al. Anti-interleukin-12 antibody for active Crohn's disease. N Engl J Med 2004;351:2069-79.
[2] von der Thuesen et al. Induction of rapid atherogenesis by perivascular carotid collar placement in apolipoprotein E-deficient and low-density lipoprotein receptor-deficient mice. Circulation 2001;103:1164-70.

2817 AKT overexpression ameliorates heart failure by phosphorilating key Ca^{2+} handling protein

P. Gallo[1], M. Santonastasi[2], M. Ceci[2], C. Scimia[1], G. Di Sciascio[1], G. Condorelli[1]. [1]*Campus Bio-Medico University, Rome, Italy;* [2]*San Raffaele Biomedical Science Park, Rome, Italy*

Cardiomyocytes (CMC) adapt to physical stress by increasing cell size while maintaining cell functionality ("physiological hypertrophy"), in contrast to maladaptation, in which cell size and functionality do not increase accordingly. The biochemical pathways involved in "physiological" hypertrophy are starting to be unraveled; Akt seems to be among the key molecules of this process. In previous studies, we and others showed that Akt overexpression increases CMC size and improves cardiac function in transgenic mice. Moreover, we determined that Akt increases inotropism and lusotropism at a cellular level and showed indirect evidence that Akt improves sarcoplasmic reticulum (SR) Ca^{2+} uptake. Here, we further investigate the molecular mechanisms of Akt on Ca^{2+} metabolism. We show that Akt overexpression 1) phosphorylates two key Ca^{2+} handling proteins, phospholamban (PLB) and ryanodine receptor (RyR), in the respective Ca^{2+}-calmodulin dependent kinase 2d (CAMK2) but not PKA site; 2) increases I_t Ca^{2+} both in transgenic animals and in wild type CMCs transduced with different active forms of Akt. Phosphorylation of PLB at the CAMK site by active Akt induces an increase in SR-Ca^{2+} uptake in biochemical assays in vitro. We further proved that an active Akt mutant directed to the SR induces PLB phosphorylation and increase in the SR Ca^{2+} uptake without inducing SERCA2 protein level upregulation and cell hypertrophy. The effects of Akt in modulating cardiac contractility were also studied in a transgenic mouse model of cardiac-specific overexpression through transverse aortic constriction. Data show that Akt decreases the negative long-term effects of banding, improving cardiac function. Thus, in this report we demonstrate that Akt improves Ca^{2+} handling by phosphorylating PLB and RyR2 and demonstrate that Akt ameliorates cardiac function also in a heart failure setting.

2818 Prostacyclin improves transcoronary myocardial delivery of adipose tissue-derived stem cells

R. Madonna[1], L. Rinaldi[1], P. Di Napoli[1], M. Massaro[2], C. Rossi[1], R. De Caterina[1,2]. [1]*Institute of Cardiology, Center of Excellence on Aging "G. d'Annunzio" University, Chieti, Italy;* [2]*Institute of Clinical Physiology, CNR, Pisa and Lecce, Italy*

Background: Transplantation of multipotent adipose tissue-derived stem cells (ASCs) into a damaged heart is a novel therapeutic approach for cardiac repair. Prostacyclin (PGI_2) exerts cardioprotection from ischemic damage and might favour the myocardial delivery of stem cells. We therefore analysed efficacy and safety of combining PGI_2 with ASC for intracoronary ASC delivery.
Methods: Hearts from 44 C57BL/6J mice were perfused with a modified Krebs-Henseleit (KH) buffer with a Langendorff perfusion apparatus. After 10 min stabilization, intracoronary infusion of bisbenzimide-prestained murine adipose tissue-derived stem cells (ASCs at first passage, $0.5x10^6$ cells/mL/min), was performed for 20 min in the presence or absence of PGI_2 (10^{-8} - 10^{-6} mol/L). We monitored coronary flow (CF), heart rate (HR), left ventricular peak pressure (LVP), +dP/dtmax, and –dP/dtmax and markers of myocardial damage (cTnI, CPK, MB-CPK, myoglobin, LDH), and nitrite and nitrate production in the coronary effluent. In parallel experiments, dose-response curves using increasing number of ACSs (10^5 - $0.5x10^6$ - $1x10^6$ - $2x10^6$ - $4x10^6$) or increasing concentrations of PGI_2 alone were performed, aimed at analysing functional and metabolic alterations. After trasfusions, the hearts were fixed and analysed at histopathology for the amount of fluorescent ASCs delivered into the myocardium.
Results: Murine hearts with coronary infusion of ASCs at $\leq 1x10^6$ cells/ml/min showed no major changes in contractility and rhythm. However, at higher doses (2-4 $x10^6$ cells/mL/min), cardiac dysfunction, with a decline in hemodynamic parameters, was observed. Perfusion with PGI_2 alone (10^{-8} - 10^{-6} mol/L) resulted in significant CF increase and nitrite/nitrate accumulation in the coronary effluent (Table). The addition of PGI_2 (10^{-8} - 10^{-6} mol/L) to ASCs concentration-dependently increased delivery and entrance of ASCs into the myocardium without affecting ventricular and metabolic functions of the perfused hearts (Table).

Table 1. Parameters at 20 min after ASCs ± PGI_2 perfusion

	KH	ASCs	PGI_2 (mol/L) without ASCs			PGI_2 with ASCs	
			10^{-8}	10^{-7}	10^{-6}	10^{-7}	10^{-6}
CF (mL/min)	3±0,3	3.3±0.2	2.9±0.1	3.7±0.2*	5.5±0.3 *	3±0.2	4.6±0.3*
nitrates (μg/mL)	3±1	1±5	0.2±1	0.5±4	10±7*	42±40*	80±5*
cTnI (ng/mL)	1.05±0.1	1.14±0.22	1±0.14	1.01±0.18	0.92±0.18	1.15±0.2	1±0.28
ASCs/0.05 mm^2	0	46±5*	0	0	0	122±15**	492 ±24**

*p < 0.05 vs KH; **p < 0.05 vs ASCs.

Conclusions: Perfusion of ASCs at doses $\geq 2x10^6$ cells/mL/min causes cardiac dysfunction. PGI_2 increases the safety and delivery of ASCs into the hearts, possibly through the elevation of nitric oxide, without adverse effects on cardiac function.

2819 Dual level of interaction between calcineurin and protein kinase C-epsilon in cardiomyocyte stretch

F. Vincent, N. Duquesnes, C. Christov, B. Crozatier. *Unité INSERM U400, Faculté de Médecine, Créteil, France*

Cellular stretch activates a number of interacting pathways such as Protein kinase C (PKC) or tyrosine kinases. In turn, they activate the Mitogen Activated Protein Kinases (MAPK) ERK and JNK, leading to the development of cardiac hypertrophy. In this study, we looked for an involvement of calcineurin and PKCε on stretch-induced ERK and JNK activations. MAPK activation was measured by Western Blot analysis using specific antibodies directed towards their phosphorylated forms in neonatal rat cardiomyocytes stretched for 15 minutes. The involved PKC isoform was shown to be PKCε since stretch induced its translocation from the cytosolic to the membrane fraction and ERK and JNK activations were blocked by a cellular transfection by a peptide specific inhibiting its activation. Both a down regulation of PKC by PMA (1μM, 24 hours) and the addition of FK506, a calcineurin inhibitor (0.1μM) reduced by more than 50% the activation of ERK and JNK. These changes were not additive, suggesting a cluster of proteins interacting with MAPK during cellular stretch. The data shown here demonstrate that calcineurin and PKC-ε co-operate at 2 levels dutring stretch. At the cytosolic level, stretch-induced translocation of PKC-ε from cytosolic to the membrane fraction was inhibited by calcineurin inhibitors showing that calcineurin is necessary for PKCε activation induced by stretch. A second level of interaction between calcineurin and PKC-ε was demonstrated by co-precipitation studies that showed that PKC-ε and calcineurin are associated in a complex which is larger during stretch. In addition, after stretch, calcineurin and PKC-ε are co-localised at the level of the perinuclear membrane. Thus, calcineurin appears to be necessary for stretch-induced PKC-ε activation after which the phosphatase and the kinase appear are colocalised at the level of the perinuclear membrane where they may finely regulate the phosphorylation level of their target proteins.

2820 Impaired mobilisation of $CXCR4^+/CD34^+$ stem cells early in acute myocardial infarction is associated with low left ventricular ejection fraction and high N terminal-pro brain natriuretic peptide levels after 1 year follow-up

W. Wojakowski[1], R. Wyderka[1], A. Zebzda[2], M. Majka[2], M.Z. Ratajczak[3], M. Tendera[1]. [1]*3rd Division of Cardiology, Silesian School of Medicine, Katowice, Poland;* [2]*Department of Transplantology, Polish-American Children's Hospital, Medical College, Jagiellonian University, Krakow, Poland;* [3]*Stem Cell Biology Program at James Graham Brown Cancer Center and Department of Medicine, University of Louisville, KY, United States of America*

Background: Stem cells are mobilized into peripheral blood early in acute myocardial infarction (AMI). In patients with low left ventricular ejection fraction (LVEF) and high levels of NT-proBNP in acute phase of AMI the mobilization of $CD34/CXCR4^+$ cells is significantly impaired. It remains unknown whether the stem cells mobilization can influence the LVEF in long-term follow-up after AMI.
Aim of the study was to correlate the early mobilization of $CD34^+$, $CD117^+$, $CXCR4^+$, c-met^+ stem cells in patients with STEMI treated with primary PCI with LVEF, NT-proBNP levels, hematopoietic cytokines, spiroergometric exercise test results in one-year follow-up.
Methods: 40 patients with STEMI (<12 hours) treated with primary PCI were enrolled. Blood samples were obtained on admission, after 24 hours and 7 days as well as after 1 year (12-16 months). Stem cells number was measured using FACS and concentrations of NT-proBNP, SDF-1, G-CSF, VEGF, IL-6 and HGF were measured using ELISA kits. Echocardiography was carried out on admission and after 1 year and ergospirometric exercise test (VO2 max., VE/VCO2 slope, VE/VCO2 peak/rest, VE/VCO2 peak, VE/VCO2 rest) after 1 year post AMI.
Results: In patients with baseline LVEF ≤ 40% as well as with NT-proBNP levels in the highest tertile the number of mobilized $CXCR4^+/CD34^+$ stem cells on admission was significantly lower in comparison to patients with LVEF >40% ($p<0.03$) and NT-proBNP levels in the lowest tertile ($p<0,001$). Moreover, patients with LVEF ≤40 after 1 year had lower baseline $CXCR4^+$ cell counts than patients with LVEF>40% on follow-up visit ($p<0.03$). Baseline number of $CXCR4^+$ cells was positively correlated with LVEF after 1 year ($r=0.55$; $p<0.03$) and in multivariate regression was independent predictor of LVEF < 40% after 1 year. The peak number of mobilized $CXCR4^+$ stem cells early in STEMI was also significantly positively correlated with the number of circulating $CD34^+$, $CXCR4^+$ and $CD117^+$ cells after 1 year ($CD34^+$: $r=0.35$, $p<0.05$; $CXCR4^+$: $r=0.38$; $p<0.03$; $CD117^+$: $r=0.4$, $p<0.02$) and patients with low baseline $CXCR4^+$ cell counts had lower number of $CD34^+$, $CD117^+$ and $CXC4^+$ cells as well as higher levels of NT-proBNP after 1 year (all $p<0.03$). The number of stem cells both on admission and at follow-up was significantly lower in patients aged > 50 years in comparison to younger subjects ($p<0.05$). No significant correlation between baseline stem cells number and exercise test results were found.
Conclusion: In STEMI patients with low LVEF and high NT-proBNP levels the mobilization of $CD34^+$, $CD117^+$, $CXCR4^+$, c-met^+ stem cells into peripheral blood is significantly compromised. The impaired mobilization of stem cells early in STEMI is associated with lower LVEF, higher levels of NT-proBNP and lower circulating stem cells number after 1 year.

e-POSTER SESSION 7

MODERATED e-POSTERS: MODULATION OF ION CHANNEL AND EXCITATION-CONTRACTION COUPLING

P2821 Cardiac nNOS regulates myocardial relaxation by stimulating phospholamban phosphorylation

Y.H. Zhang[1], M.H. Zhang[1], C.E. Sears[1], B. Casadei[2]. [1]*University of Oxford, Cardiovascular Medicine, Oxford, UK;* [2]*John Radcliffe Hospital, Dept. of Cardiovascular Medicine, Oxford, UK*

We have shown that selective gene deletion of the neuronal isoform of nitric oxide synthase (nNOS) results in a significantly impaired basal and beta-adrenergic myocardial relaxation both in vitro and in vivo. However, the mechanisms responsible for these findings remain unclear. To address this issue, we evaluated LV myocytes function in the presence of 10 μmol/L thapsigargin (TG) to disable SR function. Contraction (6Hz, 35°C) in the presence of TG remained greater in nNOS-/- myocytes; however TR50 no longer differed between groups both in basal conditions and in the presence of 1μmol/L isoproterenol (ISO). Similarly, the decay of the field-stimulated $[Ca]_i$ transient was prolonged in nNOS-/- myocytes both at baseline and in the presence of ISO, but the decay of the caffeine-induced [Ca]i transient (which does not depend on SR Ca reuptake) did not differ between groups (tau = 859.2 ± 31.8 ms vs. 980.9 ± 83.5 ms in the presence of ISO, n=15 in both groups, P=NS). These data suggest that slower SR Ca reuptake may be responsible for the impaired myocardial relaxation in nNOS-/-myocytes. It is well established that PLB phosphorylation by either cAMP-dependent protein kinase A (on Ser16) or calmodulin kinase II (on Thr17) removes the inhibitory action of phospholamban (PLB) upon the SR Ca pump (SERCA) and accelerates relaxation. Quantitative immunoblotting of LV homogenates or LV myocyte membrane subfractions showed a significant reduction in PLB phosphorylation at the Ser16 and Thr17 sites in nNOS-/- mice compared with wild type (WT) littermates (n=5 hearts per group, $P<0.01$). SERCA2a protein level did not differ between groups but total PLB was modestly decreased in nNOS-/- mice (PLB/GAPDH ratio: 0.5 ± 0.02 vs. 0.7 ± 0.005 in WT, $p<0.05$). Nevertheless, the PLB Ser16/PLB ratio remained significantly lower in nNOS-/- (ca. 40% of WT). nNOS specific inhibition with SMTC (100nmol/L) caused a significant reduction in Ser16 and Thr17 PLB phosphorylation in WT mice, with no change in total PLB. Pretreatment of isolated LV myocytes with ISO (1μmol/L) increased Ser16 PLB phosphorylation in both groups, but the PLB phosphorylated fraction remained significantly lower in nNOS-/- myocytes. Co-immunoprecipitation indicated a physical interaction between nNOS and Ser16 PLB but not with SERCA.
These findings indicate that nNOS is an important dynamic regulator of PLB phosphorylation and as such of SERCA activity and suggest that upregulation of myocardial nNOS in infarcted hearts may be an important adaptive response aimed at preserving SR Ca cycling.

P2822 S100A1 regulates the function of the cardiac ryanodine receptor

M. Voelkers[1], C.M. Loughrey[2], C. Eicher[1], A. Remppis[1], H.A. Katus[1], G.L. Smith[2], P. Most[1]. [1]*University of Heidelberg, Cardiology, Heidelberg, Germany;* [2]*Institute of Biomedical & Life Science, University of Glasgow, Glasgow, United Kingdom*

S100A1 enhances the intracellular calcium transients in cardiac as well as in skeletal muscle. In skeletal muscle, S100A1 has recently been shown to interact with the Ryanodine-Receptor (RyR). This interaction caused an enhanced sarcoplasmic calcium release in skeletal muscle. In this study we analysed the hypothesis that the calcium-binding Protein S100A1 plays a role in the regulation of the cardiac RyR. A co-localization between S100A1 and RyR could be evidenced by immunfluorescenz-microscopy in isolated adult rat cardiomyocytes. In accordance, revealed co-immunoprecipitation a calcium dependent interaction of S100A1 with the RyR. This interaction leaded in 3[H]-Ryanodin-bindings assays to a biphasic regulation of the RyR At low $[Ca^{2+}]$ (<300 nM) under diastolic conditions reduced incubation with S100A1 the open probability of the RyR, increasing $[Ca^{2+}]$ caused an increased 3[H]-Ryanodin-binding, respectively open probability. In line with this effect caused incubation with 0,1μM S100A1 at 200 nM Ca in cardiac sarkoplasmic-retikulum (SR) vesicles a significant reduction of the SR calcium leak, and in contrast caused enhancement to 400 nM Ca a significant increase in the calcium induced calcium release. An effect of S100A1 on the activity of the RyR at 150 nM Ca was investigated using the analysis of elementary calcium release events (Ca-sparks). Ca^{2+} spark morphology was measured in β-escin permeabilized cardiomyocyte at a free $[Ca^{2+}]_i$ of 150 nM using line-scan confocal microscopy (Fluo-3-fluorescence). Perfusion with 0,1 μM S100A1 reduced the average values of the spark parameters in a time-depending manner. This study brings evidence for the first time that S100A1 affects the activity of the RyR in a biphasic manner. Under diastolic conditions S100A1 seals the RyR, preventing a depletion of the SR Ca^{2+} load, during the increase of the intracellular Ca^{2+} concentration during the systole S100A1 enhances the Ca^{2+} release and improve the systolic function. Thus, S100A1 acts as a biphasic modulator of the RyR in the myocardium and the positive inotropic effects of S100A1 are in part maybe mediated by the regulation of the RyR.

P2823 The sarcolemmal calcium pump – a new dimension in the regulation of the calcineurin/NFAT pathway in the heart

M.H. Buch[1], A.H. Maass[2], A. Pickard[1], A. Rodriguez[3], S. Langer[4], J.M. Redondo[3], A.L. Armesilla[1], L. Neyses[1]. [1]*University of Manchester, Div. of Cardiology, Manchester, United Kingdom;* [2]*University of Wuerzburg, Dept. of Medicine, Wuerzburg, Germany;* [3]*Universidad Autónoma de Madrid, Centro de Biología Molecular, Madrid, Spain;* [4]*University of Colorado, Dept. Mol. Cell. and Develop. Biology, Boulder, United States of America*

The importance of the calcineurin/nuclear factor of activated T-cell (NFAT) signalling pathway in cardiovascular growth and function is well recognised. Elucidating the regulatory mechanisms of calcineurin thus has the potential to uncover new therapeutic targets. Increasing evidence supports a role for the plasma membrane calcium/calmodulin ATPase pump (PMCA) as a modulator of signal transduction pathways. We used immunoprecipitation and western blot analysis techniques to demonstrate a novel interaction between calcineurin and PMCA4b, an isoform known to be expressed in the heart. This interaction was narrowed to the region 58-143 of the catalytic domain of the calcineurin A subunit, and the region 500-575 of PMCA4b. In mammalian cells, over-expressed PMCA4b conferred a significant inhibitory effect on endogenous calcineurin activity, reflected in the transcriptional activity of NFAT, the best characterised substrate of calcineurin. The co-expression of the PMCA4b interaction peptide, however, reversed the inhibition of endogenous calcineurin activity. This suggests PMCA4b may confer its inhibitory effect through the recruitment of calcineurin to a low calcium micro-environment. PMCA4b was not, however, able to inhibit a constitutively active calcium/calmodulin independent mutant of calcineurin A signifying a calcium/calmodulin dependent mechanism. In rat neonatal cardiomyocytes, expression of an adenovirus encoding PMCA4b significantly inhibited calcineurin activity when cells were stimulated with phenylephrine, in a dose-dependent manner. Moreover, agonist-mediated cardiomyocyte hypertrophy, measured by protein synthesis and ANP transcriptional activity, was also markedly reduced. These findings provide fresh insight into the regulation of the calcineurin/NFAT pathway in cardiac hypertrophy, and may offer new potential for therapeutic interventions.

P2824 Beta adrenergic stimulation produces diastolic Ca release mainly by increasing sarcoplasmic reticulum Ca content

L. Venetucci. *The University of Manchester, Cardiovascular Research Group, Manchester, United Kingdom*

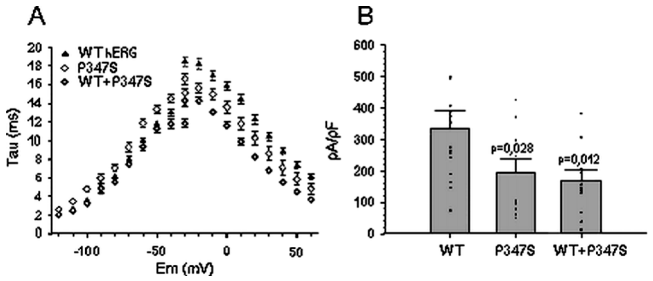
Purpose: Under various pathologic conditions the sarcoplasmic reticulum (SR) can release Ca independently from an action potential during diastole. This diastolic Ca release (also known as Ca wave) can generate arrhythmias by activating the Na-Ca exchanger (NCX) and producing delayed after-depolarisations. Although it is well established that β adrenergic stimulation can cause diastolic Ca release, the mechanisms responsible are unclear. There are two possible explanations: rise in SR Ca content or increased activation of the Ryanodine receptor (the main SR Ca release channel). The aim of this study was to clarify the main mechanism that causes the appearance of Ca waves after β adrenergic stimulation.
Methods and results: The studied was carried out on rat ventricular myocytes that were voltage clamped at -40 mV and were stimulated using 100 msec voltage steps to 0 mV. Of 38 cells exposed to 1 μM isoprenaline 28 had diastolic Ca release. The SR Ca content was quantified from the integrated NCX current produced by caffeine application. In cells showing diastolic Ca release in isoprenaline, the mean values for SR Ca content were 69 ± 11 μmol/l in control and 116 ± 12 μmol/l in 1 μM isoprenaline (n=9). In 5 cells stimulation was stopped for 2 minutes, immediately after cessation of stimulation the cells had 2 or 3 diastolic Ca release events. The SR Ca depletion caused by these Ca waves was calculated by integration of the inward current associated with the wave. The average SR Ca loss associated with these waves was 19.8 ± 3.1 μmol/l. During the remaining part of the rest period no diastolic Ca release was observed. When stimulation was restarted the Ca transient amplitude was smaller than pre rest and gradually increased. Diastolic Ca release reappeared only after the amplitude of the Ca transient had reached levels similar to pre-rest. The analysis of the Ca fluxes demonstrated that at the restart of stimulation the SR Ca content gradually increased until Ca waves occurred. After the appearance of Ca waves there was no further Ca gain.
Conclusions: β adrenergic stimulation increases SR Ca content mainly in stimulated cells. Increase in SR Ca content is the main mechanism responsible for the appearance of diastolic Ca release after β adrenergic stimulation.

P2825 Relation between acquired and congenital LQTS aetiologic components in a P347S hERG mutation: a silent genotype uncovered

J.B. Saenen[1], A. Raes[1], A. Paulussen[2], J. Aerssens[3], D.J. Snyders[1]. [1]*UA, Lab for Molecular Biophysics, Antwerp, Belgium;* [2]*CARIM, Maastricht, Netherlands;* [3]*Johnson & Johnson Pharmaceutical R&D, Department of Pharmacogenomics, Beerse, Belgium*

The long QT syndrome(LQTS) predisposes to Torsade de pointes(Tdp) and ven-

tricular fibrillation. The exact role of acquired and congenital components in the aetiology of clinical cases frequently remains unclear due to the multi-factorial nature of the disorder. Hence, differentiating high-risk patients eligible for IACD placement from acquired LQTS patients in need of conservative treatment still poses a great challenge, given its lethal potential and the physical and economical burden of IACD placement. Consequently this prompts for analysis of all aetiologic factors to allow evidence-based decision-making tailored to the individual properties of LQT-cases. We present biophysical properties of a silent hERG mutation uncovered by a drug-induced LQTS. A mutation found in KCNH2 resulted in a P347S amino acid substitution. Channel kinetics (Fig. A) revealed faster time constants for onset of inactivation but a slower recovery from inactivation for P347S compared to wild-type (WT). Co-expressing WT with P347S, mimicking heterozygosity, showed an even faster inactivation but an almost WT recovery. Upon reactivation these kinetic properties allow increased pooling of the channels into the inactivated, non-conducting, state which resulted into a reduced current during repolarisation. Administration of the suspected drugs revealed no differences in drug block yielding a true acquired aetiologic component. Transient co-expression revealed a 50% current density decline suggesting a trafficking impairment induced by P347S (Fig. B).



Figures

This study demonstrates a silent LQTS genotype in which kinetic changes along with a reduced expression level in the heterozygous situation yield a reduced IKr which merely became a phenotype when superimposed by the concomitant use of QT-prolonging drugs.

P2826 Effects of atorvastatin on hKv1.5 and Kv4.3 potassium currents

R. Gomez, L. Nunez, M. Vaquero, R. Caballero, E. Delpon, J. Tamargo. *Universidad Complutense Madrid, Pharmacology, Madrid, Spain*

Atorvastatin is a HMG-CoA reductase inhibitor (statin) widely used in the treatment of hypercholesterolemia. It has been demonstrated that statins could be useful in the prevention of the recurrence of lone atrial fibrillation (AF), after successful cardioversion. Moreover, in a canine model of AF, statins attenuated AF promotion, through mechanisms independent of the reduction in serum cholesterol levels and antioxidant properties. However, its effects on the two main human atrial repolarizing K^+ currents are unknown. In this study we have analyzed the effects of atorvastatin on hKv1.5 and Kv4.3 channels, which are the counterparts of the human atrial IKur and Ito1, respectively, stably or transiently transfected in Ltk- and CHO cells using the whole-cell patch-clamp technique.
Atorvastatin (0.01 nM-500 μM) produced a concentration-dependent block of hKv1.5 channels (IC50=4.5$\pm$1.7 μM, nH=0.2$\pm$0.01). The blockade induced by 10 nM atorvastatin, appeared in the voltage range of channel opening (25.4$\pm$4.2% at -10 mV) and, thereafter, it remained constant (26.3$\pm$3.5% at +60mV,n=10,$P>0.05$). Moreover, atorvastatin-induced block of hKv1.5 channels resulted frequency-dependent, reaching a 31.9$\pm$3.4% at 5 Hz. Atorvastatin shifted the midpoint of the activation (VhAT=-26.6$\pm$2.6 mV vs. VhC=-22.5$\pm$2.3 mV;$P<0.01$) and inactivation (VhAT=-24.5$\pm$2.2 mV vs. VhC=-20.5$\pm$1.2 mV;$P<0.05$) curves to more negative potentials, without modifying the time course of tail current deactivation (TaufC=42.0$\pm$6.9 ms;$P>0.05$).
Atorvastatin (0.01 nM-200 μM) also blocked Kv4.3 channels in a concentration-dependent manner (IC50=13.9$\pm$3.6 nM, nH=0.2$\pm$0.03). At 10 nM, the drug reduced the peak current amplitude at +50 mV by 25.2$\pm$4.1% and accelerated the time course of the fast phase of current decay (TaufAT= 16.6$\pm$1.8 ms vs. TaufC= 24.7$\pm$4.4 ms, n=6,$P<0.05$), without modifying the voltage dependence of current inactivation (VhC=-38.8$\pm$2.6 mV;$P>0.05$). The blockade induced was voltage-independent and frequency-dependent, reaching a 37.2$\pm$6.5% when pulses to +50 mV were applied at a frequency of 5 Hz. The inhibition induced by atorvastatin was not modified by vitamin C or N-nitro-L-arginine-methyl ester (L-NAME) indicating that it did not involve antioxidant actions or the activation of the nitric oxide synthase. All these results demonstrated that atorvastatin, at concentrations reached after the administration of therapeutic doses, directly block Kv4.3 and hKv1.5 channels, with this order of potency. Supported by CICYT (SAF2002-02304), CAM (08.4/0038/20011 and GR/SAL/0897/2004), Pfizer Foundation and Red RECAVA Grants.

CARDIAC ELECTROPHYSIOLOGY AND REMODELLING

P2827 (W) Beta-adrenergic activation supports IKs activation during tachycardia

M. Bondesan[1], M. Rocchetti[1], G. Mostacciuolo[1], A. Zaza[2]. *[1]Università Milano-Bicocca, Biotecnologie e Bioscienze, Milano, Italy; [2]Università di Milano-Bicocca, Dip. Biotechnologie e Bioscienze, Milan, Italy*

Particularly during tachycardia, action potential duration may seem inadequate to allow for significant IKs activation; still, IKs deficiency causes major repolarization instability. Since tachycardia is physiologically induced by beta-adrenergic (b-AR) stimulation, we have evaluated whether the latter may interact with pacing cycle length (CL) to explain this apparent paradox. We measured IKs during activity at CLs of 0.25 and 1 s, reproduced in guinea-pig ventricular myocytes by the action-potential-clamp technique (HMR1556-sensitive current, at 35C°). The time course of IKs conductance (GKs) was obtained from the ratio between IKs and membrane potential traces. Average (n=10) GKs course during the action potential plateau is shown in the figure at two CLs, in control (CONT) and with a b-AR agonist (ISO, 0.1 μM). GKs increased at shorter CL due to 1) larger instantaneous GKs, reflecting incomplete diastolic deactivation; 2) faster onset of time-dependent GKs, reflecting increased activation rate. ISO increased instantaneous GKs to a minor extent, but strongly accelerated GKs onset; the latter effect was larger at the shorter CL (+693% vs. +159%). In standard V-clamp experiments ISO slowed deactivation at -80 mV compatibly with the slight increase in instantaneous GKs, but accelerated activation too little to account for the major increase observed under AP-clamp. Thus: 1)CL-dependent increase in IKs may mostly depend on a change in activation rate, rather than on incomplete diastolic deactivation; 2) b-AR stimulation and CL shortening interact to increase IKs activation rate, thus adapting current profile to shorter repolarization;3)IKs contribution to repolarization may be underestimated if b-AR activation is not considered.

P2828 The block of transient outward potassium current lengthen action potential duration

A. Varro[1], L. Virag[2], K. Acsay[2], N. Jost[3], C. Lengyel[4], J.G. Papp[2]. *[1]University of Szeged, Dept of Pharmacology and Pharmacotherapy, Szeged, Hungary; [2]University of Szeged, Department of Pharmacology and Pharmacotherap, Szeged, Hungary; [3]Hungarian Academy of Sciences, Division of Cardiov Pharmacology, Szeged, Hungary; [4]University of Szeged, First Department Internel Medicine, Szeged, Hungary*

Previous studies suggested that the transient outward potassium current (Ito) may play an important role in controlling the repolarisation in ventricular muscle. In this study we took advantage of the observation that at high (100 μM) concentration of chromanol 293B in addition of blocking IKs largely inhibits Ito without affecting other repolarizing potassium currents like IK1 and IKr. Therefore, in the presence of full IKs block (by L-735,821) the chromanol 293B induced change of action potential and of ionic currents can be attributed to its effect on Ito. Based on this assumption, the aim of the present study was to investigate the role of Ito in cardiac repolarisation by applying the standard microelectrode and patch-clamp techniques in canine and human ventricular preparations at 37 °C.
Chromanol 293B (100 μM) in the presence of 100 nM L-735,821 (full IKs block) lengthened the repolarisation in dog ventricular muscle. In single dog ventricular myocytes the amplitude of the slow inactivation phase of Ito was 172$\pm$33 pA while the inactivation time constant was 23.5$\pm$2.5 ms (test potential 20 mV, n=12), which imply a substantial Ito current during the plateau phase of the action potential. The Ito current during the action potential plateau phase (14.6$\pm$6.6 pA at 50 ms from the upstroke, n=9) was measured as chromanol 293B sensitive current in dog left ventricular myocytes using an action potential waveform as command potential. The amplitude and inactivation time constant of the slow phase of the Ito current as a function of the test potential were also measured in undiseased human ventricular myocytes, which were similar to those found in dog (224$\pm$33 pA and 29.2$\pm$3.8 ms, test potential 20 mV, n=6).
We concluded that not only the rapid but also the slowly inactivating Ito, which carries significant outward current in the plateau phase of the action potential, may play an important role in cardiac repolarisation.

P2829 Adrenomedullin activates mitochondrial KATP channels in neonatal rat ventricular myocytes

Y. Katsube[1], M. Hajikano[2], S. Ogawa[3], R. Fukazawa[3], M. Kamisago[3], Y. Kuramochi[3], Y. Uchikoba[3], N. Sperelakis[4]. *[1]Nippon Medical School 2nd Hospital, Pediatirics, Kawasaki, Japan; [2]Nippon Medical School 2nd Hospital, Pediatrics, kawasaki, Japan; [3]Nippon Medical School Hospital, Pediatrics, Tokyo, Japan; [4]University of Cincinnati, Mol. & Cell. Physiology Dept, Cincinnati, United States of America*

Introduction: Adrenomedullin (ADM) is a potent vasodilator peptide that was originally isolated from human pheochromocytoma. It was reported that ADM exerts vasodilating action on blood vessels, and has cardioprotective and inotropic actions on the heart. However, the mechanism of action of ADM is still unclear.

Purpose: To elucidate the mechanisms for the cardioprotective and inotropic actions of ADM.
Methods: Using isolated neonatal rat (3-10 days) ventricular myocytes, whole-cell current and voltage clamp techniques were performed.
Results: The action potentials (APs) were dramatically shortened by ADM. To explore the action of ADM on APs, K^+ channel and Ca^{2+} channel currents were measured. ADM increased the outward currents, which intersected at the expected value of EK (about -75 mV). The average of the increased outward currents (at 0 mV) was 45.2 ± 12.4 pA/pF. Pretreatment with the specific ADM receptor antagonist, adrenomedullin-(22-52), prevented the effect of ADM. The increased outward currents were completely abolished by glibeclamide (which inhibits both mitochondrial KATP (mitoKATP) and sarcolemmal KATP (sarcKATP) channels), suggesting that the outward currents elicited by ADM are ATP-sensitive K^+ (KATP) channel currents. To explore the pathway of ADM for opening KATP channel, staurosporin (a protein kinase C inhibitor), wortmannin (a phophatidylinositol 3-kinase [PI3K] inhibitor), Akt inhibitor, H-89 (a protein kinase A inhibitor), and PKI (5-24) (a protein kinase A inhibitor) were examined. Pretreatment with any of these agents inhibited the action of ADM. Furthermore, to determine whether ADM increases the currents via a mitoKATP or a sarcKATP channel, 5-hydroxydecanoate (5-HD) (a selective mitoKATP channel blocker) was used. After pretreatment with 5-HD, KATP channel currents were still activated by pinacidil (which activates both mitoKATP and sarcKATP) but not by ADM, suggesting that the KATP channels activated by ADM were mitoKATP channels. To clarify the inotropic action of ADM, L-type Ca^{2+} channel current (ICa,L) was measured, but it was not increased by ADM.
Conclusions: These data suggest that: 1. ADM exerts cardioprotective action by opening mitoKATP channels not only through the PKC/PI3K/Akt pathway, but also the PKA pathway. 2. To elucidate the inotropic action of ADM, further investigations are needed.

P2830 Safety of novel atrial-selective K^+-channel blocker in experimental heart failure

H.-J. Schneider, O. Husser, M. Rihm, T. Lukowicz, A. Luchner.
Regensburg, Germany

Objective: Congestive heart failure (CHF) is often associated with supraventricular arrhythmias. The safety of many antiarrhythmic drugs in CHF is limited by pro-arrhythmic effects. The aim of the study was to characterize a newly synthesised atrial selective K^+-channel blocker (AVE0118, Sanofi-Aventis, Germany) upon heart rate, ECG-intervals and the occurrence of ventricular arrhythmias in comparison to a class III antiarrhythmic (dofetilide) and a H1-blocker (terfenadine) under control conditions as well as in experimental CHF.
Methods: For the induction of CHF, rabbits (n=6) underwent rapid right-ventricular pacing. Animals were studied at baseline (BL) and after the induction of CHF (330-380 bpm for 30d). At BL, we administered AVE0118 (1 mg/kg, Sanofi-Aventis, Germany), dofetilide (0.02 mg/kg) and terfenadine (2 mg/kg) i.v. After the induction of CHF, a second drug administration was performed. A 6-lead digitally recorded ECG was continuously recorded for 30 min after each drug administration.
Results: At BL, dofetilide and terfenadine caused a significant prolongation of QTc interval (450±30ms and 375±10ms, respectively, vs. control 310±15 ms, both $p<0.001$) while constant P-wave, PQ- and QTc-intervals were displayed after administration of AVE0118.
In CHF, LV fractional shortening was severely depressed (FS 23±7% vs. BL 53±5%, $p<0.01$) and a prolongation of P-wave (42±1ms vs. 39±1, $p<0.05$) and PQ-interval (72±3 ms vs. 65±2, $p<0.05$) was observed. Dofetilide and terfenadine caused a significant prolongation of QTc interval (365±25ms and 345±20ms, respectively, vs. control 320±10 ms, each $p<0.05$). Due to torsade-de-pointes after dofetilide and symptomatic bradycardia after terfenadine, dose-reductions were necessary. In contrast, no conduction disturbance or arrhythmia was observed after administration of AVE0118 in CHF.
Conclusion: In marked contrast to a class III-antiarrhythmic and a H1-blocker, the novel atrial selective K^+-channel blocker AVE0118 did not affect atrial conduction or ventricular repolarisation and did not induce arrhythmias at a dose for which a prolongation of atrial refractory period is well documented. Thus, atrial-selective K^+-channel blockade by AVE0118 appears safe in experimental CHF.

P2831 Effects of nitric oxide on a human atrial potassium channel (hKv1.5)

L. Nunez[1], R. Gomez[1], M. Vaquero[1], A. Garcia-Mendez[2], R. Caballero[1], A. Lopez-Farre[2], J. Tamargo[1], E. Delpon[1].
[1]*Universidad Complutense Madrid, Pharmacology, Madrid, Spain;* [2]*Cardiovascular Institute, Hospital Clinico San Carlos, Madrid, Spain*

Electrophysiological remodeling produced by atrial fibrillation (AF) is characterized by a shortening of the duration of the atrial action potential and refractory period due to changes in the cardiac channels involved in atrial repolarization. It has been demonstrated that AF downregulates the endocardial nitric oxide (NO) synthase expression and NO production. We have analyzed whether NO regulates the function of a human cardiac K^+ channel (hKv1.5) that determines atrial repolarization and refractoriness. hKv1.5 currents were recorded using the whole-cell patch-clamp technique in stably transfected Ltk- cells. S-nitroso-N-acetyl-D,L-penicillamine (SNAP) (100-500 μM) produced a concentration-dependent decrease of the hKv1.5 currents (IC50=331.5±46.6 μM) elicited by 500 ms pulses to +60 mV. Under our experimental conditions, 200 μM SNAP yielded a NO concentration of 194±13 nM tested in the cell chamber using a NO-sensitive electrode.NO did not modify the deactivation kinetics (TaufC=26.3±4.8 ms,n=8,$P>0.05$), but shifted the midpoint of the activation curve to more negative potentials (VhC=-12.0±3.2 mV vs. VhNO=-16.2±3.7 mV, $P<0.05$). Ltk- cells showed a marked expression of both endothelial NO synthase protein (30.3±3.7 AU) and soluble guanylate cyclase (20.1±2.2 AU) as measured by Western blot. The ability of Ltk- cells to generate NO was determined by confocal microscopy using diaminofluoresceine. L-arginine (10 μM-10 mM) also produced a concentration-dependent decrease of hKv1.5 currents (IC50=11.5±1.4 μM and Bmax= 21.7±1.9%). Furthermore, L-arginine did not modify the tail current deactivation (TaufC=30.5±6.1 ms,n=6,$P>0.05$) but shifted the Vh of the activation curve to more negative potentials (-21.2±1.6 mV vs. -15.2±1.6 mV, $P<0.05$). The blocking effects of SNAP were partially prevented by inhibitors of guanylate cyclase (ODQ 50 μM) and protein kinase G (KT5823 1 μM), indicating that part of the inhibitory effects of NO were mediated by the activation of the cGMP/GC/PKG pathway. The reducing agent 1,4-dithiothreitol (DTT; 5 mM) also reduced partially the inhibitory effects of SNAP, pointing to the contribution of a redox modification of NO on the hKv1.5 channel protein. Inmunocytochemistry experiments demonstrated that NO effects were not mediated by the nitration of the tyrosine residues. All these results indicate that NO decreased the hKv1.5 current an effect that would produce a lengthening of the duration of the atrial action potential. Supported by CICYT (SAF2002-02304), CAM (08.4/0038/20011 and GR/SAL/0897/2004), Pfizer Foundation and Red RECAVA Grants.

P2832 Differential expression of L-type calcium channel beta1-3-subunits may explain the distinct phenotype of the single L-type calcium channel in human heart failure

R. Hullin[1], I.F. Khan[2], J. Matthes[2], S. Herzig[2]. [1]*Swiss Cardiovascular Center of Bern, Cardiology Dept., Bern, Switzerland;* [2]*University Cologne, Pharmacology, Cologne, Germany*

The electrophysiological phenotypes of single L-type calcium channels are diverse in failing and non-failing human heart. Gene expression of β2a and β2b but not β3 subunits is altered in human heart failure and their gene products modulate single L-type calcium channel activity in a different manner. Recently, we also detected another b2 isoform (b2c) and two β1a isoforms containing exon 7a (β1aEx7A) and exon 7b (β1aEx7B) so that we determined the quantitative expression of β1 and also β2 splice variants in normal and diseased heart. In end-stage human heart failure Real-Time PCR (given are copy numbers of n=5-13 experiments; always failing DCM vs. non-failing) demonstrated an increase of β2a (3689±132 vs. 237±91, $p<0.05$), β2b (349352±7849 vs. 106743±18548, $p<0.05$), whereas b2c and β1aEx7A/Ex7B expression remained unchanged (26528±14225 vs. 6011±1575, n.s.; 48174±11197 vs. 22040±10708, n.s.; 107±61 vs. 449 ± 97, n.s.). Given this molecular background, we turned to functional co-expression of the human Cav1.2 pore (stably expressed in HEK293) with either β2a, β2b, β3a and β1aEx7A (each bicistronic pIRES-EGFP or -DsRed), in the presence of a2d-2. All β-subunits significantly increased single-channel activity versus Cav1.2 alone. Peak ensemble currents were affected in the order (n=10-14 experiments): β2b (122±35 fA) = β2a (109±25 fA) >> β3a (46±14 fA) > b1aEx7A (36±12 fA) > b2c (24±7 fA) > b1aEx7B (22±5 fA). Increase in peak ensemble currents always resulted from higher open probability and time-dependent inactivation of the particularly reconstituted single calcium channels. We conclude that β-subunits modulate channel activity distinctively. Our findings suggest that altered b-subunit gene expression may explain the distinct calcium channel phenotype observed in human heart failure.

P2833 Reduced effects of 5-hydroxytryptamine on L-type calcium current in atrial cells from patients with atrial fibrillation

D. Pau[1], A.J. Workman[1], K.A. Kane[2], A.C. Rankin[1]. [1]*University of Glasgow, Royal Infirmary, Section of Cardiology, Glasgow, United Kingdom;* [2]*University of Strathclyde, Dept. of Physiology & Pharmacology, Glasgow, United Kingdom*

Purpose: 5-hydroxytryptamine (5-HT), acting via 5-HT4 receptors, increases the L-type calcium current, ICaL, with potentially pro-arrhythmic consequences in atrial cells from patients in sinus rhythm (SR) (Pau et al., 2003). However, the effects of 5-HT on ICaL in atrial cells from patients in atrial fibrillation (AF) have not yet been studied. The aims of this study were to investigate the effects of 5-HT on ICaL in atrial cells from patients in AF, and to compare these with the effects previously observed in cells from patients in SR.
Methods: Cells were isolated enzymatically from the excised right atrial appendage of 7 consenting patients in AF undergoing cardiac surgery. Procedures for obtaining tissues were approved by the institutional ethics committee. The whole cell perforated patch-clamp technique was used at 37° C to record ICaL, using depolarising voltage-clamp steps from a holding potential of -40 mV. Values were compared using a two-tailed paired or unpaired Student's t test as appropriate, with $p<0.05$ taken as statistically significant.

Results: The density of ICaL was significantly smaller in cells from patients in AF (-2.9±0.2; n=28 cells, 7 patients) than in cells from those in SR (-4.8±0.2, $p<0.05$; 147 cells, 24 patients). In cells from patients in AF, 5-HT (1 nM-100 μM) produced a concentration-dependent increase in ICaL, with a maximum response at 10 μM, from -2.1±0.2 to -6.3±1.1 pA/pF ($p<0.05$; n=8-17 cells, 5-7 patients), with no change in the voltage dependency (peak at + 10 mV). The maximum percentage increase in ICaL produced by 5-HT (222±5%) was significantly smaller than that in cells from patients in SR (269±6%: $p<0.05$; n=17-33 cells, 9-17 patients). The logEC50 was -6.47±0.04 in cells from patients in AF, significantly higher than in cells from those in SR (-7.14±0.04 $p<0.05$), indicating a reduced potency of 5-HT. The Hill coefficient, a measure of cooperativity of the agonist with the receptor, was 0.73±0.03 in cells from patients in AF, significantly lower than in cells from those in SR (1.34±0.22; $p<0.05$).
Conclusions: These data suggest that atrial fibrillation is associated with a reduced efficacy, potency and cooperativity of 5-HT in increasing the L-type calcium current in human atrial cells. This may be due to a reduction of the density of the 5-HT4 receptors and/or L-type calcium channels (efficacy) and/or to a modification of the receptor/channel coupling (potency and cooperativity).

P2834 Does pre-operative atrial cell electrophysiology predict early post-operative atrial fibrillation?

A.J. Workman[1], D. Pau[1], C.J. Redpath[1], J.R. Russell[1], K.A. Kane[2], A.C. Rankin[1]. [1]*University of Glasgow, Cardiovascular and Medical Sciences, Glasgow, United Kingdom;* [2]*University of Strathclyde, Dept of Physiology & Pharmacology, Glasgow, United Kingdom*

Background: Atrial fibrillation (AF) is common after cardiac surgery (CS). Post-CS AF is independently predicted by old age, post-CS withdrawal of beta-adrenoceptor antagonist (beta-blocker) therapy, pre-CS AF and valve surgery. However, it is unclear whether pre-CS atrial cellular electrophysiology is predictive of post-CS AF.
Aim: To test the hypothesis that pre-CS human atrial cell action potential characteristics and the L-type Ca^{2+} current (ICaL) differ between patients who do and who do not develop post-CS AF.
Methods: Myocytes were isolated from right atrial appendages obtained from consenting patients in sinus rhythm, just prior to CS. The whole cell patch clamp was used to record action potentials (rate: 75 beats/min), the effective refractory period (ERP) and/or ICaL. Data were compared between cells from patients with and without post-CS AF, including or excluding patients with co-variables expected to influence post-CS AF incidence and/or pre-CS electrophysiology.
Results: Post-CS AF occurred within 3 days in 31 of 171 patients (18%). In cells from patients with post-CS AF, the action potential duration at 50 and 90% repolarisation and the ERP were 14±4, 218±14 and 216±12 ms, respectively (n=36 cells, 14 patients). The action potential overshoot, amplitude and maximum upstroke velocity were 61±2 mV, 141±2 mV and 190±9 V/s, respectively. The peak ICaL density, at +10 mV, was -5.2±0.5 pA/pF (n=63 cells, 20 patients). None of these values were significantly different in cells from patients without post-CS AF ($P>0.05$ for each; Student's t-test, n=208-274 cells, 71-85 patients). The patients with post-CS AF were significantly older than those without (67±2 vs 61±1 years, $P<0.05$). The incidence of post-CS AF was 15% in patients treated >7 days pre-CS with a beta-blocker, and 25% in non-beta-blocked patients. Patient-matching simultaneously for age and presence of pre-CS beta-blocker treatment revealed no significant differences in any action potential measurements, ERP or ICaL between patients with and without post-CS AF ($P>0.05$ for each). Similarly, no significant differences were detected by excluding patients either who had had a beta-blocker withdrawn or initiated within 3 days of CS, pre-CS paroxysmal AF, or CS additional to coronary artery bypass grafting.
Conclusion: Pre-cardiac surgery (CS) human atrial cell action potential characteristics, refractory period and Ca^{2+} current are not predictive of early (within 3 days) post-CS AF, whether or not accounting for co-variables expected to influence the incidence of post-CS AF and/or pre-CS electrophysiology.

P2835 Antiarrhythmic efficacy of the novel antiarrhythmic agent AZD7009 and azimilide in the dilated rabbit atria in vitro

L. Lofberg[1], I. Jacobson[1], L. Carlsson[2]. [1]*AstraZeneca R&D, Integrative Pharmacology, Mölndal, Sweden;* [2]*Astrazeneca, Dept. of Pharmacology, Mölndal, Sweden*

Background: The efficacy of azimilide and AZD7009, a new antiarrhythmic agent under development for treatment of atrial fibrillation (AF), was examined in the rabbit dilated atria.
Methods: In Langendorff-perfused hearts the right atria was acutely dilated by increasing the intra-atrial pressure from 0 to 10 cm H2O. The atrial effective refractory period (AERP) and the inducibility of AF by single premature stimuli were measured at increasing concentrations (0.1 to 3 μM) of AZD7009 (n=10) and azimilide (n=10). Time-matched control atria (n=10) were studied in parallel. In separate groups of atria, the ability of 3 μM AZD7009 (n=9) or azimilide (n=6) to terminate induced AF lasting for 30 min was studied.
Results: In non-dilated atria the AERP was 83±1.9 ms (mean±SEM, n=45) and sustained AF (AF lasting >30 s) could not be induced. Dilatation resulted in a marked reduction in AERP (to 47±1.2 ms, $p<0.001$) and 82% of the atria became inducible ($p<0.001$). As compared to the effects seen in the control atria, AZD7009 and azimilide concentration-dependently and statistically significantly increased the AERP, reduced the AF inducibility and shortened the AF duration (Table, means(SEM)). In the separate groups of atria in which the AF was allowed to last for 30 min, 3 μM AZD7009 or azimilide terminated the arrhythmia in 8/9 and 6/6 atria after 193±68 s and 288±48 s of perfusion, respectively. Prior to AF termination the average AF cycle length increased from 69±2 to 107±12 ms ($p<0.01$) and from 71±1 to 81±2 ms ($p<0.01$) during exposure to AZD7009 and azimilide, respectively. In 8/8 and 5/6 of these atria, attempts to re-induce AF failed.

	AERP (ms)			AF inducibility (%)			AF duration (s)		
	Pre-drug	0.3 μM	3 μM	Pre-drug	0.3 μM	3 μM	Pre-drug	0.3 μM	3 μM
Control	48(2)	53(2)	55(2)	70	60	70	23(4)	18(5)	21(5)
AZD7009	46(3)	61(3)	136(7)	70	10	0	22(4)	8(4)	0(0)
Azimilide	51(3)	67(4)	105(9)	80	50	0	24(4)	15(5)	0(0)

Conclusions: In the dilated rabbit atria AZD7009 and azimilide concentration-dependently increase atrial refractoriness, effectively prevent AF induction and restore normal sinus rhythm.

P2836 Modifications of VF activation patterns and VF inducibility induced by radiofrequency ablation

F.J. Chorro-Gasco[1], E. Blasco[1], A. Ferrero[1], I. Trapero[1], L.M. Such[2], L. Mainar[1], J. Sanchis[1], L. Such[2]. [1]*Clinic University Hospital, Cardiology Service, Valencia, Spain;* [2]*University, Physiology, Valencia, Spain*

Experimental and clinical data have been obtained on the effects of radiofrequency ablation (RF) upon atrial fibrillation, though very few studies have analyzed its effects upon ventricular fibrillation (VF). This experimental study analyzes the capacity of RF to interfere with the maintenance and inducibility of VF. In 19 Langendorff-perfused rabbit hearts mapping techniques were used to analyze VF induced by overpacing before and after RF induction of transmural lesions based on two sequential protocols: the first (n=9) without isolation of the zone encompassed by the lesions (anterolateral wall of the left ventricle (LV)), and the second (n=10) with isolation of the zone (posterior wall of the LV and posterior interventricular septum). The first procedure established no frequency gradients in the LV walls (anterior zone 18.3±3.8 Hz; posterior zone 17.6±3.6 Hz, ns), and VF inducibility was maintained (100% of cases at baseline and after lesion induction). The second procedure established a frequency gradient between the zone encompassed by the lesions (18.1±3.9 Hz) and the zone not encompassed by the latter (11.1±3.1 Hz, $p<0.01$), and in 5 cases total isolation of the former was achieved – with complete block of impulse entry during VF. In none of the cases was VF triggering by stimulation in the external zone prevented, though from the zone encompassed by the lesions no sustained VF episodes were recorded.
Conclusions: The RF induction of extensive and transmural lesions in the ventricle walls allows modification of the activation patterns during VF, with the establishment of frequency gradients. The exclusion of extensive zones of ventricular myocardium avoids VF induction in such zones, but not in the rest of the myocardium not encompassed by the lesions.

P2837 Repolarisation gradients in the canine left ventricle before and after induction of cardiac memory

M.J. Janse[1], E.A. Sosunov[2], E.P. Anyukhovsky[2], J.M.T. De Bakker[3], T. Opthof[3], A. Plotnikov[2], M.R. Rosen[2]. [1]*Amsterdam, Netherlands;* [2]*Columbia University, Pharmacology, New York, United States of America;* [3]*Academic Medical Centre, Experimental Cardiology, Amsterdam, Netherlands*

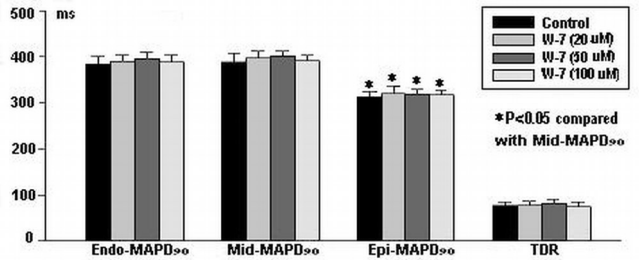
Background: Questions remain regarding the contributions of transmural versus apicobasal repolarization gradients to the configuration of the T wave in control settings and after the induction of short-term cardiac memory.
Methods and results: Short-term cardiac memory is seen as T wave changes induced by altered ventricular activation that persist after restoration of sinus rhythm. We studied cardiac memory in anesthetized, open-chested dogs paced from the ventricle for 2 hours. Unipolar electrograms were recorded from up to 98 epicardial and 144 intramural sites, and activation times and activation-recovery-intervals (ARI) measured. In separate experiments, epicardial monophasic action potentials were recorded. We found no appreciable left ventricular intramural gradients in repolarization times (activation time+ ARI) in either control conditions or after the induction of memory. In control there was a left ventricular apico-basal gradient with the shortest repolarization times in antero- basal regions and longest repolarization times postero-apically. After induction of memory, repolarization times shortened uniformly throughout the ventricular wall. Monophasic action potentials at 90% repolarization decreased by about 10 msec after induction of memory. The deeper T-wave in the electrocardiogram after induction of memory may be explained by the more rapid phase 3 of the action potential.
Conclusions: In the intact canine left ventricle at physiological rates there is no transmural gradient in repolarization. Apico-basal gradients in repolarization time, with shortest repolarization times in anterior basal areas and longest repolarization times in posterior apical regions, are important in the genesis of the T wave.

Repolarization times and monophasic action potentials at the 90% repolarization level shorten after the induction of memory.

P2838 Calmodulin antagonist inhibits torsade de pointes induced by d-sotalol without altering transmural dispersion of repolarisation in an isolated rabbit heart model

J. Pu, C. Zhang, L. Wang, R. Bai, N. Liu. *Tongji Hospital, Cardiology Department, Wuhan, China*

Background: Calmodulin is a calcium-binding protein which has been shown to be related to arrhythmias recently.The aim of this study was to evaluate the effects of W-7, a calmodulin inhibiter, on transmural dispersion of repolarization (TDR), early afterdepolarization (EAD) and torsade de pointes (TdP) induction after administration of d-sotalol in isolated rabbit heart.
Methods: TdP was induced by d-sotalol (30μmol/L), bradycardia, and hypokalemic (1.5mmol/L)/hypomagnesaemic (0.35mmol/L) solution in isolated female rabbit hearts. 36 rabbit hearts were divided into 4 groups (n= 9 each): d-sotalol alone, d-sotalol + W-7(20μmol/L), d-sotalol + W-7(50μmol/L), and d-sotalol + W-7(100μmol/L). Monophasic action potentials (MAPs) of the left ventricular epimyocardium (Epi), midmyocardium (Mid), and endomyocardium (Endo) were recorded simultaneously with ECG. The incidence of EAD and TdP were observed as well.
Results: treatment with d-sotalol alone prolonged ventricular MAP duration and QT interval, increased TDR, and evoked high incidence of EAD (9/9) and spontaneous TdP (7/9) in hypokalemic/hypomagnesaemic solution in female rabbit heart. W-7 concentration-dependently reduced incidence of TdP (4/9 in 20μmol/L; 2/9 in 50μmol/L; 1/9 in 100μmol/L). This effect of W-7 coincided with the decreased incidence of EAD(5/9 in 20μmol/L; 4/9 in 50μmol/L; 1/9 in 100μmol/L). However, the d-sotalol-induced prolongation of QT interval and TDR were not significantly altered by W-7 at the three concentration used(Figure).



MAPD90 and TDR in 4 groups (CL=1500ms)

Conclusions: in isolated rabbit hearts, calmodulin inhibiter W-7 suppresses d-sotalol-induced TdP without altering TDR but does suppress EAD. The effects observed with W-7 also suggest a possible important role for calmodulin -activated enzymes in the induction of TdP.

P2839 Suppression of cardiomyocyte hypertrophy by inhibition of the ubiquitin-proteasome system involves downregulation of cardiac signalling pathways and cell cycle regulation

K. Stangl[1], S. Meiners[1], H. Dreger[1], W. Rother[1], G. Baumann[1], V. Stangl[2]. *[1]Charite, Campus Mitte, HU, Cardiology Dept., Berlin, Germany; [2]Charite Campus Mitte, Cardiology, Berlin, Germany*

The ubiquitin-proteasome system has been implicated in the regulation of cellular proliferation. Inhibition of the proteasome results in cell-cycle arrest and growth retardation. Hypertrophy is an adaptive response of terminally differentiated cardiomyocytes to different forms of growth signals and is characterized by an increase in cell size in the absence of cell division. It is accompanied by a reentry into the cell-cycle. We hypothesized that inhibition of the proteasome prevents cell-cycle reentry and thereby affects the development of hypertrophy in cardiomyocytes.
In a model system of neonatal cardiac myocytes we investigated the effects of proteasome inhibitors on myocardial hypertrophy. Treatment with non-toxic doses of the specific proteasome inhibitor MG132 suppressed several hallmarks of cardiomyocyte hypertrophy irrespective of the hypertrophic stimuli used: reduction in cardiomyocyte size, inhibition of hypertrophy-mediated stimulation of RNA and protein synthesis, suppression of RNA and protein expression of several hypertrophic marker genes, and reduced activation of BNP-mediated luciferase activity. The hypertrophy-suppressive effects were accompanied by downregulation of several hypertrophic growth signaling pathways, such as reduced expression of calcineurin and Akt and diminished activation of Erk1/2 and nuclear factor kappa B. Moreover, we observed reduced expression of G1 cyclins and diminished cyclin D1 kinase activity, indicating reduced G1/S phase transition of hypertrophy-stimulated cardiomyocytes.
We speculate that inhibition of the proteasome may have potential therapeutic value for the prevention of cardiac hypertrophy.

P2840 Transient expression of SPARC upon myocardial infarction orchestrates fibroblast migration and tissue remodelling in the heart

R. Wu[1], M. Laser[2], H. Han[2], K. Hu[2], J. Varadarajulu[2], O. Ritter[2], C. Hauck[3]. *[1]University of Wuerzburg, Cardiology Dept., Würzburg, Germany; [2]University of Wuerzburg, Cardiology Dept., Wurzburg, Germany; [3]University of Wuerzburg, Center of Infectious Diseases, Wuerzburg, Germany*

Introduction: Expression of ECM proteins and integrin signal transduction plays an important role in remodelling after MI. SPARC, (secreted protein, acidic and rich in cysteine, also known as osteonectin or BM-40) an extracellular glycoprotein may be involved wound healing through binding to ECM proteins. The present study was designed to clarify the contribution of SPARC to remodelling after myocardial infarction and the interplay with integrin.
Methods: Adult mice received a specific av integrin inhibitor or vehicle through osmotic minipumps. Mice of each group were either sham operated or MI was induced and total heart RNA was isolated 2 days, 7 days, and 1 month after the surgical procedure for gene array analysis (SuperArray). Differentially regulated genes were confirmed by RT- PCR, Western Blot and immunohistochemistry in myocardial tissue, neonatal rat cardiocytes and fibroblasts. For migration assays a modified Boyden chamber assay was used.
Results: Microarray cDNA analysis revealed a number of genes, that were significanly upregulated 2 days and 7 days after MI including SPARC. An transient increase of SPARC protein level were observed at day 2 (2.55±0.21), day 7 (3.72±0.28) and 1 month (1.9±0.16) 2 months after myocardial infarction, SPARC expression dropped back to normal level as compared to sham-operated hearts. Immunofluorescence analysis showed an increase of SPARC in the borderzone of infarcted tissue 2 days after MI, a strong increase in the scar area 7 days after MI and a low level 2 months after MI. Integrin alpha.v inhibition abolished the upregulation of SPARC at mRNA and protein levels. SPARC was also detected in cultured fibroblasts and isolated neonatal rat cardiomyocytes. Its expression could be further stimulated by TGF-beta 1 and PDGF-BB. In vitro migration assays of mouse fibroblasts demonstrated that fibronectin–stimulated haptotaxis of fibroblasts is dependent on SPARC concentration.
Conclusion: In summary, this study provides evidence, that SPARC is strongly regulated in the infarct- and border zone after myocardial infarction, which is dependent on av integrin. Since SPARC is found to be expressed by cardiomyocytes and strongly regulates fibroblast migration, it appears to play an important role in the injured myocardium with regard to healing, scar formation, and survival.

P2841 Characterisation of an original model of myocardial infarction provoked by coronary artery thrombosis induced by ferric chloride in pig

J.M. Dogne[1], S. Rolin[2], V. Tchana-Sato[3], M. Petein[4], B. Lambermont[3], A. Ghuysen[3], J. Hanson[1], P.H. Kolh[5]. *[1]University of Liège, Medicinal Chemistry, Liège, Belgium; [2]University of Namur, Department of Pharmacy, Namur, Belgium; [3]University of liège, Hemodynamic Research Laboratory, Liège, Belgium; [4]Institute of Pathology and Genetics, Loverval, Belgium; [5]Liege, Belgium*

Background: Great advances have been made in the prevention of thrombotic disorders by developments of new pharmacological and surgical treatments. Animal models of arterial thrombosis have largely contributed to the discovery and to the validation of original treatments. The purpose of the present work was to develop and validate an original model of acute myocardial infarction provoked in pig by thrombosis of the left anterior descending (LAD) coronary artery induced by topical application of ferric chloride (FeCl3) solution (50% w/v).
Methods: Myocardial infarction, resulting from an occlusive and adherent mixed thrombus formed in the LAD coronary artery, was examined in 10 pigs at macroscopic level using dual staining technique (Evans blue Dye; triphenyltetrazolium chloride) and at microscopic level using conventional histological analyses and immunohistochemical detection of desmin. Biochemical markers (troponin T and ATP), platelet reactivity and standard hemodynamic parameters, such as stroke volume SV, ejection fraction EF, stroke work SW, and cardiac output CO were also evaluated.
Results: Each pig developed LAD coronary artery occlusion, with an average occlusion time of 23.2 ± 1.2 min. In 6 pigs, LAD blood flow linearly decreased to zero, while in the four other animals reperfusion episodes occurred before reaching a complete occlusion within 30 minutes. Estimated as percent of LV mass, risk area was 36.9 ± 2.1%, and mean infarct size was 35.3 ± 2.1%. All animals developed a transmural area of irreversible damage mainly located in the anteroseptal region of the LV. Troponine T level was 0.071 ± 0.031 μg/l at T0 and 0.997 ± 0.106 μg/l at T360. LAD coronary artery occlusion induced a progressive decrease in CO (from 57.8 ± 5.9 ml/sec at baseline to 47.3 ± 4.9 ml/sec at T360, $p < 0.05$), in EF (from 61 ± 8% at baseline to 49 ± 4% at T360, $p < 0.001$), and in stroke work (from 3069 ± 141 mmHg.ml at baseline to 1774 ± 268 mmHg.ml at T360, $p < 0.001$), at unchanged end-diastolic volume. The more progressive development of coronary artery occlusion, as compared to an abrupt ligation, was accompanied by a correspondingly progressive impairment in hemodynamics.
Conclusion: We conclude that this original porcine model of myocardial infarction is quite close to clinical pathophysiological conditions, such as thrombus formation occurring after atherosclerotic plaque rupture. This certainly constitutes a

further argument in favour of this model to assess pharmaceutical or mechanical support of an acutely ischemic heart.

P2842 Dis-regulation in the feedback loop between myocardial VEGF synthesis and receptor signalling in diabetic type 2 patients with chronic coronary heart disease

D. Torella[1], F. Sasso[2], G.M. Ellison[3], O. Carbonara[2], M. Torella[4], M. Cotrufo[4], R. Torella[2], C. Indolfi[5]. [1]*Federico Ii University, Cardiology Dept., Naples, Italy;* [2]*Internal Medicine, Medicine, Naples, Italy;* [3]*Cardiovascular Research Institute, Medicine, Valhalla, NY, United States of America;* [4]*Cardio-Thoracic Surgery, Naples, Italy;* [5]*Cardiology, Medicine, Catanzaro, Italy*

Purpose: Diabetes is a known risk factor for coronary heart disease (CHD) and is characterized by a decreased collateral vessel formation in response to coronary ischemic events. However, the role of VEGF in diabetic macroangiopathy is basically unknown. As VEGF plays a major role in the neovascularization of ischemic tissues, the aim of the present study was to evaluate the expression and the activity of VEGF and the VEGF-dependent pro-angiogenic intracellular signaling in the myocardium of diabetic type 2 patients with chronic CHD.
Methods: Biopsies of LV myocardium were obtained from 10 patients with type 2 diabetes and 10 non diabetic patients, all undergoing surgical coronary revascularization. RV myocardial samples taken from normal hearts were used as controls. VEGF and VEGF-receptors (flt-1 and flk-1) protein expression and gene transcript were evaluated by western blot, rt-PCR and real time RT-PCR. Flk-1 phosphorylation and Akt and eNOS protein expression and their phosphorylated forms were also evaluated by western blot.
Results: VEGF mRNA transcript as well as protein expression increased in non diabetic patients with CHD compared controls. Interestingly, VEGF mRNA and protein levels were 21- and 6-fold higher than controls and non diabetics, respectively. On the other hand, flt-1 and flk-1 mRNA and protein levels were significantly higher in non diabetic when compared with diabetic patients with CHD. Interestingly, the phosphorylation of flk-1, the VEGF receptor which mainly transmits the VEGF pro-angiogenic signal, was significantly blunted in diabetic compared with non diabetic patients. As a consequence, Akt phosphorylation was significantly higher in the samples from non diabetic compared to diabetic patients. Notably, eNOS protein expression was significantly reduced and its phosphorylated form was undetectable in diabetic compared to non diabetic patients.
Conclusions: During chronic CHD, there is a dis-regulation in the feed-back loop between VEGF synthesis and receptor signaling in the diabetic state. This was shown by an increased VEGF myocardial expression and a decreased expression of its receptors along with a down-regulation of its pro-angiogenic signal transduction. The latter could be partially responsible for the reduced neoangiogenesis in diabetic patients with ischemic cardiomyopathy.

CMR: ATHEROSCLEROSIS AND INFARCTION

P2843 Assessment of common and internal carotid artery vessel wall area: a feasibility study using high resolution MRI

C. Hammett[1], K.S.L. Teo[1], C. Piantadosi[1], S.M. Grieve[1], D.P. Chew[2], J. Lennon-George[1], C.A. Ellis[1], S.G. Worthley[1]. [1]*Royal Adelaide Hospital, Cardiovascular Research Unit, Adelaide, Australia;* [2]*Flinders Medical Centre, Department of Cardiology, Adelaide, Australia*

Ultrasound assessment of intima-media thickness (IMT) in the common carotid arteries (CCA) has been widely studied as a surrogate marker of subclinical atheroma. Although the presence of plaque in the internal carotid artery is a better predictor of coronary atherosclerosis and cardiac risk than IMT, internal carotid plaque can be difficult to visualise using ultrasound. MRI offers several potential advantages over ultrasound, including the ability to image the entire vessel wall in both the common and internal carotid arteries.
Aim: To assess the feasibility of common and internal carotid artery wall imaging using high resolution MRI, and to compare novel indices of vessel thickening (vessel wall area, maximal wall thickness) with MRI measures of carotid IMT.
Methods and Results: Sixty individuals (mean age 53±11, 72% male) at low to intermediate risk of cardiovascular events underwent MRI of the common and internal carotid arteries. T1 weighted images with an in-plane resolution of 0.47X0.47mm were generated using a dedicated phased-array carotid coil in a 1.5T Siemens Sonata MRI system. Images were analysed offline using ImagePro-Plus (Media Cybernetics) to determine IMT (thickness of the far wall as described for ultrasonography), cross-sectional vessel wall area, and maximal wall thickness. Statistical analysis was performed using Pearson's correlation co-efficient.
Adequate image quality for the assessment of the carotid vessel wall was obtained in all sixty patients. Both CCA maximal wall thickness ($r=0.49$, $p<0.001$) and CCA vessel wall area ($r=0.42$, $p<0.0001$) were more predictive of internal carotid thickening than CCA IMT (p=NS). There was no association of these indices of plaque burden and demographic data.
Conclusions: Assessment of the entire carotid artery wall using MRI is feasible, and novel measures of vessel thickening (vessel wall area, maximal wall thickness) may be more predictive of plaque burden than the standard measurement of IMT. Further work is needed to determine whether these measures are more predictive of cardiovascular risk than IMT.

P2844 Effect of percutaneous revascularisation of chronic total coronary occlusions on myocardial contractility and left ventricular volumes

T. Baks[1], R.J. van Geuns[2], E. Biagini[2], F. Cademartiri[2], P. Wielopolski[2], N. Mollet[2], G. Krestin[2], P. de Feyter[2]. [1]*Rotterdam, Netherlands;* [2]*Rotterdam, Netherlands*

Aim: To study the effect of percutaneous drug-eluting stent implantation for a chronic total coronary occlusion (CTO) on myocardial contractility and left ventricular volumes at 5 months follow-up.
Methods: Thirty-six patients underwent Magnetic Resonance Imaging before and 5 months after an attempt for elective percutaneous revascularization of a CTO. Cine-MRI was performed to assess myocardial wall thickening and left ventricular volumes. DE-imaging was performed to detect chronic infarction. The transmural extent of infarction was scored on a 3 points scale. Segmental wall thickening was quantified in 16 segments per patient. End-diastolic and end-systolic volume was quantified on short-axis cine-MRI images. In 27 out of 40 patients (67%), drug-eluting stent implantation was successful. The nine non-revascularized patients received optimal medical therapy.
Results: Successful percutaneously revascularized patients exhibited a significant decrease in end-systolic volume index from 33.8 ml to 31.1 ml (p = 0.027) and in end-diastolic volume index from 83.9 ml to 79.1 ml (p=0.002). Segmental wall thickening improved significantly from 21±20% to 35±35% (p=0.01) in dysfunctional segments with <25% transmural extent of infarction and improved from 18±19% to 27±20% (p=0.10) for segments with 25-75% transmural extent of infarction. Dysfunctional segments with > 75% infarction did not improve (4±33% to -9±16%; p=0.54) in segmental wall thickening. Non-revascularized patients exhibited no significant change in left ventricular volumes.
Conclusion: Percutaneous revascularization with implantation of a drug-eluting stent in patients with a chronic total coronary occlusion has a beneficial effect on myocardial contractility and left ventricular volumes. Improvement of segmental wall thickening is related to the transmural extent of infarction.

P2845 Effects of percutaneous transluminal angioplasty (PTA) and endovascular brachytherapy (EVBT) on vascular remodelling of human femoropoliteal artery: 2 years follow-up by noninvasive MR plaque imaging

R. Corti[1], R. Wyttenbach[2], M. Alerci[2], F. Mahler[3], M. Di Valentino[3], J.J. Badimon[4], V. Fuster[4], A. Gallino[3]. [1]*University Hospital Zurich, Dept. of Cardiology, Zurich, Switzerland;* [2]*Ospedale San Giovanni, Radiology, Bellinzona, Switzerland;* [3]*Ospedale San Giovanni, Cardiovascular Medicine, Bellinzona, Switzerland;* [4]*Mount Sinai School of Medicine, Cardiovascular Research Institute, New York, United States of America*

Background: Percutaneous transluminal angioplasty (PTA) of severely stenotic peripheral vascular lesions is hampered by higher restenosis rate. The effects of PTA on vascular wall as well of the anti-restenotic properties of endovascular brachytherapy (EVBT) remain unclear. Magnetic resonance imaging (MRI) allows in vivo noninvasive assessment of the vascular effects of such treatment strategies. We aimed to elucidate the vascular effect of PTA and PTA+EVBT by serial MRI.
Methods: Twenty symptomatic patients with severe stenosis of the femoropopliteal artery were randomly assigned to PTA (n=10) or PTA+EVBT (n=10, 14 Gy by g-source) and imaged by high-resolution MRI before, and 24-hours, 3-months and 2 years after intervention. An independent observer blinded to the procedure analyzed the MRI data.
Results: At 24-hours, cross-sectional MRI revealed that lumen area (+86% and +67%) and total vessel area (+47% and +34%) similarly increased in the PTA and PTA+EVBT group. All patients showed severe splitting of the atherosclerotic plaque, resulting in an irregularly shaped lumen. At 3-months, MRI revealed a significant difference in lumen area change between the PTA and PTA+EVBT group (+40% and +106%, respectively; p=0.026) and in the total vessel area (+14% and +39%, respectively; p=0.018), which was maintained at 2 years follow-up.
PTA induced plaque disruption persisted at 3 months in 50% and at 2 years in 10% in PTA+EVBT patients only.
Conclusions: After PTA, there is deep disruption of the atherosclerotic plaques and extensive remodeling process of the arterial wall. Luminal loss after PTA is partially due to inward vessel remodeling. Brachytherapy avoid inward remodeling and induces an increase in lumen area, but partially prevent healing of disrupted vessel surface.

P2846 3D-Quantification of the No-reflow phenomenon with Delayed-Enhancement MR and clinical, electrocardiographic and bioumoral correlates

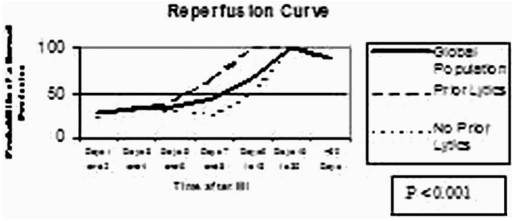
G.D. Aquaro, A. Pingitore, D. Rovai, G. Di Bella, E. Strata, D. De Marchi, C. Palmieri, M. Lombardi. *Institute of Clinical Physiology, CNR, Pisa, Italy*

Background: No-Reflow (NR) phenomenon is considered a negative prognostic index in patients with acute myocardial infarction. Delayed contrast-enhanced magnetic resonance (DE-MR) can assess the presence, the size and location of NR.
Aim: DE-MR evaluation and 3D-quantification of NR in the acute phase of ST elevation myocardial infarction (STEMI) in patient with singlevessel coronary artery disease treated with primary PTCA.
Methods: 28 patients (mean age 62±12 years, male 23) underwent MR for evaluating DE and regional and global systolic function of left ventricle (LV) 6.6±3.2 days after PTCA. Global extent of DE (GDE) was calculated by tracing short axes of LV from the mitral valve plane to the apex. A software tool, allowing semi-automatic detection of endocardial and epicardial borders and DE areas, was used for quantifying the GDE and transmural extent of DE (TDE). The NR area was defined as a black area surrounded by a hyperenhanced area. A Wall motion Score Index (WMSI, from 1=normal to 4=dyskinetic in a 17 segment model of LV) was evaluated. Sigma ST (ST) was calculated as the sum of ST elevation (mm) in the 12 ECG leads registration.
Results: There were no adverse effect during MR. Eleven patients (39%) had NR phenomenon (mean extent 8.8%±10.1) (NR group); 15 patients (53.5%) had DE without NR (HE group); 2 patients (7%) had no DE areas. History of CAD was more present in NR than in HE group (80% vs 33.3% $p<0.015$); cardiac enzymes values were similar in the 2 groups. ST was higher in NR than HE (mean 20.5±9.5 mm vs 9.8±6.8 mm, $p<0.015$). WMSI (NR 1.69±0.3 vs HE 1.33±0.2) was higher in NR than in HE. GDE was higher in NR than in HE (27.9±10.8% vs 11.2±7.21% $p<0.0001$); TDE was higher in NR than HE (31.5±13.3% vs 14±9.4% $p<0.001$); the number of LV segments with DE was higher in NR than HE (9.5±3.1 vs 6.3±3.4 $p<0.019$). At univariate analysis WMSI ($p<0.01$), GDE ($p<0.008$), TDE ($p<0.008$), ST ($p<0.01$) and history of CAD ($p<0.05$) were independent predictors of NR; at multivariate analysis GDE ($p<0.01$) was the only predictor of NR.
Conclusions: DE-MRI is a usefull diagnostic tool to evaluate and three-dimensionally assess the presence, location and size of NR, and thus may be potentially used for the early prognostic stratification in patient with STEMI.

P2847 Despite angio TIMI 3 flow after percutaneous intervention for acute myocardial infarction, MRI shows that it takes 15 to 30 days for the myocardium to reperfuse

B. Noel[1], M.C. Morice[2], J. Garot[3], Y. Louvard[1], O. Tavolaro[4], P. Dumas[1], M. Levy[1], T. Lefevre[1]. *[1]Institut Hospitalier Jacques Cartier, Institut Cardiovasculaire Paris Sud, Massy, France; [2]Institut Hospitalier Jacques Cartier, Institut Cardiovasculaire Paris Sud, Massy, France; [3]Hôpital Henri Mondor, Fedération de Cardiologie, Créteil, France; [4]Institut Cardiovasculaire Paris Sud, Quincy, France*

Introduction: Cardiovascular magnetic resonance imaging (MRI) perfusion studies performed early after successful angioplasty in acute myocardial infarction (AMI) often shows incomplete tissue reperfusion despite normal coronary blood flow by TIMI score. When performed weeks or months after AMI, MRI first-pass perfusion (FP) is usually normal. There is a clear delay in tissue reperfusion, but the kinetics of tissue reperfusion remains unknown in humans. We sought to determine the kinetics of tissue reperfusion after primary PCI in AMI.
Methods: We prospectively analyzed pts presenting with ST-segment elevation MI between July 2002 and January 2005. Included pts had TIMI 3 flow after acute PCI and MRI FP imaging within 4 months post-MI. MRI FP was performed after injection of 0.1 mmol/kg gadolinium chelate and imaging done with a Siemens Symphony 1.5 T. For FP analysis, each slice was divided into 8 segments which were then subdivided into subepicardial and subendocardial layers. Normal perfusion was defined by less than 5% of segments involved by hypoperfusion. Patients were divided into groups according to the delay between MI/reperfusion and MRI. The reperfusion curve was established by plotting the percentage of patients with normal perfusion in each subgroup.
Results: 184 MRI procedures (146 pts) were included in the analysis (40.2% had pre-hospital thrombolysis). Results are summarized in the graph below.



Reperfusion curve

Conclusions: Despite complete restoration of epicardial flow, early normal perfusion of the myocardium assessed by MRI is very uncommon. Myocardial perfusion is progressively restored and capillary blood volume at equilibrium comes back to normal between 2 and 4 weeks after MI. Thrombolytic therapy administered prior to PCI seems to accelerate reperfusion.

P2848 Which electrocardiographic patterns of necrosis predict infarct size and its transmural extent?

G. Di Bella[1], A. Pingitore[2], D. De Marchi[2], G.D. Aquaro[2], E. Strata[2], B. Favilli[2], M. Lombardi[2], D. Rovai[2]. *[1]University, Cardiology, Messina, Italy; [2]CNR, Clinical Physiology, Pisa, Italy*

Contrast-enhanced magnetic resonance imaging (MRI) allows an accurate measure of myocardial infarct size to be obtained in man.
Aim of the study: To evaluate the relationship between the different electrocardiographic patterns of necrosis and infarct size and its transmural extent by contrast-enhanced MRI.
Methods: A group of 55 patients (mean age 62 years, 4 females) with previous myocardial infarction (on average 5-year old) was studied at MRI by gadolinium-enhanced inversion recovery gradient echo sequence. The extent of delayed contrast enhancement was calculated in short-axis images of the left ventricle from the mitral valve plane to the apex. A software tool, allowing semi-automatic detection of endocardial and epicardial borders and delayed enhanced areas, was used to quantify the global and transmural extent of the infarction.
Results: Pathologic Q-waves were present in 49 patients and dominant R waves in right precordial leads were present in 19 patients (in the absence of a right bundle branch block); dominant R waves were associated to pathologic Q waves in 13 patients and were lone in 6 patients. In addition to the above patterns, 21 patients also showed a localized reduction of R wave amplitude.
Infarct size by contrast-enhanced MRI corresponded to 17±10% of left ventricular myocardium (range 2-44%). The number of Q waves (range 1 – 6/patient) was related with infarct size by MRI ($r = 0.44$); this correlation improved ($r = 0,51$) including dominant R waves in a multiple regression model; conversely, this correlation was not influenced by the inclusion of a localized R wave reduction into the model.
Furthermore, the number of Q waves did not show any correlation with the number of myocardial segments with delayed enhancement limited to subendocardial layers (inner 25% of myocardial thickness), while Q waves were related to the number of segments with infarction involving more than 25% of myocardial thickness ($r = 0,40$).
Conclusion: Both pathologic Q waves and dominant R waves in right precordial leads predict myocardial infarct size and a necrosis not limited to the inner subendocardial layers.

ECHOCARDIOGRAPHY, DOPPLER

P2849 The role of quantitative MCE and contrast enhanced MRI in the prediction of myocardial viability after primary PCI in acute myocardial infarction: a comparative study

H.S. Seo, S. Park, J.Y. Moon, E.Y. Choi, J.W. Ha, S.J. Rim, N. Chung. *Yonsei University College of Medicine, Cardiology Department, Seoul, Korea, Republic of*

Background: both quantitative myocardial contrast echocardiography (MCE) and contrast enhanced cardiac magnetic resonance imaging (MRI) can predict myocardial viability following acute myocardial infarction (AMI). We sought to compare the relative accuracy of these techniques in the assessing myocardial viability in patients with AMI undergoing primary PCI.
Method: twenty patients (age:59±10years, 16 males) with AMI who were successfully revascularised by primary PCI underwent real time MCE and MRI within 7 days after revascularisation (LAD:12, LCx:3, RCA:5). Preserved myocardial perfusion by MCE was defined as full enhancement of myocardium with microbubbles at the 10th endsystolic cardiac cycle and MCE-derived rate of microbubble velocity (β) of over 0.4 after high mechanical bubble destruction. A segment with less than 50% transmural delayed hyperenhancement on MRI was considered as viable myocardium. The improvement in contractile function was assessed by echocardiography 12 weeks later.
Results: total of 116 hypokinetic or akinetic myocardial segments were analysed. For the prediction of myocardial viability, the qualitative assessment of myocardial perfusion by MCE demonstrated a sensitivity of 72.9% and a specificity of 62.5% respectively. Segments with the rate of microbubble velocity of over 0.4 were viable after 12 weeks with sensitivity of 88.2% and specificity of 70.0%.(Accuracy: TP+TN/TP+TN+FP+FN) The transmural extent of delayed hyperenhancement of less than 50% of the whole wall thickness predicted the myocardial viability with a sensitivity of 69.8% and a specificity of 84.1%.
Conclusions: in this study, both diagnostic modalities showed comparable accuracy with MCE demonstrating superior sensitivity and inferior specificity compared to MRI. Combined assessment with quantitative MCE and MRI may provide the best diagnostic accuracy, with a sensitivity of 88.2%, a specificity of 84.1%, in the prediction of myocardial viability following acute myocardial infarction.

P2850 Microvascular and myocardial correlates of persistent ST segment elevation after PCI: results from the acute myocardial infarction contrast imaging (A.M.I.C.I) multicenter study

L. Galiuto[1], L. Agati[2], S. Funaro[3], G. Tonti[3], V. Di Bello[4], M.P. Madonna[2], B. Garramone[1], A. Scara'[1] on behalf of A.M.I.C.I. investigators. *[1]Policlinico A. Gemelli Rome, Italy, Cardiology Department, Rome, Italy; [2]La Sapienza University, Cardiology Department, Rome, Italy; [3]Catholic University, Cardiology department, Campobasso, Italy; [4]Pisa University, Cardiology department, Pisa, Italy*

Background: Microvascular and myocardial correlates of persistent ST segment elevation after PCI are still undefined. We tested the hypothesis that persistent ST segment elevation after PCI is associated with sustained microvascular obstruction and, consequently, with unresolved myocardial dysfunction and LV remodeling.
Method: A total of 109 patients with first successfully reperfused STEMI were enrolled in the Acute Myocardial Infarction Contrast Imaging (A.M.I.C.I) multicenter study. After PCI, ST-segment resolution was considered a reduction > 50% of ST-segment elevation. At day 1 and 3 months follow-up, the endocardial length of contrast defect (CD) was evaluated by myocardial contrast echocardiography (MCE) using continuous infusion of Sonovue® (Bracco) in real-time imaging. Regional wall motion scores (RWMSI), LV end-diastolic and end-systolic volumes (EDV, ESV) were calculated by echocardiography at the same time intervals.
Results: Patients with and without ST-segment resolution had similar symptoms-to-PCI time, peak CK, RWMSI and CD at day 1. At 3 months follow-up, in patients with ST segment resolution, RWMSI and CD significantly improved (1.9±0.8 vs 2.7±0.6 p<.0001 and 12.3±16.5 vs 22.6±20.3, p<.01, respectively) and EDV and ESV remained unchanged. While, in patients with persistent ST segment elevation, RWMSI and CD did not improve and EDV and ESV dilated at 3 months.
Conclusions: While at day 1 after primary PCI, patients with and without ST-segment resolution have similar microvascular and myocardial damage and LV volumes, at 3 months, unresolved ST segment elevation is associated with persistent microvascular and myocardial dysfunction and LV dilation. Thus, persistent ST-segment elevation is an early and effective indicator of sustained microvascular damage and evolving LV remodeling.

P2851 Real-time assessment of myocardial perfusion using contrast agent improves the diagnostic value of dipyridamole-atropine stress echocardiography

P. Lipiec, P. Wejner-Mik, M. Krzeminska-Pakula, J. Drozdz, L. Chrzanowski, M. Plewka, J.D. Kasprzak. *Medical University of Lodz, II Chair and Department of Cardiology, Lodz, Poland*

Aim: In patients with suspected significant coronary artery disease (CAD) the diagnostic potential of stress echocardiography (SE) based on evaluation of wall motion abnormalities (WMA) is well established. We designed this prospective study to assess if myocardial contrast enhancement (MCE) improves the diagnostic accuracy of SE by allowing concomitant evaluation of perfusion defects.
Methods: 55 patients (pts) (35 male, mean age 57±9 years) with suspected stable CAD (mean CCS class 2,5) scheduled for coronary angiography were included in this study. Prior to coronary angiography all pts underwent high-dose dipyridamole (0,84mg/kg iv over 4 minutes)-atropine (up to 1mg iv in negative cases) SE with MCE at rest and peak stress (Contrast Pulse Sequence, Siemens Sequoia 256C). MCE was performed using repeated iv boluses of 0,3-0,5ml Optison. WMA and perfusion were visually scored in 18 segments of the left ventricle. The presence of significant CAD (≥70% stenosis or ≥50% stenosis of left main coronary artery) was detected by coronary angiography.
Results: Significant CAD was present in 76% of pts (35%-1 vessel; 25%-2 vessels; 16%-3 vessels). Presence of inducible WMA had 67% accuracy (59% sensitivity, se; 86% specificity, sp) in detecting significant CAD. Concomitant evaluation of MCE provided 84% accuracy (85% se; 79% sp) using presence of any inducible abnormality (WMA or perfusion defects) as a criterion. Presence of any (inducible or resting) WMA had 85% accuracy (93% se; 64% sp). However, the optimal diagnostic accuracy was achieved using the presence of any inducible or resting abnormality (WMA or perfusion defect) as a criterion – 87% (98% se, 57% sp). The use of this criterion provided similar benefit in diagnostic accuracy in detecting significant coronary artery stenosis in analysis of individual coronary territories compared to the most accurate criterion based only on WMA (presence of any WMA), with an exception of RCA: LAD - 69% vs. 63% accuracy, Cx - 76% vs. 73% accuracy, RCA - 65% vs. 71% accuracy, respectively. The highest sensitivity (94%) in detecting 1-vessel disease was obtained using the criterion of any WMA or perfusion defect, compared to 83% sensitivity of the most sensitive criterion based only on WMA - presence of any WMA.
Conclusions: MCE with simple real-time visual assessment of perfusion defects improves the diagnostic accuracy of standard dipyridamole-atropine SE. The presence of resting or inducible WMA or perfusion defects offers the highest accuracy for detecting significant CAD.

P2852 Tissue Doppler imaging in normal and ischaemic rat models

C. Weytjens[1], T. Lahoutte[2], P.R. Franken[2], J. D'hooge[3], B. Cosijns[4], G. Van Camp[4]. *[1]Laken, Belgium; [2]AZ VUB, Nuclear Medicine, Brussels, Belgium; [3]University Hospital Gasthuisberg, Leuven, Belgium; [4]AZ VUB, Cardiology, Brussels, Belgium*

Background: Tissue Doppler Imaging (TDI) has become an important tool in the quantification of regional myocardial function. Few data are available about values of strain and strain rate in small rodents. We studied the feasibility of strain and strain rate imaging in normal rats and compared the results with two ischemic rat models.
Methods: A total of 24 male Wistar rats (age ± 24 weeks) underwent transthoracic echocardiography with M-Mode analysis of the left ventricle (LV) and TDI analysis of the anterior and inferior wall using parasternal shortaxis views. Images were recorded using a GE Vivid7 with a 13 MHz linear array transducer. Radial peak systolic velocity, strain and strain rate were measured in post processing using dedicated software (SPEQLE). In 15 normal rats reference values were obtained (group A) and the inter- and intraobserver variability for the TDI measurements in this group was tested with a Bland-Altman analysis. In 9 rats 150 mg/kg isoproterenol was injected subcutaneously at 14 weeks (group B) and in 4 rats the left anterior descendens coronary artery was surgically occluded causing anterior myocardial infarction (group C).
Results: Adequate TDI tracings could be obtained in 90% of the animals. Results of LV diameters, EF and TDI parameters are presented in Table I as mean values ± standard deviation. The inter- and intraobserver agreement for all TDI parameters in normal rats was good.

Table I

	Group A		Group B		Group C	
LVEDD (cm)	0.75 ± 0.06		0.80 ± 0.03		0.82 ± 0.08*	
LVESD (cm)	0.47 ± 0.06		0.53 ± 0.06*		0.59 ± 0.11*	
LVEF (%)	75 ± 7		70 ± 11		59 ± 24*	
	anterior wall	inferior wall	anterior wall	inferior wall	anterior wall	inferior wall
Velocity (cm/s)	-0.9 ± 0.2	2.6 ± 0.4	-0.9 ± 0.3	2.4 ± 0.4	-0.04 ± 0.03*	2.9 ± 0.7
Strain (%)	40 ± 8	48 ± 11	54 ± 10*	43 ± 12	13 ± 13*	45 ± 15
Strain rate (/s)	8.2 ± 1.7	10.2 ± 2	9.6 ± 1.7	9 ± 1	3.8 ± 3*	13.5 ± 4.4*

LVED(S)D= left ventricular end diastolic (systolic) diameter; * = p< 0.05 compared to group A

Conclusion: TDI is feasible in rats and permits a more complete characterisation of radial LV function in a normal and ischemic rat model.

P2853 Strain rate imaging accurately identifies necrotic myocardium after ischaemia-reperfusion in rabbits

H. Thibault[1], J. Loufouat[1], L. Augeul[1], E. Couture-Lepetit[1], L. Gomez[1], M. Ovize[1], G.A. Derumeaux[2]. *[1]Faculté de médecine LYON Nord, EMIU N°0226, Lyon, France; [2]Lyon, France*

Background: accurate assessment of the extension of myocardial necrosis by echocardiography remains a challenge in experimental ischaemia–reperfusion (IR). The reference method is blue dye and triphenyltetrazolium chloride (TTC) staining for measurement of the area at risk (AR) and the area of necrosis (AN), respectively. The aim of this study was to evaluate the accuracy of strain rate imaging in identifying necrotic myocardium in a rabbit model of IR.
Methods: 14 male New Zealand White rabbits underwent a 30-minute ligation of the 1st marginal branch of the LAD coronary artery followed by 72 hours of reperfusion. Echocardiography (8 MHz, Vivid 7, GE) was performed at baseline and at reperfusion (30 minutes and 72 hours). Strain rate imaging (SR, sec-1) was obtained from the mid short-axis view in the posterior (PW) and the anterior walls (AW) (SR length: 1 mm). At 72 hours, the coronary artery was reoccluded and blue dye was injected to assess the AR size. Infarct size (AN) was determined by TTC staining.
Results: blue dye localised the AR within the posterior wall and the apex in all the animals. At the level of the papillary muscles, TTC staining could identify 2 groups according to the presence of necrosis within the AR: 6 rabbits had necrosis (62±7% of wall thickness) and 8 rabbits had no necrosis. AR and AN were 31±13% and 8.3±8.5% of the left ventricle, respectively. AN/AR was 23±16%. LV ejection fraction significantly decreased from baseline (65±7%) to reperfusion (30 min: 51±12; 72 hours: 45±11%, p<0.05 vs baseline) but was not significantly correlated with the AR (r: 0.37, p: ns) and the AN (r: 0.31, p: ns). Systolic SR were obtained in all rabbits with adequate traces. As shown in the table, systolic SR significantly decreased only in the AN but not in the remote area and in the AR after 30 minutes and 72 hours of reperfusion.

Table

SR (sec^{-1})	Baseline	30 min Reperfusion	72 hour Reperfusion
Remote area (mid AW)	9.6±1	10.8±2	9.9±2
AR (mid PW)	9.05±2	10±1	8.7±2
AN (mid PW)	9.2±1	4.2±0.8*	3.6±1*

*: p<0.05 compared to baseline

Conclusion: in a rabbit model of ischaemia-reperfusion, strain rate imaging accurately identifies necrotic myocardial segments and differentiates them from stunned and normal segments.

P2854 Myocardial perfusion assessed by contrast echocardiography correlates with angiographic perfusion parameters in patients with first AMI successfully treated with primary coronary angioplasty

B. Sobkowicz[1], A. Tomaszuk-Kazberuk[2], K. Kaminski[2], K. Gugala[3], G. Mezynski[3], S. Dobrzycki[3], A. Lewczuk[2], W.J. Musial[1]. *[1]Medical Academy, Department of Cardiology, Bialystok, Poland; [2]Medical Academy, Department of Cardiology, Bialystok, Poland; [3]Medical Academy, Invasive Cardiology, Bialystok, Poland*

Background: Angiographic flow in epicardial arteries does not define accurately perfusion at a microvascular level, therefore other techniques assessing flow at a tissue level are to be preferred. In acute myocardial infarction (AMI) lack of myocardial perfusion despite recanalization of the infarct-related artery (IRA) is associated with worse left ventricular function and clinical outcome.
Aim: To compare intravenous myocardial contrast echocardiography (MCE) with angiographic methods of assessment microvascular reperfusion in patients with first AMI successfully treated with primary coronary intervention (PCI).
Methods: 100 consecutive patients (41 of them with anterior AMI) underwent primary PCI for STEMI, with restoration of TIMI grade 3 flow. Solely patients with single vessel disease were included. Baseline regional wall motion score index (WMSI) and regional contrast score index (RCSI) were calculated using a 16-segment LV model $>$ 48 hours after PCI. Optison contrast agent was administered via a peripheral vein. MCE was performed using a modality of subsequent data acquisition of triggered end-systolic images. Coronary angiograms after PCI were evaluated for corrected TIMI frame count (cTFC), TIMI myocardial perfusion grade (TMPG), and myocardial blush grade (MBG).
Results: Among 717 segments assessed by contrast echocardiography 168 (22%) revealed partial or total lack of perfusion. Patients with anterior AMI had significantly more segments with perfusion defect evaluated with MCE than patients with inferior AMI ($p < 0{,}0001$). Regional WMSI, RCSI were $1{,}6 \pm 0{,}56$, $1.4 \pm 0{,}27$ respectively. Peak CK-MB correlated well with WMSI (p=0,037). Results of angiographic reperfusion assessment techniques were as follows: mean cTFC was $25{,}2 \pm 14{,}5$, mean TMPG was $2{,}02 \pm 0{,}97$ and mean MBG was $2{,}2 \pm 1{,}16$. TMPG and cTFC correlated significantly with RCSI (p=0,031 and p=0,02 respectively). TMPG correlated with WMSI (p=0,025). MBG did not correlate with RCSI (p=0,067), but correlated with WMSI (p=0,038).
Conclusions: 1. MCE is an uncomplicated method of perfusion assessment at a microvascular level in patients with AMI at a bedside and gives additional information about actual size of myocardial infarction. 2. MCE results correlate with angiographic methods of perfusion assessment such as TMPG and cTFC estimated during primary PCI. The clinical follow-up is in progress.

P2855 Stress real-time myocardial contrast echocardiography – ready to replace single-photon emission computed tomography in its routine diagnostic applications?

P. Lipiec[1], P. Wejner-Mik[1], M. Krzeminska-Pakula[1], J. Drozdz[1], J. Kusmierek[2], A. Plachcinska[2], R. Szuminski[2], J.D. Kasprzak[1]. *[1]Medical University of Lodz, II Chair and Department of Cardiology, Lodz, Poland; [2]Medical University of Lodz, Department of Nuclear Medicine, Lodz, Poland*

Background: Myocardial perfusion at rest and during stress can be assessed using variety of techniques. Gated 99mTc-sestamibi SPECT (G-SPECT) is considered one of the reference methods. The diagnostic potential of myocardial contrast echocardiography (MCE) has not yet been fully established.
Aim: To evaluate the diagnostic value of stress MCE for detecting perfusion defects and for identifying patients with significant coronary artery disease (sCAD) in comparison with G-SPECT.
Methods: 55 patients (pts) (35 male, mean age 57 ± 9 years) with suspected stable CAD (mean CCS class 2,5) scheduled for coronary angiography were included in this prospective study. Prior to coronary angiography all pts underwent G-SPECT and high dose dipyridamole (0,84mg/kg iv over 4 minutes)-atropine (up to 1mg iv) stress MCE (Contrast Pulse Sequence, Siemens Sequoia 256C) using repeated iv boluses of 0,3-0,5ml Optison and visual scoring of perfusion in 18 segments of left ventricle. The presence of sCAD ($\geq$70% stenosis or $\geq$50% stenosis of left main coronary artery) was detected by coronary angiography.
Results: sCAD was present in 76% of pts (35%-1 vessel, 25%-2 vessels, 16%-3 vessels). Assessment of MCE was feasible in 96% of segments at rest and 94% at peak stress. Overall agreement between G-SPECT and MCE was 84% in detecting any (inducible or resting) perfusion defects and 66% in detecting inducible defects. In perfusion beds of LAD, Cx and RCA the agreement was 64%, 80% and 75% in detecting any perfusion defects and 71%, 85% and 71% in detecting inducible defects, respectively. Table 1 presents accuracy (ac), sensitivity (se) and specificity (sp) of analyzed methods in detecting sCAD and significant stenoses in individual coronary arteries.
Conclusions: Stress MCE offers acceptable agreement with G-SPECT in detecting perfusion defects. Similar sensitivity and higher specificity result in higher accuracy of MCE in identifying patients with sCAD compared to G-SPECT.
Study supported from KBN grant P05B 03623

Table 1

Criterion	Overall ac (se, sp) [%]	LAD - ac (se, sp) [%]	Cx - ac (se, sp) [%]	RCA - ac (se, sp) [%]
MCE-inducible defects	80 (78, 86)	62 (44, 79)	69 (26, 100)	67 (48, 81)
MCE-inducible or resting defects	85 (90, 71)	69 (63, 75)	72 (39, 97)	76 (91, 66)
G-SPECT-inducible defects	62 (71, 36)	55 (41, 68)	69 (30, 97)	56 (48, 63)
G-SPECT-inducible or resting defects	80 (95, 36)	64 (63, 64)	71 (35, 97)	65 (91, 47)

P2856 Relationship between myocardial perfusion assessed by contrast echocardiography and clinical and laboratory parameters in patients with AMI treated with primary coronary intervention

A. Tomaszuk-Kazberuk[1], B. Sobkowicz[1], K. Kaminski[1], W.J. Musial[1], K. Gugala[2], S. Dobrzycki[2], R. Sawicki[1], E. Skibinska[1]. *[1]Medical Academy, Department of Cardiology, Bialystok, Poland; [2]Medical Academy, Invasive Cardiology, Bialystok, Poland*

Myocardial contrast echocardiography (MCE) in AMI provides information regarding the adequacy of myocardial tissue reperfusion, as well as the spatial extent of microvascular integrity. MCE can predict recovery of left ventricular function.
Objective: to assess the relationship between myocardial perfusion defects assessed by MCE and clinical and laboratory parameters in patients with AMI treated with primary coronary intervention (PCI).
Material and Methods: 100 consecutive patients (78 men) with a first STEMI successfully treated with primary PCI. Solely patients with single vessel disease were included. 13 patients were treated with IIb/IIIa blocker (tirofiban) at the discretion of PCI operator. Regional wall motion score index (WMSI) and regional contrast score index (RCSI) were calculated using a 16-segment LV model $>$ 48 hours after PCI. Optison contrast agent was administered via a peripheral vein. MCE was performed using a modality of subsequent data acquisition of triggered end-systolic images. Perfusion assessment was qualitative (three perfusion patterns). The criterion for MCE was defined as homogenous enhancement in 50% of wall thickness in each segment. Coronary angiograms after PCI were evaluated for TIMI myocardial perfusion grade (TMPG).
Patients were divided into 2 groups according to the presence of perfusion defect assessed by MCE.
Results: group 1 consisted of 54 patients without perfusion defect, while in 44 patients (group 2) segments with loss of perfusion were found. There were no signifficant differences between both groups in respect of age and sex. Smoking was more frequent in patients with perfusion loss on MCE but the difference was at the limit of signifficance (p=0,053). In the Group 2 anterior AMI was more frequent in comparison with the patients from Group 1 (p=0,00014). Group 1 had higher ejection fraction (EF biplane), lower ESV and WMSI than patients from Group 2 (p=0,006, p=0,001, p=0,0009 respectively). Peak CK-MB correlated well with RCSI in the Group 2 (p=0,037). The patients treated with tirofiban had signifficantly lower RCSI than those who did not receive tirofiban (p=0,003). MCE perfusion results correlated with angiographic perfusion assessment by TMPG (p=0,01).
Conclusions: 1) MCE as a method of perfusion assessment is promising for early estimation of primary PCI results. 2) Anterior AMI is associated with greater extend of perfusion defect in patients treated with primary PCI. 3) Treatment with IIb/IIIa blocker is potentially associated with better myocardial tissue reperfusion in patients with AMI.

P2857 Ultrasound lung comets and plasma N-terminal proBNP in patients with dyspnoea

F. Frassi[1], S. Gligorova[1], M. Agrusta[2], L. Gargani[1], M. Emdin[1], C. Prontera[1], G. Mottola[2], E. Picano[3]. *[1]Institute of Clinical Physiology, CNR, Pisa, Italy; [2]Casa di Cura "Montevergine", Mercogliano, Italy; [3]CNR Institute of Clinical Physiology, Pisa, Italy*

Background: Ultrasound lung comet (ULC) consists of multiple comet-tails fanning out from the lung surface and originating from water-thickened interlobular septa. They are a simple echographic sign of abnormally increased extra-vascular lung water (Jambrik et al, Am J Cardiol 2004). Plasma N-terminal proBNP (NT-proBNP) concentration provides useful diagnostic and prognostic information.
Aim: To establish the correlation between ULC and NT-proBNP in a cardiological emergency department.
Methods: 63 patients (20 females; age=70 ± 11 yrs) admitted for dyspnoea underwent a simultaneous evaluation for plasma NT-proBNP (abnormal values: $>$300 pg/ml) and limited echography for ULC assessment with commercially available echocardiographic system including a portable unit. A patient ULC score was obtained by summing the number of comets in each of the scanning spaces in the anterior right and left chest, from second to fifth intercostal space.
Results: NT-proBNP values were 7033 ± 8024 pg/ml. ULC assessment could be obtained in all patients (feasibility=100%). The imaging and analysis time was always $<$ 2 minutes. ULC values were 24 ± 19. The concordance between NT-proBNP (normal/abnormal) and ULC (absent/present) was 95%. In the overall group there was a significant, albeit only fair, correlation between NT-proBNP and ULC (Figure 1).
Conclusion: In patients with dysponea, the presence and severity of ULC is somewhat correlated with plasma NT-proBNP values, expressing a link of po-

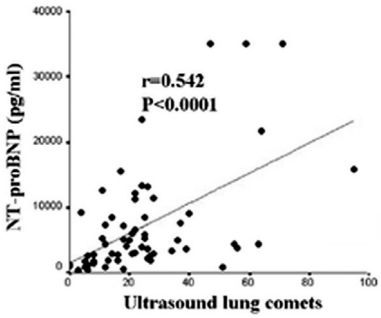


Figure 1

tential clinical and pathophysiologic value between the amount of extra-vascular lung water and cardiac endocrine expression of mechanical overload.

P2858 Utility of BNP level in patients with chronic atrial fibrillation with normal systolic left ventricular function

B.J. Kim[1], S.J. Hwang[2], K.C. Sung[2], B.S. Kim[2], J.H. Kang[2], M.H. Lee[2], J.R. Park[2]. [1]*Sungkyunkwan University School of Medi, Department of Internal Medicine, Seoul, Korea, Republic of;* [2]*Kangbuk Samsung Hospital, Cardiology, Seoul, Korea, Republic of*

There are some limitations in assessment of diastolic function in patients with chronic atrial fibrillation(AF). It is known that brain natriuretic peptide(BNP) is secreted from cardiac ventricles, reflecting left ventricular(LV) end-diastolic pressure. We studied to assess whether levels of BNP are associated with clinical and echocardiographic parameters of diastolic function in a sample of patients under study. 102 consecutive patients (65 male, 37 female. mean age 66.0±11.2 years) who showed normal LV systolic function with chronic atrial fibrillation were participated. The most frequent etiology of AF was hypertension(60%), and other etiologies were lone AF(19%), heart failure(7.9%), hyperthyroidism(7.9%), mitral stenosis(4.8%). Plasma BNP showed significantly positive correlations with transmitral early diastolic peak flow(E) velocity(r=0.341, p=0.009), ratio of E and early diastolic(Ea) velocity by mitral annular (r=0.551,p<0.001), left atrial volume index(r=0.578, p<0.001), right atrial volume index(r=0.521, p<0.001), degree of mitral regurgitation(r=0.467, p<0.001), degree of tricuspid regurgitation(r=0.418, r<0.001), and duration of AF(r=0.684, p<0.001) and negative correlations with Ea(r=-0.310, p=0.019), ratio(PVs/PVd) of systolic flow velocity and early diastolic velocity of pulmonary venous Doppler(r=-0.319, p=0.018). By multiple linear regression analysis, longer duration of AF(SB=5.26, p<0.001), larger left atrial volume index(SB=2.285, p=0.027), larger LV mass index(SB=2.095, p=0.042) independently predicted higher plasma BNP levels in this patients.
These results suggest that plasma BNP level in patients with normal LV systolic function and chronic atrial fibrillation correlates with echocardiographic Doppler parameters assessing diastolic function but is more heavily influenced by duration of AF, left atrial volume index, LV mass index.

P2859 Reduced regional systolic and diastolic functional reserve of the venous left ventricle in patients with corrected transposition of the great arteries by atrial switch: a strain rate imaging study

B. Goebel[1], R. Arnold[2], J. Kaden[3], T. Sueselbeck[3], J. Eichhorn[2], H.E. Ulmer[2], M. Borggrefe[3], T. Poerner[3]. [1]*Heidelberg, Germany;* [2]*University Hospital Heidelberg, Department of Pediatric Cardiology, Heidelberg, Germany;* [3]*University Hospital Mannheim, 1st Dept. of Medicine, Germany, Mannheim, Germany*

Background: Purpose of this study was to investigate regional myocardial function at rest and under exercise in patients with transposition of the great arteries corrected by atrial switch operation (cTGA).
Methods: The study group consisted of 25 patients (age 12-33 years) with TGA corrected at the atrial level by the Mustard or Senning technique.
Age- and gender-matched healthy subjects served as control group. All children underwent echocardiography with tissue Doppler and strain rate imaging (TDI/SRI) at rest and during a bicycle exercise test (1 W/kg body weight and 2 W/kg body weight for 5 minutes). Free wall of the systemic right ventricle (RV) and lateral wall of the venous left ventricle (LV) were scanned from apical 4-chamber-views. Longitudinal systolic (VS) and diastolic (VE) velocities, systolic strain rate (SR) and strain were determined as peak values in the basal, mid-wall and apical segments using a dedicated software.
Results: Quantitative echocardiographic data are displayed in Table 1.
Conclusions: (1) The septum and especially the free RV wall of patients with cTGA showed markedly lower regional systolic and diastolic performance indices compared to the control group both at rest and under exercise.
(2) Venous left ventricle of cTGA patients presented at rest with reduced diastolic velocities, while contractility parameters were comparable to those of the control group.

Table 1 (mean ± SD)

	Strain (%)		SR (1/s)		Vs (mm/s)		Ve (mm/s)	
	cTGA	Controls	cTGA	Controls	cTGA	Controls	cTGA	Controls
RV								
rest	15±8*	36±20	1.11±0.61*	2.89±1.69	40±27*	64±25	37±26*	86±38
exercise	13±6*	37±17	1.49±1*	3.65±1.89"	38±29*	67±34	42±27*	110±54"
Septum								
rest	20±9*	24±8	1.24±0.63*	1.91±0.69	25±12*	34±18	38±22*	85±27
exercise	23±10	28±11"	1.86±1.1*"	2.39±0.81"	31±19*	45±22"	43±22*	110±35"
LV								
rest	19±9	21±9	1.64±0.7	1.8±1.1	53±31	46±25	55±37*	94±41
exercise	18±8*	23±10	2.09±0.86*"	2.59±1.32"	76±44*	98±42"	60±23*	136±47"

p < .05: *vs. controls,"vs. rest

(3) Under exercise TDI/SRI revealed in patients with cTGA significant lower values for strain rate, strain and peak velocities in the lateral LV wall compared to healthy subjects, demonstrating a reduced functional reserve of the venous LV after correction of TGA.

P2860 Ventricular 2D-based strain values are afterload dependant: insights from an analysis of patients with transposition of the great arteries

A. Franke[1], A. Niedeggen[1], M. Becker[1], E.G. Muehler[2], H.P. Kuehl[1], R. Hoffmann[1]. [1]*University Hospital, Med. Clinic I, Aachen, Germany;* [2]*Pediatric Cardiology, University Hospital, Aachen, Germany*

Cardiac anatomy in patients (pts) with transposition of the great arteries and atrial switch (TGA) or with congenitally corrected TGA (ccTGA) allows analyzing the effect of elevated after-load on a morphological right ventricle (RV) and of reduced after-load on a morphological left ventricle (LV) in comparison to normal controls. We evaluated the effect of different after-load conditions on RV and LV using novel computer software yielding two-dimensional strain (2D strain) as an objective measure of regional contractility.
Methods: 13 pts with TGA (age 24±4 years) and 13 subjects without cardiac disease (25±4y) were included. Digital loops of LV and RV were acquired in an apical 4-chamber view (Vivid 7, GE, Horton, Norway) and 2D strain was analyzed offline (EchoPAC, GE). 2D strain software identifies intramyocardial acoustic markers and follows them over time using spatial and temporal image processing algorithms to determine regional radial or longitudinal strain. RV free wall, septum and LV lateral wall were divided into 3 segments (basal, mid, apical) each. Systolic longitudinal strain for the segments and the ventricles is given in the table.
Results: 2D strain values differ significantly between systemic and pulmonary ventricles in the individual pt. RV (= systemic ventricle) strain in TGA pts was significantly smaller than in normals (= pulmonary ventricle), LV strain in TGA pts was significantly higher than in normals. Interestingly, there were no differences between TGA-LV's and normal RV's or between TGA-RV's and normal LV's.

Negative longitudinal strain values

	TGA	Normals	Significance
global RV (6 segments)	13.2±2.5	19.1±2.9	**
RV basal free wall	15.9±6.1	24.7±9.6	*
RV mid free wall	15.7±3.6	22.7±6.5	**
RV apical free wall	13.7±5.5	21.0±6.9	**
global LV (6 segments)	19.1±5.1	14.6±3.4	*
LV basal lateral wall	24.2±8.1	14.9±6.0	*
LV mid lateral wall	21.2±7.0	14.1±5.2	*
LV apical lateral wall	19.8±14.0	10.5±7.3	n.s.

*= p<0.05; **=p<0.01; n.s.= not significant

Conclusion: Different after-load conditions in the morphological RV (and LV) can be detected by measuring 2D strain based on novel analysis algorithms.

P2861 Evaluation of cardiac functions of patients with carbon monoxide poisoning by echocardiography

N. Kalay[1], A. Gul[1], I. Ozdogru[1], Y. Cetinkaya[1], I. Ikizceli[2], I. Gul[1], A. Yalcin[1], A. Oguzhan[1]. [1]*Erciyes University Cardiology depart., Kayseri, Turkey;* [2]*Erciyes University, Emergency department, Kayseri, Turkey*

Introduction: Heart is among target organs in poisoning with carbon monoxide (CO). Myocardial damage may develop in patients exposed to CO through tissue hypoxia, direct toxicity of CO or oxidative stress. The cardiac assessment is necessary to detect cardiac damage in these patients. In this study, we aimed to investigate myocardial function in patients with CO poisoning.
Methods: The patients who were diagnosed as CO poisoning in the emergency department were included in this study. The patients who have a history of myocardial infarction, coronary artery by pass operation, hypertension, diabetes mellitus were excluded from the study. Carboxyhemoglobin (COHb) was measured at the admission to emergency department.All patients received hyperbaric oxygen treatment Patients were examined with conventional echocardiography on admission, at 24. hour and 7.day. Left ventricle ejection fraction (LV EF) and regional wall motion score index through 16 segments were measured.
Results: Twenty patients who were diagnosed as CO poisoning were included in the study (age: 39, 2± 17, 0; male 9). LVEF was below %45 in 9 patients (Group

A; mean LV EF %38,0±5,1) and above %45 in 11 patients(Group B; mean LV EF: %65,5±5,6). Twenty-four hour echo revealed a significant increase in LVEF at 8 patient of this 9 patients (mean LV EF %61,0±4,7; p=0,001) compared with initial echo and also LVEF increased at first weak(mean LV EF:%66.5±5,7 p=0.09) compared with 24. hour echocardiography. One patient did not show an increase in LVEF at 24 hours and first weak (at admission LVEF: %33, 24 hour: %36, 7. day: %35). COHb levels were significantly higher in the group A than group B (resp. COHb: 32,8 ±6,9, 23,4 ±8,6; p = 0,02). The reduction of LVEF was correlated with COHb levels (r:-0,66 p=0,002) and duration of exposure to CO (r=-0,63, p=0.005). There was a global left ventricular hypokinesia in 2 patients and segmental wall motional abnormalities in 7 patient of group A. Initial regional wall motion score index of group A was significantly higher than group B (resp. 31,2±10,2; 16,2 ± 0,6; P=0,002), also this score decreased significantly gradually in group A (initial: 31,2±10,2 vs. 24 hours: 22,4 ± 6,8; p=0,008; 24 hours: 22,4 ± 6,8 vs. 7. days:18,7±7,2 p=0,04)

Conclusion: The CO poisoning may cause myocardial stunning in patients with normal cardiac structure. This impairment can recover with hyperbaric oxygen treatment by time. However, this impairment can be persistent in some patients. Therefore echocardiographic examination is essentially to detection in these patients.

P2862 Increased TIMI frame counts in patients without significant coronary atherosclerosis but with left ventricular dysfunction during dobutamine stress echocardiography

O. Yavuzgil[1], C. Gurgun[2], M. Ildizli[2], C.S. Cinar[2], F. Ozerkan[2], H. Kultursay[2]. *[1]Izmir, Turkey; [2]Ege University Medical Faculty, Cardiology, Izmir, Turkey*

Background: Dobutamine stress echocardiography (DSE) has become a widely accepted an important clinical tool for the non-invasive diagnosis of coronary artery disease (CAD). The aim of the study was to investigate the relationship between angiographic coronary flow patterns by the thrombolysis in myocardial infarction (TIMI) frame count and DSE findings in patients without significant CAD.

Methods: The study group was consisted of 32 patients (mean age: 53±13, 81% male) who had least one positive stress test (ECG, SPECT or DSE) but without significant CAD on coronary angiography. Dobutamine was infused starting with a dose of 5 mcg/kg/min over 3 minutes with incremental steps of 5 mcg/kg/min every 3 minutes up to a maximal dose of 40 mcg/kg/min. Two-dimensional echocardiography and 12-lead electrocardiography were monitored during the infusion of the drug. Resting and peak DSE wall motion score index (WMSI) were evaluated. The TIMI frame count was determined for each major coronary artery in each patient and corrected for the left anterior descending (LAD).Group I consisted of 12 pts with positive DSE and group II consisted of 20 pts with negative DSE.

Results: DSE was positive in 12 patients (38%),in whom 16 myocardial segments were involved: of these, 12 were normokinetic and 4 hypokinetic at rest. Peak WMSI was 1.16±0.21 ($p < 0.001$ vs rest). Of the 12 patients with a positive DSE, 9 also showed diagnostic ECG changes and 4 complained of angina. Of the 20 patients with negative DSE, 1 had angina and 3 (one with angina) showed ECG changes. Corrected TIMI frame counts were shown at the table.

Corrected TFC's of the Groups

CTFC	Group I, N=12	Group II, N=20	P
LAD	36.5±25.7	23.1±14.6	0.009
Cx	35.6±20.9	24.8±11.4	0.015
RCA	25.6±5.4	21.8±5.7	0.048

LAD:Left anterior descendingCx:CircumflexRCA:Right coronary artery

Conclusions: Left ventricular dysfunction during DSE in pts without significant coronary atherosclerosis seems be related to the microvascular dysfunction which can be detected by TIMI frame count. A positive DSE in these pts needs to be investigated for the prognostic prediction.

P2863 Does myocardial jeopardy add more prognostic information to stress echo in prediction of future cardiac events in patients with natural progression of coronary artery disease

I. Nedeljkovic[1], M. Ostojic[2], B. Beleslin[2], A. Djordjevic-Dikic[2], N. Milic[2], J. Stepanovic[2], M. Nedeljkovic[2], V. Giga[2]. *[1]University Institute for CVD, Cardiology, Belgrade, Serbia and Montenegro; [2]Univ.Institute for CVD, Cardiology Dept., Belgrade, Serbia and Montenegro*

Background: Myocardial jeopardy score has been shown to be the best predictor of fatal outcome during revascularization procedures, but its role in long-term survival in patients with natural progression of coronary artery disease still remained unknown.

Objective: We sought to study the prediction of future cardiac events with modified myocardial jeopardy score (MJS) in combination with Dobutamine-Atropine (Dobatro) and Dipyridamole-Atropine (Dipatro) stress echocardiography in patients who did not undergo revascularization procedures.

Methods: From existing stress echo database, we studied 137 pts had not undergone revascularization procedures for some reason. They all underwent Dobatro (up to 40 mcg/kg/min i.v. Dob with addition of 1 mg of atropine), Dipatro (up to 0.84 mg/kg Dip with addition of 1mg of atropine) and coronary arteriography. Coronary artery disease (CAD) was present in 86 pts: 71 one-, 15 multi-vessel CAD. MJS was calculated for each vessel as a sum of all significant lesions represented as a product of: (1) myocardial kinetic status (3 for akinetic, 2 for hypokinetic, and 1 for each normokinetic myocardial segment subserved by the vessel with equal or greater than 50% diameter stenosis), (2) diameter stenosis of significantly stenosed coronary vessel (scored from 1-5), and (3) weighting flow factor for particular localization.

Results: During follow-up period was (46±22 months), 48 pts had expected cardiac events (non fatal myocardial infarction, non stable angina, or cardiac death). Of them 46 pts had positive Dobatro and Dipatro. Univariate predictors strongly associated with observed end points were: MJS >26.75 (Sn 81%, Sp 80%) according to ROC curve ($p<0.0001$), positive Dobatro ($p<0.0001$), positive Dipatro ($p<0.0001$) and the number of diseased vessels (p=0.0005). Cox regression multivariate analysis showed that myocardial jeopardy score was an independent predictor of long-term outcome (RR=1.02; $p<0.0001$). Kaplan-Meier event-free survival with combined end-points showed significantly better outcome ($p<0.0001$) for patients with lower myocardial jeopardy score (< 26.75).

Conclusion: Cardiac death and other non-fatal cardiac events are strongly associated with high myocardial jeopardy score in patients with natural progression of coronary artery disease. These findings confirmed the importance of integrated approach to coronary anatomy and amount of potentially ischemic myocardium in long- term prognostic evaluation.

P2864 Comparison of left atrial linear dimension, 2d and 3d echocardiographic estimates of left atrial size to mitral inflow and pulmonary venous flow spectral Doppler correlates

A. Gopal[1], S. Mathew[2], R.S. Toole[2], W. Schapiro[2], N. Reichek[2] on behalf of St. Francis Hospital, Roslyn, NY. *[1]St. Francis Hospital - The Heart Center, Non-Invasive Lab - Lower Level, Roslyn, United States of America; [2]St. Francis Hospital, Adult Non-Invasive Lab - Lower Level, Roslyn, United States of America*

Our previous work has shown good correlation of maximum and minimum left atrial (LA) volumes with CMR. However, the components of LA function by 3D echo has not been reported.

Methods: We compared LV diastolic Doppler parameters to 1D, 2D, and 3D estimates of LA size in 33 pts (mean age 70 yrs) with abnormal LVs (19 with aortic stenosis and 14 post-MI). 3D echo (Philips 7500) LA volumes were obtained by surface approximation from 8 apical planes(TomTec). Transmitral, pulmonary vein flow Doppler, color-M mode flow propagation velocity and TDI of the septal and lateral mitral annulus were performed.

Results: 3D LA volumes correlated only with Doppler parameters that reflect LA contraction (A vel, E/A ratio and PV systolic velocity).

Parameters	r	SEE	Regression Equation	p value
A velocity (cm/s)	0.49	27	y = - 0.5x + 134	0.0086
vs. 3D maximum LA volume	0.55	26	y = - 0.7x + 128	0.0026
vs. 3D minimum LA volume	0.41	29	y = - 2x + 132	0.0247
vs. 2D LA area	0.14	31	y = - 8x + 119	ns
vs. 1D LA linear dimension				
E/A velocity ratio				
vs. 3D maximum LA volume	0.52	1.4	y = - 0.03x - 1.3	0.0048
vs. 3D minimum LA volume	0.37	1.5	y = 0.6x - 1.1	0.0525
vs. 2D LA area	0.24	1.5	y = - 0.06x - 0.03	ns
vs. 1D LA linear dimension	0.00	1.5	y = 0.2x + 2	ns
Pulmonary vein systolic flow velocity (cm/s)				
vs. 3D maximum LA volume	0.52	13	y = 0.31x + 27	0.0266
vs. 3D minimum LA volume	0.42	11	y = 0.2 x + 38	0.0894
vs. 2D LA area	0.17	13	y = - 0.4x + 58	ns
vs. 1D LA linear dimension	0.00	11	y = 0.3x + 52	ns

Conclusions: 1) 3D LA volumes correlate with Doppler variables that reflect LA function rather than LV diastolic function in our patient cohort. 2)3D echo LA volumes correlate more closely with Doppler parameters of LA function than do linear LA dimensions or 2D LA area. 3) Our prior 3D echo/CMR correlation and current Doppler correlations suggest that 3D echo LA volume over the entire atrial cycle is a useful tool for characterization of LA function.

COMPUTERS IN CARDIOLOGY

P2865 Heteromeric Kir2.x channels are activated by proteinkinase A

C. Kiesecker[1], E. Zitron[1], D. Scherer[1], E.P. Scholz[1], S. Kathofer[1], D. Thomas[1], V.A.W. Kreye[2], C.A. Karle[1]. *[1]Medical University Hospital Heidelberg, Dept. of Cardiology, Heidelberg, Germany; [2]University of Heidelberg, Dept. of Physiology and Pathophysiology, Heidelberg, Germany*

Introduction: In human cardiomyocytes the cardiac inwardly rectifying potassium

current IK1 is essential to maintain the resting membrane potential. Modulation of IK1 by adrenergic receptors with consequent activation of proteinkinase A (PKA) plays a central role in chronic heart failure and cardiac hypertrophy. A reduction of IK1 is part of the "electrical remodeling" observed in chronic heart failure. There is an increasing body of evidence that heteromeric assembly of Kir2.1, Kir2.2 and Kir2.3 potassium channels underlies a main part of the current. However, the regulation of heteromeric Kir2.x channels by protein kinase A has not been studied yet. Therefore, we investigated the regulation of heteromeric Kir2.x channels by PKA.

Methods: Human Kir2.1, Kir2.2 and Kir2.3 channels were expressed in Xenopus oocytes and experiments were performed using two-microelectrode voltage-clamp.

Results: To induce activation of PKA, adenylate cyclase activator Forskolin (100μM) and PDE-Inhibitor IBMX (100μM) were applied simultaneously. In homomeric Kir2.1 channels (+0%) and in homomeric Kir2.3 channels (-5%) no effect was observed. However, in homomeric Kir2.2 channels (+85%) we found a marked activation of currents. In heteromeric channels all currents were activated. In heteromeric Kir2.1/Kir2.3 channels (+23%) and in heteromeric Kir2.2/Kir2.3 channels (+22%) activation was only weak. Surprisingly, however, in heteromeric Kir2.1/Kir2.2 channels (+88%) activation was as strong as in homomeric Kir2.2 channels.

Conclusion: Heteromeric Kir2.x channels are activated by upregulation of proteinkinase A. Kir2.2 channel subunits seem to play a major role in this regulation and appear to be the key element in the modulation of cardiac IK1 by PKA. These results contribute to the understanding of the adrenergic regulation of IK1.

P2866 A deterministic-statistic adventitia modelling in IVUS images

O. Rodriguez Leor[1], J. Mauri Ferre[2], E. Fernandez Nofrerias[2], A. Carol Ruiz[2], V. Valle Tudela[2], D. Gil[3], A. Hernandez[3], P. Radeva[3]. *[1]Hospital Universitari Germans Trias i Pujol, Hemodinamica Cardiaca, Badalona, Spain; [2]HU Germans Trias i Pujol, Cardiology, Badalona, Spain; [3]Universitat Autonoma de Barcelona, Computer Vision Center, Bellaterra, Spain*

Introduction: Automatic analysis of IVUS images needs accurate intima and adventitia models. There are many algorithms for a reliable intima detection but adventitia modelling has been hardly approached. Regardless of low quality in IVUS images, adventitia detection adds the difficulty of a large variety of descriptors, including image edges, points of maximum variance (calcium), bifurcations and tissue region segmentation. We describe a method for adventitia characterization based on a statistical extraction of adventitia points followed by the recovery of a closed model determined by the image geometry.

Method: The descriptors used to select adventitia points are edges (adventitia) and calcium detectors in order to discard sectors of ambiguous information. The values that best characterize each structure (adventitia and calcium) are statistically learned by means of manually segmented images. In order to enhance significant structures while removing noise and textured tissue, we use a Restricted Anisotropic Diffusion. For adventitia closing we use an Anisotropic Contour Closing to interpolate curve segments and a parametric B-spline snake for a compact explicit model.

We have applied our model to 3300 IVUS frames including bifurcations, calcium, and other kind of plaques. Automated detections have been compared to manual segmentations performed by four experts in IVUS image interpretation.

Result: Accuracy has been measured by means of the mean (MeanD) and maximum (MaxD) absolute and relative (%) positioning errors (mm) and area differences (%). Results comparing interobserver variability (INT-OBS) and automatic errors (AUT) are summarized in table 1. There is no significant difference (p=0.5307) between inter-observer and automated mean absolute distance errors.

Table 1. Results

	MaxD Abs Error	MaxD(%)	MeanD Abs Error	MeanD(%)	Area (%)
INT-OBS	0.51±0.28	0.44±0.2	0.26±0.16	0.21±0.11	7.5±3.26
AUT	0.65±0.34	0.6±0.4	0.26±0.1	0.22±0.1	9.6±3.7

Conclusion: Our model for detection of the adventitia layer in IVUS images has an accuracy comparable to manual segmentation regardless of plaque nature (calcified or not), vessel geometry and bifurcations. Robust adventitia detection represents a new trend in medical imaging with a straightforward clinical application to plaque area and vessel diameter measurements.

POSTER SESSION 5

MODERATED POSTERS: ISCHAEMIA/CORONARY ARTERY DISEASE/ACC

P2867 Echocardiographic assessment of the incidence of mechanical complications during the early phase of AMI in the reperfusion era

P. Gueret[1], K. Kalife[2], Y. Jobic[2], S. Tassan[2], C. Romeyer[2], C. Baixas[3], P. Motreff[2], D. Raufast[2] on behalf of the Study Group.. *[1]Hopital Henri Mondor, Departement de Cardiologie, Creteil, France; [2]Henri Mondor University Hospital, Cardiology, Creteil, France; [3]Henri Mondor University Hospital, Cardiology, Creteil, France*

Background: Most studies reporting the incidence of mechanical complications after acute myocardial infarction (AMI) by Doppler echocardiography (DE) were published in the eighties, before the widespread use of early revascularization by thrombolytic therapy and/or primary coronary angioplasty. The technical characteristics of DE machines have also dramatically improved, yielding better diagnostic performance.

Objectives: To assess the incidence of mechanical complications after AMI in the reperfusion era in a large cohort of patients admitted in the CCU with a STEMI.

Methods and Results: From beginning of April to end of June 2004, 908 patients (70% male, mean age 62+14y) were consecutively included in 55 french hospital centers. DE was performed on admission (median 4 hours after onset of symptoms) and at hospital discharge (median 6 days). 78% of pts were revascularized at the acute phase. The rate of death was 6.6%. Pericardial effusion (PE) was observed on DE in 6.6%, either inferior (72%) or circumferential (28%). PE was more frequent after anterior (63%) than inferior AMI (37%), and was associated with a lower left ventricular (LV) ejection fraction (EF) (44+13% vs. 51+12%, $p<0.002$). LV thrombus was found in 2.4% (22/908), mainly located at the apex after anterior AMI (21/22), and associated with a lower EF (38+10% vs 48+12%, $p<0.001$). Mitral regurgitation was observed in 28% (mild or moderate in 93% of cases), and was secondary either to LV remodelling after anterior AMI (43%) or to papillary muscle dysfunction after inferior AMI (57%) (7 ruptures). Early infarct expansion or LV aneurysm occurred in 4% essentially after anterior AMI (29/37cases) with low EF (37+13%). Septal rupture was seen in 0.98% (5/908) and acute free wall rupture in 0.8% (7/908). By multivariate logistic regression, the factors independently associated with the occurrence of mechanical complications were: lack or failure of early revascularization (OR 3.48, 98% CI 1.36-8.94), LVEF on admission $<50\%$ (OR 1.95, CI 1.42-2.67), Killip class >2 (OR 1.91, CI 1.27-2.87) and age >70y (OR 1.42, CI 1.03-1.97).

Conclusions: The current prospective study demonstrated in a large cohort of consecutive patients a favourable influence of early revascularization on the incidence of mechanical complications after AMI. It also underlined the persistent relationship between the development of these complications and depressed LV function after extensive myocardial infarction.

P2868 The quantification of infarct size by myocardial contrast echocardiography: results from the acute myocardial infarction contrast imaging (A.M.I.C.I) multicenter study

L. Agati[1], L. Galiuto[2], S. Funaro[3], V. Di Bello[4], M.P. Madonna[5], B. Garramone[2], G. Tonti[3], C. Palagi[4] on behalf of A.M.I.C.I. study group. *[1]Rome, Italy; [2]Catholic University, Cardiology, Rome, Italy; [3]Catholic University, Cardiology, Campobasso, Italy; [4]University, Cardiology, Pisa, Italy; [5]La Sapienza University of Rome, Cardiology Dept., Roma, Italy*

Background: The measurement of infarct size (IS) is an attractive surrogate end point for the early assessment of different reperfusion strategies in ST-segment elevation acute myocardial infarction (STEMI) and it may be very helpful to test the potential efficacy of new approaches. Several trials showed the dramatic impact of the IS on LV functional recovery and long-term mortality. Peak CK, electrocardiography and the extent of wall motion abnormalities after reperfusion are routinely used to measure IS, however all of them provide indirect measurement of IS. We sought to evaluate the potential of microvascular perfusion defect as compared to these more established parameters to predict soon after reperfusion LV global and regional functional recovery at 3 months follow-up

Method: A total of 109 patients with first successfully reperfused STEMI were enrolled in the Acute Myocardial Infarction Contrast Imaging (A.M.I.C.I) multicenter study. After reperfusion, peak CK, ST-segment reduction and TIMI grade were calculated. Perfusion defect was evaluated by myocardial contrast echocardiography (MCE) using continuous infusion of Sonovue Bracco SpA) in real-time imaging. The endocardial length of contrast defect (CDL%) on day 1 after reperfusion was calculated. Regional wall motion scores (RWMSI), the extent of wall motion abnormalities (WMA%), LV end-diastolic volumes (EDV), and ejection fraction (EF%) after reperfusion and at follow-up were also calculated.

Results: Peak CK and RWMSI after reperfusion significantly correlated with WMA% (r= 0.51, p=.00001 and r= 0.42, p=.00003, respectively) and EF% at follow-up (r= -0.41, p=.0001 and r= -0.67, p=.00001, respectively). However, the parameter that correlates best with WMA% and EF% at follow-up was CDL% at day 1 (r= 0.76, p=.000001 and r= -0.64, p=.00001, respectively). By stepwise

multiple regression analysis WMA% and EF% at follow-up were also predicted by TIMI grade (p=.00001) WMA% (p=.000001), however the extent of perfusion defect after reperfusion independently predicted EF and WMA% at follow-up.
Conclusions: This study shows that in patients with reperfused STEMI larger extent of wall motion abnormalities and extensive microvascular damage after reperfusion are the main determinants of global and regional function at 3 months. However, the status of microvascular perfusion after reperfusion is the most powerful predictor of EF and definitive extent of wall motion abnormalities at follow-up. The MCE assessment of IS may have important implications in patient management.

P2869 Time from symptom onset to reperfusion and influence on infarct size in patients with STEMI reperfused by prehospital fibrinolysis or prehospital initiated facilitated PCI

H. Thiele[1], M. Kappl[2], J. Niebauer[2], E. Boudriot[2], G. Schuler[2].
[1]Leipzig, Germany; [2]University of Leipzig - Heart Center, Internal Medicine/Cardiology, Leipzig, Germany

The time from symptom onset to reperfusion has strong effects on the final infarct size (IS) and subsequently on mortality for STEMI patients treated by fibrinolysis. In patients reperfused by percutaneous coronary intervention (PCI) the IS has been shown to be independent from the time from symptom onset to reperfusion and the effects on mortality are attenuated. The time from symptom onset to reperfusion and the effects on IS have not been studied for patients treated very early by either prehospital fibrinolysis or prehospital initiated facilitated PCI.
In the Leipzig prehospital fibrinolysis study patients with a STEMI were randomized to either a prehospital fibrinolytic therapy (n=82) or a prehospital initiated facilitated PCI after prehospital fibrinolysis (n=82). The time from symptom onset to reperfusion was assessed for all patients. Patients were divided into the following 3 groups defined by tertiles of the time-to-treatment interval: lower tertile (<120 min), middle tertile (120-240 min), and upper tertile (>240–360 min).
At 6 months follow-up in 134 patients cine loops of the complete heart were acquired using a steady-state free precession technique. Additionally, delayed enhancement images covering the whole ventricle were acquired after injection of Gadolinium-BOPTA using a 3 D inversion recovery gradient echo sequence. IS was determined as the percentage of the left ventricular mass.
The time interval from symptom onset to reperfusion had a significant influence on final IS for the overall patient population. In the lower tertile IS was 7.7±8.1% versus 12.1±10.6% in the middle tertile (p=0.04 versus lower tertile) and 12.7±6.9% in the upper tertile (p=0.03 versus lower tertile). In the group of patients treated by prehospital fibrinolysis the IS was 10.2±9.8% in the lower, 15.6±12.6% in the middle, and 12.8±8.5% in the upper tertile (p=0.03). In patients treated by prehospital initiated PCI the IS was 5.2±4.9% in the lower, 9.1±6.0% in the middle and 13.3±7.0% in the upper tertile (p=0.01). In patients treated by prehospital fibrinolysis alone IS was greater in the lower (p=0.006) and middle tertile (p=0.03) in comparison to facilitated PCI.
The time from symptom onset to reperfusion influences the final IS for either prehospital fibrinolysis or facilitated PCI. A prehospital initiated facilitated PCI approach is superior to prehospital fibrinolysis alone. This underlines the assumed pathophysiological link between early restoration of the flow and perfusion in the infarct related artery, which is known as the “wavefront phenomenon”.

P2870 In-hospital mortality for AMI in Switzerland: is outcome related to admission during routine duty hours versus off-hours

J.C. Stauffer[1], D.R. Radovanovic[2], A.T. Taskin[3], P.U. Urban[4], M.M. Maggiorini[5], O.B. Bertel[6], P.E. Erne[7] on behalf of AMIS-Plus investigators. *[1]C.H.U.V., Division de Cardiologie du DMI, Lausanne, Switzerland; [2]Social and Preventive Medicine, University Zurich, Zurich, Switzerland; [3]AMIS Plus Data Center, Zurich, Switzerland; [4]Clinic Latour, Cardiology unit, Meyrin, Switzerland; [5]Intensive care, University hospital Zurich, Zurich, Switzerland; [6]Hospital Triemli, Cardiology, Zurich, Switzerland; [7]Kanton Hospital Lucerne, Cardiology, Lucerne, Switzerland*

Purpose: To investigate the impact of circadian patterns on the outcome of patients treated during routine duty hours versus off-hours.
Methods: From the AMIS-Plus database, 7,368 patients with ST-elevation MI in 62 hospitals (January 1997 to December 2003) throughout Switzerland were extracted.
Results: The characteristics of the population of patients admitted to hospital during routine duty hours (7am-7pm: Pop 1) and off-hours (7pm-7am + Weekends: Pop 2) are shown in the table below. Pop 2 (Off-Hours) differs, being composed of more young male, presenting earlier and treated more often with thrombolysis than primary PCI. Despite these differences, mortality was similar. Major cardiac adverse events (re-infarction, stroke and death) occurred in 7.0% of patients who had primary PCI (p=0.997) during routine duty hours and was the same for patients who had primary PCI during off-hours. In a multivariate logistic regression model the independent in-hospital mortality predictors were age >65 y (OR 4.23 [0.36-5.9] p<0.001) and Killip class (OR 1.82 -2.81 p<0.001). Thrombolysis (OR 0.49 [0.36-0.67] p<0.001) and PCI (OR 0.30 [0.19-0.46] p<0.001) were associated with decreased mortality. Working time (OR 0.89 [0.68-1.17] p=0.41 was not related to mortality.

Table 1

	Population 1	Population 2	p value
Number of cases	3806 (51.7%)	3562 (48.3%)	p=0.003
Gender male/female	71.2%/28.8%	74.9%/25.1%	p<0.0001
Killip Class I	74.2%	74.9%	p=0.03
Killip Class II	19.2%	17.2%	p=0.03
Killip Class III	3.9%	5.0%	p=0.03
Killip Class IV	2.6%	2.9%	p=0.03
Delay (median)	4:00h	3:10h	p<0.0001
Thrombolysis	36.7%	45.8%	p<0.0001
PCI primary	26.2%	22.5%	p<0.0001
Re-infarction	4.0%	3.8%	p=0.68
Stroke	1.5%	1.6%	p=0.64
In-hospital mortality	9.2%	9.4%	p=0.68

table

Conclusions: In Switzerland, population and reperfusion strategies are different during duty hours than off-hours, with no impact on survival.

P2871 Reduction of hospital mortality in the elderly by adherence to guidelines for treatment of STEMI in clinical practice – results of MITRAplus

A.K. Gitt[1], H. Wienbergen[1], R. Schiele[1], F. Towae[1], T. Heer[1], U. Zeymer[1], M.G. Gottwik[2], J. Senges[1] on behalf of MITRAplus.
[1]Herzzentrum Ludwigshafen, MI Research Institute, Cardiology, Ludwigshafen, Germany; [2]Klinikum Nuernberg Sued, Cardiology, Nuernberg, Germany

Background: In clinical practice, elderly patients (>75 years) less often receive acute reperfusion and adjunctive medical treatment for acute STEMI and have a significantly higher hospital mortality than younger patients.
Methods: Between 1994 and 2002 consecutive patients with STEMI were enrolled into the MITRAplus Registry. We analysed, if implementation of guidelines for the treatment of STEMI improved outcome in the elderly (>75 years of age).
Results: A total of 11091 patients (26%) with STEMI were > 75 years. Reperfusion rate increased from 41% to 49% favouring primary PCI. The use of acute adjunctive treatment with betablockers, ACE-Inhibitors and statins significantly increased over the years. Hospital mortality decreased from initially 28.6% in 1994/96 to 19.9% in 2001/02 (p<0.001 for trend).

STEMI in the elderly

	1994-1996 (n=1511)	1997-1998 (n=4881)	1999-2000 (n=1527)	2001-2002 (n=1642)
Age (years, median)	81	81	80	80
Female	59.2%	57.5%	54.2%	52.0%
Prior MI	19.5%	21.5%	23.2%	22.6%
Prior PCI/CABG	na	na	9.6%	8.7%
Prior Stroke	2.7%	2.3%	7.0%	11.4%
Prehospital delay (min)	260	270	241	241
Acute Reperfusion	41.3%	29.7%	47.9%	49.4%
Thrombolysis	34.8%	23.3%	15.9%	15.4%
Primary PCI	6.5%	6.4%	32.0%	34.0%
Beta-blocker	35.5%	41.0%	66.4%	70.5%
ACE-Inhibitor	48.4%	57.8%	66.8%	64.0%
Statins	na	36.8%	39.5%	51.6%
Hospital Mortality	28.6%	27.7%	24.0%	19.9%

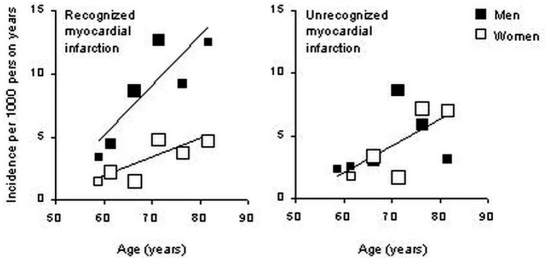
Conclusion: Between 1994 and 2002 the acute treatment of STEMI in patients > 75 years improved according to existing guidelines. This improvement in acute treatment was associated with a 30% relative reduction in hospital mortality in clinical practice.

P2872 Incidence of recognised and unrecognised myocardial infarction in elderly men and women: the Rotterdam Study

A. De Torbal[1], E. Boersma[1], J. Kors[2], G. Van Herpen[2], J. Deckers[1], B. Stricker[2], A. Hofman[2], J. Witteman[2]. *[1]Cardiology Erasmus MC, Rotterdam, Netherlands; [2]Epidemiology and Biostatistics, Erasmus MC, Rotterdam, Netherlands*

Background: Contemporary data on the incidence of unrecognised myocardial infarction among elderly subjects is limited.
Methods: We studied the incidence of recognised and unrecognised myocardial infarction in the Rotterdam Study, a population-based cohort of men and women aged 55 years and older. The baseline examination was performed during 1990-1993, with follow-up examinations during 1994-1995, and 1997-2000. Baseline 12-lead ECGs were analyzed by the Modular ECG Analysis System, and the 5,148 participants who had no evidence of prevalent infarction were subject for analysis. Incident recognised infarction was defined as the occurrence of a fatal or non-fatal event coded as I21 according to the International Classification of Diseases, 10th edition. A repeat ECG was available in 4,187 subjects. An unrecognised infarction was considered to have occurred if there was electrocardiographic evidence in the absence of a clinically recognized event.
Results: During a median follow up of 6.4 years 141 incident recognised infarc-

tions occurred, and the incidence rate of this event was 5.0 per 1,000 person years. The incidence was higher in men (8.4) than in women (3.1), and increased with age. The incidence rate of unrecognised infarction was 3.8 per 1,000 person years. Men and women had approximately similar incidence. Hence, the proportion of unrecognized infarction was lower in men (33%) than in women (54%).



Incidence of myocardial infarction

Conclusion: A high proportion of incident myocardial infarctions in elderly people remain clinically unrecognised. Since myocardial infarction is a disabling and not seldom deadly condition, our data suggest a need for periodical screening to monitor risk factors of coronary disease, and to install effective preventive treatment in the elderly.

P2873 Beneficial effect of early reperfusion therapy beyond the preservation of left ventricular function in patients with ST elevation myocardial infarction. Support for the open artery hypothesis

U. Zeymer[1], A. Gitt[2], R. Zahn[2], R. Schiele[2], R. Winkler[2], M. Gottwik[3], J. Senges[2] on behalf of MITRA-Plus investigators.. *[1]Klinikum Ludwigshafen, Medizinische Klinik B, Ludwigshafen, Germany; [2]Klinikum Ludwigshafen, Medizinische Klinik B, Ludwigshafen, Germany; [3]Klinikum Nürnberg, Medizinische Klinik 8, Nürnberg, Germany*

Background: Left ventricular ejection fraction (LVEF) is one of the most important predictors of mortality during follow-up in patients with acute ST elevation myocardial infarction (STEMI). While randomized clinical trials have shown a reduction in mortality by early reperfusion therapy, the effect of fibrinolysis and primary PCI on the preservation of left ventricular function was only modest. Therfore we sought to determine the impact of early reperfusion therapy on 1-year mortality in patients with STEMI and comparable LVEF before discharge.
Methods: We used the data from the prospective MITRA-Plus registry containing nealy 10,000 patients with STEMI and 1-year follow-up.
Results: From a total of 9934 patients 3103 were treated with primary PCI, 3856 with fibrinolysis and 2975 without early reperfusion therapy. The 1-year mortality related to LVEF and reperfusion therapy is given in the table and revealed significant differences between patients with and without reperfusion therapy in the groups with the same LVEF. Both, fibrinolysis and primary PCI remained independent predictors of mortality even after adjusting for confounding parameters such as age, gender, prior MI, Killip class and diabetes.

	No reperfusion therapy	Fibrinolysis	Primary PCI	p-value
LVEF > 55%	8.4%	2.8%	2.2%	< 0.0001
LVEF 41-55%	14.1%	.6%	4.4%	< 0.0001
LVEF < 40%	28.1%	5.2%	11.5%	< 0.0001

Conclusions: Patients treated with early reperfusion therapy have an improved midterm survival compared to patients without early reperfusion therapy despite similar LVEF before discharge. These results support the open-artery hypothesis which suggests a clinical benefit of reperfusion therapy for STEMI beyond the preservation of left ventricular function.

P2874 Transfer for primary PCI with GP IIb/IIIa inhibitor versus on-site thrombolysis in patients with acute myocardial infarction. One year follow-up of randomised open-label study

S. Dobrzycki[1], P. Kralisz[1], K. Nowak[1], H. Bachorzewska-Gajewska[1], E. Sitniewska[1], W. Kochman[1], B. Poniatowski[2], W.J. Musial[3]. *[1]Medical University, Department of Invasive Cardiology, Bialystok, Poland; [2]University Hospital, Bialystok, Poland; [3]Medical University, Dept of Cardiology, Bialystok, Poland*

Background: The best reperfusion therapy in STEMI in patient presenting to hospital without catheterization facilities has been under investigation in several trials. The delay of onset of primary PCI caused by transportation may question the benefits of this strategy over thrombolysis. Treatment with GP IIb/IIIa inhibitors for transportation for primary PCI may be the option to hold this advantage in AMI treatment.
Methods: Patients (pts) with STEMI were randomized in 13 community hospitals (20-150 km from the cath lab)to on-site thrombolysis (streptokinase) or to transportation for primary PCI with adjunctive therapy with tirofiban (10 μg/kg bolus i.v. + i.v. infusion 0.1 μg/kg/min started in the ER of hospital of admittance). All pts with cardiogenic shock were obligatory treated with primary PCI but were excluded from analysis.
Results: 401 pts were randomized into the study (200 to thrombolysis and 201 to transfer for PCI). Groups were well balanced according to basic characteristics. Results are shown in table.

Clinical outcome at 30 days and one year

		Transfer for PCI (n=201)	Thrombolysis (n=200)	p
30 day	death	12 (5,97%)	18 (9,0%)	0,23
	re-AMI	4 (1,99%)	11 (5,5%)	0,06
	stroke	1 (0,5%)	3 (1,5%)	0,3
	death/re-AMI	16 (7,96%)	29 (14,5%)	0,038
	death/re-AMI/stroke	17 (8,46%)	32 (16%)	0,021
1 year	death	16 (7,96%)	25 (12,5%)	0,12
	re-AMI	6 (2,98%)	15 (7,5%)	0,04
	stroke	2 (1%)	5 (2,5%)	0,21
	death/re-AMI	22 (10,94%)	40 (20%)	0,012
	eath/re-AMI/stroke	24 (11,94%)	45 (22,5%)	0,005

Conclusions: Outcomes at one year follow-up of two treatment strategies showed that transportation for primary PCI with adjunctive therapy with GP IIb/IIIa inhibitor- tirofiban is superior to on-site thrombolysis for patient with STEMI presenting to hospital without catheterization facilities.

RENAL PROTECTION DURING ANGIOGRAPHY

P2875 The modulation of ionic high osmolar contrast medium on renal glutathione peroxidase activity derepressed by acetylcysteine and probucol in streptozotocin- induced diabetic rats

H.W. Yen[1], H.C. Lee[1], H.Y. Chuang[2], S.H. Sheu[1]. *[1]Kaohsiung Medical University, Cardiology division/Internal Medicine Dep, Kaohsiung, Taiwan; [2]Kaohsiung Medical University, Department of Clinical Research, Kaohsiung, Taiwan*

Background: Acute renal injury is frequently identified after patients receiving coronary angiography, especially in those with diabetes. Since exogenous antioxidants such as acetylcysteine and probucol are used effectively to prevent from contrast-media-induced nephrotoxicity, we hypothesized that exogenous antioxidants would alter the renal antioxidant enzyme activities modified by ionic high osmolar diatrizoate(DTZ)in diabetes.
Methods: Four weeks after diabetes induction, these rats were divided into 3 groups. Normal rats with same age were used as control. Group 1 rats were not fed any antioxidant agent. Group 2 were pretreated with acetylcysteine (500mg/kg, bid) and Group 3 probucol (60 mg/kg, qd) orally for one week before DTZ(10ml/kg)injection. 0.9% NaCl was used as a control. Activities of glutathione peroxidase (GPx) and superoxide dismutase (SOD) were detected by spectrophotometric method at one hour after DTZ injection.
Results: Diabetic rats had higher renal GPx activity than normal rats in baseline (table). DTZ suppressed renal GPx activity significantly in both Group 1 diabetic and normal rats. This suppression disappeared in diabetic group if they were pretreated with antioxidants (table). In contrast to renal GPx, renal SOD increased insignificantly after DTZ injection in diabetics (582.4±95.3 to 602.5±69.9 U/mg, P=0.171), but significantly increased in normals (547.8±61.1 to 686.8±123.1 U/mg, p=0.011). Acetylcysteine or probucol didn't modify renal SOD remarkably(data not shown).

Renal GPx Activity after antioxidants

Antioxidants Reagents	No treatment Normal Saline (n=10)	No treatment DTZ (Group 1, n=10)	Acetylcysteine DTZ (Group 2, n=6)	Probucol DTZ DTZ (Group 3, n=6)
Normal Rats	426.3±13.9	382.0±43.7**	407.0±28.7	418.3±47.8
Diabetic Rats	647.4±80.9	497.4±115.4*	604.2±99.6***	617.3±79.1***

Renal Gpx activity (microU/mg). DTZ vs. Normal Saline: *p=0.001, **p=0.035. Group 2 or 3 vs. Group 1: ***p<0.05.

Conclusion: Acetylcysteine and probucol could derepress renal GPx activity which was suppressed by diatrizoate in diabetic rats and take renal protective effect.

P2876 Role of endothelium activation on contractility of rat tail artery after exposure to ionic and non-ionic contrast medium

G. Grzesk[1], M. Radomski[2], R. Szadujkis-Szadurski[1], L. Szadujkis-Szadurski[1], J. Kubica[2]. *[1]Collegium Medicum UMK, Dept. of Pharmacology and Therapeutics, Bydgoszcz, Poland; [2]Collegium Medicum UMK, Dept. of Cardiology, Bydgoszcz, Poland*

Background: The most important physicochemical features of water-soluble, iodinated contrast medium (CM) are their solubility, the viscosity and osmolality

of their solutions, the lipophilic or hydrophilic qualities, their electrical charge but little is known about their interactions with cellular receptor systems. We investigate the role of vascular endothelium on vascular contractility after exposure to CM: ionic (iCM) and non-ionic CM (niCM)

Materials and methods: We performed experiments on isolated and perfused rat tail artery. We investigated the contractility after stimulation of A1-adrenoceptor with phenylephrine (PHE) and vasopressin receptor with arg-vasopressin (AVP) after short exposure to CM in comparison to controls.

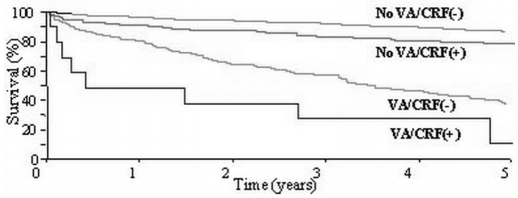
Results: Significant decrease in reactivity of smooth muscle in iCM and niCM group vs. control was observed in arteries with vascular endothelium. This effect may by significantly reduced by NO synthase inhibitors (N-nitro-L-arginine-methyl ester). In experiments performed on arteries without vascular endothelium there were no significant differences between groups. The calculated KA values for PHE (1.88 ($\pm$0.6) x10^{-7}) and for AVP (1.32 ($\pm$0.4) x10^{-7}) in groups did not differ significantly, but KA/ED50 significantly decreased. The calcium influx was inhibited from both intracellular and extracellular calcium stores.

Conclusion: Our results suggest that the both iCM and niCM stimulate the NO production by vascular endothelium. Changes in contractility are result of decrease in signal transduction between receptor and calcium channel because of increase in NO production.

P2877 Chronic kidney disease is associated with an increased risk of sustained ventricular arrhythmia during percutaneous coronary intervention and poor survival

S. Sengupta, C.S. Rihal, M. Singh, R.J. Lennon, W.K. Shen, A. Jahangir. *Mayo Clinic, Cardiology Dpt., Rochester, United States of America*

While it is known that renal dysfunction is a powerful independent predictor of cardiac arrhythmias after acute myocardial infarction, the significance of chronic kidney disease (CKD) on the occurrence of ventricular arrhythmia (VA) during transient ischemia with percutaneous coronary intervention (PCI) is not clear. Furthermore, the impact of CKD on mortality in those that did or did not have VA is not known. We therefore, sought to determine the incidence and prognosis of VA in patients (pts)undergoing PCI with or without CKD and the predictors of in-hospital and long-term mortality. Logistic regression and Cox proportional hazards models were used.



Figure

Of the 15,374 consecutive procedures performed in unselected pts (mean age 66.1$\pm$11.9 years, 71% male) at the Mayo Clinic between 1994-2003, 547 (3.6%) were performed in those who had serum creatinine level >3mg/dl at the time of PCI. Of these, 30 (5.5%) had sustained VA during PCI. Overall in hospital mortality was worse in those with VA than without VA (23% vs 1%). Independent predictors of in-hospital mortality were VA during PCI, CKD, Pre-PCI shock, history of myocardial infarction (MI), heart failure (HF), advanced age or emergency PCI. In pts who had successful PCI, presence of CKD and VA during PCI identified a group at a very high risk of death within 6 months after PCI (VA/CRF+ in Fig). The long-term mortality was higher in those who had VA during PCI (Fig). CKD, VA during PCI, history of MI, CHF, EF<40%, diabetes, lack of beta-blocker, multivessel disease, or advanced age were independent predictors of mortality at follow up. Thus, in unselected consecutive pts with CKD the incidence of VA during PCI is low, but when present identifies a group at a very high risk for death within 6 months after PCI.

P2878 Comparison of low osmolar and isosmolar contrast media utilisation in coronary angioplasty

C. Le Feuvre, G. Drobinski, A. Batisse, J.P. Collet, R. Choussat, G. Helft, G. Montalescot, J.P. Metzger. *Institut de Cardiologie Pitie-Salpêtriere, Groupe Hospitalier, Paris Cedex 13, France*

Previous studies have suggested an association between thrombus-related events and type of contrast media. In the COURT trial, a 45% reduction in in-hospital clinical events after coronary angioplasty (PCI) with unfractionated heparin has been reported with isosmolar non-ionic dimer iodixanol compared with low osmolar ionic agent ioxaglate. Our prospective single-center study aimed to compare the incidence of thrombotic cardiac events in 507 consecutive patients aleatory assigned to receive iodixanol (n=236, group 1) or ioxaglate (n=271, group 2) during PCI with enoxaparine. Patients with primary cardiogenic shock related to acute MI were excluded. PCI was performed for acute coronary syndrome in 43% and 45% out of patients in groups 1 and 2 (NS). A peak anti-Xa >0.5IU/ml was obtained in 97% in both groups, after enoxaparine 0.5 mg/kg IV or 1mg/kg BID SC. Glycoprotein IIb/IIIa inhibitors were used in 43% and 41%. Baseline clinical and angiographic characteristics were similar in the 2 groups, with 20% of diabetics. The mean volume of contrast media was 270 ml in group 1 and 277 ml in group 2 (NS). Coronary stenting was performed in 90% of patients in both groups, with direct stenting in 69% and 70%, and drug-eluting stent in 30% and 27% of groups 1 and 2 respectively. Development of large thrombi with filling defect during PCI occurred in 13 patients in group 1 and 1 patient in group 2 ($p<0.002$). Thrombotic abrupt closure of the target vessel during PCI occurred in 12 patients in group 1 and 1 patient in group 2 ($p < 0.003$). In-hospital MACE related to thrombotic event occurred in 8 patients in group 1 (cardiac death, n=2, periprocedural MI, n=6, repeat PCI, n=3) and in 1 patient (periprocedural MI) in group 2 ($p<0.03$).

In conclusion, our study does not confirm the results of the COURT trial obtained with unfractionated heparin. When using enoxaparin, thrombus-related events during PCI are more frequent with the isosmolar non-ionic dimer iodixanol than with the low osmolar ionic agent ioxaglate.

P2879 No evidence for a protective effect of acetylcysteine on contrast-induced nephropathy

E. Piccaluga[1], F.F. Ferrario[2], D. Scorza[2], A. Belloni[1], E. Cappiello[1], G. Frigeni[1], F. Benevento[1], M. Viecca[1]. [1]*Ospedale "L.Sacco", Cardiology Department, Milano, Italy;* [2]*Ospedale "L.Sacco", Nephrology and Dialysis Departement, Milano, Italy*

Background: Contrast-induced nephropathy (CIN) is one of the commonest causes of acute renal failure. Intravenous (iv) administration of saline or non ionic iso-osmolar contrast medium significantly reduce the incidence of CIN, while results on oral N-acetylcysteine (NAC) are conflicting. We compared the protective role of NAC plus saline versus saline alone in patients (pts) with moderate to severe renal insufficiency undergoing coronary and/or peripheral angiography and/or angioplasty.

Methods: We prospectively studied 200 elective, consecutive, pts (mean age 74.9 $\pm$7.3 years; 65% male, NYHA class=2) with stable chronic renal failure [baseline creatinine clearance = 55 ml/min according to the Cockroft Gault formula]. Pts were randomized to receive either oral NAC 600mg bid the day before and the day of the procedure plus saline iv 0.9% 1ml/kg/h 12-24 h before and 24 h after the procedure (group A, n = 99) or saline alone at the same time intervals (group B, n = 101). The contrast medium was non ionic iso-osmolar (iodixanol, Visipaque Amersham Health). CIN was defined as an increase in serum creatinine > 0.5 mg/dl or > 25% within 3 days after the procedure. Serum creatinine was measured at baseline, 24, 48 and 72 h after the procedure.

Results: Baseline serum creatinine (mean value$\pm$ standard deviation) was 1.44 $\pm$ 0.42 in group A and 1.75 $\pm$ 0.86 in group B; baseline creatinine clearance was 40.8 $\pm$ 9.3ml/min in group A and 37.2 $\pm$ 11.5ml/min in group B. Diabetics were 25% in both groups. The amount of contrast medium in both groups was similar (174 $\pm$ 103 ml). Overall CIN risk was 14/200 (7%). No significant difference in CIN risk was detected in group A and in group B [8/99 (8%) vs 6/101 (6%), respectively]. No statistical significant difference was detected even considering 3 subgroups of pts with higher CIN risk profile such as diabetics (4/25 vs 2/25; OR= 2.2, p=0.40), pts with a baseline creatinine clearance <42.3 ml/min, (5/54 vs 4/48; OR=1.1, p=0.87) and pts who received a contrast medium volume > 140 ml (6/59 vs 4/48; OR=1.2, p=0.46).

Conclusion: Our results show that use of an iso-osmolar contrast medium associated with an adequate iv hydration is very effective in reducing the risk of CIN in pts with moderate to severe renal impairment. In contrast, oral NAC did not produce an adjunctive effect on the prevention of CIN.

P2880 The protective effect of N-acetylcysteine in contrast-induced nephropathy is mediated by the modulation of renal endothelin-1 production

M. Boddi[1], A. Berni[2], L. Poggesi[2], M. Coppo[2], F. Fiorentino[2], S. Berardino[2], M. Bandinelli[2], G.F. Gensini[2]. [1]*Università di Firenze, Clinica Medica Generale e Cardiologia, Firenze, Italy;* [2]*Clinica Medica Generale e Cardiologia, Area Critica Medico Chirurgica, Florence, Italy*

Background: Experimental studies in contrast-induced nephropathy (CIN) reported an excessive local production of endothelin-1(ET-1), but the role of ET-1 in human CIN is still under debate. This study was aimed to investigate whether the protective effect of N-acetylcysteine (NAC) for CIN, shown in previous studies, is modulated by a reduction in local renal ET-1 formation possibly resulting in a decrease in renal vascular resistance.

Methods: We prospectively studied 21 patients (74 $\pm$ 7 yrs; 15 M, 6 F) with mild chronic renal insufficiency (serum creatinine (sCr) 1.2-2.0 mg/dL), referred to Clinica Medica for elective coronary angiography. Patients were randomly assigned to receive (1) NAC (1200 mg iv) and 0.45% iv saline infusion(1 mL/kg/h) in the 12 hrs before and after contrast dye administration (group A, n = 12; 74 $\pm$ 8 years; M/F = 7/5), or (2) iv saline infusion alone (1 mL/kg/h) (group B, n = 9; 74 $\pm$ 5 years; M/F = 8/1). In all SCr and creatinine clearance (CCr) (Cockcroft-Gault formula) were measured 24 hrs before and 24, 48, 72 hrs, 7 and 21 days after the procedure. Renal resistance index (RRI) was measured by Doppler ultrasound (Toshiba SSA 270A) under baseline and 48 hrs, 7 and 21 days after the procedure. Plasma and

urinary 24 hrs-excrection of ET-1 were evaluated by radioimmunoassay in the day before and 2 days after contrast-media administration. A rise in SCr by 0.5 mg/dL and/or 25% above baseline or a >5 mL/min increase in CCr at 48-72 hrs after contrast exposure were used as the primary and secondary outcomes.
Results: The baseline SCr was higher in group A vs group B (1.6 ± 0.2 vs 1.4 ± 0.2 mg/dL,ns). A pathological increase in SCr occurred in 2(22%) group B patients and in none of group A patients. A >5 mL/min CCr reduction occurred in 5(56%) group B patients and in 2(17%) group A patients ($p<0.05$). RRI and plasma ET-1 did not change in each group throughout the study. The baseline urinary ET-1 was higher in group A than in group B. In group A contrast administration caused a reduction in uET-1 excretion (from 6.7 to 3.7 ng/24h,ns), while in group B an increase in uET-I from 3.9 to 6.9 ng/24h (ns vs baseline).
Conclusions: In our patients with moderate chronic renal failure the occurrence of CIN seems to be facilitated by an increased local renal ET-1 production, but not by an augmentation in renal vascular resistance. NAC plays its protective role through a negative modulation of ET-1 renal production with no documentable vasodilatatory effect.

P2881 Twofold higher incidence of renal failure in 52,526 patients undergoing coronary interventions at Swedish hospitals using iso-osmolar compared to low-osmolar contrast media

B. Lagerqvist[1], P. Liss[2], P. Persson[3], P. Hansell[4], T. Nilsson[5].
[1]Akademiska University Hospital, Department of Cardiology, Uppsala, Sweden; [2]Akademiska university hospital, Department of Radiology, Uppsala, Sweden; [3]Humboldt University, Institute of Physiology, Berlin, Germany; [4]University of Uppsala, Institute of Integrative Physiology, Uppsala, Sweden; [5]Sahlgrenska university hospital, Department of Cardiology, Gothenburg, Sweden

Background: Reducing contrast media (CM) osmolality is a current strategy to minimize risk of contrast induced nephropathy (CIN). This study tests in clinical practice a previous prospective study showing reduced incidence of CIN after iso-osmolar CM (290 mOsm/kg H2O) as opposed to a low-osmolar CM (740 mOsm/kg H2O).
Methods: Hospitals were examined that principally use a single CM for Percutaneous Coronary Interventions (PCI) and coronary angiography. Iodixanol (iso-osmolar) was used in 24,085 patients, ioxaglate (low-osmolar) in 22,294 and iohexol (low-osmolar) in 6,147 subjects. Patients were evaluated from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) and rehospitalizations with a diagnosis of renal failure in the Swedish all-national "Hospital Discharge Register".
Results: Incidence of renal failure within 12 months was greatest for patients receiving the iso-osmolar CM iodixanol (1.8%). Ioxaglate or iohexol treated patients had a significantly lower renal failure incidence (0.9% and 1% respectively, $p<0.001$ vs. iodixanol). When adjusted for gender, age, diabetes, previous PCI and previous renal insufficiency the hazard ratio for iodixanol treated patients remained significantly higher than for the other two CM. Hospitals switching CM to iodixanol experienced a doubling in renal failure after cardiac interventions.
Conclusions: The occurrence of renal failure appears to be significantly greater for patients receiving the iso-osmolar CM iodixanol, than for those given ioxaglate or iohexol. The latter two CM are considerably less viscous in vitro and in vivo than iodixanol, which may be of importance for the prevention of CIN.

COMPARATIVE TRIALS USING DIFFERENT DES

P2882 Outcomes of sirolimus-eluting stents versus paclitaxel-eluting stents in patients undergoing contemporary percutaneous coronary intervention

S. Mishra[1], A. Pichard[1], L. Satler[1], R. Torguson[1], W. Suddath[1], K. Kent[1], R. Waksman[2]. *[1]Washington Hospital Center, Cardiology, Washington, United States of America; [2]Washington Hospital Center, Cardiology Research Foundation, Washington, United States of America*

Background: Sirolimus- (SES) and Paclitaxel- (PES) eluting stents have been shown to reduce restenosis compared with bare metal stents. We aimed to compare the safety and efficacy of SES to PES for patients undergoing contemporary percutaneous coronary intervention (PCI.)
Methods: The outcome of 355 consecutive patients (pts) receiving PES from the Taxus-Registry Experience at the WAshington hospital centeR with Drug-eluting Stents (T-REWARDS)registry were compared to 351 pts receiving SES from the Cypher-REWARDS registry. Clinical follow-up was carried out 30 days and 6 months from the date of implantation by telephone contact or official visit.
Results: The baseline demographics, angiographic, and procedural characteristics were similar between both groups, except pts were older in the PES group (65.6 yrs vs. 62.4 yrs, $p<0.01$), males (70.3% vs 62.2%, p=0.02) and a higher incidence of renal failure (16% vs 9.4%, $p<0.01$). Clinical outcomes at 30 days and 6 months are summarized in the table.
Conclusions: Clinical outcomes following coronary revascularization with SES or PES are safe and associated with low revascularization rates. There are no differences between SES and PES with respect to clinical events up to 6 months to support the selection of one stent over the other for contemporary PCI.

Abstract P2882 – Table 1. Event Rate SES versus PES

	Total n=706	SES n =351	PES n =355	p-value
30 day event rate				
Death (%)	0.3	0.5	0.0	0.25
Q-myocardial infarction (%)	0.4	0.5	0.3	0.50
Sub-acute thrombosis (%)	0.7	0.3	1.1	0.18
Target vessel revascularization	0.8	0.3	1.4	0.11
MACE (%)	1.3	1.1	1.4	0.50
6 month event rate				
Death (%)	1.4	1.7	1.1	0.52
Q-myocardial infarction	1.3	1.1	1.4	0.74
Late thrombosis	0.6	0.9	0.3	0.31
Target lesion revascularization	3.1	2.3	3.9	0.20
Target vessel revascularization	4.8	4.5	5.1	0.74
MACE (%)	6.6	6.5	6.8	0.90

P2883 Outcome in the real-world of coronary high-risk intervention with drug-eluting stents (ORCHID). A comparison of cypher sirolimus-eluting and taxus paclitaxel-eluting stents

S. Kumar[1], V. Suresh[2], B.D. Prendergast[2], N.H. Brooks[2], R.D. Levy[2], D.H. Bennett[2], S.G. Ray[2], H.S. Lee[2]. *[1]Wythenshawe Hospital, Cardiology Department, manchester, United Kingdom; [2]Wythenshawe Hospital, Cardiology, Manchester, United Kingdom*

Aims: The Paclitaxel (PES) and Sirolimus eluting stents (SES) differ in the drug, delivery, vehicle platform and mechanism of action.It is not known if this would be reflected in their efficacy. We present 6 month follow up data on the comparative outcome of PES and SES stents in unselected high-risk individuals from our single centre registry.
Methods: Data were collected on 439 stent implantations in 312 consecutive patients. The clinical outcome at 6 months of SES stent implantation in a consecutive cohort of 156 patients was compared to a subsequent 156 consecutive cohort who underwent PES stent implantation. Patients were clinically followed up at six months. The primary endpoint was defined as a composite of major adverse cardiac events (MACE) which was cardiac death, myocardial infarction, Coronary artery Bypass Grafting or target vessel revascularization (TVR) at 6 months. Multivariate analysis was used to predict the Odds Ratio (OR) and confidence intervals for TVR.
Results: The two groups had no significant difference in baseline demographic and clinical characteristics. A third of the patients in each group were treated for stable angina & Glycoprotein IIBIIIA inhibitors were used in three quarters in both groups.There was a high incidence of Chronic Total Occlusions in both groups(PES 17.3%,SES 20%,p NS).Multivessel intervention(PES 29%,SES 10%,$p<0.001$), bifurcation(PES 22%,SES 16%,p=NS)and small vessel stenting were commoner in the PES group. The mean stent length per lesion was 19.4±7.1mm in PES & 22.3±7.6mm in SES group.More complex lesions were treated in the PES group(B2 lesions 49% vs 46.3%;$p<0.01$). The 6 month outcome was similar in both groups with a TVR of 1.9% (SES) and 2.6% (PES, p= NS), MACE (PES 3.2%, SES 4.5%, p= NS). The incidence of sub acute stent thrombosis (SAT), causally related to premature stoppage of dual antiplatelet therapy was similar in the 2 groups (1.9%). TVR was commoner in diabetics, bifurcation stenting and vein graft intervention (OR 3.7, 4.2 and 6.9 respectively). TVR was less common in patients with longer stent length (OR 0.4) or small vessels (OR 0.6). Osteal location, Chronic Total Occlusion or previous ISR did not predict future TVR.
Conclusion: The ORCHID study shows similar efficacy and safety of PES and SES (in a similar cohort of patients)with a low intervention & MACE rate in a complex coronary intervention. It demonstrates a low incidence of SAT and underscores the importance of dual antiplatelet therapy. By including more complex patients it provides complementary information to the forthcoming REALITY study.

P2884 Clinical and angiographic predictors of major adverse cardiac events after drug-eluting stent implantation

G. Melzi[1], A. Chieffo[1], I. Iakovou[2], J. Cosgrave[2], G. Biondi Zoccai[1], M.G. Sangiorgi[2], M. Montorfano[1], A. Colombo[1]. *[1]San Raffaele Hospital, Milano, Italy; [2]Centro Cuore Columbus, Milano, Italy*

The clinical and angiographic characteristics associated with the occurrence of events following drug-eluting stent (DES) implantation, either sirolimus (SES) or paclitaxel-eluting stent (PES), remain to be fully elucidated.
Aim of the Study: To assess the predictive factors of myocardial infarction (MI), cardiac death, target lesion revascularization (TLR) and the composite endpoint of major adverse cardiac events (MACE) at one year.
Methods: The study population included all consecutive patients (pts) who underwent elective SES or PES implantation and were eligible for one year clinical follow-up.
Results: One thousand pts with 2040 lesions were analysed. Diabetes was present in 234 (23.4%) and 773 (77.3%) underwent multivessel stenting. The mean age was 62.2±10.6 years and LVEF 52.8±9.5%. In-stent restenosis was present in 273 (13.3%) lesions. The mean length of the lesion was 24.02±8.9 mm and of the stent was 27.9±13.4 mm. MACE occurred in 172 (17.2%) pts.

Multivariate analysis showed that the predictors of both MI and cardiac death were LVEF (OR 0.96; 95% CI 0.92-0.99; p=0.03) and diabetes (OR 2.88; 95% CI 1.32-6.30; p=0.008). The only predictor of TLR was diabetes (OR 1.74; 95% CI 1.06-2.85; p=0.02). Predictors of MACE were: stent length (OR 1.03; 95% CI 1.01-1.05; p=0.05), multivessel treatment (OR 1.76; 95% CI 1.09-2.84; p=0.02) and diabetes (OR 1.84; 95% CI 1.27-2.67; p=0.001).
Conclusions: In the DES era diabetes remains an important predictor of events. Interestingly in contrast to bare metal stent implantation, reference vessel diameter was not associated with repeat intervention in our cohort. Among procedural characteristics the predictors of MACE were multivessel stenting and stent length.

P2885 A prospective multicenter randomised comparison of paclitaxel versus sirolimus-eluting stents for long coronary lesion: 6-month angiographic follow-up study

S.W. Lee[1], H.S. Kim[2], J.H. Lee[3], J.H. Park[2], N.H. Lee[4], Y.H. Jo[4], I.W. Seong[3], S.W. Park[1]. *[1]Asan Medical Center, Cardiology, Seoul, Korea, Republic of; [2]Chonbuk National University Hospital, internal medicine, Jun-ju, Korea, Republic of; [3]Chungnam National University Hospital, Internal Medicine, Dae-jun, Korea, Republic of; [4]Soonchunhyang University Bucheon Hospi, Internal Medicine, Bucheon, Korea, Republic of*

Background: several drug-eluting stents (DES) have been demonstrated to significantly reduce the restensosis. It is not known, however, which of these DES, is more effective for long coronary lesion. Therefore, we performed a prospective randomized study comparing paclitaxel-(PES) and sirolimus-eluting stents (SES) for long coronary lesion (vessel size > 2.75mm. requiring long DES > 30 mm).
Methods: patients requiring long DES were randomly assigned to receive PES (Group I, n=100) or SES (Group II, n=101). The primary end point was in-segment late loss and the secondary end point was angiographic restenosis at 6 months and major adverse cardiac events (nonfatal myocardial infarction, death, target lesion revascularization) at 9 months.
Results: the baseline clinical and angiographic characteristics were similar between the 2 groups. The lesion length and mean stent length were also similar between the 2 groups (Table 1). Procedural success was 99% in group I and 100% in group II. One in-hospital death occurred in group I. In-hospital events including myocardial infarction, target lesion revascularization, or stent thrombosis did not occurred. Six-month angiographic and nine-month clinical outcomes will be obtained until meeting.

Table 1. Procedural characteristics

	Group I	Group II	P
Reference vessel size, mm	2.97±0.40	2.88±0.36	0.19
Lesion length, mm	35.3±11.7	35.4±11.3	0.98
Stent length, mm	39.3±12.7	42.6±14.3	0.15
Pre-intervention MLD, mm	0.57±0.36	0.62±0.40	0.47
Post-intervention MLD, mm	2.85±0.38	2.69±0.53	0.69
Acute gain, mm	2.28±0.50	2.25±0.48	0.74

Conclusions: treatment with PES or SES was safe and had a similarly short-term clinical outcome. The six-month angiographic and nine-month clinical outcomes will be presented at the meeting.

P2886 Comparing Cypher vs Taxus in over 2400 consecutive unselected patients: six-month results of the RECIPE Study

M. Margheri[1], C. Tamburino[2], G.M. Sangiorgi[3], G.G.L. Biondi-Zoccai[4], E. Falchetti[1], G. Vittori[1], R. Barbagallo[2], A. Colombo[3] on behalf of the RECIPE Investigators. *[1]Careggi University Hospital, Interventional Cardiology, Firenze, Italy; [2]Ferrarotto University Hospital, Interventional Cardiology, Catania, Italy; [3]EMO Centro Cuore Columbus, Milan, Italy; [4]St. Raffaele Hospital, Interventional Cardiology Unit, Milan, Italy*

Purpose: Sirolimus-eluting stents (Cypher™) and paclitaxel-eluting stents (Taxus™) effectively reduce the risk of restenosis after percutaneous coronary intervention (PCI). However, there is uncertainty on the direct head-to-head comparison of Cypher vs Taxus in unselected patients. We thus evaluated the acute and mid-term results ofa large cohort of patients undergoing Cypher and Taxus implantation.
Methods: Consecutive patients undergoing intracoronary Cypher or Taxus stent implantation from April 2002 to May 2004 were enrolled. One- and 6-month clinical follow-up was performe d(with 4 to 9-month angiographic follow-up as clinically indicated). Outcomes were adjudicated by an independent event committee, and included all-cause death, Q-wave myocardial infarction (MI), target vessel revascularization (TVR), target lesion revascularization (TLR), and stent thrombosis (ST).
Results: 2286 patients were included (1227 undergoing Cypher stenting vs 1059 undergoing Taxus stenting) with 3945 treated lesions (2265 vs 1680) for a total of 4503 implanted drug-eluting stents (2606 vs 1897). Of those, 26.8% (614) were diabetics, 9.4% (214) acute myocardial infarctions, and in 4.2% (98) patients the target vessel was an unprotected left main. Final angiographic success was respectively 99.6% and 99.5%. Overall 1-month major adverse cardiovascular events (MACE) occurred in 1.1% (25) of patients, with death in 0.7% (15), MI in 0.3% (7) and TVR in 0.4% (9), without significant difference between Cypher vs Taxus at unadjusted analysis (P>0.05). Similar event rates for the 2 stent types were also present at unadjusted 6-month analysis, with overall MACE at 5.9% (127), death at 1.4% (30), MI at 0.7% (16), TVR at 4.3% (91) and target lesion revascularization (TLR) at 3.1% (67) (P>0.05). ST rates were 0.9% for intraprocedural ST, 0.7% for subacute ST, and 0.3% for late ST (0.1% for Cypher vs 0.5% for Taxus, p=0.07). Propensity adjusted analysis balancing for differences in baseline, clinical and procedural characteristics, showed that both Cypher and Taxus provided a similarly low risk of TLR at 6-months follow-up (odds ratio 0.78, 95% confidence interval 0.46-1.32).
Conclusions: Results from this large multicenter study comparing Cypher vs Taxus shows that both Cypher and Taxus stents are safe and effective in patients undergoing PCI, including unselected as well as high-risk subjects. Propensity analysis, applied to reduce imbalances between the 2 patient populations, suggests that Cypher and Taxus were associated with similar rates of mid-term adverse events.

P2887 A randomised comparison of a sirolimus with a paclitaxel eluting stent for coronary revascularisation: twelve months results of the SIRTAX trial

S. Windecker[1], A. Remondino[2], F. Eberli[3], P. Juni[2], C. Schonenberger[2], P. Wenaweser[2], T. Luscher[3], B. Meier[2] on behalf of SIRTAX Investigators. *[1]Inselspital (Hospital), Dept. of Cardiology, Bern, Switzerland; [2]University Hospital Bern, Dept. of Cardiology, Bern, Switzerland; [3]University of Zurich, Cardiology Dept., Zurich, Switzerland*

Background: polymer-based, sirolimus (SES) and paclitaxel (PES) eluting stents have been shown to reduce restenosis compared with bare metal stents. However, differences in safety and efficacy between the SES and PES stent platform are not well established. The SIRTAX trial is a randomized, open-label study comparing the clinical and angiographic outcome between the SES and PES stent.
Methods: between April 2003 and May 2004, 1012 patients undergoing PCI were randomly assigned treatment with either the SES (n=503) or PES (n=509) stent. Patients with at least one lesion (reference vessel diameter >2.25 and <4.0 mm), which could be covered with one or more stents were eligible. There was no limitation with respect to site, amount, or length of lesions. The primary endpoint was the incidence of major adverse cardiac events (MACE) at 9 months defined as a composite of cardiac death, myocardial infarction, or target lesion revascularization. Angiographic follow-up was prespecified in 600 patients at 8 months follow-up.
Results: both groups were well matched regarding baseline clinical and lesion characteristics. A total of 1401 lesions (1.4±0.6 lesions per patient) were treated with a mean of 1.2±0.5 stents per lesion in 1012 patients. MACE at 30 days and 6 months are summarized in the table below.

Clinical outcome

	SES (n=503)	PES (n=509	P
30 Day Events			
Cardiac death (%)	0.2	1.0	0.32
NQWMI (%)	1.4	1.8	0.63
QWMI (%)	0.8	0.4	0.41
Target lesion revascularization (%)	2.2	1.4	0.21
6-Month Events			
Cardiac death (%)	0.4	1.6	0.11
NQWMI (%)	1.4	2.6	0.26
QWMI (%)	1.2	0.8	0.55
Target lesion revascularization (%)	3.2	4.7	0.20

Conclusions: coronary revascularization with the SES and PES stent appear safe and effective. Follow-up data of the clinical endpoint at 12 months will be presented at the meeting.

P2888 Rapamycin versus Paclitaxel eluting stents for complex coronary lesions: latest angiographic data from the randomised CORPAL study

A. Medina[1], J. Suarez de Lezo[2], A. Delgado[3], M. Pan[2], E. Hernandez[3], M. Romero[2], F. Melian[3], J. Segura[2]. *[1]Las Palmas de G.C., Spain; [2]Reina Sofia Hospital, Cardiology, Cordoba, Spain; [3]Dr. Negrin Hospital, Las Palmas de Gran Canaria, Spain*

Background and aims: Rapamycin- and Paclitaxel-eluting stents have been shown to significantly decrease restenosis rate. The purpose of this study was to compare both stent types in a large series of patients with coronary lesions at high risk for restenosis.
Methods: Between May/03 and October/04, 844 lesions have been treated in 652 consecutive patients with documented myocardial ischaemia secondary to coronary lesions prone to restenosis with, at least, one of the following conditions: 1) Long-diffuse stenosis (>20mm; mean 31±11mm); 2) small vessel size (<2.5mm; mean 2.4±0.2mm); 3) bifurcated lesions; 4) in-stent restenosis and 5) chronic total occlusion. Patients were randomly assigned to receive either Rapamycin- (Group I, n=434) or Paclitaxel- (Group II, n=410) eluting stents. After treatment, major adverse cardiac events were recorded at late evaluation. A follow-up cardiac catheterization was scheduled.
Results: There were no significant differences in clinical, angiographic and pro-

cedural characteristics between groups. Primary success and in-hospital course were similar in both groups of patients. Minimal lumen diameter following stent implantation was almost identical in both groups (2.59±0.5 vs 2.55±0.5 mm). Post procedural myocardical injury markers were similar in both groups either (CK 153±460 IU/L vs 140±356 IU/L; p:ns). One patient died in group I (0.2%) and 2 in group II (0.5%). Mean clinical follow-up was 13±4 months. Angiographic re-evaluations were performed on 365 lesions (43%) and intravascular ultrasound study in 124 of them. Late angiographic loss was 0.36±0.51 mm in group I vs 0.54±0.67 mm in group II (p=0.01). The incidence of binary restenosis per lesion was 22 (12%) in group I vs 35 (18%) in group II (ns). Late neointimal area was 0.62±0.7 in group I vs 1.11±1.1 mm^2 in group II ($p<0.05$). Target lesion revascularization occurred in 19 (4%)patients from group I and in 29 (7%) from group II (ns).

Conclusions: 1) No significant differences in restenosis rates or late cardiac events were observed between groups. 2) Quantitative coronary angiography showed lower rate of late loss in group I patients, as confirmed by a lesser late neointimal proliferation in the 6-month intravascular ultrasound study.

P2889 Comparison of efficacy and safety between sirolimus-eluting stent (cypher) and paclitaxel-eluting stent (taxus) on the outcome of patients with diffuse in-stent restenosis

S. Nakamura[1], T.S. Muthusamy[2], J.H. Bae[3], Y.H. Cahyadi[4], W. Udayachalerm[5], D. Tresukosol[6], S. Tansuphaswadikul[7]. *[1]New Tokyo Hospital, Department of Cardiology, Matsudo, Japan; [2]Damansara Heart Center, Department of Cardiology, Kuala Lumpur, Malaysia; [3]Konyang University Hospital, Department of Cardiology, Daejeon, Korea, Republic of; [4]Husada Hospital, Department of Cardiology, Jakarta, Indonesia; [5]King Chulalongkorn Memorial Hospital, Department of Cardiology, Bangkok, Thailand; [6]Siriaj Hospital, Department of Cardiology, Bangkok, Thailand; [7]Chest Disease Institute, Department of Cardiology, Bangkok, Thailand*

Background and Purpose: Both Sirolimus-eluting stent (Cypher™, Cordis) and Paclitaxel-eluting stent (TAXUS™, Boston Scientific) have been reported to be effective in preventing neointimal function and reducing restenosis. The aim of this study is to compare the safety and efficacy of these two types of stents on the outcome of patients with diffuse in-stent restenosis (D-ISR).
Methods: A prospective analysis of 584 patients with 668 D-ISR lesions (320 Cypher™ and 264 TAXUS™) in the high volume Asian centers after successful stent implantation (Cypher™: LMT 1.5%, LAD 44.2%, LCX 27.8%, RCA 26.5%) (TAXUS™: LMT 1.5%, LAD 44.5%, LCX 22.8%, RCA 31.2%) was performed. The study endpoints were major adverse cardiac event (MACE) at 30 days and restenosis rate at 12 months.
Results: See table for clinical results.

	Cypher	TAXUS
Number of patients	320	264
MACE at 30 days (%)	0	0
Reference diameter (mm)	2.82 ± 0.70	2.74 ± 0.72
MLD post (mm)	2.63 ± 0.66	2.52 ± 0.66
MLD at 12 months (mm)	2.54 ± 0.77	2.30 ± 0.72
Restenosis rate (%)	7.5	14.0
TVR (%)	7.5	14.0
MACE at 12 months (%)	7.5	14.0

Conclusion: The use of both stents in patients with D-ISR was equally safe with low acute complications and low incidence of restenosis.

P2890 Natural history of small and medium-sized branches after implantation of drug eluting stents. Are there any differences between Cypher and Taxus stents?

I. Iakovou[1], W. Tassanawiwat[2], J. Cosgrave[3], N. Morici[2], P. Agostoni[2], G.M. Sangiorgi[3], E. Tsagalou[2], A. Colombo[3]. *[1]Centro Cuore Columbus, EMO, Milano, Italy; [2]San Raffaele Hospital, Interventional Cardiology, Milan, Italy; [3]EMO Centro Cuore Columbus, Milan, Italy*

Background: Data regarding the fate of small and medium-sized side branches (SB)(reference vessel diameter, RVD<2mm) after implantation of drug-eluting (DES) are limited. The aim of this study was to evaluate the incidence of acute and late SB occlusion after DES implantation and identify any possible differences between the 2 types of DES currently available.
Methods: We evaluated 614 consecutive patients (812 lesions) with 1469 SB with a mean RVD of 1.46 + 0.49 mm that underwent DES implantation (N= 898; 513 Cypher stents involving 698 SB and 385 Taxus stents involving 771 SB) between April 2002 to July 2004. Angiographic follow-up was completed in 284 patients (345 lesions) 232 + 111 days after stent implantation and 6-month clinical follow-up was available in all patients. SB occlusion was defined as a Thrombolysis in Myocardial Infarction (TIMI) flow <1.
Results: Acute SB occlusion affected 148 (10%) branches in 95 patients and was not associated with death or Q-wave myocardial infarction (MI); non-Q-wave MI (defined as CK-MB elevation>3 times the upper limit of normal) occurred in 32 (5.6%) patients. There were no differences regarding the incidence of SB occlusion between lesions treated with Cypher or Taxus stents (9.6% vs. 10.5%, p=0.6). 284 SB were protected by wire placement in 119 patients. There were no differences regarding the incidence of non-Q-wave MI between the patients that had vs. the ones that had not SB protected (3.3% vs. 5.6%, p=0.4). Among the initially occluded SB, 76% spontaneously reperfused at follow-up. Late SB occlusion involved 9% of the SB without impaired antegrade flow after stenting.
Conclusions: Acute SB occlusion occurred in 10% of cases after DES implantation and had a benign course. Most acutely occluded SB underwent late spontatneous reperfusion. There were no differences regarding the incidence of SB occlusion between the 2 types of DES currently available.

P2891 Comparison of efficacy and safety between sirolimus-eluting stent (cypher) and paclitaxel-eluting stent (taxus) on the outcome of patients with small coronary arteries: multi-center registry in Asia

S. Nakamura[1], T.S. Muthusamy[2], J.H. Bae[3], Y.H. Cahyadi[4], W. Udayachalerm[5], D. Tresukosol[6], S. Tansuphaswadikul[7]. *[1]New Tokyo Hospital, Department of Cardiology, Matsudo, Japan; [2]Damansara Heart Center, Department of Cardiology, Kuala Lumpur, Malaysia; [3]Konyang University Hospital, Department of Cardiology, Daejeon, Korea, Republic of; [4]Husada Hospital, Department of Cardiology, Jakarta, Indonesia; [5]King Chulalongkorn Memorial Hospital, Department of Cardiology, Bangkok, Thailand; [6]Siriaj Hospital, Department of Cardiology, Bangkok, Thailand; [7]Chest Disease Institute, Department of Cardiology, Bangkok, Thailand*

Background and Purpose: Both Sirolimus-eluting BX velocity stent (Cypher™, Cordis) and Paclitaxel-eluting Express stent (TAXUS™, Boston Scientific) have been reported to be effective in preventing neointimal formation and in-stent restenosis. However, little is known about long-term efficacy of these 2 stents in patients with small vessel disease (reference diameter ≤ 25 mm). The aim of this study is to compare the safety and efficacy of these 2 stents on the outcome of patients with small coronary arteries (SC).
Methods: A prospective analysis of 1,360 patients with SC (758 Cypher™ and 602 TAXUS™) in five high volume Asian centers after successful stenting for SC (Cypher™: LAD 46.8%, LCX 28.0%, RCA 17.9%, HL 7.3%. TAXUS™: LAD 48.5%, LCX 22.6%, RCA 19.9%, HL 9.0%) was performed. The study endpoints were major adverse cardiac events (MACE) at 30 days, 12 months and restenosis rate at 12 months.
Results: The baseline clinical characteristics between 2 groups were similar. See table for clinical results.

	Cypher	TAXUS	p
Number of patients	758	602	–
Procedural success (%)	100	100	NS
MACE at 30 days (%)	0	0	NS
Reference diameter (mm)	2.38 ± 0.88	2.40 ± 0.90	NS
MLD post (mm)	2.42 ± 0.80	2.45 ± 0.81	NS
MLD at 12 months (mm)	2.16 ± 0.80	2.08 ± 0.77	NS
Restenosis rate (%)	11.6	13.0	NS
TVR (%)	10.6	11.6	NS
MACE at 12 months (%)	10.6	11.6	NS

Conclusion: The use of both stents in patients with small coronary arteries was equally safe with low acute complication and low incidence of restenosis.

P2892 Drug-eluting stents for the treatment of chronic total occlusion. A randomised comparison of rapamycin- versus paclitaxel-eluting stents

J.M. Segura Saint-Gerons[1], A. Medina[2], A. Delgado[2], M. Pan[3], J. Suarez de Lezo[3], M. Romero[3], E. Hernandez[2], S. Ojeda[3]. *[1]Cordoba, Spain; [2]Dr. Negrin Hospital, Cardiology, Las Palmas de Gran Canaria, Spain; [3]Reina Sofia Hospital, Cardiology, Cordoba, Spain*

Drug eluting stents have proven to be effective in reducing restenosis/reocclusion rates in patients with chronic coronary total occlusion. However, no studies comparing different drug eluting stents in this complex clinical subset are yet available.
Methods: Between May 2003 and December 04, 118 patients with angina pectoris secondary to coronary total occlusion were randomized to receive rapamycin (RES) (n=60) or paclitaxel-eluting stents (PES) (n=58) once successful recanalization was achieved (87%).
Results: There were no significant differences among groups in terms of clinical, procedural and angiographic parameters. Primary success in recanalyzed patients (93% RES vs 95% PES), and 1-month major cardiac events were similar in both groups. The immediate quantitative angiographic results were also similar in both groups. After 8±3 months follow-up, the number of major cardiac events

	RES	PES	p<
Late MLD	2.3±0.5	2.1±0.8	ns
Late % stenosis	17±14	28±25	0.05
Late loss	0.2±0.3	0.5±0.6	0.05
Binary restenosis	2 (7.4%)	6(19%)	ns
Reocclusions	0	2	ns
TLR	2 (3.3%)	4 (7%)	ns

MLD: Minimal lumen diameter

and target lesion revascularization (TLR), were not different in both groups (3% vs 7%). Late angiography was performed in 28 patients from the RES group (47%) and 28 patients from the PES group (48%). The main results obtained from serial quantitative coronary angiography are shown in the table.
Conclusions: Although there are no significant differences in overall major cardiac events and restenosis/reocclusion rates in this on-going trial, RES for coronary total occlusion is associated with lesser rate of late loss at angiographic follow-up.

P2893 Comparison of efficacy and safety between sirolimus-eluting stent (cypher) and paclitaxel-eluting stent (taxus) in patients with diabetes mellitus: multicenter registry in Asia

S. Nakamura[1], T.S. Muthusamy[2], J.H. Bae[3], Y.H. Cahyadi[4], W. Udayachalerm[5], D. Tresukosol[6], S. Tansuphaswadikul[7]. *[1]New Tokyo Hospital, Department of Cardiology, Matsudo, Japan; [2]Damansara Heart Center, Department of Cardiology, Kuala Lumpur, Malaysia; [3]Konyang University Hospital, Department of Cardiology, Daejeon, Korea, Republic of; [4]Husada Hospital, Department of Cardiology, Jakarta, Indonesia; [5]King Chulalongkorn Memorial Hospital, Department of Cardiology, Bangkok, Thailand; [6]Siriaj Hospital, Department of Cardiology, Bangkok, Thailand; [7]Chest Disease Institute, Department of Cardiology, Bangkok, Thailand*

Background and Purpose: Both Sirolimus-eluting BX velocity stent (Cypher™, Cordis) and Paclitaxel-eluting Express stent (TAXUS™, Boston Scientific) have been reported to be effective in preventing neointimal formation and in-stent restenosis. However, little is known about long-term efficacy of these 2 stents in patients with diabetes mellitus (DM). The aim of this study is to compare the safety and efficacy of these 2 stents on the outcome of patients with DM.
Methods: A prospective analysis of 868 patients with DM (508 Cypher™ and 360 TAXUS™) in five high volume Asian centers after successful stenting was performed. The study endpoints were major adverse cardiac events (MACE) at 30 days, 12 months and restenosis rate at 12 months.
Results: The baseline clinical characteristics between 2 groups were similar. See table for clinical results.

	Cypher	TAXUS	p
Number of patients/lesions	508/952	360/680	-
Age (mean/yrs)	63.8	66.9	NS
Multivessel desease (%)	78.5	78.9	NS
Procedural success (%)	100	100	NS
Number of stents (mean)	2.8	3.0	NS
MACE at 30 days (%)	0	0	NS
Lesion length (mm)	29.8 ± 12.5	31.5 ± 10.8	NS
Reference diameter (mm)	2.82 ± 0.74	2.75 ± 0.60	NS
MLD post (mm)	2.55 ± 0.78	2.54 ± 0.68	NS
MLD at 12 months (mm)	2.18 ± 0.66	2.08 ± 0.60	NS
Restenosis rate (%)	11.9	13.9	NS
TVR (%)	9.8	13.9	NS
MACE at 12 months (%)	11.9	13.9	NS

Conclusion: The use of both stents in patients with DM was equally safe with low acute complication and low incidence of restenosis.

P2894 A comparison of sirolimus-eluting stents and paclitaxel-eluting stents in different lesions in the same patient

J. Cosgrave[1], P. Agostoni[2], L. Ge[1], I. Iakovou[1], G. Biondi-Zoccai[2], M. Montorfano[2], F. Airoldi[2], A. Colombo[2]. *[1]EMO Centro Cuore Columbus, Interventional Cardiology Unit, Milan, Italy; [2]St. Raffaele Hospital, Interventional Cadiology Unit, Milan, Italy*

Purpose: Both currently available drug-eluting stents (DES) have been shown to be superior to bare-metal stents. However there is no data on the safety and efficacy of the combination of both stents in the same patient. We compared the outcome of polymeric paclitaxel-eluting stent (PES) and sirolimus-eluting stent (SES) in different lesions in the same patient.
Methods: Between March 2003 and June 2004, 84 patients were treated with a combination of both SES and PES in 278 lesions. The safety end-point was the per-patient rate of death, myocardial infarction (MI) and cumulative stent thrombosis. We compared the efficacy of the two stents by analysing the rate of target lesion revascularization (TLR).
Results: The rate of peri-procedural MI was 5.9% and no in-hospital deaths or repeat revascularizations occurred. At 1 year there were no cardiac deaths, 2 non-cardiac deaths (1 for cancer, 1 for car accident), and 1 non Q-wave MI. No episodes of stent thrombosis were documented. The per-lesion analysis showed a TLR rate of 16.1% (19/118) after SES implantation, and of 15.5% (24/180) after PES (p=0.80).
Conclusions: Implantation of different types of DES in the same patient is safe, without major adverse events either peri-procedurally or at follow-up. The TLR rate is similar between the two devices and comparable to the TLR rate of similar patients treated with a single type of DES in our institution.

P2895 Impact of sirolimus-eluting and paclitaxel-eluting stents on clinical outcome in diabetic patients with de-novo lesions

G. Stankovic[1], J. Cosgrave[2], A. Chieffo[3], I. Iakovou[2], G.M. Sangiorgi[2], N. Corvaja[2], F. Airoldi[3], A. Colombo[2]. *[1]Institute for Cardiovascular Diseases, Clinical Center of Serbia, Belgrade, Serbia and Montenegro; [2]EMO Centro Cuore Columbus, Milan, Italy; [3]San Raffaele Hospital, Milan, Italy*

Randomized trials have shown that implantation of sirolimus-eluting (SES) or paclitaxel-eluting stents (PES) in diabetic patients with de-novo lesions reduces the incidence of major adverse cardiac events compared to bare metal stents. The aim of the present study was to compare the impact of SES and PES on clinical outcome in diabetic patients with de-novo lesions.
Methods: In this observational study in-hospital and 9-month clinical outcome of 228 patients treated with SES (488 lesions) and 161 patients treated with PES (319 lesions) were compared. Major adverse cardiac events (MACE) were defined as death, non-fatal myocardial infarction (MI) and clinically-driven target vessel revascularization (TVR).
Results: Except for a higher prevalence of insulin-requiring diabetic patients in the PES group (33% vs. 21%, p=0.009), baseline clinical characteristics of two groups were well matched. Diabetic patients in SES and PES groups had similar baseline vessel size (2.60±0.58 vs. 2.63±0.62 mm), lesion length (16.7±9.9 vs. 15.6±9.1 mm), number of lesions treated (2.1 vs. 2.0), length of implanted stents (29±13 mm vs. 29±15 mm) and attained similar post procedure results.
No significant difference was observed in in-hospital events (MACE 4.4% vs. 2.5% in SES and PES group, p=0.32) and subacute (0.9% vs. 0.6%, p=0.78) and late stent thrombosis (0.9% vs. 0.6%, p=0.78). At 9-month follow-up the incidence of MACE was also similar in SES and PES groups (21.5% vs. 16.8%, p=0.25), with no difference in rate of death (3.5% vs. 1.9%, p=0.34), MI (0.9% vs. 0.6%, p=0.78) or TVR (19.3% vs. 14.9%, p=0.26).
Insulin-requiring diabetic patients treated with SES (48 patients) and PES (53 patients) had similar baseline vessel size baseline vessel size (2.57±0.59 vs. 2.69±0.61 mm), lesion length (17.7±8.9 vs. 15.9±9.4 mm), number of lesions treated (2.1 vs. 1.9), length of implanted stents (29±12 mm vs. 31±20 mm), post procedure angiographic results and rates of in-hospital (6.3% vs. 5.7%, p=0.90) and 9-month MACE (27.1% vs. 34.0%, p=0.45).
Conclusions: In diabetic patients with de-novo coronary lesions implantation of SES and PES provides similar in-hospital and 9-month clinical outcome. Our findings need to be tested in a randomized study.

P2896 One year clinical outcome after coronary stenting of very small vessels using 2.25 mm sirolimus and paclitaxel eluting stents: a comparison between the research and T-search registries

H.M. Garcia-Garcia, G.A. Rodriguez-Granillo, M. Valgimigli, J. Aoki, C.A.G. van Mieghem, A.T.L. Ong, K. Tsuchida, P.W. Serruys. *Erasmus MC, Rotterdam, Netherlands*

Background: The efficacy of sirolimus-eluting stents (SES) compared to paclitaxel-eluting stents (PES) remains unknown. We evaluated the clinical outcome after implantation of 2.25 mm diameter SES and PES.
Methods and results: Paclitaxel-eluting stents (PES) have been used as the stent of choice for all percutaneous coronary interventions as part of the prospective Taxus-Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) Registry. Ninety-two consecutive patients received at least one 2.25 mm PES (PES group) and were compared with 107 patients who received at least one 2.25mm SES as part of the RESEARCH registry. The overall population presented high risk characteristics commonly excluded from most studies. Populations were well matched. There were 2 (2.2%) sub-acute stent thrombosis in the PES group (in a 2.25mm stent) and none in the SES group. At one year, the cumulative incidence of major adverse cardiac events was 5.6%in the SES group and 18.5% in the PES group (p= 0.005). After adjustments for other significant univariate variables, female gender (adjusted OR 2.9 [95% CI 1.11-7.42], p= 0.030), presentation with acute coronary syndrome (adjusted OR 7.0 [95% CI 2.24-21.71], p= 0.001) and PES utilization (adjusted OR 2.7 [95% CI 1.00-7.15], p= 0.049) were found significant independent predictors of MACE. The presence of diabetes mellitus (adjusted OR 2.2 [95% CI 0.89-5.49], p= 0.086) presented a trend towards worse outcome.
Conclusions: In an unselected population treated for very small vessel disease, SES was associated with better 12-months clinical outcome and the use of PES, among other classical predictors, was identified as an independent predictor of adverse events.

P2897 Comparison of efficacy and safety between sirolimus-eluting stent (cypher) and paclitaxel-eluting stent (taxus) in unprotected left main coronary arteries: multicenter registry in Asia

S. Nakamura[1], T.S. Muthusamy[2], J.H. Bae[3], Y.H. Cahyadi[4], W. Udayachalerm[5], D. Tresukosol[6], S. Tansuphaswadikul[7]. *[1]New Tokyo Hospital, Department of Cardiology, Matsudo, Japan; [2]Damansara Heart Center, Department of Cardiology, Kuala Lumpur, Malaysia; [3]Konyang University Hospital, Department of Cardiology, Daejeon, Korea, Republic of; [4]Husada Hospital, Department of Cardiology, Jakarta, Indonesia; [5]King Chulalongkorn Memorial Hospital, Department of Cardiology, Bangkok, Thailand; [6]Siriaj Hospital, Department of Cardiology, Bangkok, Thailand; [7]Chest Disease Institute, Department of Cardiology, Bangkok, Thailand*

Background and Purpose: Both Sirolimus-eluting BX velocity stent (Cypher™, Cordis) and Paclitaxel-eluting Express stent (TAXUS™, Boston Scientific) have been reported to be effective in preventing neointimal formation and in-stent restenosis. The aim of this study is to compare the safety and efficacy of these 2 stents on the outcome of patients with unprotected left main coronary arteries (LMT).
Methods: A prospective analysis of 230 patients with LMT stenosis (144 Cypher™ and 86 TAXUS™) in five high volume Asian centers after successful stenting in LMT was performed. Lesion location of LMT was ostial 40 cases (17.4%), mid shaft 52 cases (22.6%) and distal 138 cases (60.0%). The study endpoints were major adverse cardiac events (MACE) at 30 days and restenosis rate at 12 months.
Results: The baseline clinical characteristics between 2 groups were similar. See table for clinical results.

	Cypher	TAXUS	p
Number of patients	144	86	–
Age (mean/yrs)	69.9	70.8	–
Procedural success (%)	100	100	NS
MACE at 30 days (%)	0	0	NS
LV ejection fraction (mean/%)	44.8	46.0	NS
Reference diameter (mm)	3.62 ± 0.94	3.48 ± 0.78	NS
MLD post (mm)	3.44 ± 0.88	3.20 ± 0.80	NS
MLD at 12 months (mm)	3.18 ± 0.77	3.06 ± 0.78	NS
Restenosis rate (%)	2.7	4.7	NS
TVR (%)	2.1	3.5	NS
MACE at 12 months (%)	2.1	3.5	NS

Conclusion: The use of both stents in patients with LMT was equally safe with low acute complication and low incidence of restenosis.

DES: TRIALS, REGISTRIES, THROMBOSIS AND EXPERIMENTAL STUDIES

P2898 Taxus II 3-years clinical follow-up: long-term data from a randomised, controlled study of polymer-based paclitaxel-eluting stents for coronary artery lesions

A. Colombo[1], A. Banning[2], S. Silber[3], K.E. Hauptmann[4], J. Drzewiecki[5], E. Grube[6], A. Wijatyk[7], M.E. Russell[7]. *[1]EMO Centro Cuore Columbus S.r.l., Dir. Cardiac Catheterization Lab., Milan, Italy; [2]John Radcliffe Hospital, Oxford, United Kingdom; [3]Internistische Klinik Dr. Muller, Munchen, Germany; [4]Krankenhaus der Barmherzigen Bruder, Trier, Germany; [5]Samodzielny Publiczny Szpital Kliniczn, Katowice, Poland; [6]Heart Center Siegburg, Siegburg, Germany; [7]Boston Scientific Corporation, Natick, MA, United States of America*

Background: TAXUS II is the phase II TAXUS trial comparing the slow- and moderate-release TAXUS stents to bare metal control stents. The primary endpoint of % net volume obstruction at 6 months as measured by IVUS was met with significant reductions in the TAXUS groups versus the control. The 2-year follow-up demonstrated the durability of TAXUS with continued low target lesion revascularization (TLR) rates and stable late loss and % net volume obstruction values in the TAXUS groups. Three-year clinical follow-up of TAXUS II will further validate the long-term safety and efficacy of the TAXUS stents.
Methods: TAXUS II is a randomized, double-blind clinical trial conducted at 38 sites comparing the safety and efficacy of the TAXUS slow-release (SR, n = 131) and TAXUS moderate-release (MR, n = 135) stents to bare control stents (BMS, n = 270) in patients with focal, de novo lesions. Clinical follow-up is being conducted annually for 5 years to assess the stability of TAXUS over time.
Results: The 3-year clinical follow-up is currently being conducted for TAXUS II to expand the long-term clinical profile of both slow- and moderate-release TAXUS stents. At 2 years, the safety and efficacy of TAXUS stents was maintained with only 1 new TLR, unrelated to restenosis, in TAXUS from 1 to 2 years. Eight TLRs were reported for BMS in the same time period. Accordingly, TAXUS groups had significantly lower TLR rates (5.5% SR and 3.9% MR vs. 15.5% BMS, P=0.0002) and MACE rates (14.2% for both SR and MR vs. 24.6% BMS, P=0.0178) than BMS at 2 years. Stent thrombosis rates were low and comparable in all groups. As of February 14, 2005, 96.6% of patients had completed the 3-year follow-up. The 3-year follow-up results will be finalized by the time of presentation.
Conclusions: The TAXUS II trial has demonstrated that TAXUS stents inhibit rather than delay restenosis out to 2 years. This benefit is accompanied by an excellent safety profile similar to that seen in BMS. The present analysis will further extend the assessment of clinical safety and efficacy outcomes of TAXUS stents out to 3 years.

P2899 (W) The new paclitaxel-eluting please stent – Results from the PECOPS-trial

M. Unverdorben[1], R. Degenhardt[1], W. Bocksch[2], D. Horstkotte[3], C. Nienaber[4], H. Schneider[4], C. Vallbracht[5], M. Wiemer[3]. *[1]Clinical Research Institute, Center for Cardiovascular Diseases, Rotenburg a.d.F., Germany; [2]Dept. of Cardiology, Charite, Medical Clinic, Berlin, Germany; [3]Cardiologic Clinic, Heart and Diabetes Center NRW, Bad Oeynhausen, Germany; [4]Dept. of Cardiology, University of Rostock, Rostock, Germany; [5]Center for Cardiovascular Diseases, Rotenburg/F, Germany*

Paclitaxel-eluting stents are associated with low coronary restenosis rates. In this trial the performance of the new paclitaxel-coated (dose: 1μg/mm²) Coroflex™-stent was investigated.
Methods: 125 patients (65.8 ± 7.6 years, lesion type A 14/125 (11.2%), type B1 85/125 (68.0%), and 26/125 (20.8%) type B2) admitted for intervention of a de-novo or restenotic coronary lesion (reference diameter: =2.25mm, <3.3mm, lesion length: <14mm, stenosis: =70%, <100%) were enrolled for elective single stent deployment.
Results: The deployment and procedural success were 117/125 (93.6%). Thirty–five of 125 (28.0%) devices were placed without pre-dilatation. In 5/117 (4.3%) subjects additional Coroflex™-stents were required for procedure related dissections. In the 112/125 (89.6%) patients treated per protocol the mean reference vessel diameter was 2.74 ± 0.52 mm and the initial stenosis was reduced from 76.1 ± 7.0% to 9.5 ± 6.1%. During the 30-day clinical follow-up, 2/125 (1.6%) premature target lesion revascularizations were performed due to stent thrombosis. In one of the patients the thrombosis occurred two days after discontinuation of clopidogrel for elective, non-study related abdominal surgery. The total MACE-rate was as low as 2.6%. One of the 125 (0.8%) patients experienced a non-ST-segment elevation myocardial infarction according to the 2001 ACC/AHA Guidelines.
Conclusion: The new Coroflex™-stent is associated with procedural results and MACE-rates comparable to other stents with active coatings. The 6-month clinical and quantitative angiographic data like late loss will be available and presented at this ESC-meeting.

P2900 Paclitaxel in-stent controlled elution study: PISCES

P.W. Serruys[1], G. Sianos[1], P. Den Heijer[2], D. McClean[3], S. Verheye[4], E. Sousa[5], J.A. Condado[6], J. Symons[7]. *[1]Thoraxcenter, Univ Hospital Rotterdam, Rotterdam, Netherlands; [2]Amphia Hospital, Breda, Netherlands; [3]Christchurch Hospital, Christchurch, New Zealand; [4]Academic Hospital of Middelheim, Antwerp, Belgium; [5]Dante Pazzanese Cardiology Institute, Sao Paolo, Brazil; [6]Miguel Perez Carreno Hospital, Caracas, Venezuela; [7]Cardialysis, CTM, Rotterdam, Netherlands*

Aim: To evaluate the safety and performance of six different formulations (2 doses normalized to a 17 mm stent and 4 release profiles) of a Paclitaxel eluting stent specifically designed for drug delivery (MedStent) with programmable pharmacokinetics in native coronary artery lesions.
Methods: 244 patients with single vessel disease received either a bare metal Conor stent (N=53) or a Paclitaxel-eluting Conor stent with one of six different release formulations (N=191): D1 (N=30): 10μg, 5-day bidirectional (abluminal and luminal) release; D2 (N=31): 10μg, 10-day bidirectional release; D3 (N=30): 10μg, 10-day abluminal (mural) release; D4 (N=31): 30μg, 10-day bidirectional release; D5 (N=39): 10μg, 30-day abluminal release; D6 (N=30): 30μg, 30-day abluminal release. The endpoints at 6 months (bare stent group) and at 4 months (eluting stent groups) were angiographic late loss, neointimal tissue volume by IVUS and the rate of Major Adverse Cardiac Events (MACE). Baseline characteristics: age 59.1±9.2y, male 70%, history of smoking 76%, diabetes 19%, hypertension 53%, dyslipidemia 66%, prior MI 38%, prior CABG 3%, prior PCI 12%. The baseline characteristics were comparable in all doses. The technical success rate was 95% and the procedural success rate 93%.
Results:

	D0	D1	D2	D3	D4	D5	D6
Dose/duration/direction	bare stent	10/5/b	10/10/b	10/10/m	30/10/b	10/30/m	30/30/m
N	50	30	29	30	30	39	29
Any MACE	4 (8.0%)	5 (16.7%)	5 (17.2%)	2 (6.7%)	2 (6.7%)	1 (2.6%)	1 (3.4%)
Late loss (mm)	0.88	0.72	0.70	0.67	0.48	0.38	0.30
Restenosis rate (%)	11.6	10.3	10.7	3.6	6.9	0.0	3.8
Obstruction volume fup (%)	26	22	20	17	12	8	5

At 6 months (bare metal group D0) and 4 months (Paclitaxel-eluting groups D1-D6)

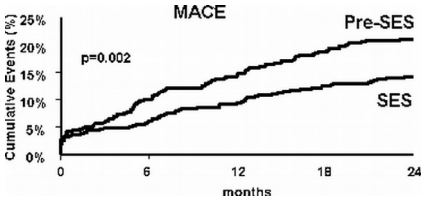
Conclusion: This novel eluting stent platform, using an erodable polymer with complete elution of low doses of paclitaxel, is safe. The inhibition of the in-stent

neointimal hyperplasia was best in the long release groups. The principal finding of this study is that, for paclitaxel, differing release kinetic profiles at similar doses appears to have profound impact on efficacy. Twelve-month clinical and angiographic data will be presented.

P2901 Sirolimus-eluting stents remain superior to bare metal stents at 2 years in the real world: long-term results from the RESEARCH registry

A.T.L. Ong, R.T. van Domburg, J. Aoki, P.W. Serruys. *Thoraxcenter, Erasmus MC (BD416), Interventional Cardiology, Rotterdam, Netherlands*

Objectives: To investigate the long term (2 year) outcome of the unrestricted utilization of sirolimus-eluting stents (SES) in an all-comers population.
Background: Despite the implantation of SES in one million patients to date, limited data exists on long term outcomes.
Methods: SES were used as the default strategy as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. Consecutive patients with de novo lesions exclusively treated with SES (n=508) were compared with 450 patients who received bare stents in the immediate preceding period (pre-SES group).
Results: Patients in the SES group more frequently had multivessel disease, more type C lesions, received more stents, and had more bifurcation stenting. At 2 years, the cumulative rate of major adverse cardiac events (death, myocardial infarction or target vessel revascularization) was 14.2% in the SES group and 21.2% in the pre-SES group (p=0.002). The 2-year risk of target vessel revascularization in the SES group and in the pre-SES group was 5.9% versus 14.0% respectively (p< 0.0001).



Cumulative Incidence of MACE

Conclusion: In an unrestricted population, the beneficial effects of sirolimus-eluting stent implantation extend out to two years compared to bare metal stents, driven by a reduction in re-intervention rates. These findings should be confirmed by the results of the large randomized trials.

P2902 Revascularisation of the proximal left anterior descending coronary artery stenosis with drug-eluting stents versus bare-metal stents versus minimally invasive direct coronary artery bypass (MIDCAB)

S.J. Hong[1], M.H. Kim[2], S.K. Ryu[3], W.J. Shim[1], Y.M. Ro[1], D.S. Lim[1]. *[1]Korea University Anam Hospital, Cardiology Department, Seoul, Korea, Republic of; [2]Donga University Hospital, Cardiology Department, Pusan, Korea, Republic of; [3]Eulji University Hospital, Cardiology Department, Seoul, Korea, Republic of*

Background: patients with significant proximal LAD stenosis are at a higher risk than those with lesions at any other locations, and they need a safe and effective means of revascularisation.
Aims: the objective of this study was to assess the clinical and angiographic outcomes of percutaneous coronary intervention (PCI) with drug-eluting stents (DESs) versus PCI with bare-metal stents (BMSs) versus minimally invasive direct coronary artery bypass (MIDCAB) surgery in the management of patients with proximal left anterior descending (LAD) coronary artery stenosis.
Methods: this was an observational retrospective cohort study including consecutive symptomatic patients (n=302) assigned to the DES group (n=77), the BMS group (n=155), and the MIDCAB group (n=70). Patients with a high-grade lesion (stenosis of > 70 percent of the luminal diameter) in the proximal LAD coronary artery (between the origin of left circumflex coronary artery and the first diagonal branch) were included in this study.
Results: in-hospital length of stay was significantly shorter in the DES and the BMS groups compared with the MIDCAB group (4.4 ± 1.2 days vs. 4.8 ± 1.9 days vs. 6.9 ± 1.2 days, p < 0.001; respectively). During the six-month follow-up period, 2.6% (n=2) in the DES group needed repeated target lesion revascularisation compared with 5.7% (n=4) in the MIDCAB group and 19.4% (n=30) in the BMS group (p < 0.001). Rates of death and myocardial infarction were similar in the three groups during the six months follow-up period. Kaplan-Meier six-month event-free survival curves (free from cardiac death, myocardial infarction, the need for repeated revascularisation) showed that 72 (93.5%) of the 77 patients in the DES group, 109 (70.3%) of 155 patients in the BMS group, and 64 (91.4%) of the 70 patients in the MIDCAB group were event-free at the six-month follow-up (Log-rank test, p = 0.007).
Conclusion: even for patients with proximal LAD stenosis, DES implantation may be more recommendable revascularisation method rather than BMS implantation and MIDCAB surgery.

P2903 Drug-eluting stents for multivessel percutaneous coronary interventions in daily practice. Mid-term results from the REAL (REgistro AngiopLastiche Emilia-Romagna) multicenter registry

F. Saia[1], A. Maresta[2], E. Varani[2], G. Piovaccari[3], F. Passerini[4], F. Castriota[5], P. Guastaroba[6], A. Marzocchi[1]. *[1]University of Bologna, Institute of Cardiology, Bologna, Italy; [2]Ospedale S. Maria delle Croci, Unità Operativa di Cardiologia, Ravenna, Italy; [3]Ospedale degli Infermi, Unità Operativa di Cardiologia, Rimini, Italy; [4]Ospedale di Piacenza, Divisione di cardiologia, Piacenza, Italy; [5]Casa di Cura Villa Maria Cecilia, Cardio-Angiologia Interventistica, Cotignola (RA), Italy; [6]Regione Emilia-Romagna, Agenzia Sanitaria Regionale, Bologna, Italy*

Purpose: We aimed to investigate the effect of drug-eluting stent (DES) utilization for multivessel percutaneous coronary intervention (PCI) in a real world scenario.
Methods: From july 2002 to june 2004, 1191 consecutive patients enrolled in the REAL (REgistro AngiopLastiche Emilia-Romagna) registry underwent elective multivessel PCI (11% of all patients treated in the same period). Among them, 674 (57%) received only bare metal stents (BMS group), 172 (14%) were treated solely with DES (DES group), and 345 (29%) with both (Mix group). The incidence of major adverse cardiac events (MACE =death, myocardial infarction and target vessel revascularisation) during follow-up was assessed.
Results: Overall, 27% of the patients were diabetics, 51% had acute coronary syndrome at admission, and 46% had 3-vessel disease. Diabetes mellitus was more common among patients treated only with DES (37.2% DES, 23.8% BMS, 26.8% Mix, p=0.002). Poor left ventricular function was evenly distributed among the 3 groups (10% DES, 8% BMS, 9% Mix, p=ns). Triple-vessel treatment was more common in the Mix group (5% DES, 6% BMS, 13% Mix, p<0.0001). The DES group had greater average lesions length (18.7±9.5mm DES, 14.6±6.2 BMS, 17.0±9.0 mm Mix, p<0.001), smaller reference diameter (2.8±0.4 DES, 3.0±0.5 BMS, 2.9±0.5 Mix, p<0.0001), and higher prevalence of left main stenting (9.7% DES, 1.7% BMS, 2.5 Mix, p<0.0001) compared to the other groups. In the Mix group, DES were most commonly used to treat the LAD and complex lesions. Procedural success was similar between the 3 groups (98.2% DES, 99.1% BMS, 98.9 Mix, p=ns). At 9-month, the cumulative incidence of MACE was 9.6% DES, 14.3% BMS, and 12.8% Mix (p=ns), and TVR was 6.5%, 8.0% and 8.1% respectively (p=ns). At multivariate analysis, only Charlson comorbidity index, left main stenting and poor left ventricular function were independent predictors of MACE, and only lesion length and 3 vessel treatment were independently associated with repeat revascularization. DES utilization was associated with a 40% reduction of MACE and 42% reduction of TVR, which were not statistically significant.
Conclusions: In this multicenter registry, DES were used in less than half of the patients undergoing multivessel PCI, mainly to treat higher risk patients and lesions, and were associated with an evident though not statistically significant reduction of MACE. Larger number of patients and longer follow-up should better clarify this aspect. Whether increasing the rate of DES utilization would further reduce the incidence of MACE remains to be investigated.

P2904 12-month results of the e-Cypher registry: assessment of real-life use of the sirolimus-eluting stent

C. Lotan[1], A.H. Gershlick[2], G. Guagliumi[3], P. Guyon[4], J. Schofer[5], J.E. Sousa[6], P. Urban[7], W. Wijns[8] on behalf of The e-Cypher Investigators. *[1]Hadassah-Hebrew University Medical Center, Heart Institute, Jerusalem, Israel; [2]University Hospitals Leicester, Cardiology, Leicester, United Kingdom; [3]A.O.Riuniti di Bergamo, Cardiology, Bergamo, Italy; [4]Centre Cardiologique du Nord, Saint-Denis, France; [5]Kardiologische Gemeinschaftpraxis, Hamburg, Germany; [6]Inst Dante Pazzanese of Cardiology, Sao Paulo, Brazil; [7]La Tour Hospital, Cardiovascular, Geneva, Switzerland; [8]Cardiovascular Center, Aalst, Belgium*

Background: The safety and efficacy of Sirolimus-eluting stents (SES) has been demonstrated in a pre-defined trial population. The e-Cypher Registry is an international, internet-based registry which aims to assess outcome of real-life clinical SES use.
Methods: Data from 15,172 patients with at least 1 Cypher® stent implanted since April 2002 were collected from 281 centers in 41 countries using a dedicated website preserving data confidentiality. Telephone interviews and/or patient visits were conducted to provide long-term clinical follow-up.
Results: Mean age of all patients was 62±11y; 78% were male, 29% were diabetics, and 57% had multi-vessel disease. Indications were stable angina (42%), unstable angina (34%) and acute MI (7%). 88% of lesions were de novo in native vessels, 12% were in-stent restenosis and 3% chronic total occlusions. Mean target vessel diameter was 2.9±0.4mm, and mean lesion length was 17.2±8.8mm. 12-months follow-up was available (n=10600) for 83% of all analyzable patients (see table).

Follow-up report

	30 days	180 days	365 days
MACE(death,MI,TLR)	1.35%	3.2%	5.9%
Death	0.57%	1.43%	2.37%
Myocardial Infarction	0.65%	0.95%	1.41%
Target Lesion Revascularization	0.42%	1.29%	2.91%
Thrombosis	0.7%	0.88%	1.11%
CABG Non-target Vessel	0.04%	0.15%	0.26%
PTCA Non-target Vessel	0.39%	1.47%	2.37%

In and out of hospital events

Conclusions: The data provided by this registry confirm safety and very low rates of MACE similar to those observed in previous randomized trials.

P2905 Sirolimus increases tissue factor expression in cultured human vascular smooth muscle cells: a risk for thrombosis associated with CYPHER stents

S. Zhu[1], H. Viswambharan[1], T. Gajanayake[1], X.-F. Ming[1], Z. Yang[2]. *[1]University of Fribourg, Dept. of Medicine, Physiology, Fribourg, Switzerland; [2]Universität Fribourg, Physiologie Institut Vaskuläre Biologie, Fribourg, Switzerland*

Background: Sirolimus-eluting stents (CYPHER stents) demonstrated remarkable efficacy in reducing restenosis rates in patients with coronary artery disease in short-to-medium term. Sub-acute and late stent thrombosis is still of concern. Recent clinical experience suggests that sirolimus-eluting stents may be prone to thrombosis. Tissue factor (TF) is critically involved in thrombosis. This study investigated the effect of sirolimus on TF expression in cultured human vascular smooth muscle cells (SMCs).
Methods: SMCs were cultured from human saphenous veins and aortas. The cells were rendered quiescent for 48 hours and then stimulated with sirolimus (20 ng/ml) over 24 hours. TF expression was analyzed by immunoblotting. The effect of sirolimus on activation of mammalian target of rapamycin (mTOR) were measured by phosphorylation of the substrate p70s6k at T389, and activation of RhoA was measured by pull-down assay. To study whether HMG-CoA reducatse inhibitors could influence the TF expression, SMC were pre-incubated with fluvastatin (1 μmol/L) for 1 hour, then stimulated with sirolimus (20 ng/ml, 24 hours).
Results: Sirolimus (20 ng/ml) increased TF protein level (2.7-fold, $p<0.01$) in cultured human SMCs in a concentration and time-dependent manner. The stimulation of TF expression by sirolimus was associated with inhibition of basal activity of mTOR. No effects of sirolimus on RhoA or p38mapk activation that are positive regulators of TF in vascular wall cells were observed. The stimulation of TF expression by sirolimus (20 ng/ml) was prevented by the HMG-CoA reductase inhibitor fluvastatin (1 μmol/L).
Conclusion: Sirolimus stimulates TF expression in human SMCs most likely via inhibition of mTOR, which could be a risk for development of stent thrombosis in patients receiving CYPHER stents. The inhibition of TF expression by fluvastatin favors clinical use of statins in patients undergoing coronary stenting.

P2906 Incidence, characteristics and outcome of subacute stent thrombosis

A. Faeh, D.J. Kurz, I. Stettler, O. Bertel. *Stadtspital Triemli, Cardiology Department, Zuerich, Switzerland*

Background: Subacute stent thrombosis (SAT) is a rare but devastating complication of percutaneous coronary intervention (PCI), with a reported incidence of about 1% under combination therapy with aspirin and clopidogrel. Here we evaluated the incidence, characteristics and outcome of this complication in all patients undergoing coronary stenting during a period of three years at a tertiary referral center.
Methods: SAT was defined as recurrent ischemia and/or myocardial infarction (MI) and documented thrombotic vessel occlusion within six month after PCI. Patients with SAT are routinely included in an on-site complication registry.
Results: Between January 2002 and December 2004 2594 patients underwent PCI and stenting. SAT occurred in 26 (1%) of all stented patients (28 vessels) after a median of 9 days. Mean age was 62.7 ($\pm$13.7) years, 69% were male. A potential trigger could be identified in 6 patients: Clopidogrel treatment was aborted in 2 patients, and 1 patient suffered SAT immediately following a driving accident with a moderate thoracic trauma; in 2 patients the initial procedure was complicated by extensive coronary dissection; one patient underwent brachytherapy. In 82.2% of cases SAT occurred in bare metal stents (BMS), while only 17.8% occurred in drug eluting stents (DES). In contrast, DES were used in 41% of the whole cohort ($p = 0.02$). Among patients subsequently suffering from SAT, the indication for the initial PCI was acute MI/acute coronary syndrome (ACS) in 80.8% of patients, while only 19.2% of SAT occurred in patients undergoing elective PCI for stable angina. In 75% of patients with SAT the left coronary artery was involved (57.1% LAD, 17.9% CX), in 21.4% the right coronary artery, and in 1 patient an arterial bypass graft. The mean length of the stented segment in which SAT occurred was 24.6$\pm$16.7mm. All episodes of SAT were treated by PCI. One patient died due to post-procedural bleeding complications.
Conclusions: In our cohort $>$80% of SAT occurred following coronary stenting during the acute or subacute phase of MI. None the less, the pathophysiology leading to SAT is heterogeneous: a triggering event was identified in 23% of cases. Drug eluting stents were not associated with an excess incidence of SAT.

P2907 Haemocompatibility, cytotoxicity and in-vivo performance of pure titanium stents in hypercholesterolemic rabbits

K. Wilczek[1], R. Wojnicz[1], A. Lekston[1], P. Walichiewicz[2], B. Duda[3], G. Nawrat[4], P. Wilczek[3], L. Polonski[1]. *[1]Silesian Centre for Heart Disease, III Dept. of Cardiology, Zabrze, Poland; [2]Institute of Oncology, Dept. of Radiotherapy, Gliwice, Poland; [3]Fundation Cardiac Surgery Developemant, Zabrze, Poland; [4]Silesian University of Technology, Gliwice, Poland*

Background: Titanium (Ti) is a non-noble metal with known good tolerance in tissue. Pure titanium has not been used as a material for intravascular stents although TiO2–coated stents are being evaluated in humans. The aim of this study was to test hemocompatibility and cytotoxicity of pure titanium in comparison to stainless steel and to compare titanium stents (TTS) with stainless steel stents (STS) in animal model.
Methods: The erythrocytes' damage in contact with tested metals and from extracts was measured spectrophotometrically as plasma hemoglobin level. Measurements of prothrombin time (PT) and partial thromboplastin time (PTT) in citrated plasma incubated with tested samples were used to screen abnormalities in coagulation pathways caused by the metals. The cytotoxicity tests were done using the fibroblast cell lines cultured with extracts of metals. Flow cytometry was used to determine the vitality of cells. The self-made titanium (Ti=99,6+%) stents were compared with stainless steel (316L) stents of the same design in 10 hypercholesterolemic rabbits. Each animal received oversized STS and TTS to left and right iliac artery. After 4-5 weeks angiography and morphometry was performed.
Results: Percent of apoptotic and necrotic cells in culture with Ti extract was low as compared to control: 5,3 and 0,6 vs 3,6 and 2,1 respectively (NS) and did not differ significantly with culture with steel extract. PT and PTT were unaffected by Ti vs controls. PT: 15,52 vs 15,07s (NS), PTT: 33,2 vs 32,3s (NS). No significant differences were observed in comparison of Ti with steel samples. No differences in hemolysis was detected between controls and tested samples for both Ti and steel. A total of 10 rabbits received 10 TTS and 10 STS stents. The in-vivo results are shown in table (mean$\pm$SD).

Morphometry and quantitative angiography

	TTS	STS	p-value
Lumen area [mm^2]	3,04$\pm$0,88	2,05$\pm$1,12	0,05
Internal elastic membrane area [mm^2]	3,95$\pm$0,76	4,08$\pm$0,53	0,721
Minimal luminal diameter [mm]	2,08$\pm$0,22	1,52$\pm$0,66	0,036
Late lumen loss [mm]	0,63$\pm$0,23	1,25$\pm$0,65	0,007

Conclusions: Titanium shows comparable to stainless steel hemocompatibility and cytotoxicity.
Titanium stents are superior to stainles steel stents in rabbit model of neointimaal hyperplasia.

P2908 Thrombosis after drug eluting stent implantation: clinical and angiographic predictors

N. Garro[1], M. Catalano[1], A.R. Galassi[1], M.E. Di Salvo[1], F. Tagliareni[1], V. Cammalleri[1], A. La Manna[1], C. Tamburino[2]. *[1]Ferrarotto Hospital, Interventional Cardiology, Catania, Italy; [2]Ospedale Ferrarotto, Istituto di Cardiologia, Catania, Italy*

Purpose: The incidence of coronary stent thrombosis is $<$ 1% in recent studies, thanks to several technical and medical advancements. Recent evidence indicates that total stent length per vessel treated is an independent factor which correlates with intraproceural stent thrombosis.
Aim: Aim of this study was to evaluate the angiographic and clinical predictors of intraprocedural, sub-acute and late thombosis after Drug Eluting Stent (DES) implantation.
Methods: From May 2002 to June 2004, 1099 coronary lesions have been treated in 678 consecutive patients (pts) with Sirolimus or Paclitaxel eluting stents. Mean pt age was 62 $\pm$ 11 y, the ejection fraction was 54 $\pm$ 10%; 247 pts (36%) were diabetics, 411 (61%) had unstable angina and 104 (15%) had acute myocardial infarction. A total of 1804 DES were implanted (1.9 $\pm$ 1.2/pt) with a mean stented segment length of 36 + 25 mm and an implantation of multiple long overlapping DES ($>$ 60 mm) was performed in 42 pts (6%). GP IIb/IIIa inhibitors were administered in 106 pts (16%). All patients were treated with dual antiplatelet therapy.
Results: Acute stent thrombosis occurred in 2 pts (0.3%), sub-acute (1-30 days) thrombosis in 6 pts (1%) and late ($>$30 days) stent thrombosis in 2 (0.4%) pts. One of these patients was pretreated with GP IIb/IIIa inhibitors administration, 5 (50%) were current smokers, 6 diabetics (60%). Nine of these patients had unstable angina and 6 had an EF $<$ 40%. Nine patients had complex and long ($>$ 28 mm) lesions. Low EF% ($p < 0.0001$), total stent lenght (mm) (p 0.02) and number of stent per vessel treated (p 0.05) were all associated with stent thrombosis.
Conclusions: Implantation of Drug Eluting Stent is safe and is associated with a relative low risk of stent thrombosis.

P2909 Subacute stent thrombosis with drug-eluting stents while on dual antiplatelet therapy: clinical and procedural characteristics of 12 cases

P. Araujo Goncalves, R. Teles, M. Almeida, R. Henriques Gouveia, J. Aniceto Silva, F. Pereira Machado, R. Seabra-Gomes. *Hospital Santa Cruz, Cardiology dept., Carnaxide, Portugal*

Little information is available regarding subacute thrombosis of drug-eluting stents (SAT), mainly because of it's low reported incidence, both in clinical trials and in registries. Some concern has arise for cases occurring while on doubled antiplatelet therapy.
Aim: To evaluate the clinical and procedural characteristics of patients (pts) submitted to PCI with drug-eluting stents (DES) that had a subacute stent thrombosis while on double antiplatelet therapy.
Methods: We report 12 cases of angiographically-confirmed subacute stent thrombosis (>24h and < 30 days) in 10 pts submitted to PCI with DES and that did not interrupted dual antiplatelet therapy. Two pts had recurrent SAT (one pt in the same lesion and the other in a different vessel).
Results: Mean age was 65 $\pm$ 10 years and 6 were men. Five pts had diabetes (2 insulin-treated). 4 pts had renal impairment at the time of the procedure. 6 pts presented multivessel disease.In 9 of the 12 SAT cases, the indication for the previous PCI was an acute coronary syndrome and glycoprotein IIb/IIIa inhibitors were used in 7 cases. In 7 of the 12 SAT cases, the patients were on LMWH before the procedure. In 2 cases there were important bleeding complications at the time of the procedure with the need for red-cell and platelet transfusions.The vessel most frequently involved was the LAD (8 cases). The stents that thrombosed were sirolimus-eluting in 7 lesions, paclitaxel-eluting in 4 and in the remaining case, both types were used to treat the same lesion. In the 12 SAT lesions, 18 stents were initially implanted. Mean length per lesion was 31.6 $\pm$ 12.9 mm and mean diameter was 2.7 $\pm$ 0.2 mm. Stents were delivered at 13 $\pm$ 4 ATMs. Predilatation was performed in all but one case.Mean time to the SAT was 7.7 $\pm$ 5.3 days. The clinical presentation was an acute ST-elevation MI in all cases.In 3 of these pts, there were other DES implanted in a different vessel in the same initial procedure that remained patent when the DES occluded. One of these patients was submitted to heart transplantation and the histology examination showed an eosinophilic inflammation in the SAT lesion that was not present in the patent lesion that received a different DES.
Conclusion: The occurrence of subacute stent thrombosis under adequate therapy raises important questions that need further investigation, namely the potential individual resistance to antiplatelet agents.

CORONARY ARTERY REMODELLING

P2910 Evaluation of four-year coronary artery response after sirolimus-eluting stent implantation by using serial quantitative IVUS and computer assisted grey-scale value analysis for plaque composition

J. Aoki[1], A. Abizaid[2], N. Bruining[3], A. Ong[3], G. Rodriguez-Granillo[3], E. Sousa[2], P. Serruys[3]. [1]*Erasmus MC, Interventional cardiology, Rotterdam, Netherlands;* [2]*Institute Dante Pazzanese of Cardiolog, São Paulo, Brazil;* [3]*Erasmus MC, Interventional cardiology, Rotterdam, Netherlands*

Background: Sirolimus-eluting stents do not affect the plaque volume behind the stent struts at 6 months. No data at later time points have been reported.
Methods: Serial quantitative IVUS and computer assisted grey-scale value analysis for plaque composition over 4 years were obtained in 23 patients in the sirolimus-eluting stent-first in man (FIM) trial.
Results: During the first 2 years, the mean plaque behind the stent struts volume (155.5$\pm$42.8 mm^{3}at post procedure, and 156.8$\pm$57.7 mm^{3}at 2 years, p=0.86) and plaque compositional change expressed as mean percent (%) hypoechogenic tissue of the plaque behind the stent struts (78.9$\pm$8.6% at post procedure, and 78.2$\pm$8.9% at 2 years, p=0.67) did not significantly change. However, significant plaque shrinking (delta plaque volume 18.4 mm^3, p=0.02) with an increase in plaque echogenicity (delta % hypoechogenic tissue; -7.8%, p<0.0001) was observed between 2 years and 4 years. The mean neointimal volume increased over four years from 0 to 8.4$\pm$5.8 mm^3(p<0.0001). However no further statistically significant change occurred between 2 and 4 years. (7.0$\pm$6.7 mm^{3}vs. 8.4$\pm$5.8 mm^3; p=0.25).
Conclusion: Shrinking of plaque behind the stent struts associated with an increase in echogenicity was observed at four year follow-up. Concomitantly no significant further increase in neointima could be demonstrated between 2 and 4 years potentially suggesting the biological phenomenon of a delayed healing response has begun to subside.

P2911 Coronary artery remodelling is related to plaque composition

G.A. Rodriguez-Granillo, H.M. Garcia-Garcia, J. Aoki, M. Valgimigli, C.A.G. Van Mieghem, A.T.L. Ong, K. Tsuchida, P.W. Serruys. *Erasmus MC, Rotterdam, Netherlands*

Background: Arterial remodeling has been related to clinical presentation and positively remodeled plaques have previously shown typical features of plaque vulnerability.
Objective: To assess the potential relationship between plaque composition and vascular remodeling using spectral analysis of IVUS radiofrequency data.
Methods and Results: Forty-one coronary vessels with non-significant (<50% diameter stenosis by angiography), $\leq$ 20 mm, non-ostial lesions located in non-culprit vessels underwent IVUS interrogation. Spectral analysis of intravascular ultrasound radiofrequency data, obtained with a 30 MHz catheter, was performed with IVUS-Virtual HistologyTM software. Remodeling index (RI) was calculated and divided into 3 groups. Lesions with RI $\geq$ 1.05 were considered to have positive remodeling and lesions with RI $\leq$ 0.95 were considered to have negative remodeling. Lesions with RI $\geq$ 1.05 showed significantly larger lipid core than lesions with RI 0.96-104 and RI $\leq$ 0.95 respectively (22.1$\pm$6.3 vs 15.1$\pm$7.6 vs 6.6$\pm$6.9, p<0.0001). There was also a significant positive correlation between lipid core and RI (r=0.83, p=0.0001) and a statistically significant inverse correlation between fibrous tissue and RI (r=-0.45, p=0.003).
Thin-cap fibroatheroma (TCFA) and fibroatheromatous lesions comprised 100% of the positively remodeled lesions, whereas negatively remodeled lesions presented a more stable phenotype, with 64% of pathological intimal thickening, 29% of fibrocalcific and only 7% of fibroatheromatous lesions (p<0.0001)
Conclusions: The results of this study support the role of plaque composition in the mechanisms of vessel remodeling. Overall, these findings may provide an explanation of why most atherothrombotic events occur in non-significant lesions.

P2912 Statin influences coronary arterial remodelling after successful coronary artery stenting: an intravascular ultrasound study

M.H. Jeong[1], Y.J. Hong[2], H.W. Park[2], W. Kim[2], Y.K. Ahn[2], J.G. Cho[2], J.C. Park[2], J.C. Kang[2]. [1]*Chonnan National University Hospital, Chief of Cardiovascular Medicine, Gwang Ju, Korea, Republic of;* [2]*Chonnam National University Hospital, Cardiovascular Medicine, Gwangju, Korea, Republic of*

Background: Statins are effective lipid lowering agents, and imaging studies have demonstrated their ability to slow progression and promote regression of atherosclerosis. However, little data are available whether statin therapy influences the post-interventional coronary arterial remodeling in patients with coronary artery disease.
Objectives: We examined the effects of statin therapy on post-interventional coronary arterial remodeling and neointimal hyperplasia (NIH) after successful stent implantation in patients with coronary artery disease.
Methods: This study included 108 patients who underwent stent implantation for angiographically significant stenosis. Patients were divided into two groups according to statin therapy (statin group; n=62, 54.7$\pm$10.7 years, male 87.1%, non-statin group; n=46, 57.5$\pm$11.2 years, male 78.3%). All patients underwent angiographic and intravascular ultrasound (IVUS) follow-up at six months.
Results: There were no significant differences in clinical and angiographic results between both groups. At six-months follow-up, the restenosis rate was 22.6% in the statin group and 28.3% in non-statin group and repeat revascularization was performed in 21% in statin group and 23.9% in non-statin group (p=0.500, 0.716, respectively). At six-months follow-up, the external elastic membrane cross-sectional area (CSA) at lesion site was significantly larger in the statin group (14.9$\pm$3.7mm^2 vs. 13.7$\pm$3.2mm^2, p=0.050) and the remodeling index was significantly higher in the statin group than that in the non-statin group (1.06$\pm$0.15 vs. 0.90$\pm$0.17, p=0.015). At six-month follow-up, the NIH CSA in the target lesion was smaller in the statin group (2.0$\pm$1.4mm^2 vs. 2.6$\pm$1.8mm^2, p=0.072) and the lumen CSA was larger in the statin group (5.5$\pm$1.6mm^2 vs. 4.9$\pm$1.5mm^2, p=0.077), but, these did not statistically significant.
Conclusions: Statin therapy may induce positive remodeling of vascular segments containing atherosclerotic plaques and may show a trend to reduce NIH after stent implantation.

P2913 Coronary remodelling is the main contributor to lumen narrowing in diabetic patients

P. Jimenez Quevedo, M. Sabate, C. Corros, A. Suarez, F. Alfonso, E. Bernardo, C. Ramirez, R. Hernandez-Antolin. *Hospital Clinico San Carlos, Interventional Cardiology, Madrid, Spain*

Background: Accelerated atherosclerosis progression is a frequent phenomenon in diabetic patients and accounts for the majority of failures of coronary revascularization procedures.
Purpose: The aim of this study was to assess the pattern of coronary remodeling of non-treated segments of coronary arteries of diabetic patients.
Methods: Serial intravascular ultrasound (IVUS) analyses from patients enrolled in the DIABETES (DIABETes and drug Eluting Stent) I and II trials were included in the plaque progression/regression substudy. Quantitative volumetric analyses were performed from motorized pullbacks (constant speed of 0.5 mm/sec), which were carried out immediately after stent implantation and at 9-month angiographic follow-up. The coronary segment eligible for serial analysis had to be located at least 10 mm distal or proximal from the previously stented segment, and thus, not subject to balloon injury during the index procedure.
Results: Forty-five diabetic patients (48 coronary segments) were included in

the study. Mean age was 67±9 years, 67% were male and 25% were insulin-dependent. Left anterior descending (46%) and right coronary (35%) arteries were most often assessed by IVUS. The coronary segment subject for the analysis measured on average 12±3 mm. Overall, during the 9-month follow-up, vessel, plaque and lumen dimensions remained unchanged (vessel volume post vs. follow-up: 82±12 mm^3vs. 87±12 mm^3; plaque volume post vs. follow-up: 48±7 mm^3vs. 46±7 mm^3; lumen volume post vs. follow-up: 45±6 mm^3vs. 52±7 mm^3, all p=ns). However, two different patterns were defined on individual analysis: 1) negative remodeling (7 segments; 15%) where vessel volume was shrunk (-70±30 mm^3), plaque volume was reduced (-34±19 mm^3), and lumen volume also decreased (-37±20 mm^3); and 2) positive remodeling (41 segments; 85%) where vessel enlargement (+22±38 mm^3) accommodated plaque increase (+10±18 mm^3) resulting in increase in lumen dimensions (+13±24 mm^3).
Conclusion: In diabetic patients, lumen increase is the result of vessel enlargement in order to accommodate plaque progression. Conversely, negative remodeling appeared to be the main contributor to lumen narrowing during follow-up.

P2914 Coronary arteries retain their capacity for compensatory remodelling beyond cross-sectional area stenosis of 40%: a serial intravascular ultrasound study

I. Sipahi, P. Schoenhagen, S.J. Nicholls, V. Ozduran, S. Kapadia, S.E. Nissen, E.M. Tuzcu. *Cleveland Clinic Foundation, Department of Cardiovascular Medicine, Cleveland, United States of America*

Introduction: Based on evidence from cross-sectional histological and imaging studies it is generally accepted that remodeling of coronary arteries is an early phenomenon during progression of atherosclerosis. These studies demonstrated that the capacity for compensatory remodeling diminishes after cross-sectional area stenosis reaches 40%.
Aim: Our aim was to validate this finding using serial coronary intravascular ultrasound (IVUS).
Methods: From the cohort of the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial, we identified 210 focal coronary lesions (single lesion per patient) at the baseline IVUS interrogations. Of these, 128 lesions that had an increase in atheroma area at the 18-month follow-up IVUS were included in this analysis. Automatic pullback and fiduciary branches were used to match the lesion site at follow-up. Atheroma area was calculated as external elastic membrane (EEM) area-lumen area and cross-sectional area stenosis as 100% x atheroma area/EEM area.
Results: Atheroma (7.2±2.6 vs. 8.8±3.2 mm^2), EEM (15.2±5.2 vs. 17.7±6.1 mm^2) and lumen areas (8.0±3.5 vs. 8.8±3.9 mm^2) increased at follow-up ($p<0.001$ for all). Median change in EEM area/change in atheroma area was 1.50 which was indicative of over-compensatory remodeling. The increase in lumen area despite an increased atheroma area was evident in lesions with both ≤40%and >40% cross-sectional area stenosis at baseline (p=0.59 for interaction). We found no correlation between cross-sectional area stenosis at baseline and change in lumen area (Fig. 1).

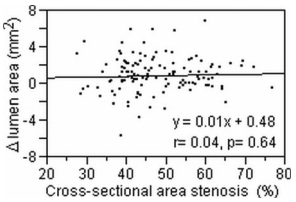


Figure 1

Conclusion: Assessment of arterial remodeling using serial IVUS revealed that compensatory (or over-compensatory) remodeling does not diminish after 40% cross-sectional area stenosis is reached.

P2915 Morphological differences between ostial, body, and distal anastomosis lesions in saphenous vein bypass grafts; an intravascular ultrasound study

K. Sano, S.G. Carlier, G.S. Mintz, K. Fujii, M. Kimura, J.R. Costa Jr, M.B. Leon, J.W. Moses. *Cardiovascular Research Foundation, Intravascular Imaging & Physiology, New York, United States of America*

Previous studies have reported that percutaneous interventions (PCI) of ostial saphenous vein graft (SVG) lesions are less likely to cause CK-MB elevation or slow or no-reflow phenomenon. However, little is known about morphological differences between lesions at different SVG locations.
Methods: We evaluated 66 de novo SVG lesions in 54 patients located at ostial (n=15), body (n=47), and distal anastomosis (n=4) by intravascular ultrasound (IVUS). SVG area (outer border of whole SVG), lumen area, wall area (SVG minus lumen area), and plaque burden (wall area divided by SVG area) were measured at the minimal lumen area (MLA) and at proximal and distal references. Remodeling index (RI) was calculated as lesion SVG area divided by average reference SVG area.
Results (see Table): The RI of body lesions was significantly greater than ostial and distal anastomosis lesion groups (1.16±0.32 vs 0.86±0.26 and 0.81±0.37; ANOVA p=0.002). Positive remodeling (RI>1.1) in ostial, body, and distal anastomosis lesions was 13.3%, 59.6%, and 25% (Chi^2 p=0.005) while negative remodeling (RI<0.9) was observed in 66.7%, 21.3%, and 75.0% (p=0.001), respectively. Plaque burden of body lesions was significantly greater than ostial and distal anastomosis lesions (0.79±0.10 vs 0.72±0.09 and 0.70±0.10; p=0.03). Importantly, when body lesions were compared to anastamotic lesions, plaques were more often soft (59.6% vs. 31.6%, p=0.04) with more ruptured plaques and the patients had more hyperlipidemia (85.1% vs. 52.6%, p=0.005) and diabetes mellitus (40.4% vs. 15.8%, p=0.07).

Table

	Ostial (n=15)	Body (n=47)	Distal anastomosis (n=4)	p
Lesion lumen area (mm^2)	4.3	4.6	6.6	0.38
Lesion SVG area (mm^2)	17.4	23.7	23.5	0.16
Lesion plaque burden (%)	72.1	78.9	70.0	0.03
Ruptured plaque (%)	13.3	31.9	0.0	0.17
Reference lumen area (mm^2)	9.3	9.3	15.0	0.01
Reference SVG area (mm^2)	20.2	20.2	30.0	0.06

Conclusion: SVG body lesions undergo positive remodeling more frequently and have larger plaque burden than lesions at the ostium and distal anastomosis. These differences might account for the different outcome after SVG PCI.

P2916 Two-year peri-stent remodelling and neointimal growth after polymer-based paclitaxel eluting stents implantation in event free patients of the TAXUS II study

J. Aoki[1], P. Serruys[2], D. Dudek[3], A. Banning[4], J. Drzewiecki[5], M. Russell[6], J. Koglin[6], A. Colombo[7] on behalf of the TAXUS II study Group. *[1]Erasmus MC, Interventional cardiology, Rotterdam, Netherlands; [2]Erasmus MC, Interventional cardiology, Rotterdam, Netherlands; [3]Jagiellonian university, Krakow, Poland; [4]John Radcliffe Hospital, Oxford, United Kingdom; [5]PSK No7 Zaklad Kardiologii, Katowive, Poland; [6]Boston Scientific Corporation, Natick Mass, United States of America; [7]Centro Cuore Colombus, Milano, Italy*

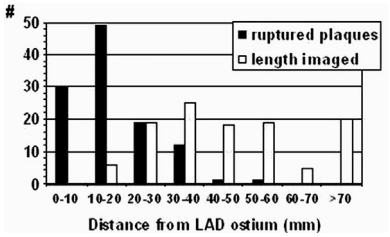
Background: While the antirestenotic effect of polymer-based paclitaxel eluting TAXUS stents are well established, long-term vascular responses inside and outside the stent beyond six months have not been evaluated yet.
Methods: TAXUS II was a randomized, double blind trial with 2 consecutive patient cohorts comparing slow-release (SR) and moderate–release (MR) with the bare metal stents (BMS) group. 161 event free patients (SR: 43, MR: 41, BMS: 77) underwent serial IVUS (post procedure, 6 months, and 2 years) analysis.
Results: At 2 years, neointimal growth inside the stent continued to be significantly suppressed in the SR and MR group, when compared to the BMS group [BMS;1.49±1.12 mm^2, SR; 0.94±0.76 mm^2 (p=0.004), MR;1.06±0.90 mm^2 (P=0.02)]. Between 6 months and 2 years, the BMS control showed a compaction of neotintima resulting in a significant decrease in mean neointimal area [delta = BMS; -0.22±1.05 mm^2 (p=0.08)]. In contrast, both the SR and MR group exhibited a slight but significant increase [delta = SR; 0.30±0.76 mm^2 (p=0.01), MR; 0.41±0.94 mm^2 (p=0.009)]. At the same time, the area outside the stent regressed in the BMS and SR groups to levels comparable to post procedure, whereas expansive remodeling only partially regressed in the MR group over the same period of time [delta(between post procedure and 2 years) = BMS; -0.34± 1.28 mm^2 (p=0.05), SR; -0.02±1.40 mm^2 (p=0.93), MR; 0.32±1.56 mm^2 (P=0.27)].
Conclusions: At 6 month, antirestenotic effects of TAXUS coincided with an increase in the area outside of the setnt. The 2-year follow-up demonstrates, that this transient increase regresses over time in both SR and MR TAXUS groups. Further follow-up is needed to assess if a similar kinetic is also present in the compaction of neointimal area inside the stent only observed in BMS at this point of time.

P2917 Spatial distribution of ruptured coronary plaques in left anterior descending artery. An intravascular ultrasound guide to detection and prevention

J. Pregowski[1], P. Tyczynski[2], G.S. Mintz[3], A. Witkowski[2], R. Waksman[4], A. Pichard[4], L. Kalinczuk[2], N. Weissman[4]. *[1]National Institute of Cardiology, Hemodynamics Department, Warsaw, Poland; [2]National Institute of Cardiology, Hemodynamics Department, Warsaw, Poland; [3]Cardiovascular Research Foundation, New York, NY, United States of America; [4]Washington Hospital Center, IVUS Core Lab, Washington, DC, United States of America*

Rupture plaque is a substrate for thrombosis, occlusion, and myocardial infarction (MI). The left anterior descending (LAD) artery subtends the largest amount of myocardium; therefore, the location of LAD plaque rupture is of particular importance in detecting vulnerable plaques and preventing MIs.
Methods: using intravascular ultrasound (IVUS)we found 160 ruptured LAD plaques. Of these, 112 ruptured plaque containing LADs had consistent automatic transducer pullback (0.5mm/s) back to the LAD ostium allowing accurated distance measurements. A ruptured plaque contained a cavity communicating

with the lumen with a residual fragment of fibrous cap. The distance between the maximal plaque cavity and the LAD ostium as well as the whole length of LAD imaged were calculated from the transducer pullback speed and duration of the pullback (mm/s x # of seconds).
Results: there were 94 males, mean age 63.8±11.7yrs. The total length of LAD imaged was 48.8±24.8mm. The frequency distribution of the location of the ruptured plaque (vs the distance from the ostium) and the length of LAD imaged is shown in the figure. The mean distance from the LAD origin to the maximal plaque cavity was 16.2±10.3mm; the maximal plaque cavity was localized to the first 20mm of the LAD in 71% and the first 30mm in 88%. Only 2 ruptured plaques were found beyond 40mm of the ostium.



Conclusion: most ruptured plaques in the LAD are located within the proximal 20mm of the LAD; and almost 90% are located within the proximal 30mm. This area of the LAD should be targeted for vulnerable (rupture-prone) plaque detection and prevention.

P2918 Influence of atherosclerotic plaque growing pattern on coronary artery remodelling-plaque angle as index of coronary artery remodelling

V. Vukcevic[1], M. Vavuranakis[2], K. Toutouzas[2], V. Spanos[2], P. Mitrovic[1], C. Stefanadis[2], M. Ostojic[1]. *[1]Clinical Center of Serbia, Institute for Cardiovascular Diseases, Belgrade, Serbia and Montenegro; [2]University of Athens, Hippokration Hospital, Athens, Greece*

Coronary artery remodeling is an important factor in the development of coronary artery (CA) stenosis. However, the exact mechanisms of atherosclerotic CA remodeling is not known.
Aim: to analyse whether coronary atherosclerothic plaques with more circumferential growth pattern may provoke a different type of CA remodeling compared with those with more focal growth form.
Methods: in 32 lesions (ls) total vessel cross sectional area (CSA), lumen CSA and maximal plaque + media thickness (PMT) was measured by intracoronary ultrasound. According to remodeling index (Ri), calculated as lesions/proximal vessel CSA, all lesions were classified into the three groups: (1) positive remodeling (Ri $\geq$ 1.05); (2) no remodeling (Ri = 0.96-1.04); and (3) negative remodeling (Ri $\leq$0.95). The extent of radial plaque growth were defined by maximal PMT, and the extent of circumferential plaque growth by the angle (plaque angle, PA) which the theoretical central point of lumen area (TCP) enclosed with the edges of the plaques. The TCP was determinate using the commercially available software, and plaque edges as the point were PMT were $\leq$0.5mm. We also used the plaque intrusion index (PIi), defined as the product of PA and maximal PMT.
Results: there were 13/32 ls (40.6%) with positive, 13/32 ls (40.6%) with negative and 6/32 ls (18.7%) with no remodeling. There were no significant differences in clinical and angiographic characteristics between patients with positive vs. negative remodeling. Ls with positive remodeling had greater PA and PIi compared with ls with negative remodeling (315.20±30.6° vs. 222.08±27.8°; p<0.0001, and 477.06±102.3 vs. 328.95±65.6; p<0.001 respectivelyrespectively). The value of Ri correlated well with PA (r=0.73, p=0.000005) and PIi (r=0.61, p=0.0003), but not with maximal PMT (r=0.028, p=0.88). By multiple regression analysis, both PA and PIi were independent predictors of Ri.
Conclusion: plaque angle and plaque intrusion index appeared as important determinants of vessel remodeling. Patients with more circumferential plaque have more frequently possitive coronary artery remodeling compared to patients with predominantly radial plaque growth pattern.

P2919 Comparison of clinical, angiographic, and intravascular ultrasound findings in saphenous vein graft and native coronary arteries plaque rupture

P. Tyczynski[1], J. Pregowski[2], G.S. Mintz[3], L. Kalinczuk[1], R. Waksman[4], A. Witkowski[1], A. Pichard[4], N. Weissman[4].
[1]National Institute of Cardiology, Hemodynamics Department, Warsaw, Poland; [2]National Institute of Cardiology, Hemodynamics Department, Warsaw, Poland; [3]Cardiovascular Research Foundation, New York, NY, United States of America; [4]Washington Hospital Center, IVUS Core Lab, Washington, DC, United States of America

Native coronary artery plaque rupture (PR) was described with intravascular ultrasounds (IVUS), but there are no similar reports in saphenous vein grafts (SVGs). We compared the clinical, angiographic, and IVUS findings in SVG vs native artery PR.

We identified 94 PRs in 76 SVGs IVUS images and compared them with the reference-lumen-area-matched native PRs (n=468). IVUS measurements were performed at the sites of the maximal plaque cavity (MPC), minimal lumen area (MLA), and distal and proximal references. Remodeling index (RI) was defined as ratio of vessel area at MPC site and mean reference. Angiographic analyses included presence of ulceration, intimal flap, aneurysm and filling defect at IVUS PR site;complex lesions contained at least one of these findings.
Clinical presentation in SVG vs native artery PR was similar (recent MI 27% vs 25%, unstable angina 42% vs 54%, stable 30% vs 21%, p=0.3), although SVG patients were older and more often hypertensive and hypercholesterolemic. Lesions in both SVGs and native arteries were angiographically complex (95% vs 94%. Rupture length and cavity area; positive remodeling; presence, location, and magnitude of calcification; and eccentricity were similar in the two groups.

	SVG	Native Artery	p
Patient age (yrs)	68.2±10.3	63.8±10.4	0.012
Hypertension	78%	61%	0.031
Hypercholesterolemia	91%	71%	0.004
Diabetes	35%	28%	0.4
Eccentric (>3)	76%	66%	0.2
Calcium at lesion site	59%	59%	1.0
Rupture length (mm)	3.6±2.1	3.6±2.2	0.8
Cavity area (mm^2)	2.9±1.9	2.9±1.9	1.0
RI	1.18±0.30	1.11±0.21	0.09
Positive remodeling	70%	75%	0.625

Although patients with SVG plaque ruptures are older with more comorbidities, the clinical presentation and angiographic and IVUS features are remarkably similar to native artery plaque rupture. This suggests that the mechanisms of plaque ruptures in native arteries and SVGs may also be similar.

P2920 Coronary calcium and matrix metalloproteinases. Volumetric intravascular ultrasound study

M. Kruk. *National Institute of Cardiology, Warsaw, Poland*

Background: Quantity of coronary calcium is associated with clinical course of atherosclerosis. However the pathomechanisms leading to the association remain less clear.
Some matrix metalloproteinases (MMPs) were shown to influence vulnerability of coronary plaques.
Therefore we correlated the quantity of coronary calcium and plaque burden as assessed by means of intravascular ultrasound (IVUS) and plasma levels of MMPs and tissue inhibitors of MMPs (TIMPs) in stable angina patients.
Methods: In 31 patients (mean age 58.2±10.1, 25 men) 94 segments within 51 major arteries not subjected to prior intervention were assessed by IVUS. Vessel and lumen area as well as coronary calcium arc were measured at 1-mm increments in 2283 coronary artery slices. Mean plaque burden (vessel area – lumen area) and mean coronary arch of calcium for each segment was then calculated. Plasma levels of MMP -2, -3, -7, -9, and TIMP –1 and –2 were measured in all patients prior to the procedure.
Results: Coronary calcium correlated with plaque burden (R=0.4,P<0.0001). Moreover there was a significant correlation between coronary calcium and TIMP-2, MMP-2, MMP-3, and MMP-9 (R=0.4, P<0.0001; R=0.3,P<0.01; R=0.3,P=0.01; R=0.2,P=0.03 respectively). Whereas plaque burden significantly correlated with TIMP-1 and MMP-9 (R=0.3,P<0.01; R=0.3,P<0.01 respectively).
Conclusion: Quantity of calcium within coronary artery wall correlates with plasma levels of enzymes contributing to plaque vulnerability.

P2921 Intravascular ultrasound findings of the RIBS II (Restenosis Intra-stent: Balloon angioplasty versus rapamycin-eluting Stenting) randomised study

F. Alfonso Manterola[1], A. Suarez[2], M.J. Perez-Vizcayno[2], A. Bethencourt[3], M. Sabate[2], J. Escaned[2], R. Hernandez[2] on behalf of The RIBS II Investigators. *[1]Madrid, Spain; [2]Hospital Clinico San Carlos, Interventional Cardiology, Madrid, Spain; [3]H Son Dureta, Cardiology, Palma de Mallorca, Spain*

Purpose: treatment of patients (P) with in-stent restenosis (ISR) remains a challenge. Drug-eluting stents (DES) are considered an attractive strategy for these P.
Methods: the RIBS II (Restenosis Intra-stent: Balloon angioplasty [BA] vs elective rapamycin-eluting Stenting) is a multicenter, randomised study designed to determine the efficacy of DES in P with ISR. From February 2003 to April 2004, 150 P with ISR were enrolled (74 allocated to BA and 76 to DES). Of these, 113 were included in a pre-defined intravascular ultrasound (IVUS) sub-study. IVUS studies (40 MHz, motorised pullback 0.5 mm/s) were systematically obtained after intracoronary nitroglycerin, before the procedure, after intervention and at 9-month follow-up (FU). Good quality IVUS images (including pre, post and FU) were available for quantitative analysis in 79 P (41 DES arm and 38 BA arm). Two pre-specified IVUS analyses were performed: the "in-segment" analysis (SEG) (lesion + treated segment + 5 mm edges) and the "in-stent" analysis (ST). Lumen (L) and neointima (NI) were measured using a validated volumetric reconstruction system (Tomtec).

Result: baseline clinical and angiographic characteristics were similar in the two arms. In the ST analysis, NI volume before intervention was similar (112±32 vs 111±30 mm^3, NS) in the two groups. However, after the procedure (7±4 vs 56±40 mm^3, $p<0.001$) and at FU (17±25 vs 90±48 mm^3, $p<0.001$) NI volume was markedly reduced in the DES group. In addition, after intervention L was larger in the DES group (215±30 vs 163±42 mm^3, $p<0.001$) and this difference was maintained at late FU (203±42 vs 120±48 mm^3, $p<0.001$). The SEG analysis showed similar results, with larger L at FU (278±71 vs 199±63 mm^3, $p<0.001$) in the DES group. Furthermore, L volume at the 5-mm edges were similar in both groups (edge L volume at FU 55±32 DES vs 61±26 mm^3 BA, NS).
Conclusion: this IVUS sub-study of the RIBS II randomised trial confirms the efficacy of DES in P with ISR. At late FU, DES provides a significantly larger lumen and a marked reduction in the extent of NI proliferation as compared with BA, without the appearance of edge-effects.

P2922 Intravascular ultrasound in the severity assessment of main stem stenosis

D.H. Koschyk, T. Heitzer, S. Willems, T. Hofmann, A. Schuchert, J. Kaehler, T. Meinertz. *University Hamburg, Heart Center, Hamburg, Germany*

Background: Angiographic evaluation of main stem stenosis is sometimes difficult, but has great impact for the decision between conservative, interventional or operative treatment. Intravascular ultrasound (IVUS) has proven the ability to accurately assess not only lumen and plaque morphology, but also stenosis severity assessment. We directly compared ANGIO and IVUS in the decision making how to treat patients with suggested main stem stenosis.
Methods: We performed IVUS in 52 consecutive patients (pt.) (37 m, 15 f., 60 ± 12 y.) with unclear severity of main stem stenosis by angiography and evidence of ischemia. In all patients the therapeutic decision was dependent on the diagnosis of significant main stem stenosis (>50% diameter stenosis).
Results: Thirty-nine pts. had multivessel coronary artery disease, 13 pts. a single main stem lesion. 83% of lesions were of eccentric mixed plaque either at the proximal or distal part. Calcification was found in 9 lesions only (arch of calcification < 60%). 33 pts. with a main stem diameter stenosis > 50% by ANGIO were selected for further treatment (bypass surgery, coronary intervention), 19 pt. with a diameter stenosis < 50% were selected to have no intervention. IVUS confirmed the ANGIO grade of stenosis in 24/33 pt. only. In 16 pt. the IVUS grade of stenosis was significantly higher or lower (< or > 50% diameter stenosis) compared to ANGIO and the initial therapeutic decision was changed. In the remaining 12 pt. the IVUS grade of stenosis was higher (up to 20%) compared to ANGIO, but within the initially planned treatment group. Based on IVUS, 28 pt. went to bypass surgery, 7 pt. with a single main stem lesion were successful dilated and stented; in the remaining 17 pt. no intervention was performed.
Conclusion: In patients with main stem stenosis, IVUS is a helpful tool either to verify or negate the finding of coronary angiography and to select patients for either bypass surgery/coronary intervention or conservative treatment.

P2923 Coronary angiography with flat-panel digital detectors increases significantly the sensitivity for calcium detection in relation to conventional fluoroscopy. A study with IVUS

J.M. De La Torre Hernandez[1], F. Sainz-Laso[2], C. Ruisanchez[2], M. Cobo[2], A. Figueroa[2], J. Zueco[2], T. Colman[2]. *[1]Santander, Spain; [2]Marques de Valdecilla, Interventional cardiology, Santander, Spain*

Purpose: Coronary calcification represents advanced atherosclerotic disease and also has implications during percutaneous coronary interventions. Angiography has been reported to yield low sensitivity for calcium detection compared with intravascular ultrasound (IVUS). We have compared the sensitivity and specificity for coronary calcium detection of two fluoroscopic equipments, one the conventional based on intensifier chains (CONV) and the other with flat-panel digital detector (FPDD).
Methods: Target lesion calcification was assessed in patients undergoing angiography by two different fluoroscopic equipments (FPDD Innova 2000 TM GE Medical Systems and CONV Advantx TM DLX 3-GE Medical Systems) and by intravascular ultrasound.
Results: In two consecutive periods (January 2002-January 2003 and February 2003-March 2004) a total of 200 consecutive patients were included, 100 in each group. Clinical characteristics were similar without significant differences between groups. In CONV group IVUS detected calcium in a 77% of cases and angiography in a 32%. Sensitivity was 41.6% and specificity 91.3%. In FPDD group IVUS reported calcification in a 79% of patients and angiography in a 57%. Sensitivity was 72% ($p<0.0001$ for comparison with CONV) and specificity was 90.4%. The higher sensitivity yielded by FPDD was significant for mild and moderate cases of calcification. In 20 randomized patients of each group the median radiation dose/area for Innova in the diagnostic angiography was 51.6 Gy/cm^2 (intercuartile range 23- 67) and for Advantx was 76 Gy/cm^2 (intercuartile range 37-107 Gy/cm^2) (p=0.03).
Conclusions: The new fluoroscopic systems based on flat-panel digital detectors increase considerably the sensitivity for calcium detection without detrimental effect on specificity. This advantage is important because may have a beneficial impact on the diagnosis and therapeutic management of patients with coronary disease.

P2924 Intravascular ultrasound assessment of the temporal effect of antiatherosclerotic therapies in coronary plaque volume. Insights from a systematic review and meta-analysis of controlled clinical trials

G.A. Rodriguez-Granillo[1], P. Agostoni[2], H.M. Garcia-Garcia[1], G.G. Biondi-Zoccai[2], E. Mc Fadden[1], N. Bruining[1], P. de Feyter[1], P.W. Serruys[1]. *[1]Erasmus MC, Rotterdam, Netherlands; [2]St. Raffaele Hospital, Interventional Cardiology Unit, Milan, Italy*

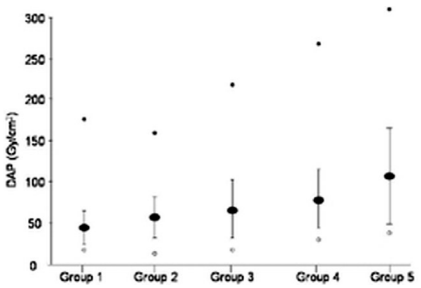
Purpose: A marked discordance is present between the clinical effects of validated medical therapies and their effects on atherosclerotic plaque volume. We performed a systematic review of all randomized controlled studies that used intravascular ultrasound to assess the temporal effect of medical therapies on coronary atherosclerotic plaque volume.
Methods: We searched PubMed for eligible studies published between 1990 and November 2004. Search key words included: "(reduc* OR regres* OR progress*) AND (ivus OR intravascular ultrasound)", where * denotes a wildcard. PubMed was searched using the method described by Biondi-Zoccai. No language restriction was used. Inclusion criteria for retrieved studies were: 1) randomized studies comparing different therapies to reduce atherosclerotic burden, 2) intravascular ultrasound (IVUS) volume analysis at baseline and follow-up. Exclusion criteria were: 1) analysis limited to cross-sectional area, 2) studies in vessels different from coronary arteries. Two investigators extracted the data independently. Data were compared using random-effect weighted and standardized mean differences. Data of interest were abstracted in pre-specified structured collection forms and reviewed twice by two of the authors.
Results: Six studies (1402 patients) were selected. At a median follow-up of 18 months (interquartile range 9-24), there were no significant differences in the change in atherosclerotic plaque volume [SMD -0.23 (95%CI -0.47–0.01, p= 0.06)]. At stratified analysis, plaque progression was significantly reduced by statin therapy [WMD -9.06 mm^3 (95%CI -14.03–-4.08, p= 0.0004)].
Conclusions: The use of statins significantly reduced plaque progression. Conversely, the overall temporal effect of other medical therapies on atherosclerotic plaque burden was not significant. Whether the discordance between the clinical effects of such therapies and their effects on plaque volume is due to a significant change in plaque composition or to deficiencies in the methodology of current IVUS studies remains unknown.

NEW TECHNIQUES OF ANGIOGRAPHIC MEASUREMENT AND VASOMOTION

P2925 Radiation dose exposure during cardiac catheterisation

A. Cioppa[1], V. Picano[1], G. Ambrosini[1], D. Kocynai[1], M.G. Andreassi[2], G. Mottola[1], P. Rubino[1], E. Picano[3]. *[1]Casa di Cura "Montevergine", Mercogliano, Italy; [2]Institute of Clinical Physiology, CNR, Pisa, Italy; [3]CNR Institute of Clinical Physiology, Pisa, Italy*

Background: Ionising radiation carries an oncogenic risk which is linearly related to the dose. An estimation of the effective dose can be obtained from the measurements of the dose-area product (DAP), which is a measure of stochastic risk and a potential quality indicator in the cath-lab (ACC/AHA Clinical Competence Statement, Circulation 2005).
Aim: To assess radiation exposure of patients in a large volume cardiac cath-lab.
Methods: A retrospective analysis of adult cardiac procedures (April to December 2004) has been carried out in order to determine the DAP and estimated risk of malignancy. We identified 5 groups: Group 1 (n=100, coronary angiography and ventriculography); Group 2 (n=50, carotid stenting); Group 3 (n=50, aortography + coronary angiography + ventriculography); Group 4 (n=100, coronary angiography + ventriculography + direct coronary stenting); Group 5 (n=100, coronary angiography + ventriculography + coronary pre-dilation and stenting). Dose-area product meter attached on the X-ray unit (Philips Polydiagnost C2 image intensifier system) has been used for the estimation of the radiation dose received by the patient.



Results: For each group, mean and standard deviation, lowest (empty dot)and highest (black dot) values are shown in the figure. Within each group, individual radiation exposure varies substantially. Average exposure in a Group 5 patient corresponds to a risk of mortality from a malignancy of about 0.5%.
Conclusion: the radiation dose varies substantially across different types of procedures and up to tenfold within the same procedure. The enhanced awareness of radiation dose might help the cardiologist to implement radiation sparing procedures eventually minimizing patient and operator radiation hazards in invasive cardiology.

P2926 Prevalence and effect of coronary stenosis vasomotion after haemodynamic provocation

M. Siebes[1], B. Verhoeff[2], M. Meuwissen[2], R.J. de Winter[2], J.A.E. Spaan[3], J.J. Piek[2]. *[1]Academic Medical Center, Medical Physics, Amsterdam, Netherlands; [2]Academic Medical Center, Cardiology, Amsterdam, Netherlands; [3]Academic Medical Center, Medical Physics, Amsterdam, Netherlands*

Background: Pathological studies have shown that most coronary artery stenoses are eccentric and partially compliant. Dynamic changes in stenosis severity are rarely considered when assessing the accuracy of diagnostic parameters of stenosis hemodynamics. Pressure gradient-flow relationships provide a way to assess the dynamic behavior of coronary artery stenoses.
Methods: We evaluated the dynamic behavior of coronary artery stenoses in18 patients before and after hemodynamic provocation by an increase in heart rate (120 bpm, pacing) and aortic pressure (+30 mmHg, iv phenylephrine) without and with pacing at sinus heart rate. Aortic pressure (Pa), and distal coronary pressure (Pd) and flow velocity (v) were measured simultaneously using a dual-sensor guide wire. Pressure drop-velocity (dP-v) relationships were constructed throughout the hyperemic response to i.c. adenosine to assess changes in the hemodynamics behavior of individual lesions. Dynamic behavior was classified based on the coefficient of variation of the pressure drop at a nominal flow velocity for all hemodynamic conditions. Standard diagnostic parameters such as coronary and fractional flow reserve (CVR=hyp v/ baseline v, FFR=hyp Pd/hyp Pa), and stenosis and microvascular resistance at maximal hyperemia (HSR=dP/v, HMR=Pd/v) were assessed.
Results: Elevated Pa resulted in a higher hyperemic flow velocity and pressure gradient (both $p< 0.05$), while pacing caused mainly an increase in baseline flow ($p<0.05$). Only 44% (8/18) of the lesions could be classified as stable (no change in dP-v relationship). The majority of lesions (10/18, 55%) responded to external hemodynamic provocation by dynamic changes in stenosis severity as demonstrated by altered dP-v relationships. Two of these lesions displayed dynamic behavior indicative of passive collapse at control, which was exacerbated by elevated Pa and alleviated by pacing. HSR and HMR generally changed concomitantly, while FFR and CVR changed in opposite directions. However, diagnostic parameters were not always congruent with the hemodynamic severity as demonstrated by the dP-v relationship, due to the combined influence of both dynamic changes in stenosis severity and changes in flow and pressure.
Conclusion: The majority of coronary artery stenoses is not fixed and changes hemodynamic severity with altered hemodynamic conditions. Dynamic stenosis behavior represents a source of variability and uncertainty in the accuracy of diagnostic parameters. The dynamic behavior can be assessed with dP-v relationships and may identify lesions prone to vulnerability.

P2927 Effects of intravenous infusion of vitamin C on L-arginine-induced dilation in epicardial coronary arteries in patients with coronary artery disease

D. Tousoulis[1], C. Xenakis[2], C. Tentolouris[2], C. Antoniades[2], A. Trikas[2], C. Tsioufis[2], C. Pitsavos[2], C. Stefanadis[2]. *[1]Athens, Greece; [2]Athens University Medical School, Cardiology Department, Athens, Greece*

Increased oxidative stress has been implicated as a potential mechanism for abnormal endothelial vasomotor function. Vitamin C is the main water soluble antioxidant in human plasma and L-arginine is the substrate for nitric oxide synthesis.
Aim: We assessed the effects of intravenous vitamin C administration on the vasomotor responses of intracoronary infusion of L-arginine in epicardial coronary arteries.
Methods: Twenty eight patients with coronary artery disease (CAD) and stable angina enrolled in the study. Eight patients received 150 mmol/min L-arginine intracoronary before and after intravenous infusion of vitamin C, 10 patients received 150 ìmol/min L-arginine intracoronary before and after intravenous infusion of normal saline, and 10 patients received intracoronary normal saline before and after intravenous infusion of vitamin C. The diameter of proximal and distal coronary artery segments was measured by quantitative angiography.
Results: Infusion of L-arginine caused significant dilation of both proximal ($4.87\pm0.96\%$, $p<0.01$ vs. NS) and distal ($6.33\pm1.38\%$, $p<0.01$ vs. NS) coronary segments. Co-infusion of vitamin C and L-arginine dilated proximal coronary segments by $8.68\pm1.40\%$, ($p<0.01$ vs. NS, $p<0.01$ vs. L-arginine), and distal segments by $13.07\pm2.15\%$, ($p<0.01$ vs. NS, $p<0.01$ vs. L-arginine). Intravenous infusion of vitamin C caused borderline increase in proximal and distal coronary segments diameter ($1.93\pm0.76\%$, and $2.09 \pm1.28\%$, respectively).
Conclusions: Our results show augmentation of the L-arginine dependent coronary segment vasodilation by the antioxidant vitamin C in patients with coronary artery disease. Thus, vitamin C may have beneficial effects on NO bioavailability induced by L-arginine.

P2928 Effect of homocysteine lowering therapy on coronary endothelial function in patients with stable coronary artery disease. A substudy of the Western Norway B-vitamin Intervention Trial (WENBIT)

O. Bleie[1], E. Strand[2], P.M. Ueland[3], H. Refsum[4], S.E. Vollset[3], J.E. Nordrehaug[5], O. Nygard[5]. *[1]University of Bergen, Institute of Medicine, Bergen, Norway; [2]Haukeland University Hospital, Heart disease, Bergen, Norway; [3]University of Bergen, Locus of Homocysteine, Bergen, Norway; [4]University of Bergen, Dept of Pharmacology, Bergen, Norway; [5]Institute of Medicine, University of Bergen, Bergen, Norway*

Purpose: Endothelial dysfunction is an early marker of arteriosclerosis. Total homocysteine (tHcy) is established as an independent risk factor for occlusive vascular disease and tHcy is also associated with endothelial dysfunction. We tested the effects of tHcy lowering therapy used in the Western Norway B-Vitamin Intervention Trial (WENBIT) on coronary endothelial function in patients with established coronary artery disease (CAD).
Methods: Forty patients undergoing elective PCI for significant CAD, were randomly assigned to daily oral treatment by a combination of 0.8 mg folic acid and 0.4 mg vitamin B-12 or placebo, and 40 mg vitamin B-6 or placebo, in a 2x2 factorial design. All patients received standard medical treatment, including statins for at least 2 months prior to inclusion. At baseline and after 9 months of treatment, coronary endothelial function was assessed by coronary angiography and doppler flow-wire during incremental (0.72 μg/min, 7.2 μg/min and 36.0 μg/min) intracoronary doses of acetylcholine.
Results: The median age of the 32 male and 8 female patients was 57 years. At baseline, we found median values of tHcy 10.4 μmol/L, creatinine 87 μmol/L, cholesterol 4.5 mmol/L and CRP 1.6 mg/L. Maximum flow achieved by acethylcholine correlated significantly to CRP ($r=0.32$, $p=0.047$), but no significant correlations were found between intacoronary flow parameters and tHcy, plasma folate or vitamin B-6. In a multiple linear regression model including age, tHcy, creatinine, total cholesterol, CRP, folate and vitamin B-6 as predictors of maximum flow, CRP was even stronger related (beta=0.39, $p=0.015$). This relation was attenuated after 9 months (beta=0.09, $p=0.6$). Treatment with folic acid and vitamin B-12 or vitamin B-6 did not influence change in coronary artery diameter, increase in average peak blood velocity (APV) or maximum flow achieved by intracoronary acethylcholine infusion.
Conclusion: In this randomised study among patients with established CAD, neither folic acid/B-12 nor vitamin B-6, given in addition to standard medical treatment, had any effect on endothelial mediated coronary tonus or flow. Inflammation is related to endothelial function, but this relation may be attenuated by continued medical therapy.

P2929 Relationship between mental stress, endothelium-dependent dilation and blood pressure in syndrome X

K. Mizia-Stec[1], Z. Gasior[1], B. Zahorska-Markiewicz[2], M. Mizia[1], A. Niedojadlo[1], P. Kumor[1], L. Goliszek[1], J. Kosmider[1]. *[1]Silesian University School of Medicine, Department of Cardiology, Katowice, Poland; [2]Silesian University School of Medicine, Department of Pathophysiology, Katowice, Poland*

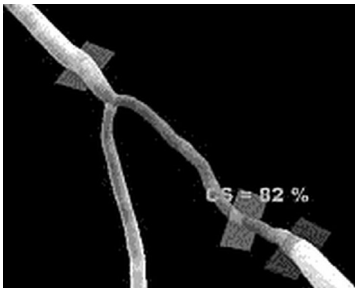
Mental stress may contribute to the pathogenesis of chest pains – both in coronary artery disease and syndrome X. It has been suggested that hemodynamic response to mental stress influences the endothelial function.
Aim: To determine whether the baseline blood pressure and the stress-induced increase of blood pressure influence endothelium-dependent flow-mediated dilatation (FMD) in patients with syndrome X.
Methods: 44 patients with syndrome X (F/M: 21/23, mean age: 55.4 ± 10.7 years) were included into the study. The endothelium-dependent FMD testing of the brachial artery was performed with high-resolution ultrasound; the result of FMD was defined as the percent change in the internal diameter of the brachial artery during reactive hyperemia related to baseline (%FMD). The %FMD was assessed before and after (10, 30, and 45 minutes) a standardized 3-minute mental stress task. Blood pressure was simultaneously monitored. The FMD% values were compared between subgroups characterized by baseline SBD, DBP, delta-SBP, delta-DBP below and over median values.
Results: In all patient groups significant decrease of %FMD measured at 10, 30, and 45 minutes after MS ($4.5 \pm 2.3\%$, $5.2 \pm 3.5\%$, $4.1 \pm 3.4\%$, respectively; $p<0.01$) was noted compared to baseline values ($7.7 \pm 4.9\%$). The impaired vasodilatation was observed independently on baseline SBP, DBP, and delta-DBP. Only in the subgroup with delta-SBP below median value (20mmHg), a significant decrease of %FMD in consecutive minutes ($4.2 \pm 2.2\%$, $4.3 \pm 3.8\%$, $3.5 \pm 3.6\%$, respectively; $p<0.001$) was found in comparison to baseline data ($8.2 \pm 5.2\%$).
Conclusion: Independently of baseline blood pressure, mental stress induces prolonged endothelial dysfunction in syndrome X. The impairment of endothelial function depends on the stress-induced increase of SBP - it is observed in

patients with mild SBP increase, probably due to less exaggerated arterial remodeling.

P2930 Bifurcation lesions in the coronary arteries: early experiences with a novel 3D imaging and quantitative analysis before and after stenting

D. Dvir[1], H. Marom[2], R. Kornowski[3]. [1]*Sheba Medical Center, Cardiology, Ramat-Gan, Israel;* [2]*Afek, Israel;* [3]*Rabin Medical Center, Petach-Tikva, Israel*

Introduction: treating coronary bifurcation lesions in the catheterisation laboratory is technically challenging. Conventional 2-dimensional (2D) angiography lacks the ability to image properly the true bifurcation geometry and/or its plaque distribution. The objectives of this study were 1) to reconstruct in 3-dimensions (3D) coronary bifurcation lesions, and 2) to analyze geometrical changes before and immediately following stenting.
Methods: the CardiOp-BTM System (Paieon Medical, Israel) is a system for 3D reconstruction of the coronary vessels and was designed as an add-on to conventional 2D angiography systems. We conducted a retrospective evaluation of 27 patients/angiograms with bifurcation lesions in the coronary arteries undergoing angioplasty procedures. After 3D reconstruction, lesions types were classified according to the European classification. Angulations between the side branch and the distal main branch of the bifurcation were measured, before and after stenting procedure.
Results: of the 27 bifurcations that were studied 26 were successfully reconstructed. In 92% of cases classification of the bifurcation in 3D was identical to that shown by the 2D angiography. Side branch involvement was found in 42% of cases based on 3D. Pre and post-stenting comparison was evaluated in 18 cases with excellent imaging. Mean angulation before stenting was significantly higher than that measured after stenting (71°±17 and 58°±18, respectively; $p<0.01$).



Conclusion: the CardiOp-BTM angiography system may provide new insight into bifurcation analysis in 3D space. The algorithm may serve as an important tool for planning of interventional procedures and accurate appreciation of interventional results in complex bifurcation lesions scenario.

P2931 A novel method for the analysis of bifurcation lesions in cardiovascular angiograms

J.C. Tuinenburg[1], G. Koning[1], A. Rares[1], J.P. Janssen[1], Y. Louvard[2], H. Pattenier[3], W. Bokhove[3], J.H.C. Reiber[1]. [1]*Leiden University Medical Center, Radiology Dept., Leiden, Netherlands;* [2]*Institut CardioVasculaire Paris-Sud, Massy, France;* [3]*MEDIS Medical Imaging Systems B.V., Leiden, Netherlands*

For coronary bifurcation stenting, there is a need for quantitative analysis of the vessel segments and its central part of the bifurcation. We developed a new bifurcation analysis method, which is able to measure the three vessel segments -each including the central part- in one analysis.
The question is whether the bifurcation analysis is an improvement compared to the individual straight analyses, and is the method reproducible?
To assess the differences between straight and bifurcation analyses with lesions “outside” the central part of the bifurcation, an analyst performed 13 bifurcation and 32 straight analyses. Additionally, 11 straight analyses with lesions “inside” the central part and the corresponding bifurcation analyses were performed. Two analysts analyzed 23 diagnostic bifurcations (interobserver variability). All analyses are performed with QVA-CMS V6.0.
The systematic error (SE) was defined by the mean signed differences (Bifurcation-Straight or Analyst1-Analyst2), and the random error (RE) by the standard deviations of these differences.
The comparison of the bifurcation and straight analyses shows that the SEs and REs of the “outside” lesions are very small. Therefore, they are considered to be similar. However, the “inside” lesions show that the obstruction diameter is smaller, the percentage diameter stenosis is larger, and the lesion length is longer for the bifurcation analysis. This confirms the intention of this new bifurcation analysis method, the ability to measure these lesions more precise. The inter-observer results show that the SEs are very small and that the REs fulfill the inter- and intra-observer variability of the QCA reference guidelines (<0.15mm). Therefore, the bifurcation analyses are considered to be reproducible.

Table 1. Results

	Bifurcation vs Straight	Bifurcation vs Straight	Inter-observer
	Outside central part (N=32)	Inside central part (N=11)	(N=23)
Obstruction D (mm)	0.00±0.10	-0.19±0.29	-0.01±0.11
Reference D (mm)	0.03±0.11	0.01±0.25	-0.02±0.13
Diameter Stenose (%)	0.25±3.85	9.41±10.41	0.02±4.11
Lesion length (mm)	0.03±1.36	2.01±2.93	-0.04±1.28

Results expressed as Systematic error±Random error.

The new bifurcation analysis shows better and reproducible results, and therefore is highly recommended above straight QCA for bifurcation analysis.

P2932 Analysis of intracoronary pressure wave forms. A new method to assess the coronary vasodilator effect of adenosine

E. Vavouranakis[1], I. Stamatopoulos[2], T. Papaioanou[2], S. Nikolopoulos[2], M. Drakopoulou[2], T. Gialernios[2], I. Karabelas[2], C. Stefanadis[2]. [1]*Marousi, Greece;* [2]*Hippokration Hospital Univ. of Athens, Cardiology, Athens, Greece*

Although coronary microcirculation plays an important role after coronary interventions, methods to evaluate it are limited. Impedance and wave reflections affect systemic arterial pressure waveforms. Whether alterations of coronary microcirculation can also produce detectable changes on intracoronary pressure waveforms, is not known.
Aim: We investigated whether intravenous infusion of adenosine can alter pressure waveform configuration along a coronary artery, by recording from proximal and distal sites simultaneously.
Methods: We studied 10 patients with normal myocardial contractile function, after optimal coronary stenting (myocardial perfusion and myocardial blush grade 3) for stable angina pectoris due to a discrete coronary artery stenosis. Intracoronary pressure was recorded by two 0.014” pressure wires (frequency response 0 – 25 Hz), from the ostium and from a distal site (at least 6 cm distal to the deployed stent). Pressure waveforms were compared and analyzed with Fast Fourier Transform (FFT, both at rest and after coronary hyperemia (adenosine at 140 μg/kg/min).
Results: Analysis of 1000 pressure waveforms showed that during hyperemia heart rate increased by 10% and pulse pressure reduced equally at both sites. However, the systolic peak wave became wider only at the distal pressure recordings during hyperemia (Figure 1). FFT showed that hyperemia compressed the amplitude of high frequency waves (on the order of 10-15 Hz) on the distal recordings, (average power spectrum per frequency from 2000±900 to 500±150, p=0.0001) (Figure 1).

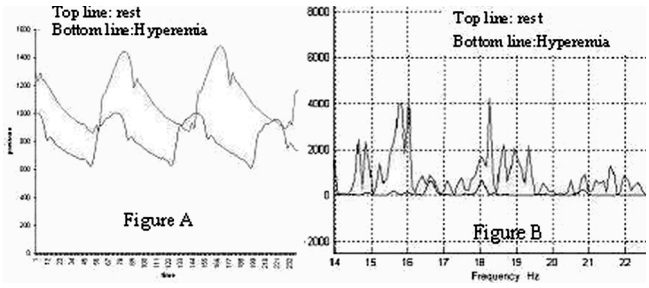


Figure 1

Conclusion: The vasodilator effect of adenosine alters intracoronary pressure waveforms probably by compressed the amplitude of high frequency waves originating from distal coronary circulation.

P2933 3D vessel analyses provide more accurate length measurement than "gold standard" quantitative coronary angiography

D. Meerkin[1], H. Marom[2]. [1]*Shaare Zedek Medical Center, Cardiology Dept., Jerusalem, Israel;* [2]*Paieon Medical, Tel-Aviv, Israel*

Background: Beyond its well established research applications,device sizing has become an important and growing clinical application of online Quantitative Coronary Angiography (QCA). In an era of drug eluting stents, accurate length assessment is important to ensure complete segment coverage while minimizing complications such as side branch jailing. The Cardiop-B system integrates 2 views to provide a 3D reconstruction of the arterial segment of interest. The aim of this study was to compare minimal luminal diameter (MLD) data to that of a validated 2D QCA (CMS-Medis) system while assessing the impact of the 3D approach on segment length analysis.
Methods: In the first phase of this study, 50 stenoses from consecutive coronary angiograms were assessed in two projections with both systems providing two data sets for the CMS-Medis system and a single data set for Cardiop-B. To compensate for varying default definitions, length was measured between clearly

defined anatomical landmarks. In a second phase, to further evaluate accuracy, a perspex phantom with a known lesion length was analyzed at increasing degrees of forshortening with acceptance criteria set at 5% from the absolute value. Correlations, accuracy and precision were determined.
Results: Phase 1 demonstrated an adequate correlation between the Cardiop-B and Medis systems when MLD was measured (1.22±0.51mm vs 1.48±0.56mm respectively, r=0.76). A stronger correlation was noted when length was measured (27.5±13.9mm vs 23.8±12.0mm, r =0.94), however Cardiop-B provided a consistently longer length ($p<0.0001$).
Phase 2: On phantom measurements the average accuracy result for the CardiOp-B system is −1.3%, length results for each degree of foreshortening, from zero to 40 degrees are within the 5% acceptance criterion that was determined for the system.
The average accuracy result for QCA-CMS is −7.8%, which was outside the acceptance criterion. Furthermore, beginning from 20 degrees of foreshortening, all QCA-CMS accuracy results are > 5%.
Conclusion: There is a good correlation of results for both systems regarding MLD data. A consistently increased lesion length was measured by Cardiop-B. Phantoms demonstrate that 3D length determination is more accurate than 2D QCA particularly in foreshortened projections, a finding with particular clinical relevance.

P2934 Coronary artery ectasia as a reflection of a generalised vascular media defect

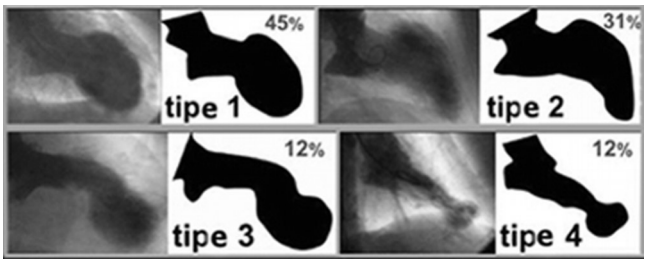
E. Triantafillidi[1], F. Panou[2], K. Kourea[2], E. Tsougkos[2], A. Antoniadis[2], I. Rizos[2], D. Kremastinos[2]. *[1]Athina, Greece; [2]University of Athens, 2nd Department of Cardiology, Athens, Greece*

Introduction: Coronary artery ectasia usually represents another form of coronary atherosclerosis. Its primary defect is a destruction of vascular media, which leads to coronary dilatation. Aim of the present study is to evaluate whether other sites of the arterial bed present anatomical and structural wall changes in patients with coronary artery ectasia.
Patients-Methods: Twelve patients with known coronary artery ectasia (group A) underwent echocardiography using M-Mode and Tissue Doppler Imaging (TDI) in order to study aortic lumen diameter and wall properties (distensibility, stiffness, TDI indices). Nine patients with coronary artery disease were the control group (group B).
Results: Both groups of patients were similar for age, gender, body surface, body mass index (BMI), smoking habit, diabetes mellitus, cholesterol, triglycerides, C-Reactive Protein, fibrinogen, office blood pressure levels (130/79 mmHg vs 128/76 mmHg), left ventricular ejection fraction and left ventricular mass.
We found that diameters of aortic root (30.9 mm vs 32.6 mm, p=0.3), aortic arch (32 mm vs 30.7 mm, p=0.5) and abdominal aorta (21.9 mm vs 22.6 mm, p=0.6) were similar in both groups. Both ascending thoracic aorta diameters, systolic and diastolic were increased in patients with coronary ectasia (systolic 38.9 mm vs 35.3 mm, p=0.06 and diastolic 37.6 mm vs 33.4 mm, p=0.03).
Ascending thoracic aortic wall properties as estimated by distensibility and stiffness indices were similar in both groups. However, a negative correlation was found in coronary ectasia patients between diastolic diameter of ascending thoracic aorta and distensibility (r= -0.88, $p<0.001$), as well as a positive correlation between diastolic diameter of ascending thoracic aorta and stiffness (r=0.8, p=0.001).
Conclusions: It seems that coronary artery ectasia co-exists with ascending aorta dilatation as well as increased stiffness of aortic wall. We suggest that coronary ectasia is not an isolated lesion but a reflection of a generalised vascular media defect.

P2935 Tako-tsubo-like apical ballooning shape: what it depends on?

J. Benezet, B. Ibanez, F. Navarro, A. Pinero, C. G Santos-Gallego, P. Marcos-Alberca, J. Higueras, J. Farre. *Fundacion Jimenez Diaz, Cardiology, Madrid, Spain*

It has been recently reported that the left ventricular (LV) akinesia in "tako-tsubo" syndrome is associated to the presence of a left anterior descending (LAD) with a long recurrent diaphragmatic segment. To test this hypothesis, we analyzed the LV morphology in 51 consecutive patients (PP) (29 men, age 66±14 years old) diagnosed with AMI for single LAD occlusion, without other coronary obstructions, and that were treated with primary angioplasty.
Methods: We established the segment occluded of the LAD and the relation between the recurrent segment and the total length of the LAD (LAD recurrence index [RI]). We identified 4 patterns of LV akinesia in these patients with AMI (Figure): 1) distal anterior wall, apex and distal diaphragmatic wall (morphology "tako-tsubo-like"), 45%, 2) distal anterior wall and apex (morphology "ballerina foot-like"), 31%, 3) apex and distal diaphragmatic wall, 12%, 4) only apex, 12%. The occlusion of the LAD was: proximal (22%), medium (55%), and distal (23%).
Results: The LAD RI related with the LV pattern was: type 1 0,21±0,02; type 2 0,06±0,04; type 3 0,20±0,04; and type 4 0,10±0,01, being the differences statistically significant between type 1 and 2 ($P<.001$), 1 and 4 (P=.002), 3 and 2 (P=.005), and 3 and 4 (P=.014). The segment occluded was proximal or medium LAD ± in types 1 and 2, and distal LAD in types 3 and 4 ($P<.001$ between 1+2 and 3+4).



Different LV Patterns

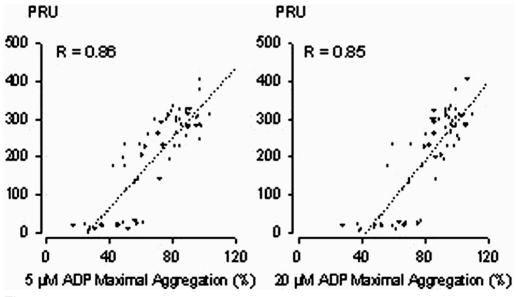
Conclusions: It can be observed an akinesia "tako-tsubo-like" type in 45% of patients with anterior AMI with a unique occlusion of the proximal or medium LAD. The development of this kind of akinesia in the acute phase depends only and exclusively of the segment of the LAD occluded (proximal or medium) and the presence of a long wrapped LAD supplying the distal diaphragmatic LV wall.

ANTITHROMBOTIC/ANTIPATELET

P2936 Correlation between platelet response units measured with a point-of-care test and ADP-induced platelet aggregation assessed with conventional optical aggregometry

N. Von Beckerath, G. Pogatsa-Murray, A. Wieczorek, A. Schomig, A. Kastrati. *DHZ Munchen, Erwachsenenkardiologie, Munich, Germany*

Background: Despite its efficacy in the prevention of ischemic events, the variable drug response to a fixed dose of clopidogrel is an issue of concern. An insufficient inhibition of the P2Y12 pathway and thus platelet function is particularly dangerous in patients treated with percutaneous coronary intervention (PCI) because insufficient P2Y12 antagonism is believed to increase the risk of stent thrombosis.
Methods: Thirty patients with suspected or proven coronary artery disease scheduled for coronary angiography were included in the study. Blood was drawn before and 4 hours after administration of a 300, 600 or 900 mg loading dose of clopidogrel. Platelet function was assessed with the "VerifyNowTM P2Y12" assay (Accumetrics, San Diego, USA) and conventional optical aggregometry. The figure shows the correlation between platelet response units (PRUs) obtained with the point-of-care test and maximal ADP(5 and 20 μM)-induced platelet aggregation.



Figure

Conclusions: Platelet response units obtained with the "VerifyNowTM P2Y12" assay correlate well with ADP-induced platelet aggregation in conventional aggregometry. The test may be helpful in tailoring antiplatelet therapy in patients scheduled for PCI.

P2937 Platelet-activating factor-acetylhydrolase G994T (exon 9) and A379V (exon 11) gene polymorphisms in relation to the onset of premature myocardial infarction in Taiwan

P.-Y. Liu[1], J.-H. Chen[1], Y.-H. Li[1], T.-H. Chao[1], L.-J. Lin[1], H.-L. Wu[2], P.-Y. Liu[3]. *[1]National Cheng Kung University Hospital, Division of Cardiology, Tainan, Taiwan; [2]National Cheng-Kung University, Department of Biochemistry, Tainan, Taiwan; [3]National Cheng-Kung University, Institute of Clinical Medicine, Tainan, Taiwan*

Background: Oxidation of low density lipoproteins is an initial step of atherogenesis that generates pro-inflammatory phospholipids, including platelet-activating factor (PAF) and its analogs. PAF is degraded by PAF-acetylhydrolase (PAF-AH), a circulating enzyme having both pro- and anti-inflammatory activities. PAF-AH

activity has been postulated to be a risk factor for premature myocardial infarction (MI). The PAF-AH has a causal role or is simply a marker of risk for MI is unclear.
Methods: All polymorphisms located in putatively functional regions were investigated in a cohort of premature MI patients onset less than 46 years of age (n = 170) and a sex-age-matched control group (n = 170). Their PAF-AH activities were evaluated by ELISA assay.
Results: The frequency of the G994T (exon 9) mutation on PAF-AH gene was similar among premature MI and the control group ($p>0.1$). The A379V (exon 11) mutation on PAF gene was less frequent in premature MI patients than in controls (p=0.02) and was associated with a lower risk of MI, suggesting that this allele might be protective against the development of premature MI. The A379V mutation was also associated with a weak increase of plasma PAF-AH activity. The modification of the enzyme function towards a more anti-atherogenic form by this A379V genetic mutation might help explain this paradoxical gene-phenotype association. Multiple logistic regression analysis showed that the A379V polymorphism was an independent risk factor (Odds Ratio (OR) 1.7, 95% CI 1.2 to 7.3, p=0.04) as were as smoking (OR 3.6, 95% CI 1.4 to 5.8, p=0.001), diabetes mellitus (OR 3.5, 95% CI 1.5 to 6.7, p=0.003) and hypertension (OR 1.9, 95% CI 1.7 to 7.7, p=0.001) for the onset of premature MI.
Conclusion: We conclude that a functional and significant association between the A379V polymorphism on exon 11 of PAF gene and premature MI exists in this Taiwanese population. This allele may be protective partially via modifying the PAF-HA enzyme towards a more anti-atherogenic function.

P2938 The P2Y12 reactivity ratio: a new method to detect response variability after clopidogrel

U.S. Tantry, K.P. Bliden, J. Yoho, K.P. Hayes, R. Kreutz, Gurbel.
Sinai Hospital of Baltimore, Center for Thrombosis Research, Baltimore, United States of America

Background: Interindividual variability to clopidogrel treatment may be related to the occurrence of stent thrombosis and ischemic events in patients receiving this drug. There is no technique available to measure the P2Y12 receptor response to clopidogrel.
Method: Five control subjects and 26 patients undergoing stenting were treated with 300 mg clopidogrel loading dose and VASP phosphorylation levels as a measure of P2Y12 reactivity ratio were measured (Biocytex, France). VASP is a marker of P2Y12 reactivity. Absolute platelet inhibition (pre-minus posy-treatment aggregation (API)) and P2Y12 reactivity ratio were calculated and results were expressed as Mean ± SD.
Results: In controls, API was 43.7±7% and 36±10% by 5 uM and 20 uM ADP respectively. VASP index was reduced significantly after clopidogrel treatment (97 ± 3 to 57 ± 15, $p<0.001$). In stent patients, API was 24=/-12 (5 uM ADP, range = 7.8-64.5%) and 16±14% (20 uM ADP, range = 0-49%); 23% and 42% were nonresponders, respectively. The post-treatment P2Y12 reactivity ratio in patients was 61 ± 24. Both API and P2Y12 reactivity ratio in patients indicate a wide range of response variability. 66% of non-responders had a P2Y12 reactivity ratio of more than 80 (r=0.64, p=<.05).
Conclusion: The P2Y12 reactivity ratio is related to blockade of P2Y12 receptor and high levels in stent patients indicate the suboptimal inhibition of P2Y12 receptors. The P2Y12 reactivity ratio can be used to identify clopidogrel nonresponsiveness in addition to conventional platelet aggregation.

P2939 Low platelet response to clopidogrel increased the risk of recurrent atherothrombotic events in patients with non-ST acute coronary syndrome after coronary stenting

T. Cuisset[1], C. Frere[2], J. Quilici[1], P.E. Morange[2], F. Barbou[2], I. Juhan-Vague[2], M.C. Alessi[2], J.L. Bonnet[1]. *[1]Hopital of Timone, Cardiology Department, Marseille, France; [2]chu timone, laboratory of haematology, marseille, France*

Background: Although clopidogrel reduces the risk of cardiovascular episodes after acute coronary syndrome (ACS) and stenting, a substantial number of ischemic events continue to occur.
Methods: In order to determine whether low platelet response to clopidogrel affects clinical outcomes, we studied platelet function profiles in 92 consecutive patients who underwent percutaneous coronary intervention (PCI) with stenting for non-ST elevation ACS. Clopidogrel was administered as a loading dose of 300 mg at least 12 hours before angioplasty. Blood samples were obtained at the beginning of the PCI and patients were stratified into four quartiles according to the platelet induced aggregation with ADP 10 μM. Patients in the highest quartile (quartile 4) were considered to be low responders to clopidogrel.We studied recurrence of cardiovascular events during a one-month follow-up.
Results: Mean±SD ADP 10μM platelet induced aggregation was respectively 82±12% in the fourth quartile, 66±4% in the third one, 56±4% in the second one and 38±8% in the first quartile. The cutt-off value between the fourth and the other quartiles was 72% of platelet aggregation. P-selectine (CD62P) expression was significantly increased in clopidogrel low responders compared with the three other quartiles (Mean Fluorescence Intensity ±SEM=0.60±0.06 vs 0.48±0.04, p=0.04 after sex and age adjustment).
Nine recurrent cardiovascular ischemic events occurred at one month: six in quartile 4 (26%), three in quartile 3 (13%) and none in the two other quartiles. Clinical outcomes were significantly associated with platelet response to clopidogrel, whereas 26% of low responders patients suffered a recurrent cardiovascular event versus only 4.5% in the three other quartiles (p=0.01 after sex and age adjustment). This difference was not affected by further adjustment for conventional cardiovascular risk factors (p=0.02).
Conclusion: A significant proportion of patients undergoing coronary stenting have an early poor response to a standard 300-mg clopidogrel loading dose. Based on a single blood sample at the time of PCI, we determined a quartile of low responders patients at high risk of recurrent cardiovascular ischemic events.

P2940 Genetic polymorphism C807T on platelets glycoprotein Ia, affects the release of sCD40L and P-selectin during the acute phase of myocardial infarction

C.A. Antoniades[1], D. Tousoulis[2], C. Vasiliadou[1], N. Koumallos[1], M. Toutouza[1], K. Marinou[1], C. Pitsavos[1], C. Stefanadis[1]. *[1]Athens University, Cardiology, Athens, Greece; [2]Athens, Greece*

Platelet membrane glycoprotein Ia (GPIa) has an important role in platelet activation during the acute phase of myocardial infarction (MI), as a receptor for collagen. Platelets activation is characterized by both the release of soluble CD40-ligand (sCD40L) and P-selectin (P-Sel). Although silent genetic polymorphism C807T affects the expression of GPIa, its actual role in platelets activation during MI is unknown.
Aim: We investigated the effect of C807T polymorphism on the release of sCD40L and P-sel during both the acute phase of MI and one year after the event, as well as in a population of age and sex matched healthy controls.
Methods: The study population consisted of 55 patients with acute MI (46.2±5.2 years old) and 235 healthy individuals (47.2±10.5 years old) of both sexes. Patients with acute MI were examined both during the acute phase of MI and one year after the event. Distribution of C807T polymorphism was investigated by genotyping DNA by PCR. Plasma levels of sCD40L and P-Sel were evaluated with ELISA.
Results: The distribution 807CC/807CT/807TT was 16/27/12 in MI and 77/120/28 in controls. During the acute phase of MI, plasma levels of both sCD40L and P-sel were significantly higher in CT+TT (16.6±1.8pg/ml and 69.8±5.2ng/ml respectively) compared to CC (3.54±0.74pg/ml and 38.9±3.98ng/ml respectively, $p<0.001$ for both). One year after the event, although plasma sCD40L and P-sel were decreased in all genotypes, they remained significantly higher in CT+TT (11.33±1.45pg/ml and 52.1±3.8ng/ml) compared to CC(4.65±0.57pg/ml and 37.5±2.8ng/ml respectively, $p<0.01$ for both). The increase of both sCD40L and P-sel from rest (at one year) to the acute phase levels was significantly higher in CT+TT compared to CC ($p<0.01$). In healthy individuals, although sCD40L was significantly lower in CC (4.19±0.48pg/ml) compared to CT+TT(5.6±0.32pg/ml $p<0.05$), there was no significant difference in P-sel levels between the genotypes (31.1±3.1 vs 35.8±1.8 ng/ml for CC vs CT+TT respectively, p=NS).
Conclusions: Genetic polymorphism C807T on platelet glycoprotein Ia, affects the release of sCD40L and P-selectin during the acute phase of myocardial infarction, an effect sustained in the same patients one year after the event. These findings suggest that C807T polymorphism may modify platelets activation, especially during the acute phase of myocardial infarction.

P2941 Mean platelet volume and risk of restenosis in type 2 diabetic patients undergoing coronary stent implantation

U. Bildirici[1], G. Kahraman[1], E. Ural[1], A. Agacdiken[2], G. Kozdag[1], T. Sahin[1], A. Vural[1], D. Ural[1]. *[1]Kocaeli University Medical Faculty, Cardiology, Kocaeli, Turkey; [2]Kocaeli University Medical Faculty, Cardiology, Kocaeli, Turkey*

Altered platelet morphology and function have been reported in patients with diabetes mellitus (DM). Mean platelet volume (MPV) is an indicator of platelet activity. The aim of this study was to compare MPVbetween DM and non-DM patients undergoing coronary stent implantation, and to determine its role in subsequent stent restenosis. A total 44 DM (12 F, 32 M, aged 61 ± 11 years) and 81 non-DM patients (60 M, 21 F, aged 59 ± 9 years) undergoing stent implantation for single vessel disease were enrolled to the study. Blood samples were collected 12 hours before and 12, 24, 48 hours and 1 month after the stent implantation. Control coronary angiography was performed after six months in all patients. The angiographic restenosis rate was 50% in DM and 28% in non-DM (p=0.02). Baseline MPV levels were significantly higher in DM patients (8.7±1.0 fL vs. 59±0.9 fL; p=0.001). No significant difference in baseline MPV was noted between patients with and without restenosis. In both groups, patients with restenosis showed a progressive increase in MVP levels, whereas in patients without restenosis it remained comparable to baseline levels (Table). In multivariate analysis, the MPV measured at the 1st month was the most significant predictor of restenosis in DM group (p=0.01) and a MPV>9 fL at 1st month was associated with an odds ratio of 9.6 for development of in-stent restenosis, with a sensitivity, specificity, positive and negative predictivity of 82%, 68%, 72% and 79%, respectively. In patients with coronary artery disease, MPV is significantly higher in DM than in non-DM.

Table 1. Change in MPV (fL)

	Before	12 h	24 h	48 h	1 month
Diabetics (n=44)					
Restenosis (+)	8.5 ± 0.8	8.6 ± 0.8	9.0 ± 1.0	9.5 ± 1.2	10.4 ± 1.4
Restenosis (-)	8.9 ± 1.1	8.6 ± 0.9	8.7 ± 0.9	8.8 ± 0.9*	8.7 ± 1.0**
Non-diabetics (n=81)					
Restenosis (+)	8.3 ± 0.8	9.1 ± 0.9	9.3 ± 0.9	9.4 ± 1.0	9.8 ± 1.2
Restenosis (-)	7.9 ± 1.1	7,9 ± 1.2**	7.9 ± 1.2**	8.0 ± 1.1**	8.0 ± 1.1**

*p=0.04, **p< 0.001 restenosis(+) vs restenosis (-), h hours, NS not significant

In both groups, increasing MPV following stent implantation is significantly related to stent restenosis. A MPV greater than 9 fL at the 1st month is a good predictor of restenosis.

P2942 Association between the PIA platelet glycoprotein GPIIIa polymorphism and extent of coronary artery disease. The role of age and diabetes mellitus

M. Gruchala[1], R. Targonski[2], W. Dubaniewicz[2], K. Chlebus[2], A. Rynkiewicz[2]. *[1]Wejherowo, Poland; [2]Medical University of Gdansk, First Department of Cardiology, Gdansk, Poland*

Background: The PIA2 allele of the gene encoding for GPIIIa subunit of the platelet membrane receptor glycoprotein (GP) IIb/IIIa has been suggested as a significant risk factor for thrombotic complications of coronary artery disease (CAD). The aim of the current investigation was to investigate the association between PIA GPIIIa polymorphism and the extent of angiographically confirmed CAD in patients from the Pomerania region of Poland.
Methods: The study was performed in 397 male Caucasian patients. All subjects had significant coronary artery stenosis confirmed by elective coronary angiography. Screening for the PIA GPIIIa genotypes was performed by polymerase chain reaction of genomic DNA, followed by NciI digestion and agarose gel electrophoresis.
Results: The genotype distribution of the PIA GPIIIa polymorphism in our study group was PIA1/A1- 75%, PIA1/A2-24% and PIA2/A2-1% with PIA1 and PIA2 allele frequencies 0.87 and 0.13, respectively. The prevalence of the homozygous PIA1/A1 genotype among subjects with multiple-vessel CAD (two or three vessels with at least 50% stenosis) was significantly higher than in patients with single-vessel disease; the odds ratio of PIA2/A2 or PIA1/A2 patients for having multiple-vessel CAD was 0.46 (95% CI 0.27-0.77, $p<0.01$). The mean CAD score for PIA1/A1 patients was significantly higher in comparison to PIA2/A2 and PIA1/A2 patients (7.58+2.20 and 6.98+2.37 respectively, $p<0.05$). The association of the PIA1/A1 genotype with multiple vessel disease was the strongest in subjects above 65 years of age in comparison to younger ones; OR 0.30 (95% CI 0.10-0.96, $p<0.05$). A trend towards increase of the PIA1/A1 genotype and PIA1 allele frequencies was observed in patients over 65 years of age with the positive history of nonfatal myocardial infarction in comparison to younger patients. Furthermore, we observed additional increase in risk of multiple-vessel CAD associated with the PIA1/A1 genotype in the presence of diabetes (OR 0.07, 95%CI 0.01-0.69, $p<0.05$).
Conclusions: Our results suggest, that the PIA1/A1 genotype of PIA GPIIIa polymorphism is associated with more severe CAD in male Caucasian patients from the north region of Poland. The association seems to be stronger in elderly and diabetic CAD patients.

P2943 Antithrombotic efficacy of BAY 59-7939 – an oral, direct Factor Xa inhibitor – compared with fondaparinux in animal arterial thrombosis and thromboembolic death models

E. Perzborn, B. Arndt, M. Harwardt, U. Lange, A. Trabandt. *Bayer HealthCare AG, Cardiovascular Research, Wuppertal, Germany*

BAY 59-7939 is a novel, oral, selective, direct Factor Xa (FXa) inhibitor in clinical development for the prevention and treatment of thromboembolic disorders. This study was performed in animal arterial thrombosis models and a thromboembolic death model to compare the antithrombotic effects of BAY 59-7939 with the indirect, antithrombin-dependent FXa inhibitor fondaparinux. Effects on arterial thrombosis were investigated in a mouse ferric chloride (FeCl3) model, in which a carotid artery was damaged by FeCl3, and in a rabbit arteriovenous (AV)-shunt model with an AV shunt between the right common carotid artery and the left jugular vein. In a mouse thromboembolic death model, thromboembolism was induced by injection of human tissue factor (Thromborel S, Dade Behring). The dose at which ≤10% of control animals survived was used, and the endpoint was the number of surviving animals. BAY 59-7939 and fondaparinux were given prophylactically, as an intravenous bolus. In order to demonstrate that both BAY 59-7939 and fondaparinux inhibit FXa in mice and rabbit plasma, FXa inhibition was measured in vitro. In the mouse FeCl3 model, BAY 59-7939 reduced the formation of arterial thrombi dose dependently (ED50 1mg/kg). At 3mg/kg, BAY 59-7939 almost completely inhibited thrombus formation (by 86±2%), compared with a 46±5% reduction with fondaparinux 10mg/kg. In the rabbit AV-shunt model, BAY 59-7939 showed dose-dependent inhibition of thrombus formation (ED50 0.6mg/kg), and almost completely inhibited thrombus formation at 3 mg/kg (by 83±7%). In contrast, fondaparinux reduced thrombus formation by a maximum of 49±4%, 50±5% and 59±3% at 1, 3 and 10mg/kg, respectively. BAY 59-7939 prevented thromboembolic death in mice in a dose-dependent manner (ED50 0.32±0.05mg/kg); almost all (97%) survived at 1mg/kg. Only 17% and 20% of mice given fondaparinux 3 and 10mg/kg, respectively, survived. In vitro, BAY 59-7939 and fondaparinux both inhibited free FXa potently: IC50 0.242±0.058μM and 0.055±0.015μM, respectively, in mouse plasma; and IC50 0.021±0.002μM and 0.041±0.015μM, respectively, in rabbit plasma. These in vitro results contrast markedly with the results in the animal models, where the direct FXa inhibitor BAY 59-7939 was significantly more effective than the indirect FXa inhibitor fondaparinux at inhibiting arterial thrombus formation and preventing thromboembolic death. The results of this study suggest that direct FXa inhibition with BAY 59-7939 may be superior to indirect FXa inhibition for the prevention of arterial thrombosis and tissue-factor-mediated thromboembolic death.

P2944 Dosing strategy in patients with renal failure receiving Enoxaparin for the treatment of non ST-segment elevation acute coronary syndrome

J.S. Hulot[1], G. Montalescot[2], J.P. Collet[2], S. Urien[1], A. Ankri[3], P. Lechat[1]. *[1]Hôpital Pitié La Salpêtrière, Service de Pharmacologie, Paris, France; [2]Pitié-Salpêtrière University Hospital, Cardiology department, Paris, France; [3]Pitié-Salpêtrière University Hospital, Hemostasis Investigations department, Paris, France*

Enoxaparin therapy is recommended for the initial treatment of patients presenting with non-ST-segment elevation acute coronary syndrome (ACS). However, little dosing information is available for the use of enoxaparin in patients with renal impairment (RI).
Methods: We conducted a population pharmacokinetic analysis (NONMEM version V, FOCE method) using anti-Xa activities measured in 532 patients (normal renal function for 34%, mild RI for 36%, moderate RI for 20% and severe RI for 10%) receiving sub-cutaneous enoxaparin (mean weight-corrected dose (±SD) 0.83±0.19 mg/kg per 12h) for an ACS. Simulations were then performed to develop a dosing strategy for patients with RI. We defined the target anticoagulation window as a maximal anti-Xa activity in steady-state conditions (Amaxss) (1)necessarily > 0.5 IU/ml and (2)optimally ranging from 0.5 to 1.2 IU/ml.
Results: A one compartment model with first order kinetics with proportional inter-subject variability (ISV) on clearance (CL/F) and volume of distribution (V/F) best fitted the data. The covariate analysis showed that enoxaparin clearance was related to renal function (serum creatinine, total body weight and gender) and volume of distribution to total body weight. Enoxaparin clearance was decreased by 31% in patients with moderate RI and by 44% in patients with severe RI resulting in a significant accumulation with the use of the standard 1 mg/kg/12h dosing regimen. Simulations showed that a first unadjusted dose of 1mg/kg followed by a regimen of 0.8 mg/kg/12h in patients with moderate RI or 0.66 mg/kg/12h in patients with severe RI should avoid accumulation of enoxaparin and keep peak anti-Xa activities between 0.5 and 1.2 IU/ml for a huge majority of patients. Moreover, compared to the recent FDA recommendation of keeping the same dose of 1 mg/kg administered only once a day in patients with severe renal impairment, this dosing strategy provides a more stable anticoagulation profile with a lower risk of under-dosing.
Conclusions: An enoxaparin dosage reduction should be considered in ACS patients with creatinine clearance < 50 ml/min. A simple dosing protocol for enoxaparin in patients with moderate or severe RI is proposed in order to prevent enoxaparin accumulation in patients with renal dysfunction while keeping most of peak anti-Xa activities in a range that would be associated with a limited thrombotic and bleeding risk.

P2945 The effect of dalteparin vs. unfractionated heparin on platelet functions and clinical course during percutaneous coronary interventions. The results of a multicentric randomised study

M. Brtko[1], I. Varvarovsky[2], P. Polansky[3], J. Maly[4]. *[1]University Hospital, Cardiac Surgery Department, Hradec Kralove, Czech Republic; [2]Hospital Pardubice, Kardio-Troll s.r.o., Pardubice, Czech Republic; [3]University Hospital, Dept. of Cardiac Surgery, Hradec Králové, Czech Republic; [4]University Hospital, Dept. of Clinical Haematology, Hradec Kralove, Czech Republic*

Background: Unfractionated heparin (UFH) commonly used during percutaneous coronary interventions (PCI) can activate platelets. This effect could be deleterious during percutaneous coronary interventions (PCI). The low-molecular weight heparins (LMWH) lack this effect.
The aim of this study: To compare the effect of LMWH – dalteparin – and UFH during PCI on platelet functions, on the occurrence of a "rebound" phenomenon after their cessation and on the clinical course of the patients with stable angina pectoris.
Methods: Dalteparin in the dose of 80 units/kg of body weight or UFH in the dose of 100 units/kg were given intravenously to 340 patients in a randomized multicentric study. The aggregation response of platelets, levels of betathromboglobulin (beta-TG), thromboxan B2 (TxB2), trombin-antithrombin complex (TAT), prothrombin degradation products (F1, F2), platelet count before and after PCI and clinical course of the patients were studied.
Results: The two goups of patients were comparable in basic demographic char-

acteristics and in the usage of antiplatelet drugs. 5 minutes after the administration of UFH the platelet aggregation was higher (compared to dalteparin) after the induction by epinephrine ($p<0,01$), thrombin and arachidonic acid (both $p<0,05$). The level of beta-TG decreased 5 minutes after dalteparin bolus from 78,3 to 63,1 ($p<0,01$), after UFH bolus from 75,9 to 71,2 IU/ml (NS). There was no significant changes in the level of TxB2 in both groups. The level of TAT decreased 5 hours after dalteparin from 14 to 8,6 mikrog/l ($p<0,05$) and increased after UFH from 11,8 to 12,2 mikrog/l (NS; between groups $p<0,05$). The level of F1,F2 did not change after dalteparin -1,1 (NS) - and increased after UFH from 1,1 to 1,6 nmol/l ($p<0,05$; between groups $p<0,05$). Platelet count decreased after the PCI in both groups (both $p<0,001$). We did not find any difference in the clinical course and in the occurrence of ischemic and haemorhagic complications of PCI between the groups.

Conclusions: The administration of the above mentioned doses of dalteparin or UFH is safe. The activation of platelets and the reactivation of coagulation cascade is less pronounced after dalteparin administration. Both UFH and dalteparin caused significant decrease of platelet count. The potencial advantages of dalteparin have no influence on the clinical course.

P2946 A randomised blinded trial comparing fondaparinux with unfractionated heparin in patients undergoing contemporary percutaneous coronary intervention: the ASPIRE pilot study

S.R. Mehta on behalf of The ASPIRE Pilot Investigators. *Hamilton Health Sciences, General Division, Hamilton, Canada*

Purpose: Percutaneous coronary intervention (PCI) is associated with an unacceptable rate of abrupt vessel closure and re-occlusion despite the use of concomitant standard therapy, including antiplatelet agents (aspirin) and anticoagulants (primarily unfractionated heparin [UFH]). We performed an international randomized blinded, controlled, parallel group pilot study of fondaparinux (Arixtra®) versus UFH trial to determine the safety and feasibility of use of fondaparinux in the PCI setting.

Methods: A total of 350 patients undergoing elective or urgent PCI were randomized to intravenously receive fondaparinux at either 2.5 mg or 5.0 mg, or UFH. Randomization was stratified for planned or no planned use of glycoprotein IIb/IIIa antagonists. All patients were pretreated with aspirin and clopidogrel, and study medications were administered at the time of guidewire insertion into the catheter. The primary safety outcome was blinded adjudicated total (major and minor) bleeding occurring within 48 h after randomization. The primary efficacy outcome was the blinded adjudicated first occurrence within 48 h after randomization of any component of the composite outcome of all-cause death, myocardial (re)infarction, urgent revascularization, and need for bail-out glycoprotein IIb/IIIa inhibitors.

Results: The incidence of total bleeding was 6.4% in the combined fondaparinux groups and 7.7% in the UFH group (hazard ratio 0.81, 95% CI 0.35-1.84, p=0.61). Total bleeding was less common in the 2.5 mg group than in the 5.0 mg group (3.4% versus 9.6%, p=0.06). The incidence of the composite efficacy outcome was 6.0% in the combined fondaparinux groups and 6.0% in the UFH group, with no significant difference in efficacy among the fondaparinux doses compared with UFH. Furthermore, fondaparinux was significantly (p=0.02) superior to UFH in inducing a sustained reduction in markers of thrombin generation, as assessed by prothrombin fragments F1+2 measured 6 and 12 hours after PCI.

Conclusions: Fondaparinux is as safe and effective as UFH in patients undergoing contemporary PCI, warranting further evaluation in the treatment of arterial thrombosis.

P2947 Effect of of enoxaparin on brain perfusion, glucose and lipids metabolism in patients with arterial hypertension and type 2 diabetes mellitus

V.B. Mychka, I.Y. Chazova, K.M. Mamyrbaeva. *Russian Cardiology Complex, Arterial Hypertension, Moscow, Russian Federation*

Goal: to study the effect of treatment with low-molecular heparin (Enoxaparin) on brain perfusion, glucose and lipids metabolism in patients with mild-to moderate arterial hypertension (AH) and type 2 diabetes mellitus (DM).

Methods: there were included 15 patients with mild-to moderate AH and type 2 DM. All patients were treated with 40 mg/day Enoxaparin subcutaneously for 6 weeks. Antihypertensive treatment remained unchanged during the study. Before and after the treatment with enoxaparin there were estimated fasting glucose, total cholesterol (TC), low-density cholesterol (LDL), high-density cholesterol (HDL), triglycerides (TG). Patients also underwent single photon emission computed tomography (SPECT) of brain with 99mTc-HMPAO at baseline and after the treatment.

Results: all patients had impaired brain perfusion level. Treatment with Enoxaparin significantly increased perfusion level in left occipital-parietal lobe from 72.78±11.49% to 75.89±11.6% ($p<0.05$), in right occipital-parietal - from 67.78±5.65% to 77.56±10.61% ($p<0.01$), left parietal - from 78.89±16.16% to 81.11±11.67% ($p<0.05$), right parietal - from 82.22±17.16% to 84.44±15.5% ($p<0.05$), left frontal-parietal – from 86.11±13.64% to 90.56±11.3% ($p<0.05$), right frontal-parietal – from 78.89±16.35% to 84.44±12.61% ($p<0.05$). Interlobular asymmetry decreased from 14±3.28 to 11±1.8 ($p<0.05$). Glucose level decreased significantly from 8.66±2.34 to 7.38±1.67 mmol/l ($p<0.01$), TC decreased from 6.61±1.46 to 6.28±0.9 mmol/l ($p<0.1$), TG decreased from 2.83± 2.6 to 2.57± 2.43 mmol/l, (p=0.3), LDL from 4.05± 1.74 to 3.7± 1.14 mmol/l, (p=0.2). HDL remained unchanged in all patients.

Conclusion: patients with type 2 diabetes and arterial hypertension have a decreased brain perfusion in occipital-parietal, parietal, frontal-parietal lobes of both hemispheres. Treatment with enoxaparin significantly increases brain perfusion level in these patients, mostly shown in occipital-parietal lobe in right hemisphere and temporal-occipital lobes in both hemispheres. Enoxaparin significantly decreases blood glucose and has neutral effect on lipids.

P2948 Reactivation of coagulation activity after cessation of the oral direct thrombin inhibitor ximelagatran is independent of time after acute myocardial infarction

C. Christersson[1], J. Oldgren[2], A. Bylock[3], A. Siegbahn[4], L. Wallentin[5]. *[1]Uppsala, Sweden; [2]University Hospital, Department Of Cardiology, Uppsala, Sweden; [3]Astra Zeneca, Göteborg, Sweden; [4]Department of Clinical Chemistry, University Hospital, Uppsala, Sweden; [5]Uppsala Clinical Research Center, Uppsala, Sweden*

Background: The placebo controlled ESTEEM trial demonstrated that long-term treatment with the oral direct thrombin inhibitor ximelagatran reduced the thrombin generation and fibrin turnover and the risk of new ischemic events after recent acute myocardial infarction, without any differences between doses from 24-60 mg bid. We have evaluated reactivation of thrombin generation and fibrin turnover, ie prothrombin fragment 1+2 (F1+2) and D-dimer, after cessation of study treatment at different times after the myocardial infarction.

Methods and Results: The patients were randomized 6 days (mean) after their myocardial infarction to one of four doses of ximelagatran or placebo twice daily for 6 months together with aspirin. F1+2 and D-dimer levels were analyzed at cessation of study treatment and 2 weeks afterwards (follow up). Patients that completed the 6 months treatment were compared with the patients with premature discontinuation of study medication. The table represent the median levels of F1+2 and D-dimer.

F1+2 and D-dimer at discontinuation

	Premature discontinuation				6 months treatment			
	n	discontinuation	follow up	p	n	discontinuation	follow up	p
			F1+2 (μmol/mL)					
Ximelagatran	83	0.83	0.97	0.001	154	0.78	0.94	<0.001
Placebo	23	1.00**	1.16	0.7	108	0.92***	0.97	0.6
			D-dimer (ng/mL)					
Ximelagatran	83	81	122	0.002	154	45	90	<0.001
Placebo	24	152*	158	0.6	108	97***	101	0.9

***p < 0.001, **p = 0.003, *p = 0.017 comparing ximelagatran vs placebo

Conclusion: The reactivation, without signs of rebound, of thrombin generation and fibrin turnover after cessation of ximelagatran is independent of time after index event and duration of treatment. This reactivation might indicate a need for further prolonged treatment.

P2949 Safety and efficacy of a new oral direct thrombin inhibitor Dabigatran in atrial fibrillation – a dose finding trial with comparison to Warfarin

L.C. Wallentin[1], M. Ezekowitz[2], T.A. Simmers[3], K.E. Pedersen[4], J. Stangier[5], G. Nehmiz[5], P. Reilly[6] on behalf of PETRO-investigators. *[1]University Hospital, Uppsala Clinical Research Center, Uppsala, Sweden; [2]Drexel University, Department of Medicine, Philadelphia, United States of America; [3]University of Amsterdam, Department of Medicine, Amsterdam, Netherlands; [4]Odense University, Deparment of Medicine, Odense, Denmark; [5]Boehringer-Ingelheim, Biberach, Germany; [6]Boehringer Ingelheim, Ridgefield, United States of America*

Oral direct thrombin inhibition might replace vitamin-K antagonists provided that its safety and efficacy can be proven in clinical trials. This dose-guiding trial investigated safety and anti-thrombotic efficacy of Dabigatran etexilate (BIBR 1048) in 502 patients with Atrial Fibrillation (AF).

Methods: Patients were randomized to 12 weeks treatment with 50, 150 or 300 mg BIBR 1048 b.i.d., combined with 0, 81 or 325 mg ASA q.d. or to Warfarin with INR 2.0-3.0. Main study endpoints were changes of D-dimer, thrombotic and bleeding events. Liver function tests were monitored every 2 - 4 weeks.

Results: The background characteristics were well balanced with mean age 69.7 years, 18% females, 4.0 years median duration of AF and with a median of 3 additional risk factors for thromboembolism. Median D-dimer level before treatment was 72 ng/ml. 464 patients completed 12 weeks treatment, 29 discontinued due to adverse events and 9 due to other causes. The ASA treatment was prematurely terminated in the 300 mg group because of an excess bleeding on this combination. Table 1 shows the results.

The ASA treatment was prematurely terminated in the 300 mg group because of an excess bleeding on this combination. Otherwise there was no relevant influence of the concomitant ASA treatment on the bleeding events. In the 300 mg group without ASA the rate of bleeding was not different from the other groups.

Table 1

Dabigatran dose mg bid	50	150	300	Warfarin
N of pts	105	166	161	70
Median change D-dimer ng/ml 28 d	+6 (p=0.03)	0	0	-1.5 (n.s.)
Thromboembolic event	2	0	1	0
Major bleeding	0	0	4	0
Major or relevant bleeding	2 (2%)	13 (8%)	17 (11%)	4 (6%)
ALT to >3*ULN	0	1	2	0

Results

Conclusion: Dabigatran 150 mg b.i.d. achieves a similar level of coagulation activity as higher doses and as Warfarin. At this dose the risk of bleeding seems low even when combined with ASA. Dabigatran appears to minimally affect liver function tests at any dose. Dabigatran 200 – 300 mg daily is therefore proposed for testing in phase III clinical trials for prevention of thromboembolic events in atrial fibrillation.

P2950 Melagatran inhibits AP-1 and NfKB activation and promotes plaque stability in advanced atherosclerotic lesions in apo E deficient mice

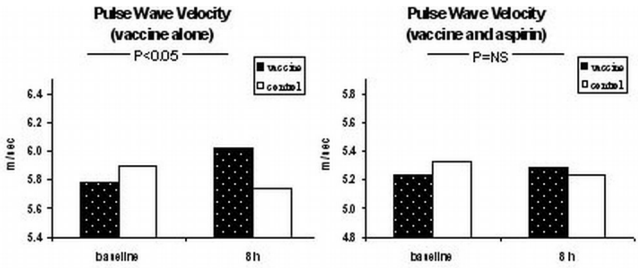
F. Bea, J. Kreuzer, M. Preusch, S. Schaab, E. Blessing. *University of Heidelberg, Cardiology, Heidelberg, Germany*

Introduction: acute coronary syndromes are related to the formation and disruption of atherosclerotic plaque. Advanced atherosclerotic lesions are characterised by the presence of a necrotic core, which is separated from the lumen by a fibrous cap. Inflammatory mechanisms are involved in processes leading to a weakening of this protective cap, resulting in plaque rupture and subsequent thrombin generation, fibrin deposition, and platelet aggregation. Thrombin not only plays a central role in thrombus formation and platelet activation, but also in the induction of inflammatory processes. Thrombin inhibition significantly reduces thrombus-related sequelae. Melagatran (M), a direct thrombin inhibitor, offers potential improvement over heparin in the clinical outcomes and risks associated with plaque destabilization and -rupture. We assessed the hypothesis that Melagatran promotes plaque stability in advanced atherosclerotic lesions via antiinflammatory mechanisms.
Methods: 28 seven months old female Apolipoprotein E deficient mice were fed a chow diet supplemented with M (500 μmol/kg/day) for 22 weeks, 26 mice received regular chow diet. At time of necropsy, the thoracic aorta was collected for subsequent gel shift analysis of the activity of the proinflammatory transcription factors activator protein (AP)-1 and NfKB. Following perfusion fixation with formalin, innominate arteries were embedded in paraffin, cross sectioned and analyzed following Movat's pentachrome staining.
Results and conclusions: activation of AP-1 (0.12$\pm$0.19 vs. 2.21$\pm$0.12; $p<0.0005$) and NfKB (1.28$\pm$0.27 vs. 2.40$\pm$0.62; $p<0.05$) were significantly reduced in the M group. Maxium lesion area were significantly smaller in the M ($246321\pm45628\mu m^2$) as compared to the placebo group ($285169\pm65063\mu m^2$; $p<0.05$). Signs of plaque instabilitiy such as thinning of the fibrous cap was observed in only 29% (8/28) treated, as compared to 65% (17/26); ($p<0.05$) control mice. Presence of a large necrotic core was observed in only 39% (11/28) in the M group and in 77% (20/26); ($p<0.05$) of the control mice. We conclude that Melagatran promotes plaque stability in advanced atherosclerotic lesions possibly through inhibition of the activation of the proinflammatory transcription factors AP-1 and NfKB.

P2951 Aspirin prevents from deterioration of arterial elastic properties induced by acute inflammation

C. Vlachopoulos[1], I. Dima[1], K. Aznaouridis[1], N. Ioakeimidis[1], N. Alexopoulos[1], M. Stratigakis[2], D. Tousoulis[1], C. Stefanadis[1]. *[1]Athens Medical School, Hippokration Hospital, 1st Cardiology, Athens, Greece; [2]Pasteur Hellenic Institute, Athens, Greece*

Purpose: large artery stiffness is an important independent prognosticator of cardiovascular risk. An association between acute inflammation and increased arterial stiffness has been suggested. Aspirin reduces cardiovascular risk and modulates the inflammatory cascade. It has not been defined whether aspirin protects from the effect of acute inflammation on arterial stiffness.
Methods: we generated a transient systemic inflammation by Salmonella Typhi vaccination in 50 healthy volunteers. In the first sub-study, 26 subjects were studied after vaccination or sham-vaccination (control group). In the second sub-study,we studied 24 subjects after they had received 1.2 g aspirin and after either vaccination or sham-vaccination. We assessed the arterial responses before and 8 hours after vaccination. Carotid-femoral pulse wave velocity (PWV) was measured as an index of aortic stiffness using an automated non-invasive device (Complior®).
Results: in the first study,inflammation produced a significant increase in PWV at 8 hours (by 0.40 m/sec,$P<0.05$,left figure) indicating an increase of aortic stiffness.In contrast,in the pretreated with aspirin group,the increase in PWV after vaccination was smaller and not significant (by 0.15 m/sec,P=NS, right figure), denoting that the effect of inflammation on arterial stiffness is reversed by aspirin. Systolic and diastolic pressures did not change significantly in any group.There were no significant changes in the control groups.



Inflammation, aspirin and PWV

Conclusion: aspirin prevents from deterioration of arterial elasticity caused by experimental inflammation, possibly by modulating the inflammatory cascade. This has important implications for the protective effect of aspirin on arterial elastic properties and on the cardiovascular system overall.

ASPIRIN RESISTANT/THIENOPYRIDINE

P2952 No impact of statins metabolised by CYP3A4 on the antiplatelet effect and the clinical outcome after a 600 mg loading dose of clopidogrel in patients undergoing elective coronary angiography

W. Hochholzer[1], D. Trenk[2], D. Frundi[2], P. Blanke[2], H.-P. Bestehorn[2], H.J. Buettner[2], F.-J. Neumann[2]. *[1]Herz-Zentrum Bad Krozingen, Bad Krozingen, Germany; [2]Bad Krozingen, Germany*

Attenuation of the antiplatelet effect of clopidogrel by concomitant treatment with the statin atorvastatin has been shown in a limited number of patients as well as in healthy subjects. The clinical relevance of this interaction is still under debate because subsequent ex vivo platelet function studies yielded conflicting results and retrospective analyses of clinical studies failed to demonstrate any clinical impact of this interaction. We therefore performed a large prospective study to investigate the interaction between statins metabolized via cytochrome P450 3A4 (CYP3A4) and clopidogrel with respect to ex vivo platelet inhibition as well as major adverse cardiac events within 30 days after stent implantation (PCI).
The study enrolled 1397 consecutive patients scheduled for coronary angiography (CA) as potential candidates for an elective PCI. Dosing regimen of lipid-lowering drugs was constant for at least 1 week before recruitment. All patients were on treatment with ASS (100 mg/day) and received a 600 mg loading dose of clopidogrel at least 2 hours before CA followed by a daily maintenance dose of 75 mg in case of PCI. Blood samples were obtained before clopidogrel, at time of CA and 24 hours after PCI. Platelet function was assessed by optical aggregometry and surface protein expression (P-selectin and activated GP IIb/IIIa by flow cytometry) after stimulation with ADP. Major adverse cardiac events (MACE: death, myocardial infarction, target lesion reintervention) within 30 days were recorded in the subset of patients undergoing PCI (n=553).
Platelet aggregation (20 μmol/l ADP) at time of CA was 50$\pm$16% (mean$\pm$SD) in patients without any statin medication (n=683), 51$\pm$15% in patients treated with atorvastatin (n=255), 51$\pm$15% in patients with simvastatin (n=335), 52$\pm$15% in patients with fluvastatin (n=43) and 52$\pm$15% in patients with concomitant use of pravastatin (n=81; p=0.41). There was no relation between platelet aggregation and the daily dose (10, 20 and 40 mg) of either atorvastatin (ANOVA p=0.70) or simvastatin (p=0.38). Determination of surface protein expression confirmed these data. The incidence of MACE within 30 days after PCI was low and not different between patients without statin medication (2.1%, 5/235), and patients treated with CYP3A4-statins (2.3%, 6/256) or other statins (3.2%, 2/62; p=0.96).
In summary, statins metabolized via CYP3A4 (atorvastatin, simvastatin) had no effect on the antiplatelet activity of a loading dose of clopidogrel 600 mg or on the 30-day-incidence of MACE following PCI.

P2953 Clopidogrel loading with eptifibatide to arrest the reactivity of PLATELETS: results of the CLEAR PLATELETS Study

Gurbel, K.P. Bliden, K.A. Zaman, M. Fissha, J.A. Yoho, K.M. Hayes, U.S. Tantry. *Sinai Hospital of Baltimore, Center for Thrombosis Research, Baltimore, United States of America*

Background: Pretreatment is not the most common strategy practiced for clopidogrel administration in elective coronary stenting. Moreover, limited information is available on the antiplatelet pharmacodynamics of a 300 mg versus a 600 mg clopidogrel (C) loading dose, and the comparative effect of eptifibatide (E) with these regimens is unknown.
Methods and Results: Patients undergoing elective stenting (n=120) were enrolled in a 2 x 2 factorial study (300 mg C $\pm$ E; 600 mg C $\pm$ E). Clopidogrel was administered immediately post-stenting. Aggregometry and flow cytometry were used to assess platelet reactivity. E added a >twofold increase in platelet inhibition to 600 mg C alone at 3, 8, and 18-24 hours post-stenting as measured by 5 uM ADP – induced aggregation ($p<0.001$). Without E, 600 mg C produced better

inhibition than 300 mg C at all time points ($p<0.001$). GP IIb/IIIa blockade was associated with lower cardiac marker release. Active GP IIb/IIIa expression was inhibited most in the groups treated with E ($p<0.05$).
Conclusions: In elective stenting without clopidogrel pretreatment, use of a GP IIb/IIIa inhibitor produces superior platelet inhibition and lower myocardial necrosis as compared to high (600 mg) or standard (300 mg) dose clopidogrel loading alone. In the absence of a GP IIb/IIIa inhibitor, 600 mg clopidogrel provides better platelet inhibition than the standard 300 mg dose. These results require confirmation in a large scale clinical trial.

P2954 Greater in vivo potency of prasugrel (CS-747, LY640315) vs. clopidogrel is not explained by differential activity of active metabolites

T. Ogawa[1], A. Sugidachi[1], T. Isobe[1], Y. Nakanishi[1], A. Kurihara[2], K. Hagihara[2], J.A. Jakubowski[3], F. Asai[1]. *[1]Sankyo, Co., Ltd., Pharmacol. & Mol. Biol. Res. Labs., Tokyo, Japan; [2]Sankyo Co., Ltd., Drug Metab. & Pharmacokinet. Res. Labs, Tokyo, Japan; [3]Eli Lilly and Company, Lilly Res. Labs, Indianapolis, United States of America*

Purpose: Prasugrel (CS-747, LY640315), a novel and potent thienopyridine type antiplatelet agent, is inactive in vitro and, like clopidogrel, requires active metabolite (AM) formation to produce in vivo antiplatelet effects. Oral dosing of prasugrel provides a 10-fold more potent antiplatelet effect than clopidogrel in experimental animals and humans (phase1). The current study was designed to determine the contribution of AM levels and inherent platelet inhibitory activity of the AMs to this greater potency following oral dosing.
Methods: The relative in vivo activities of prasugrel and clopidogrel were assessed by measurement of ex vivo ADP-induced platelet aggregation and AM levels following oral dosing. The in vitro antiplatelet effects of prasugrel AM (RS- and SR-) and clopidogrel AM (RS-) were studied using human platelets in plasma or suspended in buffer utilizing a variety of ADP receptor ligands as described below.
Results: Oral administration of prasugrel to rats resulted in inhibition of ex vivo ADP-induced platelet aggregation with more than 10-fold greater potency than clopidogrel. Consistent with the greater platelet inhibition, plasma concentration of prasugrel's AM in prasugrel-treated rats was approximately 10 times higher than that of the clopidogrel's AM in clopidogrel-treated rats, suggesting in vivo generation of AM is more efficient for prasugrel than for clopidogrel. In vitro studies indicated that prasugrel AM and clopidogrel AM inhibited ADP (10 μM)- and 2-MeS-ADP (0.1 μM)-induced platelet aggregation in washed human platelets in a concentration-related manner, with the IC50 values of prasugrel AM against ADP and 2-MeS-ADP being similar to those of clopidogrel AM. Similar results were found in human platelet-rich plasma (PRP), with IC50 values of each agent again being similar. Consistent with this data, prasugrel AM (0.03-30 μM) and clopidogrel AM (0.03-30 μM) decreased [^{3}H]-2-MeS-ADP binding to human platelets at similar concentrations. Notably, inhibition of [^{3}H]-2-MeS-ADP binding to human platelets by both AMs was partial even at the high concentrations (30 μM), suggesting high selectivity for P2Y12 receptors.
Conclusion: These results indicate that prasugrel's superior in vivo antiplatelet effect relative to clopidogrel may be due in large part to the more efficient generation of its active metabolite.

P2955 No effect of diabetes mellitus on ADP-Induced platelet aggregation after loading with 600 mg of clopidogrel

D. Sibbing, O. von Beckerath, N. von Beckerath, A. Schoemig, A. Kastrati. *Deutsches Herzzentrum Muenchen, Muenchen, Germany*

Purpose: Diabetes mellitus (DM) is associated with increased platelet activity which contributes to a higher risk of thrombembolic events. Whether clopidogrel therapy is able to suppress increased platelet activity in diabetic patients is unknown. We sought to describe platelet function in patients with and without DM after administration of a 600 mg loading dose of clopidogrel.
Methods: Blood samples of 406 patients with or without DM prior to percutaneous coronary intervention (PCI) were collected at least two hours after loading with 600 mg clopidogrel. Extra samples were available after PCI in a subgroup of 187 patients that received abciximab during intervention. Maximal platelet aggregation in response to 5 and 20 μM ADP was measured with optical aggregometry.

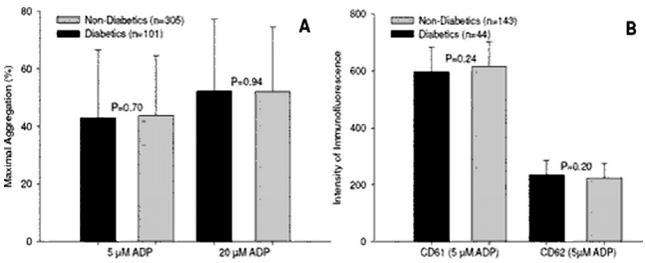


Figure 1

Surface expressions of CD61- and CD62-receptors were assessed after stimulation with 5 μM ADP with flow-cytometry.
Results: ADP-induced platelet aggregation after administration of clopidogrel did not differ between patients with and without DM (see Figure 1A). This was also true after additional therapy with abciximab (P=0.75 for 5 μM and P=0.70 for 20 μM ADP). Moreover, after abciximab CD61 and CD62 surface expression after stimulation with 5 μM ADP was similar in diabetic and nondiabetic patients (see Figure 1B).
Conclusion: These results show that the magnitude of antiplatelet effect of 600 mg loading dose of clopidogrel or abciximab in patients undergoing percutaneous coronary interventions is not influenced by the presence of diabetes mellitus.

P2956 Assessment of the best loading dose of clopidogrel to blunt platelet activation, inflammation and ongoing necrosis

G. Montalescot on behalf of the ALBION Study Investigators. *Hôpital Pitié-Salpêtrière, Institut du Coeur, Bureau 2-236, Paris, France*

Background: Previous studies such as CURE, CLASSICS and CREDO have demonstrated the benefits of adding clopidogrel to acetyl-salicylic acid (ASA) in both the short-term and long-term management of acute ischemic events. In addition, it has been shown that by administering a 300 mg loading dose of clopidogrel a significant clinical benefit can be seen within 24 hours when compared to the standard 75 mg daily dose, with no additional safety events. Recent data have also suggested that a higher loading dose of 600 mg may improve platelet inhibition. However limited randomized information is available and the optimal loading dose remains unknown.
Aim: To determine whether higher clopidogrel loading doses, including a high dose never tested before, will yield even greater and/or more rapid clinical benefit while maintaining the favorable safety profile.
Methods: ALBION is a randomized, open-label study involving ten centers in Paris, which is comparing three loading doses of clopidogrel, 300 mg, 600 mg and 900 mg, with blinded, centralized evaluation of the main evaluation criteria. Approximately 110 patients were randomized, with a target of 90 evaluable patients. Evaluation criteria: Platelet aggregation and activation in response to ADP 5 μmol/L will be evaluated using aggregometry and flow cytometry at 0, 0.5, 1, 2, 3, 4, 5, 6 and 24 hours after the loading dose. Levels of selected markers of inflammation (CRP, von Willebrand factor Ag, PAI-1 Ag and CD40-L) and necrosis (troponin I) will be assessed at 0, 6 and 24 hours. The incidence of death, MI or ischemic reoccurrence leading to revascularization or rehospitalization will also be documented, as will safety events. Major inclusion criteria: 18–85 years of age; hospitalization with ischemic symptoms (onset <48 hours) with either ECG ST or T changes and/or positive troponin; initial 250–500 mg ASA therapy, continued on low-dose ASA ($\leq$ 100 mg daily) from the next day on. Statistical methods: A sample size of 90 patients was selected to allow a statistical power of 80% (2-sided, p=0.05) for the detection via analysis of variance of a 20% difference between treatments at any specific time.
Results: Patient enrollment commenced in March 2004 and is nearly completed at the time of writing. Full baseline patient characteristics and study results will be presented at the meeting.
Conclusion: This study will provide the strongest evidence obtained so far to discriminate the various effects and the differences in onset of action of three loading doses of clopidogrel, including a high dose never tested before.

P2957 The antiplatelet effect of clopidogrel is not attenuated by treatment with CYP3A4 metabolised statins in patients with stable ischaemic heart disease

P. Vinholt[1], T.S. Poulsen[2], J. Hallas[3], P. Damkier[4], L. Korsholm[5], S.R. Kristensen[4], H. Mickley[2]. *[1]Odense University Hospital, Department of Cardiology, Odense, Denmark; [2]Odense University Hospital, Department of Cardiology, Odense, Denmark; [3]Odense University Hospital, Department of Internal Medicine, Odense, Denmark; [4]Odense University Hospital, Department KKA, Odense, Denmark; [5]University of Southern Denmark, Department of Statistics, Odense, Denmark*

Background: Recent studies suggest that cytochrome P450 (CYP) 3A4 metabolized statins may attenuate the anti-aggregatory effect of clopidogrel. These studies, however, included patients with acute coronary syndrome or patients undergoing coronary angioplasty, clinical events which per se may affect platelet function. In order to minimize the influence from potential confounders, we assessed the anti-aggregatory effect of clopidogrel, when given together with a CYP3A4 metabolized versus a non-CYP3A4 metabolized statins in clinically stable patients.
Methods and Results: Sixty-six stable patients with ischemic heart disease were included. All patients were on clopidogrel 75 mg/day and aspirin 75-150 mg/day. Thirty-three patients received a CYP3A4 metabolized statin (simvastatin 40 mg (n=17) or atorvastatin 20-40 mg (n=16), and 33 were treated with a non-CYP3A4 metabolized statin (pravastatin 40 mg). In a parallel group design, we compared platelet function in patients receiving clopidogrel and a CYP3A4 metabolized statin versus clopidogrel and a non-CYP3A4 metabolized statin. Each patient also served as his/her own control as all participants were examined at baseline and after 21 days off statin therapy. The antiplatelet effect of clopidogrel was

assessed at inclusion and 21 days after statin discontinuation. Platelet function was evaluated by two methods 1) optical platelet aggregometry after stimulation with 20 and 30 μmol/L ADP, and 2 and 4 mg/L collagen, respectively, 2) a Platelet Function Analyzer-100. The primary effect variable was maximal platelet aggregation after stimulation with 20 μmol/L ADP, and no difference in this parameter was observed among patients treated with a CYP3A4 metabolized statin compared to patients receiving a non-CYP3A4 metabolized statin (42% point (20-51) versus 35% point (25-44), p=0.92). Platelet inhibition was not improved by discontinuation of statins for 21 days. Indeed, we found that statin treatment given concomitantly with clopidogrel resulted in a lower amount of platelet aggregation when compared to clopidogrel given alone.
Conclusions: The antiplatelet effect of clopidogrel is not attenuated by concomitant treatment with a CYP3A4 metabolized statin in patients with clinical stable ischemic heart disease. Hence, our results support the view that the choice of statin should not be based on CYP3A4 metabolism when clopidogrel co-administration is required.

P2958 Prolonged clopidogrel treatment reduces lesion T-cell accumulation after PCI

K. Pels[1], C. Deiner[1], C. Loddenkemper[2], U. Rauch[1], P. Rosenthal[3], P.L. Schwimmbeck[4]. *[1]Charite - Campus Benjamin Franklin, Department of Cardiology, Berlin, Germany; [2]Charité Campus Benjamin Franklin, Pathology, Berlin, Germany; [3]Charite - Campus Benjamin Franklin, Department of Radiation Therapy, Berlin, Germany; [4]Klinikum Leverkusen, Department of Cardiology, Leverkusen, Germany*

Prolonged Clopidogrel therapy after intracoronary brachytherapy (IB) treating instent restenosis has been shown to reduce major adverse clinical events (MACE). This beneficial effect has been mainly attributed to the antithrombotic mechanism, but it is unknown whether the P2Y12 receptor antagonist mediates additional effects which contribute to the prevention of MACE.
The purpose of this study was to analyze the effect of prolonged Clopidogrel treatment on inflammatory T-cell mediated response in the intima/media (I+M) and adjacent adventitia of balloon-injured and subsequently beta-irradiated porcine coronary arteries.
Methods: 18 pigs underwent balloon injury (PTCA) in one major coronary artery followed by immediate beta-irradiation using a 90S/Y source train delivering 20 Gy at a depth of 2 mm from the source. Animals were divided into three groups (n=6 each): group I received Clopidogrel until sacrifice at day 28, group II received Clopidogrel for 28 days and was sacrificed after 3 months, and group III received Clopidogrel until sacrifice after 3 months.
Serial cross sections of coronary arteries were immunohistochemically examined.
Results: see table

T cells in vascular lesion

	$CD3^+$-cells per mm^2	
	I+M	adventitia
Group I (28 days; Clopidogrel for 28 days)	9,17 ± 1,52	10,38 ± 1,72
Group II (3 months; Clopidogrel for 28 days)	8,58 ± 1,88	10,34 ± 1,6
Group III (3 months; Clopidogrel for 3 months)	2,8 ± 1,05*	2,43 ± 0,58*

*$p < 0.05$ group III vs. groups I und II

Conclusion: Prolonged Clopidogrel therapy following PCI with IB significantly reduces T-cell accumulation in the intima/media as well as in the adventitia. This anti-inflammatory effect possibly represents an important additional mechanism of action of Clopidogrel and may be involved in reducing MACE, thereby providing additional ratio for the necessity of long term clopidogrel treatment after IB, in particular within the first 3 months after PCI.

P2959 Rebound pro-inflammatory effects following clopidogrel withdrawal in diabetic patients

D.J. Angiolillo[1], E. Bernardo[2], C. Ramirez[2], M. Sabate[2], P. Jimenez-Quevedo[2], C. Corros[2], A. Fernandez-Ortiz[2], C. Macaya[2]. *[1]University of Florida, Cardiology-Shands Jacksonville, Jacksonville, United States of America; [2]San Carlos University Hospital, Interventional Cardiology Unit, Madrid, Spain*

Background: Recently, inhibition of the P2Y12 pathway by the platelet antagonist clopidogrel has shown to have anti-inflammatory effects. In particular, the addition of clopidogrel to aspirin (ASA) is associated with a reduction in systemic markers of inflammation during the early phases of treatment. However, if a rebound pro-inflammatory response is observed following withdrawal of clopidogrel treatment is unknown. Further, diabetic patients have an enhanced inflammatory status and may be more vulnerable to these effects. Aim of the study: to assess the impact of clopidogrel withdrawal on systemic markers of inflammation in diabetic patients.
Methods: Fifty-four type II diabetic patients were studied. All patients were on long-term (12 month) combined ASA (100mg/d) + clopidogrel (75mg/d) therapy. Markers of inflammation were assessed before and one-month following clopidogrel withdrawal (patient only on ASA). Markers of inflammation included assessment of 1) high sensitivity C-reactive protein (hsCRP) by nephelometry and 2) cell surface P-selectin expression (CD62-P) in resting platelet and after ADP (2μM) stimuli by whole blood cytometry.
Results: A significant increase in all the assessed inflammatory markers was observed following clopidogrel withdrawal (Table). hsCRP values are expressed as median and interquartile range. CD-62P values are expressed as percentage of positive platelets.

	ASA+Clopidogrel	ASA	p-value
hs-CRP (mg/dL)	0.30 (0.16-0.54)	0.39 (0.18-0.69)	<0.05
CD-62P (resting platelets)	10.9 (4.2-24.8)	24.3 (6.4-47.5)	<0.001
CD-62P (ADP-induced platelets)	28.3 (18.9-42.6)	63.5 (46.3-72.7)	<0.0001

Conclusions: Clopidogrel withdrawal is associated with an increase in systemic markers of inflammation in diabetic patients. These data support the pleiotropic, anti-inflammatory, properties attributed to clopidogrel which may contribute to the clinical benefit associated with long-term dual antiplatelet treatment, especially in high risk patients.

P2960 Potent inhibition of platelet aggregation by Prasugrel (CS-747, LY640315), a novel thienopyridine antiplatelet agent, is associated with covalent binding of active metabolite to ADP receptor

A. Kurihara[1], M. Kazui[1], K. Hagihara[1], T. Isobe[2], T. Ogawa[2], A. Sugidachi[2], N.A. Farid[3], T. Ikeda[1]. *[1]Sankyo Co., Ltd., Drug Metab. & Pharmacokinet. Res. Labs., Tokyo, Japan; [2]Sankyo Co., Ltd., Pharmacol. & Mol. Biol. Res. Labs., Tokyo, Japan; [3]Eli Lilly and Company, Lilly Res. Labs., Indianapolis, United States of America*

Purpose: Prasugrel (CS-747, LY640315), a novel thienopyridine antiplatelet agent, exhibits extended activity in vivo following oral administration but not in in vitro studies. Pharmacologically, an active prasugrel metabolite is produced by cytochrome P450 enzymes after rapid hydrolysis of prasugrel to the thiolactone metabolite R-95913. In the present study, concentrations of prasugrel metabolites bound to rat platelets were determined. In addition, binding of prasugrel metabolites to the ADP P2Y12 receptor was evaluated using CHO cells expressing P2Y12 receptor.
Methods: After oral administration of prasugrel to rats, prasugrel metabolite concentrations bound to the platelets and in the plasma were measured by LC-MS method. For in vitro experiments, several prasugrel metabolites were incubated with CHO cells expressing P2Y12 receptor (P2Y12-CHO) and metabolites bound to the cells were assayed by LC-MS. Dithiothreitol (DTT; 5 mM) was added to release covalently-bound metabolites from the platelets (in vivo) or receptors (in vitro).
Results: Several metabolites of prasugrel were detected in rat plasma with S-methyl metabolite (R-100932) at highest concentration. Although the active metabolite R-138727 was detected at considerable levels in the plasma and eliminated relatively quickly, the duration of its pharmacological activity persisted longer. DTT treatment of washed platelets released R-138727 as a major component, indicating that R-138727 is covalently bound to the platelets. The concentration of platelet-bound R-138727 rapidly increased post-dosing and remained high compared to fast elimination of R-138727 from plasma. DTT-releasable binding of R-138727 to the P2Y12-CHO cells was 1.5-fold higher compared to the control CHO cells, indicating the binding of R-138727 to the receptor. The binding of other prasugrel metabolites to P2Y12-CHO cells was negligible and not significantly different from the control cells.
Conclusions: These results are consistent with previous findings that the major metabolite of prasugrel, R-138727, solely and exclusively had in vitro antiplatelet potency. The present study shows that after oral administration of prasugrel, the sulfhydryl moiety of R-138727 binds to P2Y12 ADP receptors forming a disulfide bond, leading to rapid, irreversible, and potent inhibition of platelet aggregation.

P2961 Statin therapy has an antiplatelet effect and does not interfere with the loading dose of clopidogrel in patients with ischaemic heart disease

E. Toth Zsamboki, B.J. Beres, K. Vargova, E. Fischer, E. Csoti, G. Kerecsen, I. Preda, R.G. Kiss. *Cardiovascular Research Group, SE-Hungarian Academy of Sciences, Budapest, Hungary*

Clopidogrel (CLO) is a prodrug which is -like atorva- and simvastatin- metabolized through the hepatic CYP3A4 enzyme, producing the active antiplatelet metabolite. Since patients undergoing percutaneous coronary intervention (PCI) are often on statin therapy, statins might diminish the antiplatelet effect of CLO.
We measured ADP (0.32; 0.64; 1.25; 2.5; 5; 10 μM) and collagen (1; 2 μg/ml)-induced platelet aggregation (PA) of 48 patients with stable coronary disease undergoing coronary angioplasty in citrated platelet rich plasma. Patients received 300 mg CLO loading dose, followed by 75 mg/day. Out of the 28 patients, who had previously been on statin therapy, 20 received 40 mg simvastatin and CLO loading at the same time, 8 received 40 mg atorvastatin and CLO loading; 20patients received CLO loading without statins as a control. We assessed PA before taking the drugs and 4, 24, and 96 hours later. In every group, compared to the baseline, there was a significant PA decrease 4 hours after taking CLO (ADP 0.32 μM: 6.71% versus 0.72%, 0.64 μM: 18.37% v. 11.28%, 1.25 μM: 47.1% v. 32.4%, 2.5 μM: 59.2% v. 45.5%, 5 μM: 63.1% v. 50.8%, 10 μM: 74.4% v. 64.8%, Coll 1 μg/ml: 39.3% v. 28.9%, 2 μg/ml: 57.2% v. 43.9%, p values <0.005). Importantly,

the average baseline ADP EC50 value of these 48 patients was 1.44 ± 0.52 μM explaining, that the inhibitory effect of clopidogrel is more predominant at low ADP concentrations, close to the EC50 value of the platelet P2Y12 ADP receptor.
There was no significant difference in PA levels 4 hours after taking CLO between the three patient groups (ADP EC50 values: CLO group:2.37±0.62 μM, CLO + simvastatin group: 2.25±0.5 μM, CLO + atorvastatin group: 1.84±0.84 μM; p values > 0.15, NS). Stimulated by low ADP concentrations, the level of initial PA in the statin-treated group was significantly lower than in the control group (0.32μM: control 8.6% v. statin group 5.9%, p=0,037; 1.25 μM: 57.3% v. 42.4% p=0,012).
In conclusion, atorva- or simvastatin does not reduce the antiplatelet effect of loading dose clopidogrel, routinely administered before PCI. Statin therapy has an autonomous antiplatelet effect, which is independent from CLO's and may be in correlation with the long-term pleiotropic effect of statins. Platelet aggregation measurements, performed routinely by high ADP concentrations (≥ 5μM) in citrated plasma give limited information about functionality of the clopidogrel-target P2Y12 ADP receptor and seemingly useless in assessing clopidogrel resistance.

P2962 Antithrombotic effect of clopidogrel compared with aspirin during radiofrequency catheter ablation

K. Polymeropoulos[1], V. Vassilikos[2], S. Paraskevaidis[2], P. Makris[3], T. Karamitsos[2], G. Dakos[2], S. Mochlas[2], G. Louridas[2].
[1]Thessaloniki, Greece; [2]AHEPA University Hospital, Cardiology, Thessaloniki, Greece; [3]Aristotle University of Thessaloniki, Thrombosis Laboratory, AHEPA Hospital, Thessaloniki, Greece

Aim: Thromboembolism has been reported after radiofrequency catheter ablation (RFA) as a result of hemostatic system activation. The aim of this study was to evaluate the activation of the coagulation system in relation to aspirin and clopidogrel pretreatment, during RFA procedures.
Methods: We studied prospectively 42 consecutive patients (15 men) who underwent RFA for supraventricular tachyarrhythmias in the right heart (atrioventricular nodal re-entry tachycardia n=29, atrioventricular re-entry tachycardia due to right-sided accessory pathways n=11, and typical atrial flutter n=2). Twenty-one patients were randomized to receive aspirin (325 mg loading, the day before the RFA, followed by 325 mg for one month) and twenty-one to receive clopidogrel (300 mg loading, followed by 75 mg for one month). ADP (5μg/L) induced platelet aggregation (PA) was assessed by light transmittance aggregometry and D-dimer (D-d) levels were assessed by ELISA technique. Blood samples were collected at baseline, before sheath insertion (T1), after completion of the RFA procedure (T2), 24 hours later (T3) and after 1 month (T4).
Results: A more intense inhibition of PA and significantly lower D-d values were observed by clopidogrel compared with aspirin in all stages. See table.

Table

	Aspirin	Clopidogrel	p value
T1 PA	68±7	36±12	<0.001
T2 PA	74±6	44±10	<0.001
T3 PA	76±7	47±10	<0.001
T4 PA	69±8	46±10	<0.001
T1 D-d	29±21	18±8	0.036
T2 D-d	109±15	74±15	<0.001
T3 D-d	164±95	88±30	0.002
T4 D-d	26±16	16±7	0.012

Values of platelet aggregation (%)and values of D-dimer (μg/L)

Conclusion: In this prospective clinical study, clopidogrel proved more effective than aspirin in inhibiting ADP-mediated platelet aggregation and reducing the D-dimer levels. Thus, clopidogrel treatment requires further evaluation, as it may provide possible benefits in preventing the occurrence of thromboembolic complications during RFA procedures.

P2963 Common sequence variations in the P2Y12 and CYP3A5 genes do not explain variability in the inhibitory effects of clopidogrel therapy

S.M.G. Smith[1], H.M. Judge[1], G. Peters[2], M. Armstrong[3], P. Fontana[4], P. Gaussem[4], R.F. Storey[1]. *[1]University of Sheffield, Cardiovascular Research Unit, Sheffield, United Kingdom; [2]AstraZeneca, Wilmington, DE, United States of America; [3]AstraZeneca, Alderley Park, Macclesfield, United Kingdom; [4]Hôpital Européen Georges Pompidou, Service d'Hématologie Biologique, Paris, France*

The platelet P2Y12 receptor antagonist clopidogrel reduces thrombotic events in patients with cardiovascular disease, but wide inter-patient variability is observed in clopidogrel efficacy. We determined whether P2Y12 haplotype or the CYP3A5 6986 A>G dimorphism, which influences 3A5-mediated drug metabolism, contribute to this variability.
Methods: ADP-induced optical aggregometry (OA), whole-blood single platelet counting aggregometry (WBSPC), P-selectin expression and platelet-monocyte conjugate formation was assessed at baseline, 4 hours post clopidogrel 300 mg, and following 10 and 28 days of 75 mg od in 54 patients listed for elective PCI. Patients were genotyped for P2Y12 haplotype and 3A5 6986 genotype. Further studies were performed on a separate cohort of coronary artery disease patients (n=43) prior to and 4 hours post clopidogrel 600mg.
Results: The percentage inhibition of 20μM ADP-induced OA at 4h and 10 days from baseline was 28.4±5.2 and 50.1±6.0 respectively in P2Y12 H1/H1 homozygotes (n=32), and 29.4±4.7 and 50.6±6.3 in patients with at least one copy of the H2 haplotype (n=22). The same comparisons by 3A5 genotype gave 28.9±4.3 and 50.9±5.2% inhibition in 6986 G/G homozygotes (n=40) and 28.6±6.8 and 48.7±8.3 in those with at least one copy of the 6986 A allele (n=14). There was similarly no difference between genotypes when compared by percent inhibition of 5μM ADP-induced OA, or to any of the other assays of platelet function to a range of ADP concentrations, or when assessed as delta aggregation, P-selectin or platelet-monocyte expression. Defining clopidogrel resistance as ≤ 10% inhibition of whole-blood single platelet counting aggregation induced by ADP 10μmol/L from baseline to post-clopidogrel time-points, 36% of patients were resistant 4 hours following clopidogrel 300mg and 14% following 10 days of clopidogrel 75mg daily. When clopidogrel 600mg loading dose was used, 14% of patients were resistant at 4 hours.
Conclusions: The platelet inhibitory effect of clopidogrel, either during the loading phase or at steady state, is unaffected by P2Y12 haplotype or CYP3A5 genotype. These gene sequence variations do not contribute to clopidogrel efficacy or explain the phenomenon of clopidogrel resistance. The use of clopidogrel 600mg as a loading dose achieves the same level of platelet inhibition by 4 hours as steady-state inhibition following 10 days of maintainance therapy.

P2964 The overestimation of aspirin resistance

U.S. Tantry[1], K.P. Bliden[1], J. Yoho[1], R. Kreutz[1], K.G. Guyer[2], Gurbel[1]. *[1]Sinai Hospital of Baltimore, Center for Thrombosis Research, Baltimore, United States of America; [2]IUSB, Departmwent of Chemistry, South Bend, IL, United States of America*

Objectives: This study was designed to determine the incidence of aspirin resistance in patients undergoing coronary stenting.
Background: Various studies have reported wide range of incidence of aspirin resistance using various techniques and have related this findings to the occurrence of adverse cardiovascular events.
Methods: 6 normal control subjects were studied at baseline and 24 hours after 325 mg aspirin dosing. 211 PCI patients undergoing coronary stenting and taking long term 81 - 325 mg aspirin therapy and 20 patients diagnosed with stent thrombosis were enrolled. 1 mM AA -induced platelet aggregation was measured by aggregometry (LTA) and thromboelastography (TEG) Platelet Mapping™ Assay at baseline and after procedure. Aspirin resistance was defined as > 50% AA-induced aggregation by LTA and by TEG.
Results: In control subjects, 1 mM AA-induced aggregation by LTA was 82 ± 10% at baseline and 2 ± 1% 24 hours post-treatment (p<0.001), and by TEG was 86 ± 14% at baseline and 5 ± 7% on 24 hours post-treatment- (p<0.001). In patients, 1mM AA -induced aggregation by LTA was 3 ± 2% at baseline and 3 ± 2% post-treatment (p<0.001), and by TEG was 5±9% at baseline and 6±14% post-treatment (Table). Out of 231 subjects, 1 patient with stent thrombosis met the criteria of aspirin resistance.

Table

	LTA Aggregation (%)		TEG Aggregation (%)	
	Baseline	Posttreatment	Baseline	Posttreatment
Control Subjects (n=6)	82±10	2±1	86±14	5±7
Patients (n=223)	3±2	3±2	5±9	6±14
Non-compliant PCI patients (n=7)	73±21	2±2	72±27	7±13
Aspirin Resistance (n=1)		54		85

Conclusions: Aspirin resistance is rare in patients treated with a long-term aspirin therapy as measured by cyclooxygenase specific methods. Our data suggest that the incidence reported in the literature may be an overestimate. A uniform and specific methodology and definitions are needed to evaluate and diagnose those subjects who are truly resistant to aspirin therapy.

P2965 Acetyl salycilic acid resistance: possible role of risk factors, medication and haemorheological variables

G. Feher[1], K. Koltai[2], B. Horvath[2], T. Alexy[2], Z. Marton[2], G. Kesmarky[2], K. Toth[2]. *[1]University of Pécs, Medical School, 1st Department of Medicine, Pécs, Hungary; [2]University of Pécs, Medical School, 1st Department of Medicine, Pécs, Hungary*

Introduction: Recent studies described the incidence of acetyl salycilic acid (ASA) resistance and its possible background. The aim of our present study was to compare the parameters of patients with effective platelet inhibition by ASA (risk profile, previous diseases, medication, hemorheological variables) to those with ineffective one.
Methods: 599 chronic cardio- and cerebrovascular patients were involved in our study (355 men, mean age: 64 ±11 yrs, 244 women, age: 63 ±10 yrs). Risk profile and previous diseases included BMI, smoking habits, hyperlipidemia, hypertension, diabetes mellitus, deep vein thrombosis, pulmonary embolism, ischemic vascular diseases. History of medication was related to alfa-blockers, beta-blockers, ACE inhibitors, AT-II receptor blockers, nitrates, statins, diuretics, Ca-channel blockers, NSAID, H2 receptor blockers, proton pump inhibitors, acenocoumarol, and trimetazidine. Blood was taken after an overnight fast be-

tween 8:00 and 9:00 a.m. Platelet aggregation was measured in Carat TX-4 optical platelet aggregometer. Blood hematocrit was measured by Heraeus microhematocrit centrifuge and red blood cell aggregation was detected by Myrenne aggregometer. Plasma fibrinogen was measured by Clauss method. Plasma and whole blood viscosities were measured in Hevimet 40 capillary viscosimeter.
Results: Patients with totally effective ASA inhibition had significantly lower plasma fibrinogen level ($p < 0.01$) and red blood cell aggregation values ($p < 0.05$), and more of them suffered from hypertension ($p < 0.05$) compared to the other group. In the case of effective platelet aggregation beta-blockers and ACE inhibitors ($p < 0,01$), while in the group of ineffective platelet aggregation statins were taken more frequently ($p < 0.05$).
Conclusion: The background of ineffective ASA medication is complex. Higher fibrinogen concentration increases red blood cell aggregation and can also result in increased platelet aggregation. The higher rate of hypertension can explain the difference of β-blocker and ACE-inhibitor medication, and an additive effect of these drugs may be involved in the effective antiplatelet therapy. On the other hand drug interactions with statins may play a role in the inefficient ASA bioavability.

P2966 Glycated haemoglobin level is strongly related to aspirin resistant thromboxane synthesis in patients with stable coronary artery disease

H. Omori[1], K. Murasaki[2], Y. Endo[2], K. Tanoue[2], N. Hagiwara[2], H. Kasanuki[2]. *[1]Tokyo Women's Medical University, Cardiology, Tokyo, Japan; [2]Tokyo Women's Medical University, Cardiology, Tokyo, Japan*

Background: High levels of HbA1c have been associated with increased mortality and increased risk of atherosclerosis. Aspirin reduces the risk of cardiovascular events in a broad category of high-risk patients. The primary antithrombotic mechanism is inhibition of thromboxane A2 synthesis. Recent data suggest a lower effect of prevention of cardiovascular disease with aspirin in diabetic patients as opposed to subjects with other cardiovascular risk factors. In this study, we evaluated the association between HbA1c and thromboxane biosynthesis with emphasis on aspirin resistance in patients with stable coronary artery disease.
Methods and Results: HbA1c and urinary 11-dehydro-thromboxane B2 (11-d-TXB2), a stable metabolite of thromboxane A2 were measured in 73 consecutive patients with stable angina who had taken 100mg of aspirin for previous seven or more days. HbA1c levels were divided into two groups: high HbA1c group (5.9–12.8%), and low HbA1c group (4.9–5.8%). In high HbA1c group, 11-d-TXB2 levels was significantly higher than that of low HbA1c group (36.07 ± 6.5ng/mmol Cr. versus 21.43 ± 2.7ng/mmol Cr., $P<0.01$). The odds ratio for high 11-d-TXB2 ($>$30ng/mmol Cr) versus low 11-d-TXB2 ($\leq$30ng/mmol Cr) was 2.12 in high HbA1c group compared with lower group. However, total cholesterol, triglycelide, LDL, CRP levels, BMI and age were not reached statistical significance.
Conclusion: Glycemic control reflected by HbA1c levels may contribute to the increase of thromboxane synthesis. These results provide possible explanation that effects of aspirin in diabetic patients are overwhelmed by aspirin insensitive mechanisms of platelet activation. These results also may help for tailoring therapy to control platelet activation and thrombus formation to improve disease development and prognosis.

P2967 Clopidogrel does not only reduce platelet degranulation and soluble CD40 ligand but also tissue factor in blood of patients with coronary artery disease

U. Rauch, T. Willich, C. Stellbaum, M. Hofferberth, M. Piorkowski, W. Poller. *Charite - Campus Benjamin Franklin, Cardiology and Pulmology Dept., Berlin, Germany*

Clopidogrel inhibits the platelet degranulation and the release of cytokines and pro-thrombogenic substances from the platelet alpha-granules. Circulating tissue factor (TF) and CD40L, both present in the alpha-granules of platelets, have been associated with an increased risk of thrombotic events in patients with coronary artery disease. This study aimed to assess clopidogrels' effect on platelet degranulation and on the cardiovascular risk markers, TF and soluble CD40 (sCD40L), in patients with stable coronary artery disease (CAD) and healthy individuals.
A loading dose of 300 mg clopidogrel, followed by 75 mg/d was given to 32 CAD patients and 22 healthy individuals. Thrombospondin exposure on platelets after stimulation with ADP or Thrombin Receptor Activating Peptide (TRAP) was flow cytometrically measured pre and 3 days post clopidogrel treatment. Soluble CD40L (sCD40L), TF as well as PMN-elastase in plasma were quantified by ELISA.
TF was increased in CAD and reduced by clopidogrel to the TF level found in healthy individuals (182 ± 19 vs. 149 ± 18 ng/ml, $p<0.001$). Clopidogrel also reduced sCD40L (0.43 ± 0.10 vs. 0.28 ± 0.04 ng/ml, $p=0.014$) and PMN-elastase (321 ± 34 vs. 248 ± 21 ng/ml, $p=0.035$) in CAD patients. Reduced sCD40L (0.50 ± 0.09 vs. 0.31 ± 0.05 ng/ml, $p<0.001$) and a trend towards a lower PMN-elastase (334 ± 25 vs. 283 ± 29 ng/ml, $p=0.12$) were also found in healthy individuals post treatment with clopidogrel. SCD40L correlated positively with ADP-induced platelet degranulation in healthy individuals ($r=0.448$, $p<0.001$) and CAD patients ($r=0.316$, $p=0.045$).
In conclusion, clopidogrel reduced plasma levels of TF, sCD40L, and PMN-elastase in patients with stable CAD. This correlated to clopidogrels' effect on reducing platelet degranulation. Thus, clopidogrel contributed to the reduction in the cardiovascular risk by inhibiting inflammatory and prothrombogenic substances in the blood of CAD patients.

P2968 600 mg clopidogrel increases platelet inhibition in coronary stenting

S. Hoffmann[1], R. Klamroth[2], C. Ewertsen[3], D. Andresen[3]. *[1]Berlin, Germany; [2]Institute of Hemostasis, Vivantes Friedrichshain, Berlin, Germany; [3]Institute of Cardiology, Vivantes Friedrichshain, Berlin, Germany*

Purpose: dual antiplatelet therapy with ASA and clopidogrel is the regimen of choice to prevent stent thrombosis. However, the inhibition of platelet function with these drugs shows a great interindividual variability with a potential lack of efficacy. Furthermore is the inhibitory effect of clopidogrel time dependent. Faster action is achieved due to a loading dose, however the value of loading dose of 300mg or even 600mg is yet not defined.
Methods: we examined 40 pts with a loading dose of 300mg clopidogrel and 40 pts with a loading dose of 600mg one day before elective PCI in combination with aspirin.
Blood samples were obtained immediately after PCI and platelet inhibition was studied by light transmittance aggregometry in platelet rich plasma using platelet poor plasma as a reference. We defined clopidogrel resistance as $>$ 30% after induction with ADP.
Results: the median time interval between the loading dose and PCI was $20h\pm6$ h. In the 300 mg loading dose group 60% of the pts (24/40) showed insufficient platelet inhibition at the time of PCI. With 600 mg loading dose this rate decreased to 20% (8/40). The incidence of diabetes was 26%(21/80) with no difference in both groups. None of the diabetic pts showed sufficient platelet inhibition after loading dose, even the higher dose had no effect.
Conclusion: 1.The majority of patients scheduled for elective PCI did not show sufficient platelet inhibition despite the recommended loading dose of 300 mg Clopidogrel.
2.The rate of sufficient platelet inhibition can be markedly increased with a higher loading dose of 600 mg Clopidogrel.
3.Patients with diabetes did not show any Clopidogrel effect 24h after Clopidogrel bolus, so there is a need in additional platelet inhibition in this group with complex interventions.

P2969 Partial P2Y12 receptor blockade by clopidogrel may not be overcome by increasing the clopidogrel dose

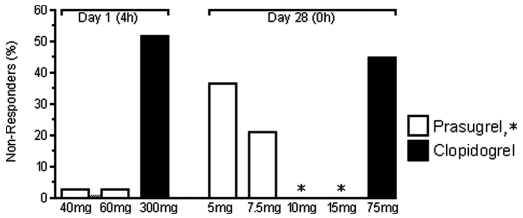
H. Judge[1], R. Buckland[2], D. Crosdale[2], R.F. Storey[2]. *[1]Sheffield University, CVRU, Clinical Sciences (North), Sheffield, United Kingdom; [2]Sheffield University, CVRU, Clinical Sciences (North), Sheffield, United Kingdom*

Clopidogrel 'resistance' has been observed in up to 30% of patients and it has been suggested that this may be associated with a higher risk of recurrent cardiovascular events. Ex vivo platelet function studies have shown that clopidogrel only partially inhibits ADP-induced responses mediated via the P2Y12 receptor. It has been suggested that this lack of response is due to the poor metabolism of clopidogrel into its active metabolite.
Studies of P2Y12 receptor blockade were carried out in normal human volunteers who received a standard clopidogrel dose regimen (300mg loading dose, 75mg daily for 7 days) and in mice fed an excessive dose of clopidogrel (100mg/kg). P2Y12 receptor blockade was assessed using radioligand binding assay (33P-2MeSADP) in the presence of an excess of the P2Y1 antagonist MRS2179, and in the absence and presence of the direct acting P2Y12 antagonist, cangrelor.
In human volunteer study, clopidogrel reduced 33P 2MeSADP binding to P2Y12 receptors by 58%. Complete P2Y12 blockade (97%) was only observed in the presence of cangrelor. However, mice fed the excessive dose of clopidogrel did not demonstrate any additional P2Y12 blockade (51% inhibition). Further inhibition was observed in the presence of cangrelor (80%).
These data suggest that a standard regimen of clopidogrel yields only partial P2Y12 receptor blockade, even at steady state, and the extent of receptor blockade may not be improved by administering a higher dose. Complete P2Y12 blockade can only be achieved in the presence of a direct acting P2Y12 receptor antagonist.

P2970 Prasugrel (CS-747), a novel thienopyridine P2Y12 receptor antagonist, results in more effective platelet inhibition than clopidogrel in aspirin-treated patients with atherosclerotic disease

L.C. Wallentin[1], T. Jernberg[2], P.T. Leese[3], A. Siegbahn[4], H. Naganuma[5], C. Payne[6], C. Darstein[7], K.J. Winters[7]. *[1]University Hospital, Uppsala Clinical Research Center, Uppsala, Sweden; [2]Uppsala Clinical Research Centre, Cardiology Department, Uppsala, Sweden; [3]Quintiles Phase I Services, Lenexa, KS, United States of America; [4]University Hospital, Internal Medicine, Clinical Chemistry, Uppsala, Sweden; [5]Sankyo Co. Ltd, Tokyo, Japan; [6]Lilly Research Centre Ltd., Windlesham, United Kingdom; [7]Lilly Research Laboratories, Indianapolis, IN, United States of America*

Background: Inadequate inhibition of platelet aggregation (IPA) is associated with an increased risk of thrombotic events after percutaneous coronary intervention (PCI). Based on preclinical studies, prasugrel (Pras) is a new potent inhibitor of ADP-mediated platelet aggregation (PA). PA, coagulation and inflammation markers were measured in this study comparing Pras with clopidogrel (Clop) in aspirin (ASA)-treated subjects with stable atherosclerotic disease.
Methods: After a run-in period on 325 mg ASA, 101 patients were randomized to 1 of 5 oral dosing regimens of a loading dose (LD) on day 1 and a maintenance dose (MD) on days 2-28: Pras - 40 mg LD with 5 mg or 7.5 mg MD, 60 mg LD with 10 or 15 mg MD; or Clop -300 mg LD/75 mg MD. Maximal PA response to 20 μM ADP was measured and IPA was calculated. Nonresponders were defined as failure to achieve $\geq$20% IPA at 4 h after the LD or at predose during MD. Plasma levels of C-reactive protein, IL-6, fibrinogen, prothrombin fragment 1+2, and D-dimer were also measured.
Results: At 4 hours after the LD, 52% of Clop patients were nonresponders compared to 3% with Pras (figure). At day 28 pre-MD, 45% of Clop patients were nonresponders, compared to 0% nonresponders for 10 mg and 15 mg Pras. Baseline levels of markers of inflammation and coagulation were low in this population and were not influenced by Clop or Pras.



Conclusion: Fewer nonresponders were observed after treatment with Pras at 40 mg or 60 mg LD and 10 mg or 15 mg MD compared to Clop (300 mg LD/75 mg MD). Prasugrel (60 mg LD/10 mg MD) is currently being evaluated in a phase 3 clinical trial. Effective IPA does not appear to influence coagulation and inflammation markers found in patients with stable atherosclerotic disease.

NUTRITION

P2971 Supplements of L-arginine attenuate the effects of high-fat meal on endothelial function and oxidative stress

W.-C. Tsai[1], C.-C. Lin[2], C.-H. Hsu[1], Y.-H. Li[1], L.-J. Lin[1], J.-H. Chen[1]. *[1]National Cheng Kung University Hospital, Department of Internal Medicine, Tainan, Taiwan; [2]National Cheng Kung University Hospita, Emergency Medicine, Tainan, Taiwan*

Background: Postprandial hypertriglyceridemia is known to cause endothelial dysfunction and increased oxidative stress. Oral supplements of L-arginine have been found to improve endothelial function. However, effects of supplements of L-arginine on the influences of postprandial hypertriglyceridemia were not studied before.
Methods: Forty young healthy men without any risk factors were equally divided into two groups. L-arginine group (age 22 $\pm$ 1 years, body mass index 23.5 $\pm$ 1.2 kg/m^2) received a standard high-fat meal and 15 gm of L-arginine. Control group (age 22 $\pm$ 1 years, body mass index 23.8 $\pm$ 0.9 kg/m^2) received a standard high-fat meal and placebo. Standard high-fat meal consisted of 900 Kcal and 50 gm of fat. Flow-mediated vasodilation (FMD), von Willebrand factor (vWF), p-Selectin, and glutathione peroxidase (GSH-Px) were measured before and 2 hours after the high-fat meal.
Results: Serum triglyceride levels were significantly increased 2 hours after the high-fat meal in both groups. In control group, FMD (10.5 $\pm$ 1.2 vs. 6.8 $\pm$ 1.4%, p $<$0.001) and GSH-Px (23.5 $\pm$ 6.2 vs. 21.9 $\pm$ 5.0 ug/ml, p = 0.029) were significantly decreased after high-fat meal. P-selectin (20.0 $\pm$ 7.7 vs. 25.9 $\pm$ 10.5 mg/l, p = 0.025) and vWF (731.2 $\pm$ 131.5 vs. 934.9 $\pm$ 133.8 mu/ml, p $<$0.001) were significantly increased after high-fat meal. In L-arginine group, FMD (10.3 $\pm$ 1.3 vs. 9.3 $\pm$ 0.9%, p $<$0.001) was slightly but significantly decreased after the high-fat meal but not GSH-Px (23.6 $\pm$ 3.6 vs. 23.0 $\pm$ 4.8 ug/ml, p = 0.468). P-selectin (20.1 $\pm$ 5.9 vs. 25.7 $\pm$ 10.2 mg/l, p = 0.001) and vWF (793.2 $\pm$ 146.0 vs. 944.4 $\pm$ 136.8 mu/ml, p $<$0.001) were significantly increased after high-fat meal. Degree of FMD attenuation following high-fat meal was significantly less in L-arginine group (1.0 $\pm$ 0.9 vs. 3.8 $\pm$ 1.5%, p $<$0.001).
Conclusions: Concomitant supplements of L-arginine improved endothelial dysfunction and oxidative stress induced by postprandial hypertriglyceridemia. However, changes of P-selectin and vWF were not affected by supplements of L-arginine with high-fat meal.

P2972 Antiatherosclerotic effects of the dietary flavenoid apigenin depend on nitric oxide

C.A. Schaefer[1], C.R.W. Kuhlmann[2], B. Wienecke[2], M.B. Schaefer[3], K. Mayer[3], H. Tillmanns[2], T. Neumann[2], A. Erdogan[2]. *[1]Giessen, Germany; [2]Justus-Liebig-University of Giessen, Dept. of Cardiology and Angiology, Giessen, Germany; [3]Justus-Liebig-University of Giessen, Lung Center, Giessen, Germany*

The dietary flavonoid apigenin has been demonstrated to induce vasoprotective effects. The aim of the present study was to examine whether apigenin-induced nitric oxide (NO) production prevents endothelial cell proliferation and migration – which are prerequisites for intima angiogenesis -, and leucocyte adhesion.
NO production was analysed using a cGMP radioimmunoassay. Apigenin caused a concentration-dependent (0.1-10 μmol/l) increase of cGMP levels with a maximum effect at a concentration of 1 μmol/l. The proliferation of human umbilical cord vein endothelial cells (HUVEC) was examined using cell counts. Compared to untreated control cells, apigenin (1 μmol/l) caused a significant reduction of cell numbers. This antiproliferative effect was completely abolished by the addition of the NO synthase inhibitor L-NMMA (300 μmol/l). In addition the effect of apigenin (1 μmol/l) was examined using a wound scratch assay. Apigenin caused a significant reduction of migrating cells and again this effect was blocked by L-NMMA. In detail migration was (in % of control): 20.1$\pm$5.8 (apigenin), 43.8$\pm$5.4 (apigenin+L-NMMA), 100.3$\pm$14.3 (L-NMMA) ($p<0.05$, n=10). The C-reactive protein-induced adhesion of [^{3}H]-labeled monocytotic U937 cells was significantly reduced by 207.2% in the presence of apigenin (1 μmol/l). The effect of apigenin was signifcantly reduced by L-NMMA ($p<0.05$, n=12).
In conclusion the results of the present study demonstrate that apigenin-induced NO synthesis is responsible for the antiatherosclerotic effects of this dietary-derived flavonoid.

P2973 Geographical influences on the association between adherence to the Mediterranean diet and the prevalence of acute coronary syndromes, in Greece

D.B. Panagiotakos[1], C. Pitsavos[2], C. Chrysohoou[2], C. Stefanadis[2]. *[1]Glyfada, Greece; [2]University of Athens, Hippokration Hospital, Athens, Greece*

Objective: We evaluated the interaction between adherence to the Mediterranean diet and region of Greece on the likelihood of having acute coronary syndromes (ACS).
Methods: During 2000-2001, a random sample of 848 patients (61 $\pm$ 10 years) with their first coronary heart disease event, and 1078 frequency matched (by age-sex) controls with no cardiovascular disease in their medical history, from all the country, entered into the study. Among several factors, adherence to the Mediterranean diet was assessed by a diet – score that incorporated the inherent characteristics of this diet.
Results: The multi- adjusted analysis showed that a 10-unit increase in the diet score was associated with a 27% (95% CI 0.66 to 0.89) decrease of the odds of having ACS. Moreover, a highly significant interaction was observed between region and diet score ($p < 0.001$). The odds ratios varied from roughly 0.5 in Southern to 1.2 or more in Northern Greek regions (p for heterogeneity < 0.05). Differences in food patterns consumed did not explain the previous findings. In addition, when we stratified our analysis by rural and urban areas we found significant differences in the estimated odds ratios (p for interaction between diet score and area = 0.01), since a 10-unit increase in the diet score was associated with 22% (95% CI 0.63 to 0.96) lower odds in urban areas and 31% (95% CI 0.48 to 0.98) lower odds in rural areas.
Conclusion: Our findings underline the significance of the Mediterranean diet on the primary prevention of ACS. Moreover, we revealed a geographical variation in importance of this dietary pattern on coronary risk, independent from the composition of food patterns consumed and the prevalence of the common cardiovascular risk factors.

P2974 Dietary supplementation with walnuts does not affect platelet-monocyte aggregation in healthy males

J.N. Din[1], A.W. Jubb[1], S.M. Aftab[1], L. Van Rensburg[2], J. Sarma[1], D.E. Newby[1], A.D. Flapan[3]. *[1]University of Edinburgh, Cardiovascular Research, Edinburgh, United Kingdom; [2]Western General Hospital, Department of Dietetics, Edinburgh, United Kingdom; [3]Royal Infirmary of Edinburgh, Department of Cardiology, Edinburgh, United Kingdom*

Purpose: A Mediterranean diet rich in alpha-linolenic acid is associated with a reduction in cardiovascular events. The mechanisms for this are uncertain. Platelet-

monocyte aggregates (PMA) are a sensitive marker of platelet activation and may contribute to the initiation and progression of atherosclerosis. We have previously shown that increased consumption of oily fish significantly reduces PMA in healthy volunteers after 4 weeks. This study assessed whether increased consumption of walnuts, a rich source of alpha-linolenic acid, would reduce PMA in healthy volunteers.

Methods: Thirty healthy males were recruited into a single-blind randomised controlled crossover trial of 4 weeks dietary walnut supplementation (15 g/day) and 4 weeks control (no walnuts). Consumption of 15 g/day of walnuts was chosen to produce a total alpha-linolenic acid intake similar to that in trials showing cardiac benefits. It also represented a realistic amount for daily consumption. Subjects completed a 3 day weighed food diary during each period to assess dietary intake of omega-3 fatty acids. Peripheral venous blood sampling was performed at baseline and at the end of each 4 week period. PMA was assessed by 2-colour flow cytometry.

Results: There was a large increase in alpha-linolenic acid intake during walnut supplementation compared to the control period (2.06±0.08 vs. 0.73±0.07 g/day, $p<0.0001$). There was no difference in the intake of eicosapentaenoic acid (0.19±0.04 vs. 0.18±0.08 g/day, p=0.82) or docosahexaenoic acid (0.25±0.05 vs. 0.24±0.06 g/day, p=0.71). Lipid profile and triglycerides were not significantly affected by walnut consumption. Walnut supplementation had no effect on PMA after 4 weeks compared to control (19.4±1.4% vs. 20.4±1.4%, p=0.46).

Conclusion: Four weeks of dietary supplementation with walnuts rich in alpha-linolenic acid does not affect PMA in healthy males. This suggests that cardiovascular benefits associated with walnuts are unlikely to be primarily mediated through effects on platelet activation.

P2975 Beneficial effects of antioxidant polyphenols contained in pomegranate juice on oxidation-sensitive gene expression and eNOS activity at the sites of perturbed shear-stress

F. de Nigris[1], L. Rossi[1], V. Sica[1], L.J. Ignarro[2], C. Napoli[3]. *[1]II Univ of Naples, General Pathology, Naples, Italy; [2]UCLA, Molecular Pharmacology, Los Angeles, United States of America; [3]University of Naples, Experimental Medicine, Napoli, Italy*

Atherosclerosis is enhanced in arterial segments exposed to disturbed flow. Perturbed shear-stress increases expression of oxidation-sensitive responsive genes (such as ELK-1, and p-JUN) in endothelium. Evidence suggests that nutritional antioxidants such as pomegranate juice (PJ) can contribute to the reduction of oxidative stress and atherogenesis. The aim of the study was to evaluate the effects of intervention with antioxidant polyphenols from PJ on oxidation-sensitive genes and endothelial nitric oxide synthase (eNOS) expression induced by high shear-stress in vitro and in vivo.

Cultured human coronary endothelial cells exposed to high shear stress in vitro and hypercholesterolemic mice were used. Intervention with PJ reduced significantly the activation of redox-sensitive genes (ELK-1 and p-JUN) and increased eNOS expression (which was decreased by perturbed shear-stress) in cultured cells and in atherosclerosis-prone areas of hypercholesterolemic mice. Moreover, PJ treatment at various degrees of the disease reduced significantly the expression of oxidation-specific epitopes and the progression of atherosclerosis in hypercholesterolemic mice.

Proatherogenic effects induced by perturbed shear-stress can be reverted by chronic treatment with pomegranate juice. This therapeutical approach may have implications for the prevention of atherosclerosis and its clinical manifestations.

DIABETES

P2976 Systolic myocardial dysfunction in asymptomatic diabetic subjects without evidence of diastolic dysfunction based on conventional Doppler interrogation. A tissue Doppler imaging study

A. Stefanidis[1], S. Bousboulas[2], K. Baroutsi[1], J. Kalafatis[1], G. Moustogiannis[1], S. Pappas[2], T. Xydas[1], E. Papasteriadis[1]. *[1]General Hospital of Nikea, 1st Cardiology Department, Piraeus, Greece; [2]General Hospital of Nikea, Diabetic Center, Piraeus, Greece*

Recent reports infer that patients with Diabetes Mellitus (DM) and diastolic dysfunction as evidenced by conventional Doppler have established systolic dysfunction when examined with Tissue Doppler Imaging (TDI) modalities.

Aim: The present study investigated using TDI if diabetic subjects with preserved diastolic function, as evidenced by conventional Doppler, demonstrate early changes of myocardial systolic deterioration.

Methods: The study population consisted of 49 consecutive diabetic (26 men, aged 53±12 yrs) and 29 control subjects (13 men, aged 53±12 yrs) with no clinical heart disease. Participants underwent full echocardiographic examination including 2-dimensional, conventional Doppler as well as TDI and stratified according to conventional Doppler in 4 groups: Diabetics with (DD, 36 persons, aged 56±9 yrs) or without diastolic dysfunction (DO, 13, 44±14 yrs) and non-diabetics with (nDD, 17, 60±11 yrs) or without diastolic dysfunction (nDO, 12, 44±8 yrs). Systolic (Sm), early (Em) and late diastolic(Am) longitudinal myocardial velocities (cm/sec), longitudinal strain (%), systolic (SSR), early (EDSR) and late diastolic (LDSR) strain rate were measured at 12 basal and medial myocardial segments and averaged. For the assessment of the combined left ventricular myocardial performance, Tei index was calculated [Tei index = (Isovolumetric Contraction+Isovolumetric Relaxation Time)/Ejection Time]. ANOVA method with Bonferroni's correction were used to assess differences between groups.

Results: Subjects with preserved diastolic function and DM (DO) had significantly lower mean systolic velocities (p:0.016), strain (p:0.001) and Tei index (p:0.031) when compared with non-diabetic patients with preserved diastolic function (nDO). Strain rate parameters between these 2 groups did not reveal significant differences.

Echo data

	Sm	Em	Am	Strain (%)	SSR	EDSR	LDSR	Ejection fraction (%)	Tei
DD	3.75±0.7	3.73±1.0	5.60±1.2	14.8±2.5	1.49±0.3	1.46±0.3	1.87±0.4	64±6	0.53±0.1
DO	4.20±0.8	5.73±1.5	4.58±1.2	15.1±2.9	1.53±0.3	1.67±0.4	1.55±0.5	63±9	0.48±0.1
nDD	4.20±0.6	4.81±1.7	4.44±1.2	17.4±2.2	1.61±0.4	1.53±0.4	1.49±0.6	67±6	0.47±0.1
nDO	5.10±0.7	6.81±0.5	3.94±0.5	19.9±2.3	1.68±0.2	1.84±0.3	1.39±0.4	65±4	0.34±0.1

Conclusion: Asymptomatic diabetic subjects with preserved diastolic function have already impaired systolic myocardial function when compared with normal subjects.

P2977 Prognostic implications of myocardial ischaemia in asymptomatic diabetic patients with no history of coronary artery disease

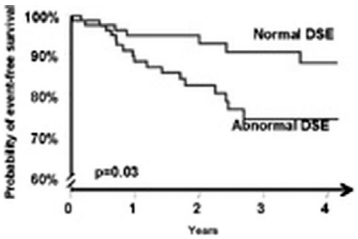
F. Sozzi[1], V. Rizzello[2], E. Biagini[2], A. Elhendy[2], E. Vourvouri[2], A. Schinkel[2], G.B. Danzi[1], D. Poldermans[2]. *[1]Ospedale Maggiore, IRCCS, Cardiology, Milan, Italy; [2]Erasmus Medical Centre, Thoraxcentre, Rotterdam, Netherlands*

Aim: to assess the value of dobutamine stress echocardiography (DSE) for the risk stratification of asymptomatic diabetic patients with no history of coronary artery disease (CAD).

Background: the prognostic significance of myocardial ischaemia in asymptomatic patients with diabetes mellitus is unclear.

Patients and methods: we studied 161 asymptomatic diabetic patients who had no history of previous myocardial infarction or revascularization. Mean age was 62±12 years, 96 men. Patients underwent DSE for evaluation of suspected CAD. Ischaemia was defined as new or worsening wall motion abnormalities. End point during follow-up was hard cardiac events (cardiac death and non-fatal myocardial infarction).

Results: ischaemia was detected in 45 (28%) patients. During a median follow-up of 5 years, 40 patients (25%) died (18 cardiac deaths) and 7 patients had non-fatal myocardial infarction (25 hard cardiac events). Survival curves in patients with normal and abnormal DSE are presented in figure. In an incremental multivariate analysis model, clinical predictors of hard cardiac events were age and hypercholesterolemia. Ischemia was incremental to clinical data (risk ratio = 2.5, 95% CI 1.1-6.3).



Cardiac events in asymptomatic diabetics

Conclusion: myocardial ischaemia assessed by DSE is an independent predictor of cardiac events in asymptomatic diabetic patients with no history of CAD.

P2978 Subclinical myocardial dysfunction in asymptomatic diabetic subjects. A tissue Doppler imaging study

J. Karantzis[1], A. Stefanidis[1], S. Bousboulas[2], K. Baroutsi[1], J. Kalafatis[1], K. Komninos[1], S. Pappas[2], E. Papasteriadis[1]. *[1]General Hospital of Nikea, 1st Cardiology Department, Piraeus, Greece; [2]General Hospital of Nikea, Diabetic Center, Piraeus, Greece*

Diabetes Mellitus (DM) substantially increases the risk of development of heart failure. Early detection of impaired left ventricular function could be very important for the prognosis in this group of patients.

Aim: The objective of the present study was to investigate the left ventricular suclinical systolic and diastolic dysfunction in patients with DM using newly developed echocardiographic techniques.

Methods: The study population consisted of 49 consecutive diabetic (43 type 2 DM, 26 men, aged 53±12 yrs, mean duration of DM 8±6 years, 23 insulin treated)

and 29 non-diabetic (non-DM) subjects (13 men, aged 53±12 yrs) with no clinical heart disease. Participants underwent full echocardiographic examination including 2-dimensional, conventional Doppler as well as Tissue Doppler Imaging (TDI). Systolic (Sm), early (Em) and late diastolic (Am) longitudinal myocardial velocities (cm/s), as well as longitudinal strain (%), systolic (SSR), early diastolic (EDSR) and late diastolic strain rate (LDSR)(1/sec) were measured at 12 basal and medial myocardial segments (apical views) and averaged. For the assessment of the combined left ventricular myocardial performance, Tei index was calculated [Tei index = (Isovolumetric Contraction + Isovolumetric Relaxation Time)/Ejection Time].
Results: Subjects with DM were found to have significantly impaired systolic and diastolic left ventricular function compared with non-DM subjects. Independent predictors of average longitudinal myocardial systolic velocities of the left ventricle were glucosylated haemoglobin (beta=-0.43, P<0.001) and age (beta=-0.33, P<0.01).Left ventricular ejection fraction, systolic and diastolic TDI parameters and Tei-index in two groups are presented in the table.

Echo data

	Sm	Em	Am	Strain (%)	SSR	EDSR	LDSR	Ejection fraction (%)	Tei
DM	3.87±0.7	4.71±1.4	5.32±1.3	15±3	1.50±0.3	1.52±0.3	1.78±0.4	64±7	0.51±0.1
non-DM	4.53±0.8	5.64±1.7	4.24±1.0	18±3	1.64±0.3	1.65±0.4	1.45±0.5	66±5	0.42±0.1
p value	0.001	0.001	0.001	0.001	0.054	0.076	0.003	0.091	0.002

Conclusion: Diabetic patients with no clinical heart disease have impaired left ventricular function at rest. Tissue Doppler Imaging is an excellent diagnostic tool for the identification of subclinical myocardial dysfunction.

P2979 Serum carboxy-terminal propeptide of human type I procollagen (PIP) is a marker of myocardial fibrosis in patients with early type 2 diabetes mellitus

S.-H. Ihm[1], H.-J. Youn[2], K.-Y. Chang[2], C.-S. Park[2], K.-B. Seung[2], J.-H. Kim[2], S.-J. Hong[2], K.-B. Choi[2]. *[1]Catholic University & the Holy Family Hosp., Internal Medicine dept, Bucheon City, Korea, Republic of; [2]The Catholic university of Korea, Internal Medicine, Cardiology, Seoul, Korea, Republic of*

Background and Objectives: This study was designed to investigate whether the serum concentration of the carboxy-terminal propeptide of procollagen type I (PIP), a marker of myocardial fibrosis, is related to the change of the ventricular filling dynamics in patients with early type 2 diabetes mellitus (DM).
Methods: Echocardiography was performed in 28 patients with type 2 DM and in 32 age-matched healthy controls, ranging from 31-69 years of age, with normal LV systolic function and ECG at rest. Subjects with diabetic complication including microalbuminuria, nephropathy (Cr > 1.3 mg/dL), severe obese (BMI > 30 kg/m^2), LV hypertrophy (LV septal thickness and/or posterior wall thickness > 12 mm on M-mode) and hypertension were excluded. The serum concentration of PIP was measured by precoated type 1 step sandwich EIA (Enzyme immunoassay) method using anti-PIP monoclonal antibody.
Results: The type 2 DM group had a lower mitral and tricuspid E/A ratio than the control group. Serum PIP was higher (P<0.05) in patients with type 2 DM than in control group.(See table) The difference in duration between transmitral forward (A) and pulmonary venous retrograde (Ar) waves (A-Ar) was considered an estimate of passive diastolic function. A-Ar was inversely related to serum PIP level in Type 2 diabetes. (r=0.43, P=0.03)

	Control (N=32)	Type 2 DM (N=28)	P value
Age	48 ± 9	52 ± 11	NS
Sex (Male: %)	47%	36%	NS
MV E/A ratio	1.17 ± 0.34	0.88 ± 0.28	< 0.01
TV E/A ratio	1.30 ± 0.25	1.15 ± 0.25	0.01
PIP (ng/mL)	109.3 ± 32.5	131.1 ± 45.6	0.04

Conclusion: These results show a relation between diastolic function and serum concentration of PIP in early type 2 DM. These findings suggest that the determination of PIP is a useful method for the screening and early diagnosis of myocardial fibrosis associated with DM.

P2980 Doppler-echocardiography as a means of early determination of diabetic cardiomyopathy for patients with diabetes mellitus type I

C.M. Schannwell[1], S. Schmidt[2], M. Schmidt[2], G. Plehn[2], B.E. Strauer[2]. *[1]Düsseldorf, Germany; [2]Duesseldorf, Germany*

Background: The early determination of the myocardial manifestation is of considerable importance, since the prognosis of patients with insulin dependent diabetes mellitus (IDDM) is generally masked by secondary cardiac complications. The aim of this study was to investigate whether young, asymptomatic patients with IDDM and persisting normal systolic left ventricular (LV) function already show a diastolic LV dysfunction.
Methods: Echocardiography was performed in 45 IDDM patients, without known cardiac disease and in 45 age- and sex matched control persons (C). Patients with a cardiac disease or long-term diabetic syndrome were excluded. Using M-mode echocardiography, morphological parameters and systolic time-intervals (fractional shortening; ejection fraction) were determined. Doppler indices were then measured: maximal early and late diastolic flow velocity (VE; VA), E/A ratio, acceleration and deceleration time (DT), isovolumetric relaxation time (IVRT).
Results: Although the left-atrial and left-ventricular dimensions, as well as the systolic functional parameters of all patients with IDDM were normal, they showed a diastolic dysfunction with a reduction of the early diastolic filling (0.58 ± 0.06 vs 0.77 ± 0.05 m/s; p < 0.01), an extension of the IVRT (129 ± 23 vs 87 ± 20 ms; p < 0.001) and an increased DT (249 ± 26 vs 187 ± 23 ms; p < 0.001).
Conclusion: Even young patients with IDDM and a normal systolic ventricular function, suffer a diastolic dysfunction. Therefore, echocardiography with measurements of systolic and diastolic functional parameters is an early, non-invasive and sensible method for the detection of diabetic cardiomyopathy.

P2981 ACE inhibitor treatment in diabetic patients prior to acute myocardial infarction may have protective effects on hospital and post-hospital morbidity and mortality

S. Ilic[1], M. Deljanin Ilic[2], D. Petrovic[1], D. Djordjevic[1]. *[1]Institute of Cardiology, Clinical Cardiology, Niska Banja, Serbia and Montenegro; [2]Institute of Cardiology, Clinical Cardiology, Niska Banja, Serbia and Montenegro*

Aim: To determine whether administration of ACE inhibitor therapy prior to acute myocardial infarction (MI) is related to infarct size, hospital and post-hospital cardiovascular morbidity and mortality and exercise capacity in hypertensive diabetic patients.
Methods: Study population consisted of 206 consecutive patients (pts) with arterial hypertension and diabtes type 2 admitted with a diagnosis of acute MI. Outcome data were compared between groups of patients receiving ACE inhibitor therapy at least three months prior to infarction (ACEI group) and those who were not (non ACEI group).
Results: One hundred and forty (68%) were receiving prior ACE inhibitor therapy. There were not significant differences in regard to age, sex, site of infarct, aspirin therapy, in two groups. Patients in ACEI group experienced smaller MI size, determined by peak creatine kinase elevation (P<0.02), and by wall motion score (14.2 ± 2.0 vs 15.8 ± 1.8; P<0.005) than pts in non ACEI group. Left ventricular ejection fraction was bigger in ACEI group than in non ACEI group (45.9 ± 8.6 vs 42.1 ± 8.3%; P<0.01). In patients receiving ACE inhibitor therapy prior to acute MI, hospital cardiovascular events were less frequent than in those who were not: ventricular fibrillation (9% vs 16%), heart failure (18% vs 26%), re-infarction (9% vs 12%), recurrent angina (13% vs 19%), vascular death (8% vs 12%). Workload on pre-discharge bicycle stress echocardiography was significantly higher (65.1 ± 16.2 vs 58.1 ± 15.6 W, P<0.05), and duration of test significantly longer (10.8 ± 4.4 vs 8.3 ± 3.4 min, P<0.01) in ACEI than in non ACEI group. There were not significant differences in regard to drug therapy including ACE inhibitor between two groups during the post-discharge six months follow-up period. After six months the incidence of post-discharge combined morbidity events (re-infarction, CHF, unstable angina, hospitalization, coronary arteriography or myocardial revascularization) were slightly higher in non ACEI than in ACEI group (46% vs 32%), as well as the cardiovascular death (8% vs 4%).
Conclusion: Our data showed that hypertensive diabetic patients who experience an acute MI, those receiving prior ACE inhibitor therapy have smaller infarct size, better global left ventricular function, less hospital and posthospital morbidity and mortality and better exercise capacity. Thus prior ACE inhibitor therapy have cardioprotective effects in hypertensive diabetic patients with acute myocardial infarction.

P2982 Beneficial modification of oxidative stress and systemic inflammation in normotensive patients with diabetes type II after angiotensin-converting enzyme inhibition treatment

E.A. Zacharis, M.E. Marketou, D. Nikitovic, G.E. Kochiadakis, E.I. Skalidis, I.K. Karalis, F. Karageorgou, P.E. Vardas. *Heraklion University Hospital, Department of Cardiology, Heraklion, Greece*

Purpose: Oxidative stress and inflammation are involved in cardiovascular complications of diabetes type II. We evaluated the effect of perindopril - an angiotensin-converting enzyme inhibitor (ACE-I) on lipid peroxides, interleukin-6 (IL-6) and tumor necrosis factor-a (TNF-a) in normotensive patients with diabetes type II.
Methods: We studied 40 normotensive patients (aged 57 ± 8 years, 22 women) with diabetes type II, a fair metabolic control (glycosylated hemoglobin < 7.5%) and a normal renal function. All patients had a normal echocardiogram and coronary angiogram. Twenty patients underwent treatment with 4 mg/day ACE -I perindopril for 6 months, while the rest served as a control group. Before entering the study and at 6 months under perindopril therapy, blood samples were taken to evaluate lipid peroxides (analyzed by a photometric assay, Oxystat, Biomedica), IL-6, TNF-a (determined by an Elisa method).
Results: No significant changes in systolic blood pressure were observed before and after treatment (124±6 mmHg versus 119±12 mmHg, p= NS).

Treatment with perindopril results in a significant decrease in lipid peroxides, TNF-a, IL-6 in patients with diabetes type II (lipid peroxides: 367 ±109 μmol/l, TNF-a: 3.3 ± 0.7 pg/ml, IL-6: 2.8 ± 0.7 pg/ml before treatment compared to 260 ± 92 μmol/l, 2.0 ± 0.86 pg/ml, 1.8 ± 0.9 pg/ml after treatment respectively, $p<0.05$ for all). No significant changes were observed in the control group.
Conclusions: Perindopril therapy has a beneficial effect on oxidative stress and cytokine serum levels in normotensive patients with diabetes type II. This may be associated with a cardioprotective action of ACE-I in diabetes type II, independently of their effect on blood pressure and may provide another important target for therapeutic intervention.

P2983 Effect of chronic sildenafil therapy on endothelial function in diabetic patients

G.M.C. Rosano[1], A. Aversa[2], C. Vitale[3], A. Fabbri[4], G. Spera[2], M. Fini[3], M. Volterrani[3]. *[1]Head Cardiovascular Research Unit, Dept. of Internal Medicine, Roma, Italy; [2]Università "La Sapienza", Internal Medicine, Roma, Italy; [3]San Raffaele IRCCS, Internal Medicine and Rehabilitation, Roma, Italy; [4]Univ. of Tor Vergata, Internal Medicine, Roma, Italy*

Phosphodiesterase-5 inhibitors (PDE5) improve erectile dysfunction and endothelial function. Diabetic patients with and without erectile dysfunction have lower response of the endothelium to PDE5 than the general patient population. Aim of this study was to evaluate the effects of chronic therapy with sildenafil (S) on endothelial function in patients with type II diabetes mellitus.
In a double-blind crossover design, 20 patients randomly received a loading dose of S (100 mg) for 3 days followed by either S 25 mg three times a day (tds) for 4 weeks or S 25 mg tds for four days followed by placebo tds for 3 weeks. Endothelial function was evaluated at baseline and at the end of each week of the study by flow mediated dilatation (FMD). Serum levels of NO, endothelin-1, CRP, IL-6, ICAM and VCAM were also measured.
After one week FMD improved significantly (>50% compared to baseline) in patients allocated to both S arms 62% and 64% respectively. In patients allocated to chronic S a progressive increase in the number of responders was noted (78%, 86%, 94% at 2,3 and 4 weeks respectively) while a progressive decrease in the number of responders was found in the placebo group (45%, 18%, 6% at 2,3 and 4 weeks respectively). At the end of the study a significant improvement in FMD compared to baseline were noted in the chronic S group (FMD from 6.8 ± 0.5 to 12.5 ± 0.7%, p=0.01 vs. baseline). A decrease in endothelin-1 levels and an increase in nitrite/nitrate levels were found in the chronic S group, (from 3.6 ± 0.5 to 2.8 ± 0.7 and from 39.1 ± 11.4 to 46.4 ± 7.3, $p<0.05$, respectively, compared to baseline). In this group significant modifications in CRP, IL-6, ICAM and VCAM levels were also found (-22%, -29%, -18%, -32%, $p<0.05$, respectively compared to baseline). No changes were observed in the placebo group.
Our results demonstrate that in diabetic patients chronic S administration improves endothelial function and reduces the indices of vascular inflammation, cronic therapy also increases the number of patients responders to the treatment suggesting that in some patients with type II diabetes there is a marked derangement of endothelial function that may be improved with a long term stimulation.

P2984 Insulin regimes which optimise postprandial glucose are associated with augmented myocardial function in patients with type 2 diabetes

H. von Bibra, U. Pischa, T. Siegmund, P.-M. Schumm-Draeger. *Stadt. Klinikum Munchen-Bogenhausen, 3. Med. Abt. (Academic Hospital Bogenhausen), Munich, Germany*

Hyperglycemia is an important cause of the predominantly diastolic dysfunction in patients with type 2 diabetes. The hypothesis was studied that myocardial function benefits from optimized postprandial glucose values in the comparison of three insulin treatment regimes.
Methods: 56 patients with type 2 diabetes were studied by ultrasound before and two hours after a standardized breakfast (48 g carbohydrates). The insulin regimes had been unchanged for 12 months and were: 1) conventional (CT) with mixed insulin 2x/d in 17 patients, 2) intensified (ICT) with a rapid acting insulin analogue 3x/d and NPH insulin 1x/d in 19 patients and 3) supplemental (SIT) with regular human insulin 3x/d in 20 patients. The three groups had comparable age of patients (64±7 years), fasting glucose and lipid values, insulin dose at breakfast (18±14 IE), hemodynamic and cardiovascular data and cardiac medication. Global systolic (Vs) and diastolic (Ve) myocardial velocities were assessed by tissue Doppler.
Results: HbA1c was comparable in CT, ICT and SIT (6,5±0.6, 6,2±0.6 und 6,4±0.7%). The postprandial increase of glucose was 57±47 mg/dl in CT, but 5±44 mg/dl in ICT ($p<0.003$) and 12±64 mg/dl in SIT ($p<0.04$). Ve was significantly decreased in CT (7.0±0.8 cm/s) vs ICT (7.9±1.4; $p<0.05$) and SIT (8.0±1.3 cm/s; $p<0.02$). Vs had similar tendencies ($p<0.08$). In all patients, there was a significant inverse correlation between the postprandial decrease of Ve and increase of glucose ($p<0.013$). Postprandially, the index of LV filling pressure was significantly higher in CT (11.8±3.9 mmHg) vs ICT (8.7±2.3 mmHg; $p<0.015$) and SIT (8.5±3.2 mmHg; $p<0.02$).
Conclusion: The studied insulin regimes modify postprandial more than fasting glucose values and demonstrate augmented myocardial function associated with optimized postprandial glucose values.

P2985 Cariporide, a selective Na^+-H^+ exchange inhibitor, reduces type 2 diabetes-associated left ventricular hypertrophy

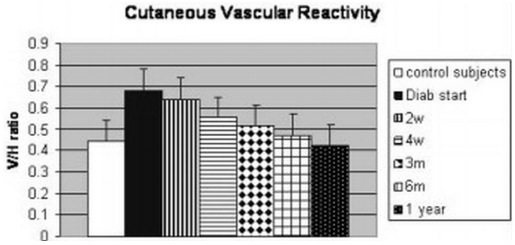
A. Darmellah[1], D. Baetz[1], F. Prunier[2], S. Tamareille[1], D. Mesangeau[3], D. Feuvray[4]. *[1]Université Paris-Sud, CNRS U 8078, Le Plessis Robinson, France; [2]Fac Méd Bichat, IFR02, Paris, France; [3]Merck-Santé, Chilly-Mazarin, France; [4]Universite Paris XI, Labo. de Physiologie Cellulaire, Orsay Cedex, France*

The Na^+-H^+ exchanger (NHE1) contributes significantly to the integrated control of intracellular pH in myocardial cells. Its potential role in the diabetic myocardium has not been established although emerging evidence is supportive of its involvement.
Aim: To study NHE1 activity, expression and regulation of activity in ventricular myocytes of type 2 diabetes-like GK (Goto-Kakizaki) rat hearts.
Methods and results: Animals (control C and GK) were fed a standard diet or diet containing 6000 ppm cariporide, a selective NHE1 inhibitor, for 13-15 wk (C-CAR and GK-CAR). There was significant hypertrophy of cardiac LV myocytes in GK rat hearts, as assessed by increased whole-cell membrane capacitance and myocyte dimension measurements, this being significantly attenuated in GK-CAR myocytes. As an index of NHE1 activity, trans-sarcolemmal acid efflux rates were determined through microepifluorescence in single cells, during recovery from intracellular acidification. Myocytes isolated from GK rat LV exhibited significantly greater sarcolemmal NHE1 activity (+100%) than myocytes isolated from control rats with an identical volume/surface area ratio. Upregulated NHE1 activity did not result from increased NHE1 protein since the protein was expressed in similar abundance in LV myocardium from GK and control rats. ERK phosphorylation (pERK), a stimulatory regulator of NHE1 activity, was also investigated. There was no change in basal level of phosphorylation of ERK and also no change in basal level of p38, another important member of the MAP kinase family. But, acidification stimulated pERK activity markedly more in GK LV myocytes than in control myocytes.
Conclusion: Cariporide treatment completely prevented the increase in NHE1 activity in GK LV myocytes and also significantly reduced LV hypertrophy, suggesting an important role for NHE1 in type 2 diabetes-associated cardiac hypertrophic process.

P2986 Improvement in vascular reactivity with Type 2 diabetes after 1 year administration of rosiglitazone

A.R. Almalty[1], S.W. Lee[2], J.S. Petrofsky[1]. *[1]School of Allied Health (Loma Linda Univ.), Loma Linda, United States of America; [2]Loma Linda, School of Medicine, Loma Linda, United States of America*

The insulin sensitizer and peroxisome proliferator-activated receptor-? (PPAR-?) rosiglitazone (RSG) has been associated with improvements in endothelial cell function. Baseline characteristics of vaso-reactivity in non-glabrous (hairy) skin of 12 subjects with type 2 diabetes were compared to 30 age matched control subjects. Subjects with diabetes were then placed on rosiglitazone (RSG) 4 mg/day and followed prospectively for one year. Reactivity was first evaluated in a 32 degree centigrade room with subjects in a horizontal posture for 30 minutes by measuring hairy skin blood flow on the calf with a laser Doppler flow meter. The subject were the tilted for 40 seconds to the 45 degree head up position and flow was remeasured. The result of the experiments showed that the ratio of blood flow under the two conditions noted above (vascular reactivity ratio) (figure 1 below) initially was approximately .42 in control subjects and 0.69 in subjects with diabetes. At baseline, these differences were significant. After 1 year, however, there was no significant difference between the groups.



Vascular reactivity

In summary, improvements in vasoreactivity was observed after administration on RSG for one year.

P2987 Diabetes mellitus is associated with increased platelet aggregation in patients on dual antiplatelet treatment

D.J. Angiolillo[1], E. Bernardo[2], C. Ramirez[2], M. Sabate[2], P. Jimenez-Quevedo[2], F. Alfonso[2], A. Fernandez-Ortiz[2], C. Macaya[2].
[1]University of Florida, Cardiology-Shands Jacksonville, Jacksonville, United States of America; [2]San Carlos University Hospital, Interventional Cardiology Unit, Madrid, Spain

Background: A broad interindividual response to dual antiplatelet treatment (aspirin and clopidogrel) has been described. In particular, some patients may have increased platelet aggregation despite using the same antiplatelet treatment regimen. Aspirin resistance has also been suggested to contribute to this phenomena. The aim of this study was to identify predictors of increased platelet aggregation in patients on dual antiplatelet treatment.
Methods: A total of 153 patients with history of coronary artery disease were included. All patients were on sustained treatment (>1 month) with aspirin (100 mg/d) and clopidogrel (75 mg/d). Platelet aggregation (PA) was assessed by light transmittance aggregometry in platelet-rich plasma stimulated with ADP (6 and 20 μM) and collagen (6 μg/ml). Aspirin resistance was defined as closure times (CT<193 seconds (s) with collagen/epinephrine coated cartridges (CEPI) using PFA-100 system (Dade-Behring), as previously reported. The patient population was divided into quartiles of PA following stimuli with ADP 6μM, ADP 20 uM and collagen 6 ug/ml (expressed as percentage of PA).
Results: Distribution of patients in each quartile of PA with ADP 6μM was as follow: 38 pts (<25.75%), 39 pts (25.75-35.5%); 39 (35.5-46.5%) and 37 pts (>46.5%); PA with ADP 20μM: 38 pts (<41.25%), 39 pts (41.25-49.0%); 38 (49.0-60.5%) and 38 pts (>60.5%) and PA with collagen 6 μg/ml was: 40 pts (<25.5%), 38 pts (25.5-40.5%); 37 (40.5-53.25%) and 38 pts (>53.25%). Multivariate analysis considering baseline demographics, risk factors, medical treatment and aspirin resistance, demonstrated that diabetes mellitus was independently associated with higher PA (corresponding with the upper quartiles of PA).
Conclusions: Diabetes mellitus is independently associated with increased PA in patients on combined aspirin and clopidogrel treatment. This may contribute to the increased atherothrombotic risk of the diabetic population.

P2988 Interaction between cardiovascular and respiratory control abnormalities in diabetes

L. Bernardi[1], C. Porta[1], A. Rinaldi[1], C. Gazzaruso[2], P. DeCata[2], P. Protti[3], R. Paltro[3], P. Fratino[4]. *[1]University of Pavia - IRCCS S.Matteo, Clinica Medica 2, Pavia, Italy; [2]IRCCS Fondazione Maugeri, Internal Medicine, Pavia, Italy; [3]IRCCS S.Matteo - University of Pavia, Clinica Medica 1, Pavia, Italy; [4]ASL Pavia, PAC, Pavia, Italy*

Diabetic autonomic neuropathy and ventilatory control abnormalities both increase cardiovascular risk. Due to reciprocal influences of cardiovascular (baroreflex) and respiratory (chemoreflex) control mechanisms, respiratory control could be impaired in diabetes by 2 different mechanisms: a) autonomic neuropathy; b) autonomic imbalance due to parasympathetic and baroreflex dysfunction, leading to sympathetic and chemoreflex activation. We hypothesised that prevalent autonomic neuropathy would depress both chemo- (particularly hypoxic) and baroreflexes, whereas prevalent autonomic imbalance would depress the baro- and enhance the chemoreflex mechanisms. In 50 type-1 diabetic subjects (33±1yr, 22 female) and in 25 age-matched controls we measured RR interval, continuous noninvasive blood pressure (Colin®), minute ventilation, oxygen saturation (SaO2) and end-tidal carbon dioxide (CO2) at rest and during progressive normoxic hypercapnia (from baseline to 55mmHg) and progressive isocapnic hypoxia (from baseline down to 80% SaO2). Baroreflex sensitivity was obtained by autoregressive spectral analysis of RR interval and systolic blood pressure ("alpha angle"), hypercapnic and hypoxic chemoreflex sensitivities were obtained by the slopes of the linear regressions linking minute ventilation to CO2 increase and to SaO2 decrease, respectively. Autonomic neuropathy was evaluated by a standard battery of cardiovascular reflex tests (deep breathing, lying-to-standing, handgrip, Valsalva manoeuvre, blood pressure changes to tilting). Mild autonomic neuropathy was present in 22/50 diabetics (average score 1.42±0.14, group N+), and absent in 28 (groupN-). Baroreflex sensitivity was reduced in the entire diabetic group (9.8±0.9 vs controls: 15.1±2.9 ms/mmHg, p<0.025), particularly in group N+ (8.5±0.9ms/mmHg, p<0.01), and not significantly in group N- (11.7±1.6ms/mmHg, p:ns). The hypoxic chemoreflex was depressed in the entire diabetic group (0.73±0.8 vs controls: 1.24±0.23 L/min/%SaO2, p<0.025), and equally reduced in group N+ (0.767±0.13 L/min/%SaO2, p<0.05) and in group N- (0.692±0.11 L/min/%SaO2, p<0.05). The hypercapnic chemoreflex was non significantly reduced in the entire diabetic group (1.86±0.19L/min/mmHgCO2, p:ns), without differences due to autonomic abnormalities. Thus, depression of both baroreflex and "peripheral" (hypoxic) chemoreflex, with mostly preserved "central" (hypercapnic) chemoreflex, indicates that cardiorespiratory control abnormalities in diabetes are mainly due autonomic neuropathy, even at an early stage of the disease.

P2989 Impact of plasma adiponectin level on left ventricular hypertrophy in patients with type 2 diabetes mellitus

R. Ogura[1], Y. Hiasa[2], Y. Ohara[2], N. Suzuki[2], T. Takahashi[2], S. Hosokawa[2], K. Kishi[2], R. Ohtani[2]. *[1]Tokushima Red Cross Hospital, Cardiology Dept., Komatsushima, Japan; [2]Tokushima Red Cross Hospital, Cardiology, Komatsushima, Japan*

Background: Adipose tissue can function as an endocrine organ by secreting adipocytokines that affect obesity-linked disorders. Adiponectin is a circulating adipose- derived cytokine that is downregulated in patients with type 2 diabetes and associated with cardiovascular diseases. Recently animal test showed that adiponectin inhibits hypertrophic signals in the myocardium through activation of AMPK signaling(Nat med. 2004 Dec; 10 Shibata Ret al.).The purpose of this study was to investigate the association of plasma adiponectin level and left ventricular (LV)hypertrophy in patients with type 2 diabetes mellitus.
Methods: seventy patients with type 2 diabetes mellitus were enrolled in this study. We compared echo-derived parameters in three groups based on plasma adiponectin status(group1;<4.5μg/ml,group2;4.5-9μg/ml,group3;>9μg/ml). Plasma adiponectin level was assessed by ELISA. End-diastolic measurements of interventricular septal thickness, LV internal diameter, and posterior wall thickness were performed employing two-dimensionally guided M-mode echocardiograms. LV mass was calculated by the equation of Devereux et al.
Results: LV mass was step-wise decreases from Group1 to Group3(239.5±76.0g vs. 175.66±97.5g vs.157.92±84.3g,p<0.05). Triglyceride and remnant lipoprotein were significantly lower in group 2,3 than group1.there were no significant differences in HbA1c and left ventricular systolic function in three groups. HDL-cholesterol was step-wise increases from Group1 to Group3(39.5±7.6 vs. 52.1±15.9 vs. 60.1±17.8mg/dl,p<0.01). Left atrium diameter was step-wise decreases from Group1 to Group3(41.2±6.2 vs. 38.6±5.0 vs. 33.7±4.6mm,p<0.01). Mitral E/A was significantly lower in group 1,2 than group3.
Conclusion: In type 2 diabetes mellitus, lowered adiponectin subjects were associated with a significantly higher prevalence of LV hypertrophy and left atrial enlargement.

P2990 Islet transplantation increases HGF and HGF-dependent pro-angiogenic signalling in diabetic mice after limb ischaemia

D. Torella[1], G. Ellison[2], A. Curcio[3], C. Spaccarotella[3], C. Manueli[4], P. Madeddu[4], A. Davalli[5], C. Indolfi[3]. *[1]Federico Ii University, Cardiology Dept., Naples, Italy; [2]Cardiovascular Research Institute, Medicine, Valhalla, NY, United States of America; [3]Cardiology, Medicine, Catanzaro, Italy; [4]National Inst of Biostruc & Biosystems, Card Med & Gene Therapy Section, Osilo, Cagliari, Italy; [5]Scientific Institute San Raffaele, Medicine, Milan, Italy*

Purpose: The delay of neo-angiogenesis in diabetes with peripheral artery disease is partially due to a decrease in hepatocyte growth factor (HGF) expression in the ischemic tissue. The aim of the present study was to assess whether pancreatic islet transplantation has a major beneficial impact on neo-angiogenesis after hindlimb ischemia in diabetic mice through HGF pro-angiogenic signaling restoration.
Methods: Streptozotocin (Stz) was administered to induce diabetes mellitus in mice. Animals were randomized into two groups: 1) Stz-induced diabetic mice; 2) Stz-induced diabetic mice in which 400 pancreatic islets taken from syngeneic mice were transplanted under the kidney capsule. Non-diabetic mice were used as the control group. Unilateral hindlimb ischemia was created by ligation of the femoral artery. Hindlimb perfusion was evaluated by laser Doppler at 28 days after surgery. After Doppler analysis, mice were sacrificed, the ischemic muscles excised and neo-capillary formation was measured by immunostaining for CD31 (specific marker for endothelial cells) and CD34 (marker for endothelial progenitor cells). Additional mice were sacrificed 3 days after hindlimb ischemia to assess HGF expression and its receptor c-met (primarily responsible for transmitting its pro-angiogenic cellular signaling) expression and activity.
Results: In diabetic mice, 28 days after surgery, blood flow in the ischemic limb was significantly reduced compared to the control mice. Transplantation of 400-islet cells rescued the impaired flow in diabetic mice compared to non-treated diabetic and control mice. At 28 days after hindlimb ischemia, capillary density was reduced in diabetic mice compared to controls. Transplantation of 400 islets significantly increased both the number of endothelial (CD31+) and endothelial progenitor (CD34+) cells, improving capillary density when compared to controls and non-transplanted diabetic mice. Finally, muscles isolated from diabetic mice at 3 days after hindlimb ischemia, revealed a strongly reduced HGF expression and a decreased c-met expression and phosphorylation, when compared to controls. Interestingly, islet transplantation in diabetic mice was associated with a significant increase of HGF expression and c-met expression and phosphorylation.
Conclusions: Islet transplantation improved neo-angiogenesis after limb ischemia in diabetic mice. This was associated with increased HGF expression in the ischemic tissue and activation of the HGF pro-angiogenic intracellular signaling pathway.

P2991 Hyperglycemia-induced apoptosis through hydrogen peroxide generation and capacitative calcium entry in human endothelial cells

S. Tamareille[1], O. Mignen[1], T. Capiod[2], D. Feuvray[3]. [1]*Université Paris-Sud, CNRS U 8078, Le Plessis Robinson, France;* [2]*INSERM, EMI-228, Lille, France;* [3]*Universite Paris XI, Labo. de Physiologie Cellulaire, Orsay Cedex, France*

People with diabetes have a 2- to 4-fold greater risk than do nondiabetic individuals of developing atherosclerosis and its complications, which include stroke, myocardial infarction, and peripheral vascular disease. Several conditions have been proposed to explain the acceleration of atherosclerosis in diabetes, including hyperglycemia (HG) and increased oxidative stress. Apoptosis is a crucial event in atherosclerosis. Previous studies have shown that HG promotes apoptosis in cultured human endothelial cells (HUVECs) in vitro.
Aim: To analyse the mechanisms by which HG initiates apoptosis in endothelial cells.
Methods and results: The increase in apoptosis is associated with a sustained increase in Ca^{2+} current resulting from capacitative Ca^{2+} entry (CCE) which is mediated by store-operated channels (SOCs). The number of apoptotic cells after prolonged (96h) high glucose (HG, 30 mmol/L) exposure was significantly reduced in the presence of CCE inhibitors. A marked increase in Ca^{2+}-dependent calcineurin (Cn) phosphatase activity also occurred after prolonged high glucose exposure. Increase in Cn activity was prevented by CCE inhibition, and selective Cn phosphatase inhibition by FK506 decreased HG-induced apoptosis. We therefore evaluated the role of reactive oxygen species in HG-elicited CCE and apoptosis. Treatment of cells with H2O2 resulted in a time- and concentration-dependent apoptosis. Treatment with ascorbic acid significantly reduced HG-induced apoptosis. In addition, negating the effects of H2O2 production using catalase was effective at reducing HG-induced apoptosis. Treatment with PP1, an inhibitor of the tyrosine kinase pp60src, which plays a role in the activation of SOCs, had a similar effect.
Conclusion: This study suggests that HG-induced apoptosis is associated with H2O2 production, which acts as an intracellular messenger by stimulating pp60src and is involved in the activation of CCE.

P2992 Estrogen improves the eNOS dysfunction in hyperglycaemia-implication for anti-atherosclerotic effect of estrogen in diabetes

T. Hayashi, A. Miyazaki-AKita, A. Iguchi. *Nagoya Univeristy Graduate Schhool of Med., Dept. of Geriatrics, Nagoya, Japan*

Introduction: hyperglycemia leading to diabetes mellitus, an independent coronary risk factor which post-menopuasal women has 3 times larger hazard ratio (risk of ischaemia attack) than male. The dysfunction of endothelial NO synthase (eNOS) plays an important role in the onset and deterioration of diabetic angiopathy. However, exact mechanisms, especially that of gender differences is still obscure.
Hypothesis: 17 beta estradiol (E2), but not testosterone improves the eNOS dysfunction in hyperglycemia, in which the effect is stronger than statin.
Methods: bovine endothelial cells (BAECs) were cultured in the medium containing various concentration of glucose. After treatment for 24-72 hours, BH4 (cofactor of NOS) level, GTPCH-I (rate limiting enzyme of de novo BH4 synthesis) activity, NOx (sum of nitrate and nitrite), O2-, mRNA and protein of eNOS and components of O2- releasing enzymes such as NADPH oxidase were determined.
Results: E2 activated the growth rate of BAECs even at high glucose concentration. In high glucose medium, oxidative stress was increased. E2, but not testosterone decreased it by restoring eNOS dysfunction through increasing the GTPCH-1 activity and BH4 level. E2 also decreased the activity of NADPH oxidase which was activated by high glucose. The effect of E2 on eNOS and NADPH oxidase were more evident in high glucose status than normal glucose status. Although statin or insulin has similar effect, the effect of E2 was more evident. Gene transfer ofestrogen receptor ERarufa increased NOx production through activation of GTPCH-1 and increase of BH4. We are evaluating the mechanism based on the fact that glycosylation modified the eNOS phosphorylation site by Akt. We ensured that estrogen and simvastatin synergistically lost the acute effect of high glucose induced eNOS inactivation through Akt pathway.
Conclusion: long term and acute treatment of estrogen was effective for showing its own anti-atherosclerotic action by improving eNOS dysfunction and regulating superoxide releasing enzyme activity in hyperglycemia.

P2993 Inhibition of platelet activation in diabetic rats by chronic treatment with the guanylyl cyclase activator HMR1766

A. Schaefer[1], U. Flierl[2], C. Vogt[2], M. Hemberger[2], M. Eigenthaler[3], U. Walter[3], G. Ertl[2], J. Bauersachs[2]. [1]*Wuerzburg, Germany;* [2]*Medizinische Klinik und Poliklinik I, Universitätsklinik Würzburg, Würzburg, Germany;* [3]*Institute of Clinical Biochemistry, Universitätsklinik Würzburg, Würzburg, Germany*

Background: Diabetes is associated with increased platelet activation contributing to the enhanced risk for atherothrombosis and thromboembolism. Under physiological conditions, endothelium-derived nitric oxide (NO) inhibits platelet activation by stimulating platelet guanylyl cyclase and cGMP. NO bioavailability and platelet sensitivity towards NO is significantly decreased in diabetes. We investigated whether chronic treatment of diabetic rats with the guanylyl cyclase activator HMR1766 would inhibit in vivo platelet activation.
Methods and results: Diabetes was induced in male Wistar rats by intravenous injection of streptozotocin. Treatment with HMR1766 or placebo was started at day 14 and continued for another 2 weeks. Thereafter, whole blood was taken from the inferior vena cava for FACSS analysis during terminal anesthesia. Compared to healthy controls, platelets from diabetic rats displayed increased fibrinogen binding on activated glycoprotein IIb/IIIa and enhanced surface expression of P-selectin indicating in vivo platelet activation. Chronic treatment with HMR1766 reversed both changes during diabetes. Furthermore, in vitro stimulation of diabetic platelets with ADP resulted in stronger expression of P-selectin than on platelets from control rats. This was suppressed by chronic treatment with HMR1766. Chronic treatment of diabetic rats with the guanylyl cyclase activator resulted in enhanced phosphorylation of platelet vasodilator-stimulated phosphoprotein, an indicator of platelet NO bioavailability and inhibitor of platelet activation.
Conclusion: Chronic activation of guanylyl cyclase by HMR1766 prevents enhanced platelet activation in diabetes and might be a promising option for future pharmaceutical treatment/prevention of cardiovascular complications in diabetes.

P2994 PPARalpha induction in adipose tissue correlates with increased insulin sensitivity and prevention of loss of left ventricular function. Effect of PPARalpha,gamma-agonist in obese dyslipidemic mice

W. Verreth[1], J. Ganame[2], A. Mertens[3], M.-C. Herregods[2], P. Holvoet[3]. [1]*Katholieke Universiteit Leuven, Cardiovascular Research Unit of CEHA, Leuven, Belgium;* [2]*Katholieke Universiteit Leuven, Department of Cardiology, Leuven, Belgium;* [3]*Katholieke Universiteit Leuven, Cardiovascular Research Unit of CEHA, Leuven, Belgium*

Objective- Obesity contributes to the clustering of the other metabolic syndrome components: hypertension, insulin resistance/type-2 diabetes and dyslipidemia. Impairment of nuclear peroxisome proliferator activated receptors (PPAR) expression is a key phase of metabolic syndrome initiation. We took advantage of the tissue-specific action of a dual PPARalpha,gamma-agonist to study the relation between PPARalpha and PPARgamma expression in adipose tissue and changes in metabolism and cardiac function in mice with combined leptin and LDL-receptor deficiency (DKO). In these mice PPARalpha and PPARgamma are downregulated and obesity, diabetes, hyperlipidemia and hypertension are associated with accelerated atherosclerosis and loss of cardiovascular function.
Methods and Results: DKO mice were treated with the dual PPARalpha,gamma-agonist (3q ([(S)-3-(4-(2-carbazol-9-yl-ethoxy)phenyl-2-ethoxy propionic acid)]) for 12 weeks starting at the age of 12 weeks. At this age, DKO have no detectable atherosclerosis and their left ventricular (LV) function (determined by echocardiography) is not different from that of lean control mice. The agonist induced PPARgamma in skeletal muscle and the heart, and PPARalpha in the adipose tissue. The latter was associated with an upregulation of the hormone sensitive lipase, GLUT-4, and FABP, resulting in increased insulin sensitivity. PPARalpha in the adipose tissue correlated with PPARgamma in the heart and with increased fractional shortening. We excluded that the effects of the agonist on PPAR expression and cardiac function were due to indirect effects of PPARdelta. Lack of increase in PPARalpha expression in liver and of PPARgamma in the adipose tissue explains the lack of effect on triglycerides and total cholesterol and thereby on atherosclerosis.
Conclusion: PPARalpha induction in the adipose tissue correlates with increased insulin sensitivity and prevention of loss of left ventricular function in the absence of a decrease in triglycerides. Our observations point to the critical role of PPARalpha in the adipose tissue as a regulator of insulin sensitivity and thereby cardiac function in the metabolic syndrome.

P2995 A rodent model of diabetic cardiomyopathy with diastolic dysfunction: haemodynamic and structural characteristics

K.A. Connelly[1], D.K. Kelly[1], Y.Z. Zhang[1], D.P. Prior[1], H.K. Krum[2], R.G. Gilbert[1]. [1]*St Vincent's Hospital, Department of Medicine and Cardiology, Fitzroy, Australia;* [2]*Alfred Hospital, Department of Medicine, Prahran, Australia*

Background: Diabetic cardiomyopathy, in the absence of coronary artery disease, is an increasingly recognized cause of diastolic dysfunction. Research into this condition has been hampered by the lack of a haemodynamically-validated animal model. The (mRen-2)27 transgenic rat develops advanced nephropathy and proliferative eye when diabetes is induced with streptozotocin (STZ), however, its cardiac pathology has not been extensively evaluated.
Methods: Six week homozygous Ren2(n=18) and non-transgenic (Sprague Dawley [SD], n=16) rats were randomized to receive STZ (diabetic) or vehicle (non-diabetic) and followed for 6 weeks. Short acting insulin (2-4 units x3 per week) was used to promote weight gain and reduce mortality. Prior to tissue collection,

animals underwent echocardiography and cardiac catheterization with pressure-volume loop acquisition.
Results: When compared with their non-diabetic counterparts, diabetic Ren 2 rats had increased lung/body weight ($p<0.05$) and evidence of diastolic dysfunction with prolonged Tau and increased end diastolic pressure volume relation (EDPVR, $p<0.01$ for both). Cardiac systolic function was not different between groups. Diabetic Ren-2 rats showed increased cardiac collagen deposition (types I and III), cardiomyocyte hypertrophy and increased phospho-Smad2 (a marker of transforming growth factor-beta activity) when compared with non-diabetic Ren-2 rats ($p<0.01$ for all parameters). No significant structural or functional changes were observed in SD diabetic animals.
Conclusions: The diabetic Ren 2 rat develops functional changes consistent with diabetic cardiomyopathy. The increased lung weight, Tau and EDPVR suggest impaired active and passive cardiac filling, consistent with diastolic dysfunction. Fibrosis, a prominent feature of this model, may be a consequence of activation of the prosclerotic cytokine, TGF-beta, by the diabetic state.

P2996 Diabetes mellitus may not have impact on heart failure mortality but it can be associated with reduced hospital admissions in patients without heart failure education and monitoring programs

E.A. Bocchi[1], F. Cruz[2], K. Alves[2], S.D. Silva[2], G. Guimaraes[2], F. Bacal[2], V. Issa[2], A.F. Ramires[2]. *[1]Sao Paulo, Brazil; [2]University of São Paulo Medical School, Heart Institute (Incor), São Paulo, Brazil*

Background: Diabetes mellitus (dbt)is a strong and independent risk factor for heart failure (CHF) and is a cause of dilated cardiomyopathy. A worse prognosis in dbt pts who develop CHF was reported in the era before beta-blocker use, mainly in dbt pts with ischemic cardiomyopathy.
Methods: We tested the hypothesis that dbt may not be a risk factor for higher mortality and hospitalization in a cohort of pts receiving treatment according recent medication guidelines for CHF. We analyzed data of the study REMADHE that was a randomized (2:1) prospective investigation, which demonstrated beneficial effects of a multidisciplinary education and monitoring program on hospitalization and quality of life in severe CHF. The intervention protocol consisted of repetitive education sessions about topics of CHF, and intensive two-week interval nurse-follow-up monitoring telephone-based. It was included 203 consecutive CHF pts in 2 groups: intervention group with 132 pts included in the intervention protocol and a control group with 71 pts. The diagnosis of type 2 or insulin-dependent diabetes mellitus was obtained in 47 pts(23%).
Results: Overall 76 pts (37.4%) died during the 653±424 days mean follow-up. The total population mortality was 30% and 39% in the dbt and non-dbt pts respectively (p=ns). The survival rate in the intervention group was at 1, 2 and 3 years 81%, 60%, 49% for non-dbt and 81%, 76% and 45% for diabetic pts (p=ns). In the control group the survival rate was at 1, 2 and 3 years 80%, 59% and 40% for the non-dbt group, and 81%, 81%, and 40% for the dbt group. In the intervention group the hospital admission days were 11±20 days for non-dbt pts and 6±16 days for dbt pts (p=0.53).In the control group the hospital admission days were 20±29 for non-dbt group, and 9±14 for dbt group (p=0.038). No differences were obtained comparing dbt and non dbt pts concerning emergency visits (intervention non dbt pts 1.1±1.6 visits versus 0.9±1.5 in dbt pts, p=ns)(control non-dbt pts had 2.9±3.8 visits versus 4.4±11.7 for diabetic pts, p=ns). A tendency for reduced mortality was observed in ischemic pts with dbt (p=0.057).
Conclusion: Dbt was not a risk factor for a worse prognosis and it was associated to reduction in hospitalization in severe systolic CHF under current guideline treatment in control group. Concepts about dbt CHF pts would be reevaluated, and the importance of factors such as education for diabetes, higher efficacy of medication, hypovolemia. and possible factors diabetes-dependent should be investigated in specific trials.

P2997 Impact of diabetes mellitus on initial and long-term clinical results of diffuse in-stent restenosis in coronary artery: multicenter registry in Japan

S. Nakamura[1], H. Sato[1], O. Hirashima[1], N. Kurita[1], M. Hirose[1], K. Hozawa[2], S. Nakamura[3], J. Koyama[3]. *[1]New Tokyo Hospital, Department of Cardiology, Matsudo, Japan; [2]Chiba Central Medical Center, Department of Cardiology, Chiba, Japan; [3]Secomedic Hospital, Department of Cardiology, Funabashi, Japan*

Background: Diffuse in-stent restenosis (D-ISR) is still a challenging problem. On the other hand, diabetes mellitus have less favorable outcomes after any form of revascularization. However, in comparison with non-diabetic patients (non-DM), the long-term clinical survival in diabetic patients (DM) underwent percutaneous coronary intervention (PCI) for D-ISR has not been validated.
Methods: To evaluate the influence of diabetes mellitus on the long-term clinical results for the treatment of D-ISR, we studied a cohort of 702 patients (822 lesions) who were treated with first D-ISR, and divided into non-DM group (n=478, male 72.4%, mean age 68.5) versus DM group (n=224, male 70.2%, mean age 66.8) respectively.
Result: See table.
Conclusion: In comparison with non-DM patients, DM is associated with significantly worse long-term PCI outcomes in patients with D-ISR.

Abstract P2997 – Table

	Non-DM (n=478)	DM (n=224)	p
In-hospital			
Procedural success (%)	98.3	98.2	NS
Clinical success (%)	97.9	97.6	NS
MACE (%)	0	0	NS
Using Cutting Balloon/rotational atherectomy	219/259	91/133	NS
6-month follow-up			
Death (%)	0	0	NS
MI (%)	0	0	NS
CABG (%)	0	5.3	<0.05
Angiographic re-restenosis (%)	27.5	51.0	<0.01
Re-PCI (%)	23.3	44.0	<0.01
Any events (%)	23.3	54.2	<0.01

P2998 Influence of diabetes mellitus in patients with long coronary lesions undergoing percutaneous coronary interventions: multicenter registry in Japan

S. Nakamura[1], H. Sato[1], O. Hirashima[1], N. Kurita[1], M. Hirose[1], K. Hozawa[2], S. Nakamura[3], J. Koyama[3]. *[1]New Tokyo Hospital, Department of Cardiology, Matsudo, Japan; [2]Chiba Central Medical Center, Department of Cardiology, Chiba, Japan; [3]Secomedic Hospital, Department of Cardiology, Funabashi, Japan*

Background: In patients undergoing percutaneous coronary interventions (PCI), diabetes mellitus (DM) is associated with poorer outcomes. On the other hand, the optimal PCI for the treatment of long coronary lesions (more than 25 mm) is still unknown. This study aimed to evaluate the influence of DM on the result of PCI in the treatment of long coronary lesions.
Methods: We studied 2,334 consecutive patients undergoing PCI for long coronary lesions, 792 (33.9%) with DM and 1,542 (66.9%) with non-DM. Stenting (bare metal stents) and rotational atherectomy were performed 1,836 patients (78.7%), 1,476 patients (53.2%), respectively. We compared the initial and long-term clinical results of the DM group and non-DM group.
Results: See table.

Table

	DM (n=792)	Non-DM (n=1542)	p
Procedural success (%)	98.5	98.8	NS
MACE at 30 days (%)	0.8	0	NS
MACE at 180 days (%)	40.5	19.8	<0.01
Angiographic restenosis at 6 months (%)	47.7	23.3	<0.01
TLR at 6 months (%)	39.8	19.8	<0.01
MACE at 1 year (%)	53.0	24.1	<0.01

MACE: major adverse cardiac event (death/CABG/MI), TLR: target lesion revascularization

Conclusions: Angiographic and clinical success rate of PCI for long coronary lesions are very high both in DM and non-DM. However, long-term clinical results in terms of restenosis, target lesion revascularization and Q-wave infarction are significantly more frequent in DM.

P2999 Impact of microvascular complications on outcome after coronary sirolimus-eluting stent implantations in diabetic patients

C. Briguori[1], G. Condorelli[2], F. Airoldi[3], A. Focaccio[4], D. D'Andrea[4], B. Golia[5], B. Ricciardelli[5], A. Colombo[3]. *[1]Clinica Mediterranea, Laboratory of Invasive Cardiology, Naples, Italy; [2]"Federico II" University, Dpt Biology, Cellular and Molecular Pa, Naples, Italy; [3]San Raffaele Hospital, interventional Cardiology, Milan, Italy; [4]Naples, Italy; [5]Clinica Mediterranea, Cardiology, Naples, Italy*

Background: We tested whether microvascular complications predict 1-year outcome after successful elective coronary sirolimus-eluting stent (SES) implantation in type 2 diabetic patients.
Methods: All consecutive type 2 diabetic patients, without any previous myocardial revascularization, who had elective SES implantation on native vessels at our Institution from April 2002 to January 2004 were analyzed. According to presence of microvascular complications, 4 groups of patients were identified: 1) group without microvascular complications, 2) group with nephropathy, 3) group with retinopathy and 4) group with both microvascular complications.
Results: Eighty consecutive diabetic patients were analyzed. Twenty-six (31%) were insulin-treated, and the remaining 54 (69%) patients were treated with oral hypoglycemic drugs.
At 15±7 months, major adverse cardiac events (MACE) occurred in 16 of the 80 (20%) patients. MACE were as follows: 3 (4%) acute myocardial infarction, 1 (1.3%) bypass-surgery, 3 (4%) death, 2 (2.7%) target-vessel revascularization and 7 (8.7%) target-lesion revascularization. MACE occurred in 3 of the 42 patients (6.7%) in the group without microvascular complications, in 3 of the 12 patients (20%) in the group with nephropathy, in 2 of the 5 patients (28.6%) in the group with retinopathy and in 8 of the 13 patients (61.5%) in the group with both microvascular complications ($p<0.001$; Figure 1). Independent predictors of MACE were: presence of both diabetic microvascular complications (hazard ratio = 34.17; p = <0.001), and age (hazard ratio = 1.10; p = 0.040), but not complete revascularization and insulin-treatment.

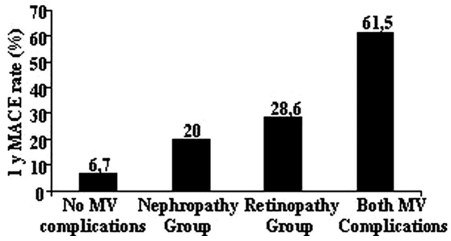


Figure 1

Conclusions: Microvascular complications represent a strong predictor of MACE following SES implantation in diabetic patients.

P3000 QT-interval dispersion in type 2 diabetic patients with previous myocardial infarction

K. Sakabe, F. Nobuo, K. Wakayama, T. Nada, H. Shinohara, Y. Tamura. *Zentsuji National Hospital, Cardiology and Clinical Research, Kagawa, Japan*

Aims: QT-interval dispersion (QTD), which reflects ventricular repolarization inhomogeneity, has been reported to increase and to have a prognostic value in patients with either myocardial infarction or diabetes. However, it remains uncertain whether diabetes lead additional QTD increase in previous myocardial infarction patients. Our aim was to compare QTD in type 2 diabetic and no-diabetic patients with previous myocardial infarction.
Methods: we investigated QTD in 89 consecutive previous myocardial infarction patients, including 22 patients with type 2 diabetes and 67 no-diabetic patients. The QTD measured with software (QTD-1) was defined as the difference in the minimum and maximum rate corrected QT-interval for any of the 12 electrocardiogram leads in which it could be reliably determined.
Results: there were no significant differences in age (70±11 vs. 70±10 years), gender (men; 13 (59%) vs. 51 (76%)), left ventricular end-diastolic volume (95±26 vs. 109±34 ml), left ventricular ejection fraction (51±7 vs. 50±20%), minimum QT-interval (364±28 vs. 362±27 ms), and maximum QT-interval (423±34 vs. 414±36 ms) between diabetic and no-diabetic patients. However, QTD was increased (67±18 vs. 58±16 ms, p=0.02) in previous myocardial infarction patients with type 2 diabetes compared to those without diabetes.
Conclusions: Type 2 diabetes led additional QTD increase in previous myocardial infarction patients. Additional increase of repolarization inhomogeneity might be implicated in the excess mortality risk of postmyocardial infarction patients with type 2 diabetes.

P3001 The realtion between type 2 diabetes mellitus, ST-elevation myocardial infarction and A1/A2 polymorphism of glycoprotein IIIa gene

A. Kozieradzka[1], K. Kaminski[1], W. Pepinski[2], J. Korecki[1], J. Janica[2], E. Frankowska[1], K. Skora[1], W.J. Musial[1]. *[1]Medical University in Bialystok, Department of Cardiology, Bialystok, Poland; [2]Medical University, Department of Forensic Medicine, Bialystok, Poland*

Glycoprotein IIIa (GpIIIa) is a membrane receptor found in various tissues. GpIIIa has two alleles: A1 and A2. According to previous studies, A2 allele is thought to be a risk factor for acute coronary events. GpIIIa's signaling cascade is modulated by enzymes called calpains, proteases that may also influence glucose metabolism. There is one small study that shows high association of A1/A2 polymorphism with type 2 diabetes mellitus (DM2). There is also known increased sensitivity of A2 form in patients with higher fibrinogen levels, condition common among diabetics.
In our research we planned to evaluate association of A1/A2 polymorphism with DM2 in a population of patients with ST-elevation acute myocardial infarction (STEMI).
The study comprised 352 individuals. From the cohort of patients hospitalised for STEMI we chose 113 patients with diagnosed DM2 (diabetic group) and 118 patients with STEMI and normal glucose metabolism (non-diabetic group).
Our control group consisted of 121 healthy persons. Genotyping was performed by restriction fragments length polymorphism (RFLP) method.
The percentage of A2 allele carriers was comparable among all groups: 20,5% (in diabetic patients), 23,4% (non-diabetic) and 21,5% (control group) (p>0,05). Actual numbers of patients and relative frequencies are shown in the Table I.
There was no significant difference in frequency of A2 allele among the groups. We have not observed any association between GpIIIa polymorphism with either DM2 or STEMI. The value of our study is limited due to the small number of patients included. Still, it is a bigger study than the previous one presenting association of A2 allele with DM2.

Table I

	STEMI and DM2 (N=113)	STEMI and normal glucose metabolism (N=118)	Healthy controls (N=121)
A1A1	90 (79.6%)	90 (76.3%)	95 (78.5%)
A1A2	20 (17.7%)	26 (22%)	22 (18.2%)
A2A2	3 (2.7%)	2 (1.7%)	4 (3.3%)

Actual numbers of patients with relative frequencies in brackets.

P3002 Cardiovascular risk factor control among diabetic patients attending community-based diabetic care clinics in Italy

F. Colivicchi[1], M. Ragonese[2], M. Ugucioni[3] on behalf of CONCORDIA study investigators. *[1]Rome, Italy; [2]ACI SMOM, Rome, Italy; [3]Osp. CTO, Cardiology, Rome, Italy*

Aim of this study was to describe the extent to which hyperglycemia, hypertension, and dyslipidemia are currently detected, treated, and controlled in diabetic patients attending community-based diabetic care clinics in Italy. The study population included 1078 consecutive patients with type 2 diabetes mellitus (48% women, mean age 69 years) enrolled in the CONCORDIA study, a quality improvement project currently conducted at 8 community-based diabetic care clinics in the Lazio region of Italy.
Clinical and medication data, as well as values of HbA1c, blood pressure, and cholesterol subfractions, were collected and entered in a prospective computerized database.
The study population showed a high prevalence of hypertension (65%), coronary artery disease (13%), peripheral arterial disease (8%) and previous cerebrovascular events (4%). Despite such findings, only 29% of patients showed adequate blood pressure control (<130/80 mmHg). Besides, optimal LDL cholesterol values (<100 mg/dl) were present in just 23% of cases. Optimal HbA1c values (<7%) were present in 59% of patients.
We conclude that cardiovascular risk factor control is the exception in diabetic patients attending community-based diabetic care clinics. Major efforts are required to improve the quality of health care currently delivered to diabetic patients.

P3003 Do age and sex have a different impact on the risk of death in diabetics with PAD?

K.J. Ishak[1], J. Caro[2], K. Migliaccio-Walle[2], I. Proskorovsky[1]. *[1]Caro Research Institute, Montreal, Canada; [2]Caro-Research Institute, Concord, United States of America*

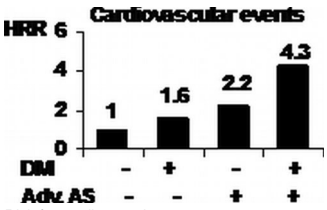
Purpose: age and sex are known risk factors for death among patients with PAD. We sought to determine whether diabetes alters the effects of these determinants.
Methods: a cohort of patients with PAD was identified from the health care records of Saskatchewan (Canada) residents diagnosed between 1985 and 1995. Follow-up ended at the time of death, departure from the province or December 2000. Data on patient characteristics and medical history were available from January 1980. Subjects were classified as diabetic if the diagnosis of diabetes was recorded prior to the index diagnosis of PAD. Other risk factors were also defined at index time. Risk of death was analysed using a proportional hazards model including age, sex and other known risk factors. Interaction terms were added to the model to test if diabetes modified the effect of age and sex.
Results: the cohort consisted of 16,440 subjects, of whom 3,172 (19.3%) were diabetic. Most (76.7%) of the 7,973 deaths occurred among diabetics. Adjusting for other risk factors, diabetes was associated with a 39.4% (95% CI: 32.2 - 47.0%) increase in the hazard of death. Diabetes reduced the effect of sex: versus females, mortality was only 17.1% higher (95% CI: 5.4 – 30.4%) in male diabetics, compared to 35% (95% CI: 28.3 – 42.2%) in male non-diabetics. Similarly, age was a weaker factor among diabetics: 6.3% per year (95% CI: 5.7 – 6.9%) compared to 10.9% (95% CI: 10.2 – 11.5%) in non-diabetics. To determine whether this is due to age and sex also being risk factors for diabetes, similar analyses for history of heart failure or atrial fibrillation were done, but no effect modification was found.
Conclusions: age and sex are strong determinants of death, but much more so among non-diabetics with PAD. Thus, once diabetes appears, the protective effect of being female or younger is significantly attenuated.

P3004 Impact of diabetes mellitus and impaired fasting glucose on the long-term prognosis of patients with atherosclerosis

C. Espinola-Klein[1], H.-J. Rupprecht[2], C. Bickel[2], K. Lackner[3], J. Meyer[2], T. Muenzel[2], S. Blankenberg[2]. *[1]Universität zu Mainz, II. Medizinische Klinik, Mainz, Germany; [2]University hospital, 2nd department of internal medicine, Mainz, Germany; [3]University clinic, Department of clinical chemistry, Mainz, Germany*

Cardiovascular risk is increased in individuals with impaired fasting glucose (IFG). The aim of this study was to evaluate the impact of manifest diabetes mellitus (DM) and IFG on the prognosis of patients with atherosclerosis.
Methods: In a prospective study we included 906 patients preceding heart catheterization. Carotid and leg arteries were examined using ultrasonographic methods. Blood samples were drawn from each subject after an overnight fasting period.
Results: Patients were compared with regard to the presence of DM (N=283, 31.2%) or IFG (fasting glucose between 110 and 126mg/dL, N=89; 9.8%). In 98

patients (10.8%) no relevant stenosis was found, 426 patients (47.0%) had CAD only and 382 patients (42.2%) suffered from CAD and peripheral stenoses (=advanced atherosclerosis). Cardiovascular events (death, infarction) after a median follow-up of 4.1 years were evaluated in 901 patients (99.4%). Presence of IFG and DM significantly increased the incidence of cardiovascular events (no DM 10.9%, IFG 13.6%, DM 23.4%, P<0.0001). Patients with advancedatherosclerosis suffered significantly more often from cardiovascular events (no stenosis 4.1%, CAD only 9.7%, advanced atherosclerosis 23.9%, p<0.0001). Prognosis was worst in patients with DM and advanced atherosclerosis (event rate 35%). The figure shows the Hazard risk ratio (HRR) for suffering a cardiovascular events.



Risk for cardiovascular events

Conclusion: Patients with IFG and DM suffered significantly more often from cardiovascular events compared to patients with normal fasting glucose. Patients with DM and advanced atherosclerosis could be identified as a high risk population with a 4-fold increase of cardiovascular risk.

P3005 Macrovascular complications of hypertensive patients with type II diabetes are independent of the presence of metabolic syndrome

J. Mourad[1], E.M. Nazal[2], Y. Gaudouen[2], A. Krivitzky[2]. *[1]Hopital Europeen Georges Pompidou, Service de Médecine Interne, Paris, France; [2]Avicenne hospital-APHP, Internal Medicine & Endocrinology, Bobigny, France*

Aim: To assess the association between the presence of a metabolic syndrome (MS) and macrovascular complications in hypertensive subjects with diabetes.
Methods: 895 hypertensive with type 2 diabetes were interviewed and examined in 113 specialized french diabetology units (mean age 63±10 years; 52% of males; mean duration of diabetes mellitus 12±9 years). Venous blood samples were collected in the fasting state for determinations of biological components of MS according to the NCEP ATPIII definition. A detailed questionnaire focusing on previous and current macrovascular complications was completed.
Results: 33.3% (n=298) of patients had at least one associated macrovascular damage: 19.5% presented angina pectoris, 13.7% had a history of myocardial infarction, 13.8% had a peripheral arterial disease and 4.9% had a history of documented stroke. According to the ATPIII definition, 131 patients had no MS, 300 patients fulfilled 3/5 factors, 270 patients had 4/5 criteria and 195 subjects had all the factors qualifying for the MS. The association between the presence of MS and macrovascular complications is detailed in the table.

	Subjects free from macrovascular damage (n=599)	Subjects with macrovascular damage (n=298)	P
Age (years)	61 ± 10	67 ± 9	0.0001
Duration of diabetes (years)	11 ± 8	15 ± 9	0.0001
HbA1c %	8.0 ±1.5	8.3 ± 3.3	0.07
HDL (g/l)	0.50 ± 0.2	0.47 ± 0.15	0.05
Serum creatinine (μmol/l)	94 ± 32	110 ± 45	0.0001
SBP (mmHg)	156 ± 14	157 ± 15	NS
DBP (mmHg)	87 ± 10	83 ± 10	0.0001
Pulse pressure (mmHg)	69 ± 14	74 ± 17	0.0001
Number of MS factors	3.6 ± 1.0	3.7 ± 0.9	NS
% of patients with MS	86.6%	89.9%	0.16

Conclusions: We found that the prevalence of the MS in a cohort of hypertensive diabetes subjects is high (85.3%)and that the MS is not associated to the presence of clinical manifestations of macrovascular damage. This result confirms that, in patients already having 2 major conventional risk factors, categorizing the presence of MS does not provide further prediction of the risk of macrovascular complications.

P3006 Is dyslipidemia among diabetics in the Middle East different from that in the West?

A. Hammoudeh[1], A. Harassis[2], H. Tarawneh[2], J. Haddad[3], Z. Mahadeen[4], M. Izraiq[5], N. Badran[6], E. Al-Mousa[5]. *[1]Ai Essra Hospital, cardiology, Amman, Jordan; [2]Khalidi Medical Center, Cardiology Department, Amman, Jordan; [3]Bader Medical Complex, Endocrinology Section, Amman, Jordan; [4]Essra Hospital, Neurology Section, Amman, Jordan; [5]Jordan University Hospital, Cardiology Section, Amman, Jordan; [6]Khalidi medical Center, Nephrology Section, Amman, Jordan*

Background and methods: Prevalence of diabetes mellitus (DM) in the Middle East is rising, and dyslipidemia in diabetics contribute to the increasing incidence of CVD in this population. Data on the prevalence of dyslipidemia in diabetics in the Middle East and whether it differs from that in the West are scarce. The Jordan Hyperlipidemia And Related Targets Study-3 (JoHARTS-3) measured levels of fasting serum cholesterol (C), triglycerides (TG), low- and high-density lipoprotein cholesterol (LDL-C and HDL-C) in mg/dl in individuals evaluated at three tertiary-care centers and outpatient clinics. None was on lipid lowering agents at the time of enrollment.
Results: Among 5000 individuals enrolled; DM was present in 1410 (40%). Women comprised 39%. Compared with nondiabetic men, those with DM had lower mean HDL-C level (38.0±10.6 vs 39.4±15.7, P=0.006) and higher mean TG level (186±78.9 vs 169±78.2, P<0.0004), but C and LDL-C levels were similar in the two groups (208 vs 207; P=0.43, and 130 vs 132; P=0.10, respectively). Similarly, diabetic women had lower HDL-C (43.8±14.2 vs 47.7±12.2, P<0.0001) and higher TG (189±78.8 vs 149±69.7, P<0.0001) than nondiabetic women. In the presence of both smoking and diabetes, the HDL-C levels are lower than levels among nondiabetic nonsmokers (36.9±10.1 vs 43.2±13.9, P<0.0001), and the TG levels are higher (201.5±80.9 vs 166.6±75.1, P<0.0001). LDL-C levels <100 were found in 19% of diabetic with CAD, and levels <70 in 5% only. With each 1g/dl increase in glycated hemoglobin (HbA1c) level; there were significant decreases in HDL-C levels (43.1 among those with HbA1c 6-7g/dl compared with 37.8 for HbA1c >10, P=.027) and significant increase in TG levels (185 to 244, P=0.02).
Conclusions: The results of this study from the Middle East confirm results of epidemiological studies from the West that diabetics have lower HDL-C and higher TG levels compared with nondiabetics. However total cholesterol and LDL-C levels are not different from nondiabetics. Poorly controlled diabetics have significantly lower HDL and higher TG levels compared with well- controlled patients.

P3007 Impaired fasting glucose is associated with greater subclinical coronary atherosclerosis in asymptomatic men without diabetes

K. Nasir[1], R.S. Blumenthal[1], R.S. Meneghelo[2], J.B. Braunstein[1], J.A.M. Carvalho[2], R.D. Santos[3]. *[1]Johns Hopkins Hospital, Cicarone Prevention Center, Baltimore, United States of America; [2]Albert Einstein Hospital, Preventive Medicine Clinic, Sao Paulo, Brazil; [3]University Sao Paulo, Heart Institute, Sao Paulo, Brazil*

Introduction: Impaired fasting glucose (IFG) is considered an intermediate stage in the natural history of disordered glucose metabolism. Recently the American Diabetic Association has proposed that the cutoff for IFG should be reduced from 110 to 100 mg/dl. In this study we evaluate whether IFG is associated with subclinical atherosclerosis as measured by coronary artery calcification (CAC).
Method & Results: We studied 539 white asymptomatic men (46±7 yrs) without diabetes (FBG<126 mg/dl as well in absence of any utilization of glucose lowering medication) who presented for electron-beam tomography in a single center. The population were calssified as 1) normal FG (NFG) with FG<100 mg/dl (n=479), and 2) IFG with FBG ≥100 mg/dl (n=60). In this study, men with IFG showed higher values of systolic blood pressure, body mass index, TG and lower HDL as compared to participants with FBG <100 mg/dl. Overall, 221 (41%) and 60 (11%) of men had any CAC and CAC≥100 respectively. The prevalence on any CAC as well CAC≥100 was significantly higher among individuals with IFG (table). In multivariate regression analyses adjsuting for CHD risk factors, compared with NFG, IFG were significantly more likely to have any CAC (OR: 1.9, 95% CI: 1.2-3.6, p=0.02) as well as CAC≥100 (2.6, 1.4-5.3, p=0.01).
Conclusion: FBG in the upper normal range appears to be an independently associated with presence and severity of CAC in apparently healthy adult men. Our finding lend support to the new IFG criteria as a risk marker for macrovascular disease.

P3008 The glucose tolerance test, but not HbA1c, remains the gold standard in identifying impaired glucose tolerance and diabetes mellitus in subjects with systemic hypertension

A.M. Salmasi, M. Dancy. *Central Middlesex Hospital, Cardiology, London, United Kingdom*

Purpose: To compare the value of the oral glucose tolerance test (GTT), glycated haemoglobin concentration (HbA1c) and fasting plasma glucose (FPG) in the identification of diabetes mellitus (DM) and impaired glucose tolerance (IGT) in hypertensive subjects who are previously not known to have DM.
Methods: 144 consecutive subjects (aged 33-83 years, median 60) who were not known to have DM and attending our Hypertension Clinic underwent a GTT, an HbA1c measurement and 24-hour ambulatory blood pressure (BP) monitoring.
Results: An abnormal GTT was detected in 94 patients (65%). FPG was not different between DM and IGT but was significantly higher than in the euglycemic subjects. A normal FPG level (<6.00mmol/l) was found in 52% (n= 33) of patients with IGT, while FPG between 6.1 and 7.00mmol/l was found in 53% (n=16) of those with DM. Using the previously published criteria of the combination of FPG > 5.7 mmol/l and HbA1c >5.9% to diagnose DM, 33% of our diabetic subjects and 75% of IGT would have been misclassified as euglycemic. The previously reported cut-off point for HbA1c of >6.1% to diagnose DM was present in 77% of

our DM and 14% (n=9) of the IGT patients. Multiple regression analysis showed that an abnormal GTT was present independently of the level of clinic or ambulatory BP, nocturnal BP dip, cholesterol level, smoking history, race or class of anti-hypertensive medication taken.

Table

	Normal GTT (n=50)	IGT (n=64)	DM (n=30)	p-value
FPG (mmol/l)	2.1-6.8 (4.9)	4.7-6.9 (5.5)**	5.0-6.8 (5.9)*	<0.0001
HbA1c (%)	4.3-6.5 (5.4)	4.8-6.5 (5.60)	5.3-7.5 (6.5)*+	<0.0001
Patients with FPG<6.0mmol/l	49 (98%)	44 (69%)	14 (47%)	<0.0001
Patients with FPG 6.1-6.9mmol/l	1 (2%)	20 (31%)++	16 (53%)++	<0.0001

** p-value<0.0001 versus normal GTT, +p-value=0.0002 versus IGT, ++p-value<0.0001 versus normal GTT

Conclusions: FPG levels or HbA1c or their combination are not accurate enough to identify DM or IGT in patients attending a hospital Hypertension Clinic. A GTT is required in these patients to reliably identify those with DM or IGT.

P3009 Increased heart rate and heart rate variability alterations are associated with subclinical inflammation in patients with impaired glucose tolerance

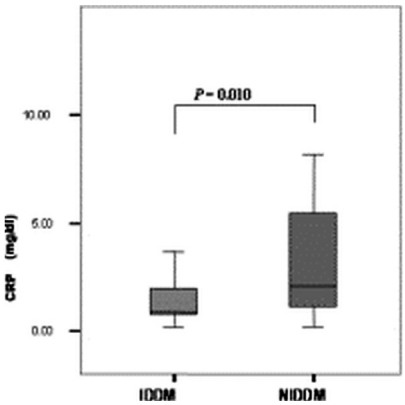
G.F. Diakakis[1], F.I. Parthenakis[1], A.P. Patrianakos[1], H.E. Mavrakis[1], E.A. Zacharis[1], E. Ganotakis[2], P.E. Vardas[3]. *[1]Heraklion University Hospital, Cardiology Dept., Heraklion, Crete, Greece; [2]Heraklion University Hospital, Dept. of Internal Medicine, Heraklion, Greece; [3]Heraklion University Hospital, Department of Cardiology, Heraklion, Greece*

Purpose: Altered cardiac autonomic tone with reduced heart rate variability(HRV) and increased inflammatory status, have been found in patients with diabetes mellitus. However there is scant information about the relationship of these parameters in prediabetic state patients. This study was designed to investigate the association of heart rate (HR) and HRV alterations, both indexes of the autonomic nervous system, with circulating levels of inflammation markers in patients with impaired glucose tolerance.
Methods: Thirty age-matched healthy indviduals were compared with 40 patients (24 men, 49.8±6.8 years) with impaired glucose tolerance diagnosed during the last year. All patients were asymptomatic, with no coherent disease, inflammation or any other risk factor for coronary artery disease. Patients and controls underwent an ambulatory 24-hour Holter recording; HR changes and time domain HRV parameters were calculated. Blood samples for proinflammatory cytokines were also taken and Interleukin- 1 (IL- 1) and 6(IL-6), tumor necrosis factor-a (TNF-a) and its soluble receptors (sTNFR) II and I were calculated by immunoassay.
Results: Patients showed increased HR(78.2±10.3 vs70.5±8.7 beats per minute, p<0.05) compared to controls. Among the time domain HRV parameters, the standard deviation of the average normal to normal intervals in all 5-min segments of the entire recording (SDANN) was decreased (97.5 ±31.1 vs 109.0±28.7 ms, p<0.05), the standard deviation of all NN intervals (SDNN) was also decreased (59.3±18.4 vs 68.5±17.2 ms, p<0.05), while the percentage of adjacent cycles differing >50ms (pNN50) showed a reduction trend (11.7±9.1 vs 15.6±13.5 ms, p = 0.27). The cytokine measurements showed that patients had elevated TNF-a (2.45±0.45 vs 1.60±0.65 pg/ml, p<0.05), sTNFRII (2.05±0.56 vs 1.41±0.55 pg/ml, p =0.15) and slightly increased IL-1b (0.41±0.12 vs 0.51±0.15 pg/ml, p<0.05) circulating levels, compared to controls. Simple linear regression analysis showed that reduced SDANN correlated significantly with TNF-a (p<0.05) and sTNFRII (p<0.05) while the increased HR correlated with IL-6 (p<0.01) and TNF-a (p<0.05) respectively.
Conclusion: Increased HR and reduced HRV are associated with elevated proinflammatory cytokine levels in patients with impaired glucose tolerance. This interaction between inflammation and autonomic nervous system alterations may constitute indexes of primary atherosclerotic process in those patients.

P3010 Different activation of acute phase response in type 1 and type 2 diabetes: an explanation for the different cardiovascular risk

S. Giubilato[1], A. Buffon[1], D. Pitocco[2], G. Liuzzo[1], L.M. Biasucci[1], G. Ghirlanda[2], F. Crea[1]. *[1]Catholic University, Department of Cardiovascular Medicine, Rome, Italy; [2]Catholic University, Internal Medicine, Rome, Italy*

There is increasing evidence that an ongoing acute-phase response is closely involved in the pathogenesis of type 2 diabetes; conversely few and conflicting data are available in type 1 diabetes.
The aim of this study was to investigate markers of systemic inflammation in type 1 and type 2 diabetic patients.
Methods: We studied 27 type 1 diabetic patients and 27 age- and sex-matched type 2 diabetic patients. All patients had no clinical evidence of microvascular or macrovascular complications and a good glycemic control on insulin therapy. Fasting venous blood sampling were collected to assess serum concentrations of high sensitivity C-reactive protein (hs-CRP), glyco-haemoglobin (HbA1c) and lipid status.
Results: Type 1 compared to type 2 diabetic patients had lower body mass index (24.3?2.3 vs 27.2?3.8 kg/m^2, p<0.002), trygliceride (79.9?17.4 vs 115.5?56.1 mg/dl, p=0.003), insulin intake (0.49?0.12 vs 0.60?0.16 UI/kg, p=0.006), HbA1c (7.4?0.8% vs 8.5?1.4%, p=0.001), as well as lower serum levels of hs-CRP (0.9, range 0.2-7.9 vs 2.1, range 0.2-50.0 mg/dl, p=0.01).
Univariate and multiple regression analysis were performed to assess the relationship between clinical and metabolic variables with hs-CRP levels. In type 1 diabetes, no variable was significantly related to hs-CRP levels. Conversely, in type 2 diabetes, BMI was directly related to hs-CRP levels (Spearman Rho, r=0.40, p=0.03) ant it was the only variable independently related to the inflammatory marker (p=0.01).



CRP levels in type 1 vs type 2 diabetes

Conclusions: Our data demonstrate that type 2 diabetes and obesity are associated with a higher degree of inflammation than type I, suggesting a pathophysiological explanation for the higher rate of cardiovascular complications in type II vs type I diabetes.

P3011 Cardiovascular autonomic dysfunction in patients with impaired glucose tolerance

T. Laitinen[1], J. Oinonen[2], J. Lindstrom[3], J. Tuomilehto[3], M. Uusitupa[4] on behalf of the Finnish Diabetes Prevention Study Group. *[1]Kuopio, Finland; [2]Kuopio University Hospital, Department of Clinical Physiology, Kuopio, Finland; [3]National Public Health Institute, Dept Epidemiology and Health Promotion, Helsinki, Finland; [4]University of Kuopio, Department of Clinical Nutrition, Kuopio, Finland*

Objective: The aim of this study was to investigate the prevalence of cardiovascular autonomic dysfunction in subjects with impaired glucose tolerance (IGT) and to characterize associations between the metabolic syndrome and cardiovascular autonomic regulation in the Finnish Diabetes Prevention Study cohort.
Materials and methods: Originally, 522 subjects overweight subjects with IGT based on two oral glucose tolerance tests were randomized to lifestyle intervention (aimed at reducing weight and increasing physical activity) and to control group. In the 2nd annual follow-up visit after the end of intervention, we performed deep breathing tests and active orthostatic tests to 322 individuals who had remained non-diabetic in each group (174 intervention, 148 control) to detect possible parasympathetic (E/I ratio = 1.1 during deep breathing) and sympathetic dysfunction (a decrease in systolic blood pressure = 20 mmHg in response to standing up). Other main examinations were anthropometric measurements, oral glucose tolerance test (OGTT), assessment of plasma glucose, insulin, glycated hemoglobin A1c, serum lipids and blood pressure.
Results: Prevalence of parasympathetic dysfunction was almost equal in intervention and control groups (33% vs. 28%, respectively, NS). Parasympathetic dysfunction was associated with parameters reflecting metabolic syndrome, such as waist-to-hip ratio and triglycerides (P<0.01, and P<0.05, respectively), and obesity such as weight and body mass index (P<0.001 for both), while it was not statistically signinificantly associated with other characteristics of metabolic syndrome including elevated blood pressure, glucose and insulin levels or glycated hemoglobin A1c. Prevalence of sympathetic dysfunction was also comparable in intervention and control groups (8% vs. 3%, respectively, NS). Sympathetic dysfunction was associated only with elevated systolic blood pressure (P<0.05).
Conclusions: We conclude that cardiocascular autonomic dysfunction is common in patients with IGT. Obesity per se or central obesity plays an important role in the pathogenesis of cardiovascular autonomic dysfunction. One reason why no differences were found between intervention and control groups in this respect could be the fact that the incidence of diabetes was more than twice as high in the control group than in the intervention group, and diabetic patients were not included in these measurements.

P3012 Increased HOMA insulin resistance is associated with increased clinical features of the metabolic syndrome

P. Ambery[1], S. Crozier[2], H. Syddall[2], D. Phillips[2], C. Cooper[2] on behalf of Hertfordshire Cohort Study Group. *[1]GlaxoSmithKline, London, United Kingdom; [2]University of Southampton, MRC Epidemiology Resource Centre, Southampton, United Kingdom*

Background: Increased HOMA-IR is strongly associated with both prevalent and incident cardiovascular disease. Both development of Type 2 diabetes and cardiovascular disease are strongly associated with number of features consistent with a diagnosis of metabolic syndrome. In this study we examine the relationship between raised HOMA-IR and increasing clinical features of the metabolic syndrome.
Methods: 1,245 men and women from the Hertfordshire Cohort Study were characterised according to number of features consistent with a clinical diagnosis of metabolic syndrome using the General Medical Services guidelines. These were BP > 145/85 or treated hypertension, HDL < 1.2mmol/l, waist > 36 inches men/>32 inches women, and fasting glucose > 6.1mmol/l or 120 min glucose > 7.0 mmol/l. Fasting insulin and glucose levels were used to determine HOMA-IR for each subject.
Results: Subjects who displayed at least 3 clinical features of the metabolic syndrome had significantly higher HOMA-IR levels compared to those with less than 3 clinical features ($P < 0.0001$). HOMA-IR was 73% higher in those with 3 or more clinical features of the metabolic syndrome, than in those with less than 3 features. Adjustment for age and sex did not substantially affect the results.
Conclusion: Easy to measure clinical parameters such as raised blood pressure, low HDL cholesterol, abnormal glucose and increased waist size may be a useful tool for clinical identification of biochemical insulin resistance, thus identifying those at increased risk of cardiovascular disease, prevalent and incident Type 2 diabetes.

ELDERLY

P3013 Favourable impact of referral to cardiologists on the control of risk factors in elderly patients with atherosclerosis seen in ambulatory general practice. The French ELIAGE-MG Survey

N. Danchin[1], S. Quentzel[2], E. Amelineau[2], J.P. Cambou[3]. *[1]Hopital Europeen Georges Pompidou (HEGP), Service de Cardiologie, Paris, France; [2]BMS, Paris La Défense, France; [3]Inserm U 518, Toulouse, France*

Background: Implementing risk factor control and secondary prevention in elderly patients is difficult. Limited data are available regarding the influence of referral to a cardiologist on the efficacy of secondary prevention in patients followed by their GPs.
Methods: ELIAGE-MG was a survey carried out in 1789 GPs from 09 to 12/2003 in France. Consecutive patients ≥70 years of age with known atherosclerosis were enrolled. In all, 3257 patients (mean age: 76±5 years; 63% men) with complete data available were included. Of them, 2760 (85%) had been referred to a cardiologist at least once over the previous 12 months.
Results: Compared with those not referred to a cardiologist, fewer were current smokers (15% vs 19%, p=0.03), had a LDL cholesterol > 115 mg/dL (60% vs 72%, p=0.001), a BMI ≥30 (14% vs 18%, p=0.03), or remained hypertensive (53% vs 59%, p=0.015). Likewise, referral to a cardiologist was associated with a higher prescription of secondary prevention medications (Table). Multivariate logistic regression analysis showed that referral to a cardiologist was independently associated with a lower risk of elevated LDL (OR: 0.61; 95% CI: 0.45-0.83, p=0.002), current smoking (OR: 0.65; 95% CI: 0.50-0.85, p=0.002), obesity (OR: 0.76; 95% CI: 0.58-0.99, p<0.05), but not of elevated blood pressure. Likewise, referral to cardiologist was associated with a higher prescription of antiplatelet agents (OR: 1.97; 95% CI: 1.58-2.44, p<0.001), beta-blockers (OR: 1.69; 95% CI: 1.35-2.12, p<0.001), statins (OR: 1.41; 95% CI: 1.11-1.80, p=0.005) or quadruple therapy (OR: 2.65, 95% CI: 1.68-4.19, p<0.001), but not of ACE-I.

On-going medications

	Antiplatelet	Beta -	Statins	ACE-I	All 4 classes
Cardiologist +	80%	49%	71%	43%	14%
Cardiologist -	67%	26%	57%	37%	5%
P value	0.001	0.001	0.001	0.01	0.001

Conclusion: In this large survey of elderly patients with known atherosclerotic disease followed by general practitioners, previous referral to a cardiologist had a positive effect on both the prescription of secondary prevention medications and control of risk factors. Overall, however, both control of risk factors and secondary prevention medications prescription remained far from optimal in this elderly population.

P3014 Pulmonary capillary wedge pressure and the blood pressure response to the Valsalva manoeuvre: normal values in healthy elderly subjects

J.J. Remmen[1], W.R.M. Aengevaeren[2], F.W.A. Verheugt[2], R.W.M.M. Jansen[3]. *[1]University Medical Center, Heartcenter, Department of Cardiology, Nijmegen, Netherlands; [2]University Medical Center, Heartcenter, Department of Cardiology, Nijmegen, Netherlands; [3]University Medical Center, Geriatric Medicine, Nijmegen, Netherlands*

Background: The blood pressure response to the Valsalva manoeuvre is related to pulmonary capillary wedge pressure (PCWP), yet this has never been studied specifically in the elderly, in whom the prevalence of heart failure is the highest. To interpret data of elderly cardiac patients correctly, we sought to obtain normal values of PCWP and of the blood pressure response to the Valsalva manoeuvre in healthy elderly subjects. In addition, we studied whether elevated PCWP (≥15 mm Hg), achieved by inflation of an anti-Gravity garment, could be diagnosed by the blood pressure response to the Valsalva manoeuvre.
Methods: 28 healthy subjects, aged 70±4 years (mean±SD) performed standardized Valsalva manoeuvres before, immediately after, and 4 minutes after anti-Gravity garment inflation, in supine and semi-recumbent position. PCWP was measured with a Swan-Ganz catheter. From the blood pressure response to the Valsalva manoeuvre, the systolic blood pressure ratio (SBPR), pulse pressure ratio (PPR), and stroke volume ratio (SVR) were calculated. The discriminatory power of these ratios to diagnose elevated PCWP was assessed with receiver operating characteristic (ROC) analysis.
Results: PCWP, mean ±SD in mmHg (5th – 95th percentiles), was 9.8±1.9 (16.7-13.3) in supine position and 8.9±2.1 (5.1-12.4) in semi-recumbent position. In supine position, SBPR, PPR, SVR, mean ±SD (5th – 95th percentiles), were 0.76±0.11 (0.57-0.98), 0.51±0.16 (0.22-0.90), and 0.42±0.11 (0.23-0.67), respectively, and in semi-recumbent position 0.74±0.10 (0.57-0.97), 0.46±0.14 (0.27-0.83), and 0.41±0.10 (0.26-0.66). In supine position at 4 minutes after anti-G garment inflation, the areas under the ROC curve for elevated PCWP of SBPR, PPR, and SVR were all above 0.85.
Conclusion: This is the first study that obtained normal values of the blood pressure response to the Valsalva manoeuvre and PCWP in healthy elderly subjects, which might be of interest for the correct interpretation of patient data. In supine position, the blood pressure response to the Valsalva manoeuvre showed significant discriminatory power in the detection of elevated PCWP, which underscores its potential in the non-invasive diagnosis of heart failure.

P3015 B-type-natriuretic-peptide-guided hospitalised management does not guarantee improved long-term prognosis in senile patients with heart failure

T. Inomata, M. Nishii, T. Koitabashi, I. Takeuchi, H. Nakano, H. Takehana, H. Shinagawa, T. Izumi. *Kitasato University School of Medicine, Internal Medicine & Cardiology, Sagamihara, Japan*

Background: We have reported B-type-natriuretic-peptide (BNP)-guided hospitalized management, in which treatment was intensified by adding some drugs to improve the status of heart failure (HF) until plasma BNP decreased below 200 pg/mL, thus reducing subsequent events of HF. It has never been elucidated, however, whether BNP-guided management has clinical significance in senile HF patients (pts) as well.
Methods: Fifty-three consecutive pts over 75 years old were admitted for HF exacerbation and managed under the BNP-guided strategy stated above in Jan, 2001-May, 2003. We investigated the relationship between subsequent cardiovascular events after discharge and plasma BNP at discharge.
Results: There was no significant difference of plasma BNP at discharge between pts with or without following readmission for HF exacerbation (379±460 vs. 342±415 pg/mL, NS; Fig. 1A). The pts with plasma BNP below 200 pg/mL at discharge did not receive a superior outcome of cardiac-event-free survival compared to those above 200 pg/mL (Fig. 1B), either. Pts who had suffered subsequent cardiovascular events after hospital discharge in spite of plasma BNP under 200 pg/mL at discharge had significantly poorer compliance of self-management such as water/sodium restriction, body weight measurement, or drug intake compared to those above 200 pg/mL (P=0.040).

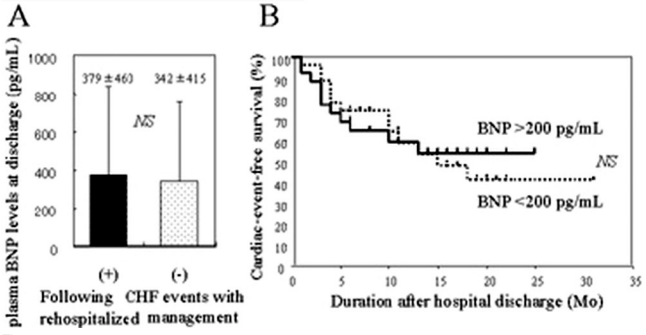


Figure 1

Conclusion: Organized disease management including basic self-control for HF as well as drug intensification under BNP-guided strategy is important for the adequate control of HF in senile pts.

P3016 Exercise testing is feasible, efficacious and cost-effective in the prediction of cardiovascular events in the very elderly as compared with Dipyridamole Tc-99m Sestamibi SPECT

L.J. Vacanti[1], A.C. Sposito[2], J.A.F. Ramires[3]. [1]*Heart Institute (InCor-DF), Zerbini Foundation, Brasilia, Brazil;* [2]*Heart Institute (InCor-DF), Zerbini Foundation, Brasilia, Brazil;* [3]*University of Sao Paulo, Heart Institute, SP, Brazil*

Purpose: To define the prognostic value and cost-effectiveness (CE) of treadmill test (TT) using the Duke treadmill score (DTS) as compared with Dipyridamole Tc-99m Sestamibi (SPECT) in patients ≥75 years.
Methods: We studied 66 individuals (40% men) with a mean age of 81±5 years. Among them, 65% had comorbidities, 28% presented with atypical chest pain and 12% with typical angina, 57% hypertensive, 38% dyslipidaemic, 28% diabetic, 48% Framinghan high risk patients and 20% with known coronary artery disease. The TT protocol was a ramped modification of the Bruce protocol. The SPECT comprised 2 stages: pharmacological stress and rest. Ischemia was diagnosed using current guidelines. Death, acute coronary syndromes and coronary revascularization were considered major cardiovascular events (MACE). We defined SPECT and TT CE ratio (american dollars) as cost per event detected by abnormal SPECT and as cost per event detected by intermediate and high DTS, respectively. The variables with a p value< 0.05 were considered statistically significant.
Results: The percent maximal predicted heart rate (MPHR) achieved was 95±9% and 88% of patients reached 85% of their MPHR. The calculated METs and the heart rate systolic blood pressure product at peak exercise was respectively: 7±2 and 24946± 4576 (bpm x mm Hg). Ischemic changes occurred in 14 (21%) subjects during TT and in 10 (15%) during SPECT and the correlation concordance was 0,63 (p< 0.01). After the 685± 118 days of follow-up 6 deaths, 1 coronary artery bypass grafting and 2 episodes of unstable angina occurred. Univariate variables associated with MACE included: age (83± 6 vs 80± 4 years; p=0.048), male gender (78% vs 33%; p=0.02), ST depression (1±1 vs 0.25± 0.6 mm; p= 0.01), intermediate and high DTS (44% vs 2%; p=0.001) and abnormal SPECT (44% vs 10%, p= 0.02). After adjustment for confounding variables high or intermediate DTS risk and age were the only variables identified as an independent predictor of MACE (HR 8.5, 95% CI 2-36, p=0.003 and HR 1.2, 95% CI 1.0-1.4, p=0.03, respectively). The CE ratio of applying SPECT in order to predict one event case was $34,440 for low risk, $14,280 for intermediate risk and $2,240 for high risk subjects, according to the Bayesian analysis of patient data. The CE ratio of applying TT for the same purpose was $7,175, $2,975 and $467, respectively.
Conclusion: TT and SPECT are comparable for assessing overall myocardial ischemia in the very elderly. The high and intermediate DTS was superior to predict MACE and represented a better cost-effectivity when compared to SPECT.

P3017 Effect of fluvastatin on cardiovascular events and lipid parameters in 2,236 elderly patients. Results from the fluvastatin pooling analysis

E. Bruckert[1], M.P. Verpilleux[2], C. Gimpelewicz[3], J.O. Logan[3], C. Ablethasuer[4], M. Bortolini[3]. [1]*Hopital Pitié-Salpétrière, Endocrinology & Metabolsim department, Paris, France;* [2]*Novartis Pharma, Clinical Development, Rueil-Malmaison, France;* [3]*Novartis, Medical Department, Basel, Switzerland;* [4]*Novartis, Medical Department, Nuremberg, Germany*

Background: Over the past few years, strong evidence supporting the use of statins in various populations has emerged. Cardiovascular disease is a major cause of morbidity and mortality in elderly patients. There is a consensus that elderly patients should be treated for dyslipidemia. This analysis was conducted to assess the lipid modulating efficacy, clinical outcome and safety profile of fluvastatin in patients =65 years old.
Methods/Patients: Data from 30 completed double-blind, randomized, placebo and active control studies, with at least 6 weeks of active treatment and daily fluvastatin doses of 20 mg, 40 mg, and 80 mg were included in a pooled database. Total cholesterol, LDL-C, HDL-C and triglycerides were evaluated at baseline and on study medication. A further analysis of clinical outcomes included only studies with duration of 1 year or longer in which clinical end points were collected and reviewed by blinded adjudication committees.
Results: The pooled database included 7,463 patients randomly assigned to fluvastatin treatment and 4,352 patients randomly assigned to placebo treatment. There were 2,236 fluvastatin patients and 1,481 placebo treated patients above 65 years of age. Mean age was 71.9 years in the placebo group and 71.1 years in the fluvastatin treated group.
Fluvastatin treatment resulted in mean reduction in LDL–C of 30.2% from baseline to Week 12 as compared to placebo (p=0.001). The clinical outcome analyses included 1421 elderly patients (706 placebo treated patients and 715 fluvastatin treated patients). In the group of fluvastatin treated elderly patients, the incidence of major adverse cardiac events (MACE) was 19.2% compared to 24.8% in placebo group: the risk of MACE was reduced by 30.0% (OR 0.70, 95CI 0.55 - 0.91, p = 0.007). Treatment with fluvastatin resulted in a statistically significant risk reduction in cardiac death and myocardial infarction of 36.0% (OR 0.64, 95%CI 0.43-0.95, p=0.027). Overall the clinical safety profile was similar in both treatment arms
Conclusions: This pooled analysis showed that fluvastatin is an effective, safe and well tolerated drug to reduce cardiovascular endpoints in elderly patients.

P3018 Evidence that early posthrombolysis stenting is more effective than a conservative ischaemia-guided approach in the elderly with thrombolysed STEMI. A GRACIA 1 substudy

P.L. Sanchez Fernandez[1], J.J. Alonso[2], A. Castro-Beiras[3], J. Blanco[4], J.A. Briales[5], F. Fernandez-Vazquez[6], G. Pena[1], F. Fernandez-Aviles[1] on behalf of Grupo GRACIA, Red Temática de Enfermedades Cardiovasculares, Spain. [1]*Hospital Clinico Universitario, ICICOR, Valladolid, Spain;* [2]*Fuenlabrada, Spain;* [3]*Hospital Juan Canalejo, Cardiologia, A Coruña, Spain;* [4]*Hospital Rio Hortega, Cardiologia, Valladolid, Spain;* [5]*Virgen de la Victoria, Cardiology, Málaga, Spain;* [6]*Hospital de León, Cardiology, León, Spain*

Background and Methods: The recently reported GRACIA 1 Study randomised patients (n=500), who presented STEMI, to angiography within 24 hours of thrombolysis followed by coronary stenting or to a conservative approach guided by ischemia. The main analysis showed that early posthrombolysis stenting was safe and preferable to the conservative strategy since it reduced the incidence of the primary endpoint of death, recurrent MI or revascularization at one-year. We report here the outcome in the elderly (≥ 75 years) subgroup (14.2% of the overall population).
Results: Compared with younger patients, the elderly had a higher absolute baseline risk profile. The incidence of the primary endpoint was 18.6% in the elderly and 12.7% in younger patients. Overall mortality was over tripled in the elderly (10.0% vs 2.6%). At one year outcome was significantly better in the elderly randomised to early posthrombolysis stenting rather than conservative approach (8.3% vs 29.4% respectively, adjusted odds ratio 0.22; 95% confidence interval, 0.05 to 0.87, p=0.03); the corresponding rates in younger patients were 10.0% vs 15.5% respectively (OR 0.61; 95% CI: 0.34 to 1.10, p=0.61). For mortality, there was an interaction between the elderly status and treatment strategy favouring early posthrombolysis stenting (5.6% vs 14.7%; OR:0.29 95% CI: 0.05 to 1.72, p=0.17). No such trend was observed in the younger patients group (2.8% vs 2.3% respectively; OR 1.16; 95%CI: 0.16 to 2.59, p =0.81).
Conclusions: These results suggest that in the elderly presenting STEMI, early posthrombolysis stenting should be preferred to a conservative strategy since it improves one-year clinical outcome.

P3019 Dementia and myocardial infarction in the community

F. Bursi[1], W.A. Rocca[2], J.M. Killian[2], S.A. Weston[2], S.J. Jacobsen[2], V.L. Roger[1]. [1]*Mayo Clinic, Division of Cardiovascular Diseases, Rochester, United States of America;* [2]*Mayo Clinic, Health Sciences Research, Rochester, United States of America*

Background: There are conflicting reports on the possible association between coronary disease and dementia.
Purpose: To examine the association between myocardial infarction (MI) and dementia in a population-based study.
Methods: Using the record-linkage system of the Rochester Epidemiology Project, 916 cases of dementia and 916 age (± 1 year) and sex matched controls were identified in Rochester, Minnesota between 1985 and 1994. Dementia was defined using the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition. From the same population, we identified all subjects who experienced an MI (defined using standardized criteria) during the period 1979-1998. We analyzed the association between dementia and MI with two separate analyses for MI preceding or following the onset of dementia (or the index year for controls). For MI occurring prior to the index year, we used conditional logistic regression (case-control analysis), while for MI occurring after the index year, we used survival analysis to account for death and censoring (cohort analysis)
Results: Before the index year, MI occurred in 35 dementia cases (3.6%) and in 33 controls (3.9%), and there was no association (OR= 1.10, 95% CI 0.67-1.80, p=0.760) between MI and dementia. However, after the index year, there was a significantly decreased risk of MI in patients with dementia compared to referent subjects (HR=0.62, 95% CI 0.41-0.94, p=0.024). This association persisted after accounting for the competing risk of death and MI.
Conclusion: In this population-based study, there was no evidence of a positive association between dementia and preceding MI. The lower risk of MI after the onset of dementia may reflect a difference in ascertainment, with MI being underdiagnosed among patients with dementia.

P3020 The influence of patients age in the acute management of atrial fibrillation

A. Martin[1], P. Laguna[2], C. Arco[2], I. Millan[3], P. Gargantilla[2], A. Lozano[2], B. Coll-Vinent[2], M. Cancio[2] on behalf of the GEFAUR investigators. [1]*Hospital de Mostoles, Emergency Department., Mostoles, Spain;* [2]*Spanish Society of Emergency Medicine, Arrhythmia Division, Madrid, Spain;* [3]*Clínica Puerta de Hierro, Biostatistics, Madrid, Spain*

Background: Patients' age is a major factor involved in the prescription of anticoagulants in atrial fibrillation (AF) in most of studies, but limited information is available about the rest of management strategies in these patients.
Objectives: We analysed the influence of patients' age in the performance and effectiveness of the management strategies(MS) of AF in the acute setting daily practice.
Methods: Prospective multicenter observational study carried out in 12 emergency departments, July-2001&Feb-2002. Elderly: >75 years. Suitability of management: Rhythm control (RhyC) if AF<48h, Rate control (RC) if HR>100 bpm and anticoagulation (ACO) following ACCP 1998 guidelines.
Results: 1481 patients included, age 74±12 y.(57%>75y),58% women. RC is less performed in the elderly (65 vs73% OR 0.7), same effectiveness, lower use of calcium/beta-blockers (6vs13% OR 0.45) and higher of digoxin (82vs65%). RhyC was attempted in 40% of AF<48 hours of duration (80% of them<75y OR 0.6), less frequently in elderly pts (34vs55% OR 0.2), with no differences in the procedure (pharmacological in 95%) or in its effectiveness. Amiodarone is more frequently used in>75 (65 vs. 39%, p=0.02) and I-C drugs in pts<75y.(47 vs. 26%, p=0.04). In the multivariate analysis the CV attempt in pts<75y was only associated with the absence of hypertension (p=0.02, OR=1.75) and dyspnoea (p=0.03, OR=2.2), as were palpitations (p=0.01, OR=3.4) in elder pts. ACO were more frequently prescribed to <75 (35vs25% OR 2.3) as was aspirin in the elderly (27 vs. 14%, p<0.001, OR=1.5). ACO prescription was associated with hypertension (p=0.01, OR=1.5) and absence of heart failure (p=0.02, OR=1.9) in <75y and to paroxysmal AF (p<0.001, OR=3.7) in the elderly. RC relieves symptomatology (p=0.005, OR=1.9) in both groups and RC and CV reduce the number of admissions (p=0.006). ACO is more suitable prescribed in <75y (concordance with guidelines 32vs20% OR 2).
Conclusions: Age is a main determinant of AF management in daily practice despite patients' risk profile and indications for treatment. Management strategies are less frequently performed in elder patients despite the fact that their effectiveness does not fall with age and they associate substantial benefits (symptom relieving and reduce hospital admission). Therefore, it is not age but the patients' clinical profile that should be decisive when management strategies are evaluated in this major group of patients with AF.

P3021 Long-term survival in patients undergoing coronary angioplasty: comparison with survival of general population

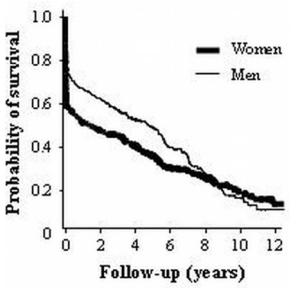
F. Ettori[1], G. Parrinello[2], O. Leonzi[1], C. Fiorina[1], G. Chizzola[1], S. Curello[3], L. Niccoli[1]. [1]*Spedali Civili, Cath Lab Cardiothoracic Dept, Brescia, Italy;* [2]*Biostatistics, University, Brescia, Italy;* [3]*University of Brescia, Cattedra di Cardiologia, Brescia, Italy*

Background: Although several studies reported early clinical outcome in patients older than 75 years undergoing coronary angioplasty (PTCA), information concerning long term survival in this group of patients, compared with survival of general population of similar age is scanty.
Patients and Methods: In order to investigate whether PTCA improves survival in patients older than 75 years, we compared survival of patients older than 75 years undergoing PTCA, with that of general population of similar age (ISTAT tables), limiting our study to one year period and Brescia province. We estimated expected survival by Hakulinen approach.
From September 2001 to December 2003, 550 patients older than 75 years underwent PTCA for acute myocardial infarction (AMI)(26%), unstable (49%) or stable angina (25%). Follow-up was completed in 438 patients (170 females). Median age was 78 years (IQR=76-81) and median follow-up 21 months (IQR=1-31 months).
Results: At the end of the study 17% of patients had had a fatal event. A higher mortality was found in patients older than 78 years (p<0.007). No difference was found concerning sex or age at time of PTCA. Figures show that, compared with general population, in patients undergoing PTCA for AMI, survival was decreased at 1 month (p<0.05), whilst in patients undergoing PTCA for unstable or stable angina survival was unchanged.
Conclusions: Our data show that, apart from an increased early mortality in patients undergoing PTCA for AMI, expected survival in old patients undergoing PTCA is similar to that of general population of similar age, thus suggesting that in older patients cardiac events do not result in additional risk.

P3022 Short and long-term prognosis of first acute ST-segment elevation myocardial infarction in older women. The PPRIMM75 Registry

H. Bueno[1], H.D. Juan[2], M. Martinez-Selles[2], E. Perez-David[2]. [1]*Hospital Univ. "Gregorio Maranon", Cardiology, Madrid, Spain;* [2]*Hospital "Gregorio Marañón", Cardiology, Madrid, Spain*

Background: The influence of gender on mortality in older patients with AMI is controversial.
Aim: To assess the independent impact of gender on short- and long-term prognosis in older patients with a first STEMI.
Methods: The clinical characteristics, hospital outcomes and long-term mortality of 395 consecutive older women (W) were compared with those of 380 men (M) with STEMI enrolled in the PPRIMM75 Registry -a prospective study designed to address the outcomes and prognosis of patients ≥75 years of age admitted to a single CCU for a first AMI- between October, 1989, and December, 2000.
Results: W were older*, had a higher* prevalence of diabetes, hypertension, and history of CHF, and lower* of smoking and history of PAD. AMI location, reperfusion rate, and LVEF did not differ between sexes. During hospitalisation, W presented higher incidences of CHF (53% vs 48%*), cardiogenic shock (23% vs 16%*), and mechanical complications (14% vs 7%*). In-hospital mortality was 36% in W and 24% in M*. Multiple logistic regression analysis controlling for age, risk factors, Killip class, delay on admission, and reperfusion therapy, selected female gender as an independent predictor of early mortality (OR: 1.57; 95% CI: 1.06 – 2.33, p=0.03). * p <0.01
Median survival time (97% complete FU)was 60 months in M and 50 months in W (p=0.006, see Graph). Cox regression analysis controlling for the factors used for hospital mortality adjustment did not select female gender as an independent predictor of late mortality (hazard ratio 0.89; 95% CI: 0.72 – 1.12)



Survival after first STEMI by gender

Conclusions: Older women have a worse short-term prognosis than older men after a first STEMI. The impact of gender seems to be only clinically relevant at the earlier phase of myocardial infarction.

P3023 Significant increase in mortality and cardiovascular events in 6880 elderly German primary care patients with peripheral arterial disease

C. Diehm[1], H.J. Trampisch[2], J.R. Allenberg[3], R. Haberl[4], B. von Stritzky[5], S. Lange[2], D. Pittrow[6], H. Darius[7]. [1]*Teaching Hospital, Internal Medicine/Vascular Medicine, Karlsbad-Langensteinbach, Germany;* [2]*Ruhr University, Dept. of Med. Inf., Biom., Epidem., Bochum, Germany;* [3]*Univ., Dept. of Vascular Surgery, Heidelberg, Germany;* [4]*Municipal Hospital Harlaching, Department of Neurology, Munich, Germany;* [5]*Sanofi-Aventis, Med. Dept., Berlin, Germany;* [6]*Inst. for Clin. Pharmacol., Tech. Univ. Dresden, Dresden, Germany;* [7]*Vivantes Hospital Neukölln, I. Med. Clinic, Berlin, Germany*

Objectives: Patients with symptomatic, but also asymptomatic peripheral arterial disease (PAD) often present with coronary artery disease (CAD). We aimed to quantify the excess cardiovascular risk borne by PAD patients compared to those without PAD in a typical primary care sample of elderly patients.
Methods: The German Epidemiological Trial on Ankle Brachial Index (getABI) is a large-scale epidemiological observational prospective 3-year study in 6,880 unselected patients = 65 years in 344 representative practices across Germany. The prevalence of PAD (defined as ankle brachial index [ABI] < 0.9) was determined with standardized Doppler sonography; CAD events (myocardial infarction, coronary revascularisation, and cardiac death) were reported by GPs and verified by hospital data.
Results: The baseline characteristics of the patients were as follows: mean age 72.5 yrs, 58% females, mean systolic/diastolic blood pressure 144/81 mmHg, 65% hypertension, 25% diabetes mellitus, 52% lipid disorders, mean ABI 1.03. The prevalence of PAD in the total sample was 18.0%. At 1 year, all-cause mortality was 2.8% in patients with PAD and 0.9% in patients without PAD (crude odds ratio [OR]: 3.0 [95% confidence interval: 2.0; 4.7]; OR adjusted for known risk factors: 2.0 [1.3; 3.3]). 1-year mortality due to CAD was 1.5% (PAD) vs. 0.3% (no PAD): crude OR 4.9 [2.5; 9.5], adjusted OR 2.5 [1.3; 4.9]. CAD events occurred in 3.7% (PAD) versus 1.4% (no PAD): crude OR 2.7 [1.8; 3.8], adjusted OR 1.6 [1.1; 2.3]. The following risk factors had a statistically significant association with 1-year CAD events: current smoking vs. never smoked: OR 2.5 [1.4;

4.3], history of CAD or cerebrovascular events vs. none: OR 2.0 [1.4;3.0], physician diagnosis of lipid disorders vs. none: OR 1.9 [1.3;2.9], age above median vs. below: OR 1.5 [1.1;2.3]), PAD vs. no PAD: OR 1.6 [1.1;2.3], homocysteine > 19.1 μmol/l vs. = 19.1 μmol/l (80% quantile): OR 1.6 [1.1; 2.3], hypertension vs. no hypertension: OR 1.6 [1.0; 2.5], HDL = 40 vs. < 40 mg/dl: OR 1.6 [1.1;2.5]. No significant associations were found for: gender, diabetes, and LDL = 130 vs. < 130 mg/dl.

Conclusions: Patients with PAD have a substantially increased risk for (short-term) all-cause mortality and CAD events. Current smoking, previous events and lipid disorders were the strongest predictors for CAD.

P3024 Impact of anaemia and renal dysfunction on cognitive function in elderly patients with heart failure

D. Del Sindaco[1], G. Pulignano[2], A. Di Lenarda[3], A. Giulivi[2], G. Cioffi[4], M. Merlo[3], G. Sinagra[3], F. Leggio[1]. *[1]IRCCS INRCA, Cardiology, Rome, Italy; [2]Rome, Italy; [3]Ospedali Riuniti, Cardiology, Trieste, Italy; [4]Villa Bianca, Cardiology, Trento, Italy*

Aim: Heart failure (HF) is often associated with cognitive impairment (CI). HF, anemia, renal dysfunction and CI are associated with mortality, impaired quality of life and disability. Aim of the study was to prospectively assess the impact of Anemia and renal dysfunction (RD) on CI in community-living elderly HF pts treated with optimized HF therapy.

Methods: . A cohort of 190 outpts aged >70 yrs (77±5, range 70-94, 53.7% males) with clinically stable HF were prospectively studied. All pts underwent complete clinical and multidimensional geriatric assessment. Cognitive status was assessed by means of Folstein Mini Mental State Examination (MMSE).

Results and Conclusions: Mean ejection fraction (EF) was 32.9±10, mean NYHA class was 2.7±0.6 (61.6% NYHA 3-4); RD (Creatinine clearance <60 ml/min) was present in 85.7%, Anemia (Hemoglobin [Hb]<12 g/dl) in 42.6% and CI (MMSE<24) in 38,9% of pts. Depressive symptoms were present in 59.8%. Pts were treated with optimized HF therapy (betablockers [BB] 52%, ACE-i/ARB 94%, spironolactone 35%). The variables significantly associated to CI were: age, female gender, Body Mass Index <21; education level <5years, depressive symptoms, anemia and severe RD (Creatinine clearance <30 ml/min). The association of anemia and severe RD showed the higher risk of CI (6,082 [2,549- 14, 542], p<0,0001). CI was also associated to disability, worse quality of life (Minnesota LHF), higher mortality (RR 2,949 [1,47-5,89]) and risk of hospitalization for worsening HF (RR 4,282 [2,266-8,092]). No association was found between CI and blood pressure, EF% or diabetes. At multivariate analysis, age (OR 1.144 [1.047-1.250]), low education level (OR 9,792 [4.157-23.064]), anemia (OR 2,492 [1,184-5,247]) and severe RD (OR 3,345 [1.369-8,175]) were independently associated to CI. Hb was split into six group and a linear relationship between Hb and CI was found, with the range 15-16.5 g/dL appearing to have the lower CI (19,4%) (p= 0,005). There was no significant interaction between anemia and BB in pts taking this therapy.

In conclusion, this study suggests that, in spite of optimized therapy: 1) CI is very common in elderly HF pts and is independently associated to anemia and renal dysfunction, rather than to ageing or other clinical and psycho-social factors alone; 2) CI is associated to worse quality of life, disability and prognosis; 3) an association between CI and Hb levels is evident. Further studies are needed to answer the question of whether optimal treatment of anemia and RD may prevent or postpone CI in HF pts.

P3025 Conventional risk factors – especially waist circumference – are strong predictors of cardiovascular health in women but not in men among 75-year old people without known diabetes

G. Nilsson[1], P. Hedberg[2], T. Jonasson[2], I. Lonnberg[3], J. Ohrvik[4]. *[1]Västeras, Sweden; [2]Central Hospital, Dept of Physiology, Vasteras, Sweden; [3]Central Hospital, Dept of Cardiology, Vasteras, Sweden; [4]Central Hospital, Dept of Clinical Research, Vasteras, Sweden*

Background: Knowledge about the importance of conventional risk factors among elderly people is scanty. Recent reports have highlighted the importance for cardiovascular disease of glucometabolic disturbances also among non-diabetics.

Methods: We studied cardiovascular health among 75-year old people (N=433; 210 men and 223 women from the general population in a defined geographical area (participation rate 70%). From this cohort we selected all patients without previously known diabetes with a complete echocardiographic examination, including left ventricular wall motion index (WMI), and an exercise test with a heart rate of at least 75% of the age predicted heart rate. The selected group comprised 304 persons (153 men and 151 women). A cardiovascularly healthy subgroup (N=105; 45 men and 60 women) was defined as persons who did not fulfil any of the following criteria: self-reported history of myocardial infarction, angina pectoris, hypertension, heart failure, atrial fibrillation or any other severe cardiovascular disease; regular cardiovascular medication; abnormal 12-lead resting ECG; exercise ECG >1mm ST-segment depression or echocardiographical abnormality including WMI <1.7.

Results: Odds ratios with 95%CI and p-value from univariable logistic regression are presented in Table 1. A forward stepwise multivariable logistic regression analysis in women resulted in the following significant risk factors: waist circumference (p=0.002), systolic blood pressure (p=0.025) and blood glucose (p=0.033).

Table 1

	Men	Women
Waist circumference per 5 cm	0.94 (0.77-1.16); 0.574	1.40 (1.17-1.69); 0.000
Body mass index per unit	0.99 (0.88-1.11); 0.848	1.18 (1.07-1.31); 0.001
Blood glucose per 0.5 mmol/L	1.00 (0.79-1.27); 0.999	1.45 (1.11- 1.89); 0.006
Triglycerides per 0.5 mmol/L	0.83 (0.65-1.08); 0.165	1.30(1.02-1.64); 0.031
HDL cholest per 0.5 mmol/L	1.20 (0.66-2.18); 0.545	0.68 (0.48-0.96); 0.030
LDL cholest per 0.5 mmol/L	0.95 (0.78-1.15); 0.596	0.91 (0.76-1.09); 0.290
Sys blood press per 10 mm Hg	1.22 (1.04-1.43); 0.014	1.19 (1.03-1.37); 0.017

Conclusion: Among 75-year old people from the general population without known diabetes, conventional risk factors, especially waist circumference, systolic blood pressure and blood glucose, are strong predictors of cardiovascular health in women but not in men.

REHABILITATION AND SECONDARY PREVENTION

P3026 The great gap between guidelines and practice in secondary prevention in the population of small towns in Poland – results of the Polish 400 cities programme

L. Wierucki[1], T. Zdrojewski[1], T. Grodzicki[2], J. Gluszek[3], K. Narkiewicz[1], A. Januszewicz[4], G. Opolski[5], B. Wyrzykowski[1] on behalf of the Working Group of the Polish 400 Cities Programme. *[1]Medical University of Gdansk, Dept. of Hypertension and Diabetology, Gdansk, Poland; [2]Jagellonian University, Cracow, Poland; [3]Medical University of Poznan, Poznan, Poland; [4]Institute of Cardiology, Warsaw, Poland; [5]Medical University of Warsaw, Warsaw, Poland*

Aim: The aim of the study was to assess the prevalence and control of cardiovascular diseases risk factors (cvd RF) in subjects with history of myocardial infarction (MI) and stroke, living in small Polish towns and villages.

Material and Methods: The Polish 400 Cities Programme (P400CP) is large scale interventional programme. The aim of medical arm of the P400CP is to increase detection and control of cvd RF in inhabitants of 418 small towns (<8 000 inhabitants) and surrounding villages in Poland, particularly in men and lower educated people. In 2003 and 2004, screening intervention was performed in 123 cities. All together, we examined 36696 subjects aged between 18 to 98. In all questionnaire interviews, blood pressure (BP) (two readings during one visit), and anthropometric measurements, as well as laboratory tests (glucose (GLU), total cholesterol (TCH) - strip tests, whole capillary blood) were performed. Material and methods: In the examined group there were 1315 subjects with history of MI (3,58%; W 2,35%; M 5,99%; p<0,001), 396 subject after stroke (1,08%; W 0,90%; M 1,43%; p <0,001) and 75 subject with history of MI and stroke (0,20%; W 0,12%; M 0,38%; p< 0,001). Mean age in subjects after MI or stroke was higher in woman than in man (W 67,1±9,28; M 64,0±9,34; p<0,001). A history of AH or newly increased BP was detected during the visit in 87% of the subjects after MI or stroke (W 88%; M 85%; ns). Only 14% of subjects with earlier detected AH were well controlled (BP<140/90mmHg) (W 11%; M 17%; p<0,01). TCH value higher than 190mg/dl or earlier detected hypercholesterolemia had 73% (W 78%; M 69%; p<0,001). Only 33% subject with earlier detected hypercholesterolemia were well controlled (TCH <190mg/dl)(W 27%; M 37%; p<0,01). Diabetes or incorrect fasting glucose (>100mg/dl) had 36% of subject after stroke or MI (W 34%; M 38%; ns). Only 32% of subject with earlier detected diabetes were well controlled (fasting GLU <100mg/dl) (W 33%; M 31%; ns) Overweight or obese were 78% of the subjects (W 76%; M 81%; p<0,01). Abdominal obesity was observed in over half examined subjects (waist: W >88cm; M >102cm)(W 70%; M 45%; p<0,001) Almost 12% of subjects were still active smokers (W 7%; M 15%; p <0,001) Conclusions: 1 There is great gap between guidelines and practice in secondary prevention in small towns in Poland, 2. This situations calls for urgent preventive and therapeutical interventions in this group. 3. High prevalence and low control of AH in participants of the P400CP confirm the decision of targeting this program to citizens of small towns and villages.

P3027 Four year follow-up of the multicentre RCT of the COACH study shows that The COACH Programme keeps patients out of hospital

M. Vale[1], V. Sundararajan[2], J. Best[3], M. Jelinek[4]. *[1]St. Vincent's Hospital Melbourne, Cardiac Investigation Unit, Melbourne, Australia; [2]Victorian Department of Human Services, Health Surveillance Section, Melbourne, Australia; [3]Deparment of Medicine, University of Melbourne, St Vincent's Hospital, Australia; [4]Cardiac Investigation Unit, St Vincent's Hospital, Fitzroy, Australia*

Background: The COACH Program (TCP) is a training program for patients with CHD whereby a health professional coach trains patients to aggressively pursue the target levels for their biomedical coronary risk factors (CRFs) while working in partnership with their own doctor(s). The Coaching patients On Achieving Cardiovascular Health (COACH) study was a multicentre RCT which showed that TCP

substantially improved CRF status at 6 months over and above usual care (UC). Although TCP targeted biomedical CRFs it also produced substantial improvements in psychological factors.
Purpose: To determine whether random assignment to TCP was associated with a difference in survival and hospital utilisation in comparison to the UC group at 4 years after randomisation. If there was a difference, we planned to evaluate which factors were most significantly associated with the reduction in hospital use.
Methods: The COACH study ended on Nov 30, 2000. After the 6 month trial, all 792 patients (398 TCP, 394 UC) received an intensive 2-hour coaching session on how to achieve the targets for their biomedical CRFs. Follow up data on hospital use and survival was obtained by linkage of the COACH data to hospital utilisation and death registry data via the linked Victorian Admitted Episodes dataset (VAED) and the linked VAED-Victorian death index dataset. To assess whether there was a statistical difference in hospital use between the groups, we calculated the rate/100 person years and 99% CI for cardiac admissions, all admissions, cardiac beddays and all beddays. A similar process was followed to assess whether there was any difference in hospital use by important covariates.
Results: There was a 92% survival in both TCP and UC patients at 4 years. The rate of beddays used for cardiac illness was 15% less than for UC patients (127 vs 149, $P<0.01$). The rate of all cause hospital admissions was 16% less in coached vs UC (105 vs 125, $P<0.01$). The rate of beddays occupied by coached patients was 20% less than UC (359 vs 448, $P<0.001$). There was no relationship between change in biomedical CRFs and subsequent bed ultilisation but improvements in anxiety levels and self reported health, mood and fitness at 6 months were highly predictive of subsequent reduction in bed usage for cardiac disease at 4 years.
Conclusions: This follow-up study has shown that TCP reduces all cause hospital readmissions and achieves large reductions in hospital stays for cardiac illness and illness of any cause. This may be due to the indirect impact of coaching on psychological status of patients with CHD.

P3028 Effectiveness of the implementation of a secondary prevention programme in patients with acute coronary syndromes

R.H. Rey, M. Rostan, C. Moreno, M. Trevisan, A. Delfante, O.O. Bazzino. *Hospital Italiano, Cardiology Dept., Martinez, Argentina*

Secondary prevention medical therapies benefits are well established but these therapies continue to be underutilized in patients with acute coronary syndromes (ACS).
This study sought to determine if a multidisciplinary program by a team that included cardiologists, a nurse, a dietitian -secondary prevention program (SPP)- focused on initiation of aspirin, beta blocker, angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor antagonists (ARA), statins, in conjunction with diet, physical activity and cigarette smoking counselling in patients with ACS is better than standard care.
SPP's patients were included before hospital discharge and followed by a team for 1 year after discharge.
Methods: Medication used rates, blood pressure measurement, lipids levels and clinical outcomes were compared in patients with ACS in the period before (January 2001 to December 2002) and the period after (January 2003 to December 2003) SPP was implemented.
Results: A total of 513 patients with ACS, 22.3% acute myocardial infarction and 77.7% non-ST-segment-elevation acute coronary syndromes (NSTE-ACS) were included. A total of 289 consecutive patients after SPP (intensive care group) and 224 consecutive patients before SPP (standard care group) were compared. Both group were matched regarding age, gender, diabetes and prior myocardial infarction.
In the intensive care group ACEi use was higher compared with the used in patients with standard care (42% to 31%; $p<0.01$). Likewise, the use of ARA (13% to 5%; $p<0.01$) and statins (80% to 49%; $p<0.01$). was twofold higher in patients in the intensive care group compared with patients receiving standard care. A reduction in levels of LDL-C was more important (108 $\pm$31 mg/dl vs. 122$\pm$37 mg/dl; $p<0.01$) and National Cholesterol Education Program goal (LDL-C $<$100 mg/dl) was more likely met in the intensive care group (69% vs. 33%; <0.01) than in standard care group. There was also a significant reduction in cardiovascular events, NSTE-ACS (6.2% vs 14.1%; $p<0.01$), percutaneous coronary intervention (2% vs 6.5% $p<0.01$), cardiovascular mortality (1.2% vs 4%;$p=0.04$) and total mortality (2.1% vs 6.2%;$p<0.01$)
Conclusion: Compared with standard care, SPP was associated with a significant increase in the use of guidelines recommended medications for secondary prevention. There was also a significant increase in patients achieving an LDL cholesterol goal and a reduction in cardiovascular events and mortalily at 1 year in patients with acute coronary syndrome.

P3029 Increased mortality after acute myocardial infarction among patients with low socio-economic status

J.N. Rasmussen[1], S. Rasmussen[2], G. Gislason[3], S.Z. Abildstrom[2], C. Torp-Pedersen[3], M. Madsen[2]. *[1]National Institute of Public Health, Copenhagen K, Denmark; [2]National Institute of Public Health, Department of Biostatistics, Copenhagen K, Denmark; [3]Bispebjerg Hospital, Department of Cardiology, Copenhagen, Denmark*

Purpose: In this population-based study linking administrative registers, we studied the long-term mortality after acute myocardial infarction (AMI) according to the individual patient's socio-economic status (SES), a field that has not received much scientific attention.
Methods: All first-time AMI patients aged 30–79 admitted in 1995–2002 in Denmark were identified through the National Patient Register. Each patient's income and education, used as indicators of SES, were retrieved from other national registers. Based on each patient's average income in the 5-year period prior to the AMI, patients were divided into 5 quintiles of increasing income. Education consisted of a five-level categorical variable of increasing length of education.
Cox regression analysis was used to calculate the relative risk of mortality between SES groups during the follow-up period from 1995 to 2003. Besides education and income, adjustments were made for age, sex, calendar year, civil status and comorbidity (established via hospital diagnoses in the 1-year period prior to the AMI). Analyses were stratified into two age groups, 30–64 and 65–79 years.
Results: Among patients aged 30–64, 23,197 patients were identified (76% male). Average time of follow-up was 4.9 years (ranging from 1 to 9 years). Mortality rate in the lowest income group was 27.8% versus 12.1% in the highest income group ($p<0.0001$), adjusted RR, 1.68 (95% confidence intervals (CI), 1.51–1.87). Mortality rate in the lowest education group was 22.0% vs. 11.5% in the highest education group ($p<0.0001$), adjusted RR, 1.45 (95% CI, 1.12–1.86).
Among patients aged 65–79, 25,539 patients were identified (61% male). Average time of follow-up was 4.6 years (1 to 9 years). Mortality rate in the lowest income group was 53.0% vs. 38.8% in the highest income group ($p<0.0001$), adjusted RR, 1.36 (95% CI, 1.28–1.45). Mortality rate in the lowest education group was 47.1% vs. 40.6% in the highest education group ($p<0.0001$), after adjustment there was no significant difference.
Conclusions: The long-term mortality after first-time AMI was higher for patients with low socio-economic status than patients with high socio-economic status; this difference was present after adjustment for comorbidity. The socio-economic inequality was more pronounced among patients aged 30–64 than among patients aged 65–79, where only income had significant influence. It remains to be established whether or not this observed difference in mortality is due to differences in severity of infarction, treatment or lifestyle.

P3030 Influence of the degree of platelet antiaggregation determined by a point-of-care test on the clinical prognosis of patients with stable chronic ischaemic heart disease

P. Alvarez-García[1], F. Worner[2], F. Bandera[2], F. Martinez-Brotons[3], J. Rodriguez[2], L. Perdigon[2], C. Rebollo[2], E. Esplugas[2]. *[1]Molins de Rei, Spain; [2]Coronary Care Unit. Cardiology, Bellvitge Hospital, Hospitalet. Barcelona, Spain; [3]Bellvitge Hospital, Haemostasia Department, Hospitalet. Barcelona, Spain*

An important percentage of patients treated with acetylsalicylic acid (ASA) are not adequately antiaggregated as determined by urinary Thromboxan B or optical platelet aggregation, and this implies a worse clinical outcome.
Objectives: to study the degree of antiaggregation, determined by a simple, fast and accessible test such as the PFA-100® analyser, in stable coronary patients treated with ASA and its influence in prognosis.
Methods: we studied patients with ischaemic heart disease chronically treated with ASA. Platelet function was assessed with the PFA-100® system, where a sample of blood is passed through an orifice reproducing the rheologic characteristics of coronary flow in a collagen membrane impregnated with epinephrine, determining the time in seconds that it takes to occlude the orifice: Occlusion Time (OT). We defined two levels of antiaggregation: maximally antiaggregated (OT $>$ 300 s, which corresponds with the upper limit of quantification) and not maximally antiaggregated (OT $<$ 300 s). Clinical follow up was done at one year and the 2 groups were compared.
Results: we included 103 patients. After confirming proper compliance of treatment with ASA, 50 (48%) presented an OT $<$ 300 s and 53 (52%) were maximally anti-aggregated (OT 300 s). At one year follow up there were no significant differences between both groups when mortality, AMI, unstable angina, hospitalisation, revascularisation or worsening of the functional class were compared separately. Nonetheless, patients with an OT $>$ 300 s presented a combination of all events of 15.7% versus 28.6% in the group with an OT $<$ 300 s ($p=0.058$).
Conclusions: patients with chronic ischemic heart disease treated with ASA who are not maximally antiaggregated according to a simple point-of-care test such as the PFA-100® analyser, show a strong tendency to have a worse clinical outcome. This must be confirmed with longer follow up.

P3031 Flow-mediated dilation as a diagnostic measure of secondary prevention in ischaemic heart disease

R. Belardinelli[1], F. Lacalaprice[2], A. Mucai[2], G.P. Perna[2]. *[1]Ancona, Italy; [2]Lancisi Heart Institute, Torrette - Ancona, Italy*

There is evidence that short-term moderate aerobic exercise training(ET) improves endothelium-dependent vasorelaxation in patients with ischemic heart disease (IHD). However, it is unknown whether flow-mediated dilation (FMD) of the brachial artery (BA) may be used as a measure of adherence to long-term ET. We studied 196 patients with IHD referred for cardiac rehabilitation. Of them, 148 (110M, 38W, mean age 58±10 years) were randomized into two groups. Group T (n=84) underwent a supervised ET program at 60% of peak VO2 three times a week for 8 weeks. Group C (n=64) was not exercised. After 8 weeks, trained patients were asked to continue to exercise at home following a program of similar intensity as that supervised. On entry, at 8 weeks and 12 months, all patients underwent a cardiopulmonary exercise testing, endothelium-dependent (ED) and endothelium-independent (EI) dilation (D) of the brachial artery (BA), and ultrasound evaluation of carotid intimal-media thickness (IMT). At 8 weeks, trained patients had significant improvements in peak VO2 (from 18.7±3.5 to 23.6±3.3 mL/kg/min), ventilatory threshold (from 9.2±3.4 to 13.1±3.3 mL/kg/min), VE/VCO2 (from 38.3±7 to 31±7) and the EDDBA (from 4.7±1.9 to 9.1±4%) as compared with controls ($P<0.05$, <0.05,<0.001 and <0.001, respectively), while the EIDBA and IMT were unchanged. At 12 months, however, 25 patients (ET-A) maintained the improvements in peak VO2, VT, VE/VCO2 and EDDBA observed after 8 weeks, while 59 patients did not, showing comparable results as controls (ET-NA). In ET-A, IMT was significantly reduced (from 0.66±0.1 to 0.58±0.1, $P<0.01$ vs ET-NA and controls). EDDBA was predictive of peak VO2 change ($P<0.001$). However, it was not predictive of IMT changes. Cardiovascular risk score was also improved in ET-A ($P<0.001$ vs ET-NA). Follow-up lasted 36±8 months. Cardiac events (PTCA, CABG, AMI, death) and new hospitalizations have been more frequent in controls (28 vs 4, and 34 vs 2, $P<0.001$ for both), and in ET-NA patients (12 and 10, respectively, $P<0.001$ vs ET-A). The EDDBA>7% (cutoff by ROC analysis, AUC 0.83) identified patients with the lowest cardiac event rate (7% vs 21%, $P<0.001$). Multivariate analysis selected peak VO2 as the strongest independent predictor of cardiac events (hazard ratio 0.67, $P<0.001$).In conclusion, long-term moderate ET maintains the improvements in functional capacity and EDDBA observed after 8 weeks. FMD-EDD was predictive of peak VO2 change, suggesting a possible role in identifying patients with a low-adherence to exercise prescription and a poor outcome.

P3032 A randomised clinical trial of comprehensive, hospital-based cardiac rehabilitation versus usual care for patients with or at risk of ischaemic heart disease (The DANREHAB Trial)

A.-D.O. Zwisler[1], A.M.B. Soja[2], S. Rasmussen[3], C. Gluud[4], L. Iversen[5], B. Sigurd[2], M. Madsen[3], J. Fischer-Hansen[2]. *[1]National Institute Of Public Health, Department Of Cardiovasculare Diseases, Copenhagen K, Denmark; [2]Bispebjerg Hospital, The Department of Cardiology, Copenhagen, Denmark; [3]National Institute of Public Health, Department of Cardiovasculare diseases, Copenhagen K, Denmark; [4]Centre for clinical Intervention, Copenhagen Trial Unit, Copenhagen, Denmark; [5]Muusmann Consult, Copenhagen, Denmark*

Introduction: Current guidelines broadly recommend comprehensive cardiac rehabilitation (CR), although evidence for CR on a wide indication may have limitations. we aimed to investigate whether hospital-based comprehensive CR is superior to usual care (UC) for patients with congestive heart failure, ischaemic heart disease or high risk for ischaemic heart disease in the modern therapeutic era of cardiology.
Method: The DANREHAB Trial was centrally randomized. The CR-intervention was an individually tailored, multidisciplinary program in accordance with the national CR guidelines (1). A detailed description of the CR-intervention is available on the web (2). The control group recieved usual care. A composite blinded register-based primary outcome measure included total mortality, myocardial infarction or first acute readmissions due to heart disease. The sample-size was calculated to 1810 participants(alpha=0.05, beta=0.20).
Results: Of 1614 eligible patients, 770 were randomized (47%): 380 to the CR-group and 390 to the UC-group. Mean age was 65 years; 36% were women; 12% were patients with congestive heart failure, 58% patients with ischaemic heart disease, and 30% were patients with high risk for ischaemic heart disease. We found no significant difference in the composite register-based outcome measure at 12-month follow-up between the to interventions. The two groups did not differ statistically for each register-based outcome measures individually either. Among the 55% of patients who were readmitted, the CR-group tended to have a non-significantly lower readmission-rate. The CR-group had significantly fewer bed–days than the UC-group in each quarter of the follow-up period (p=0.03).
Conclusion: A large-scale, high-quality, centrally randomized clinical trial on comprehensive CR can be conducted among a broadly defined patient group. Reaching the stipulated number of 1800 patients within three years was not possible. We did not find any effect on the register-based composite primary outcome at 12-month follow-up in this trial. CR seems to significantly reduce length-of-stay during readmissions.

P3033 Short-term cardiac rehabilitation after myocardial infarction – results from the acute coronary syndrom registry

B. Rauch, S. Schneider, A. Gitt, N. Liebhart, C. Juenger, R. Winkler, R. Schiele, J. Senges on behalf of the ACOS investigators. *Institut fur Herzinfarktforschung, Klinikum Ludwigshafen, Ludwigshafen, Germany*

Background: Effectiveness of short-term (3-4 weeks) cardiac rehabilitation in Germany (reha) in reducing cardiovascular risk after acute myocardial infarction has been questioned.
Methods: From the ACOS registry 9,901 consecutive patients (P) discharged alive after ST-elevation- (STEMI: 5,472 P) or Non-ST-elevation myocardial infarction (NSTEMI: 4,429 P), and either participating rehabilitation [reha(+)] or not [reha(-)] were characterized and evaluated for clinical outcome during follow-up. 67% of P with STEMI and 52% of P with NSTEMI participated cardiac rehabilitation. Recruitment of P was between June 2000 and December 2002.
Results: The table compares baseline characteristics and clinical outcome of P either participating reha or not. Multivariable analysis of long-term outcome adjusted for all parameters indicated with a star in the table (*) gave the following results; reha(+) versus reha(-): 30-days mortality: OR 0.13, 95% CI 0.08-0.22; 1-year mortality: OR 0.40, 95% CI 0.34-0.47; non-fatal reinfarction after 1 year: OR 1.02, 95% CI 0.79-1.33.

Patients characteristics and prognosis

	reha (+)	reha (-)	p-value
age (years) *	64.4	70.6	< 0.0001
myocardial infarction in history *	15.7%	26.3%	< 0.0001
diabetes mellitus *	25.6%	31.3%	< 0.0001
acute revascularization *	64.9%	45.4%	< 0.0001
ejection fraction < 40% *	18.8%	25.6%	< 0.0001
statin therapy at discharge *	82.8%	72.6%	< 0.0001
beta blocker therapy at discharge *	89.5%	84.2%	< 0.0001
total mortality after 30 days	0.4%	4.7%	< 0.0001
total mortality after 1 year	4.6%	17.6%	< 0.0001
non fatal reinfarction	3.3%	3.0%	0.37

Conclusion: P undergoing reha represent a group with optimized treatment and low risk. However, participation in reha appears to be independently associated with reduced short- and long-term mortality. Therefore, P at increased risk after STEMI/NSTEMI also should be advised to participate reha.

P3034 Home-based versus supervised centre-based cardiac rehabilitation in a multi-ethnic population: 12 months results of the Birmingham Rehabilitation Uptake Maximisation Study (BRUM)

K. Jolly[1], R.S. Taylor[2], G.Y.H. Lip[3], J.W. Mant[4], D. Lane[3], S.M. Greenfield[4], J. Raftery[5], A.J. Stevens[2]. *[1]University of Birmingham, UK, Public Health & Epidemiology, Birmingham, United Kingdom; [2]University of Birmingham, UK, Public Health & Epidemiology, Birmingham, United Kingdom; [3]University of Birmingham, Uni Dept Medicine, City Hospital, Birmingham, United Kingdom; [4]University of Birmingham, Primary Care & General Practice, Birmingham, United Kingdom; [5]University of Birmingham, Health Services Management Centre, Birmingham, United Kingdom*

Purpose: Although meta-analyses have shown benefits of rehabilitation in heart disease populations, this evidence is predominantly based on trials of the traditional model of the supervised hospital (or centre)-based programme. The UK National Service Framework goal to expand coverage of rehabilitation to all patients with heart disease demands consideration of alternative models of service delivery, in particular home-based programmes. We report here for the first time the 12-month follow up results from the largest trial of hospital versus supervised centre-based rehabilitation to date.
Methods: 525 low/moderate risk post-myocardial infarction and revascularisation patients (mean age 61 yrs, 77% male, 20% ethnic minorities) referred in the 2-year period from February 2002 to 4 inner city hospitals serving a multi-ethnic population in the West-Midlands, UK were randomly allocated to either 12 weeks of home (Heart Manual and nurse follow up) [N = 263] or usual hospital/community based rehabilitation. Primary outcomes were collected at 12-months in both groups and compared using intention to treat analysis, adjusting for baseline score, age, sex and diagnosis.
Results: At 6 months analysis revealed no significant differences in primary outcomes between home and centre-based groups for smoking cessation, exercise capacity, systolic blood pressure, Hospital Anxiety and Depression Scale (HADS) anxiety and depression scores, and total cholesterol. In a secondary analysis, statistically significant improvements in both home and centre-based groups were seen for smoking cessation, HADS anxiety, and total cholesterol levels at 6-months compared to baseline.
We will report the 12 month results for which we have 90% follow-up.
Conclusion: We have shown that home-based and supervised centre-based cardiac rehabilitation programmes equally improve outcomes at 6-months in a low risk cardiac population. The 12- month results will show whether the changes achieved by the two groups are sustained equally. If this is the case it will support the policy of increased provision of home-based programmes for selected post myocardial infarction and revascularisation patients.

P3035 Comparing access, risk factors and pharmacological treatment in traditional standardised and menu-based cardiac rehabilitation: lessons learned from Scotlands national demonstration project on CHD

S. Catto[1], G. Bowman[1], H. Whelan[2], A. Clark[3], P. MacIntyre[1].
[1]Royal Alexandra Hospital, Cardiology, Level 5, Paisley, United Kingdom; [2]University of Saskatchewan, College of Kinesiology, Saskatoon, Canada; [3]University of Alberta, Faculty of Nursing, Edmonton, Canada

Background: Cardiac rehabilitation (CR) has proven benefits in terms of mortality, morbidity and quality of life but traditional programmes are often available only to restricted groups and are not tailored to meet individual need, ability or preference. Recent government policy advocates the development of more flexible, menu-based programmes.
Aim: To compare access, risk factor control and pharmacological treatment in traditional standardised CR (TSCR) with menu-based CR (MBCR).
Methods: All patients eligible for TSCR at a Scottish district general hospital in 1999 (n=799) were studied by retrospective case note review. Data on all patients eligible for MBCR at the same hospital from May 2002-April 2003 were collected prospectively using hospital databases (n=1206). Student's two sample t-test and Chi-squared analysis identified differences between programmes.
Results: A significantly greater proportion of eligible patients were referred to MBCR (62 vs. 52%, $p<0.001$) and uptook phase 3 exercise compared to TSCR (75 vs. 58%, $p<0.001$). There was no evidence of a difference in completion rates (both 70%, p=0.89). Compared to TSCR participants, MBCR patients were less likely to smoke at the end of their involvement in CR (34 vs. 20%, $p<0.001$), smoked fewer cigarettes per day (CPD) (73 vs. 39% >10 CPD, $p<0.001$), had lower systolic blood pressure (138 vs. 132mmHg, $p<0.001$) and total serum cholesterol (5.7 vs. 4.3mmol/L, $p<0.001$) and were less likely to have hypertension (41 vs. 31%, p=0.001) and hyperlipidaemia (71 vs. 35%, $p<0.001$). A significantly greater proportion of patients referred to phase 3 of MBCR were prescribed betablockers, ACE inhibitors and statins compared to TSCR (81 vs. 34%; 65 vs. 44%, 94 vs. 72%; $p<0.001$). There was no significant difference in the proportions of patients on an antiplatelet (94% TSCR vs. 97% MBCR, p=0.26).
Conclusions: MBCR is associated with improved access, risk factor control and pharmacological treatment compared to TSCR and may offer patients improved outcome.

P3036 Impact of a training-induced differentiation of c-kit+ stem cells on left ventricular dysfunction in experimental myocardial infarction

A.H.P. Linke, V. Adams, N. Kraenkel, S. Erbs, M. Sandri, S. Gielen, G. Schuler, R. Hambrecht. *University of Leipzig, Heart Center, Department of Cardiology, Internal Medicine, Leipzig, Germany*

Background: The cytokine-mediated mobilization of c-kit+ hematopoietic stem cells has been shown to improve left ventricular function in experimental myocardial infarction. Physical exercise training induces a liberation of stem cells and endothelial progenitor cells (EPCs) from the bone marrow as well. It was the aim of the present study to determine, whether the release of c-kit+ stem cells and their training-induced differentiation is associated with a partial correction of left ventricular dysfunction in an animal model of chronic myocardial infarction.
Methods: Male Wistar Kyoto rats were sham-operated (Sham) or underwent LAD ligation (MI). Three weeks afterwards, animals of both groups were subjected to an inactive control group (Sham-C, n=10; MI-C, n=10) or a training group (Sham-T, n=10; MI-T, n=10). Animals in the training groups were running on a treadmill that was moving with a speed up to 30 m/min one hour daily for a period of four weeks. The number of c-kit+ stem cells and c-kit+/KDR+ EPCs was analysed in the non-lymphocyte fraction (CD3-) of the blood (B) by FACS and is expressed as number per 100000 "gated events". Hemodynamics were assessed by conductance catheter and echocardiography.
Results: see Table 1. There was a significant correlation between the number of c-kit+/KDR+ cells and left ventricular function in the MI-T group ($r=0.58$, $p<0.05$).

Table 1

	Sham-C	Sham-T	MI-C	MI-T
EDP (mmHg)	5±1	4±1	18±3 *	12±3 * $
EF (%)	75±2	77±3	25±4 *	34±6 * $
c-kit+ (B)	741±107	760±122	1288±130 *	1771±165 * $
c-kit+/KDR+ (B)	68±12	86±11	68±13	143±30 * $

* $p<0.05$ vs. Sham-C and Sham-T, $ $p<0.05$ vs. MI-C, EDP: end-diastolic pressure, EF: ejection fraction

Conclusion: Physical exercise training induces a differentiation of circulating c-kit+ stem cells into EPCs in an animal model of chronic myocardial infarction. This was associated with an increase in left ventricular ejection fraction in chronic MI. The ongoing tissue analysis will reveal, whether c-kit+/KDR+ cells promote neoangiogenesis in the infarct region.

P3037 Improvement of endothelial function following physical training in left ventricular dysfunction

M. Deljanin Ilic[1], S. Ilic[2], G. Kocic[3], R. Pavlovic[3], I. Stojanovic[3].
[1]Institute of Cardiology, Echo Lab, Niska Banja, Serbia and Montenegro; [2]Institute of Cardiology, Clinical Cardiology, Niska Banja, Serbia and Montenegro; [3]Medical Faculty, Institute of Biochemistry, Nis, Serbia and Montenegro

The endothelium acts to maintain vascular homeostasis and regulates vascular tone by balancing production of vasodilators, including nitric oxide and vasoconstictors. It has been demonstrated that cardiovascular (CV) diseases are associated with impaired endothelial function and that some interventions, known to reduce CV risk also, improve endothelial function.
The aim of the study was to examine the reaction of endothelium, assess through changes of circulating blood markers of endothelial function: the stable end products of nitric oxide (NOx) and S - nitrosothiols (RSNO - reservoir for bioavailable nitric oxide), that promote physical training in patients (pts) with left ventricular dysfunction (LVD).
Methods: Twenty-eight pts (21 male, 7 female; mean age 58.4 ± 8.7 years) with ejection fraction <40% were studied. In all pts, before and after short-term physical training (40 minutes of physical training daily over a period of three weeks at residential center), NOx and RSNO were evaluated and bicycle exercise test was performed. To elucidate the dynamic of nitric oxide metabolism in the circulation of pts subjected to physical training, NOx and RSNO concentration were determined according to the modified Saville-Griess method.
Results: After physical training in 21 (71%) pts NOx increased significantly (from 27.2 ± 10.3 to 56.9 ± 18.1 μmol/l, $P<0.0001$), while in 7 (25%) pts NOx decreased (from 57.6 ± 16.5 to 36.1 ± 15.1 μmol/l, $P<0.05$). Value of RSNO was significantly higher after physical training in 26 (92.8%) pts compared to baseline values (6.1 ± 2.4 vs 3.5 ± 2.1 μmol/l, $P<0.001$) while in two pts RSNO slightly decreased. Out of 28 examined pts, 27 (96.4%) had increased NOx and/or RSNO after physical training, while only one patient had reduction of both. After physical training exercise capacity and duration of test increased significantly ($P<0.05$ and $P<0.01$).
Conclusion: Residential short-term physical training in pts with LVD induced significant favorable modification of endothelial function by increased production of nitric oxide. This was documented through significant increased of NOx and RSNO and was associated with significant improvement in exercise capacity

P3038 Ambulatory exercise training in patients with chronic heart failure – influence on left ventricular remodelling and exercise capacity

A. Klecha[1], B. Bacior[1], A. Kubinyi[1], M. Pasowicz[2], P. Klimeczek[2], R. Banys[2], K. Kawecka-Jaszcz[1]. [1]Jagiellonian University, I Cardiac Department, Kraków, Poland; [2]John Paul II Hospital, Kraków, Poland

Physical training is well accepted therapy in the treatment of patients with chronic heart failure (CHF). However the influence of physical training on left ventricular (LV) remodeling process is controversial. The aim of this study was to assess the effect of 6-month physical training on exercise tolerance and selected LV parameters in CHF patients.
Material and methods: 53 patients (mean age 61,2±8,3 y) with ischemic CHF, NYHA II-III class, EF ≤ 35%, stable on standard pharmacotherapy were randomized either to a trained (A - 27 pts) or not trained group (B – 26 pts). There were no differences between groups in terms of age, sex, duration and severity of CHF. Supervised aerobic training (calisthenics, cycling at 80% VO2peak) for group A was conducted at the rehabilitation center for 6 months 3 times a week, 60 min daily. At baseline and after 6 months cardiopulmonary exercise test and cardiac magnetic resonance of the heart with estimation of LV parameters were performed in both groups.
Results: At baseline exercise capacity and LV parameters were comparable in both groups. After 6 months in group A we found a relevant improvement of exercise capacity and slight tendency towards improvement in LV parameters. In group B both exercise capacity and LV parameters remained unchanged. Results are presented in the table.

Results for group A and B

	Baseline	After 6 months	p
Group A			
VO2 peak (ml/kg/min)	14,3±2,9	19.2±3,8	< 0.01
VE/VCO2	38,4±4,1	34,3±3,9	< 0.05
Anaerobic treshold (O2 ml/kg/min)	10,4±2,5	12,9±3,2	< 0.05
LV ejection fraction (%)	27,5±4,7	30,8±5,6	NS (0,07)
LV end-diastolic volume (ml)	192±51	176±43	NS (0,06)
Group B			
VO2peak (ml/kg/min)	15,0±3,1	14,7±2,9	NS
VE/VCO2	37,5±5,3	38,0±5,1	NS
Anaerobic treshold (O2 ml/kg/min)	10,7±2,7	10,6±2,3	NS
LV ejection fraction (%)	28,3±5,9	27,7±4,6	NS
LV end-diastolic volume (ml)	179±48	187±55	NS

Conclusions: Ambulatory physical training provided for ischemic CHF patients has a positive influence on exercise capacity and no deleterious effect on LV parameters.

P3039 Exercise rehabilitation after myocardial infarction improves endothelial function partly via increase in circulating endothelial progenitor cells

N. Ikeda[1], T. Yasu[2], T. Nakamura[2], Y. Sugawara[2], N. Kubo[2], M. Saito[2]. *[1]Jichi Medical School, Integrated Medicine 1, Saitama, Japan; [2]Jichi Medical School, Integrated Medicine 1, Saitama, Japan*

Bone marrow derived endothelial progenitor cells (EPCs) are thought to exert beneficial effects on atherosclerosis, angiogenesis, and vascular repair. A recent report documented that physical activity increases the production and circulating numbers of EPCs in mice. However, little is known regarding whether EPCs in peripheral blood are enhanced by exercise training in human after acute myocardial infarction (AMI).
Aims: To explore effects of exercise training on EPC number in the peripheral blood, endothelial function and exercise capacity in patients with AMI.
Methods: Twenty patients with AMI (Killip 1) were randomly assigned to two groups: training group (30 min rapid walking daily, n = 11) or sedentary group (n = 9). Clinical background and medications of both groups were similar. Symptom-limited cardiopulmonary exercise tests were performed on 10 days, and three months after the onset of AMI. EPCs in the peripheral blood were quantified by fluorescence activated cell sorter analysis (CD34 FITC/CD133 PE/CD45 PerCP) in each group. Endothelial function was evaluated by hyperemic forearm blood flow using a strain-gauge plethysmography in the same timetable.
Results: Numbers of EPCs circulating in the peripheral blood were enhanced from 0.83 $\pm$ 0.52/μl to 0.95 $\pm$ 0.48/μl in trained group, and decreased from 0.74 $\pm$ 0.42/μl to 0.51 $\pm$ 0.28/μl in sedentary group ($p < 0.05$). Numbers of EPCs at three months after onset of AMI were correlated to anaerobic threshold ($p < 0.01$), and flow dependent vascular dilatation ($p < 0.05$).
Conclusion: Exercise training after AMI enhanced numbers of circulating EPCs, and it related to improvement of endothelial function and exercise capacity.

AF AND DRUG THERAPY

P3040 Comparative effects of carvedilol and amiodarone on conversion and recurrence rates of persistent atrial fibrillation

E.M. Kanoupakis[1], H.E. Mavrakis[1], E.M. Kallergis[1], P. Kafarakis[1], E.G. Nyktaris[1], S. Anagnostopoulos[1], E.G. Manios[1], P.E. Vardas[2]. *[1]Heraklion University Hospital, Cardiology Dept., Heraklion, Crete, Greece; [2]Heraklion University Hospital, Department of Cardiology, Heraklion, Greece*

Purpose: Pre-treatment with antiarrhythmic agents could improve cardioversion and atrial fibrillation (AF) recurrence rates in patients with persistent AF. In this prospective trial we examined the conversion and recurrence rates of persistent AF patients pre-treated with the b-blocker carvedilol or amiodarone.
Methods: One hundred forty-five patients were randomly assigned to treatment with carvedilol, amiodarone or placebo for four weeks prior to electrical cardioversion for persistent AF. The mean fibrillatory cycle length interval (FF) was evaluated before cardioversion and effective refractory period (ERP) was measured five minutes after restoration of sinus rhythm. Holter recordings were obtained from all patients on the day after cardioversion and the density of supraventricular ectopic beats was calculated.
Results: Cardioversion rates were 43/47 (91.5%) for carvedilol, 42/45 (93.3%) for amiodarone and 33/45 (73%) for placebo, making both drugs statistically superior to placebo (p=0.017). Both drugs prolonged FF and ERP in the setting of atrial remodeling due to AF and this could be related to their beneficial effect on conversion rate. Total AF recurrence rates during the first month after conversion were 27.9%, 16.6% and 39.4%, for the three groups respectively. The superiority to placebo was statistically significant only for amiodarone. Amiodarone patients also had a significantly lower density of supraventricular ectopic beats post-conversion.
Conclusions: The combination of electrical cardioversion with amiodarone or carvedilol is more effective than cardioversion alone in persistent AF patients. Amiodarone is superior in terms of sinus rhythm maintenance post-conversion. This could be related to the lower density of supraventricular ectopic beats.

P3041 Atrial fibrillation: three months of antiarrhythmic treatment keep sinus rhythm for 2 years after cardioversion

S. Juul-Moller[1], D. Anevski[2]. *[1]University of Lund, Dept. of Cardiology, Malmo, Sweden; [2]Chalmers Institute of Technology, Fraunhofer Chalmers Centre, Gothenburg, Sweden*

Introduction: Most relapse to atrial fibrillation (AF) occurs with the first 3 months after cardioversion. No study in a clinical relevant setting has until now been designed to demonstrate if intensive pharmacological treatment during this period affects the long-term prognosis.
Hypothesis: Short term treatment after cardioversion is sufficient to keep sinus rhythm in an unselected AF-population.
Methods: All patients referred for cardioversion at the Department of Cardiology, University Hospital, Malmö, Sweden, were treated based on time-guided randomisation with amiodarone for 1 month prior to DC-cardioversion and continuing for 3 months, followed by metoprolol (TR1). In case of amiodarone contraindications the treatment was metoprolol or digoxin for the whole period (2 years of follow-up). The alternative randomised treatment modality was metoprolol (TR2) only, or digoxin in case of contraindications.
Results: A total of 688 pats were included, 484 in TR1 and 181 in TR2.
No demographic differences were found between the groups. 54% of patients in TR1 received amiodarone, and 79% in TR2 received metoprolol. After 2 years 65% in TR1-group were still in SR compared to 37% in the TR2-group.
In a multivariate Cox analysis the only clinical relevant risk factors for relapse were (1) Treatment modality and (2) Duration of AF.
The hazard ratio (risk for relapse) for TR1 versus TR2 was 0,5 (P=0,0003) and for duration of AF 1,004 per month with AF prior to cardioversion (P=0,003).
Conclusion: In order to preserve SR a treatment concept including amiodarone for 1 month prior and 3 months after DC-cardioversion followed by a selective beta-blocker (metoprolol SR) seems to be an effective choice. No risk factor could be identified to define a subgroup of patients who could be excluded from this treatment.

P3042 The efficacy and safety of dronedarone as a novel rate control agent for the treatment of atrial fibrillation

J.-M. Davy[1], B.N. Singh[2], S.H. Hohnloser[3]. *[1]Hopital Arnaud de Villeneuve, Service de Cardiologie B, Montpellier cedex 5, France; [2]UCLA Medical School, Department of Medicine, Los Angeles, United States of America; [3]J.W. Goethe University, Department of Internal Medicine, Frankfurt, Germany*

Dronedarone (D) is a novel, non-iodinated benzofuran derivative with class I, II, III and IV antiarrhythmic properties whose safety and efficacy in terms of rhythm control were recently demonstrated by the pivotal EURIDIS and ADONIS trials. Moreover, preliminary data from these and other studies have also shown that dronedarone has favorable rate control properties in atrial fibrillation.
Aim: To further evaluate the efficacy in controlling ventricular rate and the safety of dronedarone in patients (pts) with atrial fibrillation (AF).
Methods & Results: The effects of D 400mg bid on rate control were prospectively assessed in the placebo (P)-controlled ERATO study, which randomized 174 pts with permanent AF whose resting heart rate was higher than 80 beats per minute (bpm) and who were receiving standard therapy (e.g. β-blockers, CCBs, digitalis, etc). Analysis of the primary endpoint (mean 24-hour Holter-monitored ventricular rate at day 14 compared to baseline) showed a difference of -11.7 bpm between the D and P arms (p value=$22x10^{-14}$). In addition, during a maximal symptom-limited exercise test on day 14, the mean ventricular rate change from baseline was 24.5 bpm lower in the D group (p=10-12), with no difference in the mean change from baseline of maximal exercise duration on day 14 compared to P. D had a favorable safety profile, with no torsades de pointes reported during the study and no statistically significant difference over P in the occurrence of treatment-emergent serious adverse events (D=16.5% vs P=13.5%) or deaths (D=2 vs P=1) during the study period.The ERATO results confirm those reported from the EURIDIS and ADONIS studies. In these 2 studies, heart rate during the first arrhythmia recurrence was significantly decreased by D. Mean heart rate recorded by TTEM was 102.3 and 104.6 bpm in the D arms versus 117.5 and 116.6 bpm in the P arms ($p<0.0001$ and $p<0.001$, respectively). The overall incidence of treatment emergent adverse events on D was not significantly different from that on P (67.4% vs 62.8%) and no pro-arrhythmic episodes or signs of extra-cardiac organ toxicity were reported.
Conclusion: Dronedarone besides being effective for sinus rhythm maintenance, effectively controls ventricular rate in a broad range of pts with AF and is well tolerated.

P3043 Observation of the temporal excitable gap measured by using autocorrelation function during cardioversion of atrial fibrillation by intravenous cibenzoline in human

A. Shimizu, Y. Yoshiga, H. Kakugawa, M. Esato, T. Ueyama, M. Matsuzaki. *Yamaguchi Univeristy School, Cardiology, Ube, Japan*

Background: We have already reported that the peak and minimum atrial fibrillation cycle lengths (AFCL) measured by using the autocorrelation function (reversed FFT analysis) reflected the mean and 5th percentile of AFCLs measured by using a computer-picked activation time, respectively, and that the minimum AFCL (min AFCL) could be used as an index the refractory period during atrial fibrillation (AF) (J Cardiovasc Electrophysiol 14:965, 2003). Class I drugs widened the temporal excitable gap in the gout and the explanation for the antifibrillatory effect of class I drugs may be a widening of the temporal excitable gap. (Wijffels MCEF, et al. Circulation 102:260, 2000).
The aim of this study was to observe the temporal excitable gap measured by autocorrelation function during cardioversion of AF by intravenous cibenzoline (CBZ) in human.
Methods: Subjects were 15 patients (61$\pm$11 years old) with induced AF (sustained $>$ 30 minutes) during electrophysiological test. Intravenous CBZ (1.4 mg/kg over 5 minutes) cardiovered AF in 8 patients (T-group), but did not in 7 patients (non-T group). Atrial electrograms for 30 seconds in the high right atrium during

AF were taken to measure AFCL by autocorrelogram before CBZ, and immediately before the termination of AF in T group or the end of CBZ in non-T group. The mean AFCL was retrieved at the point of the maximum peak of the co-efficient of the first positive autuocorrelogram and the min AFCL was chosen as the point where the first positive autocorrelogram crossed the baseline from negative to positive, as previously described. In this study, the difference of mean AFCL and min AFCL was defined as the temporal excitable gap.
Results: 1) CBZ significantly prolonged the mean AFCL (170±23 to 263±26 ms in T group; $p<0.0005$, 160±23 to 241±63 ms in non-T group; $p<0.005$) and the min AFCL (136±20 to 217±25 ms in T group; $p<0.0005$, 129±22 to 202±58 ms in non-T group; $p<0.002$) in both groups. However, there was no significant difference in the mean AFCL or the min AFCL before and after CBZ between two groups. 2) CBZ significantly ($p<0.01$) widened the temporal excitable gap from 34±7 to 46±5 ms in T-group, but not in non-T group. Furthermore, there was no significance on the temporal excitable gap before CBZ between two groups, but the temporal excitable gap after CBZ in T-group (46±5 ms) was significantly ($p<0.05$) wider than that in non-T group (39±7 ms).
Conclusion: These results suggested that the widening of temporal excitable gap was related to the cardioversion of AF by CBZ in human.

P3044 Effects of age on efficacy and safety of ximelagatran compared with warfarin in atrial fibrillation

G.A. Ford[1], P. Deedwania[2], D. Karalis[3], C.-J. Lindholm[4], W. Pluta[5], S.B. Olsson[4] on behalf of the SPORTIF III and V Investigators. *[1]University of Newcastle, Clinical Research Centre, Newcastle upon Tyne, United Kingdom; [2]University of California-San Francisco, Fresno, CA, United States of America; [3]Drexel University College of Medicine, Philadelphia, PA, United States of America; [4]University Hospital, Lund, Sweden; [5]Wojewódzkie Centrum Medyczne, Opole, Poland*

Purpose: The oral direct thrombin inhibitor ximelagatran is a potential alternative to warfarin in the prevention of stroke in patients with nonvalvular atrial fibrillation (AF). The safety and efficacy of anticoagulants are a particular concern in the elderly. We determined the influence of age on the risks and benefits of ximelagatran compared with warfarin for the management of AF.
Methods: Data were analysed from 7329 patients with AF randomized in the Stroke Prevention using an ORal Thrombin Inhibitor in patients with atrial Fibrillation (SPORTIF) III (n = 3407) and V (n = 3922) studies to ximelagatran (36 mg twice daily) or open-label (SPORTIF III) or double blind (SPORTIF V) warfarin (adjusted dose, international normalized ratio 2.0-3.0). Effect of age on the primary endpoint of stroke and systemic embolism, bleeding complications, and incidence of raised serum alanine aminotransferase (ALT) were examined.
Results: The primary event rate in patients <75 years (n = 4525) was 1.25%/year with ximelagatran and 1.28%/year with warfarin; corresponding rates in patients ≥75 years (n = 2804) were 2.23%/year and 2.27%/year. The major bleeding rate (excluding intracerebral bleeding) for ximelagatran compared with warfarin was 1.4% vs 1.8% (P = 0.23) for patients <75 years and 2.7% vs 3.6% (P = 0.13) for those aged ≥ 75 years. The number of haemorrhagic strokes was numerically lower with ximelagatran than with warfarin (<75 years: 1 vs 5; P = 0.22; ≥75 years: 5 vs 6; P = 0.77). Combined rates of minor and major bleeds were significantly lower with ximelagatran than with warfarin in both age groups (<75 years: 27% vs 35%; P < 0.001; ≥75 years: 40% vs 45%; P = 0.01). Raised serum ALT levels (>3x upper limit of normal) occurred in 6.1% of ximelagatran patients and were more common in older than in younger subjects (7.5% vs 5.3%; P = 0.007).
Conclusions: Although older patients with AF had a higher event rate compared to younger patients, fixed-dose oral ximelagatran was as effective as well-controlled, dose-adjusted warfarin in the prevention of stroke. Ximelagatran was associated with a lower overall rate of bleeding in both young and older patients but with a somewhat more frequent elevation of serum ALT in patients over 75 years.

P3045 Efficacy and safety of RSD1235 in the treatment of recent onset atrial fibrillation in ACT I, (Atrial arrhythmia Conversion Trial I), a phase III, randomised, placebo-controlled, multi-center trial

Roy[1], C. Pratt[2], D.G. Wyse[3], E. Toft[4], C. Torp-Pedersen[5], S. Juul-Moller[2] on behalf of the ACT I investigators. *[1]Montreal Heart Institute, Montréal, Canada; [2]Universitetssjukhuset I Malmo, Malmo, Sweden; [3]Libin Cardiovascular Institute of Albe, Calgary, Canada; [4]Aalborg Univ. and Aalborg Hospital, SMI, Aalborg, Denmark; [5]H:S Bispebjerg Hospital, Copenhagen, Denmark*

Objectives: To assess the effectiveness and safety of RSD1235 in the conversion of atrial fibrillation (AF) to sinus rhythm (SR).
Study Design and Methods: Patients were randomized in a 2:1 ratio of RSD1235 to placebo and stratified by AF duration of 3 hr-7 days and 8-45 days. Primary endpoint: proportion of patients (pts) with AF duration of 3hr to 7 days who had treatment-induced conversion to SR within 90 min. Secondary endpoints: time-to-conversion of AF to SR in pts with 3hr-7day AF duration; the proportion of pts with termination of AF within 90 min in pts with 8-45 days AF and in the entire group of pts with 3hr-45 day AF duration. The first infusion of study drug was given for 10 min (placebo or 3 mg/kg RSD1235), and a second 10-min infusion was given 15 min later if AF was not terminated (placebo or drug 2 mg/kg). Safety was assessed by the incidence of adverse events (AEs), vital signs, laboratory data, ECG and holter monitoring.
Results: 336 pts were randomized and received treatment (221 and 115 pts received RSD1235 and placebo, respectively). Conversion to SR in pts stratified by AF duration was as follows (see Table 1).
Of the 75 RSD1235 patients in the 3hr – 7 day group who converted to SR within 90 minutes, the median time to conversion was 11 minutes. Of these pts, only one relapsed by 24 hrs. In the 30 day interval following drug administration, serious adverse events (SAE) occurred in 21 (18%) placebo pts and in 29 (13%) pts in the drug group, with the recurrence of AF being the most common: 14 (12%) in placebo and 13 (6%) in the RSD1235 group. There were no cases of drug-related Torsades de Pointes. A transient alteration in taste was the most common non-cardiac side effect in the RSD1235 group, occurring in 66 pts (30%), vs. 1 (0.9%) in the placebo group.

Table 1

Treatment Group	Number of Pts (%) Converted to Sinus Rhythm		
	3hr-7 days (n=220)	8-45 days (n=116)	Entire Group 3hr-45 days (n=336)
RSD1235	75 (52%)	6 (8%)	83 (38%)
Placebo	3 (4%)	0 (0%)	3 (3%)

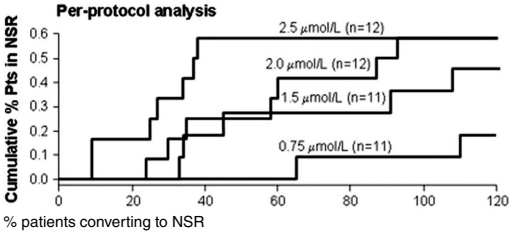
*p<0.001.

Conclusion: RSD1235 demonstrated a safe, rapid and high rate of conversion of recent onset AF to SR in this large, randomized, placebo-controlled clinical trial.

P3046 Safety and efficacy of AZD7009 given intravenously to patients for conversion of atrial fibrillation/atrial flutter

H.J.G.M. Crijns[1], I. van Gelder[2], H. Walfridsson[3], P. Kulakowski[4], A. Ronaszeki[5], V. Dedek[6], A. Malm[7], O. Almgren[7]. *[1]University Hospital Maastricht, Cardiology Dept., Maastricht, Netherlands; [2]Groningen, Netherlands; [3]Linköping, Sweden; [4]Warsaw, Poland; [5]Budapest, Hungary; [6]Ústí nad Orlicí, Czech Republic; [7]Mölndal, Sweden*

Background: AZD7009 is a novel antiarrhythmic agent with mixed K^+ and Na^+ channel-blocking properties and predominant effects on atrial refractoriness. This study (D1460C00024) assessed safety and efficacy of multiple ascending doses of AZD7009 in pts with atrial fibrillation (AF)/atrial flutter (AFl), with a special focus on tolerability during the vulnerable period around conversion to SR.
Methods: This was a double-blind, placebo-controlled, parallel-group, multicentre study of 122 pts admitted for DC cardioversion of AF/AFl of 48h – 90 days (mean, 43 days) and randomised to 7 doses of AZD7009 (n=86; target plasma levels 0.25 –2.5 μmol/L; administered as a 30-min bolus + 150-min infusion) or placebo (n=36). Pts who did not convert within 2 hrs underwent DC cardioversion, and infusion was continued during and after DC or pharmacological conversion.
Results: See Figure (% pts converting to NSR). In the 3 highest dose groups, 7/9 (78%) of pts with AF/AFl less than 1 week converted to SR on AZD7009 vs 12/26 (46%) of those with a duration >1 week. No pts converted on placebo. Prolonged infusion of AZD7009 was well tolerated except at the highest level. No case of Torsades de Pointes (TdP) according to pre-defined criteria was reported, but one case of Holter-detected asymptomatic, non-sustained polymorphic ventricular tachycardia with TdP-like features of maximally 8 beats (2s) was found. Median QTcFridericia was prolonged by AZD7009 from 404 to 480 msec at the highest dose. Corrected QTcF >550ms was seen in 4 pts at 1h and 7 pts at 3h.



Conclusions: AZD7009 showed dose-dependent efficacy of conversion of persistent AF/AFl. Prolonged infusion over 3 h was generally well tolerated.

P3047 Predominant effects on atrial versus ventricular refractoriness in man by the novel antiarrhythmic agent AZD7009

N. Edvardsson[1], H. Walfridsson[2], H. Aass[3], O. Rossvoll[4]. *[1]Pixbo, Sweden; [2]Linköping, Sweden; [3]Oslo, Norway; [4]Mölndal, Sweden*

Background: AZD7009, a novel mixed potassium/sodium channel blocker under development for atrial fibrillation (AF), has shown excellent antiarrhythmic efficacy in animal studies. It has low proarrhythmic potential and prolongs refractoriness with a predominant effect on the atria. We assessed the effects of intravenous

AZD7009 on atrial and ventricular refractoriness and hemodynamics in patients (pts) after RF ablation of AVNRT or concealed WPW syndrome.
Methods: In a double-blind study (D1460C0016), 31 pts were randomized to AZD7009 and 20 to placebo. The mean age was 57±11 (range 23-73) years and there were 31 men. Baseline measurements started 30 minutes after successful ablation. An infusion regimen designed to reach one of four target concentrations of AZD7009, or a placebo infusion was then started and repeat measurements were performed 15 min. later.
Results: The four active dose levels yielded mean pseudo steady-state plasma concentrations of 80, 300, 952 and 1620 nmol/L, respectively. At paced heart rates of 120 and 150 beats/minutes, there was a dose-dependent increase in AERP with a maximum, at the highest dose level, of 66 ms (28%, $P<0.0001$) and 74 ms (34%, $P<0.0001$). VERP increased by 38 ms (18%, $P<0.0001$) and 33 ms (17%, $P<0.0001$), reaching its maximum at the second dose level, and showed an apparent plateau pattern without further increases at higher dose levels. Linear regression confirmed the separation of the effects on the atria and ventricles. The corrected study-specific QTend and QTtop intervals increased by a maximum of 15% and 18%, while the QTend-QTtop interval did not change. A potentially clinically meaningful 11ms (10%) increase of the QRS width was seen at the highest dose level. There was a significant delay in intranodal conduction (AH interval) by a maximum of 38% at a paced heart rate of 120 bpm. No consistent effects were seen in the AV-nodal effective refractory period, the RR interval, or the right atrial, pulmonary artery, or pulmonary capillary wedge pressures. AZD7009 was well tolerated.
Conclusion: The predominant dose-dependent effect of AZD7009 on atrial refractoriness and the apparent plateau pattern in ventricular refractoriness may optimize the benefit/risk of this agent in the treatment of AF.

P3048 Pill-in-the-pocket therapy in recurrent atrial fibrillation. Dose-related effects on efficacy and rate of hospitalisation

G.L. Botto[1], P. Alboni[2], N. Baldi[3], M. Luzi[1], L. Gianfranchi[2], P. Marchi[4], M. Calzolari[5], A. Solano[6]. *[1]Sant' Anna Hospital, Cardiology, Como, Italy; [2]Civile Hospital, Cardiology, Cento, Italy; [3]Sant' Annunziata Hospital, Cardiology, Taranto, Italy; [4]Ospedale del Delta, Cardiology, Lagosanto, Italy; [5]Arcispedale SS Maria Nuova, Cardiology, Reggio Emilia, Italy; [6]Ospedali Riuniti, Cardiology, Lavagna, Italy*

The "pill-in-the-pocket" (PIP) approach is a promising strategy in the treatment of recurrent atrial fibrillation (AF) in a selected populations.
We evaluate the PIP treatment in terms of efficacy and effects on the rate of hospitalization (HSP) with regard to the type and the dose of the given antiarrhythmic drug.
After a single-step phase of in-hospital screening to exclude non-responder patients or those with side-effect, 210 patients aged 59±11 years, with none or only minimal heart disease, and history of recurrent, recent onset AF, have been teached to out-of-hospital self-administration of a single oral loading dose of flecainide (FLC) 200-300 mg or propafenone (PFN) 450-600 mg, in case of symptomatic recurrences.
During a mean follow-up of 15±5 months, 165 (79%) patients experienced 618 symptomatic episodes; 569 (92%) of which have been treated with FLC (N°=254), mean dose 3,6±0,7 mg/kg/body weight, median dose (MD) 3,75 mg/kg or PFN (N=315) mean dose 7,5±1,4 mg/kg, MD 7,5 mg/kg. Rough efficacy was 534/569 (94%) episodes, FLC 239/254 (94%), PFN 295/315 (93%). The mean time to symptoms resolving has been 113±84 min after drug administration. The rate of HSP/month has been lower during the follow-up in comparison with the year before entering the study (4.9 vs 45.6; $p<0.001$).
Arrhythmic episodes have been separated in two groups concerning the dose of the administred drug, respectively = MD (Group A, N°=322) o > MD (Group B, N°=247). The rate of persistence of AF > 6h was higher in Group A (28/322 – 8,7% vs 7/247 – 2,8%; p=0.007) as well as HSP for arrhythmia (16 - 5,0% vs 3 - 1,2%, p=0.025) or for any cause (20 – 6,2% vs 6 – 2,4%; p=0.053). Two cases of atrial flutter (1:1 AV conduction in one case) have been detected in Group A. No differences have been detected regarding the incidence of minor side effects (Group A, N°=38 vs Group B, N°=30; P=NS)
In a selected risk-stratified population of patients with recent onset AF, the PIP strategy is safe and efficacious and is able to dramatically reduce the rate of HSP. The effect of this approach isn't related to the type of administered drug, but is strongly dependent on the effectively given dose of each drug.

P3049 N3-fatty acids as prophylaxis against postoperative atrial fibrillation after coronary artery bypass surgery. A prospective and randomised study

L. Calo'[1], L. Bianconi[2], A. Meo[2], M.L. Loricchio[2], E. De Ruvo[2], M. Colivicchi[2], C. Pandozi[2], M. Santini[2]. *[1]San Filippo Neri Hospital, Cardiology, Rome, Italy; [2]San Filippo Neri Hospital, Cardiology, Rome, Italy*

Background: Postoperative atrial fibrillation (AF) is a common complication of coronary artery bypass surgery (CABG). and several studies have explored the effectiveness of pharmacological and nonpharmacological interventions for prevention of AF. There is a growing clinical evidence that n-3 polyunsaturated fatty acids (PUFAs) may have cardiac antiarrhythmic effects. Aim of this study was to assess the efficacy of preoperative and postoperative treatment with n-3 PUFAs in preventing the occurrence of AF after CABG.
Methods: 160 patients were prospectively randomized to control group (81 patients, 13 female, 64.9 ± 9.1 years) or PUFAs 2 g/day (79 patients, 11 female, 66.2 ± 8.0 years) for a minimum of 5 days before elective coronary artery bypass surgery and until the day of discharge from the hospital. The primary endpoint was the development of AF in the postoperative period. The secondary endpoint was the hospital length of stay.
Results: The clinical characteristics of the patients in the two groups were similar. Postoperative AF developed in 27 patients of control group (33.3%) and in 12 patients of PUFA group (15.2%), (P = 0.013). There was no significant difference in the incidence of non fatal postoperative complications and postoperative mortality was similar in PUFAs-treated patients (1.3%) versus controls (2.5%). After CABG, the PUFAs patients were hospitalized for significantly fewer days than controls (7.3 ± 2.1 days versus 8.2 ± 2.6 days, P = 0.017).
Conclusions: This study first demonstrate that the use of PUFAs during hospitalization in patients undergoing CABG substantially reduced the incidence of postoperative AF (54.4%) and was associated with a shorter hospital stay.

P3050 Antiarrhythmic efficacy and electrophysiological characteristics of AZD7009 in dogs with pacing-induced atrial fibrillation and remodelling

G. Duker[1], B. Andersson[1], I. Jacobson[1], G. Linhardt[1], A.C. Nordstrom[1], L. Carlsson[2]. *[1]AstraZeneca R&D, Integrative Pharmacology, Mölndal, Sweden; [2]Astrazeneca, Dept. of Pharmacology, Mölndal, Sweden*

Background: The efficacy and the electrophysiological effects of the novel antiarrhythmic agent AZD7009 were studied in dogs with pacing-induced AF and remodeling.
Methods: AF was induced by right atrial pacing (RAP, 400 bpm) for 6 weeks. Occurrence of AF was assessed weekly during the first 5 weeks and if lasting >15 min an attempt to terminate the AF by AZD7009 (9.4 μmol/kg maximum) or saline was undertaken. At week 6, the dogs were anaesthetised and prepared for an invasive electrophysiological investigation and a piece of the left atria for in vitro electrophysiology recordings was excised. Dogs not subjected to RAP were used as controls.
Results: In 11 dogs, 29 episodes of AF lasting >15 min were observed. Saline and AZD7009 terminated 1/6 and 23/23 episodes ($p<0.001$), respectively. At week 5 of RAP the number of episodes and the total dose AZD7009 for AF termination were higher than at week 1. RAP caused a significant atrial, but not ventricular, remodeling. Hence, in control dogs (n=14) the atrial and ventricular effective refractory period (AERP and VERP) were 152±4.7 and 146±2.3 ms, and in RAP dogs (n=11) 108±4.7 ($p<0.001$ vs control) and 152±3.8 ms (p=NS). In a subgroup of control dogs and in all RAP dogs AZD7009 (6.25 μmol/kg/h) concentration-dependently, and statistically significantly ($p<0.01$) increased AERP and VERP (Table). Quantitatively the effects on AERP were significantly larger ($p<0.05$). At 3 Hz, the APD90 in control and remodeled atria was 102±5.7 ms (n=5) and 88±5 ms (n=6, $p>0.05$). AZD7009 concentration-dependently prolonged the APD90 and at 10 μmol/L the increase was 48±6.5 ms (control atria, $p<0.01$) and 34±6.5 ms ($p<0.01$).

Table (Means(SEM))

	Control (n=5)		RAP (n=11)	
Cp (nmol/L)	1615(84)	2760(129)	2119(156)	3784(450)
AERP (change in ms)	71(5)	92(9)	55(14)	88(9)
VERP (change in ms)	29(2)	36(5)	18(5)	19(5)

Conclusions: In the remodeled dog atria, AZD7009 predominantly increased atrial refractoriness, retained most of its electrophysiological effects and was highly effective in terminating AF.

ELECTROCARDIOGRAPHY; 1

P3051 Heterogeneous electrical organisation of pulmonary venous antrum contributes to maintenance of atrial fibrillation analyzed by Fast Fourier Transform during electrical pulmonary venous isolation

K. Uno, K. Miyamoto, S. Sakurai, K. Nishisato, S. Yuda, A. Hashimoto, K. Tsuchihashi, K. Shimamoto. *Sapporo Medical University, The Second Department of Int. Med., Sapporo, Japan*

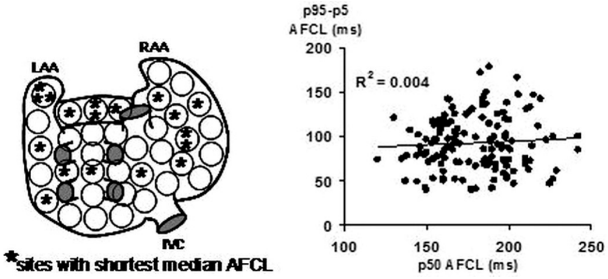
Pulmonary venous electrical isolation (PVI) eliminates triggers of atrial fibrillation (AF), but whether left atrial antrum connecting to PV ostium is responsible for sustained AF is still unclear. To examine whether electrical activity between PV ostium and PV antrum is critical for AF-maintenance mechanism, We analyzed electrophysiological activation patterns of PV ostium and PV using Fast Fourier Transform analysis (FFT) during AF. We studied thirteen paroxysmal/persistent AF patients (10 males; 59±7 yrs) deploying a 64-poles basket catheter into PV. To detect arrhythmogenic PVs, we documented spontaneous triggers after external direct current defibrillation (DC) against AF. When AF was sustained or

reinitiated after DC, PVI produced during AF according to discrete PV antrum potentials recorded by a basket catheter. Data sampling from a basket catheter were obtain during AF. After completion of every PVI, DC was performed when AF was sustained. FFT analysis of electrograms by a basket catheter during AF was performed through each PVI. (1) AF was induced in 12 cases, and AF sustained or spontaneously reinitiated in 9 cases despites of DC. (2) AF was terminated in 5 cases spontaneously when antrum potentials recorded in a basket catheter were eliminated by catheter ablation, and in 4 patients following DC. FFT of PV antrum revealed that (3) high dominant frequency was documented at small region between PV antrum and PV ostium (45% of electrode pairs of a basket catheter, not around whole electrode pairs of a basket catheter) before PVI, and that (4) AF was terminated as high dominant frequency in electrode pairs of a basket catheter of PV ostium was eliminated by PVI. (5) The peak of dominant frequency significantly decreased when antrum potentials recorded close to PV ostium were disappeared with completion of PVI ($p<0.05$). In conclusion, Heterogeneous peak dominant frequency of arrhythmogenic PV ostium activation is critical for AF maintenance. And PVI with elimination of antrum potentials of peri-PV ostium may be required to eliminate both AF initiation and maintenance.

P3052 Spatial distribution of atrial fibrillation cycle length in patients with persistent atrial fibrillation: no evidence for a driver

T.J. Van Brakel[1], N.M.S. de Groot[2], B. Koektuerk[3], M.J. Schalij[2], R.E. Accord[4], J.G. Maessen[4], M.A. Allessie[3]. *[1]University Hospital Maastricht, Cardiothoracic Surgery, Maastricht, Netherlands; [2]Leiden University Medical Center, Cardiology, Leiden, Netherlands; [3]CARIM, Physiology, Maastricht, Netherlands; [4]CARIM, Cardiothoracic Surgery, Maastricht, Netherlands*

Background: Studies in which the dominant frequency during atrial fibrillation (AF) was analyzed have suggested that in some cases persistent AF is maintained by a fast and regular 'driver' located in the pulmonary veins. We applied high density mapping to directly measure the local AF cycle length (AFCL) in patients with permanent AF.
Methods: In 9 patients with permanent AF undergoing cardiac surgery, the entire surface of both atria was mapped with a $1cm^2$ mapping probe (64 unipolar electrodes; inter-electrode distance 1.2 mm). From 30-40 locations the median AFCL and degree of irregularity was determined during 10s of AF.
Results: The average median AFCL of all electrograms was 191±40ms with a temporal variation of 100±37ms (difference between p5 and p95-values). In each patient considerable local differences in median AFCL were observed, with a spatial dispersion (maximal difference in local AFCL) ranging between 35 and 83ms (mean 54±22ms). The average median AFCL in the right atrium did not differ from the left (179±27ms vs. 176±17ms). A gradient between left and right atrium was not observed. The left figure depicts the mapped atrial regions (circles) with the fastests areas from all patients indicated by asterisks. The location of the shortest AFCL varied from patient to patient and showed no anatomically defined predeliction. There was no correlation between the median AFCL (p50) and the degree of irregularity (p95-p5), see right figure.



Conclusions: Although a considerable spatial dispersion in AFCL was present in patients with permanent AF, there was no predeliction site with a shortest and most regular AFCL. These observations do not support the hypothesis that persistent atrial fibrillation is maintained by a driver in the left atrium.

P3053 Analysis of the temporal irregularity of atrial fibrillation cycle length

N.M.S. De Groot[1], M.J. Schalij[2], M.A. Allessie[3]. *[1]Leiden University Medical Centre, Cardiology Dept., Leiden, Netherlands; [2]Leiden University Medical Center, Cardiology, Leiden, Netherlands; [3]Cardiovascular research institute, Electrophysiology, Maastricht, Netherlands*

Introduction: The exact mechanism of irregularities in atrial fibrillation cycle length (AFCL) is unknown. In this study, we investigated to what extent beat-to-beat changes in conduction of fibrillation waves can explain irregularities in AFCL.
Methods: Epicardial mapping studies of the right atrial free wall were performed during induced AF in patients (AAF, n=20, 14 male, age 31±12 yrs) with normal atria, and chronic AF (CAF) in patients with mitral valve disease (n=13, 7 male, age 66±9 yrs.) using a 244 unipolar electrode array (3.6 cm diameter). Isochronal maps were constructed during 8 seconds of AF. At the centre of the mapping area, AFCL was determined by measuring the time between activations by consecutive fibrillation waves. Temporal variation in AFCL were related with beat-to-beat changes in conduction including changes in conduction velocity, activation pathway, direction of propagation or epicardial breakthrough of fibrillation waves.
Results: Median AFCL was longer and more irregular (P95-P5)/P50) during (182±28 ms and 68±13 versus 157±27 ms and 44±17) compared to AAF. Beat-to-beat changes in conduction included "no changes in conduction" (AAF: 29±17%, CAF: 10±13%, $p<0.001$), alterations in conduction velocity/pathway (AAF: 34±15%, CAF: 14±12, $p<0.001$) changes in conduction direction (AAF: 34±15 [4-56]% versus CAF: 14±12 [0-41]%, $p<0.001$) or epicardial breakthrough (AAF: 24±22%, CAF: 66±26%, $p<0.00$). The total variation in conduction times (P100-P0) due to changes in sequence of activation under the mapping electrode was 32±17 ms during AAF and 61±21 ms during CAF.Changes in conduction in the epicardial plane accounted for 76% of the irregularities in AFCL at the centre electrode during AAF and 27% during CAF.
Conclusion: During AAF, beat-to-beat irregularity in AFCL can for a large part be explained by beat-to-beat changes in conduction of fibrillation waves in the epicardial plane within an area of 3.6X3.6 cm. During CAF, the higher degree of irregularities is caused by a higher number of epicardial waves contributing to the fibrillatory process compared to AAF.

P3054 Prognostic value of heart rate variability in patients with unstable angina

G.A. Sgueglia[1], G.A. Lanza[1], A.G. Rebuzzi[1], D. Cianflone[2], A. Sestito[1], G. Angeloni[1], F. Crea[1], A. Maseri[2] on behalf of Stratificazione Prognostica dell'Angina Instabile (SPAI) Study Group. *[1]Policlinico A. Gemelli, Istituto di Cardiologia, Rome, Italy; [2]Università Vita e Salute, Istituto di Cardiologia, Milano, Italy*

Background: Previous studies showed that a reduced heart rate variability (HRV) is of prognostic value in patients with an acute myocardial infarction. Despite the recent interest in risk stratification of patients with unstable angina (UA), the prognostic relevance of HRV in UA patients remains poorly known.
Methods: We analysed Holter ECG recordings of 583 UA patients (63±10 years, 356 men) included in the multicenter prospective Italian study "Stratificazione Prognostica dell'Angina Instabile" (SPAI) who underwent 24-hour Holter monitoring within 24 hours of hospital admission. HRV was assessed in the time-domain and in the frequency domain.
Results: During 6-month follow-up, there were 32 total deaths (6.5%). With regard to HRV variables, patients were dichotomized into those with values in the bottom quartile and those with values in the 3 upper quartiles. Low quartile values of several HRV variables were significantly associated with increased mortality at univariate Cox regression analysis (Table). On multivariate Cox regression analysis, including known clinical and laboratory prognostic variables (age, gender, cardiac risk factors, type of UA, previous myocardial infarction, ventricular arrhythmias, and serum levels of C-reactive protein and troponin I) reduced low frquency (LF) value was independently associated with both total (RR=2.32, 95% CL=1.1-4.63, p=0.03) and cardiac (RR=3.60, 95% CL=1.1-12.0, p=0.04) death.

Table

	Relative risk (95% C.L.)	P
RR interval <833 ms	2.06 (1.02-4.18)	0.044
SDNN <80 ms	1.56 (0.75-3.24)	0.23
SDANN <62 ms	1.84 (0.90-3.74)	0.09
SDNNi <39 ms	3.00 (1.50-5.99)	0.002
VLF <31 ms	3.07 (1.53-6.14)	0.002
LF <15.7 ms	3.09 (1.54-6.17)	0.001
HF <11.2 ms	1.80 (0.88-3.69)	0.11
LF/HF <1.12	3.57 (1.78-7.15)	0.0003

Conclusions: Our data, for the first time, show that decreased HRV is associated with increased mortality at 6-month follow-up in patients admitted to coronary unit because of UA, pointing out that it should be taken into account in risk stratification of these patients.

P3055 T-wave surface area: a sensitive index for transmural dispersion of the repolarisation

B. Hooft van Huysduynen, C.A. Swenne, H.H.M. Draisma, H. Van de Vooren, A.L. Antoni, E.E. Van der Wall, M.J. Schalij. *Leiden University Medical Center, Cardiology Dept., Leiden, Netherlands*

Background: Transmural dispersion of the repolarization (TDR) is caused by differences in cellular activation and action potential duration through the ventricular wall. TDR is related to arrhythmias and may be caused by various drugs that preferentially prolong the (sub)endocardial APDs. Electrocardiographic indices that reflect the TDR caused by drugs could be of great value to assess the risk of arrhythmias. Several indices of TDR have been proposed: the Tapex-Tend interval (Tae), the T-wave amplitude (Tamplitude), the T-wave surface area (Tarea) and singular value decomposition as a measure of T-wave complexity (Tcomplex-

ity). In this study we used a realistic three dimensional ECG simulation model, ECGSIM, to validate the reactions of these indices to endocardial APD lengthening.
Methods: ECGSIM consists of an equivalent double layered heart in a realistic thorax, based on MRI measurements. Using ECGSIM, we generated standard 12 lead ECGs under normal conditions and after lengthening of the endocardial APDs with 30 ms. The simulated ECGs were analyzed with a customized ECG analysis program. A blinded observer placed markers at the start and end of the T-wave. Thereafter, the program automatically calculated Tae, Tamplitude, Tarea and Tcomplexity. Tcomplexity was defined as the quotient of the more complex, higher singular values divided by the first, most simple, singular value.
Results: Lengthening of the endocardial APDs by 30 ms increased the Tae from 80 $\pm$ 7 ms to 89 $\pm$ 10 ms, an increase of 11%. Tamplitude increased from 275 $\pm$ 170 μV to 1033 $\pm$ 467 μV, an increase of 275%. The Tarea increased from 33883 $\pm$ 20084 μVms to 135955 $\pm$ 52613 μVms, corresponding to an increase of 301%. Tcomplexity increased from 0.13 to 0.30, an increase of 134%.
Conclusion: Lengthening of endocardial APDs increased Tae. However, the changes in Tcomplexity and Tamplitude were more explicit, and the increases in Tarea even more. Therefore, when assessing the arrhythmogenic side effects of drugs, Tarea may be the most sensitive measure of transmural dispersion of repolarization.

P3056 Quantifying QT lagging as a novel risk stratifier after myocardial infarction

J.K. Kanters[1], B.T. Jensen[1], S.Z. Abildstrom[1], C.T. Petersen[2], N.H. Holstein-Rathlou[2]. *[1]Elsinore Hospital, Dept. of Cardiology, Helsingor, Denmark; [2]University of Copenhagen, Dept. of Medical Physiology, Copenhagen, Denmark*

The adaptation of the QT interval is lagged and can take several minutes. The aim of the present study was to quantify QT lagging and test whether lag parameters have prognostic information.
Methods: holter recordings were done in 311 patients with an acute myocardial infarction. Ejection fraction (EF) was determined by echocardiography. Patients were followed for three years with a three year mortality of 23%. Survival analyses were performed using Cox models. The QT interval were fitted with the previous RR intervals using multiple regression (QTn = c+ci*RRn-i-1).
Results: including 50 RR intervals for fitting the QT interval reduced the mean square error from 148 to 118 msec. Multivariate Cox survival analysis revealed that the lagcoefficients: c2,c4,c5,c10,c13,c23,c28,c30,c31,c36,c38 and c40 had significant prognostic value ($p<0.0001$). A lagscore were calculated from the individual coefficients retrieved from the multivariate regression model. The hazard risk ratios from the Cox model are shown in the table.

Table

	Risk Ratio Univariate	Risk Ratio Multivariate	Survivors Median[95%CI]	Deceased Median[95%CI]
Lagscore	2.72	2.38	0.1[-1.6;1.7]	1.2[-0.5;4.5]
EF (%)	0.95	0.98	48[27;60]	36[24;60]
Age (y)	1.06	1.03	65[44;83]	76[54;89]

In conclusion QT lags adds prognostic information to EF and age.

BASIC EL- ARRHYTHMIAS MECHANISMS

P3057 A neutral endopeptidase inhibitor (NEPI) suppresses the early phase of atrial electrical remodelling in the canine rapid atrial stimulation model

R. Imaki[1], S. Niwano[2], H. Niwano[2], D. Satoh[2], T. Yoshida[2], Y. Masaki[2], T. Izumi[2]. *[1]Kitasato University, Medicine, Sagamiharashi,kitasato1-15-1, Japan; [2]Kitasato University, Medicine, Sagamiharashi,kitasato1-15-1, Japan*

Background: We previously reported that human atrial natriuretic peptide (hANP) suppresses the early phase of atrial electrical remodeling, perhaps via the action of enhanced levels of cyclic GMP (cGMP) leading reduction of calcium overload which is supposed as a main cause of the electrical remodeling. As hANP has a limitation in that it cannot be administered orally, candoxatril (Cx), a neutral endopeptidase inhibitor (NEPI) which has been shown to increase circulating levels of atrial natriuretic peptide (ANP), was evaluated in this study.
Methods: 10 beagle dogs were studied with continuous rapid atrial pacing at 400 beats per minute delivered from the right atrial appendage (RAA) for 6 hours after His-bundle ablation. 5 of these received Cx in advance, 24 mg/kg one day before and 20 mg/kg on the day of the experiment. Hemodynamics, atrial effective refractory period (AERP) and monophasic action potential duration (MAPD) of RAA were measured and blood samples were collected at the beginning and the end of the rapid pacing. Tissue RAA was also excised at the conclusion of the protocol for evaluating intracellular levels of cGMP.
Results: No significant hemodynamic changes were detected between the two groups. AERP and MAPD shortened after the rapid pacing in the control group (ERP: from 130$\pm$7 to 120$\pm$9 ms, p=0.042, MAPD: from 147$\pm$13 to 113$\pm$11 ms, p=0.021), whereas these changes were inhibited in the Cx group. The rapid pacing increased the plasma levels of ANP in the both groups (control: from 25.6$\pm$9.05 to 88.4$\pm$50.25 pg/ml, p=0.033, Cx: from 75.8$\pm$48.63 to 197.1$\pm$32.09 pg/ml, p=0.014), and values of after the rapid pacing were higher in the Cx group than the control group (p=0.004). Although the rapid pacing did not affect plasma levels of cGMP, which was higher in the Cx group than the control (34$\pm$9.9 vs. 48$\pm$10.2 pg/ml, p=0.048). There was no significant differences in the levels of active renin and angiotensin, but the rapid pacing enhanced circulating levels of aldosterone in the control group (from 61$\pm$63.2 to 256$\pm$133.1 pg/ml, p=0.027) and Cx suppressed it (from 32$\pm$26.4 to 40$\pm$20.6 pg/ml, p=0.7525). In addition, intracellular levels of cGMP were higher in the Cx group than the control group (28.1$\pm$1.60 fmol/mg vs. 44.5$\pm$12.28 fmol/mg, p=0.034).
Conclusions: Cx suppressed the shortening of ERP and MAPD with enhanced levels of intracellular cGMP as well as circulating levels of plasma ANP and cGMP. The effect of Cx might appear through the action of these factors, and could be an effective strategy for the electrical remodeling.

P3058 Nitric oxide mediates the effects of vagus nerve stimulation on ventricular fibrillation and electrical restitution in the isolated innervated heart

V.H. Patel[1], K.E. Brack[2], J.H. Coote[3], G.A. Ng[1]. *[1]University of Leicester, Cardiovascular Sciences, Leicester, United Kingdom; [2]University of Birmingham, Physiology, Birmingham, United Kingdom; [3]University of Birmingham, Neuroscience, Birmingham, United Kingdom*

We have previously shown that direct vagus nerve stimulation (VS) protects the isolated heart against ventricular fibrillation (VF) and that VS reduces the slope of the electrical restitution curve, which is a key determinant in VF initiation. Nitric oxide (NO) mediates aspects of vagal activity at the atrial level but its role in mediating the effects of VS in the ventricle has not been characterised. This study examines whether NO mediates the effects of VS on restitution and VF in the isolated innervated rabbit heart. Adult rabbits (2.2-3.0kg, n=7) were sacrificed and vagus nerves isolated at the cervical region. Restitution was studied using single ventricular extrastimuli(S2) protocol with left ventricular monophasic action potential duration (MAPD) measured. S2-MAPD were plotted against preceding diastolic intervals and maximum slope of the fitted exponential curve measured. VF threshold (VFT, mA) was determined as the minimum current required to induce VF with rapid (33Hz) pacing. Measurements were made with and without VS: at baseline (BL); with NO-synthase inhibitor, N-nitro-L-arginine (LNA, 200μM) to block NO production; with LNA and L-arginine (L-Arg,1mM) as substrate to reverse NO inhibition; with L-Arg alone and after washout.
Results (see Table, mean$\pm$SEM): VS significantly increased VFT whilst flattening the restitution curve and decreased maximum slope. These effects were blocked by LNA and reversed by L-Arg which did not have direct effects on its own. There was a significant correlation between restitution slope and VFT (r=-0.55, $p<0.0001$).

Effects of VS on Slope and VFT

	BL		LNA		LNA+L-Arg		L-Arg		Washout	
	Slope	VFT	Slope	VFT	Slope	VFT	Slope	VFT	Slope	VFT
Pre-VS	2.4	3.4	2.5	3.3	2.4	3.4	2.6	3.0	2.7	3.3
	$\pm$0.4	$\pm$0.3	$\pm$0.6	$\pm$0.2	$\pm$0.4	$\pm$0.3	$\pm$0.6	$\pm$0.4	$\pm$0.6	$\pm$0.2
VS	0.8	9.0	2.8	3.9	1.4	5.5	0.7	9.0	0.9	8.1
	$\pm$0.1	$\pm$1.1	$\pm$0.7	$\pm$0.4	$\pm$0.2	$\pm$0.6	$\pm$0.2	$\pm$1.4	$\pm$0.2	$\pm$1.2
p	0.001	<0.001	NS	NS	<0.05	<0.01	<0.05	<0.01	<0.02	<0.005

Conclusion: VS flattened the restitution curve and increased VF threshold. Inhibition of NO production with LNA blocks the effects of VS on the slope of the restitution curve and on VF threshold whilst replenishing substrate for NO production with L-Arg restores these effects. These results suggest that NO released during VS may mediate its antifibrillatory action by altering electrical restitution.

P3059 Global sequence of ventricular repolarisation during right ventricular endocardial and left ventricular epicardial pacing: monophasic action potential mapping in swine

Y. Xia[1], O. Kongstad[2], P. Platonov[2], M. Holm[3], B. Olsson[2], S. Yuan[2]. *[1]Lund University Hospital, Departmetn of Cardiology, Lund, Sweden; [2]Lund University Hospital, Departmetn of Cardiology, Lund, Sweden; [3]Johnson & Johnson, Biosense Webster, Waterloo, Belgium*

Background: Previous studies have suggested that the sequence of repolarization follows that of activation during sinus rhythm and atrial pacing. However, repolarization sequence during ventricular pacing is unknown.
Methods: Using the CARTO mapping system, global monophasic action potential (MAP) mapping of the LV and RV endocardium in total 126$\pm$35 sites were performed during RA pacing (RAP), RV apex endocardial pacing (RVEndoP) and LV laterobasal epicardial pacing (LVEpiP) in 10 healthy pigs. Local activation time (AT), MAP duration (MAPd) and end-of-repolarization (EOR) time were measured and three-dimensional global maps of the AT and EOR were constructed.
Results: 1). During RAP, the EOR sequence followed the AT sequence, with the earliest at the right/left anteroseptal/apical area, and the latest at the right or left posterior basal area. 2). During RVEndoP, the EOR sequence also followed the AT sequence. The earliest EOR started at the right apical pacing site, and prop-

agated eccentrically towards the septum and free wall, with breakthrough on the left side of the septum in either 1 or 2 regions at the apicoseptal and/or midseptal areas. The latest EOR located at the LV/RV lateral or posterolateral basal area. 3). During LVEpiP, the EOR sequence followed the AT sequence, too. The earliest EOR started at the left lateral pacing area, propagated eccentrically towards the apex and septum, with the breakthrough on the right side of the septum at the midseptal/posteroseptal regions. The latest EOR located at the right posterobasal/laterobasal areas. 4). In all the maps, MAPd and AT were negatively correlated, and EOR time and AT positively correlated (see Table, $p<0.05$-0.001).

Correlation between MAPd/EOR and AT

	n =	sites	MAPd vs. AT slope and r =	EOR vs. AT slope and r =
RAP	5	112±16	-0.45±0.13 and -0.42±0.18	0.46±0.11 and 0.44±0.14
RVEndoP	10	128±28	-0.32±0.10 and -0.32±0.04	0.51±0.13 and 0.50±0.21
LVEpiP	5	143±22	-0.35±0.10 and -0.32±0.20	0.58±0.11 and 0.55±0.17

Conclusion: In contrary to the conventional concept, the ventricular repolarization sequence is not opposite to but concordant with the activation sequence, suggesting the latter is a determinant of the former not only during normal activation sequence as reported before, but also during RV and LV pacing.

P3060 Local modifications of ventricular fibrillation complexity produced by local stretch

F.J. Chorro-Gasco[1], I. Trapero[1], J. Canoves[1], L. Mainar[1], L.M. Such[2], A. Tormos[3], J. Millet[3], A. Alberola[2]. [1]*Clinic University Hospital, Cardiology Service, Valencia, Spain;* [2]*University, Physiology, Valencia, Spain;* [3]*Polytechnic University, Electronics, Valencia, Spain*

We hypothesized that local modifications in electrophysiological properties, when circumscribed to areas of limited extent, induce few changes in the global activation process during ventricular fibrillation (VF). To test this hypothesis, we produced local electrophysiological modifications by stretching a circumscribed zone of the left ventricular wall in an experimental model of VF.

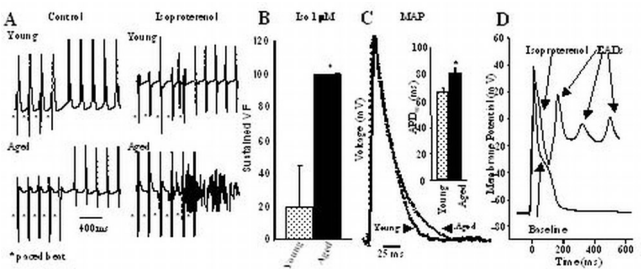
In 16 Langendorff-perfused rabbit hearts, high resolution mapping was used to analyze the VF recordings obtained with two epicardial multiple electrodes before, during and after local stretching produced with a left intraventricular device. A longitudinal lengthening of 12.1±4.5% (vertical axis) and 11.8±6.2% (horizontal axis) in the stretched zone increased the percentages of complex activation maps with three or more wavefronts and multiple block lines (21% vs 49%, $p<0.0001$), and there was also an increase in the breakthrough patterns (23% vs 37%, $p<0.01$) - without significant changes in the number of maps with reentry patterns (9% vs 9%, ns). There was a nonsignificant trend to increase the mean number of consecutive rotations (1.1±0.4 vs 1.5±0.6, ns), with a maximum number of three. Simultaneously, in a non-stretched zone, no changes were recorded in the percentages of the types of complex activation maps (24% vs 17%, ns), in the number of maps with breakthrough patterns (25% vs 20%, ns) and reentry patterns (12% vs 8%, ns), and in the number of consecutive rotations (1.1± 0.3 vs 1.0±0.2, ns) - the maximum number of rotations being 1.2. In the stretched zone, the functional refractory period during VF decreased during stretch (42±8 vs 34±4 ms, $p<0.05$), conduction velocity did not vary significantly (44.4±5.4 vs 44.6±4.9 cm/s, ns), and the wavelength showed significantly smaller values (1.9±0.4 vs 1.5±0.3 cm, $p<0.05$). No significant variations in these parameters were recorded in the non-stretched zone.

Conclusion: Local stretch increases the electrophysiological heterogeneity of myocardium and increases the complexity of VF in the stretched area, without significantly modifying occurrence of the types of VF activation patterns in the non-stretched zone.

P3061 Molecular basis for the increased vulnerability of the aged heart to arrhythmogenesis

A.S. Oberlin[1], C.C. Cabrera Aguilera[1], X.K. Liu[1], S. Raghavakaimal[2], A. Jahangir[3]. [1]*Mayo Clinic, Division of Cardiovascular Diseases, Rochester, MN, United States of America;* [2]*Mayo Clinic, General Clinical Research Center, Rochester, MN, United States of America;* [3]*Mayo Clinic, Cardiology Dpt., Rochester, United States of America*

While it is known that aging increases the susceptibility of the senescent heart to arrhythmogenesis, the molecular basis for this is not fully understood. To assess for the age-related differences in the vulnerability of the senescent heart to arrhythmogenesis, hearts from aged (24 m old) and young (6 m old) Fischer 344 rats were studied at whole heart, isolated cell level and age-related changes in expression of genes coding for proteins regulating cellular excitability and refractoriness determined by GeneChip 230 Plus2.0 arrays (Affimetrix, CA). With electrical stimulation, no sustained ventricular arrhythmia could be induced under baseline conditions, however with catecholamine challenge, sustained VF requiring defibrillation was induced predominantly in senescent animals (100% vs 20% in the young; Fig. A, B). Action Potential duration (APD) in the aged heart at baseline was longer as determined from LV epicardium (66±3 vs 80±4 ms; Fig. C) and at single cell level (77±4 vs 82±6 ms; $p<0.05$). With isoproterenol, APD shortened in the young but prolonged in the aged heart, which also demonstrated phase 3 EAD (80±5% vs 0%; Fig D) and triggered activity (50% vs 10% in young). The aged heart when compared to the young demonstrated decreased



Figure

expression of genes coding for the alpha-subunits of IKr, IKATP, If, Na^+/K^+ pump, RYR2, Calsequestrin 2 and SERCA 2 and 3 and upregulation of genes coding for KCNE1, IKAch and Beta-2 adrenergic receptor in the aged heart. Thus the increased susceptibility to arrhythmogenesis of the aged heart is partially due to decreased repolarization reserve and triggered activity due to down regulation of genes coding for proteins regulating repolarization and Ca^{2+} handling.

P3062 Prevalence and features of incessant atrial arrhythmias after heart transplantation with standard technique

B. Petracci[1], M.E. Landolina[1], F. Frattini[1], G.M. De Ferrari[1], M. Vigano'[2], R. Rordorf[1], F. Pentimalli[1], A. Vicentini[1]. [1]*Policlinico S.Matteo-IRCCS, Cardiology Dept., Pavia, Italy;* [2]*Policlinico S. Matteo IRCCS, Cardiac Surgery Dept., Pavia, Italy*

The standard technique for ortotopic heart transplantation (HTx) requires to suture the donor atrium (DA) to the recipient atrial remnant (RA); DA and RA are usually electrically isolated from each other. Little is known about the prevalence and features of atrial arrhythmias (AA) in HTx pts.

Between January 1985 and November 2004, 740 pts (age 48 ± 12 yrs, mean F.U. 80 mos) underwent HTx by standard technique in our Cardiac Surgery Dept. Sixteen/740 pts (2.2%) had incessant AA and underwent electrophysiological study and RF ablation attempt. In 10/16 (62.5%) pts, the AA originated from RA and were conducted to DA across the surgical suture; the RA arrhythmia was sustained atrial tachycardia in 6 pts, atrial fibrillation (AF) in 1 pt, and pseudo premature atrial contractions due to conduction of recipient sinus rhythm to DA in 3 pts. In 3/16 (19%) pts, the arrhythmia was a donor atrial flutter (Afl) with the critical isthmus between the atrial suture line and the tricuspid valve (TV). Two/16 (12.5%) pts had focal AA: 1 pt had frequent premature atrial contractions from the superior portion of DA, close to the suture line and 1 pt had a focal atrial tachycardia from the DA postero-lateral wall. One pt had an incessant nodal reentry tachycardia (AVNRT) from the DA. In this population, the prevalence of sustained AA was 2.2%, with a prevalence of arrhythmias due to conduction from RA to DA of 1.3%, Afl of 0.4%, AVNRT of 0.1% and focal AA of 0.4%. The only case of AF was due to interatrial conduction.

Conclusions: Interatrial conduction is responsible for most of atrial arrhythmias in HTx pts. AF prevalence is lower in HTx pts compared to general population (1%), whereas Afl prevalence is higher (0.4 vs 0.09%). The low prevalence of AF may be explained by the electrical isolation of pulmonary and cava veins from the DA; the higher prevalence of Afl is likely due to interatrial suture line which favours macroreentry arrhythmias.

P3063 Relationship between electrogram fragmentation, voltage and conduction in patients with chronic atrial remodelling

P. Sanders[1], P.M. Kistler[2], C.J. Nalliah[3], L. Szumowski[4], J.B. Morton[2], L.F. Hsu[3], M. Haissaguerre[3], J.M. Kalman[2]. [1]*Bordeaux, France;* [2]*Royal Melbourne Hospital, Department of Cardiology, Melbourne, Australia;* [3]*Hôpital Cardiologique du Haut-Lévêque, Service de Rythmologie, Bordeaux-Pessac, France;* [4]*Institute of Cardiology, Warsaw, Poland*

Background: Regions of electrogram fragmentation have been implicated in the maintenance of atrial fibrillation (AF). In patients with chronically remodeled atria due to congestive heart failure (CHF) and sinus node disease (SND), we investigated the relationship between fragmentation, voltage and conduction and compared the prevalence of these findings with age-matched controls.

Methods: 16 pts (8F; 59±17yrs) with either CHF (8) or SND (8) and 13 age-matched controls were studied. Activation, voltage and fragmentation maps were created of the RA during pacing using the CARTO system (247±62 points). Conduction velocity (CV), determined as the distance between two points expressed as a factor of the difference in the activation time. Fragmentation was defined as complex local electrical activity and quantified using validated software as the fragmentation index (FI). Each atrium was anatomically divided into 6 regions to allow an average CV, voltage and FI to be determined.

Results: Patients with CHF and SND demonstrated the following abnormalities compared to controls: (i) larger atrial size (43±9 vs 35±6mm; p=0.02); (ii) lower atrial voltage (0.89±0.4 vs 1.8±0.7 mV; p=0.0003) and increased coefficient of variation (CoV) of voltage (55±23 vs 31±29%; p=0.007); (iii) areas of electrical

silence (2.8±4.1 vs 0% of surface area; p<0.0001); (iv) reduction of CV (0.9±0.2 vs 1.4±0.6 mm/ms; p=0.006) and increased CoV of CV (43±17 vs 30±10%; p=0.01); and (v) greater FI (mean RA 8.1±1.6 vs 5.4±1.0; p<0.0001) and CoV of FI (28±15 vs 15±16%; p=0.01). Electrogram fragmentation in CHF or SND was greatest along the posterior and low septal RA and showed significant anatomic correlation with regions of low voltage (r=-0.84, p<0.0001). These regions were also observed to result in slowed conduction (r=0.57, p<0.0001).
Conclusion: Patients with advanced atrial remodeling show anatomic regions of electrogram fragmentation, which is correlated with low voltage areas and slowed conduction. These regions are not seen in age-matched controls and may form the substrate for AF.

P3064 ZP123 improves atrial conduction slowing in chronic volume overload-induced dilated atria

K. Haugan[1], T. Miyamoto[2], Y. Takeishi[2], I. Kubota[2], J. Nakayama[3], M. Hirose[4]. *[1]Zealand Pharma A/S, Cardiovascular and Safety Pharmacology, Glostrup, Denmark; [2]Yamagata University School of Medicine, First Department of Internal Medicine, Yamagata, Japan; [3]Shinshu University School of Medicine, Department of Pathology, Matsumoto, Japan; [4]Shinshu University School of Medicine, Department of Molecular Pharmacology, Asahi Matsumoto, Japan*

Background: Previously, we have shown that chronic volume overload (CVO) causes atrial conduction slowing and increases susceptibility to induction of atrial tachyarrhythmias (AT) in the rabbit heart. The exact mechanism behind this is unclear. Gap junctions are responsible for the electrotonic coupling between cardiac myocytes and the degree of gap junction intercellular coupling (GJIC) is a major determinant of cardiac conduction velocity (CV).
Purpose: To examine the role of GJIC in the pathogenesis of atrial CV slowing and for the development of AT in the setting of chronic atrial dilatation.
Methods: Chronic atrial dilatation was created in Japanese white rabbits using CVO for 8 weeks by arterio-venous shunt formation. We examined the expression of atrial gap junction proteins (connexin40 and connexin43) as well as the spatial distribution of connexin43 in sham-operated controls (n=6) and in CVO hearts (n=6) using Western blots and immunohistochemistry. Furthermore, we examined atrial CV and AT inducibility in Langendorff-perfused CVO hearts (n=13) using high resolution optical mapping before and after treatment with the selective gap junction modifier ZP123, known to increase GJIC.
Results: Protein expressions of connexin40 and connexin43 in the atrium were decreased by 32% and 72% (P < 0.01), respectively, in CVO hearts compared to control hearts. The protein expression of atrial connexin43 was homogenously down-regulated in dilated atria, thus the spatial distribution was unchanged compared to control hearts. Overall, atrial CV at pacing cycle lengths of 300, 200 and 100 ms was significantly increased after treatment with 10 nM ZP123 relative to baseline (300 ms baseline: 0.66±0.03 vs ZP123: 0.70±0.04; 200 ms baseline: 0.63±0.03 vs ZP123: 0.68±0.04; 100 ms baseline: 0.52±0.05 vs ZP123: 0.60±0.05; p<0.05, two-way ANOVA). AT was induced in 4 out of 7 ZP123 treated hearts compared to 4 out of 6 vehicle treated hearts. Thus, treatment with ZP123 had no effect on AT inducibility.
Conclusions: CVO-induced atrial dilatation is associated with marked down-regulation of atrial connexin expression. The significant effect of ZP123 on atrial CV suggests that closure of gap junction channels contribute to atrial CV slowing, however, the lack of effect of ZP123 on AT inducibility suggests that impaired gap junction intercellular communication does not account for the increased arrhythmia propensity in this model.

P3065 Arrhythmogenic pattern of coronary artery disease in patients with inducible sustained ventricular tachycardia

L. Chiriac, G. Cristian, F. Pinte, M. Iacob, R. Bolohan, I. Tintoiu. *Centrul de Boli Cardiovascular Al Armatei, Dept. of Cardiology & Arrhythmology, Bucuresti Sector 1, Romania*

Introduction: This study was performed to determine the relation between inducible sustained ventricular tachycardia (ISMVT) by programmed electrical stimulation and angiographic, clinical and echographic data in patients with coronary artery disease (CAD). The aim of this study was to explore if these inducible arrhythmias patients are associated with any specific "arrhythmogenic" pattern of CAD.
Methods and Results: 129 consecutive patients with CAD and ISMVT were evaluated by left ventriculography and coronary arteriography by standard techniques. The mean age of the patients was 46 years with a range of 21 to 72 years, 74% of them are male. A significant stenosis of the main left coronary artery LCA (>50%)appeared to be more frequent in arrhythmic patients (31%). Also proximal LAD stenosis was more frequent in the arrhythmia aptients (48%). "Main left equivalent" lesions defined as a significant stenosis of the proximal LAD and the proximal left circumflex artery was more frquent among the arrhythmia patients (51%). Using the quantitive wall motion anlysis, a strong relationship was found between the number of abnormally contracting segments and the presence of ISMVT.
Conclusions: The results suggest that ISMVT with CAD are associated with a specific arrhythmogenic pattern of coronary artery stenosis consisting of the main left coronary artery and the proximal left anterior descending artery significant stenosis.

P3066 B-blocker prophylaxis for atrial fibrillation after coronary bypass grafting in patients with neurovegetative imbalance

M. Budeus[1], H. Wienke[1], P. Feindt[2], E. Gams[2], S. Sack[1], R. Erbel[1]. *[1]West German Heart Center, Cardiology, Essen, Germany; [2]Heinrich-Heine-Universität, Thorax- und Kardiovaskular Chirurgie, Düsseldorf, Germany*

Atrial fibrillation (AF) is the most common arrhythmia after coronary bypass grafting (CABG) resulting in a prolonged hospital stay and higher costs. The withdrawal of b-blocker and a neurovegetative imbalance were identified as risk factors for AF.
In our study we performed a measuring of heart rate variability (HRV) among 142 consecutive patients with b-blocker therapy before CABG in order to identify a collective who had an increased risk due to a withdrawal of b-blocker medication. A neurovegetative imbalance was defined as a HRV below 30 ms. Patients with a neurovegetative imbalance were divided into patients with and without a continuously b-blocker therapy. Patients with a HRV above 30 ms were also divided in a group with and without a continuously b-blocker therapy.
AF occurred in 39 of 142 (27%) patients after surgery. The collective of neurovegetative imbalance without a continuously b-blockerhad a higher incidence of AF (14/26 patients, 54%) than patients with neurovegetative imbalance and a continuously b-blocker therapy (7/33 patients, 21%; p < 0,009), patients with a HRV above 30 ms and a continuously b-blocker therapy (8/40 patients, 20%; p < 0,004) or without a continuously b-blocker therapy (10/43 patients, 23%; p < 0,01). Patients with a neurovegetative imbalance had a significantly higher incidence of diabetes mellitus (47 vs. 14% of patients; p < 0,0001). The diagnostic value of neurovegetative imbalance and b-blocker withdrawal achieved a specificity of 78%, a sensitivity of 54%, a positive predictive value of 36%, a negative predictive value of 88% and an accuracy of 73% for identifying patients being at risk of AF.
The results of our study suggest that patients with a neurovegetative imbalance had a high risk of AF after CABG as a result of a withdrawal of a b-blocker therapy. A continuous b-blocker therapy reduces the risk especially in patients with a neurovegetative imbalance and should always be practised.

P3067 The relationship between arrhythmias and C-reactive protein levels in patients with acute myocardial infarction

I. Dursun, K. Durna, K. Soylu, S. Yuksel, B. Tascanov, O. Gulel, O. Yesildag, M. Sahin. *Ondokuz Mayis University Hospital, Department of Cardiology, Samsun, Turkey*

Objectives: The arrhythmias are common and deadly complication in patients with acute myocardial infarction(AMI). Several studies have demonstrated that high levels of C-reactive protein (CRP) is associated with poor prognosis and extended infarct size. Furthermore, it's well known that the imbalance of serum potassium concentration is associated with ventricular arrhythmias in these patients. The aim of present study was to investigate the relationship between arrhythmic events and CRP levels in patient with AMI.
Methods: 90 patients with acute ST-segment elevation myocardial infarction included the study (74 male, 55±11 years). The new onset arrhythmias during AMI were monitorised and recorded. The patients were divided into two groups: group 1 (n=42) included patients with new onset arrhythmias and group 2 (n=48); without arrhythmias. Potassium levels during admission and CRP levels at the next day were measured from the venous blood samples. Echocardiographic examination was performed within the first week and peak creatine kinase MB (CKMB) was measured in blood sample to evaluate infarct size.
Results: Baseline clinical characteristics were similar in both groups. CRP levels were significantly higher in group 1 (group 1; 65,99 ± 73,07 mg/dl, group 2; 30,92 ± 35,78 mg/dl, p<0,005). Ventricular arrhythmias was the most commonly detected arrhythmia (45%) in group 1. Also, AV blocks in 24%, atrial fibrillation in 17%, bundle brunch blocks in 7% and bradycardia in 7% of cases were observed. There were no significant difference between the two groups regarding potassium levels (p=0,10). In group 1, potassium levels were significantly lower in patients with ventricular arrhythmias (ventricular tachycardia and ventricular fibrillation) than patients without ventricular arrhythmias (3,7 ± 0,6 mEq/L versus 4,1± 0,5 mEq/L, p <0,05). Peak CKMB levels were significantly increased in group 1 (380 ± 258 mg/dl versus 255 ± 178 mg/dl, p<0,05). But, LVEF were similar in both group(%46 ±10 versus %46 ± 8, p=0,67).
Conclusions: CRP and peak CKMB levels were significantly increased in patients with arrhythmias following AMI than non-arrhythmic patients in our study. Potassium levels were associated with ventricular arrhythmia like previous studies. These findings suggest that, infarct size and inflamation as well as electrolyte imbalance, contribute to development of major arrhytmic events.

P3068 Autonomic dysfunction in asymptomatic patients with TTR met30+

J.P. Freitas[1], R. Santos[2], M. Carvalho[2], F. Rocha-Gonçalves[3]. *[1]Porto, Portugal; [2]Hospital Sao Joao, Centro de Estudos da Funcao Autonomica, Porto, Portugal; [3]Hospital de São João, Serviço de Cardiologia, Porto, Portugal*

Autonomic failure (AF) induces disabling orthostatic symptoms. Short-term heart rate (HR) and blood pressure (BP) orthostatic patterns are well characterized in these patients but data with long term blood pressure and heart rate monitoring is lacking. The aim of this study was to access circadian HR and BP variation in AF patients.

We studied 8 patients with severe AF (7 with familial amyloidotic polyneuropathy TTRmet30+ and 1 with pure autonomic failure) Group A, and 2 control groups (8 asymptomatic patients TTRmet30+: Group B, and 16 normal aged matched controls: Group C). All groups underwent 24 HR and BP monitoring.

Twenty-four hours-SBP and 24h-DBP were similar in all groups (114.5±10.6 and 73.2±6.7; 123.0±6.2 and 79.0±9.5; 118.6±10.1 and 71.4±9.4 mmHg for groups A, B and C, respectively). BP dipping was attenuated or even inverted ($p<0.01$) in AF patients (SBP and DBP differences between day and night: -1.6±11.6 and 3.3±6.3; 10.0±1.0 and 11.7±1.5; 15.6±7.9 and 16.2±5.8 mmHg; for groups A, B and C, respectively; $p<0.01$).

Although mean 24h HR were similar between patients and controls (80.9±14.0; 87.0±4.6; 80.7±5.2 bpm for groups A, B and C, respectively), there were striking differences in heart rate variability among groups (max-min 24h-HR difference: 46±16; 89±11 and 91±9 bpm; pNN50: 0±0; 6±2 and 12±6%; SDRR: 68±24; 128±10; 148±32 ms for groups A, B and C; $p<0.01$).

There were significant differences between normal controls and asymptomatic TTRmet30+ controls in mean HR, diastolic blood pressure dipping and NN50; $p<0.05$.

Autonomic failure can be suspected by simple twenty four hours blood pressure evaluation and by heart rate monitoring. Asymptomatic TTRmet30+ patients may show already some degree of autonomic impairment, namely concerning early vagal dysfunction.

P3069 Muscle sympathetic nerve activity in patients with Chagas disease

C.E. Negrao[1], A.C. Santos[2], M.U.B. Rondon[2], B. Ianni[2], C.E. Rochitte[2], C. Mady[2], A.C.P. Barretto[2], H.R. Middlekauff[3]. *[1]Sch Phys Educ and Sports USP, Heart Institute (InCor) Univ SPaulo Med Sch, Sao Paulo, Brazil; [2]Heart Inst (InCor) Univ SPaulo Med Sch, Sao Paulo, Brazil; [3]Univ California Los Angeles Med School, Dept Cardiology, Los Angeles, United States of America*

Purpose: Two hypothesis have been advanced to explain the progression of heart failure (HF) in Chagas' Disease. 1) Remodeling, in which acute segmental cardiac dysfunction reaches a critical threshold, leading to remodeling, neurohumoral activation, and the common pathway of end-stage heart disease. Or, 2) The Neurogenic Hypothesis in which direct parasite damage to parasympathetic neurons during acute phase leads to early, unopposed sympathetic nerve activation, and progressive HF. To help distinguish between these hypotheses, we used the sensitive technique of microneurography to measure sympathetic nerve activation at rest and during exercise in patients with Chagas' Disease and normal ejection fraction (EF) vs patients with HF.

Methods: Three advanced HF groups (NYHA II-III) were studied: Chagas' Disease (n=15), ischemic cardiomyopathy (n=15) and idiopathic cardiomyopathy (n=15). Seven age-paired Chagas' Disease patients without HF and normal EF, and 15 normal controls (NC) were also studied. Muscle sympathetic nerve activity (MSNA) was directly measured from the peroneal nerve at rest and during handgrip exercise.

Results: MSNA was similar among all 3 HF groups (52±4, 52±3 and 50±3 bursts/min p=NS). MSNA was greater in HF patients when compared with Chagas' Disease patients without HF (52±3 vs 22±2 bursts/min p=0.001). MSNA in Chagas' patients with normal EF and NC was not different. During handgrip exercise, peak MSNA was the same in all 3 HF groups. Peak MSNA during exercise in the Chagas' patients with normal EF was lower than in patients with Chagas' Disease and HF, and not different from NC.

Conclusions: Sympathetic activation measured directly is not elevated in patients with Chagas' Disease with normal EF. These findings support the concept of remodeling and neurohumoral activation as a common pathway following significant cardiac injury.

P3070 Effects of direct sympathetic and vagus nerve stimulation on action potential alternans in the innervated isolated heart preparation

V.H. Patel[1], K.E. Brack[2], J.H. Coote[3], G.A. Ng[1]. *[1]University of Leicester, Cardiovascular Sciences, Leicester, United Kingdom; [2]University of Birmingham, Physiology, Birmingham, United Kingdom; [3]University of Birmingham, Neuroscience, Birmingham, United Kingdom*

We have previously shown that sympathetic stimulation (SS) steepens the action potential duration (APD) restitution curve and lowers the threshold for ventricular fibrillation (VF) in the isolated heart whilst vagus nerve stimulation (VS) has opposite effects. The restitution hypothesis suggests that a steep restitution curve facilitates oscillations and degeneration into fibrillation, which may be the mechanism underlying autonomic modulation of VF. This study examines the effects of SS and VS on alternans of APD in the isolated innervated rabbit heart preparation. NZW rabbits (2.4 - 3.1 kg, n=5) were sacrificed with thoracic spine and sympathetic outflow preserved and vagus nerves isolated. Monophasic action potentials were recorded from the left ventricular free wall and duration measured at 50% repolarisation (MAPD). Ventricular pacing was carried out with 50-beat trains and the MAPD of the last 2 paced beats were measured. This was repeated with progressively shorter cycle lengths (CL) [by 10 ms from 300 to 200 ms; by 5 ms from 200 ms] which caused alternans, defined as a variation of >5% in MAPD of sequential beats. Shorter CL caused increasing alternans and eventually VF. Peak alternans level was noted as was the range of CL with alternans before VF (Alternans Range). Effects with SS and VS were compared with baseline (BL).

Results (mean±SEM): Alternans occurred at longer CL and peak alternans level was greater with SS when compared with BL. CL at which VF occurred was not altered with SS but Alternans Range was greater than BL. VS caused a decrease in Alternans Range.

Effect of SS and VS on Alternans

	BL	SS	VS
CL at alternans (ms)	123.0 ± 7.8	139.0 ± 8.4**	119.0 ± 9.1
Peak Alternans level (%)	15.4 ± 3.2	32.5 ± 9.9*	13.7 ± 2.9
CL at VF (ms)	77.0 ± 4.1	81.0 ± 6.2	81.0 ± 8.9
Alternans Range (ms)	41.0 ± 7.0	53.0 ± 6.2*	33.0 ± 7.3***

Compared with BL: * $p<0.05$ ** $p<0.01$ *** $p<0.005$

Conclusion: Sympathetic stimulation caused alternans at longer pacing cycle lengths with greater degree of alternans. It also caused a wider range of cycle lengths where alternans occurred whilst vagus nerve stimulation shortened this range. These results suggest that the dynamic variation in action potential duration may be a key mechanism in the autonomic modulation of VF initiation.

P3071 Increased baroreflex sensitivity (BRS) after dietary supplements of polyunsaturated fatty acids (PUFA)

A. Radaelli[1], A. Viola[2], M. Cazzaniga[2], R. Raco[1], M.G. Signorini[3], A. Azzellino[4], A.U. Ferrari[5]. *[1]Azienda Osp Vimercate, Divisione Cardioriabilitazione, Seregno (MI), Italy; [2]Universita di Milano-Bicocca, Clinical Medicine, Monza, Italy; [3]Politecnico, Bioingegneria, Milano, Italy; [4]Politecnico, Ingegneria Ambientale, Milano, Italy; [5]Centro Fisiologia Clin. e Ipertensione, Clinica Medica Generale, Milano, Italy*

The mechanism underlying the PUFA-related prevention of sudden death (SD) is unknown. Since low BRS is a risk factor fo SD, it may be that the PUFA-related cardioprotection depends on a restored BRS; however, the effects of PUFA on BRS are unknown and their assessment was thus the goal of the present study.

Methods: Patients with post-MI systolic left ventricular (LV) dysfunction (age: 60±5 years, mean±SEM; ejection fraction: 35.0±1.4%; peak VO2 16.5±2.0 ml.kg-1.min-1; all on otpimized ACE-inhibitors and beta-blocker therapy) underwent i) continuous blood pressure (BP, Finapres) and R-R interval (RR, by EKG) recordings for 15 min to derive variability parameters and ii) baroreflex testing by the neck suction (NS) technique (slopes of the regressions relating the peak depressor and bradycardic responses to carotid sinus baroreceptor stimulations (CSBS) at -20 and -40 mmHg stimulus intensity). Assessments were performed before and after randomized treatment for 4 months with PUFA (2 g/die, n=15) or placebo (Pl, n=10).

Results: Baseline mean BP (MAP) and RR were unaffected by either treatment (PUFA, MAP from 91.3±3.7 to 92.0±4.1 mmHg; RR from 921±29 to 978±39 msec, both p=ns; Pl, MAP from 92.3±3.1 to 90.4±3.6 mmHg; RR from 954±37 to 952±34 msec, both p=ns). BRS: the depressor response to CSBS increased significantly after PUFA (from 0.09±0.01 to 0.16±0.01 mmHg.mmHg-1, $p<0.001$) but not after Pl treatment (from 0.07±0.005 to 0.10±0.008 mmHg.mmHg-1, p=ns). A similar pattern was observed for the bradycardic response to CSBS, which increased from 1.25±0.9 to 1.69±1.1 msec.mmHg-1 ($p<0.04$) after PUFA but not after Pl (from 1.87±1.1 to 1.44±1.0 msec.mmHg-1, p=ns). Overall RR variability was enhanced after PUFA (variance from 845±123 to 1264±225 msec2, $p<0.02$) but not after Pl (data not shown). MAP variance was also unaltered after vs before either treatment. RR spectral powers were also markedly increased after PUFA (MF from 50.4±21.0 to 190.0±51.1 msec2, $p<0.004$; HF from 238±84 to 363±119 msec2, $p<0.02$) but not after Pl (data not shown). MAP spectral powers were again unaltered after vs before PUFA or Pl. Bivariate analysis showed an increased alpha (HF) baroreflex index after PUFA (from 8.99±1.4 to 12.2±1.2 msec.mmHg-1, $p<0.02$) but not after Pl (from 9.0±1.9 to 6.5±1.6 msec.mmHg-1, p=ns).

Conclusions: high dose PUFA treatment for 4 months is accompanied by a marked increase in BRS and in RR variability in LV dysfunction patients. Performance of "ad hoc" studies to shown whether these changes contribute to the cardioprotective (antiarrhythmic) properties of PUFA is prompted

LEFT VENTRICULAR ASSIST DEVICE

P3072 Efficacy of ventricular assist devices in children

A.T. Fuchs[1], S. Zysk[2], C. Rinker[2], R. Kozlik-Feldmann[2], J. Sachweh[3], S.H. Däbritz[4], H. Netz[2]. *[1]University Hospital Grosshadern, Department of Paediatric Cardiology, Munich, Germany; [2]University Hospital Grosshadern, Department of Paediatric Cardiology, Munich, Germany; [3]University Hospital, Pediatric cardiac surgery, Aachen, Germany; [4]University Hospital Grosshadern, Cardiac surgery, Munich, Germany*

Ventricular assist devices are successfully used in the treatment of end-stage cardiac failure in the pediatric population. This retrospective study evaluates early and late results of the implantation of ventricular assist device systems in children as bridge to recovery or bridge to transplant.

38 patients (pts) received assist devices, with ages ranging from 2 days to 23 years. There was size differences with weights ranging between 2.7 and 75 kg. 26 pts were supported with ECMO with 8 pts weighing less than 3 kg, 7 pts with Medos, 2 pts with Berlin Heart and 3 pts with Novacor. Pts were supported with an average of 4.2±3.2 days (ECMO), 18.2±8.0 days (Medos), 14.1±19.6 days (Berlin Heart) and 8.3±11.8 days (Novacor). Diagnosis were in 22 pts congenital heart diseases and in 16 pts acquired heart disease. Indications for implantation of the ECMO were postcardiotomy heart failure in 18/26 pts, reanimation in 3/26 pts and non-operation related cardiac failure in 5/26 pts, the indication for the use of the Medos, Berlin Heart and Novacor assist device was bridging to transplant in DCM in all pts.

Primary myocardial recovery was only observed in 12/26 of the ECMO pts. 11/38 pts underwent transplantation (27% of the ECMO patients (5/18), 28% of the Medos pts. (2/7), all Berlin Heart pts. (2/2) and 67% of the Novacor pts. (2/3)). 20/38 pts (52.6%) were discharged and are long-term survivors.

These results demonstrate the efficacy and necessity of an assist program at a centre for pediatric cardiology.

P3073 The Swedish experience of left ventricular assist device as a bridge to heart transplantation

A. Cabreira[1], C.-H. Bergh[2], B. Kornhall[3], L. Wiklund[4], H. Granfeldt[5], U.G. Dahlstrom[6]. *[1]Atvidaberg, Sweden; [2]Sahlgrenska University Hospital, Department of Cardiology, Gothenburg, Sweden; [3]Lund University Hospital, Department of Cardiology, Lund, Sweden; [4]Sahlgrenska University Hospital, Department of Thoracic Surgery, Gothenburg, Sweden; [5]Linkoping University Hospital, Department of Thoracic Surgery, Linkoping, Sweden; [6]Linkoping University Hospital, Department of Cardiology, Linkoping, Sweden*

Background: Left Ventricular Assist Device (LVAD) as a bridge to heart transplantation (HTx) has been in use since 1992 in Sweden.

Aim: The aim of this study is to compare the long-term outcome in patients who were heart transplanted with or without previous mechanical support.

Methods: Sixty-four patients, from 3 medical centres (Linköping University Hospital, Sahlgrenska University Hospital and Lund University Hospital), who were treated with LVAD as a bridge to HTx were studied. Thirteen patients were excluded, 7 died before transplantation, 3 were weaned from LVAD without HTx. In 2 patients the case records were missing and 1 patient with hypertrophic cardiomyopathy was excluded. The remaining 51 patients were matched concerning gender, age and etiology of heart failure with 51 patients who had been transplanted without prior LVAD-treatment.

Results: Each group consisted of 42 males and 9 females with a mean age of 44 years (range 15-63). Fifteen with ischemic etiology and the remaining dilated cardiomyopathy/myocarditis. Thirty-seven patients received their device as an urgent bridging and fourteen received it more electively. The mean time of LVAD support was 182 days (range 10-873). During LVAD support the most common complications were: bleeding (n=17), infections (n=31), device complications (n=14). The mean time on the waiting list for HTx was 7 months for the device group and 4 months for the matched controls. Both groups were comparable concerning postoperative bleeding, infections and cardiac arrhythmias. Rejection (grade 3A/3B) was more common in the LVAD group (n=38) compared to the control group (n=22). Serious infections occurred in 9 patients in the LVAD group and 7 in the control group. Malignancies were diagnosed in 3 patients in the LVAD group and 7 in the control group. The mean follow-up time after HTx was in the LVAD group and the control group 57 months (range 1-139) and 83 months (range 2-195), respectively. Eleven patients died within three months (5 in the LVAD group and 6 in the control group) and no further died in any of the two groups during the first year.

Conclusions: The most critical period for both groups seems to be within the first 3 months following HTx. Although there were differences between the two groups concerning occurrence of serious rejections and malignancies, there were no increased mortality the first year in patients supported with LVAD prior to the transplantation.

P3074 Use of a percutaneous 16 F axial flow pump in high-risk coronary angioplasty

M. Ferrari. *Jena, Germany*

Background: Minimal-invasive circulatory assist devices are well established in interventional cardiology. They are indicated for hemodynamic stabilization during high-risk coronary angioplasty (PCI) when the target vessel supplies more than 50% of the vital myocardium. Axial flow pumps are powerful left ventricular assist devices (LVAD) decompressing the left ventricle independently of the cardiac function or rhythm. However, the flow rate is often limited by the diameter of the pump cannula. The implantation of present devices with flow rates $>$ 3 l/min requires a surgical approach to the femoral artery. Recently, a novel 16 F pump was developed for percutaneous implantation by Seldinger's technique. We describe its first clinical use.

Methods: The novel axial flow pump (AMED) can create a constant flow rate up to 3.3 l/min. Guided by an Amplatz guide wire, the 16 F pump cannula is advanced with its tip into the left ventricle using percutaneous insertion. Afterwards, the inner guiding pigtail catheter is replaced by the impeller pump. The device is driven by an external motor connected to the drive line of the pump at the distal end of the sheath. We percutaneously implanted the AMED device in 8 patients who underwent high-risk PCI. Follow-up examination was performed 30 days after the procedure.

Results: All patients (67 ± 9.9 years) suffered from severe three vessel disease. The left ventricular ejection fraction measured by echocardiography was 35% ± 19.8%. In 6 patients we performed a PCI of the left main coronary artery. In the remaining 2 patients the last remaining vessel was treated. We were able to implant the AMED pump in all 8 patients without any complication in less than 15 minutes. PCI was performed without complications in all patients. The average time of support was 12±10.2 hours (2h – 24h). All patients were free of angina pectoris at 1 month follow-up. The LVEF increased to 44% ± 21.5%.

Conclusions: The novel 16 F AMED axial flow pump provides sufficient circulatory support in patients who undergo high-risk PCI. This device allows to perform PCI in high-risk patients with satisfying 1-month-results. The AMED pump can be implanted easily within less 15 minutes by percutaneous approach.

P3075 A new LVAD for intrathoracic implantation and partial left ventricular unloading

S. Christiansen[1], A. Perez-Bouza[2], H. Reul[3], R. Autschbach[1]. *[1]University of Aachen, Cardiothoracic Surgery, Aachen, Germany; [2]Inst. for Pathology, University of Aachen, Aachen, Germany; [3]Inst. for Cardiovascular Technology, University of Aachen, Aachen, Germany*

Objective: Currently available left ventricular assist devices (LVAD) are associated with a significant number of complications, especially device pocket infections and thromboembolic events. Therefore, we tested the newly developed microdiagonal blood pump (MDP) as continuous flow LVAD for intrathoracic implantation and partial unloading of the left ventricle.

Methods: The MDP consists of a brushless DC-motor which drives the mixed flow impeller by means of a magnetic coupling system. Inside the pump, the blood stream simultaneously serves to cool the integrated electric motor. A central feature of this implantable pump is the use of blood-immersed bearings, thus eliminating the need for seals. To enhance the fluid motion around the bearings and to prevent stagnation of blood flow in these critical regions, washout holes have been placed into the rotor hub.

It was implanted in six calves for seven days each. The inflow conduit was anastomosed to the left atrium and the outflow conduit to the descending aorta with the pump placed in the left pleural cavity. Pump flow was adjusted to 2-3 L/min. Anticoagulation was done by intravenous heparin administration with a partial thromboplastin time of 100 s postoperatively. Follow-up was done by hemodynamic and echocardiographic data, daily blood samples and histologic examinations of all inner organs.

Results: Systemic and pulmonary artery pressures did not change during the whole test period. Due to partial unloading of the heart, left ventricular enddiastolic (4.1 => 3.6 cm) and endsystolic (3.2 => 2.8 cm) diameters as well as the ejection fraction (57 => 42%) decreased postoperatively and did not change during the test period. Due to operative reasons, the hemoglobin value (13.2 => 11.9 g/dL) and platelet count (550.000 => 350.000/μL) decreased perioperatively but recovered within the test period. Renal and liver function was slightly impaired perioperatively, indicated by temporarily enhanced values of bilirubin and creatinine but both organs recovered completely within the test period. The MDP did not produce a significant hemolysis (the free hemoglobin did not increase during the test period). Wound infections and thromboembolic events did not occur.

Conclusions: These trials demonstrate that the MDP provides a reliable partial unloading of the left ventricle without a significant hemolysis or thromboembolic events. The technique of intrathoracic implantation may help to avoid device pocket infections.

P3076 Impact of age on survival after implantation of left ventricular assist device

E.V. Potapov[1], M. Pasic[2], Y. Weng[2], M. Jurmann[2], J. Stein[2], R. Hetzer[2]. [1]*Deutsches Herzzentrum Berlin, Cardiothoracic and Vascular Surgery Dept., Berlin, Germany;* [2]*Deutsches Herzzentrum Berlin, Cardiothoracic and Vascular Surgery, Berlin, Germany*

Background: Implantation of LVAD prevents death in critically ill patients. The impact of age on outcome may be crucial but is still not well defined. We evaluated impact of age on outcome after LVAD implantation.
Methods: Since June 1987 LVADs were implanted in 403 patients. Patients were divided into four age groups: ^{3}60 years old (n=116); between 40 and 60 years old (n=204); between 18 and 40 years old (n=117) and $<$18 years old (n=56). We compared early outcome (30-day survival or HTx or weaning from LVAD during first 30 days) and late outcome (HTx, weaning, support $>$6 months in patients with definitive therapy or continuing support in others) among groups.
Results: Age was not related to early outcome (area under the ROC curve 0.56, p=0.7). Negative late outcome was more likely in older patients (area under the ROC curve 0.66, p$<$0.001). The highest risk for negative late outcome was in the oldest group (OR 2.5), while the best late outcome was observed in children (OR 0.5). In all patients emergency LVAD implantation was a risk factor for early (OR 1.9) but not for late outcome (OR 1.1), while postcardiotomy surgery was a risk factor for both outcomes (OR's 5.6 and 2.0, resp.). Emergency implantation negatively influenced late outcome (OR 2.2) in older patients only. Gender and ischemic heart disease did not influence either outcome.
Conclusion: Advanced age does not affect early outcome but is a significant risk factor for late outcome after LVAD implantation. In patients over 60 years old the decision for LVAD implantation should be made as early as possible.

P3077 Clinical follow-up of patients with transient circulatory support with a percutaneous left ventricular assist device (TANDEMTM heart)

R. Hullin[1], M. Schmid[2], S. Jakob[3], H.U. Rothen[3], J. Takala[3], T. Carrel[4], B. Meier[2], S. Windecker[2]. [1]*Swiss Cardiovascular Center of Bern, Cardiology Dept., Bern, Switzerland;* [2]*Swiss Cardiovascular Center of Bern, Cardiology Dept., Bern, Switzerland;* [3]*University Bern, Intensive Care, Bern, Switzerland;* [4]*University Bern, Cardiovascular Surgery, Bern, Switzerland*

Background: Recovery of myocardial function after revascularization of occluded coronary arteries often requires several days. During this time, patients may have low cardiac output and develop cardiogenic shock. The percutaneous left ventricular assist device may offer a treatment option for these patients by providing an active circulatory support.
Objective: Assessment of 30 day outcome in patients with cardiogenic shock supported by a percutaneous left ventricular assist device admitted from 11/2000 to 11/2004.
Study design: Prospective follow-up of the post-interventional clinical course.
Results: A total of 24 patients (mean age: 60 years, 19 males) were included in the present analysis Patients were divided into three distinct categories with group I: TANDEM support post cardiac cardio-pulmonary resuscitation (n=9); group II TANDEM support for cardiogenic shock without CPR (n=11); group III TANDEM support for hemodynamic support at time of intervention (n=4). 30 day mortality in groups I/II/III was 77%, 45%, 0%, respectively. Mean TANDEM support was 2.2/6.1/1 d in the three groups. Recovery occurred in 2/9 group I patients, 8/11 group II patients and 3/4 group III patients. Permanent assist devices were implanted in 3/11 group II patients and 1/4 group III patients. Cardiac index at admission was not different between group I/II (2.06 vs. 2.17 L/min/m^2) and highest in group III (2.56 L/min/m^2; p=0.02). However, cardiac index during TANDEM support was not different between groups (2.75-2.94 L/min/m^2, p=n.s.). Venous oxygen saturation was significantly different between groups and lowest in group 1 (56%), followed by group 2 (62%), and highest in group 3 (68%; p$<$0.02). Two patients suffered from cerebrovascular embolism, 1 patient from arterial embolism in the lower extremity.
Conclusion: Transient hemodynamic support with the TANDEM heart may allow-for myocardial recovery in patients with cardiogenic shock. Cardiogenic shock in combination with cardiopulmonary resuscitation pre-implantation is associated with a poor prognosis. However, all other cardiogenic shock patients appear to benefit with either recovery or bridge to permanent assist device implantation or cardiac transplantation.

P3078 Medium-term echocardiographic assessment of heart failure patients with an axial flow LVAD

X.Y. Jin[1], A.P. Banning[2], L. Wu[3], P. Poole-Wilson[4], J.R. Pepper[5], S. Westaby[6]. [1]*Oxford Heart Centre, Dept. of Cardiac Surgery, Oxford, United Kingdom;* [2]*John Radcliffe Hospital, Dept of Cardiology, Oxford, United Kingdom;* [3]*John Radcliffe Hospital, Surgical Echo Lab, Cardiac Surgery, Oxford, United Kingdom;* [4]*NHLI, Imperial College London, Dept of Cardiac Medicine, London, United Kingdom;* [5]*NHLI, Imperial College London, Academic Cardiac Surgery, London, United Kingdom;* [6]*John Radcliffe Hospital, Dept Cardiac Surgery, Oxford, United Kingdom*

Background: Non pulsatile axial flow LVADs have been recently used to treat end-stage heart failure patients. The changes in clinical cardiovascular physiology following implanting an axial flow LVAD have not been fully elucidated. The aim of this study was to assess medium-term performance of the Jarvik Flowmaker LVAD, left ventricular remodelling, systemic haemodynamics and its response to pump speed test.
Methods: Five patients (all male, age 61$\pm$6 yr) with end-stage non-ischaemic DCM received a Jarvik Flowmaker LVAD, and were prospectively studied by Doppler echocardiography before, then 1, 6, 12 months and annually after the operation. Systemic blood pressure, heart rate, LV EDD, ESD, wall thickness/EDD ratio (T/R ratio), LV ejection fraction; LA size, MV filling time, MR degree and AR degree were all measured. LIMA flow velocity time integral (LIMA-VTI) and LVAD outlet graft flow velocity time integral (LVAD-VTI) were also quantified. The changes in BP, LIMA-VTI and LVAD-VTI with different LVAD pump speed were also recorded.
Results: The echo follow up for each case ranged from 6 to 52 (mean 24$\pm$18) months. All patients had improvement in NYHA class (from IV to I-II). Compared with pre-op echo, there was no significant changes in HR, BP, LV ESD, T/R ratio, LVEF, LA diameter, MV flow velocity, MV filling time or MR degree during the follow up (all p$>$0.05). LV EDD, LV SVI, and AR degree increased with follow up time (r=0.65, 0.52, 0.45; p=0.0001, 0.006, 0.028). LIMA-VTI increased significantly after LVAD implant independently from follow up time. LVAD-VTI did not change post-operatively. Pump speed test confirmed that 10k rpm produced most desirable systemic BP and LIMA flow pattern. LVAD regurgitation volume during pump switched off accounted for 10% of its normal forward flow.
Conclusion: The axial flow LVAD improves cardiac output, systemic perfusion and relieves symptoms in end-stage heart failure patients. Pulsatile systemic flow and blood pressure can be achieved when LV contraction is coupled with LVAD flow. LV adverse remodelling process appears to be halted, though not reversed, by the axial flow LVAD. Study the changes in cardiovascular hemodynamics with different pump speed helps defining both LVAD hydrodynamic performance and the best speed setting for individual patient.

P3079 Ventricular assist device before heart transplantation in cardiogenic shock patients: more than 15 years of experience

G. Reyes[1], R.H. Rodriguez Abella[1], G. Cuerpo[1], J. López[1], A. Heredero[1], A. Pinto[1], J. Palomo[2], J. Yañez[2]. [1]*Hospital "Gregorio Maranon", Cardiac surgery, Madrid, Spain;* [2]*Hospital Gregorio Marañón, Cardiology, Madrid, Spain*

Objectives: Ventricle assit devices may be the only option in patients with cardiogenic shock. In some patients heart recover cannot be expected and heart transplantation may be the only solution. In the present study we report our experience in the last 16 years of ventricle assit devices as a bridge to heart transplantation after cardiogenic shock.
Methods: Every patient receiving heart transplantation after a ventricular assist devices between August 1988 and December 2004 were included. Baseline clinical characteristics, postoperative morbidity and mortality data were analysed. Also 5 years survival was analysed.
Results: Mean age was 51,8$\pm$8,5 years. Male/Female ratio was 13/9. Reasons for heart transplantation were:postcardiotomy ventricular dysfunction in 8 patients (36,4%), myocardial infarction in 5(22,7%), primary graft dysfunction in 8 (36,4%) and dilated miocardiophaty in one(4,5%). Ventricular assist devices were placed in left side in 12 patients (54,5%),right side in 1 patient (4,6%) and biventricular in 9 patients (40,9%). Different types of ventricular assist devices were used: "Abiomed 5000" in 13 patients,"Biomed CM" in 9 and "BioMedicus" in one.Mean waiting time to transplantation was 5 days (median 4; IQR: 4.5). Main hospital complications were:Neurological (n=7), infectious (n=12), renal (n=3),severe hemorrhagic (n=3) and respiratory (n=2). Mortality before discharge was 40, 9%. Kaplan-Meier analysis showed 1 year survival of 54% and 5 year survival of 31% (Figure 1). 1 year survival after discharge was 92,3%.

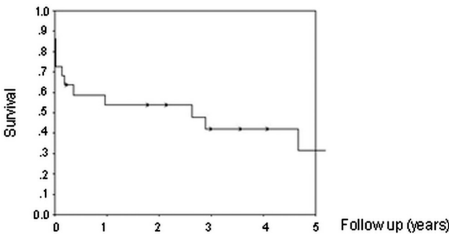


Figure 1

Conclusions: Medical treatment offers poor results in cardiogenic shock. In our experience the use of a ventricular assist devices as a bridge to transplantation can be a good alternative.Hospital survival is 60% and in this group 1 year survival is 92.3%

P3080 Prediction of right ventricular dysfunction after implantation of left ventricular assist devices

E.V. Potapov[1], M. Dandel[2], Y. Weng[2], M. Pasic[2], M. Jurmann[2], R. Hetzer[2]. *[1]Deutsches Herzzentrum Berlin, Cardiothoracic and Vascular Surgery Dept., Berlin, Germany; [2]Deutsches Herzzentrum Berlin, Cardiothoracic and Vascular Surgery, Berlin, Germany*

Right ventricular failure (RVF) after left ventricular assist device (LVAD) implantation is a serious complication. Although no internationally agreed definition of RVF exists, its incidence has been reported as between 10 and 50% in LVAD patients. The prediction of RVF before surgery remains difficult.
In a retrospective study based on LVAD implantations performed in our institution between January 2002 and December 2004 111 patients who received an LVAD for chronic end-stage heart failure were evaluated. Patients requiring an LVAD for postcardiotomy heart failure were excluded from the study. The patients were divided into two groups: group I (n=102) with normal RV function after LVAD implantation and group II (n=9) with RVF after implantation. Patients were defined as having RVF if two or more of the following criteria were met during the first 24 hours after LVAD implantation: MAD $<$55 mmHg, CVP $>$16 mmHg, mixed venous saturation $<$55%, CI $<$2l/min/m^2, inotropic support $>$20 units or need for righ ventricular assist device. Preoperative echocardiographic findings (RV diameter and ejection fraction) and laboratory and hemodynamic parameters were analyzed. In addition, 30-day survival was compared. The parameters analyzed showed no differences between groups. The overall 30-day survival rate was 80%. Patients who survived for $>$30 days had preoperatively less inotropic support (p=0.007), lower WBC (10.4$\pm$3.9 vs. 14.7$\pm$4.5, p$<$0.001) and lower serum creatinine (1.4$\pm$1.03 vs. 2$\pm$1.17, p$<$0.038) only.
Thus, as expected, preoperative signs of inflammation and poor renal function indicate a high 30-day mortality; however, RVF after LVAD implantation cannot be predicted on the basis of routine preoperative evaluation.
In conclusion, the prediction of RVF remains difficult despite sophisticated echocardiographic and laboratory evaluations. New approaches to predicting RVF after LVAD implantation should be evaluated in future studies.

P3081 Should the outflow graft of axial flow devices be anastomosed to the ascending or descending aorta? A clinical comparison of results in patients with the two approaches

J. Mueller[1], M. Jurmann[2], T. Drews[2], M. Pasic[2], Y. Weng[2]. *[1]Berlin Heart, Berlin, Germany; [2]Deutsches Herzentrum Berlin, Cardiac Surgery Dept., Berlin, Germany*

Objective: Small axial flow devices for left heart support provide the implanting surgeon with the option to place the device intrapericardially or intrapleurally. It is still a matter of dispute whether the anastomosis of the outflow graft of axial flow devices to the descending or the ascending aorta is optimal. We have compared the outcome after placement in the two positions.
Methods: Fifty-eight patients were implanted with the axial blood pump Incor (Berlin Heart) between June 2002 and December 2004. In 11 (Desc group) the pump was placed intrapleurally, anastomosing the outflow graft to the descending aorta and in 47 (Asc group) in the pericardium anastomosing the outflow cannula to the ascending aorta.
Results: Mean age of the patients was 59 years in the Desc group and 53 in Asc group. In the Des group, 7 had ischemic heart disease and 4 dilated cardiomyopathy, in the Asc group 11 and 34, respectively. The rate of TIAs and strokes was higher in the Asc group; however, the difference was not significant. The number of patients who died on device was higher in the Desc group (not significant).
Conclusion: Patients with an axial flow device in lateral position have a higher risk of dying on device, but a lower risk of thromboembolic events. The higher death rate may be additionally influenced by their higher age, cause of heart failure and status at the time of implantation. The lower rate of thromboembolic events may be related to the retrograde perfusion of the upper aortic segment.

CARDIAC TRANSPLANTATION

P3082 Effects of ACE inhibitor therapy versus valsartan on cellular markers of cell growth, metabolism and survival in the transplanted human heart: the valsartan in cardiac transplantation trial

M. White[1], L. Voisin[2], H. Ross[3], J.L. Rouleau[4], L. Whittom[5], G. Pelletier[1], N. Racine[1], S. Meloche[2]. *[1]Montreal Heart Institute, Cardiology Dept, Montreal, Canada; [2]University of Montreal, Department of Pharmacology, Montreal, Canada; [3]The Toronto Hospital, Research Center, Toronto, Canada; [4]University of Montreal, Research Center, Montreal, Canada; [5]Montreal Heart Institute, Research Center, Montreal QC, Canada*

Background: Both angiotensin converting enzyme (ACE) inhibitor and angiotensin receptor blocker (ARB) therapy provided some beneficial impacts on morbidity and in some studies on mortality in patients with hypertension, in left ventricular (LV) dysfunction post-myocardial infarction and in chronic heart failure. The mechanisms for the pharmacologic action of both types of agent are quite distinct. The effects of ACE inhibitor therapy vs substitution for an ARB valsartan on cardiac cellular mechanisms have not been investigated in the human heart.
Methods: Twenty-six stable long-term cardiac transplant recipients aged 51.8$\pm$12 years, 48.4$\pm$46.5 months following transplantation were recruited. All subjects were treated with a calcineurin inhibitor and exhibited well controlled hypertension without any evidence of LV hypertrophy on echo. The patients were on a stable dose of ACE inhibitors for at least 3 months and were randomized to continue on ACE inhibitor therapy (n=8) vs substitution for valsartan (n=18) titrated to 160 mg o.d. Endomyocardial biopsies for the monitoring of rejection plus 2 extra-pieces of 3 to 5 mg were harvested at the time of randomization and after 9months of therapy. Angiotensin type (AT) I and II receptors, and ANF mRNA were measured by real-time quantitative polymerase chain reaction (PCR). The total expression level and activity of the MAP kinases ERK1/2, JNK and p38, and the protein kinases AKT and mTOR was measured by immunoblotting. Results for selected markers are presented in the table.

Table 1

	AT1	AT2	ERK-1	mTOR	AKT
ACEI (n=8)					
BSL	0.04$\pm$0.03	0.02$\pm$0.02	0.51$\pm$0.56	0.70$\pm$0.25	0.46$\pm$0.25
9 months	0.05$\pm$0.02	0.02$\pm$0.03	0.70$\pm$0.67	0.79$\pm$0.41	0.51$\pm$0.35
Valsartan (n=18)					
BSL	0.03$\pm$0.02	0.01$\pm$0.01	0.72$\pm$0.91	0.92$\pm$0.29	0.47$\pm$0.24
9 months	0.04$\pm$0.02	0.01$\pm$0.01	0.46$\pm$0.78	0.95$\pm$0.23	0.39$\pm$0.21

Data are mean$\pm$SD; P=NS for all markers.

Conclusions: The substitution of valsartan for ACE inhibitor therapy provides similar effects on cellular mechanisms involved in the regulation of cell growth metabolism and survival in the transplanted human heart. Accordingly, a similar cardio-protective effect is expected with both ACE inhibitor and valsartan.

P3083 New onset diabetes after heart transplantation. Incidence and risk factors in a cohort of 307 patients

J. Garcia-Lara[1], M.G. Crespo-Leiro[2], M.J. Paniagua-Martin[2], I.P. Garrido-Bravo[2], J. Muñiz[3], E. Vazquez-Rey[2], R. Campo-Pérez[2], A. Castro-Beiras[2]. *[1]A Coruna, Spain; [2]Servicio de Cardiologia, Hospital Universitario Juan Canalejo, A Coruña, Spain; [3]Universidad de A Coruña, Instituto de Ciencias de la Salud, A Coruña, Spain*

Background: New onset diabetes (NOD) is a frequent complication after heart transplantation (HT), being immunosuppression (IS) a well known risk factor. Nowadays, IS post-HT is changing and the real contribution of each IS regimen on NOD is still unknown.
Objective: To know the incidence of NOD and risk factors in our cohort.
Patients and methods: We carried out a historic cohorts study in all patients who underwent HT from 1991 to 2003 in our institution and were: older than 18 years, diabetes free before HT and $>$ 1 year survival. We analyse the prevalence of NOD according to ADA Criteria at 1,3,5,7 and 10 years. Independent variables: Sex, BMI pre HT, basal IS (considering 4 groups: A. Ciclosporin A (CsA)+ Azathioprine (Aza)+ steroids (ste), B. CsA+ Mycophenolate Mofetil (MMF)+Ste, C. Tacrolimus (FK)+ Aza+ ste, D. FK+ MMF+ est, E. Others) and cumulative Ste dose.
Results: We examine a cohort of 307 patients, (mean age 55 years, 84% males) with a mean following period of 68 months. 100% still treated with steroids one year after transplantation. NOD incidence at 1,3,5,7 and 10 years was 16%, 15%, 16%, 22% and 22% respectively. Basal IS regime was A n= 194, B n= 96, C n= 6, D n= 4 and E n= 7. Group C, D and E were excluded from the analysis due to the small number of patients (resulting distribution displayed in table 1). Multivariate analysis showed that patients who develop NOD were older than those who didn't (OR 1.04; CI 1.01- 1.07; p= 0.021), and followed IS regime A vs B (OR 2.31; CI 1.16- 4.6, p= 0.016).

Table 1: Basal IS in our series.

Basal IS	No NOD	NOD	Total
CsA+ Aza+ Ste	141 (73%)	52 (27%)	193
CsA+ MMF+ Ste	81 (85%)	14 (15%)	95

CsA: Ciclosporin A; Aza: Azathioprine; Ste: Steroids; MMF: Mycophenolate Mofetil; NOD: New onset diabetes; IS: Immunosupression

Conclusions: In our cohort, prevalence of NOD is 16% at 1 year and 22% at 10 years, with accumulated incidence of 23% after a mean following period of 68 months. Development of NOD was associated with age and CsA+ A za+ ste based IS versus CsA+ MMF+ ste. Greater series of patients are needed for testing the effect of other IS regimes.

P3084 Heart transplantation provides long-term survival benefit in stable outpatients with heart failure

B. Meyer[1], D. Moertl[1], M. Huelsmann[1], R. Pacher[1], R. Berger[2]. *[1]Medical University of Vienna, Department of Cardiology, Vienna, Austria; [2]Univ. Klinik für Innere Medizin II, Abteilung für Kardiologie, Vienna, Austria*

Background: we recently demonstrated that in stable chronic heart failure (CHF) patients with optimized medical therapy, heart transplantation (HTx) does not pro-

vide additional survival benefit in the short term (2 years). The aim of this study was to compare the outcome of these stable outpatients with patients post HTx in the long-term.
Methods: between January 1995 and September 1997, 318 potential HTx candidates (NYHA class III or IV, left ventricular ejection fraction [LVEF] <35%) were evaluated in our heart failure center. After 3 months of therapeutic optimization 126 patients were stable outpatients with maximally up-titrated RAAS-antagonists and β-blockers. Seventy of the 318 patients underwent HTx between January 1995 and December 1997. Outcome of these two patient groups was compared after an observation period of six to nine years.
Results: using the endpoint death or urgent HTx in stable outpatients and death in patients after HTx, Kaplan Meier analysis revealed a significant difference between groups in favour of patients after HTx ($p<0.005$). Stratifying stable outpatients according to their LVEF one year after medical optimization, patients with an LVEF >40% (36 patients) had a similar survival compared to patients after HTx. In CHF patients with an LVEF <40% (61 patients) one year after medical optimization survival was worse compared to patients after HTx regardless of the functional class.
Conclusion: not in the short term (2 years) but in the long term (>6 years) HTx seems to provide additional survival benefit in stable CHF patients except in patients whose LVEF improves to 40% or above after medical optimisation.

P3085 Right ventricular function long-term after cardiac transplantation is not affected by elevated pulmonary vascular resistance pre-transplant

A. Wahl[1], M. Feller[1], F. Merz[2], E. Wigger[1], C. Stoupis[3], J.P. Schmid[1], P. Mohacsi[1], R. Hullin[4]. [1]*Swiss Cardiovascular Center of Bern, Cardiology Department, Bern, Switzerland;* [2]*Swiss Heart Center Bern, Cardiology, Bern, Switzerland;* [3]*University Bern, Radiology, Bern, Switzerland;* [4]*Swiss Cardiovascular Center of Bern, Cardiology Department, Bern, Switzerland*

Background: Acute right ventricular (RV) failure is a severe complication post-transplant usually attributed to an elevated recipient pulmonary vascular resistance (PVR). Whether RV function long-term is different in heart transplant recipients with normal or elevated PVR pre-transplant is unknown.
Methods: Forty three orthotopic cardiac allograft recipients after biatrial HTx underwent both cardiac catheterization with endomyocardial biopsy and cardiac MRI assessment long-term post-transplant. MRI measured RV volumes using contiguous short axis slices (1.5 T Siemens, breath-hold cine steady state free precession technique, manual contour drawing). As histological parameter for RV remodeling post-transplant collagen content was assessed in trichrome stained sections of myocardial biopsies.
Results: Pre-transplant PVR ranged from 35 to 615 dyn.sec.cm-5. PVR >240 dyn.sec.cm-5 in patients responded always either to oxygen or prostacyclin infusion. Patients were divided into 2 groups according to pre-transplant PVR: group 1 (PVR ≤ mean PVR; n=28), and group 2 (PVR>mean PVR; n=15). Pre-transplant PVR was significantly different between groups (113 vs. 322 dyn.sec.cm-5; $p<0.0001$). Groups did not differ with respect to mean age, interval to cardiac transplantation (1714 vs. 2086 days), donor heart ischemic time, donor age, number of episodes of cardiac allograft rejections or acute RV dysfunction (4/28 vs. 4/15). One year post-transplant PVR in group 2 patients was significantly lower and not different to group 1 patients (93 vs. 106 dyn.sec.cm-5; n.s.). Long-term post-transplant PVR in both groups remained low (115 vs. 125 dyn.sec.cm-5; n.s.). Cardiac MRI long-term post-transplant revealed no significant differences between groups with respect to RV enddiastolic (138 vs. 128 ml) and endsystolic volumes (53 vs. 55 ml) and RV systolic function (ejection fraction 62 vs. 57%). RV enddiastolic pressures (RVEDP) post-transplant were similar (4 vs. 6 mmHg) and as was collagen content in myocardial biopsies. However, cardiac output was higher in group 1 (7.2 vs. 5.7 l/min; p=0.009).
Conclusion: PVR normalizes within 1y post-transplant in HTx survivors with pre-transplant elevated PVR. Long-term post-transplant RV systolic function, RVEDP and collagen content of cardiac allografts are not affected by an elevated pre-transplant PVR. For the first time, our data demonstrate that HTx recipients with higher PVR pre-transplant have a favorable prognosis for normal RV function long-term.

P3086 Mortality in patients referred for heart transplantation the classical and new risk stratification factors – a prospective registry based analysis

J. Korewicki[1], T. Zielinski[1], A. Browarek[1], M. Zembala[2], M. Zakliczynski[2], J. Sadowski[3], P. Przybylowski[3], M. Garlicki[4] on behalf of POLKARD HF collaboration. [1]*Institute of Cardiology, Heart Failure and Transplantation, Warsaw, Poland;* [2]*Kardiochirurgii i Transplantologii, Katedra i Oddzia[3] Kliniczny, Zabrze, Poland;* [3]*Szpital.im Jana Pawla II, Klinika Chirurgii Serca i Naczyn, Krakow, Poland;* [4]*CSK MSWiA, Klinika Kardiochirurgii, Warsaw, Poland*

Advanced heart failure is known as a disease with a very poor prognosis. The impact of recent improvement in therapy on survival of those patients is still not well known.
Aim of the study: To determine the survival prognosis of patients with advanced heart failure referred as candidates for cardiac transplantation and the value of NT proBNP and hs CRP assessment in the risk stratification.
Patients and methods: A prospective study from all transplantation centers in Poland based on data of 384 patients mean age 49,5 ± 10 referred as candidates for heart transplantation in 2004 from the POLCARD HF registry was done. Classical risk factors included in the risk score proposed by Aaronson and potential new risk factors N terminal proBNP (brain natriuretic peptide) and hs CRP (C-reactive protein) were analyzed. Kaplan Meier curves of risk of death or composite end point (death or transplantation) were analyzed stratified on the Aaronson risk score, NTpro BNP, hsCRP values.
Results: The survival up to 300 days in patients with Aaronson high risk score was 72%, medium risk score 87%, low risk score 92%. –log-rank test p =0.0001. When stratified according to the levels of NT-proBNP the survival was in high risk(> 5000 pg/ml) pts -78%, medium risk (2000-5000)-83%, low risk (<2000)-92% log rank test p=0.018, according to hs CRP high risk (>5) 88%, medium risk (89%), low risk (<1)-93%. Log-rank p=0,4
The survival with freedom of the composite end-point(death or transplantation) was analyzed for the same set of stratifying variables- Aaronson risk score: high-58% medium 76%, low- 82%. Log-rank test p=0.0004; NTproBNP high -57%, medium 68%, low- 82% logrank p=0.005; hsCRP high- 60%, medium -69%, low-81% log rank p=0,16.
In Cox proportional hazard model analyses the level of NTproBNP was an independent risk factor for death ($P< 0.0065$) and the composite end point (death or transplantation –$p <0.005$) when analyzed in the model together with the Aaronson risk score.
Conclusions: The survival of patients with end stage heart failure on modern therapy is higher than expected
NT proBNP levels should be included in the model of risk of death assessment of patients with advanced stage heart failure.
The potential role of hs CRP in risk stratification of patients with advanced heart failure need to be further investigated.

P3087 Dendritic cells after heart transplantation. Impact for coronary endothelial dysfunction

S. Kofler[1], J.-O. Kim[1], C. Grimm[1], B. Meiser[2], I. Kaczmarek[2], M. Weis[1]. [1]*University Hospital Munich-Grosshadern, Cardiology Dept., Munich, Germany;* [2]*University hospital-Grosshadern, cardiac surgery, Munich, Germany*

Indirect allorecognition, namely the presentation of donor antigens by recipient's dendritic cells (DCs) to naïve T cells (TCs), is involved in chronic transplant rejection. We characterized circulating and myocardial invaded dendritic cells (DC) in patients after heart transplantation (HTx). Moreover, association of myocardial DCs with structural and functional coronary changes was investigated during a longitudinal study.
Methods: PBMC and myocardial DCs were quantified using real-time PCR in 10 patients during the first year after HTx. Immunfluorescence labeling in cardiac biopsies was investigated in 16 heart transplant patients during a longitudinal study (1-24 months follow-up). It was performed using 1) DC antibodies against CD1a, Fascin and CD209; 2) antibodies against T-cells (CD3) and endothelial cells (ECs; PECAM-1). The respective fluorescent index was calculated based on the total cell number and/or number of ECs using quantization software analysis. Moreover, association of myocardial DCs with structural coronary changes (IVUS) and coronary epicardial and microvascular endothelial function (quantitative angiography, i.c. Doppler) was detected.
Results: CD1a and CD123 gene expression in PBMCs is highly upregulated in transplant recipients ($p<0.001$ versus healthy controls). DC invasion in the human myocardium is detectable early after heart transplantation, further increases during the first 6 months, and decreases constantly thereafter. Myocardial DCs are expressing markers of immaturity and maturity as well. 10-70% of the DCs in myocardial biopsies are time-dependently clustering with activated TCs. Patients with epicardial and microvascular endothelial dysfunction during follow-up had significantly elevated CD209-positive DCs early after HTx compared to patients with normal coronary endothelial function. Intimal hyperplasia was not associated with myocardial DC infiltration.
Conclusions: DCs are frequently invading the cardiac allograft with a peak during the first 6 months, thereby stimulating vascular inflammation. The myocardial clustering of DCs with TCs suggests that TC-activation may occur inside the allograft. CD209 positive DCs are an early marker for allograft epicardial and microvascular endothelial dysfunction.

P3088 The haemodynamic evaluation of inhaled aerosolised iloprost in heart transplant candidates with pulmonary hypertension

S.D. Braun[1], H. Schroetter[2], R. Marquetant[2], A. Schmeisser[2], R.H. Strasser[2]. [1]*University of Technology, Cardiology, Dresden, Germany;* [2]*University of Technology, Cardiology, Dresden, Germany*

Introduction: Secondary pulmonary hypertension (PH) in patients (P) with left heart failure is associated with increased mortality. Prior to heart transplantation (HTX) the information about the pulmonary vascular response (PUVResp) to vasodilator exposure is of great importance for the management of postoperative

right-heart failure. In contrast to the routinely used vasodilators, such as nitric oxide (NO), oxygen (O) and nitroglycerin (N), there is no valid information about the efficacy and safety of the aerosolized stable prostaglandin analog iloprost (ILO) for testing the PUVResp in pulmonary-venous hypertension.
Methods: In 30 HTX candidates (54+12 years) with dilated (n=14) or ischemic (n=16) cardiomyopathy (EF<25%) and PH, the PUVResp was tested with O/N (6l/min oxygen/10min + 0.8mg s.l. N) and ILO after 20 min washout (inhalation; 10 μg., Nebutec IR). Measurement of hemodynamics (H) was performed by using a pulmonary artery catheter (PA, Swan-Ganz-Catheter; cardiac output measurements by Fick techniques) and a femoral artery (FA) catheter. Big Endotelin-1 (B-ET1) was measured with ELISA from PA and FA blood samples pre- and post ILO.
Results: In comparison with the baseline values the inhalation of ILO lowered the specific pulmonary parameters, such as the transpulmonary pressure gradient (TPG) (14.6±5.7 mmHg vs. 9.5±3.71 mmHg; p<0.0001), the mean pulmonary-artery pressure (mPAP) (36.3±7.1 mmHg vs. 30.07±8.1; p<0.001) and the pulmonary-vascular resistance (PVR) (305.8±111.2 dyn s cm^{-5} vs. 192.7±61.4 dyn s cm^{-5}; p<0.0001). The mean TPG and PVR with ILO were significantly lower than with O/N (9.5±3.71 mmHg vs. 12.2±4.8 mmHg and 192.7±61.4 dyn s cm^{-5} vs. 245.4±102.7 dyn s cm^{-5}, p< 0.001, respectively). The reduction of TPG and PVR to < 12mmHg and < 250 dyn s cm^{-5}, respectively, as the most positive predictive values for the PUVResp prior HTX was obtained in 28 (93%) patients with ILO vs. 21 (70%) with O/N (p<0.01). Big-ET1 levels in PA, FA and the Big-ET1 av-ratio were not correlated to the ILO effects on TPG and PVR, but were correlated to PCWP (r=0,6). In contrast to O/N, ILO lowered sligthly the mean arterial pressure and systemic resistance and increased left ventricular stroke volumen (p<0.05). Side effects of ILO were slight flush (20%), and asymptomatic descrease of SaO2 (94% vs. 91%), potentially due to an increase in ventilation-perfusion mismatch.
Conclusion: Inhalation of ILO was highly more efficacious with an responder rate of 93% than conventional application of O/N for reducing of critical parameters of PUVResp prior HTX. Big-ET1 levels were not correlated to TPG and PVR pre and post ILO but to PCWP.

P3089 Impact of right ventricular assistance device on clinical outcome after heart transplantation in patients with severe pulmonary hypertension

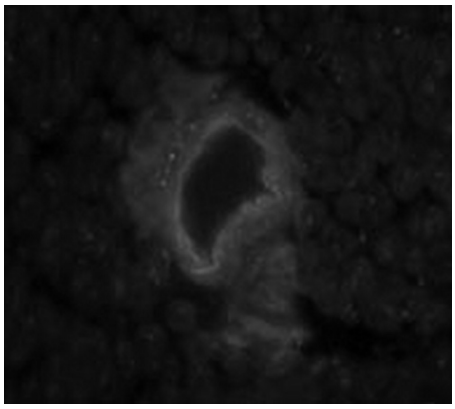
J.P. Gueffet, S. Pattier, O. Baron, M. Burban, T. Petit, M. Treilhaud, D. Duveau, J.-N. Trochu. *Thorax Institute, Cardiology, Nantes, France*

Right-sided heart failure (RHF) accounts for about 50% of cardiac complications after heart transplantation (HTx). Severe preoperative pulmonary hypertension (PHT) is the predominant cause of right ventricular dysfunction after HTx. The purpose of this study was to evaluate the impact of the implantation of a right ventricular assist device (RVAD) with a centrifugal pump (BioMedicus) in cardiac transplant patients with severe pre-HTx PHT.
Between January 2000 and July 2003, 85 patients underwent heart transplantation. Among them, 8 (52±6 years, EF 22±5%, serum creatinine 144±50μmol/L) required the implantation of a RVAD because of a severe PHT detected during the pre-transplant hemodynamic evaluation (pulmonary vascular resistance (PVR) = 5.9±1.7 UW, transpulmonary gradient (TPG = 18±4 mm Hg). Despite the high level of pulmonary pressure, these 8 patients were listed on the HTx waiting list because PHT was reversible after a prolonged (> 24 hours) pharmacological test (PVR = 2.2± 0.4 UW and TPG = 11±4 mmHg). Four patients had a pre-emptive implantation of the RVAD during surgery, i.e. the use of the RVAD was programmed before HTx based on the results of the pre-HTx hemodynamic evaluation. The 4 remaining patients required RVAD between 20 min and 10 hrs after the end of extracorporeal circulation because of right ventricular dysfunction.
Mean duration of support was 150±61 hrs. The most prevalent complications were infection (100%) and bleeding (62%). Two patients, in whom RVAD had to be secondarily implanted because of RHF, died from multi-organ failure before discharge. The 6 remaining patients survived to discharge, one died 6 months later of a cerebral haemorrhage, and the others are still alive.
In conclusion, HTx should be considered despite severe PHT, with the use of a prolonged pharmacological preoperative test, which allows the detection of reversible PHT, and the resort to a pre-emptive strategy with the implantation of a RVAD during HTx.

P3090 The origin and the pathogenesis of donor transmitted cardiac allograft vasculopathy (CAV): a novel alloimmune independent model

M. Yousufuddin[1], H. Ratliff[1], M. Yamani[2]. *[1]West Virginia University, Robert C. Byrd Health Sciences Center, Charleston, United States of America; [2]Cleveland Clinic Foundation, Kaufman Center for Heart Failure/Trans, Clevleand, OH, United States of America*

Heart transplant recipients with CAV have cardiac ang II type 1 receptors (AT1R)up-regulation, which may represent a remnant of systemic AT1R activation in the donor prior to organ harvesting.
Design: In part-A, we examined AT1R mRNA transcripts in cardiac biopsies (EMBx) at 1-yr after transplantation (Tx) in 44 recipients, who had paired IVUS imaging within 4-wks and at 1-Yr after Tx to assess changes in maximal intimal thickness(CMIT) and plaque volume (CPV).Allo-immune response was assessed as average biopsy score (ABS) based on EMBx histology through 1st-yr Post-Tx.In part-B, this experiment was extended to 28 donors and corresponding recipients with serial examinations for AT1R mRNA in lymphocytes-derived from donor spleen and in transplanted hearts at 1-wk and 1-yr post-Tx.A CMIT of >0.3 mm in 1-yr defines CAV.
Results: The AT1R mRNA transcripts at 1-yr after Tx were correlated with CMIT (regression coef [RC] 1.7,P<0.0001) and CPV (RC1.25;P=0.002). Patients with CAV(n=21) at 1-yr had higher cardiac AT1R than those (n=23) who did not develop CAV (3.7±2.9; 1.6±1.7 fold; P=0.006). AT1R at 1-yr post-Tx predicted CAV progression (sensitivity 75%, specificity 83%). AT1R mRNA in the donor lymphocytes prior to Tx and in the corresponding transplanted hearts were elevated in recipients who developed CAV and correlated with CAV progression. ABS was not related to CAV. Immunofluorescence studies confirmed AT1R expression in patients with CAV (figure).



Colocalization of AT1R and vWF

Conclusions: AT1R are activated in the donor and potentially initiates vascular damage prior to organ harvesting. AT1R up-regulation in transplanted heart may represent a remnant of this activation in the donor. The data support a novel concept for the origin of CAV from the donor and an alloimmune-independent mechanism for its progression.

P3091 Cardiac hepatopathy before and after heart transplantation

W. Dichtl[1], W. Vogel[2], K. Dunst[3], H.F. Alber[1], W. Grander[1], G. Laufer[3], O. Pachinger[1], G. Poelzl[1]. *[1]Medical University Innsbruck, Clinical Division of Cardiology, Innsbruck, Austria; [2]Innere Medizin, Gastroenterologie/Hepatologie, Innsbruck, Austria; [3]Herzchirurgie, Universitätsklinik für Chirurgie, Innsbruck, Austria*

Background: Chronic cardiac hepatopathy is a common entity in patients evaluated for heart transplantation. Hepatic injury is caused by severe heart failure due to prolonged recurrent congestion and/or impaired arterial perfusion. No data are available on the reversibility of cardiac hepatopathy in patients undergoing heart transplantation (HTX).
Methods: Data of 56 consecutive adult patients undergoing HTX in the years 2000-2002 at the University Hospital of Innsbruck were analysed retrospectively. The following parameters were evaluated at the time of listing and three, six and twelve months after HTX: Plasma levels of gamma-glutamyl-transferase (GGT), alkaline phosphatase (AP), bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and total plasma protein.
Results: When listed for HTX, only 12% of all patients analysed (n = 42) had physiological values throughout the seven laboratory parameters assessed. Pathological levels of GGT, AP, bilirubin, AST, ALT, LDH and total plasma protein were detected in 66.6%, 29%, 50%, 16.7%, 10%, 40% and 18% of all patients, respectively. Accordingly, median plasma levels of GGT, bilirubin and LDH were elevated, whereas the mean plasma level of AP was at the upper normal range. In contrast, median plasma level of AST and mean plasma levels of ALT and total plasma protein were not elevated: GGT (median 109.0; range 634.0 U/l; n = 36), AP (mean 120.2 ± 78.9 U/l; n = 29), bilirubin (median 1.3; range 16.1 mg/dl; n = 32), LDH (median 226.0; range 2355.0 U/l; n = 33), AST (median 29.0; range 145.0 U/l, n = 36), ALT (mean 28.3 ± 20.8 U/l, n = 36), total plasma protein (mean 7.2 ± 1.1 g/dl; n = 25). Within three months after HTX, elevated parameters except LDH significantly ameliorated: GGT (median 59.0 range 1160.0 U/l; p = 0.011), AP (92.2 ± 75.2 U/l; p = 0.016), bilirubin (median 0.9; range 8.1 mg/dl; p = 0.004), LDH slightly increased (median 281.0; range 543.0 U/l; p = 0.039), but there was a delayed improvement of this parameter after six and twelve months post HTX.
Conclusions: End-stage heart failure is characterized by a cholestatic liver enzyme profile with elevated plasma levels of GGT and bilirubin. These parameters significantly improve within three months after HTX. Therefore, chronic cardiac hepatopathyseems to be a benign, potentially reversible disease.

P3092 Cardiac graft growth after heart transplantation in children

S. Di Filippo[1], F. Sassolas[2], J. Ninet[3], A. Bozio[2]. [1]*Hôpital Cardiovasculaire Louis Pradel, Cardiologie Pédiatrique Dept., Lyon 03, France;* [2]*Hôpital Cardiovasculaire, Cardiologie Pédiatrique, Lyon Cedex 03, France;* [3]*Hopital Cardiologique Louis Pradel, Cardiothoracic Surgery, Lyon, France*

Objective: The aim of this study was to assess anatomic changes of cardiac allograft and compare them to linear growth in pediatric heart-transplant patients.
Methods: From 1987, 53 pediatric heart transplantations (HT) were performed in a single center. The study group included 17 recipients (8 males and 9 females) who were less than 13 years old at the time of HT (2 days to 13 years, mean= 5.7 years, median= 5 years) and whose follow-up was more than 18 months post-transplant (18 months to 12 years, mean= 6.1 years, median= 5.8 years). The donor age varied from 7 days to 13 years (mean= 5.9 years, median= 3 years); the weight ration donor/recipient varied from 0.91 to 4.5 (mean= 1.63, median= 1.39). Measurements were collected every month during the first post-transplant year, every 2 months after one year, and included: linear growth parameters (weight, height) and echocardiographic parameters (end-diastolic left ventricle (LV) diameter, end-systolic LV diameter, interventricular diastolic thickness, left posterior wall diastolic thickness). Body surface area (BSA), LV mass (g) and LV mass index (g/m^2) were calculated.
Results: Mean BSA increased from 0.68 m^2 to 0.94 m^2 during follow-up. Thirteen patients had normal and 4 had moderate-impaired linear growth. Maximum linear growth was observed in infants less than 5 years old (18.2% every year).
Diastolic LV diameters, systolic LV diameters and LV mass increased linearly with BSA in all the cases. LV mass index increased in the first post-transplant month (mean= 168.2 g/m^2) and decreased later to reach normal range within the first six months post-transplant. LV echographic measurements ranged within normal value for age beyond the sixth postoperative month.
Conclusion: In our experience, cardiac graft grows linearly with BSA in children and mid-term and long-term graft measurements range within normal value for age.

P3093 Evolution of CMV specific IgG and IgM antibody titles in long-term follow up of heart transplant recipients and their relation to PCR DNA detection of CMV

C. Economidou, J. Terrovitis, E. Prifti, Z. Margari, E. Avdikou, C. Charitos, V. Petrocheilou, J. Nanas. *Athens, Greece*

Introduction: Cytomegalovirus infection is a frequent source of morbidity after orthoptic heart transplantation. There is a significant number of available immunoassays for the detection of CMV specific IgM and IgG antibodies, but a large number of false positive results reduce their diagnostic value. We sought to determine the evolution of the titles of the CMV specific IgG and IgM antibodies with 3 immunoassays in a prospective virological and serologic follow up of heart transplant recipients and compare the results to PCR-DNA detection of CMV.
Methods: Thirty cardiac transplant recipients (25 males, 5 females) were screened for CMV every week during the first 2 months, twice a month until the 6th month after transplantation and once a year thereafter. The following immunoassays were performed: IMxCMV IgM assay (Abbott), Mini Vidas CMV IgM, IFA CMV IgG and PCR CMV Oligoditect kit.
Results: CMV status of donor (D) and recipient (R) before transplantation was: Group1(R+/D+) n=5, group 2(R-/D+) n=5,group 3(R+/D-) n=9,group 4(R-/D-) n=11. Patients were followed for 1-144 months (mean 50.4, median 30). During the follow up, 6 patients (16.6%) experienced active CMV infection (5 from group1, 1 from group 2). The rest, (23/24, 95%) had high titles of IgG antibody ($>$160, x4 up the title before the transplantation) from day 50 (48d-60d) and kept the titles until the end of the follow up period. 23/24 (95%) had high titles of IgM antibody (1.00-2.45, x2-3 times up the title before transplantation) from day 60 and kept the titles for at least 3 years (47%), without clinical signs of active CMV infection. For those with follow up of more than three years after transplantation, 3/18 (16%) had false positive titles of IgM by mini Vidas IgM CMV detection versus 10/18 (55%) with IMxCMV IgM (p=0.216). With PCR-DNA detection, all of them (24/24) were negative for DNA-CMV.
Conclusion: None of the tested ELISAs could reliably diagnose active CMV infection, because of the high number of false positive results, probably due to cross-reactions. Mini Vidas CMV IgM produced less false positive results. PCR - DNA detection remains the gold standard for the diagnosis of CMV active infection/disease.

P3094 Risk factors for the presence of early detected (within 1. months after orthotopic heart transplantation) allograft coronary artery disease

M. Kocik[1], I. Malek[2], B. Janek[2], M. Zelizko[2], J. Pirk[3]. [1]*General Faculty Hospital, IV. clinic of internal medicine, Prague, Czech Republic;* [2]*IKEM, Dep. of Cardiology, Prague, Czech Republic;* [3]*IKEM, Dep. of Cardiovascular surgery, Prague, Czech Republic*

Introduction: Despite not being proofed, allograft coronary artery pathologic findings detected very early after orthotopic heart transplantation (OHTx) are regarded to represent donor transmitted lesions. Therefore the aim of the study was to identify possible risk factors for the presence of allograft coronary artery disease (aCAD) detected very early after OHTx (within 1 months after OHTx) in order to elucidate its origin. Study population and methods: Study population consists of 83 OHTx recipients (65 m, 18 f, mean age 50.55$\pm$11.04 years) with intravascular coronary ultrasound (IVUS) examinations performed very early after OHTx (mean time 29.81$\pm$12.45 days) Impact of number of factors describing different phases of peri- and early postOHTx period (donor characteristics, recipient characteristics, surgical procedure, early postOHTx period (CMV, rejections, infection, etc.)) on development of early detected allograft coronary artery disease was evaluated. Results: Higher recipients body mass index (p=0.008), higher donor age (p=0.0001), donor cause of death (p=0.01), donor history of hypertension (p=0.005) and higher incidence of clinically manifested acute rejections (p=0.02) were found to correlate in univariate analysis with the presence of early detected allograft coronary artery disease.
Conclusions: The results of the study strongly support the importance of donor characteristics on the presence of early detected allograft coronary artery disease. Univariate analysis shows on possible modifying effect of clinically manifested acute rejection on the development of early detected allograft coronary artery disease.

P3095 Sirolimus (SRL) treatment in Calcineurin-Inhibitor (CNI) Nephrotoxicity in heart transplantation: preliminary results of a multicenter registry in Spain (RAPACOR Study)

M.G. Crespo-Leiro[1], J.F. Delgado[2], N. Manito[3], G. Rabago[4], E. Lage[5], J.M. Arizon[6], E. Roig[7], J. Palomo[8]. [1]*H. Juan Canalejo, Cardiology, La Coruna, Spain;* [2]*H. 12 de Octubre, Cardiology, Madrid, Spain;* [3]*R.S. Belvitge, Cardiology, Barcelona, Spain;* [4]*C.U.N., Cardiology, Pamplona, Spain;* [5]*H. Virgen del Rocio, Cardiology, Sevilla, Spain;* [6]*H. Reina Sofía, Cardiology, Cordoba, Spain;* [7]*H. Clinic, Cardiology, Barcelona, Spain;* [8]*H. Gregorio Marañon, Cardiology, Madrid, Spain*

Background: SRL is a non nephrotoxic immunosuppressive drug with antiproliferative properties that could play a role in CNI nephrotoxicity and graft vascular disease (GVD) in heart transplantation (HT).
Methods: a multicenter registry of heart receptors who received SRL through a compassionate use after therapies based on calcineurin inhibitors (CNI), has been created in Spain in order to characterize efficacy and safety. We present a subanalisys of the patients converted to SRI due to renal dysfunction (RD). The objective was to perform a progressively withdrawal of CNI. SRL was introduced using an initial daily dose of 2.0 mg/day, searching a target through blood levels between 8-12 ng/ml.
Results: of the 120 HT patients included, the reasons to introduce SRL were renal function impairment in 71 patients (59,2%), GVD in 64 (53,3%), distinct neoplasias in 25 (20,8%), refractory reject in 5 (4,2%) and neurotoxicity in 4 (3,3%). Of the 71 patients (91,5% male) (median age 63,9 years) with signs of calcineurin-inhibitor renal toxicity, 53,5% presented additional patology (neoplasia, refractory rejection etc). The initial immunosuppression was based on cyclosporine in 63,4% and tacrolimus in 36,6%. SRL was started on a median of 72 months (range: 0.1-182) post transplant, and the follow-up was 10,7 months (0,1-26). Median first through SRL levels achieved was 6.8 ng/ml (range: 2.5-33,5). CNI withdrawal was progressive and was achieved in 63% at 6th month and 68,4% at 12th month. Mean creatinine clearance of patients recruited due to nephrotoxicity changed from 38,9 ml/min at baseline to 33,2 ml/min at 12th month (p=0.731). Performing a subanalysis with regard to the baseline creatinine $<$ 2,5 mg/dl (n=49;69%) or $>$ 2,5 mg/dl (n=22;31%), the mean creatinine changed from 1,9 to 1,9 mg/dl (p=0.439), and from 3,6 to 5,0 mg/dl (p=0.392), respectively and the GFR from 45,3 to 47,4 ml/min (p=0.594), and from 24,9 to 20,6 ml/min. (p=0.954). Survival of patients with RD at 12th month was 90,7%.
Conclusion: a registry of HT recipients treated with SRL has been developed. Most of the patients were included due to renal function impairment. Improvement in CNI related nephrotoxicity may require an earlier introduction of SRL and a shorter time of concomitant use with CNI.

P3096 Younger heart transplant recipients are at higher risk of coronary vasculopathy (CAV) late onset

M.W. Zakliczynski[1], M. Swierad[2], M. Maruszewski[3], H. Zakliczynska[3], A. Kosakowska-Baranska[3], A. Lekston[4], M. Zembala[3]. [1]*Silesian Centre for Heart Disease, Heart Transplant Outpatient Clinic, Zabrze, Poland;* [2]*Silesian Center for Heart Disease, 1st Dept. of Cardiology, Zabrze, Poland;* [3]*Silesian Center for Heart Disease, Cardiac Surgery and Transplantation, Zabrze, Poland;* [4]*Silesian Center for Heart Disease, 3rd Dept. of Cardiology, Zabrze, Poland*

Aim: Aim of this study was to analyze an influence of potential risk factors of coronary lesions development on presence and time of onset of CAV.
Material and methods: Inclusion criteria were: OHT before the end of 1998, and at least 1 protocol coronary angiography (CAG) performed after OHT (1st CAG – 12 months after OHT, consecutive CAGs – every 12-24 months). 132 OHT recipients were included: 114M/18F; age median – 46 y. The following potential risk factors of CAV were under evaluation: heart failure etiology (ischaemic vs. others),

age (above vs. below median), sex, post-transplant diabetes, arterial hypertension, hyperlipidaemia, overweight, high frequency of cellular rejection during the 1st year after OHT (>2 episodes of significant rejection), and occurrence of late cellular rejection episodes. Using Kaplan-Meier curves time of onset of any CAV lesion, or time to occurrence of clinical event related to CAV (death, myocardial infarction, or coronary angioplasty) were compared among groups characterized by presence of factors mentioned above. Statistical significance was assessed using log-rank test.

Results: Shorter time to onset of any CAV (statistically significant – p=0.023), or clinically significant CAV (trend – p=0.07) was found in group of male OHT recipients. Time to onset of any or clinically significant CAV was also shorter in patients with ischaemic aetiology of heart failure, however a difference did not reach the statistical significance (p=0.09 and p=0.07, respectively). Surprisingly, occurrence of clinically significant CAV was higher in a group of patients under 46 y. of age (p=0.01). This difference was achieved due to high frequency of new onset of clinically significant CAV over 5 year after OHT in younger patients.

Conclusions: Diagnosis of de novo CAV later than 5 years after OHT is more characteristic for patients below 46 y. of age. CAV develops earlier in male OHT recipients. The influence of ischaemic aetiology of heart failure on CAV development is not unequivocal.

P3097 Reversibility of early endothelial dysfuction implies less development of cardiac allograft vasculopathy in heart transplantation

S. Lopez-Fernandez[1], J.A. Gomez Hospital[2], A. Cequier Fillat[1], N. Manito Lorite[1], J. Roca Elias[1], C. Martorell Adrian[1], R. Marin Perez[1], E. Esplugas[1]. *[1]Hospital de Bellvitge, Cardiology, Barcelona, Spain; [2]Barcelona, Spain*

Objetive: Coronary endothelial dysfunction (ED) may be an early marker of cardiac allograft vasculopathy (CAV) after heart transplantation (HT). This study tested whether changes in endothelial function at first year of follow-up can correlate with less development of CAV.

Methods: We included successful HT recipients that at first month and at first year of follow-up underwent a coronary angiography and endothelial function (EF)study. If any coronary angiographical lesions were observed at this study, patient (pt) was excluded. EF was assessed by infusion of serial increasing doses of acetylcholine (ACh) in the left anterior descending coronary artery.ED was defined as a paradoxical decrease of coronary diameter greater of 4% of the studied artery in response to Ach.

According to the results, four groups of patients were defined:

Group 1: Normal endothelial response in both studies.

Group 2: Early ED that became normal function in second study.

Group 3: Normal EF became ED.

Group 4: Early ED that remained in second study.

A third coronary angiogram was performed at long-term follow-up. Development of CVA was considered when any coronary lesion could be identified.

Results: 41 HT recipients were included with a mean age of 42±6 years old. 36 patients (88%) were males. Distribution of pt according to EF evolution was:

– Group 1: 26 pts (63%)
– Group 2: 6 pts (15%)
– Group 3: 3 pts (7%)
– Group 4: 6 pts (15%)

The third angiogram was performed at long-term follow-up (mean time=6,8±1,5 years) We found that 13 pts (32%) had developed CVA and 28 pts had normal coronary arteries. Distribution among the groups can be seen in Figure 1.

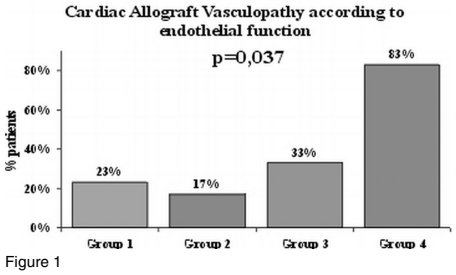


Figure 1

Conclusion: Reversibility of early ED implies better long-term CAV outcomes in HT recipients.

P3098 Increased peripheral chemoreceptor sensitivity and exercise ventilation in heart transplant recipients

A. Ciarka[1], N. Cuylits[1], K. Narkiewicz[2], B. Najem[1], M. Lamotte[1], J.P. Degaute[1], R. Naeije[3], P. van de Borne[1]. *[1]Erasme Hospital, Dept. of Cardiology, Brussels, Belgium; [2]Medical University of Gdansk, Diabetology and Hypertension, Gdansk, Poland; [3]Physiology Institute, Brussels, Belgium*

Background: Augmented peripheral chemoreceptor sensitivity increases the ventilatory response to hypoxia in congestive heart failure patients. Peripheral chemoreceptor sensitivity is positively related to exercise hyperpnea. Heart transplant recipients (HTR) disclose an increased ventilatory response to exercise. Effects of cardiac transplantation on peripheral chemoreflex control of ventilation are unknown. We tested the hypothesis that peripheral chemoreceptor sensitivity is increased in HTR and linked to exercise hyperpnea.

Material and methods: We determined the ventilatory, muscle sympathetic nerve activity (MSNA), and circulatory responses to isocapnic hypoxia 7±1 years after transplantation in 19 HTR with a normal left ventricular ejection fraction of 60±2%. Results were compared to 11 closely matched control subjects. Sixteen patients and 10 controls underwent cycle ergometer exercise tests.

Results: HTR, in comparison with control subjects, disclosed higher MSNA (52±4 vs. 34±3 burst/min, $p<0.01$) and faster heart rates (83±4 vs. 68±3 bpm, $p<0.01$) during room air breathing. The increase in ventilation during hypoxia was higher in HTR than in the controls 3.1±0.3 vs. 1.6±0.3 L/min, $p<0.01$, respectively). The rise in MSNA was also more marked during hypoxia in the HTR (32±6%) than in the controls (11±5%, $p<0.01$). The ventilatory response to exercise, characterised by the regression slope relating ventilation to CO2 output, was steeper in HTR (38±2 vs. 29±1 L/mmHg in the controls, n=16, $p<0.01$). Exercise hyperpnea was related to the larger ventilatory response to isocapnic hypoxia (r=+0.57, n=16, $p<0.05$).

Conclusion: Peripheral chemoreceptor sensitivity is increased in HTR and is related to exercice hyperpnea after heart transplantation.

P3099 Cause of donor death and risk of donor transmitted coronary artery disease in clinical heart transplantation

M. Kocik[1], I. Malek[2], B. Janek[2], M. Zelizko[2], J. Pirk[3]. *[1]General Faculty Hospital, IV. clinic of internal medicine, Prague, Czech Republic; [2]IKEM, Dep. of Cardiology, Prague, Czech Republic; [3]IKEM, Dep. of Cardiovascular surgery, Prague, Czech Republic*

Introduction: Atraumatic intracranial haemorrhage as cause of donor's death is reported to represent a risk factor for future development of graft vasculopathy. The reason for this observation has not been explained yet. Current study suggests, that particular cause of donor death could represent a risk factor for transition of donor related coronary artery disease (DRCAD). This postulate could help us to understand the correlation between cause of donor death and development of graft vasculopathy.

Study population and methods: Study group represents 66 heart transplant donors, with intravascular coronary ultrasound (ICUS) examination performed early after orthotopic heart transplantation (OHTx) in corresponding recipients. Donors were divided into 3 groups according to the cause of death: group A- cranial trauma (50 donors), group B- atypical intracranial haemorrhage (11 donors) and group C- typical intracranial haemorrhage (5 donors). The differences in the incidence of DRCAD as assessed by early ICUS between these subgroups were studied.

Results: Significantly higher incidence of DRCAD was observed in group of donors died of typical intracranial haemorrhage in compare to remaining two groups (C/A/B= 5/19/5: $p=0.025$, C/A=5/19: $p<0.01$, C/B=5/5: $p<0.05$). No significant difference in the DRCAD incidence was observed between groups A (cranial trauma) and B (atypical intracranial haemorrhage).

Conclusions: Typical intracranial haemorrhage as a cause of donor's death represents a risk factor for transmition of donor related coronary artery disease.

P3100 Malignancies during long-term follow up after heart transplantation: first results of the German heart transplantation tumour data base

K. Pethig[1], C. Bara[2], T. Dengler[3], N. Hiemann[4], T. Stadlbauer[5], A. Rahmel[6], H.U. Stempfle[7]. *[1]Friedrich Schiller University Jena, Dept. of Internal Medicine I - Cardiology, Jena, Germany; [2]Hannover Medical School, Dep. of Cardiothoracic Surgery, Hannover, Germany; [3]Dep. for Cardiology, University of Heidelberg, Heidelberg, Germany; [4]Dep for Cardiothoracic Surgery, German Heart Center, Berlin, Germany; [5]University of Giessen, Giessen, Germany; [6]Heart Center Leipzig, Leipzig, Germany; [7]Dep for Cardiology, University of Munich, Muenchen, Germany*

During long term follow up after heart transplantation (HTx) an increasing incidence of malignancies had to be observed over recent years. However, little is known about the time course of malignant disease, a potential relation to immunosuppressive therapy, pattern of organ involvement and impact on prognosis of heart transplant recipients.

In 2004, the German Working Group on Heart Transplantation established an internet based Tumor Data Base. A total of 18 heart transplant centres participate in this survey, documenting each patient transplanted in their program.

Results: So far 1634 patients (pts) with a mean follow up of 7.1 ± 3.9 years after HTx (1329 male, mean age 50 ± 12 years) were evaluated in the data base. Underlying disease before HTx was dilated CMP in 954 pts (58%), ischemic CMP in 573 pts (35%) and other in 107 (7%) pts. A total of 889 pts were treated with an antibody induction therapy early after transplantation. Immunosuppressive therapy was administered in form of Cyclosporine in 63%, Tacrolimus in 24%, Sirolimus/Everolimus in 6%, Azathioprine in 38%, Mycophenolate Mofetil in 28%,

and Steroids in 84% of pts. In 320 out of 1634 pts (20%) 517 solid malignancies were observed. The highest incidence was found for skin cancer (53%), followed by lymphomas (15%), lung cancer (12%), urogenital- (9%) gastrointestinal cancer (7%). Malignancies were identified as the cause of death in 24% of all deceased patients in this cohort. A potential association to immunosuppressive therapy and clinical follow up after manifestation of disease is under further evaluation.
Conclusion: Results of this study focussed on long term follow up confirmed the predominence of skin cancer in heart transplant recipients, followed by lymphomas and solid cancer. In contrast to the Cincinnati Transplant Tumor Registry, post-transplant lymphoproliferative disorders were statistically less common in the German Tumor Data Base. Further analysis is aimed to develop new surveillance strategies in order to prevent or at least anticipate the manifestation of malignant disorders.

P3101 Is routine coronary angiography and revascularisation indicated among patients undergoing evaluation for lung transplantation?

I. Ben-Dor, D. Shitrit, M.R. Kramer, Z. Iakobishvilli, G. Sahar, A. Battler, D. Hasdai. *Rabin Medical Center, Petach Tikva, Israel*

Background: Coronary angiography (CA) is advised for pts considered for lung transplantation (LTx), and residual significant coronary artery disease (CAD) is a contraindication to LTx.
Aim: To review CAD prevalence among LTx candidates, the time interval CA-to-LTx/death, and post-revascularization outcomes.
Methods: We followed all LTx candidates from 1997 who underwent CA. Significant CAD was defined as >70% diameter stenosis.
Results: Of the 118 candidates (68.3% males and median (25th, 75th interquartiles) age 58[53-61]), 59 underwent LTx, 56 were LTx-eligible, and 3 were excluded due to CAD. Significant CAD was in detected in 21(17.7%) pts, non-significant CAD in 21(17.7%) and anatomically normal coronary arteries (NCA) in 76(64.4%). There were no significant differences in the demographic or clinical profile among pts with or without CAD, except for fewer males in the NCA group (p=0.03). Among 21 pts with significant CAD, 12(57.1%) underwent successful PCI, 1 had failed PCI, and 8(38%) had no intervention. Of the post-PCI pts, 1 had periprocedural MI, 1 had subacute stent thrombosis, and 1 had symptomatic in-stent restenosis. The median time interval between CA and LTx/death/last-visit among the 115 candidates was 166[48-410] days; among significant-CAD pts 174[124-369] days and among post-successful-PCI pts 124[100-173] days. Death occurred while on the wating list post-CA in 30(53.5%) pts during a median follow-up of 312[46-664] days and after LTx in 14(23.7%) pts during a median follow-up of 142[73-304] days, without any difference in outcome based on severity of CAD in the two groups (p=0.7 and p=0.6, respectivly).
Conclusion: The prevalence of significant CAD among LTx candidates is low and cannot be predicted by risk factors. Revascularization may be associated with complications and the time interval revascularization-to-LTx my be long. Converesely, certain pts with significant CAD underwent LTx without complications. The practice of routine CA and revascularization prior to LTx should be reconsidered.

P3102 Effect of vitamin C supplementation on the coronary hypersensitivity to serotonin in cardiac transplant recipients. Relation to vessel wall morphology

G. Berkenboom[1], N. Preumont[2], O. Pradier[3], Y. Carpentier[2], M. Goldman[3], J.L. Vachiery[2], M. Antoine[2]. [1]*Erasme hospital, Cardiology, Brussels, Belgium;* [2]*Erasme hospital, Cardiology, Brussels, Belgium;* [3]*Erasme Hospital, Immunology, Brussels, Belgium*

Coronary hypersensitivity to serotonin promotes platelet aggregation entailing the progression of the atherosclerotic process. This abnormality is a common finding in cardiac transplant recipients and may be triggered by reactive oxygen species (ROS). Therefore, we aimed determining whether this hypersensitivity is reversible after acute supplementation with vitamin C (vit C) and whether the effect of this superoxide anion scavenger is influenced by morphological changes such as intimal hyperplasia.
Methods: Intracoronary (IC) injections of serotonin (5HT, 3 μg), bradykinin (Bk, 600 ng) and nitroglycerin (ISDN 200 μg) were performed in 21 cardiac transplant recipients (1 year post Tx) with normal coronary angiography; the 5HT injections were repeated after IC vit C supplementation (40 mg/min for 14 min). In the segments where 5HT effects were the most pronounced, the diameter changes were measured by quantitative angiography and the vessel wall morphology was studied by intravascular ultrasound (IVUS).
Results: The IVUS examination revealed moderate to severe intimal thickening (IT, total area minus luminal area/total area) 25±2%, compatible with early stage of graft vasculpathy in 9 patients (group 1). In this group, the hypersensitivity to 5HT remained unchanged after IC vit C supplementation: from -21±3% (% of baseline) to -25±3%; whereas in the other 12 patients with mild IT (9±1%; group 2), the hypersensitivity to 5HT was attenuated from -20±5% to -4±6% (P<.002). In contrast, the responses to Bk and ISDN were not significantly different: 17±2% vs 16±2% (in group 2) and 21±3% vs 23±3% (in group 2), respectively. The 2 groups were similar with regard to recipient and donor ages, pre-transplant coronary artery disease prevalence, number of rejections episodes, cholesterol plasma levels, statin and ACE inhibitor treatments but not for high sensitivity CRP plasma levels (1.6±0.2 mg/l vs 6.9±2.6 mg/l in group 1, P<.05). Proinflammatory cytokines (IL-6 and IL-8) plasma levels were also higher in group 1.
Conclusion: At 1 year post Tx, the morphological changes, compatible with early stage of graft vasculopathy, are accompanied by a hypersensitivity to 5HT unresponsive to vitamin C, despite a relatively preserved endothelial function (unaltered response to Bk). These morphological and functional alterations seem to be associated with persistent immune activation.

P3103 The assessment of the right atrial function after heart transplantation using bicaval anastomoses. A strain (rate) imaging study

C.F. Sirbu[1], P. Claus[1], J. D'hooge[1], B. Bijnens[1], M.F. Mattei[2], J.P. Villemot[2], G. Sutherland[3], F. Rademakers[1]. [1]*University Hospital Gasthuisberg, Cardiology Dept, Leuven, Belgium;* [2]*University Hospital Brabois, Cardiac surgery and transplantation, Nancy, France;* [3]*St George's Hospital, Cardiology, London, United Kingdom*

Background: Orthotopic heart transplantation (HTX) using bicaval anastomoses allow a more physiological atrial function with beneficial effects. However, the different degrees of right ventricular (RV) dysfunction related to the RV pressure overload after transplantation with heterogeneous recovery may influence the right atrial (RA) function. Strain rate imaging is a new technique that may provide additional insights into regional myocardial function and could improve the understanding of these changes.
Aims: To assess the RA contractile, reservoir and conduct functions using the strain (e) and strain rate (SR) indicators after HTX with bicaval anastomoses.
Methods: 18 patients with bicaval HTX (group A) and 18 healthy subjects age matched with the transplanted heart (group B) underwent a standard transthoracic echocardiography (TTE) followed by a 2D colour myocardial velocity imaging (2D CMVI) study. M-mode of the lateral tricuspid annulus (TLA) was obtained from apical 4 chamber view. The Doppler indicators of the tricuspidian inflow were also assessed. The RA longitudinal function was studied for the mid portion of the lateral RA wall from apical 4 chamber view. The peak values of e and SR for the longitudinal deformation of the lateral RA wall were calculated for the RA contractile, reservoir and conduit periods using dedicated software (SPEQLE) and were used as indicators of the RA function.
Results: Table 1 shows the results in comparison between the 2 groups.There was a signifficant difference between groups relating to TLA: 1.65+/0.39(group A)and 2.25+/0.43(group B)(p<0.01). The strain rate indicators for the RA contractile function in group A (peak strain=-20.3+/11,peak SR=-4.96+/2.57)were lower than in group B(peak strain=-38.1+/15.6,peak SR= -5.83+/1.97)(p<0.01)The same results were showed for the RA reservoir function in group A(peak strain=43.56+/20, peak SR =4.4)vs groupB (peak strain=95.4+/35, peak SR= 7.6+/2.8) and for the conduit function in group A(peak strain=-23.8+/12and peak SR -5.2+/2.6°VS group B(peak strain=-64+/28, peak SR= -7.4+/2)
Conclusions: The strain rate imaging allows to quantitate RA function in HTX patients.The values of e/SR indicators are significant reduced as against the normal subjects, this may be related to the RV pressure overload and to the hight sensitivity of the RV to ischemia.

P3104 Effect of receiving a heart-lung transplant in Eisenmengers syndrome analysis of a cohort entered on to a waiting list

A. Bertolotti[1], L. Favaloro[1], M. Diez[2], M. Peradejordi Lastra[1], F. Klein[1], R.R. Favaloro[1], M. Diez[1]. [1]*ICYCC Favaloro Foundation, Transplante Dept/Cardiology Div., Buenos Aires, Argentina;* [2]*ICYCC Fundacion Favaloro, Transplante Dept/Cardiology Div., Buenos Aires, Argentina*

Reliable information on variables predicting mortality in patients with Eisenmenger's Syndrome on H-LTx waiting list (WL) is essential to establish the criteria for the correct management of the WL.
Objective: To determine clinical and hemodynamic data predicting mortality in patients with Eisenmenger's syndrome on H-LTx WL.
Methods: From 1992 to 2003, 58 patients were included on H-LTx WL for Eisenmenger's syndrome (mean±SD age 29.1±12 years, 25 patients[43.1%] were men). Forty-two patients(72.4%) presented simple cardiac anatomy(atrial or ventricular septal defect, patent ductus arteriosus). New York Heart Association (NYHA) functional class (FC) III or IV was present in 21 patients(36.2%) at admission and in 44 patients(76%) on WL. The predominant symptoms at admission were dyspnea (n=37; 63.7%) and congestive heart failure (n=9; 15.5%) Pulmonary artery systolic pressure was 107±25 mmHg and pulmonary artery mean pressure was 70±16 mmHg. Right ventricular ejection fraction was 32±13% and transpulmonary gradient was 61±20 mmHg. Permanent oxygen therapy was instituted in 43 patients(74.1%). Clinical record prominent features included hemoptysis(n=20; 34.5%), cerebrovascular accident(n=3; 5.2%), syncope(n=10; 17.2%), brain abscess(n=3; 5.2%), and pregnancy(n=18; 31%). Survival was analyzed by the Kaplan-Meier method. Cox test was used for the analysis of late mortality predictors. Odds ratio(OR) was estimated with a 95% confidence interval(CI).
Results: Mean WL time was 4.3±3 years. Eleven patients(19%) died on WL and 10(17.2%) were transplanted. Thirty-four patients(58.6%) were hospitalized for heart failure. Overall survival on WL at 1, 3, 5 and 8 years was 86±4%, 71.4±6%,

63.5±6% and 53.8±8. Survival of transplanted patients at 1, 3 and 5 years was 54.5±15%, 36.3±15% and 36.3±15%. Predictors of mortality on WL were(OR, 95% CI, p): NYHA CF IV (9.6, 2-44, P=.004), hospitalization for heart failure (6.6,1.2-34, P=.02).
Conclusion: In our study group the need for hospitalization for heart failure and functional class IV were the variables predicting mortality in patients with Eisenmenger's syndrome on H-LTx WL. Considering the better survival of stable patients in relation to transplanted ones it would be reasonable to consider only the patients who presented NYHA FC IV or hospitalisation for heart failure to be included on WL to receive a HLTx.

P3105 Left ventricular hypertrophy after heart transplantation. Role of growth factors and cytokines

A. Vierheilig, T. Wissmann, M. Muscholl, M. Weis. *University Hospital Munich-Grosshadern, Medizinische Klinik und Poliklinik I, Munchen, Germany*

Left ventricular hypertrophy (LVH) develops frequently after human heart transplantation (HTx). Pathophysiological mechanisms for LVH include immunosuppression-induced hypertension and cardiac denervation. The impact of cytokines and growth factors, often upregulated due to chronic immune activation, on load-independent transplant hypertrophy is not well defined. We hypothesized that myocardial growth factors and inflammatory mediators contribute to LVH after HTx. We investigated circulating angiotensin II (AT-II), Endothelin-1 (ET-1), Insulin-like growth factor (IGF-1), Transforming growth factor (TGF-β), Fibroblast growth factor (FGF) and inflammatory markers (monocyte count, fibrinogen) in patients 1-48 months after HTx. Left ventricular mass (LVM) and geometry, systolic and diastolic left ventricular function were investigated by a blinded observer using echocardiography (n=31 patients during the first year; n= 120 > 2 years after HTx). LVH was defined as LVM >143 g/m^2 in men and LVM > 105 g/m^2 in women. LVH was detectable in 51% of all the patients. LVM increased from 154 g/m^2 during the first year to 170 g/m^2 in patients > 2 years after HTx. Progression of LVH over time was dependent on LVM changes during the first 12 months after HTx. IGF-1, TGF-β and FGF serum levels were significantly elevated in HTx-recipients with LVH ($p<0.05$). IGF-1, FGF and fibrinogen levels during the first 12 months after transplantation predicted development of LVH over time (FGF: 27.23 pg/ml versus 15.02 pg/ml in patients without LVH; $p< 0.01$; IGF-1: 23 versus 29 ng/ml; Fibrinogen: 431 versus 354 mg/l in patients without LVH; $p< 0.05$). Monocyte count and immosuppressive treatment (cyclosporine or tacrolimus) were not associated with LVH, whereas AT-II levels were inversely correlated to LVH ($p<0.05$).
Summary: TGF-β, IGF-1, FGF-1 and fibrinogen levels (but not AT-II and monocytes) are elevated in heart transplant patients with LVH. Initially elevated IGF-1, FGF-1 and fibrinogen levels are predicting progression of LVH during follow-up.

P3106 Conversion from cyclosporine A to tacrolimus after heart and heart lung transplantation in children

A.T. Fuchs[1], S. Reichel[2], J. Diterich[2], C. Rinker[2], S. Zysk[2], U. Roemer[2], R. Kozlik-Feldmann[2], H. Netz[2]. *[1]University Hospital Grosshadern, Department of Paediatric Cardiology, Munich, Germany; [2]University Hospital Grosshadern, Department of Paediatric Cardiology, Munich, Germany*

In a prospective study we investigated the effects of conversion from Cyclosporine A (CsA) to tacrolimus (TAC) in pediatric recipients of cardiac allografts. Side effects of CsA led to a switch in the immunosuppressive regimen.
22 heart (HTx) and 3 heart lung (HLTx) transplanted patients (pts) with stable graft function were assigned to the conversion to TAC. Indications for the switch to TAC were severe hypertrichosis in 7 pts, gingival hyperplasia in 5 pts, renal insufficiency in 5 pts, hypertonia in 3 pts, hyperlipidemia in 3 pts and atopic eczema in 2 pts. Demographic data: n=25, 15 boys and 9 girls, weight 47.5±20.9 kg, age 10±7.5 years (yrs), follow-up time 23.4±4.5 months. Diagnosis leading to transplantation were dilative cardiomyopathy: n=8, restrictive cardiomyopathy: n=3, Kawasaki Disease: n=1, idiopathic pulmonary hypertension: n=1, congenital heart disease: n=12.
Renal insufficiency was evaluated in values of serum creatinine and creatinine clearance, atopic eczema was assessed by calculating the Scorad score, hypertrichosis by calculating the Ferriman-Galway-Index. TAC was introduced directly with doses adjusted to a range of 8-10 ng/ml. Concomittant immunosuppressive therapy, consisting of mycophenolate mofetil and low dose steroids in the heart-lung-transplanted patient was maintained after the switch. Hypertrichosis (Ferriman Galway index) and gingival hyperplasia had strongly resolved in all pts 3 months after the switch. Renal function improved in terms of a decreased serum creatinine 3 months after the switch. Hyperlipidemia and hypertonia improved 3-6 months after the switch. Atopic eczema disappeared in 1 pt and remained unchanged in the other one.
Conversion from CsA to TAC in pediatric heart transplanted pts is effective. CsA related side effects improved within a few months, resulting in a better quality of life and in an improved cardiovascular risk profile.

P3107 Nuclear mean grey level and chromatin distribution in cardiocytes during acute cellular rejection of the transplanted heart

M.W. Zakliczynski[1], J. Nozynski[2], D. Konecka-Mrowka[2], D. Lange[3], M. Zembala[2]. *[1]Silesian Centre for Heart Disease, Heart Transplant Outpatient Clinic, Zabrze, Poland; [2]Silesian Center for Heart Disease, Cardiac Surgery and Transplantation, Zabrze, Poland; [3]Institute of Oncology, Dept. of Pathology, Gliwice, Poland*

Background: Distribution and staining of nuclear chromatin its are thought to be a sensitive indicators of changes in physiology, mitotic status, and pathology of cells. However, the use of these parameters in cardiopathology, and especially in cardiac transplantation, is very rare and poorly described. The aim of the study was to compare cardiomyocytes status in heart transplant recipients suffering from moderate acute cellular rejection and subjects without signs of active cellular rejection.
Material and methods: 129 endomyocardial biopsy samples from 43 heart transplant recipients (no later than 6mo. after surgery) were under evaluation. Overall, 3235 cartdiomyocytic nuclei were analyzed using Quantimet image analysis system, for assessing the mean grey level. 1584 nuclei were found in biopsies without signs of rejection or with non-significant rejection (ISHLT grade 0, 1A and 1B), whereas the remaining 1651 nuclei were measured from biopsies showing ISHLT grade 3A (significant rejection). Additionally, the chromatin distribution was assessed in all eligible nuclei. The results of grey level assessment were, as follows (no/non-significant rejection vs. significant rejection): mean – 135.449±52.338 vs. 179.634±18.353; median – 112.536 vs. 182.633; lower quartile 85.933 vs. 164.299; upper quartile – 203.955 vs. 194.640 ($p<0.01$, Student T test). Fine granular regular distribution of nuclear chromatin was found in 70 vs. 20% of nuclei ($p<0.0001$), clumps and regular distribution in 10 vs. 30% of nuclei ($p<0.003$), marginalization in 7 vs 48% of nuclei ($p<0.0001$, all chi-square test).
Conclusion: Inflammatory stimulation of cardiomyocytes during acute cellular rejection of the transplanted heart influences the chromatin distribution in the nuclei. These cytologic changes may have an additional value, when assessing a severity of cellular rejection.

P3108 Prognostic indicators in patients with end-stage heart failure who are on the waiting list for cardiac transplantation

H. Duygu[1], M. Zoghi[2], S.N. Nalbantgil[1], U.T. Turk[2], B.K. Kirilmaz[2]. *[1]Ege university medical school, Cardiology, Izmir, Turkey; [2]Ege university medical school, Cardiology, Izmir, Turkey*

Background: Heart failure is one of the most common and fatal diseases despite improvements in recent years. Cardiac transplantation is the last change in treatment of refractory heart failure and suitable donors should be found in the shortest time possible.
Objective: This study aimed at evaluating the patients (pts) with end-stage heart failure who are on the waiting list and determining the patients who should be prioritized in cardiac transplantation due to poor prognostic factors by comparing clinical and laboratory characteristics of the patients surviving and died while waiting on the waiting-list for cardiac transplantation.
Methods: 60 pts (mean age: 56 ± 11 years, 47 males) who were on the waiting list over the period of 6 years were investigated in 2 groups. Group I (n= 26, 17 males, mean age: 44 ± 17 years) was consisted of pts who were still receiving medical therapy and waiting for a suitable donor (group II, n = 34, 30 men and 4 women, mean ages: 46 ± 5 years). Demographic characteristics, clinical status (according to the UNOS criteria), medical therapies, risk factors for coronary artery disease, ECG findings (QRS time and corrected QT dispersion), echocardiographic data and hemodynamic parameters (aortic systolic pressure, left ventricular end-diastolic pressure, pulmonary arterial systolic, mean pressures and pulmonary capillary wedge pressure and transpulmonary gradient) of both groups were compared.
Results: Whereas no significant difference was found in age, risk factors for atherosclerosis and etiologies of heart failure between two groups, the rate of female pts in the group I was found to be greater than in the group II ($p = 0.04$). The rate of the patients with IB status was significantly greater in group I ($p = 0.01$). QTcd value was 62 ± 8 msn in the group I and 50 ± 5 msn in the group II ($p < 0.001$). QRS interval was significantly longer in the patients in the group I than those in the group II (180 ± 22 msn vs. 142 ± 10 msn,
$p < 0.001$). The right ventricular functions were more poor in group I (p=0.002). In the group I, right ventricular ejection fraction were
30 ± 10%, whereas this finding were 38 ± 9% in the group II. Transpulmonary gradient was 8 ± 2 mmHg in the group I and 6 ± 1 mmHg in the group II (p=0.03).
Conclusions: The clinical status, female gender, poor right ventricular functions, higher systolic pulmonary arterial pressure, wide QRS interval and increased QT dispersion are the strongest determinants of mortality in the patients on the waiting list for cardiac transplantation.

P3109 Soluble adhesion molecules and graft coronary artery disease

M. Kocik[1], I. Malek[2], J. Kvasnicka[3], O. Vilicky[4], T. Kvasnicka[5], I. Malikova[3], J. Pirk[6]. *[1]General Faculty Hospital, IV. clinic of internal medicine, Prague, Czech Republic; [2]IKEM, Dep. of Cardiology, Prague, Czech Republic; [3]1st Medical Faculty,Charles University, Dep. of clinical heamotology, Prague, Czech Republic; [4]IKEM, Dep. of nephrology, Prague, Czech Republic; [5]1st Medical Faculty,Charles University, III. clinic of internal medicine, Prague, Czech Republic; [6]IKEM, Dep. of Cardiovascular surgery, Prague, Czech Republic*

Introduction: Graft vasculopathy (GV) still represents the most important risk factor for long term survival after orthotopic heart transplantation (OHTx). Adhesion molecules are regarded to play an important role in its pathogenesis. Current study was designed to investigate, whether elevated plasma levels of soluble forms of ICAM-1, P-selectin, E-selectin correlate with the presence of GV as diagnosed by intravascular coronary ultrasound (ICUS) in OHTx recipients one year after OHTx.
Methods: Study population consists of 27 OHTx recipients (21 males, 6 females, age 49.04±11,69 years). Control group form 40 healthy individuals (30 males, 10 females, age 52±4.89 years). ICUS examinations were performed in all recipients one year after OHTx. Plasma levels of sICAM-1, sP-selectin, sE-selectin using ELISA method were determined in control group and in OHTx recipients at the time of ICUS.
Results: Significantly higher plasma levels of sICAM-1 and sP-selectin were found in OHTx recipient as compared with control group (sICAM-1, ng/mL: 326.46±81.03 vs. 292.3±74.39, p=0.0002, sP-selectin, ng/mL: 210.06± 112.6 vs. 167.21± 80.83, p=0.0002). sE-selectin plasma levels did not differ between both groups (sE-selectin, ng/mL: 47.08±19.54 vs. 47.12±17.5, p=0.81). GV was detected in 11 OHTx recipients (10 males, 1 female, age 49.64±1.47 years). No differences in plasma levels of tested soluble forms of adhesion molecules were observed between recipients with GV and without GV. (sICAM: p=0.55, sP-selectin: p=0.72, sE-selectin p=0.15).
Conclusions: Despite being elevated in OHTx recipients, plasma levels of sICAM-1 and sP-selectin do not correlate with the presence of morphologic sighs of GV. Thus soluble adhesion molecules' plasma levels can not be used as an non-invasive marker of GV in OHTx recipients.

P3110 Evaluation of coronary artery angiography in allograft coronary artery disease diagnosis

M. Kocik[1], I. Malek[2], B. Janek[2], M. Zelizko[2], J. Pirk[3]. *[1]General Faculty Hospital, IV. Clinic of Internal Medicine, Prague, Czech Republic; [2]IKEM, Department of Cardiology, Prague, Czech Republic; [3]IKEM, Department of Cardiovascular Surgery, Prague, Czech Republic*

Introduction: Thought intravascular coronary ultrasound (IVUS) is regarded to represent a gold standard in allograft coronary artery disease (aCAD) diagnosis, coronary artery angiography (CAG) is still used as a screening method in aCAD surveillance programs. The aim of the study was to evaluate the clinical role of CAG in aCAD surveillance programs after orthotopic heart transplantation (OHTx)
Study population and methods: Study population represents 52 OHTx recipients (47 male, 5 female, mean age 50.8±10.9 years) with CAG and IVUS of graft coronary arteries performed at the same time (mean time after OHTx 36.5±27.9 months). CAG findings and different CAG diagnostic criteria of aCAD were compared to IVUS findings (presence/absence of aCAD, aCAD significance), which was regarded as a reference method.
Results: Using strict diagnostic criteria aCAD was recognised by CAG in 32 out of 36 OHTx recipients as assessed by IVUS, which results in CAG sensitivity 89%, specificity 100%, negative predictive value (NPV) 80%, positive predictive value (PPV) 100% in aCAD diagnosis. In case of significant (hemodynamicaly important stenosis of allograft coronary arteries) aCAD as assessed by IVUS, CAG reached 100% sensitivity, 18%specificity, 100% NPV and 44%PPH in aCAD diagnosis.
Conclusions: Despite underestimating the seriousness of aCAD (sensitivity 43%, NPV 83% of significant stenosis diagnosis), the CAG is reliable method in aCAD diagnosis in case of significant stenosis of allograft coronary arteries (sensitivity 100%, NPV 100%). CAG represents relatively reliable method even in aCAD diagnosis at all, when strict angiographic criteria are applied (sensitivity 89%, NPV 80%). Importantly, the sensitivity and NPV of CAG in aCAD diagnosis rise with the time after OHTx.

P3111 Prognostic value of symptoms in heart transplant patients with cardiac allograft vasculopathy diagnosed by angiography

I.P. Garrido Bravo[1], M.G. Crespo-Leiro[2], M.J. Paniagua[2], J. Garcia-Lara[2], J. Salgado[2], R. Calvino[2], J.M. Vazquez-Rodriguez[2], A. Castro-Beiras[2]. *[1]A Coruña, Spain; [2]Hospital Juan Canalejo, Cardiology, A Coruña, Spain*

Background: Controversy exists regarding the management of patients with cardiac allograft vasculopathy (CAV) detected by angiography. Severe angiographic CAV has been proposed as a predictor of CAV related death or retransplantation but other factors may be related with a poor prognosis.
Methods: To investigate this issue we analyzed 48 patients who underwent heart transplantation from April 1991 to January 2003 with an angiography showing CAV. CAV was classified as mild, moderate, or severe according to Costanzo classification. Other variable examined were age, sex, diabetes mellitus treated with insulin, presence of symptoms of CAV (heart failure, syncope, chest pain) before and after pharmacological symptomatic treatment, ECG changes, left ventricle ejection fraction (LVEF), cardiac index and mortality related to CAV at one year or retransplantation.
Results: After one year follow up 14 patients dead related to CAV and 3 patients underwent retransplantation. Mild CAV was present in 20 patients, moderate in 17 and severe in 11. CAV-related events (death or retransplantation) actuarial incidence at one year was 25% (5/20, 1 asymptomatic and 4 symptomatic) in mild CAV, 18% (3/17, all symptomatic) in moderate CAV and 73% (8/11, 1 asymptomatic and 7 symptomatic) in severe CAV. After excluding 2 patients who underwent revascularization, those patients who dead because CAV or retransplantation were more symptomatic before (59% vs. 6%, p<0,001) and after (71% vs 8%, p<0,001) treatment, showed more ECG changes (58% vs. 22%, p= 0,014) and a more incidence of severe angiographic CAV (75% vs. 26%, p<0,001) and have lower LVEF (59±14 vs. 47±16, p=0,014) and cardiac index (3,1±1,7 vs. 2,5±1,2, p=0,038). No significant differences were found in other variables (age, sex, diabetes). Those variables that showed on univariate analysis a significant association were included in a multivariate analysis to predict mortality or retransplantation related to CAV at 1 year; only the persistence of symptoms after treatment was related with a poor prognosis (OR: 14,107, CI 95% [2,998-66,376], p=0.001).
Conclusions: Although severe angiographic CAV incidence is higher in poor prognostic patients is not an independent predictor. Only the persistence of symptoms after pharmacological symptomatic treatment is related with mortality or retransplantation related to CAV.

P3112 Semiquantitative myocardial perfusion of native and transplanted heart assessed by single-photon emission computed tomography: can we use the same reference database?

B. De Chiara[1], E. Roubina[1], M. Frigerio[2], R. Sara[3], P. Silva Orrego[2], O. Zoccarato[4], E. Vitali[2], O.A. Parodi[1]. *[1]Niguarda Ca' Granda Hospital, CNR Clinical Physiology Institute, Milan, Italy; [2]Niguarda Ca' Granda Hospital, Cardiology Dept., Milan, Italy; [3]Niguarda Ca' Granda Hospital, Nuclear Medicine Service, Milan, Italy; [4]Nuclear Medicine Dept., S. Mauggeri Foundation Medical Center, Veruno, Italy*

Background: The analysis of bull's eye map has been developed to quantify the information obtained from single-photon emission computed tomography (SPECT). It is usually generated from a commercial reference database which includes subjects with <5% probability of coronary artery disease. Aim of the present study was to compare the common reference database (C) with one obtained from heart transplant (HTx) recipients, in which SPECT is currently used in the detection of coronary allograft vasculopathy.
Methods: Dipyridamole stress-rest sestamibi SPECT imaging was performed in 29 HTx recipients (52±12 years, 20 male), which were included according to the following criteria: HTx performed one year before, normal left ventricular ejection fraction and coronary angiography, normal SPECT imaging according to visual analysis, normal clinical status. These patients generated the HTx reference database. Bull's eye map was reconstructed by standard methods; each map was normalized for peak myocardial activity (100%). Then, the map was divided into 17 segments according to the American Heart Association standardized segmentation for tomographic imaging. Stress and rest C (n=50) and HTx maps were compared to point out differences in regional perfusion.
Results: Perfusion in the anterior and septal walls were significantly higher in HTx than in C (p<0.0001) both in stress and rest images. Conversely, perfusion in inferolateral wall was significantly lower in HTx than in C during stress (p<0.0001), but not in resting condition. Differences in anteroseptal wall were found even when bull's eye maps were analyzed separately in men and in women, while in inferolateral wall they were present only in men.
Conclusions: Semiquantitative analysis of stress perfusion imaging by bull's eye maps indicates that antero-septal walls are more perfused in "normal" HTx recipients at one year after transplantation than in normal subjects, while the inferolateral wall is less perfused. The use of bull's eye reference database of HTx recipients instead of a standard reference map could improve the accuracy of SPECT technique in the detection of coronary allograft vasculopathy.

IMAGING IN VALVE DISEASE

P3113 Rest and stress echocardiographic predictors of mortality in patients with left ventricular dysfunction and functional mitral regurgitation

E. Agricola[1], A. Meris[1], M. Oppizzi[1], T. Bombardini[2], M. Pisani[1], G. Fragasso[3], E. Picano[2], A. Margonato[1]. *[1]San Raffaele Hospital, Division of Noninvasive Cardiology, Milano, Italy; [2]CNR, Institute of Clinical Physiology, Pisa, Italy; [3]San Raffaele Hospital, Heart Failure Unit, Milano, Italy*

Background: In patients with left ventricular dysfunction, the prognosis is related to the presence and severity of functional mitral regurgitation (FMR) that is a dynamic condition and can be studied during exercise.
Aim: To identify the potential predictors of death in patients with FMR, by considering all known potential rest and stress echocardiographic variables.
Methods: Thirty-seven consecutive patients (mean age 67±9 years) with left ventricular dysfunction (mean ejection fraction (EF) 29.3±7%) and at least mild MR (mean effective regurgitant orifice (ERO) 16.7±14.7 mm^2, range 4.5 to 48 mm^2) were enrolled. All patients underwent symptoms-limited exercise echo (30 watt/3 minute step). At rest and during exercise end-systolic (ESV), end-diastolic (EDV) volumes, EF, ERO and systolic pulmonary artery pressure (sPAP) were calculated. Moreover, we assessed the presence of contractile reserve evaluated by the non-invasive force-frequency relation during maximal exercise: the force was determined at each step as the ratio of systolic pressure (cuff sphygmomanometer)/end-systolic volume (biplane Simpson rule/body surface area). Finally, the presence of interstitial pulmonary edema (comet score) at rest and immediately after exercise as result of impairment of hemodynamic response to exercise was evaluated by the echographic chest examination. The end point was cardiac mortality. To detect independent predictors of cardiac death, we performed a multivariate Cox regression procedure according to the unmodified forward stepwise analysis. ROC curve analysis was performed to determine the cut off values of the independent predictors.
Results: The mean follow up was 21±3 months, during this period 8 patients (21.6%) died. At multivariate analysis, baseline ESV ($?^2$ = 8, p= 0.004), exercise change in EDV ($?^2$ = 5.6, p= 0.01) and ERO >20 cm^2 at rest ($?^2$ = 4.8, p= 0.02) were the only independent predictors of death, whereas other clinical (NYHA class) and rest/stress echocardiograpohic variables did not enter in the model. Patients with an ESV >95 ml/m^2, stress EDV >120 ml/m^2 or ERO >20 cm^2 at rest had significantly lower survival estimates than those with ESV <95 ml/m^2 (40% vs 92.6%, p=0.0001), stress EDV <120 ml/m^2 (50% vs 88.9%, p= 0.006) or ERO <20 cm^2 at rest (50% vs 92%, p=0.002).
Conclusion: In patients with left ventricular dysfunction and FMR, simple rest and stress echocardiographic parameters provide independent prognostic information useful for clinical management.

P3114 The role of TEE during operation on modifying the procedure of surgery in patients under repairing and replacing mitral valve operation

N. Aslanabadi[1], M.D. Mirinejad[2], M.D. Parvizi[2], M.D. Sajjadieh[2]. *[1]Tabriz University of Medical Sciences, Shahid Madani Heart Hospital, Tabriz, Iran (Islamic Republic of); [2]Tabriz university of medical sciences, Shahid Madani heart hospital, Tabriz, Iran (Islamic Republic of)*

Background and Objectives: Repair of mitral valve and maintaince of mitral apparatus is associated with fewer mortality and thromboemboli and better LV function. TEE immediately after repair operation plays an important role on measurement of residual requrgitation and prevention of redo operations. This is one of the routine monitors in cardiac surgery in most developed centers.
This study reviews the inpact of this monitor on repairing and replacement of MV to determine the significance of each.
Methods: 143 cases out of which 87 patients received repair (60.8%) and 56 received replacement of MV (39.2%) during a 3 year period were selected.
Immediately after the operation, the cardiologist performs TEE and if repair is satisfactory the operation is terminated otherwise redo repair or replacement is suggested.
Results: out of 87 repair operations 57 (65.5%) and out of 56 replacements 50 cases (89.2%) were satisfactory. Unsuccessful operations were detected by TEE and by modifying the procedure from repair to replacement and from replacement to reconsideration, all cases led to success.
Conclusion: During operation and immediately after MV repair and replacement TEE has crucial role on the prevention of redo operation and seems essential on all repair and replacement operations.

P3115 Mitral annular systolic velocity reflects the left atrial appendage function in mitral stenosis

M. Cayli[1], M. Kanadasý[2], M. Demir[2], E. Acartürk[2] on behalf of MSAF. *[1]cukurova univesity, cardiology, adana, Turkey; [2]Çukurova University School of Medicine, Cardiology, Adana, Turkey*

The left atrial appendage (LAA) has close anatomic relation with lateral annulus and LAA dysfunction is independent predictor of thromboembolism.

Aims: To investigate whether there is a relation between annular velocities obtained by tissue Doppler imaging (TDI) and LAA function and to determine if the annular velocities can predict the presence of the inactive LAA in mitral stenosis (MS).
Methods: Eighty-five patients with isolated MS (69 female and 16 male; mean age: 43.9 ± 10.1) were evaluated with transthoracic echocardiography. The lateral mitral annular systolic (S wave) and diastolic (E and A waves) velocities were recorded by using TDI. All patients underwent TEE. Inactive LAA was defined as the peak LAA emptying velocity <25 cm/s. Patients were divided into three groups; group I (n=43): sinus rhythm and peak LAA emptying velocity ≥ 25 cm/s, group II (n=15): sinus rhythm and peak LAA emptying velocity <25 cm/s and group III (n=27): atrial fibrillation.
Results: Thrombus was detected in 12 patients only in group III and spontaneous echo contrast (SEC) was detected in 48 patients. Both annular S wave and peak LAA emptying velocity were decreasing from group I to group III, while SEC frequency and SEC density were increasing from group I to group III. There was a positive correlation between LAA emptying velocity and S wave (p<0.001, r=0.682). Age, left atrial dimension, mitral valve area, transmitral mean and peak gradient, annular systolic and diastolic velocities were evaluated on multivariate regression analysis with backward elimination. Only S wave was found to be independent predictor for the presence of inactive LAA (p=0.001, odds ratio=0.143, 95% CI=0.047-0.434). In patients with sinus rhythm, the cut-off value of S wave was 13.5 cm/s, obtained by the ROC curve analysis, for prediction of presence of inactive LAA with a sensitivity of 95.3% and a specificity of 93.3%.
Conclusions: There is a positive correlation between annular systolic velocity and LAA emptying velocity in MS. Annular systolic velocity is an independent predictor for the presence of inactive LAA and assessment of annular systolic velocity is useful and reliable tool in estimating inactive LAA in MS patients with sinus rhythm.

P3116 Atherosclerosis of the aorta is common in patients with severe aortic stenosis: an intraoperative transoesophageal echocardiographic study

D. Weisenberg[1], Y. Sahar[1], G. Sahar[2], Y. Shapira[1], Z. Iakobishvili[1], B.A. Vidne[2], A. Battler[1], A. Sagie[1]. *[1]Rabin Medical Center, Cardiology Department, Petah Tikva, Israel; [2]Rabin Medical Center, Cardiothoracic Surgery Department, Petah Tikva, Israel*

Objective: Several studies have recently reported an association between aortic valve calcification and atherosclerosis of the cardiovascular system, suggesting that aortic valve calcification may represent an atherosclerosis-like process. Hence, the aim of the present study was to determine whether there is a similar association between aortic stenosis and aortic atheromas.
Methods: We evaluated the records and the echocardiographic videotapes of 91 consecutive patients with severe aortic stenosis who underwent intraoperative transesophageal echocardiography before aortic valve replacement to measure the presence and characteristics of aortic atheromas. There were 50 men (55%) and 41 women (45%). The mean age was 71.9 ± 9.4 years (range 34-91). These patients were compared with 91 sex-and age-matched patients without aortic stenosis who underwent transesophageal echocardiography for various indications. Aortic atheromas was defined as localized intimal thickening of >3 mm. A lesion was considered complex if there was plaque extending> 5 mm into the aortic lumen and/or if it was protruding, mobile or ulcerated.
Results: The aortic stenosis group had significantly higher rates of aortic atheromas (85% vs.37%, P< 0.001) and complex atheromas (47% vs 9%, P< 0.001), as compared with the control group. In the vast majority of patients in the aortic stenosis group the aortic atheromas were localized in the aortic arch (60 patients, 66%; 50% being complex aortic atheromas) and in the descending aorta (70 patients, 77%; 45.7% being complex aortic atheromas); in only 4 patients (4.4%) the aortic atheromas were localized in the ascending aorta (50% complex aortic atheromas).
Conclusions: There is a strong association between the presence of severe aortic stenosis and the presence and severity of aortic atheromas, suggesting that aortic stenosis may be a manifestation of the atherosclerotic process. These findings imply 1) Aggressive atherosclerotic risk-factor modification for patients with aortic stenosis may be advisable. 2) Consider evaluation of the aorta by transesophageal echocardiography prior to aortic valve replacement in selected patients.

P3117 Can live three-dimensional transthoracic echocardiography highlight the pathophysiological mechanism of mitral insufficiency?

F. Rigo[1], E. Polesel[2], A. Venturini[2], D. Mangino[2], A. Asta[2], M. Terrini[2], C. Zussa[3]. *[1]Hospital, Umberto I Hospital, Mestre-Venice, Italy; [2]Umberto I°, Cardiac Surgery, Mestre-Venice, Italy; [3]Umberto I° Hospital, Cardiac Surgery, Mestre-Venice, Italy*

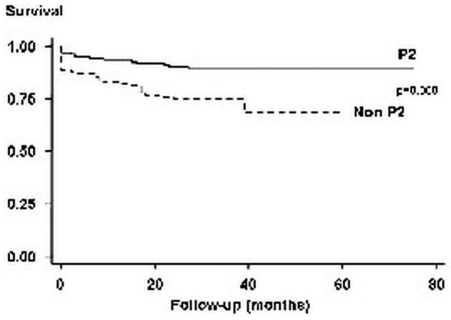
Background: Real time three-dimensional transthoracic echocardiography (3-DE) represents the most recent non-invasive diagnostic application in ultrasound. Theoretically, it offers better opportunities for correct diagnosis of the functional mechanism of mitral valve insufficiency, which
represents the most common condition to be resolved through surgical repair.

Methods: From April 2004 we evaluated 51 patients consecutively, 37 male mean age 61±12 years undergoing a surgical mitral valve repair procedure for mitral prolapse. Each of them underwent a common 2-D echo-doppler (2-DE) evaluation, a 3-DE analysis and an intraoperative transesophageal evaluation (TEE-IP). In particular, we adopted the Carpentier classification to focus on the mitral valve, subdividing the two leaflets into three segments (A1,A2,A3,P1,P2;P3): in the functional mechanism of mitral regurgitation we included the anterior and posterior commisure and tried to look for the possible presence of chordal rupture. We matched the 2-DE, 3-DE and TEE-IP with each other and with anatomical intraoperative findings. We employed an apical or parasternal approach for 2-DE and 3-DE, using the second harmonic (1,6 MHz-3,2 MHz). We classified the quality of images as excellent, good, sufficient and poor in function of complete visualization of all the mitral valve segments.
Results: The respective sensitivity, specificity and diagnostic accuracy was 74%-68%%-73% for 2-D TTE, 87%-82%-86% (p<0,001) for 3-DE and 94%-85%-93% for TEE-IP(p=NS).
The feasibility of 3-DE was excellent in 23/51 pts (45%), good in 12/51 pts (24%), sufficient in 12/51 pts (24%) and poor in 4/51 pts (7%).
Conclusion: 3-DE represents a new Echo application
that, after a short learning curve, allows us to obtain
a multiplane cardiac image and therefore a more
complete functional mitral valve anatomy which is very close to anatomical surgical views. In particular, 3-DE offers additional anatomical information about anterior mitral leaflet, the commissure and moreover about chordal rupture.
3-DE facilitates a more complete recognition of mitral valve anatomy, allowing a correct interpretation of functional mechanism of mitral regurgitation in a few minutes. This overcomes the limitation of 2-DE and, in the near future, could reduce the employment of TEE before the intraoperative time.

P3118 Precise localisation of valve prolapse by trans-thoracic echocardiography: influence on long-term postoperative outcome

J.L. Monin[1], P. Dehant[2], C. Roiron[1], M. Monchi[3], G. Fernandez[4], P. Clerc[4], R. Houel[5], P. Gueret[1]. *[1]Hôpital Henri Mondor, Service de Cardiologie, 8ème étage, Créteil, France; [2]Clinique Saint Augustin, Cardiology, Bordeaux, France; [3]Institut Médical Jacques Cartier, Intensive Care Medicine, Massy, France; [4]Clinique Saint Augustin, Cardiac Surgery, Bordeaux, France; [5]Institut Médical Jacques Cartier, Cardiac Surgery, Massy, France*

Background: Mitral valve repair is a major incentive to early surgery in case of severe mitral regurgitation (MR), the feasibility of which is largely based on echocardiographic analysis. Postoperative outcome implications of the precise localization of prolapsed segments by trans-thoracic echocardiography (TTE) in degenerative MR are not well known.
Methods and results: Consecutive patients (n=279; 181 men; median age, 68 years [quartiles: 61-74]) operated on for MR were prospectively enrolled in two tertiary centers. Etiology of MR assessed by TTE was degenerative (valve prolapse or flail leaflets) in 190 patients, cardiomyopathy in 49 (including 29 of ischemic origin), rheumatic disease in 24 or endocarditis in 16 patients. For the whole group, valve repair was performed in 237 patients (85%) and replacement in 42 (bioprosthesis, n=22; mechanical, n=20). The feasibility of repair was strongly influenced by the etiology of MR; it was significantly higher for degenerative MR and lower for rheumatic disease and endocarditis (p=0.0001). Long-term survival was significantly better for degenerative MR compared with the other groups (p=0.0025). Furthermore, in the subgroup of degenerative MR, patients with isolated P2 prolapse had a significantly better outcome as compared with patients with non-P2 lesions (p=0.008, Figure).



Conclusion: The precise localization of the prolapsed segments by TTE has a strong influence on postoperative outcome; single P2 lesions having a significant better prognosis as compared with all other lesions.

P3119 The annular systolic velocity in estimating spontaneous echo contrast and thrombus in mitral stenosis

M. Cayli[1], M. Kanadasý[2], M. Demir[2], E. Acartürk[2] on behalf of MSAF. *[1]cukurova univesity, cardiology, adana, Turkey; [2]Çukurova University School of Medicine, Cardiology, Adana, Turkey*

The changes of mitral annular functions direct influence the left atrial (LA) functions. It is known that the mitral annular functions are impaired in mitral stenosis (MS).
Aim: To determine if annular velocities obtained by tissue Doppler imaging (TDI) can predict the presence of spontaneous echo contrast (SEC) or thrombus in MS.
Methods: Eighty-five patients with MS (69 F and 16 M; mean age: 43.9 ±10.1) were evaluated with transthoracic echocardiography. The lateral annular systolic (S wave) and diastolic (E and A waves) velocities were recorded by using TDI. All patients underwent transesophageal echocardiography. The severity of SEC was graded from 0 to 4+.
Results: Mean mitral valve area (MVA) was 1.58±0.4 cm^2. Thrombus was detected in 12 patients (10 of them in left atrial appendage and 2 of them both LA and left atrial appendage) and SEC was detected in 48 patients. S wave was correlated negatively with severity of SEC and the patients with thrombus had lowest S wave. However, E and A waves showed no correlation with severity of SEC or thrombus. Age, atrial fibrillation (AF), LA dimension, MVA and S wave were evaluated on multivariate regression analysis with backward elimination. Age, LA dimension and S wave were found to be independent predictors for the presence of SEC, while AF, MVA and S wave were independent predictors for the presence of thrombus (table). In the ROC curve analysis, the cut-off values of S wave was 13.5 cm/s for prediction of SEC (sensitivity: 100% and specificity: 89.6%) and 10.6 cm/s for prediction of thrombus (sensitivity: 89.6% and specificity: 83.3%).

Table

	SEC			Thrombus		
	p	OR	95% CI	p	OR	95% CI
Age (years)	0.02	1.23	1.04-1.46	0.4	0.95	0.85-1.07
AF (%)	0.2	5.64	0.39-82.33	0.004	21.4	2.74-167.47
LAD (mm)	<0.05	1.24	1.01-1.53	0.5	1.05	0.91-1.20
MVA (cm^2)	>0.05	0.008	0.00-1.09	0.009	0.002	0.00-0.199
S wave (cm/s)	0.001	0.33	0.18-0.63	0.01	0.55	0.35-0.87

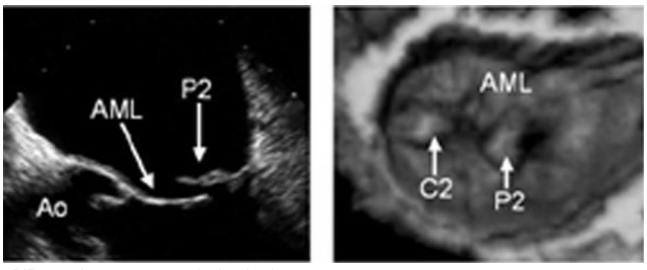
SEC: Spontaneous echo contrast, OR: Odds ratio, CI: Confidence interval, LAD: Left atrial diameter, MVA: Mitral valve area, AF: Atrial fibrillation.

Conclusion: S wave is an independent predictor for both SEC and thrombus. Annular systolic velocity is a reliable and useful parameter in estimating SEC and thrombus in MS.

P3120 Three-dimensional image reconstruction is superior to conventional transoesophageal echocardiography for conceptualisation prior to mitral repair surgery

S. Müller[1], L. Müller[2], H. Alber[1], W. Dichtl[1], M. Frick[1], W. Laufer[2], O. Pachinger[1], T. Bartel[3]. *[1]University Innsbruck, Department of Cardiology, Innsbruck, Austria; [2]University Innsbruck, Department of Cardiac Surgery, Innsbruck, Austria; [3]University of Innsbruck, Department of Cardiology, Innsbruck, Austria*

Background: We comparatively tested the diagnostic value of transoesophageal echocardiography (TEE) and three-dimensional image reconstruction (3DIR) to particularise mitral valve dysfunction of type II. TEE is not optimal to safely assign complex lesions of definite valvular segments.
Methods: In 74 patients (mean age 59 ± 13 years) with mitral regurgitation due to type II valve dysfunction, TEE and 3DIR were performed and analyzed by 2 experts prior to repair surgery. Leaflet segments and commissures were displayed in short-axis en-face and long-axis views. Echocardiographic results were intraoperatively validated and sensitivity (SE), specificity (SP), positive predictive value (PPV), negative predictive value (NPV), and accuracy (AC) calculated with respect to all segments, Barlow's disease and combined lesions. Interobserver variability was also determined.
Results: Although superiority reached not always a significant degree ($p < 0.05$), SE, PPV, NPV, and AC of 3DIR were found to be higher than those of TEE throughout all segments. SP was higher with respect to P2 lesions. The clearest advantages of 3DIR over TEE were demonstrated for SE regarding to com-



3DIR reveals 2 segments to be involved

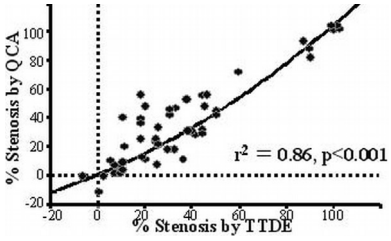
missural and bileaflet defects ($p < 0.05$). Interobserver agreement on 3DIR was stronger than on TEE results (Kappa-values: 0.52 vs. 0.82; $p < 0.0001$). There were 16 (23%) disagreements on TEE images but 5 (7%) on 3DIR readings, only.
Conclusion: The more complicated the lesions (Figure) are, the more superior is 3DIR to TEE and should be therefore employed in order to evaluate and to safely localise particular pathology in type II mitral valve dysfunction prior to repair.

CORONARY SURGERY

P3121 Noninvasive and quantitative evaluation of the patency of internal mammary artery bypass graft to the left anterior descending artery by Transthoracic Doppler Echocardiography

N. Mizukami[1], S. Minagoe[2], Y. Otsuji[2], T. Yuasa[2], K. Nakashiki[2], I. Maruyama[3], R. Sakata[4], C. Tei[2]. *[1]Kagoshima university, Division of clinical Laboratory, Kagoshima, Japan; [2]Kagoshima university, Cardiovascular Medicine, Kagoshima, Japan; [3]Kagoshima university, Laboratory and Vascular Medicine, Kagoshima, Japan; [4]Kagoshima university, Thoracic and Cardiovascular Surgery, Kagoshima, Japan*

Background: Transthoracic Doppler echocardiography (TTDE) enables quantitative evaluation of left anterior descending (LAD) artery stenosis by continuity equation, however, feasibility of TTDE to assess the anastomosis of internal mammary artery (IMA) to LAD has not been fully investigated.
Methods: In 66 consecutive patients (48 men and 18 women, age 67±10 years) with recent or previous coronary artery bypass grafting (CABG) using IMA graft to LAD (left IMA in 59 patients and right IMA in 7 patients), the distal IMA flow at the anastomosis was visualized and the %stenosis was evaluated by the continuity equation using the anastomotic and pre-anastomotic flow velocity by TTDE. When the anastomosis flow was not visualized by TTDE, the proximal IMA flow from the supraclavicular approach was evaluated and the diastolic to systolic mean velocity ratio (D/S ratio) < 0.25 was considered as anastomotic occlusion. % stenosis of the anastomosis was also evaluated by quantitative coronary angiography (QCA).
Results: 1) Distal IMA flow at the anastomosis was visualized and applied for continuity equation in 50 (76%) patients. In 4 of the remaining 16 patients, proximal IMA flow by TTDE showed total occlusion pattern. Therefore, quantitative evaluation by TTDE was applicable in these 54 (82%) patients. 2) In the 54 patients with the applicable evaluation, % stenosis by TTDE showed significant and good correlation with that by QCA ($r^2 = 0.86$, $p<0.001$)(Figure). 3) In all the remaining 12 patients with a patent proximal IMA pattern but without visualized anastomotic flow, the patency was confirmed by angiography



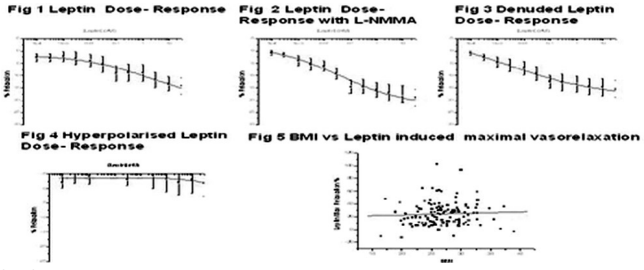
% Stenosis: Doppler Echo vs. Angiography

Conclusions: TTDE enables direct visualization and quantitative evaluation of the anastomotic patency in the majority of patients with IMA graft to the LAD.

P3122 The adipocyte derived peptide hormone leptin is an endothelial independent vasodilator in humans: implications for vascular homeostasis

A. Momin[1], A. Shah[2], D. Grieve[2], C. Driver[3], A. El-Gamel[4], J. Desai[4], R. Sherwood[3], M. Kearney[2]. *[1]London, United Kingdom; [2]GKT School of Medicine Kings College, Cardiovascular Division, London, United Kingdom; [3]Kings College Hospital, Biochemistry Department, London, United Kingdom; [4]Kings College Hospital, Cardiothoracic Department, London, United Kingdom*

It has been suggested that leptin, the adipocyte-derived peptide hormone has vasoactive actions in animal models. We sought to define the mechanisms and determinants of leptins vascular actions in humans. We examined the effect of leptin (0.0001-100nM) on ex-vivo vascular function in saphenous vein rings (SV) taken from 131 patients (age 65.7±0.7) undergoing elective CABG. Mean maximal relaxation to leptin in the whole population was 24.5±1.6% and all rings relaxed fully to sodium nitroprusside. Relaxation to leptin was unaffected by the nitric oxide synthase inhibitor L-NMMA(0.1mM) (n=8, 17.4±3.4 vs 17.8±3.3%, P=NS) and endothelial denudation(n=8, 17.4±4.4 vs 22.5±3.0%, P=NS). Since the central effects of leptin are thought to be mediated through opening of potassium channels we explored the possibility that its vascular effects are mediated in a similar fashion. In the presence of KCl (30mM) to inhibit hyperpolarisation, the vasodilator effect of leptin was completely blocked (n=10, 12.6±5.6 vs 0.08±4.1%, P<0.001). The only independent correlate of leptin mediated vasodilatation was TNF-a (R=0.23, P<0.05). Markers of total fat mass (BMI) or visceral fat (waist) had no relationship with leptin-mediated vasorelaxation, supporting tissue specificity of leptin resistance.



Leptin

Conclusion: Leptin is an endothelial independent vasodilator in humans, leptin mediated vasorelaxation is mediated by smooth muscle hyperpolarisation. The independent and positive correlate of leptin-mediated vasorelaxation is the cytokine TNF-a. These results may have implications for blood pressure regulation in different inflammatory conditions in humans such as sepsis and obesity.

P3123 Preoperative creatinine clearance is a better predictor of mortality after cardiac surgery than creatinine

A. El-Gamel[1], W. Jamal[1], L. John[1], J. Desai[1], M. Kearney[1], O. Wendler[2]. *[1]King's College Hospital, Cardiothoracic Surgery, London, United Kingdom; [2]King's College Hospital, Consultant Cardiothoracic Surgeon, London, United Kingdom*

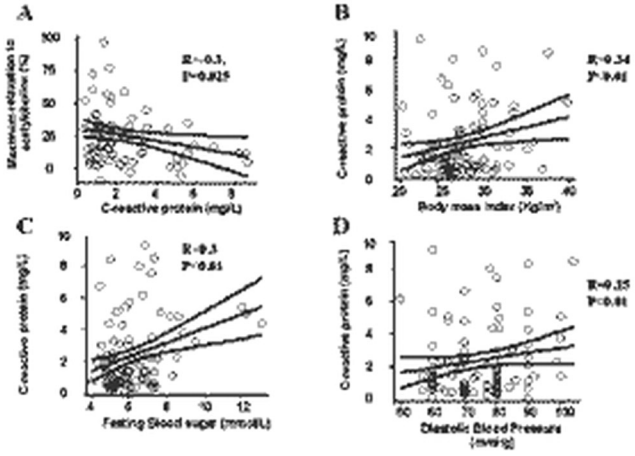
Background: Serum creatinine (Cr) is an accepted marker of renal dysfunction before cardiac surgery. However, a number of patients (pts) with normal preoperative Cr suffer from postoperative renal failure with its high mortality. Creatinine clearance (CrC) is known to be more accurate in the early diagnosis of renal failure. In this prospective study we analysed if CrC is a prognostic tool to identify patients with an increased mortality after cardiac surgery.
Patients and Methods: Between 04/2002 and 09/2004 a total of 2000 consecutive pts with isolated CABG (n=1345) or aortic/mitral valve replacement ±CABG (n=655) were included into the investigation. In all pts Cr and CrC were determined preoperatively. CrC identified the pts into group I (CrC <70 ml/min; n=754) and group II (CrC =70 ml/min; n=1246). Univariate and multivariate analysis were used to identify risk of mortality.
Results: The groups showed no differences due to age, sex, on-bypass procedures and artherosclerosis. Group I showed a higher incidence of hypertension (n=543 vs. n=342; p=0.01) and aortic stenosis (n=302 vs. n=99; p=0.02), wherease diabetes mellitus was more frequent in group II (n=125 vs. n=432; p=0.02). In 433 pts of group I the preoperative Cr was normal (sensitivity: 24%). In group II 40 pts had raised Cr (specificity: 96.7%). In-hospital mortality with 5.6% was significantly higher in group I (n=42) compared to 0.7% in group II (n=8; p<0.001). If CrC was <40 ml/min the in-hospital mortality rose to 49% (n=26/58). Multiple regression analysis identified CrC to be the only strong predictor of in-hospital mortality.
Conclusion: Preoperative Cr shows a high specificity but a very low sensitivity to exclude renal impairment before cardiac surgery. Reduced CrC is a strong predictor for postoperative mortality after cardiac surgery.

P3124 C-reactive protein is an independent predictor of endothelial function in patients with coronary artery disease treated optimally with statins

A. Momin[1], A. Shah[2], D. Grieve[2], C. Driver[3], J. Desai[4], A. El-Gamel[4], R. Sherwood[3], M. Kearney[2]. *[1]London, United Kingdom; [2]GKT School of Medicine Kings College, Cardiovascular Division, London, United Kingdom; [3]Kings College Hospital, Biochemistry Department, London, United Kingdom; [4]Kings College Hospital, Cardiothoracic Department, London, United Kingdom*

Novel risk factors for coronary artery disease(CAD)have emerged, among which C-reactive protein(CRP) has been suggested to be linked to endothelial dysfunction(ED). The relationship between CRP and ED in CAD patients(pts) treated with statins is unclear. The aim of this study was to explore the role of CRP as a predictor of ED in pts optimally treated with statins. We recruited consecutive pts undergoing elective CABG. Endothelial function was assessed ex vivo in saphenous vein (SV) rings obtained at CABG.
Of 115 pts, 99 (mean age 66±0.9; 90% male) were optimally treated with statins, cholesterol levels <5.0 mmol/L (mean 3.1±0.7) and triglycerides 1.2±0.1 mmol/L. BMI 26.9±0.4 kg/m^2, waist 99.8±1.0 cm, systolic BP 138.7±2.2 mmHg, diastolic BP 74.3 ± 1.1 mmHg, fasting glucose 6.2 ±0.2 mmol/L, and CRP 2.4±0.2 mg/L. Vascular reactivity of preconstricted SV rings was assessed in 77 pts. Maximal relaxation to the endothelium-dependent vasodilator acetylcholine (Ach; 10-9-10-

4 mol/L) was 25.5 ± 2.3%. All rings relaxed fully to SNP. In univariate analysis, CRP(r=-0.3), waist(r=-0.19) and BMI(r=-0.2) were inversely correlated with relaxation to Ach(all P<0.05). In multivariate analysis, the only independent predictor of relaxation to Ach was CRP(r=-0.3; P=0.025). Relaxation to SNP was not associated with any variable. In multivariate analysis to assess correlates of plasma CRP, the only independent predictors were BMI (r=0.34), diastolic BP (r=0.25) and fasting glucose (r=0.3) - all P<0.01.



CRP

In statin-treated CAD pts with low cholesterol levels undergoing CABG, CRP is the only independent predictor of ED. These data support a link between CRP and endothelial dysfunction even in pts treated with currently recommended doses of statins.

P3125 Fate of sequential anastomose is better than individual anastomose on diagonal branches of left anterior descending artery

B.S. Oz[1], M. Yokusoglu[2], C. Bolcali[1], M. Uzun[2], E. Kuralay[1], O. Baysan[2], E. Isik[2], H. Tatar[1]. *[1]GMMA, CV Surgery, Ankara, Turkey; [2]Gulhane Military Medical Academy, Cardiology Department, Ankara, Turkey*

Despite many advances and understanding of early and late graft patencies, sequential or individual coronary artery by-pass grafting still continues to be cornerstone of coronary revascularization practice. We applied sequential and individual coronary artery by-pass grafting techniques to diagonal branches of LAD artery. Here we reported our early and mid-term angiographic outcome of our patients in whom CABG was performed with radial artery or saphenous vein to diagonal branches of LAD in sequential or individual techniques.

A total of 296 coronary anastomose of diagonal branches of LAD were assessed in 296 patients in an average of 49.4±13.2 months after operations. The diagonal artery anastomosis was done sequentially in 101 patients (saphenous vein in 83 patients, and radial artery in 18 patients) and individually in 195 patients (saphenous vein in 148 patients, and radial artery in 47 patients)

The total patency rate of sequentially conduits were markedly higher than individual ones on diagonal branches (89.2% versus 67.8%; p=0.001) and also patency rates of sequential radial artery anastomose was better than sequential saphenous vein anastomose (91.4% versus 79.2%; P=0.001)

We compared the sequential and individual by-pass grafting technique in a small diameter coronary artery – diagonal branch of LAD to understand the effect of distal runoff. The patency of a sequential anastomose generally superior than individual anastomose regardless on the type of conduit (radial or saphenous). The cause of this effect may be the better runoff for distally located anastomose with better quality and larger diameter than the diagonal branch of sequential anastomose. But technical difficulties about performing a sequential anastomose makes it risky especially at high risk patients.

In conclusion; sequential by-pass grafting in a small diameter coronary artery such as diagonal branch of LAD is superior to individual anastamose regardless of the type of conduit. Within sequential anastomose, radial artery conduit is better than saphenous vein. However, difficulties in sequential anastomose procedures are still the main limitation of this technique.

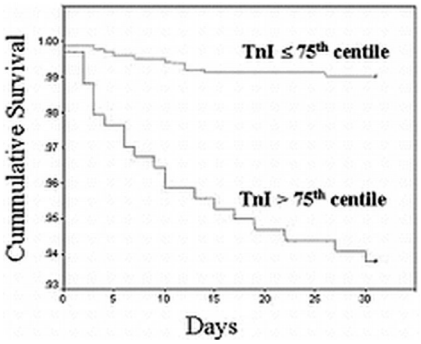
P3126 Clinical significance of cardiac troponin I release following cardiac surgery

B.L. Croal[1], B.H. Cuthbertson[2], T. Fazal[1], R.R. Jeffrey[3], K.G. Buchan[3], G.A. Gibson[3], H. El-Shafei[3], G.S. Hillis[4]. *[1]Aberdeen Royal Infirmary, Department of Clinical Biochemistry, Aberdeen, United Kingdom; [2]Aberdeen Royal Infirmary, Anaesthesia and Intensive Care, Aberdeen, United Kingdom; [3]Aberdeen Royal Infirmary, Department of Cardiac Surgery, Aberdeen, United Kingdom; [4]Aberdeen Royal Infirmary, Department of Cardiology, Aberdeen, United Kingdom*

Interpretation of cardiac biomarker levels following cardiac surgery is complicated by background release in this setting and the paucity of data exploring the implications of any elevation. The current study explored the factors associated with, and the clinical consequence of, cardiac troponin I (cTnI) release following cardiac surgery.

Methods: The study cohort consisted of 1,413 consecutive patients undergoing cardiac surgery (coronary artery bypass grafting and/or valve surgery) in a regional centre. Blood samples for cTnI were taken post-operatively (0 h) and at 24 h. Further samples were taken at 48 and 72 h if clinically indicated. Clinical data were collected and vital status recorded at 30 days.

Results: cTnI levels peaked at 24 h, with progressively higher levels found as the number of vessels grafted increased (p <0.001). Patients undergoing valvular surgery had the highest TnI levels (p <0.001). Median cTnI levels among patients that died within 30 days were 11.9ng/mL vs 4.3ng/mL (p <0.001), and remained independent predictors after adjusting for other prognostic variables (p <0.001). Using the 75th centile for each operation type (number of grafts/valvular surgery) as a cut-off, survival curves were constructed for 30-day mortality (Figure, p <0.001).



Figure

Conclusion: Higher levels of cTnI are seen with an increasing number of bypass grafts or with valvular surgery. Patients with a cTnI above the 75th centile for their operation type are at a substantial increased risk of mortality at 30 days.

P3127 Influence of pre-operative moderate renal dysfunction on clinical outcome in coronary artery bypass surgery; a new parameter in pre-operative risk score? The Nijmegen experience

I. Plesiewicz, S.C. Wouters, G.A.M. Pop, F.W.A. Verheugt, L. Noyez. *Heart Centre UMCN St Radboud, Nijmegen, Netherlands*

Purpose: The CORRAD score is a scoring system for evaluation of pre-operative risk in coronary artery bypass surgery (CABG) and has shown an even better predictive power than the EURO and Parasonnet risk scores. Recently, it has been demonstrated that moderate renal dysfunction (MoReD) resulted in worse outcome after cardiac surgery. We investigated if MoReD should be included as a new parameter in the CORRAD score.

Methods: In 627 consecutive patients, from the CORRAD database, who underwent CABG between January 2003 and September 2004, we analyzed in-hospital mortality and morbidity after surgery. MoReD was defined as creatinine clearance (CrCl) >60 and < 80 ml/min (using Cockroft-Gault formula) or as serum creatinine level (SCrL) >124 and <178 μmol/L. Univariate analysis and logistic regression were performed to check the association between MoReD, estimated by CrCl and SCrL, and in-hospital mortality and morbidity.

Results: In univariate analysis, when renal function was estimated by CrCl,among patients with MoReD a significantly higher mortality was observed than among patients with normal renal function(6/174 pts vs 2/341 pts; OR= 6.054; p<0.013). Logistic regression analysis revealed that MoReD was an independent predictive risk factor for in-hospital mortality after CABG (p=0.05; OR= 0,12). No significant predictive power was found when MoReD was defined by SCrL.

Conclusion: The CORRAD score should include MoReD as an independent preoperative risk factor in CABG patients and MoReD should be estimating by creatinine clearance, using the Cockroft-Gault formula, rather than serum creatinine level.

P3128 Killip class predicts the need for coronary artery bypass graft surgery in non-ST segment myocardial infarction

M. Vasconcelos[1], R. Almeida[1], L. Mariano[1], C. Gavina[1], T. Pinho[1], A. Ferreira[2], M.J. Maciel[1], F. Rocha-Goncalves[1]. [1]*Hospital S. Joao, Cardiology, Porto, Portugal;* [2]*Hospital S. Joao, Internal Medicine, Porto, Portugal*

Introduction: The management of non-ST elevation acute coronary syndromes (NSTEMI) in hospitals with catheterisation laboratory facilities, namely the use of clopidogrel, is influenced by the probability of surgical revascularisation. Our aim was to find clinical predictors of indication for coronary artery bypass graft surgery (CABG) in this group of patients (pts).
Methods: We studied 586 pts (62.7±11.9 years-old, 69.8% males) consecutively admitted in our cardiology department with NSTEMI. All of the assessed clinical and laboratory parameters were obtained during the first 48 hours. The study end point was CABG during index hospitalisation.
Results: Prevalence of cardiovascular risk factors in our population was high (hypertension in 64.3%, diabetes mellitus in 32.3%, current or previous smoking in 44.7%, dyslipidaemia in 70.1%, body mass index > 30 kg/m^2 in 20.6%). Thirty-seven percent had known cardiovascular disease, 6.2% had Killip classes III/IV and 28.3% had left ventricular systolic dysfunction (LVSD). Multivessel and/or left main coronary artery disease was found in 65.9%. CABG was performed in 17.9% (15.8% of pts in Killip classes I/II and 50% of pts in classes III/IV). Variables associated with CABG in univariate analysis were: smoking (OR 0.621, 95%CI 0.408-0.943), Killip classes III/IV (OR 5.339, 95%CI 2.363-12.064) and troponin I (OR 0.986, 95%CI 0.972-0.999). Multivariate analysis, using a stepwise binary logistic regression method, revealed that the only independent predictor was Killip class (OR 5.976, 95%CI 2.602-13.725) with sensitivity=17.3%, specificity=96.2%, positive predictive value=49.3% and negative predictive value=80%.
Conclusion: Our study shows that NSTEMI pts presenting in Killip classes I or II have a low probability of CABG during hospitalisation. Therefore, according to current guidelines for ACS management, early clopidogrel use in this group can be decided prior to knowledge of coronary anatomy based only in a clinical predictor.

P3129 Effects of Ca^{2+} sensitiser levosimendan on flow in internal thoracic and radial arteries in patients undergoing CABG – preliminary results

I. Knez[1], S. Schweiger[2], I. Ovcina[2], S. Huber[2], D. Dacar[2], B. Rigler[2], P. Rehak[3], W. Toller[4]. [1]*University Clinic of Surgery, Cardiac Surgery, Graz, Austria;* [2]*University Clinic of Surgery, Cardiac Surgery, Graz, Austria;* [3]*Surgery, Biomedical Engineering & Computing, Graz, Austria;* [4]*Anesthesiology, Cardiovascular Anesthesia, Graz, Austria*

Objective: Spasm due to surgical harvesting is a major concern with the use of arterial conduits in coronary artery bypass surgery (CABG).We evaluated the effect of inotropic agents on in vivo radial artery (RA) flow compared with internal thoracic artery (ITA) flow and set this data in relation to observed hemodynamic changes.
Design: Prospective,randomized,double-blind,clinical trial, statistical power stratification for 15 patients per group.
Setting: University hospital.
Methods: 45 patients (32 males and 13 females) undergoing primary CABG,mean age of 58±3 years were enrolled in this study and randomized to 3 groups receiving a loading dose of Levosimendan (12μg/kg/min), Dobutamine (5μg/kg/min) and physiologic saline as control group (ml) over 10 minutes. RA and ITA flows (in ml min^{-1}), aortic (AP),pulmonary artery (PAP),pulmonary capillary wedge (PCWP) pressures (in mmHg) and heart rates (HR in beats min^{-1}) were measured at baseline (T0), 5 (T1) and 10 minutes (T2) after test drug administration.
Results: Flows in ITA (15.4-22.4-30.1 vs 19.6-21.5-22.6; p<0.000001*) and in RA (13.14-21.21-29.9 vs 13.9-15.1-16.1; p<0.000001*) significantly increased in Levosimendan vs Dobutamin patients. Hemodynamics remained absolutely stable in Levosimendan and control groups, a statistically significant deterioration was found in Dobutamin patients.

Hemodynamics: analysis of variance

Drug tested	HR				AP			
	T0	T1	T2	P	T0	T1	T2	P
Levosimendan	53.7	52.3	53.3		76	72	70	
NaCl 0.9%	56.2	56.5	56.9		76	79	78	
Dobutamin	53.8	61	66	0.0029*	82	85	93	0.0056*

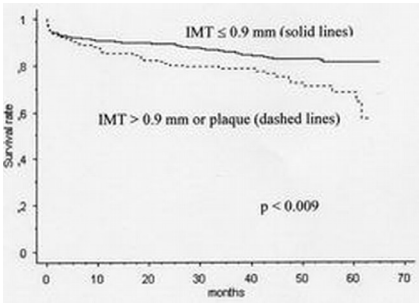
	PAP				PCWP			
	T0	T1	T2	P	T0	T1	T2	P
Levosimendan	18.4	17.7	17.5		12.1	10.6	11.1	
NaCl 0.9%	16.5	16.5	16.7		10.9	10.8	10.8	
Dobutamin	16	19	21.4	0.000006*	11.6	13.1	14.1	0.00019*

Conclusions: This in vivo study concludes that in arterial grafts used for CABG intravenous Levosimendan causes higher flows comparing to Dobutamin.Levosimendan is significantly superior to Dobutamin as far as protection from vasospasm due to surgical harvesting of ITA, especially RA is concerned.

P3130 Usefulness of the carotid intima-media thickness measurement as a prognostic marker in patients undergoing coronary bypass surgery. A prospective study

J. Guilloux, V. Aboyans, P.H. Lacroix, C. Yildiz, M. Laskar. *Thoracic & Cardiovascular Surgery, Limoges, France*

Background: In primary prevention, carotid-IMT is a valuable cardiovascular risk marker but its interest in secondary prevention has been less studied.
Objectives: We hypothesized that common carotid intima-media thickness (CCA-IMT) could be used for peri-operative and long-term risk stratification in candidates for coronary artery bypass grafting (CABG).
Methods: We prospectively enrolled 609 patients (66.8 ± 9.2 years) for preoperative CCA-IMT measurement and follow-up. The primary end-point combined long-term cardiovascular death, non-fatal acute coronary syndromes, stroke, secondary coronary revascularization and peripheral arterial surgery. The secondary end-point was the 1-month post-operative death. Univariate and multivariate analysis were performed by usual methods.
Results: A subgroup of 150 patients (24.6%) was individualized with a CCA-IMT above 90th percentile (>0.90 mm) or presenting plaques in their CCA. At one month, there was no significant difference in the prevalence of elevated CCA-IMT between deceased patients and survivors (16.7% vs 24.9%, p=ns). During a mean follow-up of 41.8 ± 16 months, 121 patients (19.8%) met the primary endpoint. High CCA-IMT was predictive (OR=1.67, 95%CI 1.14 – 2.46, p=0.009) in the univariate analysis (figure). In the multivariate analysis, age (OR=1.03, 95%CI 1.00-1.05, p=0.029) concomitant valvular surgery (OR=2.17, p=0.003) arrhythmia (OR=2.20, p=0.021), and peripheral arterial disease (OR=2.41, p<0.001) were significant independent prognostic factors whereas CCA-IMT failed to remain independently significant.



Kaplan-Meier actuarial survival

Conclusions: Pre-operative CCA-IMT provides prognostic information for candidates to CABG. However clinical data present stronger prognostic values.

P3131 A comparison of complete and incomplete revascularisation in angioplasty and surgery during five years of follow up in CAD patients in MASS II (The medicine, angioplasty or surgery study) trial

A.F. Gois[1], J. Borges[2], N.H.M. Lopes[2], B.A. Gersh[3], W.A. Hueb[2], L.B. Puig[4], S.A. Oliveira[4], J.A.F. Ramires[5]. [1]*Sao Paulo, Brazil;* [2]*Heart Institute - InCor, Chronic Coronary Disease, Sao Paulo, Brazil;* [3]*Mayo Clinic, Cardiovascular Division, Rochester, United States of America;* [4]*Heart Institute - InCor, Cardiovascular Surgery, Sao Paulo, Brazil;* [5]*Heart Institute - InCor, Sao Paulo, Brazil*

Background: Completeness of revascularization has been shown to improve short and midterm outcome. However, the widespread use of angioplasty has minimized the importance of such approach. The aim of this study was to assess the independent contribution of completeness revascularization to longterm outcome in patient with CAD and preserved left ventricular function
Methods: From the MASS II study, a randomized trial comparing treatment for individuals with CAD and preserved ventricular function, we analyzed 391 patients during five years of follow up. Off all patients, 193 were randomized to PCI and 198 to CABG, based on intention to treat principle. The primary end point was considered as the composite events: cardiac related death, myocardial infarction and unstable angina requiring revascularization.
Results: The two groups had similar clinical characteristics. Of all patients, 227 had complete revascularization and 164 had incomplete revascularization. The composite event free probability rates were: 77.9% for complete and 71.3% for incomplete revascularization (p=0.134).The mortality rate was 10.37% and 12.20% for complete and incomplete revascularization, respectively (p=0.016)
Conclusion: In the MASS II trial, incomplete revascularization was associated with similar outcome compared to complete revascularization, when we analyze mortality and primary end points during five years follow up.

e-POSTER SESSION 8

MODERATED e-POSTERS:
NEW ULTRASOUND TECHNIQUES

P3132 Intracardiac echocardiographic guidance in transcatheter closure of patent foramen ovale: a feasibility study

G. Girod, J.M. Meier, A. Delabays, E. Eeckhout. *CHUV, Dépt. Médecine, Div. Cardiologie, Lausanne, Switzerland*

Background: Transoesophageal echocardiography (TEE) has been successfully used for guiding transcatheter device closure of atrial septal defect and patent foramen ovale (PFO). However, the use of TEE for device closure requires general anesthesia. Experience with intracardiac echocardiography (ICE) guidance to perform PFO closure is limited so far.
Methods: We prospectively collected data of 81 consecutive patients (F: 43%, age: 27-73 y.) referred for percutaneous closure of PFO after cryptogenic stroke (78%), transient ischaemic attack (18%), paradoxical embolism (2%) or platypnea-orthodeoxia syndrome (2%). All pts underwent trans-thoracic (TTE) and TEE during work-up. Interatrial septal aneurysm (> 11 mm excursion in TM mode) was present in 72% of the pts. PFO closure with PFO-Star in the 22 first pts (Cardiac Inc, Burnsville, MN) and Starflex occluder in 59 pts (NMT Medical Inc, Boston, MA) was achieved under fluoroscopy and systematic TEE control (62 first pts) or intra-cardiac ultrasound AcuNav catheter (Acuson-Siemens Co, Mountain View, CA) in the last 19 pts.
Results: All pts had successful device placement. The pts with TEE guidance necessitated all general anesthesia, whereas pts with ICE were all awake. TEE guided device implantation revealed 1 partial expansion of the device at the wrong side of the septum in 1 pt, and motivated device's withdrawal in order to change its size in 3 pts. ICE provided adequate views of the PFO and surrounding structures and the various stages of device deployment. There was no complication related to the use of AcuNav catheter, and adequate evaluation of the size and deployment of the device was achieved in all pts. The median fluoroscopy time for pts with TEE guidance was 9.8 minutes (range 3.3-20 min.) and 9.2 minutes (range 5-21 min.) for pts with ICE guidance (NS). Mean in hospital stay was 1 day less in the ICE group of pts than in the TEE group, thanks to the absence of general anesthesia.
Conclusion: ICE provides excellent images of the PFO and surrounding structures and is a safe alternative to TEE-guided percutaneous PFO closure. ICE improves the safety of this percutaneous technique, without the disagreement and risk of general anesthesia required by TEE guidance. Finally, it tends to reduce in hospital stay.

P3133 Two-Dimensional Strain Imaging – a new method for angle independent quantification of myocardial deformation

C. Rost[1], B. Stolle[1], G. Wasmeier[1], F.A. Flachskampf[1], W.G. Daniel[1], J.U. Voigt[2]. *[1]University Erlangen, Medical Clinic II, Erlangen, Germany; [2]University Erlangen, Medical Clinic II, Erlangen, Germany*

Background: Conventional tissue Doppler (TD) based echocardiographic assessment of myocardial velocity and deformation is angle dependent. New algorithms are based on frame-by-frame grey-scale 2D image analysis (2DA) and, thus, allow to measure motion and deformation in any given direction within the image. In this study we validated such a new algorithm against conventional Doppler measurements.
Methods: In 15 consecutive patients we acquired simultaneously tissue Doppler and grey scale data from the parasternal long axis (PLAX) and apical 3 chamber views (3CH) (TVI-mode, Vivid 7, GE Vingmed, Norway). Only data from the basal posterior segment in both PLAX and 3CH were evaluated. Longitudinal myocardial systolic and diastolic velocities and over all segmental strain during the cardiac cycle were obtained by TD in 3CH and by 2DA in PLAX and 3CH (EchoPac, GE Vingmed, Norway). Radial parameters were measured by TD in PLAX and by 2DA in PLAX and 3CH.
Longitudinal and radial measurements in 2DA were compared between PLAX and 3CH acquisitions and against conventional TD.
Results: Velocity data from TD and 2DA analysis showed a good correlation for transversal (PLAX r=0.95, 3CH r=0.84, both $p<0.01$) and longitudinal (PLAX r=0.77, 3CH r=0.91, both $p<0.01$) measurements. In Bland-Altmann analysis, 2DA values tended to be lower than TD measurements (bias -0.2 to -0.4). Comparison of 2DA data from PLAX and 3CH showed an excellent concordance (r=0.87, $p<0.01$, bias +0.06). 2DA Strain data also correlated well with TD based measurements (r=0.77 to 0.92, $p<0.01$, bias -0.2 to -0.3). Correlation among strain measurements in 3CH and PLAX was good (r=0.79, $p<0.01$, bias +0.08).
Conclusion: Velocity and deformation measurement results based on 2D image analysis are comparable to conventional Doppler based data, however, tend towards lower absolute values, particularly in hard to scan patients. 2DA measurements directed parallel to the ultrasound beam were more robust than those perpendicular to it. We conclude, that the new method of velocity and deformation measurements by analysis of 2D images is feasible and, with further improvement, may be used for myocardial function assessment by echocardiography.

P3134 Levosimendan echocardiography: a novel test for assessing left ventricular contractile reserve in patients with heart failure

C. Cianfrocca[1], F. Pelliccia[2], V. Pasceri[1], A. Auriti[1], C. Pristipino[1], S. Ficili[1], G. Richichi[1], M. Santini[1]. *[1]San Filippo Neri Hospital, Cardiology, Rome, Italy; [2]Roma, Italy*

The assessment of contractile reserve is crucial to improve risk characterisation in heart failure. Dobutamine stress echocardiography is commonly used to this end although its clinical value is limited by the widespread use of beta-blockers and the frequent side effects. Levosimendan is a new calcium-sensitizing agent with positive inotropic and vasodilatory effects which does not cause adrenergic stimulation.
Aim: To ascertain if levosimendan compares favorably with conventional dobutamine echocardiography in evaluating LV contractile reserve in patients with heart faillure
Methods: We studied 12 patients (6 males, age: 60±8 yrs) with LV ejection fraction<30%. Treatment included digoxin (7 patients), beta-blockers (10 patients), ACE-inhibitors (8 patients) and diuretics (9 patients). All patients underwent echocardiography either on dobutamine (5 and 10 mg/kg/min by 5 min intervals) or on levosimendan (24 mg/kg/min in 10 min), one-day apart. Along with measurements in LV ejection fraction, we recorded Doppler tissue imaging velocities in 5 different LV regions as well as transmitral LV filling velocities.
Results: LV ejection fraction was identical at baseline before starting dobutamine or levosimendan infusion (26±12% and 25±15%, NS). At peak stress, conversely, LV ejection fraction was slightly higher with levosimendan than with dobutamine (41±19% vs 35±18%, p=0.07). Similarly, LV regional velocities measured using Doppler tissue imaging and transmitral LV filling velocities increased more with levosimendan than with dobutamine. Identification of contractile reserve by levosimendan was concordant with dobutamine in 8/12 patients. In 2 patients, an increase in LV ejection fraction>10% was detected with levosimendan but was not seen with dobutamine, while 2 patients had an ejection fraction increase>10% with levosimendan but did not tolerate dobutamine because of palpitation. Duration of stress echocardiographic examinations was similar with levosimendan and dobutamine (20±5 vs 23±6 min, NS). At 10 mg/kg/min doses of dobutamine, heart rate and systolic blood pressure were higher than at peak levosimendan. Significant side effects on drug infusion or at the recovery occurred with dobutamine only (i.e. ventricular ectopic beats in 3 patients and headache in 1 patient), but were not observed with levosimendan.
Conclusion: Levosimendan echocardiography is a novel stress test for identification of contractile reserve in patients with heart failure whose feasibility, safety and diagnostic accuracy are at least similar to those of standard dobutamine echocardiography.

P3135 Coronary flow reserve detected by transthoracic echocardiography on left anterior coronary artery and right coronary: feasibility, results and clinical impact

F. Rigo[1], M. Richieri[2], S. Gherardi[3], V. Cutaia[2], P. Della Valentina[2], M. Celestre[2], C. Zussa[4]. *[1]Hospital, Umberto I Hospital, Mestre-Venice, Italy; [2]Umberto I° Hospital, Cardiology, Mestre-Venice, Italy; [3]Bufalini Hospital, Cardiology, Cesena, Italy; [4]Umberto I°, Cardiac Surgery, Mestre-Venice, Italy*

Background: Coronary flow reserve (CFR) can be measured by transthoracic echocardiography (TTE) during vasodilator stress on the mid-distal left anterior descending (LAD) artery. Recently, the investigation of the right coronary artery (RCA) has been proposed. Aim of our study was to evaluate the feasibility and clinical usefulness of the investigation of both arteries.
Methods: Starting from January 2002, 446 subjects (302 males; age=63±14 years) suspected of having coronary artery disease were evaluated by stress echocardiography. TTE (S3-S8 probe, second harmonic 3,6-7 MHz, HP 5500-7500, Philips technology). The mid-distal LAD coronary artery was imaged from a modified apical two-chamber view and the distal tract of RCA was focused by looking at the diaphragmatic left ventricular wall. The peak diastolic coronary flow velocity of each coronary artery was recorded by pulsed Doppler. CFR was calculated as the ratio of rest/peak diastolic flow velocity (0,84 mg over 10 m'). All patients underwent coronary angiography within six months.
Results: Interpretable rest-peak signals were obtained in 403/446 for LAD (92,6%) and in 306/446 (68,6%). The mean CFR value of LAD was 2,31±0,6 (range:1,1-4,9) and 2,43±0,5 (range:1.2-4,5)for RCA (p=0.16). Sensitivity, specificity and accuracy values are summarized in table. By matching patients with pathological CFR value (<2) with pts. with normal CFR(>2), we found that a close CFR value in both coronary arteries is a good predictor of microvasculature dysfunction ($p<0.001$)

	ExT	CFR-LAD	CFR-RCA
Sensitivity	61,2%	91,8%	89,3%
Specificity	62,6%	82,2%	71,6%
Positive predictive value	49,8%	85%	74,2%
Negative predictive value	61,7%	93,2%	85,2%
Accuracy	60,9%	89,9%	82,7%

Conclusion: In our experience coronary artery flow imaging and flow reserve assessment are highly feasible in LAD and reasonably good for RCA, which re-

vealed a lower sensitivity value and, in particular, less specificity. Promising clinical information is given by similar behaviour of the CFR in both coronary arteries, which, when reduced, appears to be a good marker of microvasculature dysfunction.

P3136 Modulation of caveolar trafficking of endothelial cells by diagnostic cardiac ultrasound

V. Lionetti[1], A. Fittipaldi[2], F.A. Recchia[1], M. Giacca[2], E. Picano[3]. *[1]Scuola Sant'Anna, Pisa, Italy; [2]Scuola Normale, Pisa, Italy; [3]CNR Institute of Clinical Physiology, Pisa, Italy*

Background: Diagnostic ultrasound (US) is reported to increase intracellular oxidative stress in vitro. However, it remains unclear how ultrasound mechanical energy is transduced to ROS production. Caveolae are small flask-shaped invaginations in the plasma membrane involved in signal transduction and the intracellular transportation of lipid raft-associated molecules. It has been recently demonstrated that oxidative stress modulates endothelial function by regulating caveolae formation.
Aim: to investigate in vitro the effects of diagnostic cardiac ultrasound on the modulation of caveolar trafficking in human endothelial cells.
Methods: As a specific marker of caveolar trafficking we used the basic domain of HIV-1 Tat protein, which is known to be internalized only by caveolar vescicles. Human umbilical vein endothelial cells (HUVEC) were cultured in an appropriate medium and incubated for 90 minutes, before being exposed to ultrasound, with 2μg/ml HIV-1 Tat basic domain fused to the enhanced green fluorescent protein (EGFP) purified as a GST recombinant fusion protein (GST-Tat11-EGFP) or 2μg/ml GST-EGFP recombinant fusion protein, a marker of endothelial plasma membrane integrity. Cells were analyzed by flow cytometry after sham (transducer off) exposure to ultrasound and after 5', 15' and 30' of ultrasound irradiation with 1.3 MHz cardiac portable ultrasound scanner (Philips Optigo, mechanical index 1.5).
Results: Analysis of the flow cytometry profiles and of the mean cellular fluorescence values showed a significant enhancement of GST-Tat11-EGFP cellular internalization only following 30' of ultrasound exposure ($p<0.05$ for ultrasound irradiation versus sham), but not GST-EGFP.
Conclusion: In a human endothelial cell culture diagnostic cardiac ultrasound may modulate caveolar trafficking according to the duration of ultrasound exposure, without disruption of the cell membrane integrity.

P3137 Distribution of ultrasonic radiofrequency signal within the atherosclerotic plaque discriminates lipid-rich human coronary disease

T. Tsunoda[1], H. Hara[2], R. Iijima[2], T. Yoshitama[2], M. Nakamura[2], T. Tsuji[2], R. Nakajima[2]. *[1]Toho University Ohashi Hospital, Cardiovascular Medicine, Tokyo, Japan; [2]Toho University Ohashi Hospital, Cardiovascular Medicine, Tokyo, Japan*

Background: Lipid accumulation within the coronary plaque is an important process of disease vulnerability. However, tissue characterization based on gray-scale (GS) intravascular ultrasonics (IVUS) image has large limitation inability to distinguish fibro-lipidic region. Radiofrequency (RF) signal analysis may provide more accurate information discriminating troublesome coronary plaque.
Method: We analyzed 29 zones of intermediate severity plaques in human coronaries acquired from autopsies. Blinded pathologist classified them into two histologic subgroups, no lipids (group N) and with lipids (group L). One hundred (10x10) of tiny region of interests (ROI) were placed on the targeted zone. RF signals from 50MHz transducer within each ROI were digitized at 240MHz in 12 bit resolution. Mean power of integrated backscatter (IB) amplitudes and their intra-plaque distribution were automatically calculated. Variance of IB values for all ROIs, and those with lateral and axial direction distribution were compared between the groups.
Results: Conventional GS-IVUS showed extremely low detection sensitivity (46%) for existing lipids, while high specificity (88%). Large intra-plaque variance of IB amplitudes and variance for axial direction were powerful parameters detecting lipids (Table). The cut-off value (32) of total variance could discriminate lipidic from non-lipidic plaque with high sensitivity (84.6%) and specificity (75%).

Comparison of group N and group L

	Average power (dB)	Total variance among all ROIs	Variance for lateral direction	Variance for axial direction
Group N	30.4±6.9	27.8	7.7	7.8
Group L	29.5±5.5	38.8	5.1	17.4
p value	NS	0.02	NS	0.015

Conclusions: According to coronary atheroma formation, tissue composition becomes heterogeneous and contains multi-layered lipids. Compared with conventional GS-IVUS analysis, present RF technique could portray complex histologic architecture and detect early stage of lipidic plaques more accurately.

CELL THERAPY IN ISCHAEMIC HEART DISEASE: ANGIOGENESIS AND MYOGENESIS

P3138 Mesenchymal stem cells from adult adipose tissue with the potency of myogenesis and cardiovascular tissue repair

R. Madonna[1], J. Willerson[1], Y. Geng[2]. *[1]University of Texas Houston Medical School, Internal Medicine, Houston, United States of America; [2]University of Texas Houston Medical School, Internal Medicine, Houston, United States of America*

Background: Recent studies have shown evidence that the stromal compartment of adipose tissue contains multipotent stem cells that are capable of developing into myogenic cells in culture.
Aim: To test the potential of adipose tissue-derived mesenchymal stem cells (MSCs) to develop into myogenic cells and promotes myocardial repair.
Methods and Results: MSCs were isolated and cultured from adult porcine adipose tissue by enzymatic digestion. Markers for cardiac myogenesis and cellular survival were analyzed by immunocytochemistry and immunoblotting. In primary cultures with cardiomyogenic media for 15-20 days, MSCs formed colonies and expressed myocardin-A, a key transcription cofactor for myogenic cell development, and cardiac cytoskeletal proteins, including cardiac sarcomeric actinin and myosin. For longer period of culture time, smooth muscle-specific markers, such as SM-alpha-actin, were detectable in the cultures. Similar to embryonic stem cells, MSCs from the adult adipose tissue produced high levels of telomerase and its activities, as assessed by immunoblotting, RT-PCR, and TRAP assays. Further studies with MSC transplantation into the heart with experimental infarcts created by coronary ligation demonstrated the survival, proliferation and differentiation into cardiac and vascular myocytes in the damaged myocardium. In the regions with MSC transplantation, neovascular tissue was generated and large numbers of myofibroblasts appeared with strong signals for SM-alpha-actin and cardiac actinin. Electromechanical mapping revealed significant mechanical improvement of the injected segments and elevated voltage changes in the hearts 4 weeks after MSC transplantation. Pathological examination showed reduced scar tissue and increased neovascularization. There was no major abnormality in electrophysiology in the hearts.
Conclusion: MSCs from adult adipose tissue are multipotent stem cells, which are capable of survival and differentiation into cardiac and vascular myocytes. When transplanted into the myocardium with ischemic injury, MSCs may help tissue repair and functional improvement by enhancing both cardiac and vascular myogenesis.

P3139 Human Sca-1+ cardiac progenitor cells differentiate into cardiac myocytes in vitro

M.J. Goumans[1], A. Smits[1], P. van Vliet[1], C. Seinen[1], R.J. Hassink[2], A. Brutel de la Riviere[3], P.A. Doevendans[2]. *[1]Univeristy Medical Center, Cardiology Lab. of Exp. Cardiology, Utrecht, Netherlands; [2]Heart Lung Center Utrecht, Cardiology, Utrecht, Netherlands; [3]Heart Lung Center Utrecht, Cardiothoracic Surgery, Utrecht, Netherlands*

Background: A population of cardiac stem or progenitor cells has been identified in human hearts. Although the existence of primitive cells in the heart has been recently reported, there is little information about the characterization of cardiac progenitor cells (CPCs). The aim of this study was to isolate CPCs from human hearts and elucidate the differentiating capacity of CPCs into cardiomyocytes.
Methods: Human foetal hearts and biopsies from patients undergoing coronary artery bypass surgery were used as the source. Sca-1+ cells were purified from small cell population (diameter < 70 um) of enzymatically disaggregated hearts. To induce differentiation, the isolated cells were cultured in different cardiogenic media and differentiation towards cardiac muscle-like cells was determined by expression of cardiomyocyte-specific markers from 2 weeks after induction, by RT-PCR and immunofluorescent staining against cardiac markers like troponin I, tropomyosin, and sarcomeric a-actinin.
Results: We isolated a progenitor stem cell population from both foetal and human hearts, expressing several stem cell markers that are CD34-, CD45-, Sca-1+, CD105+, CD107low and Isl-1+. They also express the early cardiac transcription factors Gata-4 and Nkx2.5. When CPCs were cultured they gradually lost the expression of Sca-1 and CD107 over time. Treatment with 5-Azacytidine or oxytocin for 4 weeks resulted in the differentiation of a percentage of the CPCs into spontaneously beating cells in which cross striations were observed and the expression of the cardiomyocyte markers ?-actinin and troponin-I. We examined the gene expression of cardiac transcriptional factors in CPCs by RT-PCR. Two weeks after treatment, cardiac transcription factors such as MEF2c were expressed, while Isl-1 expression was no longer present. When grown in endothelial differentiation medium, CPCs were able to differentiate into endothelial cells.
Conclusion: The human heart harbours a population of cardiac progenitor cells. These cells are capable of differentiating towards a cardiomyocyte phenotype in vitro, and may be able to regenerate damaged hearts.

P3140 Stem cell transplantation enhances functional and myocardial remodelling of cardiomyocytes in chronic non-ischaemic heart disease

J. Garbade[1], A. Schubert[2], C. Lipinski[2], H. Aupperle[3], T. Walther[2], J.F. Gummert[2], S. Dhein[2], F.W. Mohr[2]. *[1]Herzzentrum Leipzig, Heartsurgery, Leipzig, Germany; [2]Herzzentrum Leipzig, Heartsurgery, Leipzig, Germany; [3]University of Leipzig, Vet. Pathology, Leipzig, Germany*

Objective: Recent studies have suggested the ability of bone marrow cells (BMCs) to enhance cardiac function in acute and chronic ischemic heart disease, but its effect in non-ischemic cardiomyopathy is still unknown. This study evaluates the hypothesis that epimyocardial application of autologous BMCs in doxorubicin-induced cardiomyopathy improve contractility and induce myocardial regeneration.
Methods: Heart failure was induced in White New Zealand rabbits by injection of doxorubicin (3mg/kg weekly for 6 weeks). They were divided into 4 groups: transplant group (Tx, 1.5-2.0x10^6 BMC, n=15), control group (DoxM, medium injection, n=10), healthy group (n=10) and diseased group (without therapy, n=6). Cells were isolated by bone marrow aspiration and labelled with fluorescent dye Vybrant/DiI prior to transplantation. Cardiac function using conductance method, 256-channel mapping and immunohistochemical studies were carried out. Additionally, cell proliferation (Ki67) and apoptosis (Bax, p53, Bcl-family) were investigated four weeks after transplantation.
Results: Both, the maximum dP/dt (2115.25±203.74 vs. 1434.63±195.25 mmHg/s, Mean±SEM, p=0.03) and minimum dP/dt (-1481.0±161.27 vs. -1021.36±114.69 mmHg/s, Mean±SEM, p=0.029) were improved in cell-treated group vs. DoxM-group. This was associated with a lower isovolumetric relaxation-time, with a sharper slope of the left ventricular developed pressure-volume-curve and a reduced slope of the end-diastolic pressure-volume-relation in the Tx-group. A 256-channel mapping revealed no arrythmogenic focus due to cell-injection. On histology, engrafted cells were found in all treated animals. Few BMCs stained positiv for cardiospecific markers: troponin I, a-actinin and connexin43. A higher fraction of Ki67 positive cardiomyocytes was noted in cell-treated hearts. Pro-apoptotic makers Bax and p53 were decreased and antiapoptotic Bcl-family was increased in Tx-group.
Conclusion: Autologous BMC transplantation improves heart function and restores the myocardial reconstitution in doxorubicin-induced cardiomyopathy. Transdifferentiation, induction of cardiomyocyte proliferation and reduced apoptosis are involved, but the dominant process responsible for myocardial revival is unclear

P3141 Adeno Cyr-61 enhances angiogenesis in a porcine model of chronic myocardial ischaemia

E. Teiger[1], S. Champagne[1], J. Su[2], F. Rouzet[3], R. Bazeli[3], D. Le Guludec[3], L. Hittinger[2], P. Merlet[3]. *[1]Hopital Henri Mondor, Unite de Cardiologie Interventionnelle, Creteil, France; [2]Inserm, U660, Créteil, France; [3]University hospital Bichat, Nuclear Medecine, Paris, France*

Background: Cyr61 (CCN1) is an immediate early gene encoding a cystein-rich heparin-binding protein that is associated with extracellular matrix and cell surface, and has been demonstrated to be a potent proangiogenic factor in vitro and in vivo in the rabbit ischemic hindlimb model. No data are available on the in vivo efficacity of Cyr61 genetherapy on a model of chronic myocardial ischemia.
Goal: This study aimed to evaluate in vivo the angiogenic effect of direct intramyocardial human Cyr61 transfer in an adenoviral context, in a porcine model of chronic myocardial ischemia.
Method: For this purpose, 14 swines underwent placement of an ameroid constrictor around the left circumflex coronary artery and, after randomization, these animals were separated in 2 groups which received epicardial injections of 5*108 infectious units of an adenovirus carrying either the Cyr61 gene (Ad-Cyr61) or no transgene (Ad-null). Myocardialperfusion was assessed 4 weeks later using sestamibi-Tc 99m SPECT imaging at stress (rapid cardiac pacing, 200 b/min) and at rest. Two observers, unaware of the therapeutic status of the pigs, measured semi-quantitatively the importance of abnormalities of myocardial perfusion. They estimated on the Bull's eye images the extent (E, in % of the global surface) and the degree (I, difference in intensity between the mean value obtained in the normal areas of the myocardium and the mean value obtained in the defect, expressed in %) of the ischemic defect.
Results: In the Ad-Cyr61 group the ischemic defect measured on the myocardial SPECT perfusion images was much more smaller and less important than that found in the Ad-null group: for E (4.4±9.8 in Ad-Cyr61 vs. 24±19.3% in Ad-null, P=0.02) and for I (12.8±28.6 in Ad-Cyr61 vs.75.2±9.4% in Ad-null, P=0.02).
Conclusion: Cyr61 gene transfer appears potent in stimulation myocardial angiogenesis, thereby promoting great improvement in tissue perfusion in the ischemic myocardium as assessed by myocardial perfusion SPECT imaging. These findings suggest that Cyr61 could be a therapeutic candidate for treating severe myocardial ischemic disease.

P3142 Dose-dependent contribution of CD34-positive cell transplantation to concurrent vasculogenesis and cardiomyogenesis for functional regenerative recovery post myocardial infarction

H. Iwasaki[1], A. Kawamoto[2], M. Ishikawa[2], A. Oyamada[1], S. Suehiro[3], T. Asahara[2]. *[1]Riken Kobe Institute CDB, Stem cell translational research, Kobe, Japan; [2]Institute of Biomedical Research, Regenerative Medicine, Kobe, Japan; [3]Osaka City University Graduate School, Cardiovascular surgery, Osaka, Japan*

Multi-lineage developmental capacity of the CD34+ cells, especially into cardiomyocytes (CMCs) and smooth muscle cells (SMCs), is still controversial.
Aim: we performed a series of experiments to prove our hypothesis that vasculogenesis and cardiomyogenesis post myocardial infarction (MI) may be dose-dependently enhanced following CD34+ cell transplantation.
Methods: Peripheral blood CD34+ cells were isolated from total mononuclear cells of a patient with limb ischemia by apheresis after 5-day administration of G-CSF. PBS, 1x10e3 (Low), 1x10e5 (Mid) or 5x10e5 (High) CD34+ cells were intramyocardially transplanted after ligating LAD of nude rats (n=12 in each group). Functional, histological and gene expression outcomes were compared among the groups.
Results: Functional assessments using echocardiography and a micro-tip conductance catheter at day 28 revealed dose-dependent preservation of LV function by CD34+ cell transplantation. Necropsy examination also disclosed dose-dependent augmentation of capillary density and dose-dependent inhibition of LV fibrosis (% fibrosis area: High, 16.0±2.6; Mid, 22.4±1.9; Low, 30.7±3.9; PBS, 31.5±0.7%, respectively. $P<0.01$ for High vs Mid and Mid vs Low). Immunohistochemistry for human-specific brain natriuretic peptide (BNP) demonstrated that human CMCs were dose-dependently observed in ischemic myocardium at day 28 (High, 2480±149; Mid, 1860±141; Low, 423±9; PBS, 0±0/mm^2, respectively. $P<0.05$ for High vs Mid and Mid vs Low). Immunostaining for smooth muscle actin (SMA) and human leukocyte antigen or Ulex europaeus lectin type 1 also revealed dose-dependent vasculogenesis by human endothelial cell (EC) and human SMC development following CD34+ cell transplantation (SMC: High, 895±95; Mid, 180±11; Low, 0±0; PBS, 0±0/mm^2, respectively. $P<0.01$ for High vs Mid and Mid vs Low) (EC: High, 3373±363; Mid, 980±211; Low, 226±35; PBS, 0±0/mm^2,respectively. $P<0.05$ for High vs Mid and Mid vs Low). RT-PCR indicated that human specific gene expression of CMC (BNP, cardiac troponin-I, myosin heavy chain and Nkx2.5), SMC (SMA and sm22alpha) and EC markers were dose-dependently augmented in MI tissue.
Conclusion: The collaborative multi-lineage differentiation potential of CD34+ cells into not only EC but CMCs and SMCs was enhanced by cell dose escalation, and conduced to heart regeneration in terms of the functional and histological recovery through vasculogenesis and cardiomyogenesis.

P3143 Synergy between cellular cardiomyoplasty and cardiac angiogenesis for treatment of myocardial infarction

L. Ye[1], K.H. Haider[2], S.J. Jiang[2], R.S. Tan[3], R.W. Ge[4], P.K. Law[5], S. Aziz[6], E.K.W. Sim[1]. *[1]National University of Singapore, Surgery, Singapore, Singapore; [2]University of Cincinnati, Department of Pathology, Cincinnati, United States of America; [3]National Heart Center, Department of Cardiology, Singapore, Singapore; [4]National University of Singapore, Department of Biological Sciences, Singapore, Singapore; [5]Cell Transplants Singapore Pte Ltd, Singapore, Singapore; [6]Washington Adventist Hospital, Washington, United States of America*

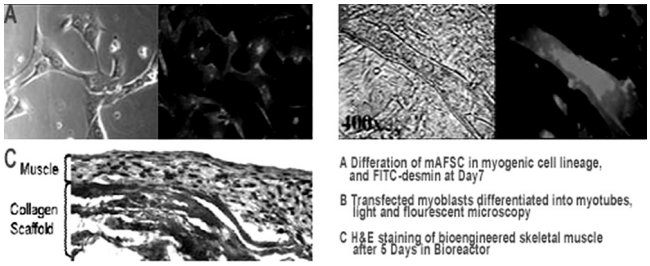
Introduction: Recently, angiopoietin-1 (Ang-1) has been seen as a new and promise angiogenic factor for therapeutic angiogenesis. We compared the effectiveness of only Ang-1 with Ang-1+VEGF165 delivery for therapeutic angiogenesis through skeletal myoblasts.
Methods: Human skeletal myoblasts carrying Lac-z gene were transduced with adenoviral bicistronic vectors carrying only Ang-1 (Ad-Ang-1) or Ang-1+VEGF165 (Ad-Bic). Myocardial infarction was created in pigs by coronary artery ligation and grouped as DMEM injected (group-1 n= 6), null adenoviral vector transduced myoblast transplanted (group-2 n= 5), myoblast carrying Ang-1 transplanted (group-3 n=6) and myoblasts carrying Ang-1+VEGF165 transplanted (group-4 n=7). After 3-weeks, 5ml DMEM with or without 3x10^8 cells were intramyocardially transplanted. Animals were immunosuppressed for 6-weeks using Cyclosporine-A. Pigs were euthanized and hearts were explanted at 6-weeks post-treatment and processed for histological studies.
Results: Transduced myobalsts efficiently secreted VEGF165 and/or Ang-1 as revealed by dual fluorescent immunostaining and RT-PCR. Extensive survival of the Lac-z expression skeletal myoblasts was observed in pig heart. Average vascular density at low power field (x100) by double immunofluorescent staining for vWFactor-VIII and smooth muscle actin in group-4 (45.2±2.95; 38.6±2.13) and group-3 (39.3±3.09; 34.7±2.52) was significantly higher than group-1 (16.18±0.91, $p<0.05$; 7.88±0.52, $p<0.05$) and group-2 (26.57±2.09, $p<0.05$; 20.14±1.68, $p<0.05$) at 6-weeks post-treatment. Mature blood vessel count and regional blood flow in group-4 was the highest (86.33% and 2.91 ml/min/g), followed by group-3 (85.26±2.86%; 2.73±0.03ml/min/g) as compared with other two groups. Significantly improved EF was achieved by group-3 (49.22± 5.92%,

p=0.037) and group-4 (50.5%, p=0.015) as compared with group-1 and -2. There was no significant difference was achieved between group-3 and group-4.
Conclusion: Ang-1 delivered by skeletal myoblasts can achieve the same effectiveness for therapeutic angiogenesis as simultaneous delivery of Ang-1+VEGF165 via skeletal myoblasts for cardiac repair.

P3144 Cellular and angiogenesis therapy for congenital heart disease

S. Neshat Vahid, A. Milanessi, G. Christ, A. Atala, S. Soker.
Wake Forest University Health Sciences, Institute for Regenerative Medicine, Winston-Salem, United States of America

In this study we investigated the feasibility of cell therapy for myocardial diseases using mouse amniotic fluid-derived cells (mAFSC). Mouse amniotic fluid was collected at E11.5 and a subpopulation of cells was isolated based on expression of stem cell markers. To induce differentiation we treated the cells with 5-azacytidine. We further infected the cells with adenoviral vector encoding for human VEGF165 (Ad-VEGF). RT-PCR, immunohistochemistry and Western blot analyses were used to evaluate the phenotypic characteristics of the cardiomyocyte-like cells and VEGF-expression. Finally, the cardiomyocyte-like cells were seeded on collagen sheets and placed in a bioreactor system with cyclic strain stimulation mimicking the wall motion of the heart muscle, in order to promote maturation. Stem cells were successfully isolated from mouse amniotic fluid and were positive for alkaline phosphatase, Thy-1 and OCT4. Within 2 weeks in cardiomyocyte inducing medium, they expressed cardiac specific markers. RT-PCR analysis showed expression of transcription factors involved in fetal ventricular cardiomyocyte development (Nkx 2.5, GATA 4, MEF-2C). MAFSC infected with Ad-VEGF165 expressed VEGF. The bioengineered cardiac muscle tissue, retrieved from the bioreactor, showed adequate contractility and appropriate response to cardio-active pharmacological agents in organ bath studies.



Differentiation of mAFSC

In this study, we demonstrated that mAFSC can be differentiated into a cardiomyogenic lineage and can be genetically modified to express angiogenic growth factor. The stimulated release of VEGF will increase cardiac tissue perfusion and survival of cardiomyocytes. This is a promising approach of cell therapy for the treatment of variety of cardiac diseases such as congenital hypertrophic cardiomyopathy.

P3145 Tacrolimus seem to inhibit discordant xenorejection of human embryonic stem cells: a study in the human-to-pig model

K.H. Grinnemo[1], A. Mansson-Broberg[2], X. Hao[2], A.J. Siddiqui[2], O. Hovatta[2], C. Sylven[2], M. Corbascio[2], G. Dellgren[2]. *[1]Huddinge University Hospital, Cardiothoracic surgery, Stockholm, Sweden; [2]Stockholm, Sweden*

Objective: To be able to use human embryonic stem cells (hESCs) for cardiomyoplasty, it is important to circumvent the anticipated immune response. In this study we transplanted hESCs to pig myocardium and studied the immune response as well as the survival of the stem cells.
Methods: hESCs were injected through a left thoracotomy into the anterolateral wall of the left ventricle of domestic mini-pigs (25 kg). The stem cells were injected together with microcarriers (Microsphers S) to simplify the tracing of the injection area. The pigs were randomised to immunosuppression with Tacrolimus given daily po or without. We aimed towards a concentration of Tacrolimus of 5-10 ng/ml. The pigs were euthanized during a follow-up period of 2 weeks. The hearts were freeze-sectioned and the stem cells were identified by fluorescence in situ hybridisation (FISH). The immune response was studied using Htx/eos and antibodies towards macrophages.
Results: The hESCs could only be identified in the hearts where we have used immunosuppression. The stem cells seemed to have migrated from the injection area, marked with microcarriers, into the surrounding myocardium. In the group not treated with Tacrolimus, no hESCs were identified and there was a massive infiltration of macrophages in the area were cells had been injected.
Conclusion: Survival of hESCs was only observed when immunosuppression was used in this discordant xenotransplantation model. A xenorejection seems to have occurred in non-immunosuppressed animals, supported by the evidence of massive infiltration of macrophages surrounding the transplanted hESCs. Tacrolimus seem to inhibit the xenorejection of hESCs in the human-to-pig xenomodel although the number of surviving hESCs was low.

P3146 Survival and organ distribution of mononuclear and mesenchymal bone marrow cells after transplantation in acute and chronic myocardial infarction in rats

J. Mueller-Ehmsen[1], B. Krausgrill[2], K. Schenk[2], V. Burst[3], J.W. Fries[4], J. Hescheler[5], R.H.G. Schwinger[2]. *[1]University of Cologne, Dept. of Internal Medicine III, Koeln, Germany; [2]University of Cologne, Dept. of Internal Medicine III, Cologne, Germany; [3]University of Cologne, Dept. of Internal Medicine IV, Cologne, Germany; [4]University of Cologne, Dept. of Pathology, Cologne, Germany; [5]University of Cologne, Inst. of Neurophysiology, Cologne, Germany*

Transplantation of autologous bone marrow cells is a promising new therapeutic option after myocardial infarction (MI). Here, we determined in rats the survival and organ distribution of transplanted cells, and their dependence on cell type, cell number and time of application.
Mononuclear (MNC) or mesenchymal (MSC) bone marrow cells (male Fischer 344 rats) were injected into the border zone of MI (syngeneic females) immediately or 7 days after LAD ligation (10^5 or 10^6 cells in 3x17 μl). After 0h, 48h, 5d, 3wk and 6wk, DNA of heart, lung, liver, spleen, kidney, blood, bone marrow, brain and skeletal muscle was isolated and the number of male donor-cells determined (real-time PCR, Y-chromosome).
The percentage of surviving donor-cells in the heart decreased rapidly from 34-80% of injected cells (0h) to 0.3-3.5% (6 wks) independent from cell type, number and application time (table). The absolute number of surviving cells increased about 10-fold after increasing injected cell number (10^6 vs. 10^5). Early after injection, a significant number of MNC and MSC were found in the lungs (126±48 and 140±3 per million cells), whereas only few or none were found in all other organs. At later times only few cells were detectable in the lungs, but the number of MNC (not MSC) in the spleen increased up to 603±173 cells per million (6 wks, few or no cells in all other organs).

Heart: detected cells in % grafted

	0 h	48 h	5 d	3 wks	6 wks
MNC 10^5	34.1±9.9**	4.9±2.0**	3.3±1.7#	2.5±1.0	1.5±0.6
MSC 10^5	80.1±24.5	46.0±10.2	23.7±7.4	3.3±1.0	2.0±0.8
MNC 10^6	–	5.6±0.6	6.8±2.2	1.6±0.9	1.2±0.6
MSC 10^6	–	21.2±4.8	10.0±3.3	4.7±1.8	3.5±1.2
MNC 10^6, late	–	8.0±3.4	11.6±5.7	4.1±1.2	0.3±0.1
MSC 10^6, late	–	27.6±8.3	4.6±3.9	1.5±0.6	2.2±1.1

All n=4-5; late: injection time 7 d after infarction. **P<0.01, #P=0.06 vs. MSC 10^5.

Although, the absolute number of persistent cells in the heart can be increased by increasing cell number, the percentage of overall mid-term survival and persistence remains low independent from cell type, number and time of application. Few cells can be detected in other organs, but MNC seem to proliferate in the spleen. The low survival of grafted cells may limit their therapeutic impact.

P3147 Safety and potential efficacy of granulocyte-colony stimulating factor in the acute myocardial infarction (the Rigenera study)

A.M. Leone[1], B. Garramone[2], M.B. Giannico[2], S. Brugaletta[2], A. Giordano[3], L.M. Biasucci[2], A.G. Rebuzzi[2], F. Crea[2]. *[1]Università Cattolica del Sacro Cuore, Medicina Cardiovascolare, Rome, Italy; [2]Istituto di Cardiologia, Roma, Italy; [3]Istituto di Medicina Nucleare, Rome, Italy*

Background: Intracoronary administration of bone marrow stem cells (BMSC) appear to improve post-infarction myocardial function. Nevertheless this invasive approach is not widely applicable. The Granulocyte-Colony Stimulating Factor (G-CSF) could improve post infarction myocardial function through mobilization of BMSC into peripheral blood.
Methods: in a open label study 10 patients with a first large anterior acute MI and a LVEF <45% 5 days after a successful primary angioplasty received G-CSF for 5 days. Myocardial perfusion and function was assessed by Gated-SPECT prior to G-CSF administration and 3 and 6 months after the acute event. Repeat coronary angiography was performed at 6 months. Circulating CD34+ cells, markers of thrombosis (platelet/monocyte aggregates and D-dimers) and of inflammation (C-reactive protein and IL-6) were measured at baseline and 5 and 10 days after starting G-CSF.
Results: CD34+ cell count increased from 5.68±3.47 to 45.46±29.79 cells/μl (p=0.004) while platelet/monocyte aggregates, D-dimers, C-reactive protein and IL-6 did not change significantly. At 3 months LVEF from 31±10 to 37±9% (p<0.05) and summed perfusion score decreased from 30±6 to 17±7 (p=0.002). At 6 months LV function and perfusion did not show further changes. Two patients had in-stent restenosis at coronary angiography at 6 months.
Conclusions: G-CSF therapy in patients with large anterior AMI is safe and well-tolerated and might improve post-infarction myocardial function and perfusion.

P3148 Intracoronary transplantation of circulating progenitor cells after recanalisation of chronic coronary artery occlusions: impact on coronary vasomotion and left ventricular remodelling

S. Erbs[1], V. Adams[2], H. Thiele[2], F. Emmrich[3], R. Kluge[4], K. Kendziorra[4], G. Schuler[2], R. Hambrecht[2]. [1]*University of Leipzig - Heart Center, Department of Cardiology, Leipzig, Germany;* [2]*University of Leipzig - Heart Center, Department of Cardiology, Leipzig, Germany;* [3]*University of Leipzig, Institute of Immunology, Leipzig, Germany;* [4]*University of Leipzig, Department of Nuclear Medicine, Leipzig, Germany*

Background: Several clinical studies have convincingly demonstrated that transplantation of blood-derived circulating progenitor cells (CPC) augments left ventricular regeneration after acute myocardial infarction. It is unknown, however, whether CPC transplantation exerts beneficial effects also in patients (pts) with chronic myocardial ischemia. Therefore, it was the aim of this randomised, double-blind, placebo-controlled study to evaluate the impact of an intracoronary application of CPCs on coronary vasomotion and left ventricular remodelling in pts after successful recanalization of a chronic coronary total occlusion (CTO).
Methods: Twenty-six pts (age 63±2 years, LV-EF 53±2%) were enrolled after recanalization of a CTO. They were subcutaneously injected with G-CSF (filgrastim) (10 mg/kg/d) for a period of 4 days in order to increase the number of CPCs in the peripheral blood. Mononuclear cells were isolated from 406±13 mL blood and cultured for 4 days in endothelium-specific medium to select CPCs. Ten days after recanalization, 69.6±15.5 Mio CPCs were infused into the target vessel in patients randomised to the treatment group, whereas patients in the control group (C) received intracoronary injection of serum. Immediately before CPC/serum application (B) and 3 months after recanalization endothelium-dependent vasodilation in response to acetylcholine (Ach) and coronary flow reserve (CFR) in response to adenosine (2.4 mg/min) were measured in the reopened target vessel. Left-ventricular diameter and function were assessed by magnetic resonance imaging. Myocardial metabolism was determined by FDG-PET.
Results: Intracoronary application of CPCs resulted in a significant attenuation of paradoxic vasoconstriction in response to Ach (7.2 mg/min) by -72% from –0.87±0.12 mm at B to –0.24±0.09 mm after 3 months ($p<0.01$ vs. B and C) and in an increase in CFR by 43% from 2.3 ±0.3 at B to 3.3 ±0.5 after 3 months ($p<0.01$ vs. B and C). The improvement in microvascular function was associated with a significant reduction of hibernating segments (from 3.50±0.80 at B to 2.50±0.65 at 3 months, $p<0.05$ vs. C) and an augmentation in LV-EF by 14% (from 51±4 to 59 ±3%; $p<0.05$ vs. B and C). All of the above-mentioned parameters remained unchanged in C.
Conclusion: Intracoronary transplantation of CPCs after successful recanalization of CTO improves both macro- and microvascular function, which leads to the recruitment of hibernating myocardium and, thereby, contributes to an increase in left-ventricular function.

P3149 Does intracoronary bone marrow cell delivery damage myocardial microcirculation?

M. Baltali[1], H. Ozdogu[2], M. Aydin[3], A.F. Yapar[3], C. Boga[2], I. Kozanoglu[2], H.T. Kiziltan[4], H. Muderrisoglu[5]. [1]*Adana, Turkey;* [2]*Baskent University, Adana, Hematology, Adana, Turkey;* [3]*Baskent University, Adana, Nucleary medicine, Adana, Turkey;* [4]*Baskent University, Adana, Cardiovascular Surgery, Adana, Turkey;* [5]*Cardiology, Baskent University, Ankara, Turkey*

Selective intracoronary delivery of autologuos bone marrow cells (BMC) represents an effective approach for the repair of infarcted myocardium. However, as shown in animal studies, BMC administration into the coronary artery may impair myocardial microcirculation.
Aim: We evaluated if defective perfusion of myocardium due to the compromise of coronary microcirculation occur in patients undergoing intracoronary BMC administration.
Methods: Our study group consisted of six stable patients (four men, mean age 59.6±10 years) with a history of myocardial infarction and subsequent revascularisation. The mean left ventricular ejection fraction was 32.2±13%. We obtained two separate scintigraphic examinations using intracoronary administration of Tc-99 macroaggregated albumin (MAA) to determine the defective myocardial perfusion due to the occlusion of coronary microvasculature. The baseline examination was performed two days before the intracoronary BMC delivery and the second examination immediately (within 10 minutes) after the procedure. A 20-segment model was used for the interpretation of scintigraphic findings. Compared with the initial findings, an additional defective tracer uptake detected by the second MAA examination was considered to be due to myocardial microvasculatory perfusion compromise which occurred during the procedure.
Results: For the intracoronary BMC delivery, 278.2±33 ml of bone marrow was aspirated from the posterior iliac crest. The final preparation of BMC contained $7.7x10^8 \pm 8.7x10^8$ nucleated cells (viability 98%). During the procedure, a mean amount of 15.8±7 ml BMC containing solution was injected during each delivery into 8 coronary arteries supplying 49 myocardial segments in total. Baseline scintigraphic evaluation using Tc-99m MAA revealed absent or reduced tracer uptake in 7 myocardial segments. Compared with the baseline findings, the second scintigraphic examination showed defective Tc-99m MAA uptake in 8 additional myocardial regions. No pathologic increase of troponin I or CK-MB levels was observed after the procedure, and the patients were discharged without major complications.
Conclusion: Our study revealed that absent or reduced myocardial Tc-99m MAA uptake may be observed after intracoronary administration of BMC, suggesting a compromise of myocardial microvasculature. However, this finding is not necessarily associated with myocardial injury, since a pathologic increase of cardiac biomarkers was not detected after the procedure.

P3150 Stem cell perfusion alters cardiac contractility in apolipoprotein-E mice: a study in the Langendorff perfusion model

Q. Zhang[1], J. Lin[2], S. Li[2], W.F. Shen[3], Y.J. Geng[2]. [1]*Shanghai Ruijin Hospital, Cardiology Department, Shanghai, China;* [2]*Texas Heart Institute, Heart Failure Research Lab, Houston, United States of America;* [3]*Shanghai Ruijin Hospital, Department of Cardiology, Shanghai, China*

Objective: Stem cell coronary delivery has been recently used for treating myocardial infarction and ischemic injury. This study was aimed at comparing the cardiac hemodynamics in the hearts of apolipoprotein-E-null (apoE-null) and wild type (WT) control mice.
Methods: Hearts isolated from apoE-/- mice (apoE group, n=9) and WT mice (WT group, n=13) were retrograde perfused on a Langendorff model. After stablization and ischemia preconditioning GFP transfected embryonic stem cells (ESC) were infused with different concentration (1 $x10^6$ cells/ml/min and 2.5 x 10^6 cells/ml/min) in both groups. Hemodynamic performance were recorded including coronary flow(CF), heart rate(HR), left ventricular peak pressure(LVP), +dp/dt max, -dp/dt max, left ventricular end diastolic pressure(LVEDP), and left ventricular developing pressure(LVDP).
Results: Both groups showed significant changes in the hemodynamic parameters when the hearts were infused with the higher doses of cells. ApoE-/- group displayed the worse outcomes, compared to the WT group (see table).

Hemodynamic alterations at 30 minutes

	ApoE group		WT group	
	1×10^6 cells/ml/min	2.5×10^6 cells/ml/min	1×10^6 cells/ml/min	2.5×10^6 cells/ml/min
CF	1.77 ±0.88	1.57 ±0.82	3.15 ± 1.33	2.08 ±0.74
HR	274 ±59	238 ±73	302 ±64	287 ±74
LVP	101.6 ±46.7	109.1 ±47.7	118.1 ±52.1	99.9 ±53.6
+dp/dt max	2421 ±1228	2336 ±999	2938 ±1532	2653 ±1649
-dp/dt max	1489 ±549	1399 ±432	1963 ±859	1659 ±802
LVEDP	16.2 ±20.3	19.0 ±21.7	8.7 ±2.1	13.0 ±14.8
LVDP	93.0 ±42.0	93.9 ±42.6	111.8 ±53.2	97.6 ±50.1

Conclusion: Intra-coronary infusion of ESC at high rates may compromise cardiac hemodynamics, especially in the artherosclerosis-prone hearts.

P3151 Regeneration of human heart function in chronic coronary heart disease with chronic myocardial infarction: controlled study with intracoronary autologous mononuclear bone marrow cell transplantation

M. Koestering[1], M. Brehm[1], T. Zeus[1], C. Antke[2], G. Koegler[3], P. Wernet[3], H.-W. Mueller[2], B.E. Strauer[1]. [1]*Cardiology, Duesseldorf, Germany;* [2]*Nuclear Medicine, University Duesseldorf, Duesseldorf, Germany;* [3]*Institute for Transplantation, University Duesseldorf, Duesseldorf, Germany*

Introduction: Remodeling of the left ventricle (LV) after myocardial infarction (MI) represents a major cause of infarct-related heart failure and death. After acute myocardial infarction transplantation of bone marrow cells (BMCs) improve cardiac function.
We investigated cardiac performance of intracoronary transplantation of autologous BMCs in patients with chronic ischemic heart disease, suffered from transmural myocardial infarction
Methods and Results: We treated 22 consecutive patients (48±13 years) with chronic myocardial infarction (5 months to 8 years old) by intracoronary transplantation of autologous bone marrow mononuclear cells (BMCs) and compared them with a consecutive enrolled representative control group (n=20, 52±10 years). After 3 months in the transplantation group, infarct size was reduced by 30%, and global left ventricular ejection fraction (+15%) as well as infarction wall movement velocity (+57%) increased significantly ($p<0.001$), while in the randomized control group no significant changes were observed during 3 months follow-up in infarct size (27±9 to 26±9%), in left ventricular ejection fraction (51±10 to 52±10%) and in wall movement velocity of infarcted area (1.88±0.76 to 1.91±0.79cm/s). PTCA alone had no effect on left ventricular function in this chronic coronary patients. After bone marrow cell transplantation, there was an improvement of maximum oxygen uptake (V=2max, +11%) and of regional 18F-Fluor-Desoxy-Glucose (FDG) uptake (PET) into infarcted tissue (+15%).
Conclusions: These results demonstrate that regeneration of infarcted and chronically avital tissue can be realized in humans by selective intracoronary bone marrow mononuclear cell transplantation. This regeneration is most probably due to neogenesis of cardiac tissue, of both myocytes and of coronary blood vessels.

P3152 Unchanged LV function, but reduced scar size in some cases after autologous bone marrow cell therapy during bypass surgery in patients with myocardial infarction

J. Mueller-Ehmsen[1], P. Tossios[2], C. Scheid[3], N. Uenal[4], M. Schmidt[5], B. Rueckriehm[6], U. Mehlhorn[2], R.H.G. Schwinger[4]. *[1]University of Cologne, Dept. of Internal Medicine III, Koeln, Germany; [2]University of Cologne, Dept. of Cardiac Surgery, Cologne, Germany; [3]University of Cologne, Dept. of Internal Medicine I, Cologne, Germany; [4]University of Cologne, Dept. of Internal Medicine III, Cologne, Germany; [5]University of Cologne, Dept. of Nuclear Medicine, Cologne, Germany; [6]University of Cologne, Dept. of Radiology, Cologne, Germany*

Cardiac cell therapy is an attractive novel strategy to support cardiac regeneration after myocardial infarction (MI). The aim of this ongoing study is to establish a hybrid intervention of isolating mononuclear bone marrow (BM) cells, aortocoronary bypass surgery (ACB) and cell injection in patients with chronic MI, and to investigate the therapeutic potential of such strategy.
18 patients with transmural scar were enrolled (63±3 years, 15 male), who underwent elective ACB-surgery 2.1±0.6 months post MI. Infarct area and hibernating myocardium were identified by Tc-99m-MIBI Single-Photon Emission Computed Tomography (SPECT) and F18-FDG-Positron-Emission-Tomography (PET). LV function was assessed by SPECT and MRT. During surgery, 10 ml of sternal BM were obtained, and mononuclear cells (MNC) were isolated. At the and of surgery MNC were injected into the the center and the border zones of the infarct (10 injections, 2 ml total volume containing 6.6±1.3 x 10^7 MNC (FACS analysis: 1.9±0.2% CD34+; 0.02±0.005% CD34+/KDR+, 0.8±0.2% CD133+ and 0.8±0.2% CD34+/CD133+). No major complications attributable to cell therapy were observed.
17 patients were evaluated at three months after cell therapy and ACB (15 male). In ergometry they performed 104±10 W for 6.2±1.4 min. without angina or ECG changes. Global LV function at rest remained unchanged (MRT, 36.7±4.5% vs. 32.1±3.1% prior to surgery, P=0.4; SPECT 41.0±3.0% vs. 39.5±2.4%, P=0.7), as well as LV function during dobutamine stress test (10μg/kg*min) (MRT, 36.2±3.8% vs.29.3±3.6%, P=0.2). In 5 of 17 patients (29%) scar size was reduced (PET, average reduction 60.0±6.1%), but also in these patients no improvement in global LV function was observed (47.8±4.5% vs. 39.4±5.7%, P=0.3). 6 months follow up is currently underway.
The results show that mononuclear cells from bone marrow can be recovered, isolated and injected during a single hybrid intervention together with ACB-surgery without additional risk for the patient. Scar size was reduced in about 30% of the patients possibly reflecting an enhanced regeneration of the infarcted tissue. Nevertheless, global LV function remained unaffected in all patients, also in those with improved vitality. Thus, the therapeutic benefit of BM cell transplantation may be limited, at least under the specific conditions of this study at 3 months follow up.

P3153 PET-evidenced homing following intracoronary transplantation of non-mobilized CD34+ blood stem cells after acute myocardial infarction

D. Blocklet, M. Toungouz, M. Lambermont, P. Unger, N. Preumont, E. Stoupel, J.P. Degaute, G. Berkenboom. *U.L.B. Hopital Erasme, Brussels, Belgium*

Several studies have shown marginal increase in left ventricular function in patients receiving autologous CD34+ stem cells after acute ST-elevation myocardial infarction (MI). The benefit of this therapy remains controversial: improved function may be related to recovery of viable myocardial cells and re-stenosis has been observed after intra-coronary (IC) administration of mobilized blood stem cells. To assess the contribution of injected stem cells to functional improvement, an essential step is to demonstrate their homing in the affected myocardial area. In the present study, we tested the feasibility of non-mobilized CD34+ blood cells collection for IC administration. We also used PET to test the myocardial homing of these cells after IC transfusion.
Methods: 6 (3 male, 3 female) patients with a first large anterior myocardial infarction (time to revascularization 25±11 h, mean±s.e.m.) and successful reperfusion (3 primary PTCA and 3 rescue PTCA) underwent a large volume cytapheresis 9±3 days after the acute event. After CD34+ selection (Isolex 300i device, Baxter), 14.9 ± 3.6 millions CD34+ were obtained. Half of them were labelled with FDG (cell viability after radiolabelling > 95%). The labelled and non-labelled cells were infused into the LAD (2 proximal, 4 middle) through the central lumen of an over-the-wire balloon catheter (placed at the stent level). After 2 hours, PET images were obtained.
Results: 6±1% of the injected radioactivity was detected within the limits of the infarcted area. At 3 months, echocardiography revealed a slight increase in left ventricular ejection fraction from 56±3% to 60±3% (NS) and a significant (P<0.05) improvement in wall motion score index from 1.64±0.12 to 1.27±0.10. At 6 months, no adverse event occurred (no re-stenosis, no ventricular arrhythmias).
Conclusions: IC transplantation of non-mobilized CD34+ stem cells is feasible after an acute MI. PET imaging is a valuable technology for the detection of stem cell homing in the infarcted area. From the preliminary experience here reported, IC administration of non-mobilized CD34+ blood stem cells appears safe; it leads to stem cell myocardial homing and it might bring some improvement in ventricular function after acute myocardial infarction.

CARDIAC IMAGING AND MSCT

P3154 Diagnostic accuracy of 64 slice computed tomography compared with invasive angiography: feasibility of this non-invasive modality on the clinical practice

M. Ehara[1], O. Kato[1], T. Matsubara[1], M. Trashima[1], E. Tsuchikane[1], T. Ito[1], M. Kawai[2], T. Suzuki[1]. *[1]Toyohashi heart center, Cardiology, Toyohashi, Japan; [2]Toyohashi Heart Center, Radiology, Toyohashi, Japan*

Background: The purpose of present study is to investigate whether 64-slice computed tomography (64-MSCT) is feasible for evaluation of coronary artery disease as the daily practice.
Methods: Sixty-one consecutive cases underwent angiography using SOMATOM Sensation 64 Cardiac. In approximately 60% stenting was previously performed. All underwent conventional coronary angiography (CAG) within interval of 1 month. None was administered beta-blockers. Scan time was 13.7 seconds and amount of contrast material was 72.7 ml, on average. Coronary artery was classified according to AHA classification, and accuracy to detect more than 50% stenosis on CAG was analyzed segment by segment.
Result: In total, 843 segments were visible by 64-MSCT. Segment-based accuracy was shown in the table.

Segment-based Accuracy

Seg	n	Sensitivity	Specificity	PPV	NPV	Accuracy
Total	843	90.5	95.3	90.8	95.2	93.7
#1	59	96.2	97.0	96.2	97.0	96.6
#2	56	95.9	93.8	92.0	96.8	94.6
#3	55	85.0	94.6	89.5	92.1	91.2
#4AV	56	75.0	95.3	81.8	93.2	90.9
#4PD	53	61.5	100.0	100.0	89.6	91.2
#5	53	93.8	91.9	83.3	97.1	92.5
#6	52	100.0	87.5	94.7	100.0	96.2
#7	46	100.0	86.7	94.1	100.0	95.7
#8	55	100.0	100.0	100.0	100.0	100.0
#9	50	87.5	96.2	95.5	89.3	96.2
#10	49	84.6	97.3	91.7	94.7	97.3
#11	51	90.9	93.1	90.9	93.1	93.1
#12	53	83.3	93.0	76.9	95.2	93.0
#13	54	86.4	84.4	79.2	90.0	84.4
#14	50	100.0	90.0	71.4	100.0	90.0
#15	47	66.7	95.5	100.0	97.7	95.5

PPV: Positive predictive value, NPV: Negative predictive value

Conclusion: 64-MSCT, which realizes higher temporal and spatial resolution than current scanner, is a feasible and practical modality with less scan time, contrast material and without use of beta-blockers.

P3155 Effective radiation dose of cardiac computer tomography angiography. A comparison between 64- and 16-slice technology

J. Hausleiter[1], T.S. Meyer[2], M. Hadamitzky[1], S. Martinoff[2], A. Schoemig[1]. *[1]Deutsches Herzzentrum, Department of Cardiology, Muenchen, Germany; [2]Deutsches Herzzentrum, Department of Radiology, Muenchen, Germany*

Background: Contrast-enhanced, multi-slice computer tomography (CT) is a new method for imaging patients with suspected coronary artery disease. With the use of 64-slice cardiac CT the spatial and temporal resolution increased significantly, which enlargens CT diagnostic capabilities. However, the also increased radiation dose is a limitation of this technique. An ECG-dependent dose modulation algorithm has been developed to reduce the dose in CT angiographies (CTA) of the coronary arteries. The purpose of the present retrospective investigation was to estimate and compare the effective radiation dose of non-invasive coronary CTA with 16- and 64-slice technology.
Methods: Cardiac CT angiographies were performed with state of the art multislice CT systems (Sensation Cardiac 16 and 64, Siemens, Germany). Indications for CTA were among others the presence of atypical chest pain, pathological stress tests in asymptomatic patients, high risk for coronary heart disease and the assessment of bypass grafts or the thoracic aorta. The effective radiation dose was estimated from the "dose-length-product" for each patient.
Results: The radiation dose was estimated in 298 patients with coronary CT angiography. 200 and 98 of them were investigated with Cardiac 16 and Cardiac 64 systems, respectively. ECG-dependent dose modulation was used in approximately 85% of patients. The mean radiation dose with 16-slice scanner was 6.5 ±1.9mSv, the mean radiation dose with 64 was 10.5 ±2.3mSv.
Conclusions: The calculated dose estimates were obtained in a heterogenous patient population including long scan ranges for visualization of bypass grafts or the thoracic aorta. The increase in spatial and temporal resolution with the latest generation of CT-scanners with 64-slice technology is associated with an

increase of radiation dose. Nevertheless this dose is comparable to other non-invasive procedures such as myocardial szintigraphy (approximate dose 10 - 20mSv). All means to reduce the dose of cardiac CT investigations, including the careful selection of patients, meticulous planning of the investigation and effective algorithms such as the ECG-dependent dose modulation should be used in all patients whenever possible.

P3156 Clinical value of CT coronary angiography in patients with a high prevalence of coronary artery disease

N.R.A. Mollet[1], F. Cademartiri[2], C.A.G. Van Mieghem[2], G. Runza[2], M.P. Freericks[3], J.P. Kerker[3], G.P. Krestin[4], P.J. De Feyter[2]. *[1]Erasmus Medical Center, Departements of Cardiology and Radiology, Rotterdam, Netherlands; [2]Erasmus Medical Center, Cardiology and Radiology, Rotterdam, Netherlands; [3]Ikazia Hospital, Cardiology, Rotterdam, Netherlands; [4]Erasmus Medical Center, Radiology, Rotterdam, Netherlands*

Objective: To determine the value of 16-slice CT coronary angiography (CTCA) in the work-up of patients with stable angina pectoris as compared to stress-ECG and conventional coronary angiography (CA).
Background: The clinical value of in the evaluation of patients suspected of coronary artery disease (CAD) is unknown.
Methods: During a 6 month-period, 62 consecutive patients with first presentation of stable angina and ≥2 cardiovascular risk factors, or patients with recurrent angina after myocardial infarction and an ≥3-month asymptomatic period, were included. Other inclusion criteria: sinus heart rhythm and ability to breath hold for 20 seconds. Exclusion criteria: contra-indications to iodinated contrast material and patients who previous underwent a conventional angiogram. Patients were recruited in a community hospital, and underwent stress-ECG and, irrespective of these results, conventional CA. CTCA was performed on an outpatient basis in a university hospital prior to conventional CA.
Results: The prevalence of patients with significant CAD was 77%. Sensitivity of CTCA to detect significant CAD was 100% (95%-CI: 91-100), specificity was 92% (95%-CI: 61-99), and positive and negative predictive values were 98% (95%-CI: 87-99) and 100% (95%-CI: 71-100), respectively. Sensitivity of stress-ECG was 78% (95%-CI: 62-92), specificity was 67% (95%-CI: 34-90), and positive and negative predictive values were 89% (95%-CI: 73-93) and 47% (95%-CI: 22-72), respectively.
All patients with significant CAD were correctly classified on CT, whereas 13 patients remained undetected by stress-ECG (9 false negative and 4 inconclusive stress-tests). Absence of significant CAD was correctly ruled out by CTCA in 13 of 16 patients. CTCA had a large impact on the likelihood of CAD (positive and negative likelihood ratios: 12.0-0.0), whereas stress-ECG had a small impact (positive and negative likelihood ratios: 2.3-0.3).The agreement between conventional CA and CTCA to detect patients with significant CAD was very good (0.91).
Conclusions: CTCA has an important impact on the likelihood of significant CAD in patients with a high pre-test likelihood and a negative stress-ECG examination.

P3157 Multidetector computed tomography: a new promising non invasive method to rule out coronary artery disease

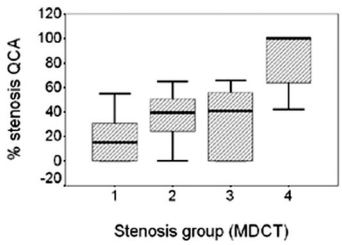
G. Pontone[1], D. Andreini[2], G. Ballerini[1], E. Nobili[1], M. Gamberini[1], A. Succu[1], C. Quaglia[1], M. Pepi[1]. *[1]Centro Cardiologico "Monzino", IRCCS, Milan, Italy; [2]Centro Cardiologico Monzino, Cardiology, Milan, Italy*

Background: Multidetector computed tomography (MDCT) is a promising technique for non-invasive coronary, venous and artery graft evaluation, although few data on consecutive patients concerning the accuracy of this new method are avaible. This study was designed to evaluate the diagnostic performance of MDCT for detection of significant lesions in all coronary tree and in coronary-aorta bypass graft (CABG).
Methods: two-hundred-fifty four consecutive patients (177 male, 63±9 years), with or without history of coronary artery disease (CAD) were evaluated by MDCT (GE Medical System Ligth Speed Pro 16x0.625 mm, 400 msec time rotation, 100±15 cc Iomeron 400 mg/ml at 4.5 ml/sec). Ninty-nine patients with heart rate above 65 beats/min received intra-venous dose of metoprolol (4.55±1.65 mg). The average heart rate was 58±7 beats/min. MDCT scan was acquired during breath hold (about 20 seconds) and evaluated with multiple approach including volume rendering, multiplanar reconstruction and vessels analysis by three blinded observers. In ninty-two patients conventional selective coronary angiography was performed and evaluated by blinded reviewer. The diagnostic accuracy of MDCT to detect significant stenoses (≥50% diameter reduction) was tested in all coronary segments in according to AHA/ACC classification and in CABG (fifteen patients: 15 left mammarian artery, 1 radial artery, 15 venous graft).
Results: the global feasibility of MDCT was 88.2%, but if we exclude small vessels (diameter ≤ 1.5 mm), it reached 96%. In comparison to conventional angiography the sensitivity, specificity, positive and negative predictive value were high for all vessels (respectively 94%, 84%, 81% and 94%). The accuracy for CABG was about 100%.
Conclusions: our results indicate high diagnostic accuracy of 16-slice MDCT. Considering the excellent negative predective value, this method could be promising in ruling out CAD. Further studies needed to test the feasibility of MDCT in subgroups of patients in which the exclusion of CAD is strategic in therapeutic management (Ex: dilated cardiomyopathy, aneurysm of ascending aorta and valvular diseases with surgical treatment indication).

P3158 Diagnosis of coronary in-stent restenosis using new generation multi-detector row spiral computed tomography

Halon[1], T. Gaspar[2], S. Adawi[1], N. Peled[2], J.E. Schliamser[1], R. Rubinshtein[1], B.S. Lewis[1]. *[1]Lady Davis Carmel Medical Center, Dept. of Cardiology, Haifa, Israel; [2]Lady Davis Carmel Medical Center, Department of Radiology, Haifa, Israel*

Background: Non-invasive imaging of coronary stents has proved difficult due to imaging artifacts caused by metallic stent struts. We examined the accuracy of a new generation 40 slice multi-detector CT scanner (MDCT) (Brilliance 40, Philips Medical Systems) in the diagnosis of in-stent restenosis (ISR) in an unselected patient cohort referred for repeat invasive coronary angiography (ICA) due to recurrent angina pectoris.
Methods: We examined 65 pts (63.1±11.6 yr, 73.8% male) with 111 stents (diameter 3.3±0.5mm). One quarter (17 pts, 26.2%) had acute MI and 12 (18.5%) prior CABG. Scanning was performed with 70ml IV contrast and MDCT images reconstructed using retrospective ECG gating. Gold standard for restenosis was =>60% narrowing by quantitative analysis of ICA. Reformatted MDCT images were examined in 2D long and short axes and luminal narrowing grouped from 1-4. Five stents (4.5%), unassessable by MDCT, were excluded from current analysis.
Results: Prevalence of restenosis on ICA was 24.6% (pts) and 16.0% (stents). MDCT groups 1 and 4 sharply differentiated restenosis (Figure). MDCT Group 1 excluded restenosis. Sensitivity of MDCT Group 4 for restenosis was 71%, specificity 97%, positive predictive value 80%, negative predictive value 95%, predictive accuracy 92%.



QCA % stenosis for each MDCT group

Conclusions: 1. The 40 slice MDCT scanner allows systematic assessment of ISR in symptomatic pts. 2. High negative predictive value makes MDCT a useful clinical tool in the exclusion of in-stent restenosis.

P3159 Image quality and diagnostic accuracy of 16-slice multi-detector computed tomography for the detection of coronary artery disease in obese patients

C. Burgstahler[1], T. Beck[2], A. Kuettner[3], M. Heuschmid[3], A.F. Kopp[3], C.D. Claussen[3], S. Schroeder[2]. *[1]Eberhard-Karls-University, Department of Cardiology, Tuebingen, Germany; [2]Eberhard-Karls-University, Department of Cardiology, Tuebingen, Germany; [3]Eberhard-Karls-University, Department of diagnostic Radiology, Tuebingen, Germany*

Background: Cardiac multi-slice computed tomography (MSCT) scanners permit visualization of the coronary arteries with an overall good sensitivity and specificity. However, in obese patients (pts), who are at higher risk to develop coronary artery disease (CAD), image quality of MSCT is supposed to be limited. At present, there no data whether the accuracy of MSCT depends on the body mass index (BMI). Thus, we compared the catheter-controlled MSCT results from normal weight and obese pts in a cohort of 117 pts with regard to sensitivity (sens), specificity (spec), positive predictive value (PPV), negative predictive value (NPV) and image quality.
Methods and material: 21 normal weight pts (group I: BMI<25, 64.6±11.1 years, number of risk factors 2.1±1.1), 60 pts with mild overweight (group II: BMI 25-30, 64.6±8.9 years, number of risk factors 3.4±1.0) and 36 obese pts (group III: BMI >30, 63.0±8.5 years, number of risk factors 3.4±0.9) were examined by MSCT (Sensation 16 Speed 4 D®, Siemens, Germany, gantry rotation time 375 ms) and invasive coronary angiography. MSCT results were compared blinded to the results of the coronary angiography with regard to the presence or absence of a significant stenosis (>50%) in a modified AHA 13 segment (sgt) model. Image quality was assessed on a qualitative scale between 1 (very good) to 5 (blurred) for each sgt.
Results: Sens, spec, PPV and NPP were statistically not different in all three groups (I: 0.88/0.97/0.91/0.96, II: 0.83/0.97/0.88/0.95, III: 0.87/0.99/0.96/0.96). 3 pts (group I 1, group II 2) had to be excluded from analysis due to technical problems. Group I had significantly less risk factors ($p<0.001$) and image quality was significantly better than in group II and III ($p<0.05$). Group II and III did not differ with regard to risk factors or image quality.

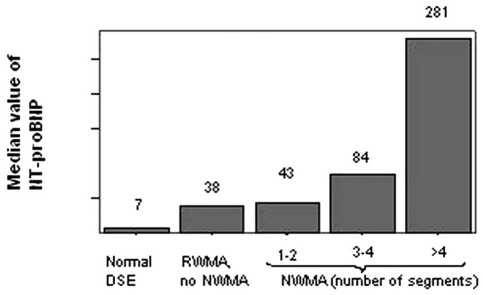
Conclusions: Overweight and obesity have an impact on MSCT image quality but did not hamper the diagnostic accuracy. Thus, MSCT is a non-invasive method to detect CAD irrespective to the BMI. These retrospective data have to be confirmed in larger prospective trials.

ECHOCARDIOGRAPHY/DOPPLER

P3160 Pre-test plasma N-terminal pro-B-type natriuretic peptide is associated with the extend of stress induced myocardial ischaemia during dobutamine stress echocardiography

H.H.H. Feringa[1], J.J. Bax[2], R. De Jonge[3], A.F.L. Schinkel[4], O. Schouten[1], A.H. Van de Meiracker[4], H. Boersma[4], D. Poldermans[5]. *[1]Erasmus MC, Vascular Surgery, Rotterdam, Netherlands; [2]University hospital Leiden, Cardiology, Leiden, Netherlands; [3]Erasmus MC, Clinical Chemistry, Rotterdam, Netherlands; [4]Erasmus Medical Centre, Cardiology Dept., Rotterdam, Netherlands; [5]Erasmus MC - Anesthesiology, Rotterdam, Netherlands*

Background: Plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) is secreted by the heart in response to wall stress. We hypothesized that NT-proBNP levels are elevated in patients with coronary artery disease, which can be detected as new wall motion abnormalities (NWMA) during dobutamine stress echocardiography (DSE).
Aim: To determine the relation between the extend of stress-induced new wall motion abnormalities and circulating NT-proBNP-levels.
Methods: NT-proBNP level was measured in 170 consecutive patients prior to DSE. Cardiac risk factors were recorded at the time of DSE. During DSE, rest wall motion abnormalities (RWMA) and NWMA were scored using a 5-point, 16-segment model.
Patients were divided into three groups according to DSE results: group 1: no RWMA and no NWMA, group 2: RWMA and no NWMA, group 3: RWMA + NWMA
Results: In this study population (mean age 59±13 years, 70% male), median NT-proBNP level was 13.3 (interquartile range: 5.1-46 pmol/L). Median NT-proBNP levels were 7, 38 and 52 pmol/L in group 1 (97/170, 57%), group 2 (45/170, 26%), and group 3 (28/170, 16%), respectively ($p<0.0001$). In group 3, NT-proBNP levels were associated with the extend of NWMA, with median values of 43, 84 and 281 pmol/L in patients with 1-2, 3-4 and >4 ischemic segments, respectively (p=0.03).
Using multivariable analysis, NT-proBNP >80 pmol/L (after adjustment for cardiac risk factors and RWMA) was significantly associated with the occurrence of NWMA (OR: 5.9, 95% CI: 1.9-18).



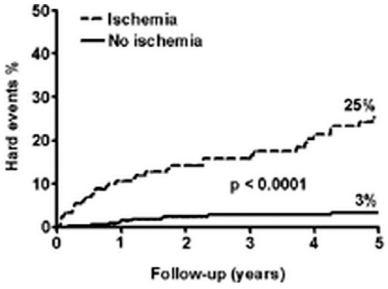
Figure

Conclusion: Elevated levels of NT-proBNP are associated with the extend of NWMA during DSE, irrespective of the presence of RWMA.

P3161 Prognostic value of stress echocardiography in chest pain patients with intermediate-to-high threshold ischaemia on exercise ECG

L. Cortigiani[1], R. Bigi[2], P. Landi[3], F. Bovenzi[1], E. Picano[4]. *[1]Ospedale C. di Marte, Cardiologia, Lucca, Italy; [2]University School of Medicine, Cardiology Unit, Milan, Italy; [3]Institute of Clinical Physiology, CNR, Pisa, Italy; [4]CNR Institute of Clinical Physiology, Pisa, Italy*

Aim: To determine the prognostic implication of stress echo findings in patients with intermediate-to-high threshold ischemia on exercise ECG.
Methods: 719 chest pain patients (age 58±10 yy; 471 men), showing =1 mm ST-segment depression in =2 contiguous leads at =75 watt (mean 108±26) bicycle exercise workload, underwent dipyridamole (n=587) or dobutamine (n=132) stress echo. Those with known coronary artery disease, left bundle branch block, paced rhythm, left ventricular hypertrophy or strain pattern on resting ECG, digitalis or antiarrhythmic therapy were excluded.
Results: Ischemia (new wall motion abnormalities) at stress echo was found in 319 (44%) patients. During a median follow-up of 33 months, there were 47 deaths, 23 nonfatal infarctions, and 94 late (>3 months from stress echo) coronary revascularizations. Out of 11 clinical and echo covariates, ischemia at stress echo (HR=3.41, 95% CI=2.03-5.72, $p<0.0001$), age (HR=1.04, 95% CI=1.01-1.07, p=0.004), and smoking habit (HR=2.16, 95% CI=1.26-3.71, p=0.005) were independently associated with hard events (death, infarction). 5-year hard event rate was 27% in patients with and 3% in those without ischemia at stress echo (Figure). Independent indicators of major events (death, infarction, late revascularization) were ischemia at stress echo (HR=3.63, 95% CI=2.50-5.27, $p<0.0001$), male gender (HR=2.04, 95% CI=1.21-3.44, p=0.007), and smoking habit (HR=1.56, 95% CI=1.08-2.24, p=0.02). 5-year major event rate was 44% for patients with and 7% for those without ischemia at stress echo.



Conclusions: Stress echo allows effective risk stratification in chest pain patients with intermediate-to-high threshold ischemia on exercise ECG. In particular, the negative test result is predictive of low rate of future events.

P3162 Risk stratification by treadmill exercise echocardiography

P. Pinon[1], J. Peteiro[2], L. Monserrat[1], J. Marinas[3], A. Bouzas[1], M. Pineiro[1], A. Castro Beiras[1]. *[1]Juan Canalejo Hospital, Cardiology, A Coruña, Spain; [2]A Coruna, Spain; [3]Juan Canalejo Hospital, Unit of Codification, A Coruna, Spain*

Although exercise echocardiography (EE) has value forthe diagnosis of CAD, it's no clear whether it may be useful for risk assessment in all categories of patients.
Aims: To determine whether: 1) there is an incremental value of exercise echocardiography over clinical, exercise and rest echocardiographic variables for the prediction of events according to the pre-test probability of coronary artery disease (CAD); and 2) the number, location of the diseased territories, and nature of the disease affect the risk stratification.
Methods: 2436 patients (mean age 62±12 years, men 65%) referred for EE were followed for 2.1±1.5 years (median 2 years). There were 120 hard events (45 non fatal myocardial infarctions and 75 cardiovascular deaths) before any revascularizacion procedure. Based on a pre-test score, previous myocardial infarction (MI) or revascularizations, 1242 patients were considered as having high, 1038 moderate, and 156 low pre-test probability of CAD. Additionally, 556 patients without angina, previous MI or revascularization procedures were separately analysed.
Results: There were 89 events in the 1203 patients with abnormal EE vs. 31 events in the 1233 with normal EE ($p<0.0001$). Variables independently associated to hard events were male gender (RR=1.7, 95%CI=1.1-2.8, p=0.02) Mets(RR=0.9, 95%CI=0.9-1.0, p=0.01), heart rate x blood pressure(RR=0.94, 95%CI=0.91-0.98, p=0.002), resting wall motion score index (RR=2.5, 95%CI=1.5-4.1, $p<0.0001$) and number of involved territories at exercise (RR=1.4, 95%CI=1.2-1.7, p=<0.0001; final Chi-square=170, incremental p value of exercise echo <0.0001). The incremental value of exercise echo over other variables was found in patients with high pre-test probability of CAD (final Chi-square=105, incremental value of exercise echo p=0.01), moderate (final Chi-square=52, incremental value of exercise echo p=0.03), and low (final Chi-square=6, incremental value of exercise echo p=0.02) and also in the subgroup that had neither angina nor previous MI or revascularization procedures (final Chi-square=49, incremental value of exercise echo $p<0.0001$).
Conclusions: Exercise echocardiography has incremental value over clinical, exercise and resting echocardiographic variables in patients with different pre-test probabilities of CAD.

P3163 Dobutamine stress echocardiography in left ventricular apical ballooning syndrome

M. Previtali[1], L. Scuteri[1], S. Panigada[2], E. Baldini[1], L. Lanzarini[1], A. Repetto[1]. *[1]Pavia, Italy; [2]Pavia, Italy*

Purpose: left ventricular apical ballooning syndrome (LVABS) is an acute ischaemic syndrome mimicking myocardial infarction in the absence of significant coronary disease, characterised by severe but reversible stunning-like apical wall motion abnormalities (WMA) in which dynamic intraventricular obstruction (DIOB) has been proposed as a possible pathogenetic mechanism. The purpose of the study was to evaluate response to dobutamine stress echocardiography (DSE) in pts with LVABS in order to assess the role of myocardial stunning and of DIOB in its pathogenesis.
Method: 12 pts, all women, aged 70 ± 8 years fulfilling the criteria for LVABS underwent DSE (5-20 mcg/kg/min) at 9 ± 14 days from admission. During DSE

WMA were evaluated on a 16-segment model of LV and a score from 0 = normal to 4=dyskinesia was assigned to each segment; development of DIOB and acute mitral regurgitation was monitored by Color, PW and CW Doppler.
Results: during DSE heart rate increased from 72±14 to 100±20 bts/min (p<.0002), systolic blood pressure (BP) increased from 135±20 to 138±33 (ns) and diastolic BP from 73±8 to 74±15 mm Hg (ns);end-diastolic and end-systolic volumes decreased from 92±28 to 79±24 ml (p<.05) and from 39±16 to 29±16 ml (p<.05) and ejection fraction increased from 57±10 to 64±12% (p< .05). WM score index improved from 1.35± .34 to 1.24±.37 (p =.09); of the 8 pts with persistent WMA, apical WM normalised in 3 pts and improved in 3, while after a transient recovery apical WM worsened in the 2 pts who developed a severe DIOB. In these 2 pts severe DIOB (peak gradient 150 and 98 mmHg)was associated with systolic anterior motion of anterior mitral leaflet and grade 4 mitral regurgitation; a moderate DIOB (38 mm Hg) was observed in 1 pt. All changes returned to baseline after intravenous propranolol. No pt had chest pain or other major symptoms;positivisation of negative T waves in the anterior leads occurred in 2/12 pts.
Conclusion: 1)In LVABS apical WMA are caused by myocardial stunning which may be reversed by inotropic stimulation with dobutamine; 2) Dynamic intraventricular obstruction elicited by sympathetic stress can be documented in 25% of pts with LVABS and can play a significant pathogenetic role, leading to the development of severe mitral regurgitation and acute left ventricular failure.

P3164 Chronotropic incompetence is an independent predictor of repeat revascularisation after the first percutaneous coronary intervention

D. Orlic, M. Ostojic, A. Dikic-Djordjevic, I. Nedeljkovic, B. Beleslin, J. Stepanovic, S. Stojkovic, M. Nedeljkovic. *Institute for Cardiovascular Diseases, Belgrade, Serbia and Montenegro*

Objectives: The study sought to determine predictive value of chronotropic incompetence (CI) for repeat revascularization (TVR) among patients referred for stress echocardiography following the first percutaneous coronary intervention (PCI). Background: Although CI has been shown to be predictive of an adverse prognosis, its value as a predictor of TVR has not been explored.
Methods: Consecutive patients (468 men and 51 women; mean age 54.5±8.9 y) who were not taking beta blockers and were referred for symptom-limited exercise echocardiography between 2 and 4 months after the first PCI were followed for a mean of 6.2±2.8 months after the PCI. Chronotropic incompetence was assessed as 1) failure to achieve 85% of the age-predicted maximum heart rate, and as 2) low chronotropic index (CRI =< 0.80). Echocardiographic ischemia (Echo+) was defined as new or worsening systolic wall motion abnormalities in ≥ 2 segments, and electrocardiographic ischemia (ECG+) as depression of ST segment ≥ 1 mm in ≥ 2 contagious leads. Angiography was indicated in patients with Echo and/or ECG signs of ischemia and TVR performed (target and non-target lesion revascularization) if diameter stenosis was ≥ 50%.
Results: Target vessel revascularization was performed in 81 patients. Failure to reach 85% of the age-predicted maximum heart rate was found in 51 (11.6%) patients with no TVR and in 48 (59.3%) patients with TVR, and was predictive of TVR by univariate analysis (RR 11.04, 95% CI 6.49 to 18.77, p<0.001). Low CRI was found in 162 (37.0%) patients with no TVR and in 63 (77.8%) patients with TVR, and was associated with TVR (RR 5.96, 95%CI 3.41-10.42, p<0.001). Multivariate analysis identified independent predictors of TVR as follows: ECG+ (RR 2.43, 95%CI 1.01-5.87, p=0.049), Echo+ (RR 20.55, 95%CI 8.10-52.16, p<0.001), failure to reach 85% of the age predicted maximum heart rate (RR 4.54, 95%CI 2.13-9.66, p<0.001) and low CRI (RR 2.37, 95%CI 1.07-5.23, p=0.03).
Conclusion: Chronotropic incompetence, assessed by either failure to reach 85% of the age-predicted maximum heart rate or low chronotropic index, is an independent predictor of TVR following the first PCI.

P3165 Impairment of primary haemostasis at rest in hypertrophic cardiomyopathy is highly predictive of the severity of obstruction during exercise echocardiography

T. Le Tourneau[1], S. Susen[1], A. Millaire[2], A.S. Polge[3], P. de Groote[2], G. Deklunder[3], C. Bauters[2], B. Jude[1]. *[1]INSERM ERI-9, University of Lille, Lille Cedex, France; [2]Hopital Cardiologique, Cardiologie C, Lille, France; [3]Hopital Cardiologique, Service d'EFCV, Lille, France*

Background: shear stress is considered as the main determinant of Willebrand factor (VWF) impairment in aortic stenosis. High outflow velocity in hypertrophic cardiomyopathy (HCM) might impaired primary hemostasis. However, the magnitude of the outflow gradient may vary rapidly with a number of physiological alterations. In HCM with no or moderate obstruction at rest (≤50 mmHg), we sought to evaluate 1) the relationships between outflow gradient and VWF impairment, and 2) the effect of exercise on outflow gradient and VWF.
Methods: we enrolled 35 patients (44±16 yrs, 23 males) with either obstructive (HOCM, 6) or non obstructive (HCM, 29) hypertrophic cardiomyopathy. Cardiomyopathy was considered as obstructive in the presence of an outflow gradient ≥30 mmHg at rest. A semi-supine symptom-limited exercise echocardiography (EE) was performed. Latent (or provocable) obstruction was defined as a peak gradient <30 mmHg at rest and ≥30 mmHg with EE. Selected parameters of primary hemostasis reflecting VWF abnormalities were evaluated under basal conditions and within 1 hour after EE.
Results: outflow gradient increased significantly during or immediately after EE (from 13±13 to 42±47, p=0.0001). Twenty-two patients had no obstruction, 6 patients had moderate obstruction at rest (>30 and ≤50 mmHg) and 7 patients had latent obstruction. Under basal conditions, shear-induced platelet adhesion (PFA 100®) was prolonged in HOCM compared with HCM (264±55 vs 150±55 s, p< 0.0001). VWF-collagen binding activity (VWF:CB) and the percentage of high molecular weight multimers (%HMW) of VWF were significantly reduced in HOCM compared with HCM (59±18 vs 113±49, and 4.8±1.3 vs 11.0±1.9% respectively, p<0.0001). There was no change in %HMW after EE, but a slight decrease of PFA 100® and an increase in VWF:Ag and VWF:CB (all p<0.05). PFA 100® or %HMW were correlated with the outflow gradient at rest (r=0.56 and r=-0.61 respectively, p=0.001). However the better correlation was found between either PFA 100® or %HMW at rest and the maximal value of peak gradient during EE (r=0.72 and r=-0.76 respectively, p<0.0001). Finally, the maximal value of peak gradient during EE was the only independent predictor of either PFA 100® or %HMW alteration at rest (both p<0.01).
Conclusion: moderate obstruction (>30 and ≤50 mmHg) at rest in HOCM leads to an impairment of primary hemostasis related to type IIa Von Willebrand acquired syndrome. Moreover primary hemostasis impairment at rest is highly predictive of the maximal value of peak gradient during exercise echocardiography.

P3166 Can cardiovascular risk factors affect the clinical value of coronary flow reserve for diagnosis of a significant left anterior descending artery stenosis?

L. Ascione[1], M. Accadia[2], C. Sacra[2], A. D'Andrea[3], M. De Michele[4], G. Granata[2], P. Guarini[5], B. Tuccillo[2]. *[1]S. Maria di Loreto Hospital, Division of Cardiology, Naples, Italy; [2]S. Maria diLoreto Hospital, Division of Cardiology, Naples, Italy; [3]G. Rummo Hospital, Division of cardiology, Benevento, Italy; [4]Moscati Hospital, Division of Cardiology, Aversa, Italy; [5]Villa dei Fiori Hospital, Division of Cardiology, Acerra, Italy*

Background: A value of coronary flow reserve (CFR) < 2, noninvasively determined, has provided a useful tool for diagnosis of a significant left anterior descending artery (LAD) stenosis in selected populations. However recent studies have showed that cardiovascular risk factors affect CFR reducing its value for diagnosis of a significant LAD stenosis (SLS).
Methods: 383 patients (mean age 59±10 years, 72% men, 20% diabetics, 56% hypertensives, 24% dyslipidemic, 53% smokers), without previous anterior myocardial infarction, underwent transthoracic echocardiographic CFR evaluation. Blood flow velocity was measured in the mid distal part of LAD at rest and during infusion of high dose dipyridamole (0.84 mg/kg i.v.) in 6 minutes using high frequency transducer. CFR was calculated as the ratio of hyperemic to basal peak diastolic flow velocity. All patients underwent coronary angiography in a week after CFR evaluation. SLS was defined according to the presence of LAD stenosis > 50%. Study population were divided in high score (HSP) and low score (LSP) patients according to the presence of more than two cardiovascular risk factors (such as diabetes, hypertension, hyperlipidemia, smoke and age > 65 years).
Results: CFR value wasn't significantly different between HSP and LSP (2,17 ± 0,70 vs 2,26 ± 0,66 n.s) while patients with SLS had a significantly reduced CFR value compared to patients without SLS (1,84 ± 0,68 vs 2,4 ± 0,5, p < 0,0001). In 241 patients without SLS, a multivariate logistic regression analysis showed that hypertension (beta:-0.4; p<0,005), age (beta: -0.2; p< 0,05), diabetes (beta:-0.38; p<0.005) and number of risk factors (beta:-0.27; p<0,01) were independent factors influencing CFR. In 142 patients with SLS, LAD stenosis (beta:-0.32; p<0.001) was the only independent predictor of a reduced CFR in a multivariate logistic regression analysis.
Conclusion: Our results suggest that cardiovascular risk factors don't reduce the clinical value of CFR evaluation for diagnosis of SLS. In fact even if cardiovascular risk factors can reduce CFR in patients without SLS, a CFR value < 2 is a reliable cut-off point for the detection of SLS.

P3167 Quantitatively evaluation of marrow mesenchymal stem cells implantation

R. Guo[1], X.- Chen[2], Q. Zhou[2], J.L. Chen[2]. *[1]Renmin Hospital of Wuhan University, Division of Echocardiography, Wuhan, China; [2]Renmin Hospital of Wuhan University, Division of Echocardiography, Wuhan, China*

Objective: The change of regional motion function and the left ventricular(LV) function after marrow mesenchymal stem cells (MSCs) implantation in ischemic myocardium measured tissue Doppler imaging(TDI) has not be reported. This study also explored the value of MSCs implanation in ischemic myocardium.
Methods: Myocardial infarction was created in 30 rabbits by left anterior descending coronary artery ligation, which were divided into two groups randomly: implantation group(group A) and control group(group B).The diastolic diameter of LV (LVDd),the anterior thickness of LV wall(AW),the ejection function(EF)and the systolic and diastolic peak velocity of anterior wall in LV (Vs?VE?VA)were measured by two-dimension echocardiography and tissue Doppler imaging before 1 day and 1 week after infarction, as well as 4 weeks after implantation.

Result: Comparing with groug B, LVDd of group A was smaller 4 weeks after MSCs implantation(12.2±1.9mm vs14.9±2.2mm, P<0.01), and EF was higher (67.3± 10.2%vs54.6±9.6%, P<0.01). Failed wall segmental motion performance produced by AMI was significantly improved in implantation group 4 weeks after cell implantation (Vs 9.2±1.9cm/s,VE 11.1± 2.7cm/s),higher than control group (Vs 7.6±2.1 cm/s, VE 9.5±2.6cm/s, P<0.05, respectively).
Conclusions: TDI is a valid and sensitive method for detecting of regional myocardium motion and cardiac function in ischemic myocardium after MSCs implantation.

P3168 Comparison of myocardial tissue Doppler with color M mode flow propagation velocities in hypertensive left ventricular hypertrophy.

S.J. Park, C.H. Kwak, J.Y. Hwang. *GyengSang National University Hospital, Internal Medicine(division of cardiology), Jinju, Korea, Republic of*

Introduction: Abnormalities of left ventricular (LV) relaxation and diastolic filling have been reported in patients with hypertension (HTN) by mitral inflow pulsed wave Doppler velocities. Doppler tissue imaging (DTI) and color M-mode flow propagation (FP) velocities are useful for assessment of LV diastolic function regardless of laoding conditions. The purpose of this study was to compare DTI and FP in patients with HTN.
Methods: Conventional 2D echocardiography with Doppler was performed in 200 subjects: HTN (n=100, age 66±17 years, 46 males) and normal controls (NC, n=100, 50±12 years, 46 males). 2D echo measurements included: LV ejection fraction (EF), LV mass index (LVMI); mitral inflow pulsed wave Doppler indices included E/A wave ratio, deceleration time and isovolumic relaxation time intervals. Tissue Doppler early diastolic myocardial (Em) velocity was recorded at the septal annulus; color M-mode flow propagation (FP) velocity was obtained in the apical 4 chamber view. Subjects with HTN were divided into two groups: left ventricular hypertrophy (LVH: LVMI=134 g/m^2 in men and =110 g/m^2 in women).
Results: Among patients with HTN, 65 met criteria for LVH (HTN+LVH). Although the NC group was significantly younger than the HTN+LVH group, there was no age difference between HTN+LVH and HTN+NLVH (non-LVH) (n=35) groups. By design, the HTN+LVH group had significantly higher LVMI compared to both HTN+NLVH and NC groups, although the LVEF was similar across all three groups (HTN+LVH: LVMI 165.3±32 g/m^2, EF 65± 13%; HTN+NLVH LVMI 115±22.2 g/m^2, EF 62.9± 13.9%; NC: LVMI 113±17 g/m^2, EF 66± 8%). Although all Doppler variables except FP allowed discrimination between HTN+LVH and NC groups, only TDI Em at the septal bases was significantly different both between HTN+LVH and HTN+NLVH groups and between HTN+NLVH and NC groups. There were no statistically significant differences in color M-mode FP velocities across any of the groups.
Conclusions: In the presence of LVH and preserved left ventricular systolic function, TDI Em velocities are more sensitive than color M-mode FP velocities in detecting abnormal left ventricular relaxation.

P3169 Can right ventricle Tei-index be used as a tool to detect presence of increased pulmonary vascular resistance (PVR) in patients with systemic sclerosis (SSc)?

M.H. Sander[1], M.C. Vonk[2], F.H.J. van den Hoogen[2], F.W.A. Verheugt[3], A.P.J. van Dijk[1]. *[1]Radboud University Medical Centre, Department of Cardiology, Nijmegen, Netherlands; [2]Radboud University Medical Center, Department of Rheumatology, Nijmegen, Netherlands; [3]Radboud University Nijmegen Medical Centre, Department of Cardiology, Heartcenter, Nijmegen, Netherlands*

Background: Pulmonary arterial hypertension (PAH), defined as systolic pulmonary arterial pressure (PAP)=35 mmHg, is a fatal complication of some autoimmune diseases, especially SSc. To diagnose PAH echocardiography (echo) is used as a screening tool; the diagnosis has to be confirmed by right heart catheterization (RHC). In our cohort of patients with SSc we have found a sensitivity of 90% of echo for predicting PAH. Therefore, measurements that can enhance the accuracy of echo are needed to prevent unnecessary catheterizations (cath) and missed diagnoses. The Tei-index incorporates elements of both systolic (syst) and diastolic (diast) phases in the assessment of global ventricular function. An increase in the Tei-index results from a (progressive) ventricular dysfunction, and it has been used to differentiate normal subjects from patients with varying degrees of LV and RV dysfunction and to provide prognostic information for a variety of myocardial conditions. In this study the RV Tei-index is compared with the PVR in patients with SSc.
Aim: Can RV-Tei-index be used as a tool to detect presence of increased PVR in SSc patients?
Methods: Patients with SSc (n=76) and other connective tissue diseases (n=10) in whom echo was performed in 2004 were included. Tei-index was calculated as (IVCT+IVRT)/RV-ejection time in all patients using Doppler-echo. Echo syst PAP was calculated from tricuspidal regurgitation-velocity and RA pressure estimation. 38 patients had a RHC in which PAP and PVR were obtained.
Results: 86 patients (58±12 years;59 female) were included; mean Tei-index 0.34±0.21 (mean±SD) (normal value in literature=0.28±0.04). Echo syst, diast, mean PAP were 44±23 mmHg, 15±8 mmHg, 25±13 mmHg respectively, and 46 patients had an echo syst PAP=35 mmHg.
The correlation between echo syst PAP and Tei-index was 0.56(p=0.000), SEE=19.2 mmHg, and did not increase statistically significantly when changing the cut-off point of the PAP value for having PAH.
In the 38 patients who had a RHC correlation of syst measured PAP and Tei was 0.67(p=0.000), SEE=17.4 mmHg. Mean PVR was 7.07±5.51 Wood units, and using multiple regression analysis only the measured PVR with cath was independently and significantly correlated with the Tei-index; r=0.78(p=0.000), SEE=3.50 Wood units.
Conclusion: The RV Tei-index has a significant, but weak correlation with non-invasively determined PAP in SSc patients. A strong independent correlation between invasive PVR and RV Tei-index is present in SSc patients. These findings suggest that in failing RV's PVR and NOT syst PAP indicates the severity of disease.

P3170 Is Tei index the new echocardiographic golden standard for predicting the death in children with idiopathic dilated cardiomyopathy?

V.M.P. Azevedo[1], F.M. Albanesi Filho[2], M.B. Castier[2], M.A. Santos[1], M.O.M. Cunha[3]. *[1]National Inst. Cardiology Laranjeiras, Pediatric Cardiology Dept., Rio de Janeiro, Brazil; [2]University of Rio de Janeiro State, Cardiology, Rio de Janeiro, Brazil; [3]National Institute of Cancer, Pediatric Dept, Rio de Janeiro, Brazil*

Background: Tei index evaluates ventricular systolic and diastolic function. It is useful predicting evolution in patients with ventricular dysfunction. It remains doubtful whether it is the new golden standard in predicting the death in children with idiopathic dilated cardiomyopathy (IDCM), compared to others 91 echocardiographic parameters.
Purpose: To compare Tei index as an independent marker of death with others 91 echocardiographic parameters in children with IDCM.
Patients: 55 consecutive children with IDCM (13 deaths) underwent 92 echocardiographic studies from January 1996 to August 2003.
Methods: Left ventricle Tei index (LVTei) were compared to echocardiographic parameters from dimension of cavities and derivates functions (26 parameters), Doppler estimation of valve regurgitation (3) and pressure (5), mitral (19) and tricuspid (19) inflow curves analysis, left atrium posterior wall motion (7), left ventricle posterior wall motion (9), isovolumetric relaxation time, aortic acceleration velocity and right ventricular Tei index (RVTei). The dichotomous data were evaluated by chi-square and calculated the confidence interval of 95% (CI95). Descriptive data were evaluated by Student's t test and correlation by Pearson method. Multivariate analysis by groups of variables was performed by Cox's method. After the first step of Cox's method, the significant variables were select and compared with LVTei, with grouping according by mitral regurgitation. Alpha=0.05 and beta=0.80 were considered for statistical significance.
Results: age=3.36 years old (zero to 15.4, median=1.06 year), 24 males (43.6% - CI95 30.5% to 57.6%)(p=0.18) and 34 black (61.8% - CI95 47.7% to 74.3%)(p=0.0132). LVTei and RVTei had a higher correlation (r=0.82, p<0.001); therefore RVTei was discharged from analysis. After the first step of Cox's method they were significant: LVTei (p=0.0222), left ventricle ejection fraction (p=0.0377), distance of mitral E point and ventricular septum (p=0.0394), mitral deceleration time (p=0.0022), LV A wave velocity (p=0.0441), tricuspid E wave acceleration time (p=0.0464), duration of systolic period (p=0.0007), fiber circumferential short velocity (p=0.0382) and left ventricle end-diastolic dimension/body surface area (p=0.0439). Multivariate analysis showed LV Tei index to be an independent marker of death (p=0.0011).
Conclusions: In children with IDCM the LV Tei index is an independent marker of death and it has the potential to be the new golden standard in the evaluation of mortality.

P3171 Changes in myocardial performance indexes induced by surgical ventricular restoration in ischaemic dilated cardiomyopathy

S. Castelvecchio[1], P. Dabic[1], C. Santambrogio[1], M. Di Donato[2], L. Menicanti[1]. *[1]Istituto Policlinico San Donato, Centro Cardiovascolare Malan, San Donato Milanese, Italy; [2]auniversity of Florence, Critical Care Medicine, Firenze, Italy*

Background: Surgical Ventricular Restoration (SVR) in post-infarction cardiomyopathy improves systolic function by a reduction in ventricular volumes and an increase in ejection fraction (EF) of the left ventricle (LV). Little is known on the effects of SVR on diastolic function and global performance of the LV.
Aim: to assess diastolic function and global myocardial performance before and late after SVR in pts with post-infarction ischemic dilated cardiomyopathy.
Method: 80 pts (67 M/13 F, mean age 66 ± 9) with previous anterior myocardial infarction (AMI) underwent SVR between January 2002 and June 2004. Transthoracic two-dimensional and pulsed Doppler echocardiography was performed before and late after surgery (mean time from surgery 12,2 ± 3,6 m). Surgical procedure was performed on arrested heart using a Mannequin filled with 50-60ml/m^2 of saline to size and re-shape residual cavity (Chase Medical, Texas). CABG was associated in all pts and mitral repair for mitral regurgitation in 12 pts (15%).

We evaluated echocardiographic parameters of diastolic function (E/A ratio, DT, IVRT) and we graded the diastolic dysfunction according to the diastolic filling pattern (DP 1 to 4). Moreover, we evaluated the myocardial performance index (MPI =ICT+IRT/ET where ICT=isovolumic contraction time, IRT=isovolumic relaxation time and ET=ejection time) for the assessment of the overall systolic and diastolic function and the total isovolumic time (t-IVT=[60-(total ejection time+total filling time]) which is considered a predictor of exercise capacity.
Results: Operative mortality rate was 3.7%. (3 pts). End-diastolic and end-systolic volumes improved at late control (from 192 ± 66 to 158 ± 57 ml, $p <$ 0,002 and from 127 ± 53 to 96 ± 44 ml $p <$ 0,0004, respectively), as well as EF (from 33,6 ± 8,3 to 40,2 ± 9,6%, $p <$ 0,0002). A restrictive diastolic pattern (DP 3 and 4) was observed in 16% of pts, pre-operatively. ANOVA showed that pre-operative E/A ratio and restrictive DP were significantly associated with operative mortality. MPI and t-IVT showed a significant reduction(from 0,74 ± 0,25 to 0,57 ± 0,22, $p<$0,009 and from 11,8 ± 4,5 to 9,9 ± 3,6, $p<$0,05, respectively), without any significant change in E/A ratio, DT and IVRT. An improvement of the NYHA class was observed at follow-up (from 2,4 ± 0,6 to 1,68 ± 0,6, $p <$ 0,0001.
Conclusion: Pre-operative diastolic dysfunction affects operative mortality. SVR does not affect negatively diastolic function 1 year after surgery. Myocardial performance, as evaluated by MPI and t-IVT, shows a significant improvement.

P3172 Left atrial systolic reserve in idiopathic vs. ischaemic dilated cardiomyopathy

I. Moyssakis[1], D. Papadopoulos[1], G. Kelepesis[2], E. Gialafos[1], V. Votteas[1], F. Triposkiadis[2]. *[1]Laiko Hospital, Cardiology Department, Athens, Greece; [2]Unversity Thessaly, Cardiology, Larissa, Greece*

Purpose: There are studies indicating more pronounced left atrial systolic dysfunction at rest in idiopathic (IDDC) vs ischemic dilated Cardiomyopathy (ISDC). It was hypothesized that similar would be the findings with regards left atrial systolic reserve.
Methods: Twenty-six patients with IDDC, 28 with ISDC and 25 normal controls underwent low dose Dobutamine stress echocardiography (5-10 μg/kg/min IV). Left atrial volumes were echocardiographically determined at rest and after stress at mitral valve opening (maximal, LA max), electrocardiographic P wave (onset of atrial systole, LAp) and mitral valve closure (minimal, LA min) from the apical 4- and 2-chamber views (biplane area-length method). Left atrial systolic function was assessed with the left atrial active emptying volume (ACTEV)=Vp-Vmin and fraction (ACTEF)=ACTEV/Vp.
Results: LAmax at rest was similar in IDDC and ISDC and greater than control (54.2±12 vs. 48.5±18 vs. 27.1±6.3 cm^3/m^2 respectively $p<0.001$) and did not change during stress (53.9±13.8 vs. 46.9±16,2 vs.25.8±5.9 cm^3/m^2, $p<0.001$). ACTEV at rest was similar in IDDC and ISDC and greater than control (8.6±3,5 vs. 9.7±2.9 vs. 6.1±2.2 cm^3/m^2 $p<0.01$) but during Dobutamine infusion it remained unaltered in idiopathic (10,8±4.6 cm^3/m^2, p=NS vs rest) and increased in ischemic cardiomyopathy (11.8±3.3 cm^3/m^2, $p< 0.05$) and control. (13.1±3.2 cm^3/m^2, $p<0.01$). ACTEF was lower in IDDC than ISDC and control at rest (20±10% vs. 33±8% vs. 36±10%, $p<0.001$). Dobutamine infusion was associated with no significant increase in ACTEF in IDDC (25±12%, p=NS vs. rest) and with an increase in this variable in ISDC (39±10%, $p<0.05$) and control (49±12%, $p<0.01$).
Conclusions: Dobutamine infusion is associated with an increase in left atrial active emptying volume and fraction in ISDC and no significant changes of these indices in IDDC. These findings indicate reduced left atrial systolic reserve in the latter.

P3173 Do geometry of left ventricular outflow tract determine transmitral inflow velocity patterns?

S.Y. Yoo, S.G. Ahn, J.H. Choi, S.Y. Choi, M.H. Yoon, G.S. Hwang, S.J. Tahk, J.H. Shin. *Ajou University School of Medicine, Cardiology Department, Suwon, Korea, Republic of*

Background: aging is an important factor to determine transmitral inflow velocity pattern. Geometry of left ventricular outflow tract (LVOT) such as aortoseptal angle (ASA) was changed with age. An anterior vortex within left ventricle (LV) developed interacting with mitral valve motion and inflow velocity. We hypothesised that geometry of LVOT may influence transmitral inflow pattern.
Methods: healthy 115 (61 men, 37 ± 15 years) individuals were enrolled. Echocardiography was performed to measure LV mass, thickness, left atrial (LA) size, ASA, early (E) and late (A) transmitral inflow velocity, and deceleration time (DT). ASA was measured at mid-diastole in apical long-axis view according to a method as the open angle between the edge of the interventricular septum and axis perpendicular to the aortic annulus. The relation between transmitral inflow velocity patterns and LV geometric parameters was analysed by regression analysis.
Results: simple regression analysis demonstrated a significant correlation between transmitral inflow parameters with age and geometric parameters (Table). Multiple regression analysis, taking into consideration age, ASA, LA size and LV mass index showed that only age was an independent predictor for E, A, DT, and E/A ratio (r2 = 0.210, Beta coefficient (β) = 0.459, $p <0.001$; r^2 =0.427, β = 0.654, $p <0.001$; r^2 =0.227, β =-0.476, $p <0.001$; r^2 =0.436, β = -0.661, $p <0.001$, respectively).

Table 1

	Mean±SD	r Coefficient			
		E (cm/sec)	A (cm/sec)	DT (msec)	E/A ratio
Age (years old)	37 ± 15	-0.475†	0.663†	0.464†	-0.670†
ASA (degree)	135 ± 13	0.395†	-0.546†	-0.480†	0.514†
LA size (mm)	35 ± 5	-0.229*	0.515†	0.319*	-0.443†
LV mass index(g/BSA)	92.7 ± 20.0	-0.225*	0.491†	0.277*	-0.423†

*$p < 0.05$, †$p < 0.001$

Conclusion: transmitral inflow velocity patterns underwent various influences. Although ASA, a parameter of LVOT geometry is a factor influencing LV inflow velocity, its significance is limited.

P3174 X syndrome revisited

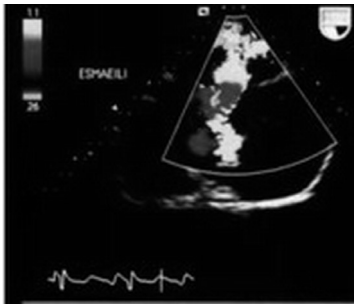
C. Cotrim[1], O. Simoes[1], M.J. Loureiro[2], P. Cordeiro[1], M. Iala[1], H. Vinhas[1], J. Guardado[1], M. Carrageta[1]. *[1]Cardiology, Almada, Portugal; [2]Cardiology, Almada, Portugal*

Introduction: It is reported that the development of intraventricular gradients (IVG) on exertion seldom occurs. We performed exercise stress echocardiography in a 23-year-old athlete with atypical angina, a positive treadmill ECG and normal rest echocardiogram, and without angiographically demonstrable coronary disease. During stress echocardiography he developed IVG of 105mmHg and systolic anterior movement of the mitral valve (SAM).
Purpose: To evaluate IVG and mitral valve SAM during stress echocardiography in pts with positive exercise ECG testing and normal coronary angiography.
Methods: We conducted a prospective evaluation of 64 patients (pts), mean aged 50,3±12, 5 years (age range, 20 to 75 years), 35 were women. All pts had positive exercise ECG treadmill testing, normal rest echocardiogram and no coronary artery disease on coronary angiogram (cardiac X syndrome). They all underwent stress echocardiography with 2D and Döppler echographic evaluation before, during and after treadmill exercise.
Results: Döppler evidence of IVG was found in 22 pts, mean aged 44,8±14,3 years (age range, 20 to 72 years), 14 men (Group A). This group developed IVG with a mean end-systolic peak of 101±41 mmHg (30 to 180mmHg) accompanied by mitral valve SAM (figure 2) in 16 pts. GIV development was complicated by symptomatic hypotension in two of these pts. The 42 pts in Group B, mean aged 53,2±10,5 years, with an age range from 34 to 75 years, ($p<0,05$ vs group A), 15 of them men, didn't develop IVG and three of them developed left ventricular segmental wall motion abnormalities.
Conclusions: 1. A significant number of pts with X syndrome developed IVG during upright exercise. These pts (Group A) are mainly males and younger than those who didn't develop IVG. 2. The authors propose that the development of mitral valve SAM and IVG on exertion might be associated with ST segment downsloping during stress testing in pts without epicardial coronary disease. 3. Pts with positive exercise ECG testing and normal epicardial coronary blood flow can develop new regional wall motion abnormalities during exercise.

P3175 Quantitation of left-to-rigth shunt in patients with secundum ASD by PISA method

M. Esmaeilzadeh[1], M. Maleki[2], F. Noohi[2], Ojaghi[2], A. Mohebbi[2]. *[1]Shahid Rajaee Heart Center, Dept. of Cardiology, Tehran, Iran (Islamic Republic of); [2]Shahid Rajaee Heart HospitaL, Echocardiography, Tehran, Iran (Islamic Republic of)*

Objectives: The aim of this study is to evaluate the accuracy of the PISA method for quantitation of the degree of shunt flow in patients with secundum ASD.
Methods: We studied 48 consecutive patients with secundum ASD, who were refered to our echocardiography department for evaluation of suitability for device closure.There were 33 (70%) females and 15(30%) males aged between 18-54 years (mean: 32.5±4.2 years).The defect size was between 12-40 mm (mean: 26±6 mm).In all the patients, the degree of left to right shunt(QP/QS) was measured by continuity equation and PISA methods. Qp would be equal to QS adds ASD volume, measured by PISA.The patients were classified into three groups based on their defect size (small, moderate, and large) and the degree of the shunt.



ASD - PISA

Results: QP/QS by continuity equation was between 1.7- 4.5/1 (mean: 2.91), and by PISA method was between 1.6-4.8/1(mean:2.92). There was no significant difference between the degree of shunt estimated by the continuity equation and PISA methods in terms of the defect size and the degree of shunt (PV=0.179). The correlation coefficient between two methods was significant(r=0.92, PV=0.0001)
Conclusions: This study shows PISA could be as an accurate alternative method of the continuity equation for quantitation of the degree of shunt flow in patients with secundum ASD. This method is highly recommended in patients with pulmonary stenosis, significant pulmonary regurgitation and poor image view of pulmonary valve.

COMPUTERS IN CARDIOLOGY

P3176 Validation of a new semi-automatic method for lumen and media-adventitia borders detection in sequential intravascular ultrasound images

G.D. Giannoglou[1], I.S. Hatzizisis[1], V.G. Koutkias[2], I. Kompatsiaris[3], P. Diamantopoulos[4], N. Maglaveras[2], G.E. Parcharidis[1], G.E. Louridas[1]. *[1]AHEPA University Hospital, 1st Cardiology Department, Thessaloniki, Greece; [2]Aristotle University of Thessaloniki, Laboratory of Medical Informatics, Thessaloniki, Greece; [3]Center for Research and Technology, Informatics and Telematics Institute, Thessaloniki, Greece; [4]University of Sussex, Department of Engineering and Design, Sussex, United Kingdom*

Purpose: The purpose of this study is to describe and validate a new semi-automatic method for lumen and media-adventitia (EEM) contour detection in sequential intravascular ultrasound (IVUS) images.
Methods: The ultrasound data set was obtained with a 40 MHz, 2.6F sheath-based catheter at an automatic pullback speed of 0.5 mm/sec and the images along with the ECG were directly digitized at a rate of 30 frames/sec. The lumen and EEM borders were detected in each frame with a custom-developed algorithm, which was based on active contour models, also known as snakes. The first step of the procedure included the consecutive initialization of two snakes for lumen and EEM borders respectively in the first frame. The snakes deformed automatically by minimizing their energy function to capture the corresponding boundaries and then were applied to the next frames of the sequence. The final output was reviewed by the user and, if it was not the optimal, the above steps were iterated starting from the frame where the detected boundary diverged from the actual one. The intra- and inter-observer agreement for manual and semi-automatic segmentation was assessed by two independent experts, who initially and a month apart performed manual and semi-automatic tracing in fifty randomly selected images. The comparing parameters were lumen cross-sectional area (LCSA) and EEM cross-sectional area (EEMCSA). The semi-automatic segmentation of the fifty images compared with reference manual (average of two experts) for the same parameters with linear regression and Bland-Altman analysis.
Results: The intra-observer correlation coefficients for LCSA and EEMCSA were 0.986 and 0.997 respectively for manual and 0.963 and 0.995 respectively for semi-automatic segmentation. The inter-observer r-values for LCSA and EEMCSA were 0.964 and 0.981 respectively for manual and 0.969 and 0.988 respectively for semi-automatic segmentation. All r-values were statistically significant ($p<0.0001$). Linear regression analysis for comparison of semi-automatic with reference manual segmentation yielded the equations $y=0.93x+0.224$ and $y=1.014x-0.144$ for LCSA and EEMCSA respectively ($p<0.0001$). Bland-Altman analysis of the new method versus the reference manual resulted in relative differences for LCSA and EEMCSA of $-3.4\pm17.9\%$ and $-0.3\pm8.6\%$ respectively. The average analysis time for the entire set of fifty images was reduced significantly by 75% (from 60 to 15 minutes).
Conclusions: Our new method provides an accurate, feasible and time-saving assessment of coronary lumen and EEM borders in serial IVUS images.

P3177 Complex assessment of aortic morphology and wall texture by IVUS and neural networks-based approach – in-vitro correlation study with histology

L. Chrzanowski[1], J.D. Kasprzak[1], K.S. Jedrzejewski[2], J. Drozdz[1], M. Strzelecki[3], M. Ciesielczyk[1], P. Lipiec[1], M. Krzeminska-Pakula[1]. *[1]Medical University of Lodz, II Chair and Department of Cardiology, Lodz, Poland; [2]Medical University of Lodz, Chair of Morphology, Lodz, Poland; [3]Technical University of Lodz, Institute of Electronics, Lodz, Poland*

IVUS has been shown to correlate well with histology (HIST) and angioscopy, but the data on large elastic arteries imaging are scant. Neural networks (NN) are helpful in ultrasound image processing, and their potential to identify HIST from sonographic texture (TXR) appearance needs further validation.
Aim: to compare IVUS measurements (MMs) of the aorta (Ao) with reference method – HIST and to evaluate the feasibility of NN-based approach for the TXR analysis.
Methods: human thoracic Ao specimens were examined in-vitro by 10 MHz IVUS and matching HIST sections were stained with rezorcine to visualize elastic fibres of media (EFIM). Diameter, intima-media thickness (IMT) and cross-sectional area (CSA) were measured at 45 matching regions of IVUS and HIST; 291 parameters (PRs) of image TXR were calculated from pixel-, 2nd order histogram, gradient- and run length matrix. 3 optimal discriminators were selected and separation was assesed for 2 vectors of each PR from 36 matching IVUS still frames and digitized HIST images by linear and NN-based approach.
Results: good correlation was observed for CSA (r=0.98) and aortic lumen diameter (ALD)(r=0.82), while discrepancy - for IMT (r=0.67) - all $p<0.0001$. The IVUS TXR PRS showed good correlation with HIST ($r>0.8$). In HIST datasets, NN discriminated best calcified specimens and those with increased amount of EFIM. At IVUS, only calcium-reach segments were easily identifiable, with positive trend in correct recognition of EFIM overload (Fig. 1).

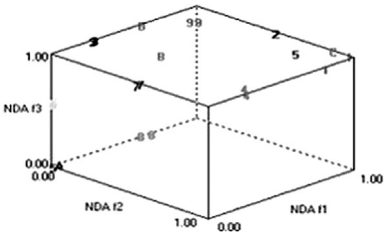


Figure 1

Conclusions: ALD and CSA by IVUS correlate well with HIST, while IMT shows poor agreement. The use of NN is feasible for TXR analysis of IVUS Ao images. NN-based approach correctly identifies calcified tissue and may facilitate detection of subtle abnormalities in aortic wall.

e-POSTER SESSION 9

MODERATED e-POSTERS: FUNCTIONAL MITRAL REGURGITATION: THE ROLE OF ECHOCARDIOGRAPHY

P3335 Long-term outcome of patients with heart failure and dynamic functional mitral regurgitation

P.L. Lancellotti[1], P.G. Gerard[2], A. Ancion[2], L.A. Pierard[2]. *[1]CHU Sart Tilman, Service de Cardiologie, Bâtiment B 35, Liège, Belgium; [2]University Hospital, Cardiology Dept., Liège, Belgium*

Aims: In patients with heart failure and chronic ischaemic mitral regurgitation (MR), the mortality risk is related to the quantified severity of MR at rest and its dynamic changes during exercise. The impact of dynamic MR on long-term mortality, hospital admission for heart failure and major adverse cardiac events has never been investigated.
Methods and Results: We prospectively studied 161 patients with chronic ischaemic left ventricular (LV) dysfunction and at least mild MR who underwent quantitative measurement of the effective regurgitant orifice (ERO) of MR at rest and during semi-supine exercise test and who were followed up for 37 ± 9 months. The 20 patients who underwent surgery were censored at the time of operation. Of the 141 patients who were treated medically, 23 died, 22 required hospitalization for heart failure, 4 had nonfatal myocardial infarction and 11 developed unstable angina. By multivariate analysis, an exercise-induced increase in ERO by ≥ 13 mm^2 and a greater increase in transtricuspid pressure gradient during exercise emerged as predictors of mortality and of hospital admission for heart failure. MR severity under basal conditions (ERO ≥ 20 mm^2) was an independent predictor of only cardiac death. Greater LV volumes at rest and lack of contractile reserve during exercise were additional independent markers of poor outcome.
Conclusion: In patients with ischaemic heart disease and LV dysfunction, large exercise-induced increases in MR identify patients at high risk of morbidity and of death.

P3336 Ischaemic mitral regurgitation is an important determinant of E over Em in patients with stable coronary artery disease

J.H.A.J. De Sutter, A.K. Ascoop, N.R. Van de Veire, T.C. Gillebert. *University Hospital Gent, Dept. of Cardiovascular Diseases, Ghent, Belgium*

Background: The ratio of early diastolic transmitral velocity (E, obtained by transmitral Doppler) to early diastolic medial annulus velocity (Em, obtained by Tissue Doppler Imaging) or E/Em is increasingly used to estimate left ventricular (LV) filling pressure noninvasively. We studied the relationship between E/Em and severity of ischemic mitral regurgitation (IMR) in a large population of patients with coronary artery disease (CAD).
Methods: We studied 849 consecutive stable CAD patients (age 67 ± 10 years, 76% men). LV diameters, left atrial (LA) diameter and LV mass were determined by 2D echocardiography. LVEF was graded as 1 (LVEF>55%), 2 (LVEF 41-55%), 3 (LVEF 26-40%) or 4 (LVEF<26%). Em was determined at the medial annulus using pulsed wave TDI and E/Em was calculated. IMR was graded as absent or

trace (n=212, 25%), mild (n=395, 46%), moderate (n=207, 24%) or severe (n=35, 5%).

Results: Results of LVEF class, LV and LA parameters (indexed for body surface area), Em and E/Em according to severity of IMR are given in the table. An even mild increase of IMR was clearly associated with a decrease of Em and increase of E/Em ($p<0.001$). Multivariate linear regression analysis including IMR, LVEF grade, LV and LA dimensions, age, gender and LV mass, showed that E/Em was mainly determined by IMR and LVEF class, followed by age, gender and LV mass (all $p<0.01$).

	IMR trace (n=212)	IMR mild (n=395)	IMR moderate (n=207)	IMR severe (n=35)	p value ANOVA
LVEDDind (mm/m^2)	23.5±4.0	25.0±4.3	27.0±4.3	31.7±5.7	0.001
LVESDind (mm/m^2)	16.2±4.5	17.3±4.5	19.5±5.1	26.1±7.6	0.001
LAind (mm/m^2)	17.4±6.4	19.1±7.9	22.3±6.4	22.0±9.1	0.001
Em (cm/se)	5.9±2.0	5.7±2.2	5.0±1.8	4.7±1.9	0.001
E/Em	11.9±4.8	12.8±5.5	15.1±7.0	16.7±7.5	0.001
LVEFclass	1.5±0.8	1.7±0.9	2.1±1.0	3.0±1.1	0.001

Conclusion: IMR is an important independent determinant of E/Em in patients with stable coronary disease. Even mild to moderate IMR is associated with an increase of this noninvasive marker of LV filling pressure.

P3337 Preserved papillary muscle function with significant adjacent left ventricular wall remodelling contributes to ischaemic mitral regurgitation in patients with prior inferior myocardial infarction

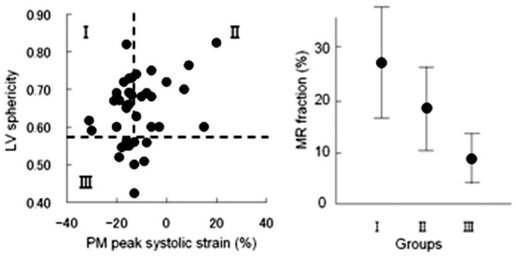
T. Uemura[1], Y. Otsuji[1], K. Nakashiki[2], B. Yu[1], A. Kisanuki[1], S. Minagoe[1], R. Levine[3], C. Tei[1]. *[1]Kagoshima University, Cardiovascular center, kagoshima, Japan; [2]Kagoshima University, Cardiovascular center, Kagoshima, Japan; [3]Massachusetts General Hospital, Cardiac Ultrasound lab., Boston, United States of America*

Background: In the genesis of chronic ischemic mitral regurgitation (MR), left ventricular (LV) remodeling causes outward displacement of the papillary muscle (PM) to induce leaflet tethering and MR. However PM contractile dysfunction with its systolic elongation can potentially attenuate leaflet tethering. Therefore, we hypothesized that significant adjacent LV wall remodeling with preserved PM function contributes to ischemic MR in patients with prior inferior myocardial infarction (MI).

Methods: In 40 patients with prior inferior MI, PM function was evaluated by longitudinal systolic shortening by tissue Doppler strain imaging, adjacent LV wall remodeling was measured by LV sphericity or short-to-long axis dimension ratio in the apical 2-chamber view, and MR was quantified by Doppler echocardiography. Patients were then classified into 3 groups: group I with significant LV remodeling but good PM function, group II with significant LV remodeling and PM dysfunction, and group III without significant LV remodeling.

Results: 1) Compared to patients without adjacent LV remodeling (group III), those with LV remodeling (group I+II) had significantly greater MR fraction (23±13 vs. 7±5%, $p<0.01$).

2) Among the patients with adjacent LV wall remodeling (groupI+II), those with preserved PM function had greater MR fraction (28±14 vs. 17±8%, p=0.01).



Conclusion: Preserved PM function with adjacent LV remodeling contributes to ischemic MR in patients with prior inferior MI.

P3338 Prognostic significance of myocardial viability during stress-echo in patients with severe ischaemic heart failure and papillary muscle distortion for postoperative mitral valve competence

N. Maroz-Vodolazskaya, O. Kardash, V. Shumovetz, I. Vodolazhskiy, I. Ostovskiy. *Scientific-Practical Center Cardiology, Cardiovascular Surgery, Minsk, Belarus*

One of the important leadings of the mitral valve surgery in patients with coronary artery disease is a preservation of the normal physiology and mobility of the mitral valve apparatus. Septal-lateral annular dilatation has been shown to be the principal cause of the leaflet malcoaptation for DCMP.

The estimation of link between the myocardial viability in area of papillary muscle and left ventricular (LV) remodeling on the mitral valve (MV) competence after its surgery in patients with ischemic heart failure was aimed.

Cohort of 21 patients (LVEF 0.31±0.04, NYHA 3.1±0.5, mitral regurgitation (MR) >3 degree, systolic pulmonary artery pressure (PAP) 50±6.9 mm Hg, EDV 245.2±45.6 ml, WMI 2.56±0.34, was undergone low dose dobutamine echo before open heart surgery. All patients were operated in similar condition with CABG (mean shunts 2,9±0,4), LV plasty (for apical aneurysm – 12 cases, for diffuse LV dilatation – 14 cases) and MV plasty (durable original ring- 16 pts, Calafiore-10 pts). Mean follow-up was 5,5 months (1-12 months). Two patients (9.5%) died before discharge, one patient (4.76%) - at 6 months after surgery.

MR was assessed with biplane color Doppler, VTI of the MR jet in CW, diameter of "vena contracta". The angle between the MV axis and antero-lateral papillary muscle (ALPM) axis (Angle) and diastolic spherical index (SI, gr.1-0,82 and gr.2-0,76, p between group >0,05) were applied for estimation of LV remodeling.

For whole cohort the positive inotropic response of LV was revealed (p=0.0004, pair t-test). Accordingly dobutamine function of ALPM (16-segments model) the patients were divided on to 2 groups: 1- 11 pts with the no dynamics of contractility (scar), 2 –15 pts with improving of the contractility of akinetic segment or induced ischemia of the hypokinetic segment (viable myocardium). Groups were similar in the size of LV, MR degree, LVEF, SI, MV procedure.

At 7 day after surgery all patients demonstrated significant improving of the LV pump function (p=0,003), WMI (p=0,0002), decreasing of MR degree (p=0,004), improving of the functional status ($p<0,001$). In spite of similar basal condition and surgery groups were different in the dynamics of MR early after opeation (MR grade 2,1±0,4 in gr.1 and 0,9±0,3 in gr.2, p between groups 0,01).

So, bypass grafting leads to improving of the LV wall contractility and decreasing of the MR. The positive inotropic response of ALPM segment followed by statistically significant improving of the mitral valve closing function in spite of basal papillary muscle distortion and non elliptic form of the LV.

P3339 The degree of functional mitral regurgitation predicts NT-proBNP plasma levels in patients with either ischaemic or idiopathic dilated cardiomyopathy

F.L. Dini, E. Cabani, S. Banti, U. Conti, S.M. De Tommasi. *Santa Chiara Hospital, Cardiovascular Diseases Unit 2, Pisa, Italy*

Background: It has been clearly demonstrated that NT-proBNP plasma levels increase with the degree of mitral regurgitation (MR) in patients with primary mitral valve disease. However, it is not clear whether there is an association between the severity of functional MR and NT-proBNP in patients with dilated cardiomyopathy.

Aim: To focus on the relationships between the degree of functional MR and NT-proBNP plasma levels in patients with either ischemic or idiopathic dilated cardimyopathy.

Methods: We studied 211 patients (24% female) diagnosed with either ischemic or idiopathic dilated cardiomyopathy submitted to a complete Doppler and echocardiographic study. The eligible patients had to have a left ventricular (LV) end-diastolic volume >75 ml/m^2 and a LV ejection fraction (EF) <45%. They were subsequently divided into groups according to the color-coded maximal MR jet area in the left atrium assessed in two planes from the apical window: no or trivial MR (group 1, n=83), mild-to-moderate MR (≤5 cm^2, group 2, n=73), severe MR (>5 cm^2, group 3, n=55). At the time of enrollment, a bood sample was drawn for measurement of NT-proBNP plasma levels.

Results: The prevelence of coronary artery disease was 55%. Mean LV EF and NT-proBNP plasma levels were 31±6% and 1326±558 pg/ml. Forty-three percent of patients were in NYHA class >2. At linear regression analysis, significant correlations with NT-proBNP plasma levels were found with EF (r: 0.28), mitral E/A ratio (r: 0.35), mitral E wave deceleration time (r: 0.31), tricuspid regurgitant jet-derived pulmonary artery systolic pressure (PASP) (r: 0.33) and MR jet area (r: 0.40). Stepwise multiple regression analysis showed that MR jet area was the most potent independent predictor of NT-proBNP plasma levels followed by EF and PASP (multiple R value: 0.47). Patients with severe MR exhibited higher NT-proBNP plasma levels as compared to those with mild-to-moderate MR and those with no or trivial MR ($p<0.01$, group 1 vs group 3).

Conclusions: In patients with either ischemic or idiopathic dilated cardiomyopathy, the degree of MR at color Doppler imaging was found to be the most important predictor of NT-proBNP plasma levels. Since natriuretic peptides are powerful predictors of prognosis, this information may be helpful for establishing patient's therapeutic strategy.

P3340 3D real time vs 2D transthoracic echocardiography in mitral regurgitation assessment before revascularisation after myocardial infarction

P. Scislo[1], J. Kochanowski[2], P. Suwalski[2], R. Piatkowski[2], D. Kosior[2]. *[1]Warsaw, Poland; [2]The Warsaw Medical University, Dept of Cardiology, Warsaw, Poland*

Correct assessment of mitral regurgitation (MR) at patients (pts) after myocardial infarction qualified to coronary artery by-pass grafting (CABG) is a critical factor for extending the operation to mitral valve surgery or not. We compare results techniques used for this evaluation 2D transthoracic echo (2D TTE) and real time 3D transthoracic echo (3D TTE) with reference method multiplane transesophagial echocariography (TEE).

We analyzed 45 pts with MR after MI, referred to echo before CABG.

Each pts had independent assessment of MR by 2D TTE and 3D TTE by 2 inde-

pendent sonographers (in 1 case randomly, one of them made 2D TTE, second 3D TTE). After TTE in each pts TEE were done for MR verification.
The TTE and TEE were realized using Philips Sonos 7500 with D2 software package and with Philips iE33. All studies were recorded digitally for further re-assessment. For MR quantification we used method of regurgitation fraction, mild MR <20%, moderate 20-40%, severe >40% in best view.
Results: All TTE results we compare with reference method - TEE. In TEE we found 1+ MR in 15 (33%) pts, 2+ MR in 22 (49%), 3+MR 8 (18%) pts. In 2D TTE we found 1+ MR in 20 (44%) pts, 2+ MR in 20 (44%), 3+MR 5 (12%) pts. In 3D TTE we found 1+ MR in 14 (31%) pts, 2+ MR in 23 (47%), 3+MR 8 (22%) pts.

Table 1

	2D	3DRT	
Correct	35	43	p=0,013
Incorrect	10	2	Chi2=6,15

Conclusion: Real time 3D TTE is a better diagnostic method than 2D TTE in MR assessment because of opportunity of spatial reconstruction.

INFLAMMATION AND PLAQUE REMODELLING

P3341 Transcriptional suppression of CRP expression in hepatocytes by ligand-induced activation of liver-X receptors

F. Blaschke[1], Y. Takata[2], E. Caglayan[2], C. Lyon[2], E. Fleck[3], R. Tangirala[2], W. Hsueh[2]. *[1]University of California, Endocrinology, Diabetes, Hypertension, Los Angeles, United States of America; [2]University of California, Endocrinology, Diabetes, Hypertension, Los Angeles, United States of America; [3]Deutsches Herzzentrum Berlin, Kardiologie und Innere Medizin, Berlin, Germany*

C-reactive protein (CRP) is the prototypic acute phase protein and an independent risk predictor of future cardiovascular events. Recent clinical trials suggest that strategies to aggressively lower cardiovascular risk should beside cholesterol also include monitoring and lowering serum CRP levels. We demonstrate here that the Liver X receptors (LXR alpha and beta), members of the nuclear hormone receptor superfamily and important regulators of cholesterol homeostasis and inflammatory gene expression in macrophages inhibit cytokine-induced expression of CRP. Treatment of primary human hepatocytes and Hep3B cells with the synthetic LXR agonists T0901317 or GW3965 (0.1 – 5 μM) dose-dependently reduced cytokine (IL-6 10 ng/ml plus IL-1β 20 ng/ml) induced CRP mRNA and protein expression as determined by Northern blotting, quantitative real-time PCR and ELISA assay. Transient transfection of the human CRP promoter (- 964 bp to + 9 bp) in Hep3B cells revealed that LXR activation by T0901317 and GW3965 dose-dependently inhibited CRP promoter activity. Co-transfection of LXRa/RXR expression vectors further increased LXR ligand-mediated CRP promoter repression, indicating a LXR receptor-dependent mechanism. Sequence analysis of the 5'-flanking region of the CRP gene did not reveal the presence of potential LXR response elements, indicating that the mechanism for this effect is likely to be indirect. Analysis of truncated CRP promoter constructs using systematic series of 5'-deletions revealed that a region between –256 to -125 relative to the initiation site is required for the ability of LXR to inhibit CRP promoter activity. This region contains a binding site for the hepatocyte nuclear factor-1 alpha (HNF-1a). Overexpression of wild-type HNF-1a increased CRP promoter activity, whereas expression of a dominant-negative HNF-1a mutant resulted in a significant reduction of both basal and IL-6/IL-1β induced CRP promoter activity. However, electrophoretic mobility shift experiments demonstrated that LXR ligands did not affect HNF-1a DNA binding capacity, suggesting that LXR ligands might affect binding of coactivator and corepressor complexes to HNF-1a, thus modulating HNF-1a transcription activity. In summary, our results demonstrate that ligand activation of LXR represses CRP gene transcription in hepatocytes. These results define a novel function of LXRs in the control of liver CRP gene expression and support the potential utility of LXR ligands in modulating inflammatory gene responses and inhibiting the development of atherosclerosis.

P3342 Statins reduce C-Reactive protein in hepatocytes: new evidence for anti-inflammatory effects of statins

C. Arnaud, V. Braunersreuther, S. Steffens, F. Burger, F. Mach. *Geneva University Hospital, Division of Cardiology, Geneva, Switzerland*

Background: Recent clinical trials showed that C-reactive protein (CRP), a major acute-phase protein, is a powerful independent predictor of future cardiovascular events. Besides its predictive role in determining cardiovascular risk, CRP could exert direct proatherogenic effects. CRP is mainly produced by hepatocytes in response to interleukin-6 (IL-6), and is then released into the systemic circulation. HMG-CoA reductase inhibitors, or statins, have been shown to significantly reduce cardiovascular events and mortality in patients with or without coronary artery disease, and are well known to reduce plasma CRP levels in humans. However, the mechanism by which statins reduce plasma CRP remains unknown.
Methods and Results: In this study, we report that atorvastatin (0.1 and 1 μM), simvastatin (1 μM) and pravastatin (10 and 20 μM) reduce IL-6-induced CRP release in human hepatocytes. We demonstrate by ELISA and real-time quantitative RT-PCR that statins reduce both protein and RNA levels of IL-6-induced CRP in hepatocytes. These effects are reversed by mevalonate and mimicked by an inhibitor of the geranylgeranyltransferase. IL-6-induced CRP production requires the binding of IL-6 to its cognate receptors, which results in activation and phosphorylation of the transcription factor STAT3. We provide evidence that statins reduce this IL-6-induced phosphorylation of STAT3 in hepatocytes.
Conclusion: These results demonstrate that statins reduce IL-6-induced CRP production directly in hepatocytes, via inhibition of protein geranylgeranylation. We further show that statins act via inhibition of STAT3 phosphorylation. These findings bring new evidences for direct anti-inflammatory properties of statins, which may help to better understand their great clinical benefits.

P3343 Does plasma concentrations of adiponetin predict severity of coronary artery disease?

A.A.M. Farrag[1], Y. Baghdady[2], A. Rizk[3], H. Yehia[2], M. Gamil[4], A. El-Naggar[3]. *[1]Giza, Egypt; [2]Cairo University, Cardiovascular Medicine, Cairo, Egypt; [3]Cairo University, Critical Care Dept., Cairo, Egypt; [4]Cairo University Hospital, Internal Medicine Dept., Cairo, Egypt*

Purpose: Adiponectin is an adipocyte derived plasma protein that shows a number of anti-atherogenic properties. It is abundantly present in the circulation and also accumulates in the injured arteries. This study was designed to determine whether a decreased plasma adiponectin level is associated with the extent of atherosclerosis in patients with coronary artery disease (CAD).
Methods: Plasma concentrations of adiponectin were measured in 97 patients with CAD and 22 age and sex matched healthy controls. All patients underwent coronary angiography for clinical purposes. Patients were divided into two groups according to the number of coronary plaques causing >50% diameter stenosis by quantitative angiography (QCA): group 1; ≤3 plaques (n= 47) and group 2; >3 plaques (n=50) with a particular focus on the relation between plasma adiponectin concentrations and the presence or absence of cine-angiographic evidence of coronary calcification (a marker of heavy atherosclerotic burden).
Results: Plasma concentrations of adiponectin in patients with CAD were significantly lower than in control group (4.6 ± 3.7 vs 7.3 ± 2.4 ug/ml, p= 0.03). Patients in group 2 had a significantly lower plasma adiponectin level than patients in group 1 (3.6 ± 2.7 vs 5.7 ± 4.5 ug/ml, p= 0.05). Patients with calcified lesions had also a significant lower level of plasma adiponectin than patients with no evidence of cine-angiographic calcification (3.4 ± 1.9 vs 5.2 ± 4.3 ug/ml, p= 0.05). On the other hand, plasma adiponectin level showed a significant negative correlation with body mass index (BMI) (r= -0.313, p= 0.015). Multiple regression analysis showed that plasma adiponectin concentrations correlated independently with increased number of coronary plaques >3 (p= 0.05).
Conclusion: The present study showed that decreased plasma adiponectin concentrations can predict severity of CAD and may be related to increased atherosclerotic burden.

P3344 Decreased mRNA expression of peroxisome proliferator activated receptor-a and -d in blood monocyte of patients with severe coronary artery disease

J.Y. Hwang[1], H.G. Seo[2], S.J. Park[1], C.H. Kwak[1], J.R. Park[1]. *[1]Gyeong-Sang National University, Internal Medicine, Jinju, Korea, Republic of; [2]Gyeongsang Institute of Health Science, Pharmacology, Jinju, Korea, Republic of*

Numerous basic research indicates that activation of peroxisome proliferator activated receptors(PPAR) family, consisting of PPAR-alpha, -delta and –gamma, may beneficial effects on initiation and progression of arterial atherosclerosis. Especially each of PPARs is known to influence the lipid uptake and efflux, inflammatory mediator production in macrophage.
Aim: To explore the activities of individual PPAR subfamily protein in blood monocytes of patients with severe atherosclerosis, comparing with those of mild or disease free subject determined by coronary angiography.
Method: Monocyte rich buffycoat layer was isolated from blood samples of seventeen patients with two or three coronary artery disease and seventeen control subject. all extracted mRNAs were analyzed simultaneously by quantitative real time reverse transcription polymerase chain reaction using subfamily specific primer

	Mild or Disease free control subject (N=17)	Coronary artery disease group (N=17)	P value
Age, year	56 ± 13	63 ± 9	0.108
Body weight, kg	63 ± 8.7	65 ± 6.7	0.428
Hypertension, number (%)	5 (29)	9 (52)	0.163
Diabetes mellitus	3 (17)	6 (35)	0.244
Total cholesterol, mg/dl	192 ± 31	193 ± 54	0.018
Smoking	5 (29)	6 (35)	0.714
PPAR-alpha expression ratio	1174.4 ± 460.0	261 ± 157.0	0.003
PPAR-delta expression ratio	191.1 ± 55.4	82.4 ± 60.6	0.001
PPAR-gamma expression ratio	28.7 ± 11.5	21.3 ± 10.8	0.642

Results: mRNA expression of PPAR-alpha and -delta were markedly decreased in patients with coronary artery disease than in mild or disease-free control subject. The mRNA expression of PPAR-gamma showed statistically no significant difference between both groups (Table).
The expression level of PPAR-alpha, PPAR-delta and PPAR-gamma showed the positive correlation (PPAR-alpha and -delta, r=0.61, P<0.0001; PPAR-alpha and -gamma, r=0.715, P<0.0001; PPAR-delta and –gamma, r=0.71, P<0.0001)
Conclusion: This result suggests that decreased activity of PPAR-alpha and PPAR-delta in human monocytes may be related with atherosclerotic disease progression

P3345 Postprandial, but not postabsorptive low-density lipoproteins increase the surface expression of intercellular adhesion molecule-1 in human endothelial cells

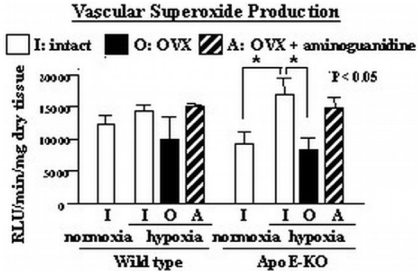
P. Marschang, C. Goetsch, R. Kirchmair, S. Kaser, C.M. Kaehler, J.R. Patsch. *Innsbruck Medical University, Department of Internal Medicine, Innsbruck, Austria*

Background: The magnitude of postprandial lipemia has been identified as independent risk factor for the development of coronary artery disease. One of the first steps in atherogenesis is the adherence of leukocytes to the endothelium, which is mediated by adhesion molecules. We tested the hypothesis that postprandial low-density lipoproteins (LDL) may be more effective than postabsorptive LDL in upregulating adhesion molecules on the surface of endothelial cells.
Methods: LDL were isolated from human plasma before and after ingestion of a standardized fatty test meal. We used flow cytometry and Northern blotting to quantify cell adhesion molecules in human aortic endothelial cells. The adherence of leukocytes to endothelial cells was analyzed with a monocyte adhesion assay.
Results: Incubation of endothelial cells with postprandial, but not postabsorptive LDL induced a twofold increase of intercellular adhesion molecule-1 (ICAM-1) surface expression. No differences were observed for E-selectin and vascular cell adhesion molecule-1. We found increased amounts of ICAM-1 transcripts in endothelial cells treated with postprandial LDL. The adhesion of monocytes to endothelial cells was increased after pretreatment with postprandial, but not postabsorptive LDL.
Conclusions: Postprandial, but not postabsorptive LDL increase the surface expression of ICAM-1 in human aortic endothelial cells. The increase of ICAM-1 appears to be due to de novo synthesis and leads to increased adhesion of monocytes. In conclusion, the upregulation of ICAM-1 by postprandial LDL may explain part of the proatherogenic effect of high postprandial lipemia.

P3346 Endogenous estrogen suppresses exacerbation of atherosclerosis by regulating MMP-9 activity and iNOS production in apoE-KO mice exposed to hypoxia

T. Hayashi[1], T. Mori[2], N. Tazawa[3], D. Nakano[3], K. Sohmiya[1], Y. Okada[4], Y. Matsumura[3], Y. Kitaura[1]. *[1]Osaka Medical College, 3rd Department of Medicine, Takatsuki, Osaka, Japan; [2]Osaka Medical College, 3rd Department of Medicine, Takatsuki, Osaka, Japan; [3]Osaka Univ of Pharmaceutical Sciences, Department of Pharmacology, Takatsuki, Japan; [4]Osaka Medical College, Pathology, Takatsuki, Japan*

Background: We have reported that hypoxia accelerated the development of atherosclerosis in apolipoprtein E-knochout (apoE-KO) mice. The role of inducible nitric oxide synthase (iNOS) in the pathophysiology of atherosclerosis has been known. The aim of this study was to examine the vascular superoxide production (O2-) and the effect of endogeneous estrogen on the development of atherosclerosis in apoE-KO mice when exposed to hypoxia.
Methods: Female apoE-KO (n=35) and wild-type (n=40) mice at 6 weeks of age were divided into sham-operated or ovarectomized (OVX) group. The OVX mice were subdivided into two groups with or without supplement of the NOS inhibitor aminoguanidine (1%, wt/vol). All animals were kept under hypoxia (oxygen, 10.0±0.5%) or normoxia. Three weeks later, O2- production, matrix metalloproteinase (MMP)-9 and NADPH diaphorase activity in the thoracic aorta were evaluated.
Results: In the wild-type mice no atherosclerosis was found, and both hypoxia and OVX had little effect on the O2- production. In apoE-KO mice, hypoxia developed prominent plaque formation, accompanied by increased O2- production and MMP-9 activity. The OVX to apoE-KO mice progressed atherosclerosis, and increased MMP-9 and iNOS in the artery. However, vascular O2-, after OVX, significantly decreased in the apoE-KO mice under hypoxia, which was increased again after treatment with the NOS inhibitor (Figure).
Conclusion: In apoE-KO mice, endogenous estrogen suppresses the acceleration of atherosclerosis through the regulation of MMP-9 activity and iNOS production.



Figure

P3347 Homocysteine stimulates vascular smooth muscle cell proliferation by increasing endothelin-1 expression

T.-H. Cheng[1], J. Liu[1], H. Yang[1], J. Chen[2]. *[1]Taipei Medical University-Wan Fang Hospital, Cardiology Department, Taipei, Taiwan; [2]National Taiwan University Hospital, Department of Internal Medicine, Taipei, Taiwan*

Purpose: Homocysteine is a sulfur-containing amino acid produced from methionine during processing of dietary protein. It has gained considerable attention recently because elevated concentration of total homocysteine are believed to be associated with an increased risk of cardiovascular disease, including coronary artery, cerebrovascular, and peripheral vascular disease. There is evidence that homocysteine can induce vascular smooth muscle cell proliferation in vitro. However, the molecular mechanism(s) of homocysteine in the pathogenesis of cardiovascular diseases remains to be further examined. In the present study, we investigated whether endogenous endothelin-1 (ET-1) mediates homocysteine-induced vascular smooth muscle cell proliferation and explore its molecular mechanism in culture system.
Methods: Cultured rat aortic smooth muscle cells were stimulated with homocysteine, [3H]thymidine incorporation and the ET-1 gene expression was examined. Antioxidants pretreatment on homocysteine-induced extracellular signal-regulated kinase (ERK) phosphorylation were performed to elucidate the redox-sensitive pathway in proliferation and ET-1 gene expression.
Results: Homocysteine increased DNA synthesis which was inhibited with ETA receptor antagonist (BQ485). Homocysteine was found to increase vascular smooth muscle cell ET-1 expression in a time- and dose-dependent manner. Co-transfection of dominant negative mutant of Ras, Raf and MEK1 attenuated the homocysteine-increased ET-1 promoter activity, suggesting that the Ras-Raf-ERK pathway is required for homocysteine-induced ET-1 gene. Truncation and mutational analysis of the ET-1 gene promoter showed that activator protein-1 (AP-1) binding site was an important cis-element in homocysteine-induced ET-1 gene expression. In addition, homocysteine activated the transcription factor AP-1, as well as the phosphorylation of ERK. Inhibition of ERK (with UO126) significantly suppressed homocysteine-induced ET-1 expression, implicating these pathways in the response to homocysteine. The ability of both N-acetylcysteine and diphenyleneionium (antioxidants) to inhibit homocysteine-induced ET-1 production suggested involvement of intracellular redox pathways.
Conclusions: Homocysteine regulates ET-1 in vascular smooth muscle cells, suggesting it may have a role in the vascular changes associated with hypertension and vascular disease.

P3348 DHT has proatherogenic effects on human endothelial cells via activation of the proinflammatory NFkB by the androgen receptor

K.C.Y. McGrath, A. Death. *Heart Research Institute, Sydney, Australia*

Purpose: There is a gender difference in the incidence of cardiovascular disease, with men having a 2-4-fold higher risk. We have been investigating whether constant exposure to male hormones, androgens, may underlie the earlier onset of cardiovascular disease in men. We have demonstrated that exposure to the potent androgen, dihydrotestosterone (DHT), increases endothelial vascular cell adhesion molecule-1 (VCAM-1) expression, which subsequently enhances monocyte adhesion. This is a key early step in atherosclerotic lesion formation. The aim of this study was to delineate the molecular mechanism via which DHT regulates VCAM-1 expression.
Methods: Human umblical vein endothelial cells (HUVECs) were isolated and cultured from male and female donors. Androgen receptor (AR) levels were up-regulated in female HUVECs by transfection with an AR cDNA expression vector and down-regulated in male HUVECs by transfection with an AR siRNA expression vector. Protein levels were measured by western blot analysis, mRNA by real-time RT-PCR and NF?B activity by luciferase assays. HeLa (AR –ve) cells were cultured and transfected with an NF?B-luciferase reporter vector or VCAM-1 promoter-luciferase reporter vector. Protein-protein interactions were analysed by co-immunoprecipitation.
Results: Higher levels of AR expression (3-fold increase compared to controls, P<0.05) in female HUVECs resulted in an up-regulation of VCAM-1 expression (2-fold, P<0.005). Treatment of these female cells with DHT (400nM) for 48 hours significantly enhanced monocyte adhesion (1.5-fold, P<0.05). By contrast, lower levels of AR (3-fold, P<0.05) in male HUVECs resulted in the repression of VCAM-1 expression in response to DHT (5-fold, P<0.05). In keeping with these findings, HeLa cells transfected with the AR cDNA expression vector significantly

increased NF?B activity and VCAM-1 transcription. Together, these findings suggested AR and NF?B interact. However, AR was found to not physically interact with NF?B (co-immunoprecipitation), but instead was shown to induce degradation of the NF?B inhibitor, I?Ba. DHT (400nM) in an AR-dependent manner, reduced I?Ba levels by 1.5-fold ($P<0.05$), which led to enhanced NF?B activation by 2-fold ($P<0.05$).
Conclusions: In summary, our data demonstrate that the potent natural male androgen, DHT, via its specific receptor (AR), increases I?Ba degradation resulting in increased NF?B activation. In turn, NF?B upregulates endothelial VCAM-1 expression and this enhances monocyte binding to the endothelium. This mechanism could underlie the higher propensity of young men to develop atherosclerosis and should be considered when developing androgen-based hormone treatment for men and women.

P3349 Effect of low density lipoproteins on the proteomic profile of cytoskeleton-related proteins in human vascular smooth cells

M. Garcia-Arguinzonis, T. Padro, E. Pena, V. Llorente-Cortes, L. Badimon. *Hospital Sant Pau., Cardiovascular Res. Center, CSIC-ICCC, Barcelona, Spain*

Coronary atherosclerosis is the most frequent cause of ischemic heart disease, being the lipid-rich and soft plaques, with low content in smooth muscle cells (SMC), the most prone to rupture. Phenotypic modulation of SMC is therefore a key event in plaque progression. In this study, we investigated the effect of low density lipoproteins (LDL), usually bound to extracellular matrix in atherosclerotic lesions, on the phenotypic profile of cytoskeleton-related proteins in the SMC and their migratory response after wound healing.
Methods: Cultured human coronary SMC were incubated in the presence/absence of 100μg/ml LDL during a period of 24h. Proteins, obtained by sequential extraction (cytosol-fraction and urea/detergent-soluble fraction) were analysed by a proteomic approach. Thus, protein separation was achieved by 2D-electrophoresis (2-DE) and differential analysis using the PDQuest and Image Master Platinum software. Characterization of proteins was performed by mass spectrometry (MALDI-TOF). Confocal mycroscopy was used for intracellular protein localization and cell migration studies were performed in vitro by the wound healing technique.
Results: We identified >12 cytoskeleton-related protein species affected in their distribution and/or detection level by the presence of LDL. Interestingly, detection of the two non-sarcomeric isoforms and the smooth muscle isoform of the myosin regulatory light chain (MRLC) were reduced and their level of phosphorylation altered in LDL-treated cells. In addition, the distribution pattern of the non-regulatory myosin light chain isoforms was markedly different in the 2D-gels of the LDL-treated cells. SMC-migration after wound healing was strongly decreased in the presence of LDL (30±11 μm/h in control vs. 16±4 μm/h in LDL group). By confocal microscopy, SMC exposed to LDL in comparison with control cells showed a) lower MRLC/actin co-localization and b) increased desorganization of cellular actin.
Conclusion: LDL seems to potentiate SMC phenotypic changes by myosin light chain-mediated mechanisms, which might contribute to the progression and complication of atherosclerosis.

P3350 Modulation of dendritic cells by flavonoids

T. Nickel, C. Grimm, J.O. Kim, M. Weis. *University Hospital Munich-Grosshadern, Medizinische Klinik und Poliklinik I, Munchen, Germany*

Arteriosclerosis is an inflammatory disease. Dendritic cells (DCs) are crucial for the regulation of the immune system and represent up to 10% of the cells in the plaque area. Recently, the anti-inflammatory and vasoprotective potential of flavonoids, a heterogenic group of polyphenols (high concentrations of which are in soja-products, tea, wine and vegetables), has become a focus of interest. We examined the impact of different flavonoids on 1) DC adhesion on endothelial cells (ECs), 2) expression of DC-adhesion molecules, 3) DC-cytokine expression, and 4) DC phagocytosis capacity.
Methods: Murine DCs (immortal, myeloid DCs; DC2.4) and autologous murine aortal ECs were incubated with the isoflavanol Epigallocatechin-3-gallate (Epi), the flavone Genistein (Gen) and the flavonole Quercetin (Quer) at 0.1-10μM. DC adhesion on ECs in response to 24h flavonoids (± preincubation of TNFa (10ng/ml) or oxLDL (10μg/ml) for 48h) was analyzed using fluorescent assays. Expression of the adhesion molecules ICAM-1 and DC-SIGN on human monocyte derived DCs was detected using FACS-analyses. Endocytosis capacity of FITC-Dextran was used as a marker of phagocytosis. IL-12 and IL-10 cytokine-secretion from human DCs (± flavonoids)was measured by ELISA.
Results: DC adhesion was significantly reduced by Epi (-18%; $p<0.05$), Quer (-25%; $p<0.01$), and Gen (-19%; $p<0.05$). Stimulated DC adhesion by TNFa and ox-LDL was significantly reduced up to 50% by Epi and Quer ($p<0.01$), but not using Gen. Whereas the baseline ICAM-1 expression on DCs was not effected by flavonoids, all 3 substances reversed the oxLDL induced ICAM-1 upregulation ($p<0.05$). The endocytosis capacity of Dextran was reduced significantly by Quer (-49%), Gen (-38%) and Epi (-24%). TNFa stimulated endocytosis (+100%) was completely blocked by Gen, Quer and Epi ($p<0.01$).
Furthermore, flavonoids increased DC secretion of IL-10 (Epi 110%, Quer 106%, Gen 90%; $p< 0.01$) and partially reversed decreased IL-10 release mediated by TNFa and oxLDL stimulation ($p<0.05$). No effect was detectable on Il-12 release.
Conclusion: Flavonoids diminish endothelial DC-adhesion, downregulate ICAM-1 expression on DCs, reduce DC phagocytosis capacity and stimulate release of the anti-inflammatory cytokine IL-10. Modulating DC-activity by flavonoids may contribute to the anti-inflammatory and anti-atherosclerotic effects of flavonoids.

P3351 HSP27 proteolysis, an index of remodelling in vulnerable atherothrombotic plaques

J.L. Martin-Ventura, J.B. Michel, O. Meilhac. *INSERM U698, CHU Xavier Bichat, Paris, France*

Background: We recently reported that carotid atherosclerotic samples release less heat shock protein 27 (HSP27) relative to control endarteries. In agreement with this results, plasma HSP27 levels are decreased in atherosclerotic patients in relation to healthy subjects, suggesting that plasma HSP27 could be an index of atherosclerosis (Circulation 2004; 110:2216-9). Based on our observations and on published work showing that vulnerable atherosclerotic plaques secrete proteases, we hypothesized that the diminished HSP27 released by atherosclerotic plaques and eventually in plasma, would be due to the proteolysis of the protein.
Methods and results: Recombinant HSP27 (40 mg/mL) was incubated with different proteases [elastase (150 nM), plasmin (125 nM), thrombin (100nM)] in vitro. HSP27 was degraded in a dose and time-dependent manner by elastase and plasmin, but not by thrombin (Western-blot). HSP27 proteolysis was prevented by incubation with different inhibitors (elastase inhibitor III, HLEi, and a1-antitrypsin for elastase and VFK and aprotinin for plasmin). Mass spectrometry analysis by SELDI-TOF corroborated the results obtained by Western-blot, showing peaks of HSP27 degradation at similar molecular masses.
In addition, when mammary control endarteries were cultured in the presence of plasmin or elastase, the released HSP27 was proteolyzed into fragments similar to that observed after incubation with these proteases and recombinant HSP27 in vitro. Furthermore, we incubated vulnerable atherosclerotic plaques (as a source of proteases) with recombinant HSP27 for 24 h. Atherosclerotic plaques in tissue-culture were able to degrade recombinant HSP27, displaying the same fragments of HSP27 as those observed after incubation in vitro with elastase and plasmin. In addition, both aprotinin and HLEi inhibitors were able to diminish HSP27 degradation. Finally, co-incubation of mammary endarteries and vulnerable atherosclerotic plaques lead to HSP27 proteolysis.
Conclusions: We have shown that HSP27 is proteolyzed by different enzymes released from vulnerable atherosclerotic plaques. Our results suggest that soluble HSP27 levels could reflect a pathological vascular remodeling process, in which the final balance between proteases and antiproteases could determine the degradative process of the extracellular matrix. The characterization of the HSP27 fragments resulting from elastase/plasmin proteolysis in atherosclerotic plaque conditioned medium and eventually in plasma could provide a direct index of plaque instability and associated risk of rupture.

P3352 Enhanced antioxidant capacity and decreased migratory response to OX-LDL render human internal mammary arteries immune to atherosclerosis

V.S. Mahadevan[1], M. Campbell[1], P.P. McKeown[1], U. Bayraktutan[2]. *[1]Royal Victoria Hospital, Department of Medicine, Belfast, United Kingdom; [2]Royal Victoria Hospital, Department of Medicine, Belfast, United Kingdom*

Human internal mammary arteries (IMA) are relatively immune to atherosclerosis despite being exposed to the same atherogenic agents as the coronary arteries (CA). The current study investigated the putative causes of IMA immunity using vascular smooth muscle cells (VSMC) from both arteries. IMA VSMC were isolated from patients (n=12) undergoing coronary bypass surgery using the explant technique. The pro-oxidant [NAD(P)H oxidase] and anti-oxidant [eNOS, superoxide dismutase, catalase and glutathione peroxidase] enzyme activities as well as superoxide anion and nitrite productions were determined by specific assays. VSMC migrations were investigated using the Dunn chamber. As illustrated in table 1, significant increases in antioxidant enzyme activities and a marked decrease in NAD(P)H oxidase activity were detected in IMA VSMC ($p<0.05$). Similar alterations were observed in nitrite and superoxide anion levels, respectively. While both sets of VSMC migrated towards serum ($p<0.01$), neither oxidized-low-density-lipoprotein (LDL) (25 or 100 μg/ml) nor native-LDL (100 μg/ml) af-

Table 1

	IMA VSMC	CA VSMC
eNOS (pmol L-citrulline/mg protein/min)	1.56 ± 0.25 *	0.39 ± 0.09
Glutathione peroxidase (U/mg protein)	43.6 ± 3.1 *	20.3 ± 1.2
Superoxide dismutase (mU/mg protein)	142 ± 26 *	99 ± 5
atalase (U/mg protein)	264 ± 30 *	210 ± 13
AD(P)H oxidase (pmol superoxide anion/mg protein)	0.42 ± 0.11 *	1.33 ± 0.16
Nitrite (nmol/mg protein)	34.42 ± 1.28 *	19.99 ± 1.23
uperoxide anion (pmoles/million cells)	237 ± 18 *	329 ± 34

Data are expressed as mean±SEM from 4 different experiments. *$P<0.05$ difference between IMA and CA VSMC.

fected the chemotactic ability of IMA VSMC. However, in CA VSMC high dose ox-LDL produced significant chemotaxis that was inhibited by both pravastatin (0.1 μmol/L) and enalapril (1 μmol/L). Enhanced intrinsic antioxidant enzyme activities along with diminished NAD(P)H oxidase activity may render IMA relatively immune to atherosclerotic disease. Statins and angiotensin converting enzyme inhibitors exert antiatherogenic effects partly by suppressing the ox-LDL-mediated migration of CA VSMC.

P3353 MMP-2 activity is associated with stable and MMP-9 activity with unstable atherosclerotic lesions: a role for different EMMPRIN glycosylation forms

J.P.G. Sluijter[1], A.H. Schoneveld[2], F. Moll[3], J.P. de Vries[4], J. Verheijen[5], R. Hanemaaijer[5], D.P.V. de Kleijn[2], G. Pasterkamp[2]. *[1]University Medical Centre Utrecht, Experimental Cardiology Laboratory, Utrecht, Netherlands; [2]University Medical Centre Utrecht, Experimental Cardiology Laboratory, Utrecht, Netherlands; [3]University Medical Center, Department of Vascular Surgery, Utrecht, Netherlands; [4]Saint Antonius Hospital, Department of Vascular Surgery, Nieuwegein, Netherlands; [5]Biomedical Research, TNO Quality of Life, Leiden, Netherlands*

Introduction: Matrix metalloproteinase (MMP) synthesis and activation are important features in atherosclerotic plaque destabilization. Extracellular matrix metalloproteinase inducer (EMMPRIN) stimulates the production of several MMPs, and glycosylation of EMMPRIN (45kD and 58kD) seems to be critical for MMP induction. We studied EMMPRIN (45kD and 58kD) levels and MMP-2 and 9 activity in relation to plaque characteristics in human atherosclerotic plaques.
Methods: Carotid atherosclerotic plaques were collected from patients (n=150) that underwent endarteriectomy and categorized as fibrous, fibro-atheromatous or atheromatous. In addition, sections were stained for smooth muscle cells (SMC) and macrophages and analyzed semi-quantitatively and categorized as no/minor (-) or moderate/heavy (+). Adjacent segments were used to isolate total protein to assess MMP-2 and MMP-9 activity (activity assay) and EMMPRIN levels (Western blotting).
Results (see Table 1): MMP-9 activity was increased in more atheromatous plaque phenotype ($p<0.001$), whereas MMP-2 activity was higher when a more fibrous phenotype was addressed to the lesions (p=0.007). Moreover, macrophage rich lesions revealed higher MMP-9 acivity, whereas SMC rich lesions showed higher MMP-2 activity and more EMMPRIN 45kD. Interestingly, regression analysis revealed that EMMPRIN 45kD was associated with MMP-2 activity (all $p<0.005$), whereas EMMPRIN 58kD was related to MMP-9 activity (all $p<0.001$).

Table 1

	SMC			Macrophages		
	–	+	p-value	–	+	p-value
EMMPRIN (45kD)	21±32	27±36	0.005*	30±41	19±27	0.03*
EMMPRIN (58kD)	89±115	62±102	0.39	65±93	78±120	0.79
MMP-2	3.9±2.6	6.1±5.0	0.008*	5.4±4.6	5.1±4.2	0.86
MMP-9	3.8±3.5	2.8±3.3	0.04	2.0±2.2	4.4±4.0	0.001*

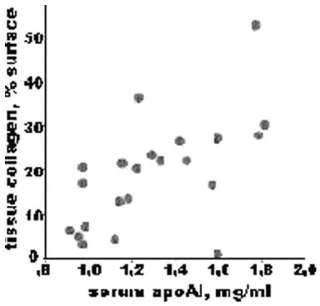
EMMPRIN levels, MMP-2 and 9 activity related to SMC and macrophage staining (EMMPRIN levels are mean arbitrary units±sd, MMP activity in ng/mg±sd)

Conclusions: MMP-9 activity was associated with more inflammatory lesions, whereas MMP-2 activity was higher in stable plaques. Different EMMPRIN glycosylation forms are associated with either MMP-2 or MMP-9 suggesting that EMMPRIN glycosylation may play a role in MMP regulation and plaque destabilization.

P3354 High apolipoprotein AI in serum is associated with more stable coronary atherosclerotic plaques

M. Levin[1], J. Solem[2], T. Karlsson[2], L. Grip[2], O. Wiklund[3], P. Albertsson[2]. *[1]Sahlgrenska University Hospital, Wallenberg Laboratory, Göteborg, Sweden; [2]Sahlgrenska University Hospital, Department of Cardiology, Gothenburg, Sweden; [3]Sahlgrenska University Hospital, Wallenberg Laboratory, Goteborg, Sweden*

Although plasma lipoproteins are well recognised as risk factors for coronary heart disease, the role of lipoproteins for the regulation of plaque composition and plaque stability is not known.
Aim: To analyze the relation between serum lipids and lipoproteins and tissue composition in human coronary atherectomies.
Method: 29 patients with stable angina pectoris were randomised to treatment with atorvastatin 80mg/day or placebo when put on a waiting list for PCI with directed atherectomy. Atherectomy specimens were obtained from 22 subjects, 11 in each group. Average treatment period was ten weeks. Serum lipids, lipoproteins and plasma inflammation markers were analyzed at randomisation and at PCI. Atherectomy specimens were analyzed with immunohistochemistry and quantitative image analysis.
Results: As expected, atorvastatin reduced LDL (-63%) and apoB (-45%). There was a very consistent correlation between apoAI and tissue markers for plaque stability (apoAI vs. collagen: r=0,56**; vs. macrophages in tissue r=-0.56**; vs. MMP9 expression r=0.61**). Similar correlations were seen for serum apoAI levels before treatment, at randomisation. No correlations were seen between tissue composition and LDL or apoB.



apoAI/Collagen

Conclusion: High serum apoAI is associated with a stable plaque phenotype in coronary atherectomies. Thus, apoAI may be a candidate clinical marker for stable, and less rupture prone, coronary plaques.

P3355 ED-B fibronectin targeted near infrared imaging detects atherosclerotic lesions in ApoE deficient mice

M. Roser[1], C. Perlitz[2], T. Dietrich[3], P. Stawowy[3], U. Thanabalasingam[3], M. Graefe[3], M. Schirner[2], K. Graf[3]. *[1]Deutsches Herzzentrum Berlin, Cardiology Dept., Berlin, Germany; [2]Schering AG, Berlin, Germany; [3]Deutsches Herzzentrum Berlin, Cardiology, Berlin, Germany*

The aim of this study was to examine the expression of ED-B fibronectin in a murine model of moderate atherosclerosis to investigate its relevance for imaging of early atherosclerotic lesions. Apolipoprotein-E-null (ApoE-/-) mice and control mice (C57Bl6) were fed with normal chow up to 10 months, leading to modest focal atherosclerosis in the aorta and supraaortic arteries. Sudan red staining and immunohistochemical analysis of the vessel wall using antibodies against ED-B (AP19), CD31, CD68 and actin was performed in mice at age 3, 7 and 10 months (n=15). ED-B immunoreactivity was observed in focal atherosclerotic lesions, but absent in non-atherosclerotic arteries or control animals. Histomorphometry revealed correlation of ED-B expression with the increase in atherosclerotic plaque lesion size and number. Immunohistochemical analysis revealed strong interstitial immmunoreactivity and identified mainly smooth muscle and endothelial cells as ED-B positive cells. In contrast, no immunoreactivity was detected in control mice and in wall areas free of atherosclerosis in younger ApoE mice.
Imaging for atherosclerotic plaques in-vivo was performed with AP19 anti ED-B, labeled with near infrared (NIR) fluorophores and injected intravenously into atherosclerotic ApoE-/- (n = 14) or normal wild-type mice (n = 4) at the age of 10 months. Mice were killed 24 hours after injection and NIR fluorescence was analysed in thoracical aorta and supraaortic arteries. NIR-signals demonstrated a strong intensity in focal plaque lesions, whereas no signal was found in undiseased aortas from control mice or in mice injected unspecific NIR fluorophores (n=3). NIR-signal positive areas significantly correlated with histological plaque lesion expression ($p<0.05$). Signal intensity in supraaortic areas strongly correlated with plaque lesion area ($p<0.05$).
Conclusion: This study demonstrates, that plaque imaging using antibodies labeled with near infrared fluorophores is feasible in a model of focal atherosclerosis.

P3356 Blocking of angio-associated migratory cell protein reduces smooth muscle cell migration and neointima formation after vascular injury in hypercholesterolemic apolipoprotein E knockout mice

F. Vogt[1], A. Zernecke[2], M. Beckner[3], N. Krott[1], A.-K. Bosserhoff[4], R. Hoffmann[1], C. Weber[2], R. Blindt[1]. *[1]University Hospital RWTH Aachen, Medical Clinic I, Aachen, Germany; [2]University of Aachen, Cardiovascular Molecular Biology, Aachen, Germany; [3]Pittsburgh University Medical Center, Pathology, Pittsburgh, United States of America; [4]University Hospital Regensburg, Pathology, Regensburg, Germany*

Purpose: The recently discovered 52kDa-protein angio-associated migratory cell protein (AAMP) was shown to participate in angio- and cancerogenesis. It is predominantly expressed in cells with a strong migratory phenotype. The aim of this study was to investigate the contribution of AAMP to neointimal formation after vascular injury.
Methods: AAMP contents of smooth muscle cells (SMCs) with a quiescent or migratory phenotype were quantified by Western blot analysis. Migratory potential of SMCs transiently transfected with AAMP sense expression vectors and influence of anti-AAMP-antibody on migratory potential of SMCs was examined using modified Boyden chamber assays. Subcellular localisation of AAMP in SMCs was examined by use of confocal scanning laser microscopy. In vivo expression of the protein was investigated in tissue sections from the porcine coronary restenosis model by immunohistochemistry. Apolipoprotein E knockout (apoE-/-) mice fed a 1% cholesterol diet were treated with anti-AAMP-antibody and neointimal lesions in wire-injured carotid arteries were quantified histomorphometrically.

Results: In vitro, protein lysates of SMCs with a migratory phenotype showed an increased AAMP expression (34.9 ± 6.0 intensity/area) compared to the quiescent phenotype (3.8 ± 0.3; P<0.01). The migratory potential of AAMP sense transfected SMCs was increased (51.9 ± 4.1 cells/area) compared to mock transfected cells (32.5 ± 2.3; P<0.01). Anti-AAMP antibody reduced migratory potential of medial (21.5 ± 4.0 cells/area) or neointimal (74.4 ± 11.6) SMCs compared to control (49.7 ± 3.8 or 164.5 ± 20.6, respectively; P<0.001). Subcellular localisation analysis of AAMP in migratory or AAMP transfected SMCs revealed a preferentially membrane-localised AAMP distribution along the membranous filopodia and lamellopodia. In vivo, SMCs of the neointima and media showed a significantly stronger expression of AAMP compared to undilated control arteries. Treatment of apoE-/- mice with anti-AAMP-antibody reduced neointimal area compared to isotype control (42.060 ± 2.756 or 78.650 ± 3.073 μm^2; P<0.01).
Conclusions: AAMP was upregulated in SMCs with a migratory phenotype, AAMP overexpression led to an increase of migratory potential, and treatment with anti-AAMP-antibody reduced SMC migration and neointima formation. The subcellular localisation of AAMP indicates a functional link to regulation processes of the actin cytosceleton. These data indicate a possible contribution of AAMP to SMC migration during development of atherosclerosis and restenosis after vascular injury.

RISK STRATIFICATION WITH CARDIAC CT

P3357 Multislice computed tomography for the risk stratification in patients with chest pain syndrome

S. Kimura[1], T. Kakuta[2], O. Kuboyama[2], T. Yonetsu[2], T. Umemoto[2], H. Fujiwara[2], M. Isobe[3]. *[1]Tsuchiura Kyodo Hospital, Cardiovascular medicine, Tsuchiura, Japan; [2]Tsuchiura Kyodo Hospital, Cardiovascular medicine, Tsuchiura, Japan; [3]Tokyo Medical & Dental university, Cardiovascular medicine, Tokyo, Japan*

Introduction: In the emergency department (ED), the subset of patients with chest pain who had non-diagnostic ECG findings for myocardial ischemia requires meticulous follow-up observation by ECG monitoring and blood sampling. We investigated the diagnostic efficacy of noninvasive coronary angiography with 16-detector multislice computed tomography (MSCT) in these patients.
Methods: One hundred-four consecutive patients presenting to ED with chest pain suggestive for myocardial ischemia who showed non-diagnostic or normal ECG findings were examined by MSCT (16x0.75mm detector collimation, 0.42-s rotation time, retrospectively ECG-gated) before the results of biomarkers were obtained. MIP, MPR, and cross-sectional images were assessed by two investigators for coronary anatomy if there was any significant coronary stenosis for myocardial ischemia. The patients with significant coronary stenosis detected by MSCT were admitted and underwent conventional coronary angiography (CAG) within 48 hours from admission. The high risk patients in whom MSCT detected multivessel coronary artery disease or left main stenosis were immediately transferred to emergent catheterization lab irrespective of TIMI Risk score. The remaining patients without significant stenosis in MSCT were watchfully observed at outpatient basis without admission.
Results: MSCT images were unassessable in 3 patients due to severe coronary calcification and/or motion artifacts, and these patients were excluded from the analysis. In the remaining 101 patients, MSCT diagnosed 19 patients with multivessel disease, 2 patients with left main disease, and 18 patients with single vessel disease, and these patients underwent CAG. The diagnostic accuracy of MSCT for significant coronary stenosis was 93%. One patient without significant stenosis in MSCT was admitted because of biomarker positive, and CAG revealed culprit lesion in this patient. Other sixty-one patients without significant stenosis in MSCT were biomarker negative and followed up without admission, and no cardiac event was observed up to 3 months. The frequency of biomarker positive patients with significant stenosis in MSCT was 21%, and 2.3% in patients without significant stenosis in MSCT.
Conclusion: MSCT combined with cardiac biomarker may efficiently risk-stratify the patients with chest pain with normal or nondiagnostic ECG findings at ED.

P3358 64-slice cardiac CT in triage and management of patients presenting with chest pain to the emergency department

R. Rubinshtein[1], D.A. Halon[1], T. Gaspar[2], R. Jaffe[1], B. Karkabi[1], M.Y. Flugelman[1], N. Peled[2], B.S. Lewis[1]. *[1]Lady Davis Carmel Medical Center, Department of Cardiovascular Medicine, Haifa, Israel; [2]Lady Davis Carmel Medical Center, Department of Radiology, Haifa, Israel*

Purpose: we examined the role of a new generation, fast (5-8 sec) 64-slice multidetector cardiac CT scanner (MDCT) in the assessment and triage of pts presenting to the emergency room (ER) with chest pain.
Methods: contrast enhanced MDCT scans (Philips, Brilliance 64) were performed in 26 ER pts with chest pain of uncertain etiology. Presumptive diagnosis, decision to hospitalize and intended management (intensive therapy/urgent intervention vs medical management) were recorded before MDCT by 2 senior cardiologists based on routine ER data analysis. Change in diagnosis, management and disposition following MDCT findings were noted.
Results: before MDCT scanning, primary diagnosis was chest pain of cardiac origin (ACS) in 18 pts, hospitalization recommended in 22 and early angiography planned in 14 (Table). Following MDCT, diagnosis of ACS was changed in 9/18 (50%) pts (6 normal MDCT/patent stents, 3 alternative diagnoses), hospitalisation cancelled in 7/22 (32%). Early intervention was postponed in 8/14 (57%) (2 alternative diagnoses, 2 distal vessel disease, 4 normal MDCT/patent stents) but advanced in another pt (1/12, 8%), so that decision regarding intervention changed in 9/26 (35%) pts. Important extra-cardiac diagnoses (chronic aortic dissection, left subclavian stenosis proximal to LIMA graft and pancreatic tumor) were made in 3 pts.

Impact of MDCT on triage and management

	Pain of cardiac origin (ACS)	Hospitalization required	Intensive management/intervention
Before MDCT	18/26(69%)	22/26(85%)	14/26(54%)
After MDCT	9/26(35%)	15/26(58%)	6/26(23%)
Change in diagnosis/management	9/18(50%)	7/22(32%)	(8+1)/26(35%)
p value	0.01	0.03	0.02

N=26

Conclusions: 1. Rapid 64 slice MDCT scanning made a major contribution to the triage of pts presenting to the emergency room with chest pain of uncertain etiology. 2. The primary diagnosis and decisions regarding hospitalisation and management were refined after MDCT scan in a third to half the pts.

P3359 Calcium-scoring in asymptomatic persons: is there a difference between 4-slice and 16-slice MSCT? Results in 6.000 consecutive persons

S. Finsterer[1], M. Rothmeier[1], C. Mayer[1], P. Lochow[1], S. Silber[2]. *[1]Heart Diagnostic Center, Cardiology Practice and Hospital, Munich, Germany; [2]Cardiology Practice and Hospital, Munich, Germany*

Background: Calcium scoring with the Multi-Slice CT (MSCT) is increasingly performed for coronary risk assessment. 16-slice MSCT (16-S MSCT) has mostly replaced the older 4-slice CT (4-S MSCT). The question is whether the reference percentile distrubutions obtained with the 4-S MSCT can also be applied to the 16-S MSCT since there are differences in the thickness of the slices (2.5 mm vs. 1.5 mm) and rotation times (500 ms vs. 420 ms). The goal of the study was to compare the results of the 4-S MSCT with those of the 16-S MSCT in a consecutive patient population.
Methods: 6.000 consecutive persons were analyzed, 4.518 with the 4-S MSCT and 1.482 with the 16-S MSCT. The persons were asymptomatic for coronary artery disease (CAD). Image acquisition was prospectively triggered to 60% of the RR-interval to reduce the radiation exposition. The slice thickness of the 4-S MSCT was 2.5 mm (4 x 2.5 mm) and 1.5 mm with the 16-S MSCT (16 x 1.5 mm). The calcium score was calculated according to the Agatston-Score (high risk was defined as a score above the 75th percentile, depending on age and sex).
Results: Women represented 24.5% of the 4-S MSCT group and 27.4% of the 16-S MSCT group. The mean age is shown in the table. Compared to the 4-S MSCT there was a lower calcium score in the 16-S MSCT: Table 1

Table 1

	4-slice male	4-slice female	16-slice male	16-slice female
Age	54.4±9.8	58.4±9.9	56.2±10	58.0±8.8
Score (absolut)	227.1±577	83±283	174±378	67.0±266
High risk	23.1%	25.3%	21.1%	21.1%

Conclusions: There is some doubt whether the average percentiles of the calcium score evaluated with 4-S MSCT can be applied to the 16-S MSCT. Today, 4-, 16-, 32-, 40- and 64-slice MSCT are used and probably will need individually percentile distribution curves to avoid a misclassification of asymptomatic persons.

P3360 Progression of coronary calcification despite intensive lipid-lowering therapy: a randomised controlled trial

E.S. Houslay[1], S.J. Cowell[2], D.B. Northridge[3], J. Burton[4], J.R. Reid[4], N.A. Boon[2], D.E. Newby[2] on behalf of The SALTIRE trial investigators. *[1]University of Edinburgh, Cardiovascular Research, Edinburgh, United Kingdom; [2]Royal Infirmary of Edinburgh, Cardiology, Edinburgh, United Kingdom; [3]Western General Hospital, Cardiology, Edinburgh, United Kingdom; [4]Borders General Hospital, Radiology, Melrose, United Kingdom*

Objectives: The objective was to confirm whether aggressive lipid-lowering alters the progression of coronary artery calcification.
Background: Observational studies have suggested that statin therapy may induce regression of coronary calcification. In a substudy of patients with calcific aortic stenosis, we evaluated the effect of intensive lipid-lowering therapy on coronary calcification.
Methods: In a double blind randomised controlled trial, 105 patients with calcific aortic stenosis and coronary calcification were randomized using the minimization technique to atorvastatin 80 mg daily or matched placebo. Coronary calcification was assessed annually by helical CT.

Results: Forty nine patients were randomized to atorvastatin and 56 to placebo with a median follow-up of 24 months (range = 19-30). Baseline characteristics and coronary calcium scores were similar in both groups. Atorvastatin therapy was associated with a 53±19% reduction in serum low-density lipoprotein cholesterol concentrations ($P<0.001$) whilst there was no change with placebo (7±32%, P=0.99). The rate of change in coronary calcification was 42±73%/yr (0.09±0.11 logAU/yr) in the atorvastatin group and 29±37%/yr (0.06±0.11 log AU/yr) in the placebo group (P=0.12, atorvastatin vs placebo). The difference in the rate of progression was 13%/yr (95% confidence intervals, -9 to +36%/yr; P=0.24). There was no correlation between serum low-density lipoprotein concentrations and the rate of progression of coronary calcification (r=0.05, P=0.62).
Conclusion: In contrast to previous observational studies, this randomised controlled trial has shown that intensive lipid lowering therapy does not have a major effect on the progression of coronary artery calcification.

P3361 Multislice cardiac CT is cost effective as a screening method in patients with an intermediate Framingham risk score

B. Shivalkar[1], O. Oszcharlak[2], R. Salgado[2], I. Goovaerts[3], P. Parizel[2], C. Vrints[3]. *[1]UZA, Cardiolgy, Edegem, Belgium; [2]University Hospital Antwerp, Radiology, Edegem, Belgium; [3]University Hospital Antwerp, Cardiology, Edegem, Belgium*

Purpose: A cost effective screening may allow improved effectiveness at a decreased cost. Use of multislice cardiac CT (MSCT) as a screening test has been suggested in a select population with intermediate Framingham risk score (FRS). We sought to assess the cost effectiveness of MSCT as a diagnostic strategy in patients with intermediate FRS.
Methods: One hundred and fortyeight asymptomatic patients including 47 with PFH (male/female, age 56±12 years) with low to intermediate FRS had a MSCT (Siemens, 16-rows) for coronary artery calcium scoring (CACS, Agatston score) and CT angiography (CTA), as well as carotid intima media thickness measurement (IMT), and biochemical analysis (lipid, fibrinogen levels, C-reactive protein). The coronary arteries were divided in to 12 segments similar to conventional coronary angiography (CA) for grading of luminal stenosis. Exercise ECG was considered a standard non invasive screening test for asymptomatic patients with an intermediate FRS, and we used weighted averages from published data for the sensitivity (68%) and specificity (77%). A standard exercise ECG cost € 75, and MSCT € 210. Cost effectiveness was calculated as total direct costs divided by number of correctly diagnosed patients. Data are given as mean ±SD.
Results: Ninetytwo of the 148 patients had a positive CACS (241±527), of whom 34 had a PFH (CACS:251±593). Significant correlation was found between CACS and age, IMT, systolic blood pressure and total cholesterol ($p<0.05$), In the subgroup with PFH stepwise regression analysis showed that increased IMT predicted likelihood of CACS (p= 0.01). In 40 patients with either a significant CACS (>400) or evidence of soft plaque and a >50% stenosis on CTA, CA was performed. High CACS predicted likelihood of at least one significant coronary stenosis on CA (p=0.01). The overall agreement for 454 coronary segments between CTA and CA was 88% (kappa = 0.62). The sensitivity and specificity were respectively 77 and 89%, with a predictive accuracy of 88%. The calculated cost effectiveness for exercise ECG and MSCT was respectively, € 3657 and € 3301.
Conclusions: In patients with a low FRS but PFH a strong association was found between CACS and IMT. MSCT is a cost effective test compared to the standard exercise ECG test for detection of CAD in patients with PFH and intermediate FRS.

P3362 Non-cardiac findings in non-invasive coronary imaging with multidetector computed tomography

Y. Onuma[1], K. Tanabe[1], M. Hatori[1], K. Ibukuro[2], H. Fukuda[2], H. Nakajima[1], K. Hara[1]. *[1]Mitsui Memorial Hospital, Department of cardiology, Tokyo, Japan; [2]Mitsui Memorial Hospital, Department of Radiology, Tokyo, Japan*

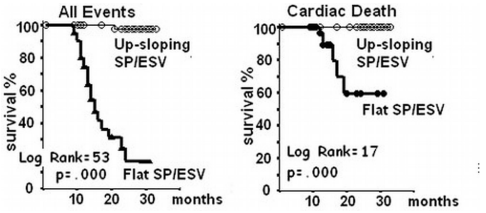
Purpose: Multidetector computed tomography (MDCT) is now accepted as a useful modality to detect coronary stenosis in selected population. We investigated the prevalence of non-cardiac findings in patients referred to coronary MDCT.
Methods: Between July 2004 and January 2005, 200 consecutive patients who have symptoms of chest angina or known coronary stenosis or prior history of coronary bypass graft underwent 16-slice (Sensation 16, Siemens Medical solution; scan parameters, 370ms gantry rotation, 16*0.75-mm-slice collimation) or 64-slice MDCT (Sensation 64, Siemens Medical solution; scan parameters, 330ms gantry rotation, 64*0.60-mm-slice collimation). Plain CT of the chest was simultaneously scanned to perform scoring for calcification of coronary artery by cardiologists. The same images were reviewed in multiplanar reconstruction with lung and soft tissue windows by radiologists.
Results: Consecutive 200 patients were enrolled in this study. Non-cardiac findings were pointed out in 101 patients (50.5%). These include liver cysts (15), fatty liver (2), cholelithiasis (6), renal cysts(8), renal stone (1), emphysema (10), pulmonary nodule (17), pleural thickening (4), lung mass suspected of malignancy (5), calcification of the lung (5), infiltration of the lung (17), bulla (9), lymph node swelling (2), goiter (4), thyroid cyst(1), thyroid tumor(1), breast tumor (1), thoracic aortic aneurysm (2), dissecting aorta(1). Up to now, one patient was diagnosed as breast carcinoma by aspiration biopsy.
Conclusions: Fifty point five percent of patients referred to coronary MDCT had non-cardiac findings. 11 patients should be under careful clinical follow-up or under further investigation. Collaboration of radiologists and cardiologists is important to avoid missing potentially important pathology.

ECHOCARDIOGRAPHY/DOPPLER

P3363 Negative stress echo: further prognostic stratification with left ventricular contractility assessment

T. Bombardini[1], M. Galderisi[2], E. Agricola[3], E. Pasanisi[1], L. Pratali[1], E. Picano[4]. *[1]Institute of Clinical Physiology, CNR, Pisa, Italy; [2]Università Federico II, Cardiology Dept, Naples, Italy; [3]San Raffaele Hospital, Milan, Italy; [4]CNR Institute of Clinical Physiology, Pisa, Italy*

Background: Patients with negative stress echo are a low risk subset. However, the potentially prognostically relevant information on global contractile reserve of the left ventricle is missed by standard regional wall motion assessment and can be obtained by Force-Frequency Relationship (FFR) evaluation.
Aim: to assess the relative prognostic value of FFR in patients with negative stress echo.
Methods: We enrolled 99 consecutive patients (age= 61±14 years; 81 males, baseline left ventricular ejection fraction 47±14%, Wall Motion Score Index = 1.43±0.48 at baseline and peak stress) with negative stress echo by standard regional wall motion criteria. To build the FFR, the force was determined at rest and peak stress as the ratio of the systolic pressure (SP, cuff sphygmomanometer)/end-systolic volume (ESV, biplane Simpson rule) index. All patients were followed-up on medical therapy.
Results: There were 25 events: 6 deaths and 19 worsening of NYHA class of >-1 grade. Patients with and without events had different baseline left ventricular ejection fraction (33±12% vs 52±12%, $p<.05$), SP/ESV index (2.8±3.1 vs 6±2.7, $p<.05$), delta (rest-stress) SP/ESV index (0.65±0.51 vs 5.9±4.7, $p<.05$). Using Cox proportional hazard model the only independent predictor of total events was SP/ESV index change (rest-stress) <1.5 mmHg/ml as determined by ROC analysis cut-off (RR 51,9, p=0.001). The overall survival and event-free survival was lower in patients with delta SP/ESV index <1.5 (flat SP/ESV in figure).



Conclusions: in patients with negative stress echo, a preserved global contractility response can be easily identified through stress-induced variation in SP/ESV index, with powerful further risk stratification.

P3364 Prognostic value of dobutamine stress echocardiography in patients with right ventricular pacemaker

X.A.J.C. Dechenne[1], A. Rousseau[2], M. Simon[3], T. Simon[2], E. Bogino[3], P. Dehant[3], C. Chauvel[3]. *[1]clinique saint-augustin, echocardiography department, bordeaux, France; [2]Hopital Saint-Antoine, URCEST, Paris, France; [3]Clinique Saint-Augustin, echocardiography department, Bordeaux, France*

BACKROUND: The aim of this study was to evaluate the prognostic value of dobutamine stress echocardiography (DSE) in patients (pts) with pacemaker (PM) according to mortality and cardiac events.
Method: From 1998 to 2004, we performed DSE in all pts with ventricular pacing at rest and referred for stress echocardiography. DSE was performed using standard protocol (steps of 2 min., maximal dose 40 gamma/kg/min dobutamine ± 1.5mg atropine). Ischemia was defined as a new or worsening wall motion abnormality during the test, in at least 2 adjacent myocardial segments. We collected events by phone or mail. Global mortality (D), cardiac death (CD) and cardiovascular events (CVE) needing hospitalization (myocardial infarct (MI), acute coronary syndrome (ACS), arrhythmia, heart failure (HF)) were recorded. We established prognostic value of DSE for each event.
Results: 95 consecutives pts (73 M, 73 ± 8 years, rest EF 57 ± 13%) were included in the study. 58% had known coronary artery disease (CAD), 22% had previous MI, 20% diabete mellitius. Indication for DSE was: diagnostic evaluation (50%), follow-up of a known CAD (40%), before surgery (6%) and viability (4%). The heart rate (HR) was 68 ± 12 bpm at baseline and reached 129 ± 20 bpm (88 ± 13% MPHR) at stress peak. The peak HR was > or = 85% MPHR in 63 pts (66%). We stopped the test for: target HR (58%), maximal dose (20%), arrhythmia (4%), malaise (8%), angina (6%), maximal HR of PM (2%). DSE demonstrated

ischemia in 14 pts (15%). Events recorded after a median follow-up of 49 [38 – 59] months were: D 10 pts (11%) including 6 CD (6%), CVE 8 pts (7 ACS, 1 HF) (8%). Survival at 12, 24 and 48 months was 98, 98 et 94% respectively. Cardiovascular event free survival (CD + CVE) at 48 months was better in pts with negative vs positive DSE (87 vs 67%, p= 0.047). Survival was higher in pts reaching 85% MPHR than the others ($p<0.05$). The prognostic value for CD or MI at 12 months of a negative DSE (> or = 85% MPHR) was 98% (figure). These pts had also less coronary events (CD + MI + ACS) at 24 months (96% vs 90%, p = 0.046).
Using multivariate analysis, after age and sex adjustment, a positive DSE in pts with known CAD was associated with an increase of CVE (OR = 3, p = 0.041), in diabetics OR = 2.9 (p = 0.035). The number of ischemic segments was also an independent marker of CVE (OR = 3.28, p = 0.049).
Conclusion: In our population, a negative DSE at target HR has an excellent prognostic value. DSE is useful tool for the detection and follow-up of CAD in patients with implanted pacemaker.

P3365 Diagnostic and prognostic value of stress echo-pacing in patients with implanted AAI pacemaker

E. Plonska-Gosciniak[1], Z. Kornacewicz-Jach[2], M. Lewandowski[2], A. Wojtarowicz[2], M. Peregud[2], T. Rozpara[2]. *[1]Szczecin, Poland; [2]Medical University, Szczecin, Poland*

Aim: The aim of this study was to assess the utility, safety and prognostic value of echocardiographic stress test (EST) in non-invasive diagnosis of ischemic heart disease in patients (pts) with implanted pacemaker, with and without left ventricle hypertrophy.
Method: EST was performed in 40 patients (mean age 60±10 years, from 43 to 78) with pacemaker. Using external programming system heart rate was accelerated by 10 beats in every 3 minute till reaching maximal heart rate. The examination was conducted only in patients with physiological stimulation of right atrium by AAI mode. Angiographically significant coronary artery stenosis size was accepted as over 50% artery diameter.
Results: Mean duration time of performed examination was 13±4 min. No adverse events were observed. The quality of stress echo visualization was good in every case. Heart rate at rest and at maximal stimulation were respectively 68±8 and 132±13 per minute ($p<0,0001$) and systolic blood pressure pressure 140±13 and 142±13 mmHg (ns). In 10 (25%) pts the result was positive, in 24 (60%) – negative, and in 6 (15%) – non-diagnostic. Non-diagnostic result of the test was due to pacemaker limitation (1pts), and not achieving Wenckebach point (5 pts). Test specificity was 95%, sensitivity - 69%, accuracy – 85%. Significant occlusion in coronary angiography were observed in 40% pts (including 1-vessel disease – 12,5%). In left ventricle hypertrophy group (n=19), the EST accuracy was 87% (without significant difference with non-hypertrophy group). In the group with beta blockers therapy (n=16) the observed accuracy was 93%. The follow-up time was 963 + 497 days. Ten (25%) pts with positive EST died, suffered myocardial infarction, nonstable angina or revascularization during follow-up. The prognostic value of positive EST result for cardiac events was 80%, and for negative – 100%. None of the pts with negative stress echo result suffered any cardiac event.
Conclusions: EST is a safe, short lasting examination with good quality of echo visualization. This method seems to be of important value in diagnosing the ischaemic heart disease in pts with pacemaker, also with left ventricle hypertrophy and obligatory beta blockers medication. Pts with negative EST have a very good prognosis.

P3366 Noninvasive diagnosis of coronary artery disease in humans by quantitative stress testing using myocardial contrast echocardiography: comparison with angiography

R. Vogel, A. Indermühle, P. Meier, S. Windecker, B. Meier, C. Seiler. *University Bern, Cardiology, Bern, Switzerland*

Background: Stress echocardiography is an everyday clinical tool for the noninvasive detection of significant coronary artery disease (CAD). However, the qualitative evaluation of stress tests entails considerable interobserver variability and a truly quantitative approach is desired. The hemodynamic relevance of coronary artery stenoses can be determined quantitatively by the coronary vasodilator reserve (CVR) defined as the ratio of myocardial blood flow (MBF, ml/min/g) during hyperemia to MBF at rest. Recently, we have shown that MBF and CVR can be obtained from quantitative myocardial contrast echocardiography (qMCE). Objective of this study was to test whether qMCE can be used for the assessment of coronary artery disease in humans.
Methods: 25 patients (18 men) eligible for pharmacologic stress testing underwent qMCE at rest and during adenosine-induced hyperemia (140mg/kg/min), and subsequently quantitative coronary angiography. MBF of septal, lateral und inferior regions was calculated from ultrasound contrast destruction/refill sequences using the volumetric model of contrast agent kinetics.
Results: Mean±SD patient age was 60±9 years; 7 patients had no CAD. One and two vessel disease was present in 11 and 7 patients, respectively. No patient had three vessel disease. Stenosis severity varied between 0-95% (29±35%) diameter reduction. qMCE was successfully performed in 73 of 75 territories. MBF at rest and during hyperemia ranged between 0.402-1.768ml/min/g (0.993±0.339ml/min/g), and 0.659-6.735ml/min/g (2.450±0.989ml/min/g). CVR varied between 0.72-6.04 (2.61±0.98) and progressively decreased with increasing stenosis severity (r^2 =0.32, $P<0.0001$). Using a regional CVR threshold below 2.13, a significant stenosis of the respective coronary artery defined as ≥ 50% diameter stenosis was detected with 88% sensitivity and 89% specificity. A CVR below 2.04 in any of the three territories detected the presence of relevant CAD with 94% sensitivity and 88% specificity.
Conclusion: Quantitative stress testing based on myocardial blood flow measurements derived from myocardial contrast echocardiography is a new method for the noninvasive and reliable assessment of coronary artery disease in humans.

P3367 Basal left ventricular segments are important for long-term recovery of global function in heart failure patients

M. Scharin Tang[1], B. Andersson[2]. *[1]Sahlgrenska Universitetssjukhuset, Cardiovascular institute, Gothenburg, Sweden; [2]Sahlgenska Universitetssjukhuset, Cardiovascular institute, Gothenburg, Sweden*

Background: The aim of this study was to elucidate whether different regions of the left ventricle respond differently to beta-blockade treatment, and if regional contractile reserve (CR) assessed with dobutamine stress echocardiography (DSE) could be used to predict long-term global improvement during treatment.
Methods: Twenty-two patients with cardiomyopathy were treated with metoprolol, 136±26 mg daily during 6 months. Echocardiographic evaluation was performed at rest and during DSE, before and after treatment. Regional left ventricular (LV) function was evaluated in three areas of the ventricle: basal, mid, and apical areas as well as global LV function.
Results: The ability of regional and global CR to predict long-term improvement in global LV function (EF >5 units) was assessed by constructing ROC-curves for sensitivity and specificity (Figure 1). The largest area under the ROC curve was found for CR in the basal area (0.87), and in LV global function (0.82), whereas the curves from the mid and apical areas were poorer (0.54 and 0.52, respectively). The CR in the basal area predicted improvement in global LV function with sensitivity 89%, specificity 77%, and accuracy 82%, $p<0.01$. Global CR predicted improvement in global LV function with sensitivity 78%, specificity 77%, and accuracy 77%, $p<0.05$.

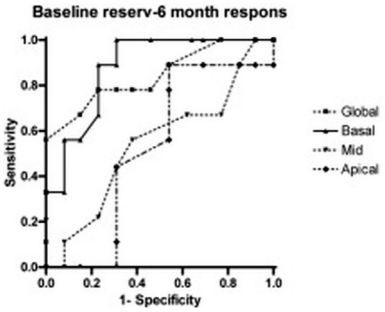


Figure 1

Conclusions: To predict long-term improvement in LV global function during beta-blocker treatment, assessment of CR in the basal part of the left ventricle was superior to assessment of global CR and other areas. These results imply that LV basal function and CR is of major importance for the function of the heart and for the potential to recover during treatment.

P3368 Efficacy of sublingual captopril before dobutamine stress echocardiography in hypertensive patients: a double-blind, placebo-controlled study

A. Rodrigues, V.T. Hotta, F. Borges -Neto, L.M. Trindade, J.M. Santos, W. Mathias Jr. *Heart Institute (InCor), Department of Echocardiography, Sao Paulo, Brazil*

Background: While limiting hypertension may result in prematurely terminating dobutamine stress echocardiography (DSE), high initial blood pressure (BP) levels may lead to cancellation of scheduled patients. A fast-acting and safe antihypertensive drug might prove useful to save DSE in case of uncontrolled hypertension.
Objective: We sought to determine the efficacy of sublingual (SL) captopril in lowering BP before DSE to increase the feasibility of this examination
Methods: . We consecutively assessed all patients > 18 years referred to DSE for ischemia evaluation, in a randomized, double-blind, placebo-controlled fashion. Patients with initial BP levels above 160/110 mmHg were randomized either to captopril (CAP) or placebo (PLA) groups. After 15 minutes, only patients who decreased BP below these predetermined levels undertook the examination.
Results: Six hundred and fifty four patients referred to DSE were screened and

152 (23.2%) were found to have BP above the predetermined levels. Out of these, 98 met inclusion criteria and were randomized. Clinical characteristics such as age (63±12 vs 64 ±11 years), diabetes (23% vs 33%), hypertension (88% vs 94%), dislipidemia (31% vs 33%) and chronic renal failure (18% vs 12%) were comparable for both PLA and CAP groups. Anti-hypertensive drugs usage was similar for both groups (beta-blockers = 27% vs 21%, angiotensine-converting inhibitors =23% vs 19%, diuretics = 44% vs 43%, and calcium-channel blockers =14% vs 18%). Initial systolic blood pressure (SBP) was 177 ±15 mmHg and 180±17 mmHg, while diastolic blood pressure (DBP) was 102 ± 15 mmHg and 103 ± 15 mmHg for PLA and CAP respectively (p = NS). In 32.7% (CAP) and 28.6% (PLA) of the patients a small but significant decrease in systolic (4 and 7%, respectively) and diastolic (5 and 8%, respectively) BP was observed following drug administration. Hypertension was responsible for DSE termination in 4 patients in the PLA group compared to none in the CAP group (p = NS). The frequency of adverse effects during the examination was comparable for both groups.

Conclusion: This study shows that both SL captopril and placebo are equally effective in increasing DSE feasibility in about one third of the hypertensive patients, and suggests that a significant psychological basis may mediate hypertension associated with this examination.

P3369 Extension and trasmural entity of myocardial necrosis are major determinants of coronary flow reserve impairment after acute myocardial function treated with primary coronary angioplasty

R. Montisci[1], M. Ruscazio[2], C. Sarais[3], F. Corbetti[4], L. Cacciavillani[3], M. Perazzolo Marra[3], L. Meloni[1], S. Iliceto[3]. [1]*University of Cagliari, Chair of Cardiology, Cagliari, Italy;* [2]*Centro Gallucci, Dept. of Cardiology, Padova, Italy;* [3]*University of Padova, Department of Cardiology, Padova, Italy;* [4]*University of Padova, Department of Radiology, Padova, Italy*

Background: Following acute myocardial infarction, the microcirculation can be damaged and the dilatory capacity impaired, with a reduction of coronary flow reserve (CFR) in the infarct related artery. We hypothesized that, in patients with acute myocardial infarction the reduction of CFR is inversely related to the entity of necrosis as assessed by gadolinium contrast enhanced cardiac magnetic resonance (GE-MRI).

Methods: Thirthy three consecutive patients (mean age 59±11) with anterior acute myocardial infarction underwent CFR assessment in the left anterior descending coronary artery with adenosine transthoracic echocardiography and GE-MRI 5±3 days after primary coronary angioplasty. A 17-segment model of the left ventricle was used to analyze both wall motion abnormalities and trasmural extent of necrosis at GE-MRI as assessed by hyperenhancement (HE) extent. A necrosis score was derived for each segment in the predicted risk area (myocardial segments supplied by left anterior descending coronary artery) considering HE thickness extent (1: no HE; 2: HE < 25%; 3: HE < 25 < 50%; 4: HE > 50% < 75%; 5: HE trasmural > 75): In each patient a wall motion score index (A-WMSI) and a necrosis score index (A-NSI) were calculated in the risk area. According to CFR values, 11 patients were classified into a normal or preserved CFR group (>2.5,group A), and 22 into an impaired CFR group (<2.5, group B).

Results: An inverse correlation was detected between CFR and myocardial necrosis extent (r=-0.44, p=0.009). Myocardial necrosis extent (A-NSI) was greater in group B than in group A (3.66±0.94 vs 2.39±0.96,p=0.001). In patients of group B 18/22 (88%) showed a large myocardial necrosis extent (A- NSI I>3), but only 4/11 in group A (36%; p<0.05). On the contrary, A-WMSI was similar in the two groups (2.20±0.29 vs. 2.03±0.34; p=ns), and no correlation was found between CFR and A-WMSI (r=-013,p=ns). However, it was better in preserved CFR patients at follow-up echo (1.55±0.41 vs 1.84± 0.27; p<0.005). Furthermore, an inverse correlation was found between CFR and A-WMSI at follow-up echo (r=-0.43, p=0.05).

Conclusions: CFR is inversely correlated with myocardial necrosis extent detected by GE-MRI after primary coronary angioplasty. Thus, a preserved CFR can be considered an expression of myocardial salvage as demonstrated by the extent of residual viable myocardium at GE-MRI and by the recovery of regional myocardial function at follow up.

P3370 Left anterior descending coronary artery velocity parameters at rest predict dobutamine stress echocardiographic regional wall motion abnormalities

D. Sharif[1], A. Sharif-Rasslan[2], C. Shahla[1], A. Khalil[1], U. Rosenschein[1]. [1]*Bnai Zion Medical Center, Dept. of Cardiology, Haifa, Israel;* [2]*Technion, Technology and Science, Haifa, Israel*

Velocity profiles at rest are used to assess peripheral arterial stenosis. Furthermore, diastolic velocity profiles and pressure half times (P1/2t) are used to evaluate valvular disease. Recently, sampling of left anterior descending coronary artery (LAD) velocities by transthoracic-echo (TTE) Doppler became possible.

Aim: To test the hypothesis that diastolic p1/2t and flows at rest predict ischemia in the territory of LAD before dobutamine stress echocardiography (DSE).

Methods: In 150 patients, age 58.6±10.6 years, with suspected coronary artery disease undergoing DSE evaluation, TTE-Doppler sampling of LAD blood velocity was attempted, DSE was performed in the usual manner. Measurement of diastolic (VD) and systolic (VS) LAD velocities, and their ratios and calculation of diastolic (FD) and systolic flow (FS) and their ratios, were performed.

Results: 1) Major diastolic component with short pressure half time (p1/2t) and rapid deceleration in 137 subjects without left ventricular (LV) wall motion abnormality (WMA) after DSE in the LAD territory. 2) Increased systolic component with long p1/2t and slow deceleration in 7 patients and LV wall motion abnormalities, indicating LAD-territory stenosis (see table). 3) In 6 patients, LAD velocities could not be recorded and apical WMA in the LAD territory were observed.

LAD velocity predictors of WMA

	VD/VS	FD/FS	P1/2t
WMA	1.12± 0.34	1.5± 0.6	341± 88
NO-WMA	3.9± 4.7	5.1± 2.3	164 ± 38
P- value	<0.02	<0.00002	<0.001

Conclusions: Baseline LAD velocity profile may predict myocardial wall motion abnormalities in the territory of the LAD during DSE.

P3371 Aortic valve sclerosis screening using a hand-held ultrasound device and its correlation to coronary artery disease

E.C. Vourvouri, E. Biagini, V. Rizzello, A.F.L. Schinkel, F.B. Sozzi, G.E. Parharidis, J.R.T.C. Roelandt, D. Poldermans. *Erasmus MC, Thoraxcenter, Cardiology Department, Rotterdam, Netherlands*

Background: Aortic valve sclerosis (AVS), mitral annulus calcification (MAC) and aortic root sclerosis (ARS) have been demonstrated to be markers of coronary artery disease.

Purpose: 1.To evaluate the diagnostic potential of a hand-held ultrasound device (HD; SonoHeart, SonoSite Inc) for screening for AVS, MAC, ARS in patients with known or suspected coronary artery disease (CAD). A standard echocardiographic system (SE) was used as a reference. 2. To evaluate the relation between AVS, MAC and ARS and CAD assessed as rest or stress induced new wall motion abnormalities during dobutamine stress echocardiography (DSE).

Methods: Ninety-one patients (53% men, mean age 62±13 years) were referred for the evaluation of known or suspected CAD. All patients were examined with a HD and a SE to assess AVS, MAC and ARS by two independent cardiologists. AVS was scored using a 4-point grading scale:1=normal, 2=mildly sclerotic, 3=moderately sclerotic and 4=severely sclerotic, with calcifications. MAC and ARS were defined as an increased echoreflectance and thickness of the mitral annulus and aortic root wall respectively. Subsequently all patients were evaluated for rest and stress induced wall motion abnormalities during DSE by a third independent observer.

Results: AVS, MAC and ARS were present in respectively 41%, 34% and 43% of patients using SE and 41%, 26% and 40% of patients using the HD (p=NS). There was a good to excellent agreement between the two imaging devices for the evaluation of the sclerosis of all aortic valve cusps (right cusp 86%, k=0.67, left cusp 96%, k=0.79, non coronary cusp 90%, k=0.77). The agreement for the assessment of MAC and ARS were respectively 92%, k=0.82, and 92%, k=0.84. During DSE, wall motion abnormalities at rest and ischemic segments at peak were respectively present in 54 (59%) and 17 (19%) of patients. There was a poor correlation between the grade of AVS and the number of dysfunctional segments at rest (r=0.1) or the number of ischemic segments at peak DSE (r=0.11).

Conclusion: Hand-held echocardiography is a reliable and accurate screening tool for AVS, MAC and ARS. There was no correlation between the grade of echo-assessed AVS and coronary artery disease detected by DSE.

P3372 Bedside evaluation of left ventricular dimension and function by hand-carried ultrasound device: a comparison with standard echocardiography

A. Posteraro, P. Trambaiolo, A. Salustri, F. Papetti M Piccoli, E. Cerquetani R Teoli, E. Amici, G. Pastena E Rinaldi, G. Gambelli. *P.O.I. Portuense, Cardiology Unit, Rome, Italy*

Background: Aim of this study was to evaluate the potential value of hand-carried ultrasound (HCU) devices for the bedside evaluation of left ventricular (LV) dimension and function in patients with different cardiac pathologies.

Methods: Three-hundred-forty-five patients admitted to our Center for different reasons (early after cardiac surgery= 256; ischemic heart disease= 50; heart failure= 39) were enrolled in this prospective study. HCU studies were performed by the referring staff cardiologist (4 level-1 and 4 level-2, according to ASE requirements), using a commercially available device (OptiGoTM, Philips, Andover) which allows 2-D and Color flow Doppler imaging. Patients were evaluated at bedside, during the consultation round, for focused assessment of LV dimension and function. LV dimensions were visually estimated during the HCU exam and defined as normal, mildly enlarged, and grossly enlarged. Left ventricular ejection fraction (LVEF) was visually estimated and categorized into 3 groups: <31%, 31-50%, >50%. A standard echocardiographic (SE) exam with a high-end system (Sonos 5500, Philips, Andover) was performed within 24 hours from the HCU. Indexed left ventricular end-diastolic volumes (iEDV) and LVEF (modified Simpson's method) were calculated and compared with the data obtained at HCU.

Results: HCU was feasible in all patients, with a mean time of < 3 minutes. iEDV

at SE was significantly larger in patients with "grossly enlarged" compared to patients with "mildly enlarged" and "normal" left ventricle (84±40 ml/m^2 vs 57±20 ml/m^2 vs 46±15 ml/m^2, respectively; p<0.01). The agreement between LVEF visually estimated by HCU and quantitated by SE was as 282/345= 0.82.

Table 1. Results

LVEF	<31% (HCU)	31-50% (HCU)	>50% (HCU)
<31% (SE)	17	3	0
31-50% (SE)	13	62	14
>50% (SE)	1	32	203

The agreement between LVEF visually estimated by HCU and quantitated by SE was as 282/345= 0.82.

Conclusions: HCU devices allow to perform a targeted, bedside evaluation of left ventricular dimension and function, within minutes during the consultation round. Data obtained with visual estimation from HCU device are closely related to those quantitatively obtained from standard high-end echocardiography.

P3373 The Heart in the City: screening on population of pre-clinical markers of heart failure by hand-held echocardiography

M. Galderisi[1], P. Ballo[2], P. Innelli[3], G. Giannotti[2], S. Lunghetti[2], G. de Simone[3], O. de Divitiis[3], S. Mondillo[2]. *[1]Naples, Italy; [2]Siena University, Cardiology, Siena, Italy; [3]Federico II University, Clinical and Experimental Medicine, Naples, Italy*

Purpose: the "Heart in the City" is a project designed by Naples and Siena University, for a screening on population of pre-clinical markers of heart failure by using hand-held echocardiography (HHE).
Methods: in 3 cities (Naples, Siena, Striano [Salerno]) 280 individuals (115 women, mean age = 58.8 years) were assessed by HHE (Sono Heart, Sono Site) of limited tools (M-mode and 2D- with only linear measurements, bidirectional power Doppler) and low cost. Participants also filled out a questionnaire indicating risk factors, cardiac pathologies and drugs. Anthropometric data, blood pressure (BP) and heart rate were recorded. Data of left ventricular (LV) dimensions and wall thickness, left atrial dimension, "visual" ejection fraction (EF), wall motion score index (WMSI) and valve heart disease were collected into an echo report. In the present study, after excluding 35 patients with known cardiac disease (coronary artery disease, more than mild valve disease, primary cardiomyopathy, atrial fibrillation), we selected 255 subjects: 184 normotensives and 71 hypertensives taking antihypertensive drugs by at least 1 year.
Results: hypertensives had older age (p<0.0001), higher body mass index (BMI) (p<0.005) and higher systolic and diastolic BP (p<0.0001 and p<0.05 respectively). They showed in comparison with normotensives higher septal thickness (p<0.0001), LV end-diastolic dimension (p<0.05), LV mass index (LVMI) (49±14.8 versus 41.7±13.4 g/m$^{2.7}$, p<0.001) and left atrial dimension (LAD) (p<0.0001), while relative diastolic wall thickness was similar between the 2 groups. Visual EF was lower (p<0.05) and WMSI higher (p<0.01) in hypertensives. In the overall population EF, LVMI and LAD were related with systolic BP (r=-0.23, p<0.001; r=0.29, p<0.0001 and r=0.25, p<0.001), diastolic BP (r=-0.18, p<0.01; r=0.19, p<0.01 and r=0.28, p<0.0001) and pulse pressure (r=-0.17, p<0.01; r=0.24, p<0.001 and r=0.13, p<0.05). Among these relations only that between systolic BP and EF remained significant after correction for age and BMI (r=-0.15, p=0.04).
Conclusions: HHE are able to detect alterations of both structure and function involving the hypertensive heart. LV systolic function has a negative association with systolic BP, crude expression of LV afterload. In relation to the found wall motion abnormalities, it is conceivable that at least part of these alterations could be ascribed to silent myocardial ischemia. Pre-clinical markers of heart failue can be unmasked by HHE in a population free of overt coronary artery disease.

P3374 Hand-carried ultrasound devices in outpatient clinic reduce standard echocardiographic need

P. Trambaiolo, A. Posteraro, A. Salustri, F. Papetti, E. Amici E Cerquetani, M. Piccoli G Pastena, R. Teoli, G. Gambelli. *P.O.I. Portuense, Cardiology Unit, Roma, Italy*

Background: Aim of this study was to assess the potential value and the cost-effectiveness of hand carried ultrasound (HCU) devices in the outpatient cardiology clinic for reducing the need of standard echocardiography (SE).
Methods: From September 15th to December 15th, 210 consecutive patients referred to the outpatient clinic of our Center for elective cardiac evaluation were screened and enrolled in this prospective study. Eight cardiologists of the staff (4 level-1 and 4 level-2, according to ASE requirements), after clinical history, EKG and physical examination, required other diagnostic exams for proper evaluation of the patient. If a SE was specifically indicated, a HCU examination was immediately performed by the same cardiologist using a commercially available system (OptiGoTM, Philips, Andover) capable of 2-D and Color flow Doppler imaging. Then, the cardiologist re-evaluated the clinical scenario in order to confirm or cancel the SE request according to the information provided by the HCU exam.
Results: The HCU exam was performed in 106/210 (50%) patients, with a mean examination time < 3 minutes. In 32% of these patients (34/106), SE request was cancelled because cardiologists were satisfied by HCU information. In the remaining patients (72/106; 68%), SE was confirmed because of the following reasons: Doppler evaluation of diastolic function (28/72; 39%); quantification of valvular pathology (21/72; 29%); left ventricular regional function (14/72; 20%); poor image quality (6/72; 8%); assessment of pulmonary arterial systolic pressure (3/72, 4%). According to actual costs (SE = 60 Euro's, HCU = 3 Euro's), the use of HCU allowed to save 1938 Euro's in the study period.
Conclusions: In patients referred to an outpatient cardiology clinic, a HCU device with limited 2-D and Color flow Doppler imaging: 1. avoids to perform high-end SE in one out of three patients, without significant prolongation of the cardiac consultation time;
2. permits to save 914 Euro's every 100 screened patients.

P3375 New generation ultra-portable Doppler and echocardiographic machine allows an accurate diagnosis in CCU: preliminary experience

M. Ladouceur[1], S. Ederhy[2], G. Dufaitre[1], E. Di Angelantonio[1], S. Janower[1], N. Hammoudi[1], A. Cohen[1]. *[1]Assistance Publique Hopitaux de Paris, Saint Antoine University Hospital, Paris, France; [2]Saint antoine, Cardiologie, Paris, France*

Background: New generation portable Doppler echocardiography (PE) machines, including all capabilities have been recently introduced and seem attractive due to their size and portability. We aimed to compare the diagnostic value of a PE examination, when performed by an individual with minimal echocardiographic training, in patients admitted to a CCU with various clinical presentations, to standard state-of-the-art equipment machines (SE).
Methods: We used a PE (ultra portable VIVIDi) to evaluate patients admitted in a CCU, and compared the results with SE (VIVID7). The 38 critically ill patients (mean age 68±12) were studied with each machine. All studies were done and interpreted separately in blinded fashion. Doppler echocardiographic examinations included 4 and 2-chamber views with Doppler interrogation of all valves and determination of left ventricular (LV) diameters and mass (LVM), volumes, ejection fraction, filling pressure based on mitral flows (E/A, E/Ea), and pulmonary pressures (Vmax TR).Overall concordance in all measurements and diagnosis was determined using the Kappa test and pearson correlation.
Results: The table shows the main correlations for some critical parameters measured with both PE and SE. Pearson correlations varied from 0.223 (posterior wall thickness) to 0.933 (LVEF). PE did not miss any significant valvular regurgitation (≥ grade2) or stenosis. The overall concordance for the main echocardiographic diagnosis was 83% (Kappa coefficient 0.764, p < 0.001).

Measurement concordance between PE and S

Parameters	Pearson correlation	p Value
Left Ventricular Mass	0.755	<0.001
Left atrial area	0.720	<0.001
Biplane LVEF	0.933	<0.001
E/A	0.892	<0.001
E/Ea	0.726	<0.001
E/Vp	0.547	0.003
Valvular regurgitation(≥grade2) Yes/No	0.612(Kappa)	0.004
VmaxTR	0.691	<0.001

Conclusion: This preliminary study support the recommendation that a new generation ultra-portable echocardiographic machine equipped with all capabilities allow an accurate diagnosis in a CCU setting.

P3376 Doppler evaluation of cardiac allograft dysfunction in long-term heart transplantation recipients with normal coronary angiograms

F. Tona[1], A.L.P. Caforio[1], A. Gambino[2], A. Angelini[3], A. Ramondo[1], G. Thiene[3], G. Gerosa[2], S. Iliceto[1]. *[1]Cardiology, University of Padova, Padova, Italy; [2]University of Padova, Cardiovascular Surgery, Padova, Italy; [3]University of Padova, Cardiac Pathology, Padova, Italy*

Chronic cardiac allograft dysfunction with normal coronary angiograms is poorly understood. We studied Doppler-derived systolic and diastolic function indexes in long-term heart transplantation, to identify early noninvasive markers of allograft dysfunction.
Methods: We studied 154 stable heart transplantation recipients (125 male, aged 51 ± 13 years) with normal left ventricular echocardiographic ejection fraction (63 ± 6%), free from acute rejection and without allograft vasculopathy. Doppler parameters were: mitral E and A wave velocities, E/A ratio, mitral deceleration time (DT), isovolumic relaxation time (IVRT), isovolumic contraction time (IVCT), ejection time (ET) and Tei index (IVCT + IVRT/ET). Mean follow up from heart transplantation to Doppler examination was 6.6 ± 4.3 years. Rejection scores (RS) on endomyocardial biopsy were calculated (ISHLT grades: 0=0; 1A=1; 1B=2; 2=3; 3A=4; 3B=5; 4=6) in the first year, in the second year and during the whole follow-up. RS including only severe grades (≥3A) were also calculated. Pearson's test was used to correlate quantitative data.
Results: E/A ratio and Tei index were inversely related with donor age (r=-0.198, p=0.02 and r=-0.232, p=0.004 respectively) and directly related with mean time from heart transplantation (r=0.190, p=0.03 and r=0.309, p<0.0001 respectively). IVRT was inversely related with ischemic time and with RS in the second year (r=-

0.213, p=0.01 and r=-0.202, p=0.02). DT was inversely related with RS in the first year, in the whole follow up, and with RS including only severe grades in the first year and in the whole follow-up (r=-0.207, p=0.002; r=-0.261, p=0.01; r=-0.224, p=0.006 and r=-0.220, p=0.04 respectively). Tei index was directly related with all RS and RS for severe grades in the first year (r=0.209, p=0.01 and r=0.242, p=0.005 respectively).
Conclusion: These correlations suggest a progressive impairment of myocardial performance, directly associated with acute rejection burden, in long-term heart transplantation recipients free from cardiac allograft vasculopathy and with normal left ventricular ejection fraction. This may indicate early graft dysfunction, reflecting subtle chronic rejection changes.

P3377 Tissue Doppler imaging improves dobutamine stress echocardiography analysis by novice readers in heart transplant patients

H. Thibault[1], R. Ciobanu-Jurcut[1], S. Thivolet[1], D. Brunet[1], L. Sebbag[1], M. Ovize[1], G.A. Derumeaux[2]. *[1]Lyon University - EMIU O226, Louis Pradel Hospital, Lyon, France; [2]Lyon, France*

Background: Cardiac allograft vasculopathy,a major long-term complication in heart transplant patients, can be diagnosed by dobutamine stress echocardiography (DSE). However, DSE is strongly dependent on the reader's experience. This study aimed to compare novice reproducibility of DSE analysis by wall motion score (WMS) and by systolic velocity (Vs, cm/sec), strain rate (SRs, sec-1) and end-systolic strain (Ses, %), respectively.
Method: 30 heart transplants (mean time since transplantation: 7 ± 2 years) underwent a DSE (Vivid 7, GE). Two novices and an expert independently analyzed WMS at rest and at peak using a 16-segment model (kappa test). Then, the 2 novices mesured Vs, SRs and Ses within the basal and mid segments from the 3 apical views at rest and at peak (Bland and Altman test). In addition, Vs, SRs and Ses were compared in normal and abnormal segments (based on the expert analysis).
Results: Interpretation of WMS was feasible in 395 segments. At rest, the agreements on WMS were poor between the 2 novices (Kappa: 0.40) and between the 2 novices and the expert (novice 1: 0.21 and novice 2: 0.26). At peak, Kappa values did not improve between the novices (0.28) and between the novices and the expert (0.33 and 0.23, respectively).
Vs, SRs and Ses were measured on 360 segments. At peak, Vs was significantly lower in abnormal than in normal segments for the 2 novices. In contrast, SRs and Ses could not distinguish normal from abnormal segments (Table, * p<0,05 versus normal).The agreement on Vs values was excellent and better than SRs and Ses. Mean difference between the 2 novices was: - for Vs: 0.04± 0.04 cm/sec at rest and 0.09± 0.09 cm/sec at peak.
– for SRs: 0.12±0.03 sec-1 at rest and 0.5± 0.07 sec-1 at peak.
– for Ses: 1.9±0.3% at rest and 2.6±0.4% at peak.

Expert diagnosis	NOVICE 1		NOVICE 2	
	Normal segments	Abnormal segments	Normal segments	Abnormal segments
peak DSE Vs (cm/sec	9.1±0.2	7.6±0.3 *	9.1±0.2	7.2±0.3 *
peak DSE SRs (sec-1)	-2.8±0.09	-2.4±0.1	-2.2±0.08	-2.1± 0.1
peak DSE Ses (%)	-17.2±0.5	-16.5±0.6	-14±0.5	-14.5± 0.6

Conclusion: In heart transplants, WMS analysis by novice is not reliable. In contrast, Vs but not SRs and Ses improves DSE reproducibility and accurately differenciates normal from abnormal segments.

P3378 Contrast enhancement increases the prognostic value of dobutamine stress echocardiography in the prediction of cardiovascular outcome in heart transplant recipients

M. Kung[1], S. Stoerk[1], F. Weidemann[2], P. Jung[1], C. Spes[3], C.E. Angermann[1]. *[1]Med. Klinik und Poliklinik II, Cardiology, Wuerzburg, Germany; [2]Med. Klinik und Poliklinik I, Cardiology, Wuerzburg, Germany; [3]Staedt. Krankenhaus Neuperlach, Cardiology, Munich, Germany*

Background: dobutamine stress echocardiography (DSE) is an established method for transplant vasculopathy (TVP) surveillance after heart transplantation (HTX) while strain rate imaging allows the detection of regional left ventricular functional abnormalities. Contrast enhanced imaging improves endocardial visibility. It is unknown to which extent contrast enhanced and strain rate imaging may increase the diagnostic yield of DSE. We estimated the independent and incremental prognostic value of these modalities in post HTX patients.
Methods: we studied 83 consecutive HTX recipients (55.3±10.4y, 15f) with DSE, who were included irrespective of native image quality. Native and contrast enhanced (Optison®) digitally stored cineloops of apical 2-, 3- and 4-chamber views were analysed for wall motion abnormalities (WMA) at rest and under stress. Two alternative definitions of an abnormal DSE were used: Type A: >1 segment with new/progressive WMA in native or contrast DSE; type B: >2 abnormal segments in native or contrast DSE. The incremental value was assessed comparing ROC curves derived from Cox regression models. In a subgroup Colour Doppler myocardial imaging (CDMI) data were obtained from the mid segment of the lateral wall. From each segment peak systolic strain and strain rate were extracted by postprocessing the CDMI data. Cardiovascular interventions and deaths were monitored.
Results: during a median follow-up of 3.6years 25 cardiac events occurred (15 PTCA/stent, 10 cardiac deaths). Type A and B with contrast, sex, hemodialysis, and hyperlipidemia were univariate predictors for cardiac events (all P<0.15). Native DSE, strain and strain rate were not predictive. In separate multivariate models, type A (HR 0.26, 95%CI 0.11-0.73, P=0.009) and type B (0.20, 0.05-0.52, P=0.001) remained predictive for TVP together with dialysis and hyperlipidemia (all P<0.05). Using all routinely obtained clinical information resulted in an area under the ROC curve of 0.81. Adding contrast DSE increased the area under the ROC curve (P<0.05), yielding an excellent discriminate power of 0.94.
Interpretation: contrast enhanced, but not native DSE proved a powerful predictor of future cardiovascular events in consecutive HTX recipients not selected for native image quality. No prognostic value was found for strain and strain rate values. In conclusion, contrast enhanced DSE facilitated the identification of HTX recipients at risk and, thus, may improve post HTX monitoring.

COMPUTERS IN CARDIOLOGY

P3379 Bedside recording of the patients medical history and diagnostic findings using mobile devices with an integrated expert system

S. Urban[1], K. Kronberg[1], J. Riesmeier[2], M.S. Claus[2], M. Eichelberg[2], G.-H. Reil[1]. *[1]Klinikum Oldenburg, Kardiologie, Oldenburg, Germany; [2]OFFIS e.V., IUK-Systeme im Gesundheitswesen, Oldenburg, Germany*

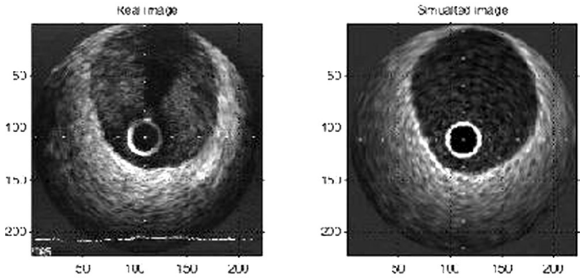
Background: mobile device technology has developed rapidly in the last couple of years. Today, many institutions already use these types of devices for data acquisition in various fields. Usually, the access to the local network is provided by means of wireless network connections. Within the cardiology department of the Klinikum Oldenburg mobile devices are used to record the patient's medical history and the results of the physical examination directly at the bedside.
Method: for this project the mobile device "skeye.pad" from skeye.webpanel running on Windows CE has been selected. The display of this web panel has a resolution of 800 x 600 pixels which is more than a personal digital assistant typically provides.
Based on the Microsoft. NET framework input masks for acquiring the medical history of a patient have been designed. The graphical user interface controls a self-learning expert system which also uses previously entered medical cases as its knowledge base. Diagnoses and typical symptoms can be selected from a list which is sorted by the frequency of occurrence. Depending on the selected diagnosis the expert system proposes appropriate diagnostic procedures and medications.
The user is guided through the entire process of data acquisition in a step-by-step manner. This approach ensures that all data is collected correctly and completely. In addition, a navigation bar allows the user to open a particular input mask directly. Finally, the entered data and generated diagnostic codes are summarised. The user can then either confirm or modify the data.
The whole application can be controlled by fingertips – the use of an input pen is optional. All input masks and data structures can be modified using a simple administration tool, i. e. no programming skills are required. Furthermore, the core architecture of the application is highly modular which facilitates the development of future extensions.
Results: the bedside recording of the patient's medical history and diagnostic findings eliminates the need for manual transfer of data from the conventional patient record into the cardiology information system. All data can be retrieved from any authorised workstation in the department at any time. In combination with the electronic reports from cardiac catheter and echocardiography examinations discharge letters can be generated automatically.
Conclusion: the use of mobile devices can significantly improve the workflow in a hospital department. However, this requires a software which implements a medical knowledge base and an intuitive, self-explanatory user interface.

P3380 Empirical intravascular ultrasound simulation system

O. Rodriguez Leor[1], J. Mauri Ferre[2], E. Fernandez Nofrerias[2], E. Tizon[3], A. Tovar[2], V. Valle Tudela[2], M. Rosales[3], P. Radeva[3]. *[1]Hospital Universitari Germans Trias i Pujol, Hemodinamica Cardiaca, Badalona, Spain; [2]HU Germans Trias i Pujol, Cardiology, Badalona, Spain; [3]Universitat Autonoma de Barcelona, Computer Vision Center, Bellaterra, Spain*

Intravascular ultrasound (IVUS) images give very important information for diagnostic and therapy in atherosclerotic vessels. IVUS analysis is made without considering the principles for the image generation. We propose a physical model for simulating IVUS images.
Method: The model is based on a discrete representation of the tissue by individual scatterers elements with given spatial distribution and Backscattering Differential Cross Section (DBC). It uses the emission and reception principles of the ultrasound waves while crossing radially a simulated coronary artery, con-

sidering spatial scatterers distribution, DBC distribution, influence of the cardiac pressure in the scatterers distribution, influence of catheter movement and critical appearance of IVUS parameters (spatial resolution, optimal ultrasound frequency, optimal attenuation coefficient, beam number influence, etc).
We have used 20 real IVUS images in which lumen, intima, and adventitia were manually delimited in order to generate 20 images using our model.
Simulated and real images were compared in global and local form using different quantitative parameters (average grey level projection (AVG), region of interest analysis (ROI) and local spectral density of the grey level average projection (LSD)).
Result: Comparison between real and simulated data showed the following correlation: AVG R=0.93; different ROI (transition intima to lumen and adeventitia) R=0.90; LSD R=0.87 (Px) and R=0.85 (Py).



Real and simulated artery

Conclusion: Our model simulates IVUS images with high precision. IVUS image simulation, considering not only vessel structures but physical parameters of ultrasound can contribute to a better interpretation of IVUS images by enhancing the interpretation of physical parameters of IVUS in image formation.

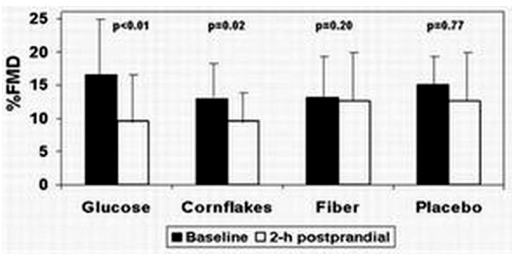
POSTER SESSION 6

MODERATED POSTERS: EXERCICE/EPIDEMOLOGY/PREVENTION/ PHARMA/NURSING

P3381 The acute effect of various glycemic index dietary carbohydrates

T. Lavi[1], A. Karasik[1], M.S. Feinberg[2], M. Shechter[2]. *[1]Sheba Medical Center, The Endocrinology Unit, Tel Hashomer, Israel; [2]Sheba Medical Center, The Heart Institute, Tel Hashomer, Israel*

Background: Data relating the acute effect of various glycemic index dietary carbohydrates on endothelial function has not yet been explored.
Methods: We prospectively assessed endothelium-dependent flow-mediated vasodilation (FMD) of the brachial artery in 34 consecutive healthy non-diabetic volunteers [26 normoglycemic (NGT) and 8 impaired glucose tolerance (IGT)] without known CVD. All subjects were studied on 4 separate mornings, 1-2 weeks apart. At each visit, after an overnight fast and discontinuation of all medications for > 12 hours, endothelium-dependent brachial artery FMD and endothelium-independent nitroglycerin-mediated vasodilation (NTG) were assessed non-invasively, using high resolution (15 MHz) linear array ultrasound, after which subjects randomly received one of 3 carbohydrate-based meals, each with a different glycemic index (glucose, cornflakes, fiber) or placebo (water). Two hours postprandial a repeat endothelial function test was performed.
Results: The 2 groups were comparable regarding gender, age, body mass index, lipoproteins and C-reactive protein. Fasting blood glucose and blood glucose, after a 75g glucose-loading test, were significantly higher in the IGT group compared to NGT. Baseline %FMD was not significantly different in all 3 carbohydrate-based and placebo meals in both study groups. However, it was significantly reduced 2 hours postprandial in the glucose-base and cornflakes meals (figure).



Conclusion: Carbohydrate meals with high glycemic index significantly suppress endothelial function in the brachial artery in NGT and IGT subjects, suggesting a mechanism whereby high glycemic index may enhance CVD risk.

P3382 Decline in aerobic fitness of Canadian children over the past 23 years; a retrospective comparison

K.E. Reed, D.E.R. Warburton, H. Macdonald, C.L. Whitney, H.A. McKay on behalf of Action Schools! BC. *University of British Columbia, Human Kinetics, Vancouver, Canada*

Background: Anecdotal and empirical evidence suggests that physical fitness has declined in youth in recent years. However, not all investigations show this decline, and several studies from Europe even show an increase in physical fitness. Thus, the aim of this study was to compare the aerobic fitness (AF) of Canadian children in 2004 with that of Canadian children in 1981.
Methods: This was a cross sectional comparison of 2 data sets (1981 and 2004). Participants (2004 cohort, n=252), aged 9-11, completed Leger's 20m Shuttle Run Test. Performance of children in 2004 was converted to Z-scores, then to 1981 equivalent percentiles, derived using data extracted from Leger's original study (n= 2151 children of comparable age/sex). Data from 2004 were compared to data from 1981 using one-sample t-tests. Statistical significance was set at $p<0.05$.
Results: AF is lower, at all ages, in both boys and girls in 2004 compared with normal values from 1981. Statistical significance between cohorts (1981 and 2004) was achieved for girls aged 9, boys aged 10 and 11 years (Fig. 1). Mean AF of children in 2004 is equivalent to the 19th percentile of the 1981 cohort. Therefore the average fitness of a child in 2004 is more than 30 percentiles lower than age and sex matched children of 23 years ago.
Figure 1 shows aerobic fitness of children in 1981 and 2004, in sex and age categories

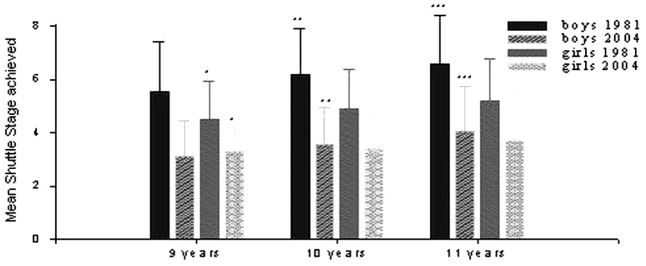


Figure 1. Aerobic fitness in 1981 and 2004 (* indicates $p<0.05$)

Conclusion: Aerobic fitness, assessed by running performance, is substantially lower in children today than 23 years ago. AF has declined more in young boys than in young girls. As aerobic capacity is associated lower prevalence of cardiovascular disease risk factors, even during youth, it is imperative that this decline in fitness is addressed.

P3383 Strong prognostic value of C-reactive protein and albuminuria for the risk of mortality in the general population

H. Hillege[1], E.M. Stuveling[2], F.W. Asselbergs[3], S.J.L. Bakker[2], R.T. Gansevoort[4], R.O.B. Gans[2], P.E. de Jong[4], D. de Zeeuw[5]. *[1]University Medical Center, Trial Coordination Center/Cardiology, Groningen, Netherlands; [2]University Medical Center, Internal Medicine, Groningen, Netherlands; [3]University Medical Center, Cardiology, Groningen, Netherlands; [4]University Medical Center, Internal Medicine/Nephrology, Groningen, Netherlands; [5]University Medical Center, Clinical Pharmacology, Groningen, Netherlands*

Background: Increased levels of both C-reactive protein (CRP) and urinary albumin have seperately been associated with an increased risk of total and cardiovascular (CV) mortality in the general population. It is not known whether CRP and albuminuria can be substituted for each other as risk predictors or that they are additive in predicting total and CV mortality.
Methods: We conducted a prospective study on CV risk factors with a median follow-up of 1709 days in the city of Groningen, the Netherlands, comprising of 8,592 men and women, aged 28-75 years old. These subjects were identified in the Prevention of Renal and Vascular Endstage Disease (PREVEND) study during 1997-1998.
Findings: Crude and multivariate analyses showed that both CRP and albuminuria increased and added to the absolute and relative risk of total, CV and non-CV mortality: CRP: hazard ratio for CV 1.19 (95%CI 1.00-1.41) and non-CV 1.29 (1.15-1.43); albuminuria: CV 1.23 (1.09-1.39) and non-CV 1.14 (1.04-1.27) per 2-fold increase of their levels, respectively. This increased risk appeared to be independent of classical risk factors and of each other. Diabetes, elevated blood pressure and total cholesterol did not add prognostic information to the multivariate model, whereas smoking and male gender increased the risk approximately 2-fold.
Conclusions: CRP and albuminuria contribute independently to the CV risk profile, and are additive, in the general population. CRP and albuminuria provide more information about CV risk than conventional risk factors, suggesting that strategies aimed at lowering both markers may be effective in primary prevention. The relative risks of CV death are comparable with increasing levels of both mark-

ers, although albuminuria provides a more accurate marker of CV death relative to CRP. CRP and albuminuria were as strongly related to CV death as to non-CV death.

P3384 Is the volume of procedures still an issue in the era of PCI with systematic stenting?

M.C. Morice[1], C. Spaulding[2], N. de Vernejoul[3], B. Lancelin[4], S. Elhadad[5], M. Monchi[6], E. Lepage[3], S. Fosse[3]. [1]*Institut Hospitalier Jacques Cartier, Institut Cardiovasculaire Paris Sud, Massy, France;* [2]*Hôpital Cochin, Paris, France;* [3]*Agence Régionale Hospitalière, Paris, France;* [4]*Centre Chirurgical Marie Lannelongue, Le Plessis-Robinson, France;* [5]*Centre Hospitalier de Lagny, Marne-la-Vallée, France;* [6]*Institut Hospitalier Jacques Cartier, Institut Cardiovasculaire Paris Sud, Massy, France*

Background: The effect of hospital volume on angioplasty complications has been well described. However, it was suggested that the use of stenting was likely to neutralize the volume-outcome relation.
Methods: In 2000, the hospital agency of the Paris region set up a registry of all PCI procedures performed in this region. Completeness of the registry database was achieved in 2001. Both internal and external audits were carried out on data quality.
Results: In 2002, 105 550 PCI procedures were performed in 220 centers in France;19% of these procedures were performed in the 44 centers implanted in the Paris region (10% of procedures (P) in 14 centers performing $<$250 P/year, 14% in 9 centers with 250-400 P/year, 30% in 12 centers with 400-600 P/year and 46% in 9 centers with $>$ 600 P/year. The registry population included in 2001 and 2002 comprised 33,393 pts (37,848 procedures)22% female, mean age 64, 19% of whom had AMI and 2% cardiogenic shock. Stenting was performed in 86.9% of patients. Death occurred in 2.2% of pts (5.6% with AMI and 0.8% without AMI). Multivariate analysis showed that mortality predictors were: age ($p<0.0001$), female gender (0.0045), center activity volume (0.018), highest risk pts (with circulatory arrest or cardiogenic shock) $p<0.0001$, and AMI $<$ 24 h ($p<0.0001$). However, the following interactions were found: hospital volume/highest risk patients, p=0.0560; age/highest risk patients, p=0.0001 and warranted a case control analysis (propensity score) comparing centers performing $<$400 cases/year and those performing $>$ 600 cases/year: Overall mortality was significantly higher in low-volume centers (2.4% vs. 1.9%, p=0.038) and to an even greater extent in high-risk patients (8.4 vs. 6.3%, p=0.0110), but not significantly different for low-risk pts (0.6 vs. 0.6, p=0.8). Rates of complications were significantly higher in low-volume centers for the general population (p=0.002), high-risk (p=0.003) and low-risk pts (p=0.016).
Conclusion: In the era of systematic stenting, PCI can be performed safely and successfully in most patients. However, these data demonstrate that patient safety is still related to hospital volume.

P3385 Cost-effectiveness of neonatal ECG screening the long QT syndrome

P.J. Schwartz[1], S. Quaglini[2], C. Rognoni[2], C. Spazzolini[3], S. Mannarino[4], S.G. Priori[5]. [1]*IRCCS S. Matteo/University of Pavia, Dept. of Cardiology, Pavia, Italy;* [2]*University of Pavia, Dept. of Computer Science and Systems, Pavia, Italy;* [3]*IRCCS S. Matteo/University of Pavia, Dept. of Cardiology, Pavia, Italy;* [4]*IRCCS Policlinico S. Matteo, Department of Pediatrics, Pavia, Italy;* [5]*IRCCS Fondazione S. Maugeri, Molecular Cardiology Laboratories, Pavia, Italy*

The long QT syndrome (LQTS) is a life-threatening genetic disorder with a high incidence of sudden death as first symptom, beginning already in the first year of life. Our recent molecular evidence in 200 victims of Sudden Infant Death Syndrome (SIDS) points to 10-15% of SIDS being actually due to LQTS. As very effective treatments are available, early diagnosis would allow identification of the affected individuals, including family members, and institution of life-saving therapy. Our ongoing prospective study of neonatal ECG, based on 31,000 infants, demonstrates that besides LQTS several serious cardiovascular malformations can be identified and surgically corrected prior to irreversible cardiac damage or death. These considerations raise the controversial issue of widespread neonatal ECG screening and, indeed, some European countries are considering its introduction as part of the services offered by their National Health Systems. Accordingly, we have carried out an economic evaluation using a decision analysis approach, including Markov models and Monte Carlo simulations, and have tested the cost-benefit of introducing neonatal ECG screening in a country such as Italy with approximately 550,000 births per year. The necessary data or estimates (such as prevalence of LQTS, mortality in treated or untreated patients, probability of expensive non-pharmacological therapies, and so on) were derived from published reports or from our own large databases. The main finding is that the cost per year-of-life saved is of 6,860 Euros. Based on current standards this figure is "very cost-effective". The cost to save one life (70 years) is approximately 500,000 Euros. Given the implications of this finding, and for additional caution, we performed a multivariate sensitivity analysis varying all data by $\pm$ 30% and found that the cost for year-of-life saved was still low, between 4,000 and 15,000 Euros. These figures do not consider the uniquely tragic emotional trauma due to the sudden death of a child. Thus, screening with ECG every infant born in a large European country is highly cost-effective. European tax-payers should be informed about the cost-benefit ratio of neonatal ECG screening.

P3386 Plasma oxidised low density lipoprotein: a strong predictor for acute coronary heart disease events in apparently healthy middle aged men from the general population

C. Meisinger[1], J. Baumert[1], N. Khuseyinova[2], H. Loewel[1], W. Koenig[2]. [1]*National Research Center for Health, Institute of Epidemiology, Neuherberg, Germany;* [2]*University of Ulm Medical Center, Department of Internal Medicine II, Ulm, Germany*

Purpose: Oxidized low density lipoprotein (oxLDL) is thought to play a key role in the inflammatory response in the arterial vessel wall.
Methods: In a prospective nested case-control study, the association between plasma oxLDL and risk of an acute coronary heart disease (CHD) event was investigated in men without prevalent CHD or diabetes mellitus at baseline. Subjects came from two population-based MONICA/KORA Augsburg surveys conducted in the years 1989/90 and 1994/95 with follow-up in 1998 (mean follow-up time 5.6 years; SD 2.6). OxLDL was determined by ELISA in 88 men with incident CHD and in 258 age- and survey-matched controls. Hazard ratios (HR) were estimated from Cox proportional hazard models.
Results: Baseline mean plasma oxLDL concentrations were significantly higher in subjects who subsequently experienced an event compared to controls (109.8 (SD 32.1) vs 92.8 (SD 28.1) U/L; $p<.001$). After adjustment for age, survey, smoking, hypertension, obesity, physical activity, education, and alcohol consumption, the HR for a future CHD event comparing the top tertile of the oxLDL distribution to the bottom tertile was 3.79 (95% confidence interval 2.07-6.95; $p<.001$). Plasma oxLDL was the strongest predictor of CHD events compared to a conventional lipoprotein profile, and other traditional risk factors for CHD. When both oxLDL and C-reactive protein were simultaneously assessed in the same model, they still independently predicted future CHD events even after multivariable adjustment.
Conclusions: Elevated concentrations of oxLDL are predictive of future CHD events in apparently healthy men. Thus, oxLDL may represent a promising risk marker for clinical CHD complications and should be evaluated in further studies.

P3387 Long-term cost effectiveness of early and sustained antiplatelet therapy with clopidogrel following percutaneous coronary intervention (CREDO trial): a five European country analysis

W.S. Weintraub[1], O. Bouin[2], E. Veledar[1], G.P. Kolm[1], S. Gabriel[2]. [1]*Emory Center For Outcomes Research, Emory West, Atlanta, United States of America;* [2]*Sanofi-Aventis, Paris, France*

Background: The Clopidogrel for the Reduction of Events During Observation (CREDO) trial showed that clopidogrel loading prior to percutaneous coronary intervention (PCI) followed by 1-year treatment after PCI reduced the combined risk of death, myocardial infarction (MI) or stroke. The purpose of this study was to evaluate the economic impact of clopidogrel based on CREDO in Switzerland, Belgium, Italy, France and Spain.
Methods: We used clinical outcomes and resource use from CREDO combined with external survival data to assess the long-term cost-effectiveness of clopidogrel.
2116 patients undergoing planned or probable PCI were randomized to clopidogrel loading before PCI plus 1 year therapy vs placebo. All patients received clopidogrel day 0 to 28. At one year 89 (8.45%) patients in the treatment and 122 (11.48%) in the placebo arm had an event (RRR 26.9%, 95% CI 3.9%-44.4%). Hospitalizations were assigned a Diagnostic Related Group (DRG), and unit costs were developed in each country and applied to all patients. Lost life expectancy associated with death, MI and stroke was estimated from Saskatchewan Health Database (SHD) survival data, discounted 3%. The SHD contains comprehensive longitudinal health care data for the entire population of the Canadian province of Saskatchewan. The incremental cost-effectiveness ratios (ICER) were expressed as cost per event prevented (EP) and as cost per life year gained (LYG).
Results: The cost/EP at one year with clopidogrel vs placebo were € 16,742 in Switzerland, € 15,765 in Belgium, € 16,205 in Italy, € 15,884 in France and € 18,442 in Spain. Long term results are consistent in the 5 countries and well below the threshold commonly accepted ($<$30,000euros/LYG) (see table, currency in Euros).

Long Term Cost-Effectiveness

	Added Cost	LYG With	ICER	%$<$30,000/LYG
Country		Clopidogrel	(Cost/LYG)	
Switzerland	506	0.1920	2,696	97.8
Belgium	477	0.1920	2,483	98.7
Italy	490	0.1920	2,552	98.7
France	480	0.1920	2,502	98.7
Spain	558	0.1920	2,905	98.4

Conclusion: Clopidogrel used prior to PCI and for 1 year thereafter is a cost effective strategy.

P3388 Baseline ApoB predicts benefit of intensive statin therapy in patients with ACS: an analysis from PROVE IT-TIMI 22

K.K. Ray[1], C.P. Cannon[2], D.J. Rader[3], R. Cairns[4], C.H. McCabe[2], F.M. Sacks[5], E. Braunwald[2]. [1]*British Heart Foundation International Fellow, TIMI Study Group, Boston, United States of America;* [2]*Brigham & Women's Hospital, Medicine, Boston, United States of America;* [3]*University of Philadelphia, Medicine, Philadelphia, United States of America;* [4]*Nottingham Clinical Reseach Institute, Nottingham, United Kingdom;* [5]*Harvard Medical School, Harvard School of Public Health, Boston, United States of America*

Background and Aims: apolipoprotein B (ApoB) is the major protein in atherogenic lipoproteins. Some studies have suggested that Apo B may be a useful predictor of cardiovascular outcome in patients with stable coronary disease. However, its ability to predict risk in acute coronary syndrome (ACS) patients is unknown.
Methods: the PROVE IT-TIMI 22 study compared intensive therapy (atorvastatin 80mg) vs standard therapy (pravastatin 40mg) in patients with ACS. The endpoint of the study was death, MI, unstable angina, stroke and revascularization >30 days. Baseline ApoB levels were available in 3683 patients and at 4 months in 2998 patients. Treatment efficacy was assessed across quartiles of baseline levels of ApoB.
Results: at enrollment the mean ApoB level was 102 mg/dl. At 4 months, compared with standard therapy, intensive therapy was associated with a significantly greater reduction in ApoB (32% vs 8% reduction, p<0.0001) resulting in a lower achieved ApoB (69 mg/dl vs 92 mg/dl, p<0.0001). There was a gradation of clinical benefit of intensive therapy over standard therapy with increasing quartiles of baseline ApoB (fig 1).

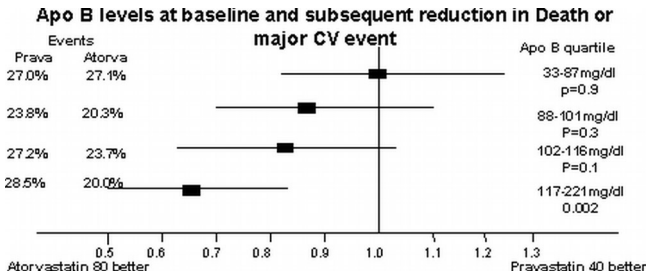


Figure 1

Conclusion: baseline levels of ApoB predict benefit from intensive statin therapy in patients with ACS, with the greatest benefit of intensive therapy in those with the highest levels of ApoB at baseline.

LONG-TERM RESULTS OF BRACHYTHERAPHY

P3389 3-year follow-up after intracoronary beta-radiation therapy for in-stent restenosis reveals considerable delayed recurrent restenosis

E. Iofina[1], P. Radke[2], R. Langenberg[2], A. Franke[2], R. Schubert[3], P. Hanrath[2], R. Hoffmann[2]. [1]*University Hospital RWTH Aachen, Medical Clinic I, Aachen, Germany;* [2]*University, Medical Clinic I, Aachen, Germany;* [3]*University, Department of Radiation Therapy, Aachen, Germany*

Background: Intracoronary radiation therapy (IRT) has proven to be highly effective to reduce recurrent in-stent restenosis (ISR) over a 12 months period. Whether the beneficial effect from radiation is sustained over long-term period remains a concern. This study sought to evaluate the effectiveness of IRT during a 3 year follow-up period.
Methods and results: 130 consecutive symptomatic patients (pts; mean age 63±11 years, 78% males) with 131 in-stent restenotic lesions (>10 mm length)were treated with IRT (non-centered β-emitter, Novoste). The mean radiation dose was 21.1±3.1 Gy at a distance of 2 mm from the radiation source. Additional bare metal stents at the stent margins before IRT due to dissection or remaining stenosis were implanted in 16 lesions (12.4%). 6-months clinical and angiographic follow-up were obtained in 100% and 80% of pts respectively. Binary angiographic restenosis rate was 22% in stent (29% in lesion) with an in-stent late loss of 0.49±0.62 mm. 98% of pts underwent 36-months clinical follow-up. Target lesion resvascularization (TLR) at 6 months follow-up was performed in 23 cases (18%). MACE (death, myocardial infarction, any revascularisation) was observed in 24 pts (19%). At 36-months follow-up TLR increased to 27% (35 cases) and MACE rate was 30% (38 pts). In a subgroup of pts(N=15) with clinically driven recurrent angiography (6-36 months, mean 18±7 months) 14 pts had restenosis; late loss in stent increased from 0.43±0.55 mm at 6 months to 1.03±0.85 mm at repeated angiography (P=0.044) (in lesion: 0.47±0.54 mm to 1.27±0.76 mm, P=0.005). TLR for IRT failure included drug-eluting stents (Cypher®) in 15 cases, recurrent IRT in 9 cases, bypass surgery in 7 cases and angioplasty in 4 cases. Angiographic follow-up after treatment of recurrent in-stent restenosis was obtained in all pts treated by PCI. Recurrent ISR was observed in 3 cases (20%) after drug-eluting stents, 3 cases (33%) after IRT and 2 cases (50%) after angioplasty.
Conclusion: There is a considerable number of delayed recurrent restenosis post IRT for ISR. This is due to ongoing late loss more than 6 months post IRT. Drug-eluting stent placement appears at least as effective as recurrent IRT for treatment of recurrent ISR.

P3390 Very late (3-years follow-up) failure of coronary beta-irradiation for the treatment of in-stent restenotic lesions

T.M. Schiele[1], B. Poellinger[2], W. Haimerl[2], J. Rieber[3], A. Koenig[3], E. Duehmke[2], U. Siebert[4], V. Klauss[3]. [1]*Munchen, Germany;* [2]*Ludwig-Maximilians-University, Radiation Therapy and Radiooncology, Munich, Germany;* [3]*Ludwig-Maximilians-University, Cardiology Dept., Munich, Germany;* [4]*Harvard School of Public Health, Harvard Center for Risk Analysis, Boston, United States of America*

Background: Vascular brachytherapy (VBT) has been convincingly shown to reduce the rate of repeat in-stent restenosis (ISR) and of major adverse cardiovascular events (MACE) at 6 to 9 months after the index procedure. Yet there is evidence that the restenosis process is prolonged and causes MACE even at 2 years post procedure. Even longer follow-up intervals following beta-VBT are not very well described. Thus the aim of our study was to characterise the clinical 3-years follow-up after VBT using 90Sr/90Y.
Methods: Irrespective of the clinical status all patients (PT) having undergone VBT for ISR were prospectively enrolled into a clinical follow-up schedule at 6, 12, 24 and 36 months (mo). Complete 3-years follow-up is available for 106 PT.
Results: The PT (age 64.0±10yr, 82% male) revealed a high incidence of cardiovaskular risk factors. Angioplasty was performed predominantly (76%) with the cutting balloon (balloon/artery-ratio 1.19±1.1; maximal inflation pressure 13.2±5bar). The mean radiation dose was 21.4±2Gy, fractionation was necessary in 2 cases (1.9%). The length of the treated stented segment measured 32.4±18mm (reference lumen diameter 3.1±0.6mm, minimal lumen diameter pre intervention 0.7±0.6mm, post intervention 2.9±0.7mm, acute lumen gain 2.2±0.8mm). All PT received clopidogrel for at least 6 months, most of them for 1 year. After 3 years 2 (1.9%) PT had died (non cardiac), all 5 (4.7%) cases of myocardial infarction took place within the first year. Four (3.8%) instances of late thrombotic occlusions were observed within the first 6 months, 1 additional (0.9%) within the first year. The revascularisation rate of the target lesion revealed a maximum during the first year, decreased during the second year, and, interestingly, again showed an increase during the third year (6mo: 8.5%; 12mo: 3.8%; 24mo: 1.9%; 36mo: 3.8%). This time course was true also for the target vessel revascularisation rates (6mo: 12.3%; 12mo: 6.6%; 24mo: 2.8%; 36mo: 7.5%). The cumulative MACE-rate after 3 years was 35.8%.
Conclusion: While severe MACE like late thrombotic occlusions or myocardial infarction were confined to the first year of follow-up after VBT revascularisation procedures of both the target lesion and the target vessel were necessary during the subsequent follow-up period, notably in the third year of follow-up. These findings may be regarded as indicative for a continuous slow failure of VBT to effectively inhibit neointima formation.

P3391 Five years after intracoronary radiation for the prevention of in-stent restenosis: not as hot as we thought

L. Gruberg[1], M. Suleiman[2], S. Pechersky[2], E. Nikolsky[2], E. Grenadier[2], M. Boulus[2], W. Markiewicz[2], R. Beyar[2]. [1]*Rambam Medical Center, Heart Institute, Haifa, Israel;* [2]*Rambam Medical Center, Department of Cardiology, Haifa, Israel*

Intracoronary radiation therapy (IRT) has been the treatment of choice for the prevention of restenosis and revascularization procedures in patients with in-stent restenosis. The aim of the present study was to analyze the clinical and angiographic characteristics of patients who had recurrence of in-stent restenosis despite IRT. We retrospectively analyzed data of all patients who underwent IRT (n=133) at our institution between 3/1999 and 1/2004. Patients who had either target lesion revascularization (TLR) or need for CABG during the follow-up period were considered as failed IRT (n=47; 35.3%). We compared them to patients who had successful IRT (n=86, 64.7%) during the same time period. Both groups were similar regarding baseline clinical characteristics. Clinical and angiographic characteristics are shown in the table. A total of 56 patients (42.1%) required TLR, CABG or TVR and 67 patients (50.4%) either died or had TLR, TVR or CABG.

	Failed IRT (n=47)	Successful IRT (n=86)	p
Age (years)	60 SD 10	61 SD 11	0.5
Male (%)	83	80	0.7
Diabetes (%)	45	40	0.7
Hyperlipidemia (%)	79	81	0.7
# Prior Restenosis (%)	1.7 SD 0.7	1.4 SD 1.0	0.02
Baseline TIMI 0-1 (%)	19	7	0.03
New Stent (%)	30	18	0.1
MLD Baseline (mm)	0.91 SD 0.54	0.68 SD 0.45	0.6
MLD Final (mm)	2.09 SD 0.71	2.1 SD 0.66	0.9
Lesion Length (mm)	21 SD 12	20 SD 9	0.7

By multivariate analysis, baseline TIMI 0/1 flow was an independent predictor of restenosis (OR:3.6, CI=1.1-11.6, p=0.02). The number of prior restenosis showed a strong trend (OR:1.7, CI=0.96-3.0, p=0.06).
Conclusions: 1) One-third of patients who underwent IRT for in-stent restenosis, required reintervention due to failed IRT. 2) A totally occluded artery at the time of the procedure was an independent predictor of IRT failure. 3) Baseline and final vessel diameters did not seem to play a role in the process. 4) Half of all patients had a major event (death or revascularization) during the follow-up period.

P3392 Avoiding bypass surgery for recurrent in-stent restenosis by intracoronary brachytheraphy with beta-radiation: results of a 3-year follow-up

S. Silber[1], P. Lochow[2], I. Krischke[2], C. Drexler[2], S. Staerk[2], B. Bosnjak[2], A. Witzgall[2]. [1]*Cardiology Practice and Hospital, Munich, Germany;* [2]*Cardiology Practice and Hospital, Munich, Germany*

Background: Recently presented 5-year follow-up of the gamma-1 study showed no significant difference between placebo and brachytherapy. These results raise the question whether the long-term results was related to gamma-radiation only or applies also to beta-radiation.
Methods: This is an analysis of the prospective and continuous clinical follow-up of our patients which were treated with brachytherapy for in-stent restenosis. The 3-year follow-up was asessed in 170 consecutive patients. The rate of death, myocardial infarction, re-PCI of vessel treated with brachytherapy, PCI of a different vessel was compiled and the MACE rate calculated. 35.3% of the patients had a first, 36.5% had a second, 12.9% had a third and 15.3% had at least a fourth in-stent restenosis. The dose was 18.4 Gy at 2 mm from the center of the radiation source in vessel diameter from 2.5 to 3.5 mm and was 23.0 Gy in vessel diameter 3.5 to 4.0 mm, 20 Gy in 1 mm from the center of the radiation source.
Results: The mean age was 61±9 years. The treated stent diameter was 3.03±0.36 mm (2.25-4.0) and the stent length was 23±12 mm (8-60). The radiated vessel length was 54±21 mm (30-120).

Table 1

parameter (%)	1 year	2 years	3 years
cardiac death	0	0	0
free of infarct	97.7	95.3	94.1
free of PCI - target vessel	74.7	63.5	58.2
free of PCI - other vessel	87.1	84.7	3.5
free of CABG	94.1	89.4	87.1
free of MACE	64.1	53.5	50.6

Conclusions: The 3-year follow-up of "real world" intracoronary brachytherapy with beta-radiation in patients with mainly recurrent in-stent restenosis shows that good results are maintained. The re-PCI of the target vessel continously declined. Thus, bypass surgery could be avoided in 87% of the patients within the 3-year follow-up period.

P3393 Superior benefit in diabetics after intracoronary radiotherapy with a 188rhenium liquid-filled PTCA balloon system in in-stent restenosis

U. Koeckeritz[1], K. Reynen[1], J. Kropp[2], G. Wunderlich[2], J. Kotzerke[2], R. Strasser[1]. [1]*Herzzentrum Dresden - Kardiologie, Dresden;* [2]*Technische Universität, Klinik für Nuklearmedizin, Dresden, Germany*

Background: In cases of in-stent restenosis, only brachytherapy and drug eluting stents have been shown to reduce the rate of repeat restenosis. Since the rates of restenosis remain high, a better patient selection may be useful. To obtain selection criteria we analyzed our brachytherapy patients with regard to the presence of diabetes.
Methods and Results: From May 2000 to January 2004, 164 patients (mean age 64 ± 10; 126 male, 38 female) with symptomatic in-stent restenosis were included in a prospective, randomized, double-blind trial to test the efficacy of intracoronary brachytherapy with a 188Rhenium liquid-filled PTCA balloon system. Immediately after successful repeat PTCA, a standard PTCA balloon catheter was inflated at low pressure (3 atm) either with liquid 188Rhenium in order to reach 30 Gy at 0.5 mm depth of the vessel wall or with NaCl-solution to perform sham procedure. At six months after the index procedure, repeat angiography was performed in 156 of the 164 patients (rate 95%). 164 patients completed the one-year follow-up. Although all patients profit by brachytherapy, this study shows a greater benefit in diabetics. In diabetic p atients, the late loss was significantly lower in the radiation than in the placebo group despite the small number of patients leading to a lower restenosis rate at six months and a higher event-free survival rate (death, myocardial infarction, TVR) at one year.
Conclusions: In diabetic patients, intracoronary radiation therapy with the liquid-filled beta-radiation emitting 188Rhenium balloon system shows a superior benefit compared to non-diabetic patients.

Table 1

	Diabetics brachytherapy	Diabetics placebo	Non-diabetics brachytherapy	Non-diabetics placebo
n	34	22	44	56
MLD before intervention (mm)	0,53 ± 0,34	0,53 ± 0,39	0,51 ± 0,30	0,51 ± 0,34
MLD after intervention (mm)	1,71 ± 0,26	1,79 ± 0,42	1,81 ± 0,35	1,74 ± 0,25
MLD at follow-up (mm)	1,44 ± 0,56	1,19 ± 0,62	1,31 ± 0,65	1,21 ± 0,66
Reference diameter (mm)	2,42 ± 0,36	2,41 ± 0,50	2,44 ± 0,37	2,38 ± 0,32
Late loss (mm)	0,28 ± 0,58*	0,60 ± 0,46*	0,49 ± 0,51	0,54 ± 0,61
Late loss index	0,24 ± 0,57	0,47 ± 0,35	0,41 ± 0,42	0,43 ± 0,47
Rate of restenosis (%)	18*	41*	30	39
Event free survival (%)	86	68	85	75

* p<0.05 comparing brachytherapy and placebo patients

P3394 Stenting versus stenting with adjunctive beta vascular brachytherapy in patients with de novo long lesions

C. Pappas[1], M.I. Papafaklis[1], C.S. Katsouras[2], D.N. Nikas[1], P. Tsekeris[3], J. Kalef-Ezra[4], L.K. Michalis[2]. [1]*Michailidion Cardiac Center, Ioannina, Greece;* [2]*Medical School, University of Ioannina, Department of Cardiology, Ioannina, Greece;* [3]*University Hospital of Ioannina, Department of Radiotherapy, Ioannina, Greece;* [4]*Medical School of Ioannina, Department of Medical Physics, Ioannina, Greece*

Vascular brachytherapy (VBT) after stent implantation for de novo lesions of low risk for restenosis is contra-indicated. However, little knowledge is available about the impact of VBT combined with stenting for de novo lesions of high restenotic risk (e.g. long lesions).
Aim: To evaluate the long-term efficacy of beta VBT in patients undergoing bare metal stenting of de novo long lesions.
Methods: From March 2000 to July 2002 74 patients (76 de novo long lesions >20mm) who underwent successful stenting were randomly assigned to receive (group A: beta VBT & bare metal stent group) or not receive (group B: bare metal stent group) beta (90Strontium/90Yttrium) radiation. All patients were treated with indefinite administration of aspirin (100mg od) and clopidogrel (75mg od). Clinical follow-up was then scheduled at 1, 6, 12 and 24 months after the index procedure and coronary angiogram was performed if clinically indicated (anginal symptoms and/or positive functional test). All major adverse cardiac events [death, myocardial infarction (MI), target vessel revascularization (TVR)] and the anginal status of every patient were recorded.
Results: Baseline clinical and angiographic characteristics were similar between the two groups. At 2 years, 3 deaths, 4 MIs and 14 TVRs (1 in-hospital) occurred in the VBT & stent group, whereas in the stent group, there were 1 death, no MIs and 2 TVRs. Four late thrombotic events were reported all in group A. Furthermore, recurrent angina during the two years of follow-up appeared in 12 patients of group A and only in 2 of group B (OR: 8.75, p=0.003). Computation of Kaplan-Meier 2-year mortality and event-occurrence curves and comparison of group A vs. B using the log-rank test revealed significant differences for the total MACE (48.7±0.08% vs. 8.1±0.045% respectively, p<0.001) and TVR rates (37.7±0.08% vs. 5.4±0.037% respectively, p<0.001).
Conclusion: VBT after stenting of long lesions (>20 mm) seems to be associated with a high MACE event and repeat revascularization rate compared with bare metal stents only. Late thrombotic events post VBT remain a problem regardless of the combined administration of antiplatelet agents.

NONCORONARY INTERVENTION

P3395 Carotid clamping time as a risk factor for early restenosis after carotid endarterectomy

L.A. Malek[1], A.K. Malek[2], J. Leszczynski[2], S. Toutounchi[2], M. Elwertowski[2], P. Domagala[3], M. Spiewak[3], M. Skorski[2]. [1]*Medical University of Warsaw, 1st Department of Cardiology, Warsaw, Poland;* [2]*Medical University of Warsaw, General and Thoracic Surgery, Warsaw, Poland;* [3]*Medical University of Warsaw, Warsaw, Poland*

Background: Success of carotid endarterectomy (CEA) is limited by a significant rate of early restenosis, but published works on risk factors responsible for that outcome present conflicting data.
Aim: To find or confirm risk factors of early restenosis after CEA.
Methods: Prospective analysis included 497 primary procedures on symptomatic and asymptomatic patients. Baseline demographics, clinical history, surgical procedure parameters and peri-operative complication rates were assessed by qualified personnel. Post-operative follow-up was done at 6, 12 and 24 months with clinical assessment and duplex ultrasound. The presence of a restenosis 70% was considered an event.
Results: Early restenosis occurred in 71 (14.3%) patients. Univariate analysis disclosed longer carotid clamping time (p=0.002), higher rate of peri-operative strokes (p=0.05) and a lower number of operations with the use of shunt (p=0.03) as related to early restenosis. To facilitate clinical interpretation we proposed a threshold value for CCT with means of ROC. The area under the curve relating carotid clamping time (CCT) to early restenosis was 0.617 (95% CI 0.573-0.660) and the highest likelihood ratio corresponded to a value of 18 minutes. CCT was the only independent predictor of early restenosis in a logistic regression model including all significant variables with CCT divided by calculated threshold level (OR=2.25; CI 1.2-4.1; p=0.008).
Conclusions: We propose a carotid clamping time (CCT) as a novel risk factors for early restenosis.

P3396 Catheter PFO closure in 140 consecutive patients: a prospective study with contrast transcranial Doppler

E.O. Eustaquio Onorato[1], F. Casilli[2], M.M.M. Marcel Mbala-Mukendi[1], E.M. Eva Morandi[3], G.P.A. Gian Paolo Anzola[3]. [1]Humanitas Gavazzeni, Cardiology, Bergamo, Italy; [2]Humanitas Gavazzeni, Cardiology, Bergamo, Italy; [3]S. Orsola FBF Hospital, Neurology, Brescia, Italy

Purpose: Catheter PFO closure is increasingly being performed and monitored with transthoracic or transesophageal echocardiography, whereas contrast-enhanced transcranial Doppler(ce-TCD), which probably represents the most suitable tool to quantify right-to-left shunt (RLS) in the brain vessels, has systematically overlooked. Aim of this study is to prospectively assess efficacy and safety of catheter PFO closure using ce-TCD.
Methods: A total of 140 consecutive patients (mean age, 46±13 years; male/female ratio, 63/77) with PFO-related large RLS and no other recognized cause of focal cerebral ischemia underwent catheter closure. TCD was done preoperatively and 1 month after the procedure in all patients, after 3 months in 120, after 6 months in 112, and after 1 year in 104 patients.
Results: The procedure was successful in all patients. During Valsalva strain, a large shunt ("shower" pattern if more than 25 bubbles and "curtain" pattern if uncountable bubbles) was still detectable in 31 of 140 (22%), 15 of 120 (13%), 9 of 112 (8%) and 9 of 104 (9%) patients at the 1-,3-,6-, and 12-month visits, respectively. Periprocedural and postprocedural complications included atrial fibrillation in 8% and scintillating scotomata in 6% of patients. During the 1-year follow-up period, only 1 transient ischemic attack was recorded in a patient with paroxysmal atrial fibrillation and complete PFO closure.
Conclusions: Catheter PFO closure in patients with cryptogenic stroke and large RLS may be less successful than reported previously. Ce-TCD appears the ideal tool to follow up the closure process and to identify early, during follow up, those patients who will be left with a significant shunt. Atrial fibrillation is more common than believed previously and may underlie the occurrence of further cerebrovascular events despite complete PFO closure. Irritative visual phenomena may occur as a consequence of nickel toxicity.

P3397 Application of gamma-irradiation after surgical coronary artery reconstruction: a new approach for end-stage coronary artery disease?

C.J. Beller[1], A. Becker[2], J. Kosse[2], R. Krempien[3], L. Seres[2], I. Berger[4], S. Hagl[2], G. Szabo[2]. [1]University of Heidelberg, Cardiac Surgery, Heidelberg, Germany; [2]University of Heidelberg, Cardiac Surgery, Heidelberg, Germany; [3]University Heidelberg, Clinical Radiology, Heidelberg, Germany; [4]University Heidelberg, Pathology, Heidelberg, Germany

Background: Coronary artery endarterectomy represents a surgical therapeutical option in an increasing number of patients with advanced coronary artery disease. The mid-term results are compromized by early restenosis due to neointima formation. The aim of this study was to evaluate a new treatment option - endarterectomy with consecutive gamma-irradiation - in a rat carotid endarterectomy model.
Methods: 33 adult male Sprague-Dawley rats underwent left carotid endarterectomy with removal of intima. After the operation rats a single dose of external gamma-irradiation (Ir192) at 15 Gray (n=13) and 20 Gray (n=10) or received no radiation (control, n=10) was applied. After 3 weeks, carotid arteries were perfusion-fixed in vivo, prepared as histologic cross-sections and vessel compartment areas were measured. Transmission electron microscopy and immunohistochemical staining were used to confirm neointima formation.
Results: After 3 weeks, neointima formation was 0,07 mm^2 ± 0,04 mm^2 in the control group. In the treatment groups, a significant neointima reduction was observed (0,003mm^2 at 15 Gy and 0,0007 mm^2 at 20 Gy, $p < 0,0001$). Additionally, a significant reduction of intima/media ratio was observed (control: 2,75; 15 Gray: 0,1; 20 Gray: 0,01; $p < 0,0001$). However, in the irradiated carotid arteries a significant inflammatory response was detected in the vessel wall, even with areas of focal medial necrosis (p= 0,003).
Conclusions: External gamma-irradiation significantly suppressed neointima formation in a rat model of surgical vessel reconstruction. Application of gamma-irradiation may be therefore a new concept to inhibit intimal hyperplasia after coronary endarterectomy in patients. However, further studies are necessary to determine the optimal dose for clinical application.

P3398 4-years follow-up of catheter PFO closure using intracardiac echocardiographic guidance in 439 patients

E.O. Eustaquio Onorato[1], F. Casilli[2], M.M.M. Marcel Mbala Mukendi[1], L.P. Luigi Pedon[3], A.C. Antonio Carrozza[3], M.Z. Mario Zanchetta[3], G.P.A. Gian Paola Anzola[4]. [1]Humanitas Gavazzeni, Cardiology, Bergamo, Italy; [2]Humanitas Gavazzeni, Cardiology, Bergamo, Italy; [3]Cittadella Hospital, Cardiology, Cittadella, Padova, Italy; [4]S. Orsola FBF Hospital, Neurology, Brescia, Italy

Purpose: To assess the safety and feasibility of percutaneous interventional closure of patent foramen ovale (PFO) with or without atrial septal aneurysm (ASA) with different PFO occluder devices (ODs) in patients (pts) with ischemic cerebral events due to presumed paradoxical embolism using intracardiac echocardiographic (ICE) monitoring alone.
Methods: Between June 1999 and December 2004, 439 pts aged 48 ± 15 years (range 14-75; F/M 1.44) underwent transcatheter closure of PFO using different ODs. All pts were submitted to a pre-study full cardiological and neurological examination including CT/MR imaging and contrast-enhanced transcranial Doppler (ce-TCD). Pre-procedurally thromboembolic events (ThEE) were: 202 ischemic stroke (46%), 288 TIA (65%) and 46 peripheral and coronary arterial embolism (10%). Atrial septal aneurysm (ASA) was observed in 170 pts (38%). 3 pts suffered from platypnea-orthodeoxia syndrome; 2 pts from refractory hypoxemia. 195 pts were migraineurs with/without aura (44%). The procedures were performed with local anaesthesia under fluoroscopic and ICE guidance. Antiplatelet therapy was given in all pts for 6 months.
Results: The devices (398 Amplatzer PFO Occluder, including 12 Amplatzer Multifenestrated Septal Occluder; 7 Gore Helex Septal Occluder; 4 PFO Star X and 30 Cardia Intrasept Devices) were placed correctly in all pts. Femoral haematoma was observed in 12 cases (2.7%), with no need for blood transfusion or surgical repair. Atrial fibrillation was detected in 10 pts (2.27%). One patient with Brugada syndrome underwent implantable defibrillator device. Major complications observed during follow-up period were: 1 early post-procedure death due to fatal massive pulmonary thromboembolism (PTE); 5 late no-procedure related deaths (2 due to respiratory failure; 1 due to a fatal massive PTE; 1 sudden death and 1 case of suicide); 1 case of pericardial effusion with cardiac tamponade; 3 cases of epileptic (partial) disorder and 1 case of transient aphasia due to presumed recurrent ThEE. No fatal stroke and/or major stroke were observed. No device embolization, infective endocarditis or device thrombosis occurred.
Conclusions: Transcatheter closure of PFO with or without ASA is safe and effective; it ensures high closure rate, avoiding life-long anticoagulation therapy. The combination of ICE imaging and ce-TCD represents a major advance in interventional cardiology for successful deployment of ODs, avoiding the need of TEE and general anaesthesia or sedation. Long-term follow-up results appear favourable with respect to recurrent ThEE.

P3399 Prevalence of Eustachian valve in adults: relation to patent foramen ovale and to interatrial septal aneurysm. A prospective French study

R.N. Sachs[1], K. Lahmi[1], K. Zerhouni[1], J.C. Charniot[1], J.Y. Artigou[1], J.P. Albertini[2]. [1]Avicenne Hospital, Cardiology, Bobigny, France; [2]Avicenne Hospital, Biochemistry, Bobigny, France

Background: The eustachian valve (EV) is a remnant embryonic right valve of the sinus venosus. Embryologically, the EV directs oxygenated blood from the inferior vena cava across the patent foramen ovale (PFO) into the systemic circulation. Inter-atrial septal aneurysm (IASA) is frequently associated with PFO.
Aim of the study: To assess the prevalence of persistent EV in an adult population undergoing transesophageal echocardiography (TEE), and its relation to inter-atrial septal abnormalities (SA).
Methods: 103 consecutive patients underwent TEE for different diagnoses including valvular disease, stroke and endocarditis. The presence of EV, PFO and IASA was evaluated with two-dimensional transesophageal echocardiography, color Doppler and contrast echocardiographic studies.
Results: EV was found in 50 patients (49%). SA in 26 Patients (25%), PFO in 18 patients (17%) and IASA in 15 patients (15%). EV was found in 88% patients with SA ($p<0.0001$)), in 67% patients with PFO ($p<0.02$) and in 53% patients with IASA (NS). Clinical assessments did not influence significantly these relationships.
Conclusion: Persistent EV is a frequent finding in adult patients with SA and mainly PFO. A persistent EV may participate to the mechanism of a paradoxical embolism by directing the inflow blood from the inferior caval vein towards the interatrial septum.

P3400 Implication of atrial septum aneurysm associated with patent foramen ovale in cryptogenetic stroke

M.T. Gonzalez-Alujas[1], Z. Gomez-Bosch[2], M. Rubiera[3], E. Santamarina[3], C. Orihuela[2], A. Evangelista[2], H. Garcia del Castillo[2], J. Soler-Soler[2]. [1]Barcelona, Spain; [2]Vall d'Hebron Hospital, Dept. of Cardiology, Barcelona, Spain; [3]Vall d'Hebron Hospital, Dept. of Neurology, Barcelona, Spain

Aim: To ascertain whether the presence of atrial septum aneurysm (ASA) implies a worse prognosis in patent foramen ovale (PFO)
Methods: 112 patients with cryptogenetic stroke were studied clinically, by MRI and by echocardiography. Embolic and atherosclerotic risk factors, scattered lesion pattern by MRI, assymptomatic previous emboli and follow-up recurrences were assessed. PFO was determined and quantified using agitated saline solution by transthoracic echocardiography (TTE) and transoesophageal echocardiography (TOE). ASA was diagnosed when >15 mm.
Patient were followed 32±29 m. and treated with antiagregant, anticoagulant therapy or post-closure device.
Results: 76 had PFO, 24 isolated and 52 with ASA (displacement: 20±4 mm). Characteristics and statistical values are in the table.

Statistical values of characteristics

	PFO+ASA (52)	isolated PFO (24)	p
Age	47±14	43±14	n.s.
MRI: scattered	19 (37%)	5 (20%)	n.s.
Recurrence/assymptomatic emboli	17 (33%)	1 (4%)	0.01
Shunt moderate-severe	42 (84%)	8 (33%)	0.0001
PFO diameter (mm)	4.43±2.82	2.42±1.50	0.002
Complicated aortic atherosclerosis	0	2 (9%)	n.s.
Right cardiac disease and/or deep venous thrombosis	7 (14%)	1 (4%)	n.s.

PFO+ASA vs isolated PFO

Conclusions: Patent foramen ovale with atrial septum aneurysm in cryptogenetic stroke is associated more frequently with an emboli pattern by MRI; FOP size and shunt severity is greater and more frequently associated with assymptomatic emboli and recurrence is high. Atrial septum aneurysm in PFO defines the group with the greatest embolic risk candidates for more agressive therapy.

P3401 Patent foramen ovale – the prevalence and treatment in patients with a suspected embolisation within the central nervous system

L. Golan[1], A. Linhart[2], J. Horak[2], T. Palecek[2], P. Rekova[3], D. Svackova[3], Z. Hlubocka[2], M. Aschermann[2]. *[1]The Charles University Hospital, IInd Department of Internal Medicine, Prague 2, Czech Republic; [2]The Charles University Hospital, IInd Department of Internal Medicine, Prague, Czech Republic; [3]The Charles University Hospital, Department of neurology, Prague, Czech Republic*

Background: Patent foramen ovale (PFO) is a frequent congenital heart defect. In most cases it is asymptomatic, but it harbours a risk of paradoxical embolism, especially when associated with interatrial septal aneurysm (IAS). We have no clinical evidence that a treatment of PFO decreases the risk of paradoxical embolism. That is why we were interested in the prevalence of PFO among patients with a suspected embolization within the central nervous system and in the treatment strategies in our hospital.
Methods: We performed a retrospective case-control study. Cases were patients examined by transesophagial echocardiography (TEE) because of a suspected embolization within the brain. Patients with atrial fibrillation, atrial flutter or intracardiac thrombi were excluded. We assessed the prevalence of PFO and IAS in cases and in patients examined by TEE from other indications (controls). We also evaluated the treatment strategies of PFO in cases.
Results: From October 2000 till November 2004 we examined 123 patients with a suspected embolization within the brain and 221 controls. We found PFO (or atrial septal defect) in 36 patients (29.3%) and in 53 controls (24.0%); the difference was not statistically significant. The simultaneous finding of PFO and IAS was found in 23 cases (18.7%) and 18 controls (8.1%); the difference was statistically significant ($p<0.05$). In 12 patients the PFO was successfully closed percutanously with an endovascular occluder, other patients were treated with anticoagulation and/or antiplatelet therapy.
Conclusion: The prevalence of PFO in patients with a suspected embolization within the central nervous system is similar to other patients examined by TEE. However, the simultaneous finding of PFO and IAS is more frequent and may constitute an increased risk of paradoxical embolization. Different strategies of PFO treatment are used (anticoagulation and/or antiplatelet therapy or endovascular occlusion). Evidence from clinical trials is necessary to help us to choice an optimal treatment strategy.

P3402 Transcatheter occlusion of PFO and ASD in cryptogenic stroke

M. Balbi[1], G. Pongiglione[2], M. Marasini[2], M. Del Sette[3], G. Gnecco[4], L. Casalino[4], A. Barsotti[4]. *[1]Genova, Italy; [2]Istituto G.Gaslini, Paediatric Cardiology, Genova, Italy; [3]University of Genova, Neurology, Genova, Italy; [4]University of Genova, Cardiology, Genova, Italy*

Paradoxical embolism trough a patent foramen ovale (PFO) can lead to an embolic stroke in young adults.
Trans-esophageal echocardiography (TEE) have shown the high prevalence of PFO (with or without associated atrial septal anerysm) in patients with cryptogenic stroke.In the last years percutaneous PFO closure has been used in adult population but there are no data from randomized trials.
Between August 2001 and January 2005, 138 patients with presumed cryptogenic cerebral or peripheral thromboembolic events were evaluated by a team of neurologists, cardiologists and paediatricians, and 79 of them (42 female, mean age 45,5years range 17 to 70) had a transcatheter PFO or ASD occlusion: 30 had a single previous transitory ischemic attack (TIA), 23 a single previous stroke, 15 presented recurrence of TIA or stroke, 2 had peripheral embolism and 9 had others indications.
We used 67 PFO occluder (64 Amplatzer 18-25mm, 2 Cardia, 1 Helex) and 12 Atrial Septal Occluder (Amplatzer 22-36 mm.). Before catheter closure, patients received antibiotic prophylaxis, heparin e.v., deep sedation. Catheter closure have been done with fluoroscopic and TEE (in two cases with intracardiac echocardiography) guidance; the average procedure duration was 40 min, the average fluoroscopy duration was 3 min.
Procedural success was obtained in 79 patients (100%); device reposition during procedure was necessary in 12 patients (15%); none procedural complications and minimum residual shunt in 7 patients (9%). Sixtynine patients have been evaluated with TEE at three months: there were no
device embolization or thrombosis (0%),minimum residual shunt in 1 patients (1,5%). During the mean clinical follow up of 27 months (range1 to 41 months) there were no stroke recurrence; two recurrence of TIA occurred: the first in a patient within 96 hours from the procedure (incomplete occlusion), and the second in a patient with a pulmonary arterovenous fistula too.
Our initial experience shows that percutaneous closure of PFO and ASD is a safe procedure. Our optimal peri-procedural results (none major or minor complications) despite the initial learning curve is probably due to the collaboration of specialists of different areas (cardiologists, neurologists, interventionist pediatricians) during the selection of patients candidate to the PFO closure and during the execution of the procedure. Beside, clinical follow-up shows the efficacy of percutaneous closure of PFO: none stroke recurrence despite interruption of medical therapy (anticoagulation/antiaggregation) after 6 months from procedure.

P3403 4-year follow-up of intracardiac echocardiography transcatheter atrial septal defect closure

M. Zanchetta[1], L. Pedon[1], M. Zennaro[1], A. Carrozza[1], E. Onorato[2]. *[1]Department of Cardiovascular Disease, Cittadella, Italy; [2]Gavazzeni "Humanitas" Clinic, Division of cardiology, Bergamo, Italy*

Purpose: Intracardiac echocardiography (ICE) evaluation of secundum atrial septal defect (ASDs) shows several advantages over transesophageal echocardiography (TEE). Aim of our study was to describe the 4-year results of transcatheter ASDs closure using the Amplatzer Septal Occluder (ASO) and ICE as the sole imaging tool both to select the device size and to monitor the procedure.
Methods: Between July 2000 and May 2003, one hundred and thirty five consecutive eligible patients with hemodinamically significant ASDs (male/female=45/90; mean age 42.2 ± 19.2 years; BSA 1.71±0.7 m^2; mean pulmonary arterial pressure 30.4 ± 11.5 mmHg; mean Qp/Qs ratio 2.1 ± 0.6) underwent transcatheter closure using the ASO under fluoroscopic and continuous ICE monitoring.
ICE was performed by the same interventional team (i.e. a single operator use) using a commercially available 9F-9MHz Ultra ICETM catheter-based ultrasound transducer (EP Technologies, Boston Scientific Corporation, San Jose, CA, USA). Two standardized orthogonal sections were used to obtain ICE-derived fossa ovalis measurements and to assess optimal device deployment: the first one is the transverse section on the aortic valve plane in the short axis of the body, and the second one is the longitudinal section on the 4-chamber plane in the long-axis of the heart. This latter view was also used to monitor all of the stages of the device deployment. The majorand the minor axes of the fossa ovalis on these two orthogonal planes were measured, using end-diastolic frames.
The ICE derived mathematical modeling, the geometric assumption and the ASO calculator software may be downloaded free of charge from the following website (www.ulss15.pd.it/sito/ospedale_cit/cit_cardioASO.htm).
Results: In all cases, we obtained an optimal evaluation of ASDs axes on the two orthogonal planes, leading to an optimal device size selection (mean size 25.0±6.7 mm). Moreover, the ICE allowed us to monitor device deployment and to verify the effectiveness of the ASDs stenting by ASO. During a mean follow-up period of 34.5±14 months, the shunt-free survival rates were 97.7%, 97.7%, 97.0%, 97.1%, 97.5% and 98% at 24 hours, 1 and 3 months, and 1-2 and 3 years, respectively. There were no complications related to the procedure as well as to the use of ICE.
Conclusions: ICE is an effective and safe alternative to TEE and balloon sizing maneuver during ASDs transcatheter closure procedures, allowing us to avoid the need of general anesthesia and leading to a similarly high percentage of occlusion rate with respect to the conventional method.

P3404 Migraine treatment: a case-control study

E.O. Eustaquio Onorato[1], F. Casilli[2], M.M.M. Marcel Mbala-Mukendi[2], E.M. Eva Morandi[3], G.P.A. Gian Paolo Anzola[2]. *[1]Humanitas Gavazzeni, Cardiology, Bergamo, Italy; [2]Humanitas Gavazzeni, Cardiology, Bergamo, Italy; [3]S. Orsola FBF Hospital, Neurology, Brescia, Italy*

Purpose: Recent evidence has suggested the association between migraine, right-to-left shunt (RLS) brought about by patent foramen ovale (PFO) and stroke. Aim of this preliminary case-control study was to compare catheter PFO closure vs medical treatment in patients with migraine and PFO.
Methods: Twelve consecutive female patients scheduled to undergo catheter closure of PFO because of recent TIA or stroke and who had also migraine according to the International Headache Society criteria (IHS) were age and sex matched to twelve consecutive patients attending the headache outpatient clinic who also had PFO. Mean age were 35±13 and 32±12 years old respectively. Twelve were treated with conventional antimigraine preparation (NSAIDs, 5-HT1 agonists) and twelve underwent catheter PFO closure. All patients underwent a pre-study full neurological examination, CT or MR imaging and contrast-enhanced transcranial Doppler (ce-TCD) to evaluate RLS. Large shunts ("shower" pattern if more than 25 bubbles and "curtain" pattern if uncountable bubbles) were detected in all patients. A semiquantitative scale was used to note the severity of the migraine, by

indicating the frequency, duration and intensity of the attacks and the occurrence of aura in the prodromal phase. The migraine composite score was calculated by summing up the partial scores of each category. After the first visit or discharge, patients were given a headache diary and told to record the duration, intensity, frequency of the attacks and the number of episodes preceded by aura as well as their response to treatment. After one year of the first visit or discharge, the patients were reassessed.
Results: The total score in the two groups was 7 at the beginning of the study. Catheter closure was successful in all patients. At one-year follow-up, a decline in the severity of migraine, with reduction in frequency, intensity and duration was observed in both groups, with a total score of 4.6 in the medically treated group (7 vs 4.6, t=1.79, p=0.016) and 4 in the catheter closure group (7 vs 4, t= 1,79, p= 0.003), the difference being statistically significant in both groups. By contrast, the aura disappeared in 8/10 patients (80%) in the catheter closure group and only 4/10 (40%) among the medically treated group (p= 0.01 on c2=9.5).
Conclusions: Our preliminary results seem to suggest that overall PFO closure is as equally effective as medical treatment in reducing the frequency, duration and intensity of migraine attacks, whereas it is significantly more effective in reducing the incidence of the prodromal aura.

P3405 Procedural and clinical outcomes in adults undergoing transcatheter closure of atrial septal defects with multiple devices

V.S. Mahadevan, N. Gomperts, K. Haberer, E.M. Horlick, L. Benson, P.R. McLaughlin. *Toronto General Hospital, Congenital Cardiology Unit, Toronto, Canada*

Purpose: Transcatheter closure of secundum atrial septal defects (ASD) is widely performed in adults. A proportion of these patients have multiple defects and may require more than one device to achieve complete septal closure. The outcomes in such patients have not been previously well described.
Methods: Four hundred and eighty patients underwent transcatheter ASD closure in our institution between June 1990-February 2005, of which 28 required more than one device for complete septal closure. We report on the procedural and clinical outcomes in these patients. Right ventricular (RV) measurements were done using the apical four chamber echocardiographic view. An Amplatzer® septal occluder (ASO) (AGA Medical Corp. Golden Valley, MN) was used in all but one patient in whom a Cardioseal® (NMT Medical, Boston, MA) device was employed.
Results: There were 19 (68%) females and mean cohort age was 44 (range 21-76) years. Pre procedure transesophageal echocardiography (TEE) showed more than one defect in 17 (61%) patients. In 11 (39%) patients the defect was detected during intraprocedure echocardiography. The mean diameter for the largest defect by the pre procedure TEE was 13.8±5mm and 6.4±3.2mm for the second defect. Based on intraprocedure echocardiography, two devices were deployed in 24 (86%) patients and three devices in four (14%) patients. Stretched mean diameter was 19.4±5.0mm and 14.2±5.6mm for the largest and second defect respectively. All patients except one had successful deployment of the devices in a single procedure. Largest mean ASO device diameter was 22±6mm and 17±6mm for the second defect. There were no procedure related deaths. On follow up echocardiography between 3-6months after closure, a small residual leak was seen in 7 (25%)of patients and none were felt clinically to be of hemodynamic consequence. Mean RV diameter fell from 47.6±5.72 mm to 40±4.3mm ($p<0.05$) post procedure and RV systolic pressure fell from 39±5 to 32±4mmHg ($p<0.05$).
Conclusions: Transcatheter closure of multiple ASD's using more than one device in a single procedure, is feasible with excellent procedural and short term outcomes. Significant decreases in RV size and systolic pressure were seen in this group following device closure of the ASD. Long term outcome data and the effect of residual leaks needs to be assessed.

P3406 Closure rates of interventional occlusion in atrial septal defects at different training levels

R.S. von Bardeleben[1], C. Halcour[2], C. Kampmann[3], M. Ries[2], S. Mohr-Kahaly[4], H.J. Rupprecht[5], G. Horstick[2] on behalf of PFO Study Group. *[1]University of Mainz, II.Med.Clinic Cardiology, Mainz, Germany; [2]Johannes-Gutenberg-Universität, II. Medizinische Klinik, Mainz, Germany; [3]University Mainz Medical Center, Dep Pedicatric Cardiology, Mainz, Germany; [4]Inst. Cardiology, Wiesbaden, Germany; [5]II.Med. Klinik, Klinikum, Rüsselsheim, Germany*

Introduction: Interventional PFO and ASD closure procedures in patients with and without addiditional atrial septal aneurysm (IASA) have been reported to significantly reduce the risk of recurrent thrombembolic events. The aim of the present study was to evaluate the impact of three different training levels in respect of time to definite closure on mid-term follow up.
Methods: Since 1999 until 2004 306 consecutive patients were included in this non-randomized, prospective study (61% men, mean age 52 years, BMI 25,8). All patients had a history of symptomatic PFO or ASD and underwent a defect closure using the Amplatzer PFO/ASD occluder, CardioSeal/Starflex and Gore Helex devices. The interventional cardiologists were subdivided in three groups with an experience of less than 15 (LE), 15-44 (ME), 45 or more procedures (HE).
Results: During a mean follow up of 24 months transesophageal and transthoracic echocardiographic controls were performed at day one, one month and three/six months, in case of residual shunts one and two years after intervention. The closure rates after one month were 82, 92 and 84% and after one year 98, 95 and 96% for LE/ME/HE. The number of more complex interventions, the rate of ASD and ASA in the high experience group was significantly higher ($p<0,05$). Correcting the data for only PFO closures without septum abnormalities the closure rates increased to 82, 98 an 92% at one month and 91, 98 and 100% respectivly.
Conclusion: Interventional closure of different septal defects is a new and promising technique in symptomatic patients. More than 80% of all definite closures already occurred within 1 month even with less experienced interventional cardiologists. Corrected for the severity of the interatrial defect highly experienced cardiologists achieved a higher closure rate of simple PFO defects while the overall short-term closure performance is affected by cases with more complex anatomy involving ASA or multiple ASD.

P3407 Percutaneous closure of a patent foramen ovale: single centre experience using different types of devices and mid-term outcome

M. Post, K. Van Deyk, W. Budts. *University Hospitals Leuven, Cardiology, Leuven, Belgium*

Introduction: Patent foramen ovale (PFO) has been identified as a source of paradoxical embolism and cryptogenic stroke. Low recurrence rates of ischemic stroke after percutaneous closure have been described. We report our single centre experience using four different types of devices.
Methods: All patients, who underwent a percutaneous PFO closure in the University Hospitals Leuven between 02-1999 and 12-2003, were included. The primary endpoint was defined as reoccurrence of stroke, transient ischemic attack (TIA), or a peripheral thrombo-embolic event. The periprocedural and mid-term complications were reported.
Results: One-hundred and twelve patients, mean age of 52.1±12.5 years (63 male/49 female), were included in the study. Indications for closure were cryptogenic stroke (91.9%), peripheral embolism (4.5%), obligate right-to-left shunt in Ebstein anomaly (1.8%), platypnoe syndrome or brain abscesses (both 0.9%). Cardioseal/Starflex® was used in 12, the Amplatzer PFO occluder® in 35, PFOStar/CardiaStar® in 64, and Helex® in one patient. The primary endpoint occurred in 1.8% for stroke and 2.8% for TIA during a median follow up of 1.9 years, range 4.9 years. Periprocedural complications were dislocation of the device (0.9%), transient arrhythmias (15.5%), aspiration pneumonia (0.9%), inguinal haematoma (3.6%), and an allergic reaction on medication (1.8%). Mid-term complications were perforation of device (0.9%), persistent transient arrhythmias (6.3%) and thrombus formation on the device (0.9%). No significant differences in outcome or the occurrence of any type of complication could be documented between the different types of devices.
Conclusion: Percutaneous PFO closure seems to be a highly efficient and relatively safe procedure, independent of the type of device used for closure.

P3408 Interventional closure of double/multiple atrial septal defects with Amplatzer device

M. Szkutnik, J. Bialkowski, J. Kusa, J. Baranowski, P. Banaszak, B. Zeifert, M. Zyla-Frycz, A. Lenarczyk. *Silesian Center for Heart Disease, Congenital Heart Dis. & Paediatric Cardiology, Zabrze, Poland*

Among 426 patients (pts), in whom interventional closure of atrial septal defect (ASD) was performed in our Center, we selected pts with double ASD or multiple defects localized on aneurysmatic interatrial septum (IAS). Our strategy of closure of such defects is described.
Material and method: Between October 97 and January 2005y 56 pts with double/multiple ASD were treated with Amplatzer Septal Occluder (ASO). There were 38 pts with double ASD and stable septum and 18 pts with multiple (2 or more) defects inside the floppy aneurysmatic IAS. The age of patients ranged from 0,8 to 44 (mean 27,5) years (y). Different type of double ASD were distinguished depending on size of both defects and the distance between both fenestrations. In 2 pts with 2 distant (more than 10 mm) and significant defects 2 devices were implanted. In the rest single ASO was used. In 29 pts bigger ASD and smaller one with the distance between them 3 to 7 mm were recognized. The first one was 16,1 (from 8 to 28) mm of diameter and the second - 2,9 (from 1,5 to 7) mm. In this group oversized ASO was implanted to stent larger ASD, with intention to close neighbouring smaller fenestration with left retention disc. In 5 pts with 2 defects (of different sizes) lokalized close to each other (in distance of 3 mm) - both defects were joined to a single one during stretching procedure (a kind of balloon atrioseptostomy was performed). In 2 pts closure of main ASD was attempted leaving remote, small (1-2 mm) fenestration located close to IVC. Residual shunt through this small defect was "a priori" accepted. In 18 pts with perforated aneurysm of IAS, the entire entrance of aneurysm was stented with ASO implanted to the largest defect.
Results: In all cases the procedures were completed without any complications. In 2 patients in whom two devices were implanted, complete closure of shunt was confirmed after 24 hours. In remaining 54 pts, in whom single ASO was applied,

closure rate (estimated by Color-Doppler TTE) was 55,3% after 24 hours, 77,5% after 3months, 96,9% after 1 y and 98,9% after 6 y of follow-up. All residual shunts were of no haemodynamic consequence.
Conlusions Transcatheter closure of double and multiple ASD with ASO is an effective method of treatment. Strategy of the procedure depends on morphology of ASDs. Residual shunts though frequently seen in early follow up tend to diminish and disappear with time.

P3409 Incidence of thrombus formation on patent foramen ovale and atrial septal defect closure devices

R. Maier[1], O. Luha[1], D. Paetzold[1], N. Watzinger[1], J.I. Stein[2], K. Niederkorn[3], A. Beitzke[2], S. Horner[3]. [1]*Department of Medicine, Division of Cardiology, Graz, Austria;* [2]*Department of Pediatrics, Division of Pediatric Cardiology, Graz, Austria;* [3]*Department of Neurology, Graz, Austria*

Background: Device closure of patent foramen ovale (PFO) or small atrial septal defects (ASD) is a suitable therapy for well selected patients after an embolic event. The procedure itself is safe and effective, however, a few potential complications have to be kept in mind. Amongst them, thrombus formation on the closure device is of major importance. In the literature there is ongoing controversy, whether differences exist between various devices regarding the risk of thrombus formation. Therefore, we reviewed our own patient registry (TACET = The Austrian Paradoxical Cerebral Embolism Trial) with respect to this particular question.
Patients and Methods: In our institution, 112 patients (53 male (47%); mean age 43 ± 11 years; age range 15 – 63 years) underwent PFO and/or ASD transcatheter closure between October 2002 and July 2004. All patients had suffered a cerebral embolic event and were considered for PFO/ASD closure because of a spontaneous or provokable right-to-left shunt during contrast transoesophageal echocardiography (TEE). We used an Amplatzer occluder in 48 (43%), a CardioSeal in 28 (25%), a CardiaStar in 22 (19.5%), and a StarFlex in 14 (12.5%) patients. Device deployment was performed with TEE-guiding. All patients had a transthoracic echocardiogram (TTE) the day after the procedure, and a thorough TEE follow-up six months later. Periprocedurally, enoxaparin (1mg/kg subcutaneously bid) was administered to each patient. In addition, 5,000 IU of unfractionated heparin were injected intravenously in the cath lab. Antiplatelet therapy, started with the embolic event, was maintained for at least six months after the procedure.
Results: The postprocedural TTE study was unremarkable in all patients. In two cases (1.8%), six-month TEE follow-up revealed a small thrombus (1x1 mm) on the left atrial side of the device. Both patients had received an Amplatzer occluder. Antiplatelet therapy was maintained for another six months in both patients. None of them suffered a recurrent embolic event, and no more thrombus could be detected by repeated TEE.
Conclusions: With current anticoagulation regimen the incidence of thrombus formation on PFO and ASD closure devices is low. In contrast to reports in the literature, thrombi may occur on Amplatzer devices as well. A period of six months of antiplatelet therapy seems to be adequate in most patients, however, thorough TEE evaluation is mandatory before termination.

P3410 Tailored neuroprotection assures safety of carotid artery stenting

P. Pieniazek[1], P. Musialek[2], A. Kablak-Ziembicka[2], T. Przewlocki[2], R. Motyl[3], A. Lesniak-Sobelga[2], K. Zmudka[4], W. Tracz[2]. [1]*Krakow, Poland;* [2]*Jagiellonian University, Dept. of Cardiac and Vascular Diseases, Cracow, Poland;* [3]*Jagiellonian University, Dept. of Neurology, Krakow, Poland;* [4]*Interventional Center, John Paul II Hospital, Krakow, Poland*

Background: Registry data indicate that neuroprotection increases safety of carotid artery stenting (CAS), but the criteria for maching the neuroprotection system to the particular patient and lesion have not been fully established. Material and methods: Between January 2001 and January 2005 we performed CAS in 194 patients (pts) (age 44-81 years, mean 64±9 years, 65% symptomatic). All procedures were done with neuroprotection (in 2 pts CAS was not performed due to inability to place a neuroprotection device). Before CAS all patients underwent angio-CT and extra- and intracranial duplex Doppler to evaluate plaque content/morphology and the anatomy/function of intracranial circulation.
Results: We have implanted 208 stents in 203 carotid arteries. Distal neuroprotection (filter devices or PercuSurge/GuardWire) was used in 152 (75%) procedures whereas proximal systems (PAES, Mo.Ma) in 51 (25%) procedures. 'Direct' stenting was performed in 78% cases. The degree of stenosis (% lumen diameter reduction, QCA) was 75.5±10.8% before and 17.2±8.9% after CAS ($p<0,001$). The minimal lumen diameter increased from 1.43±0.55 to 3.76±0.6,8mm ($p<0,001$). Independent histopathologic examination of the captured debris showed embolic particles in 72%. In the periprocedural period, 2 (1.0%) patients had hyperperfusion syndrome leading to a minor stroke, 1 (0,5%) had a minor ishaemic stroke, 5 (2.6%) TIA, and 10 (5.2%) hypotension requiring dopamine infusion. Long-term follow up of all patients (mean 22.1 months) showed 7 (3.6%) deaths due to cardiovascular events, 2 (1.0%) noncardiovascular deaths, and restenosis in 4 (2,0%) pts. Statistical analysis indicated that that the risk of post-CAS mortality was due to coexisting coronary artery disease but not to the presence of neurological symptoms prior to CAS.
Conclusions: CAS with tailored neuroprotection is safe, has a high procedural success rate and a low complication rate. Our data indicate that intention to stent directly (i.e. without predilatation) does not have any negative impact on the outcome of CAS. Identification of embolic particles in ¿ of procedures reinforces the need for temporary brain protection during CAS. Optimal pre-procedural patient evaluation requires non-invasive assessment of extra- and intracranial circulation (duplex Doppler and angio-CT), so that the most appropriate neuroprotection system can be selected for the particular patient and lesion.

P3411 Is carotid angioplasty and stenting under protection becoming the gold standard treatment of a carotid stenosis?

M. Henry[1], I. Henry[1], A. Polydorou[2], A.D. Polydorou[2], E. Le Borgne[1], M. Hugel[1]. [1]*Cabinet de Cardiologie, Nancy, France;* [2]*Panteleimon General Hospital, Athens, Greece*

Purpose: Carotid Angioplasty and Stenting (C.A.S.) is emerging as an alternative treatment for carotid artery stenosis. Cerebral protection devices should be routinely used to reduce distal embolization of debris which may result in neurological deficit. Recent studies have shown that C.A.S. has superior short-term outcomes than Carotid Endarterectomy (C.E.A.) in high surgical risk patients (H.R.). It is not clear however, whether low surgical risk patients (L.R.) are also at lower risk. We compared short-term outcomes of C.A.S. in H.R. and LR. patients.
Methods: We analyzed all C.A.S. performed under protection devices. HR factors included age=80 yrs, post surgical restenosis, prior neck surgery or radiation, contralateral occlusion, low/high anatomic lesion, unstable or severe coronary/heart diseases, severe commorbidities. Patients were followed for 30 days.
Results: In our series of 701 C.A.S., 514 were performed under protection devices in 472 patients (m: 362, F:110). Mean age: 70.9±9.2 yrs using occlusion balloon (n=330), filters (n=178), reversal flow technique (n=6). 334 (65%) were found to be at HR and 180 (35%) at LR. 64% of the lesions were symptomatic. HR and LR patients had similar success rate of protection device deployment (99% both), and stent placement (100% both).
There was no statistical difference between occlusion balloon and filter for 30 day death and stroke rate (0.3% vs 0.6)and embolic events (1.4% vs 1.1%). the 30 day outcomes are shown in the table.

Table

	Total n=514	High risk n = 334	Low risk n = 180	P value
T.I.A.	6 (1.2%)	4 (1.2%)	2 (1.1%)	N.S.
Minor stroke	1 (0.2%)	1 (0.3%)	0	N.S.
Major stroke	1 (0.2%)	1 (0.3%)	0	N.S.
Retinal embolus	2 (0.4%)	0	2 (1.1%)	N.S.
Hyperperfusion syndrome	3 (0.6%)	2 (0.6%)	1 (0.6%)	N.S.
Death	3 (0.6%)	2 (0.6%)	1 (0.6%)	N.S.

Conclusions: C.A.S under protection is safe with favourable low event rate in HR and LR patients. LR patients have a trend toward lower death and stroke rate after C.A.S. compared to C.E.A., but it is not statistically significant. C.A.S should be enlarged to L.R. patients. C.A.S. is becoming the gold standard treatment of a carotid stenosis.

P3412 Percutaneous transluminal angioplasty and stenting of extracranial vertebral artery stenoses

M. Henry[1], I. Henry[2], A. Polydorou[3], A. Polydorou[3], M. Hugel[1]. [1]*Cabinet de Cardiologie, Nancy, France;* [2]*Polyclinique, Bois-Bernard, France;* [3]*Panteleimon General Hospital, Athens, Greece*

Purpose: To evaluate the safety and efficiency of percutaneous interventional treatment (angioplasty/stenting) in patients with symptomatic vertebral artery (VA) stenosis.
Material and methods: 60 VA angioplasties were attempted in 58 vessels in 55 patients by femoral approach using coronary techniques (M:40, F: 15) mean age 67,5 ± 6,8 years (22-84) right 29 left 31. All patients had multivascular diseases (carotid stenoses: 39, subclavian stenoses: 11, renal stenoses: 10, peripheral vascular diseases: 15, coronary diseases: 38). 58 lesions were atheromatous, 2 inflammatory diseases. Mean lesion length: 9,4 ± 2,5 mm (5-14), mean arterial diameter: 4,6 ± 0,6 mm (4-6). 55 lesions were located at VO segment (ostium) 4 at V1 segment and 1 at V2 segment.
Indications for angioplasty included: dizziness (55), bilateral weakness (9), visual changes (8), diplopia (8), drop attacks (8), TIA (5), ataxia (4).
A protection device (filter) was used in 3 patients. 11 subclavian artery angioplasties were performed at the same time of VA angioplasty.
Results: Technical and clinical success 53/55. There were 2 failures in elderly patients with very tortuous calcified arteries. 6 lesions were treated by angioplasty alone (3 VO lesions in our first 3 patients, 2 V1 lesions and 1 V2 lesion). 1 patient with inflammatory disease was treated by cutting balloon alone. 51 lesions were stented with balloon, expandable stents (peripheral stents: 16, coronary stents: 35). 2 V1 lesions were treated with self expandable stents. We observed no per

or post-procedure neurological complications. Angiographic success, defined as ≤20% residual stenosis without in hospital emergency surgery, stroke and death: 58/60 lesions (97%).
Post-procedure arterial diameter: 4,55 ± 0,8 mm (4-6). Mean residual stenosis 2,2 ± 3,5%. 4 patients developed symptomatic restenosis during the follow-up (mean follow-up: 27,3 ± 26,1 months). 3 after PTA alone, 1 after PTA and stent (1 occlusion was treated medically, the 3 stenoses were successfully treated with balloon angioplasty).
Conclusion: Endovascular treatment of V.A.S. can be performed safely and effectively with a high technical success rate, a low complication rate and a durable clinical success in patients with symptomatic V.A.S. Stents seem to improve and long-term results.

P3413 Cutting balloon angioplasty versus stenting for superficial femoral artery: multicenter registry in Japan

S. Nakamura[1], H. Sato[1], O. Hirashima[1], N. Kurita[1], M. Hirose[1], K. Hozawa[2], S. Nakamura[3], J. Koyama[3]. *[1]New Tokyo Hospital, Department of Cardiology, Matsudo, Japan; [2]Chiba Central Medical Center, Department of Cardiology, Chiba, Japan; [3]Secomedic Hospital, Department of Cardiology, Funabashi, Japan*

Background: Treatment and maintaining long-term clinical patency of superficial femoral artery (SFA) atherosclerotic lesions is still one of the most challenging endovascular treatments in terms of restenosis.
Methods: To compare the efficacy and safety of Cutting Balloon angioplasty (CB) versus stenting for treatment of SFA disease, we studied 342 patients with 405 lesions (male 75.1%, mean age 71.0 years): 242 patients with 285 lesions received stenting (Palmaz stent 32.8%, Wall stent 67.2%) and 100 patients with 120 lesions received CB.
Results: See table for immediate and long-term clinical outcomes between stenting and CB.

Table

	Stenting (n=242)	CB (n=100)
In-hospital		
Procedural success (%)	100	100
Lesion length (mean/mm)	52.6	58.8
Reference diameter (mean/mm)	6.3	6.2
Balloon or stent/artery ratio	1.20	1.04
Follow-up at 6 months		
Symptom recurrence (%)	37.2	20.2
Re-intervention (%)	37.2	18.0
Angiographic restenosis (%)	42.1	*20.0

*p<0.05 vs Stenting.

Conclusion: These data show that Cutting Balloon angioplasty seems to offer better long-term clinical outcomes than stenting. Randomized trial is needed.

P3414 Percutaneous transluminal angioplasty of the subclavian arteries

M. Henry[1], I. Henry[2], A. Polydorou[3], A. Polydorou[3], M. Hugel[1]. *[1]Cabinet de Cardiologie, Nancy, France; [2]Polyclinique, Bois-Bernard, France; [3]Panteleimon General Hospital, Athens, Greece*

Purpose: To review feasibility, safety and long-term results of sub-clavian artery angioplasty.
Methods: Over 14 years, 237 patients (males: 135, mean age: 64±12y) underwent percutaneous treatment for sub-clavian artery occlusive disease. Indications for treatment were upper limb ischemia (n=125), vertebrobasilar insufficiency (n=128), coronary steal (n=11) and anticipated coronary bypass surgery in asymptomatic patients (n=26). 192 arteries were stenosed and 45 occluded. Mean % stenosis was 81.9±7.6, mean lesion length was 23.8±8.8 mm. Percutaneous techniques included retrograde femoral (n=163), brachial artery (n=47) access or both (n=14), and in 4 cases, the "pull through technique". An isolated balloon angioplasty was performed in 59 cases. We implanted 132 balloon expandable stents, 32 self-expandable stents.
Results: Technical success was obtained in 223 lesions (94%). Only 31 occlusions were recanalized (69%). Four periprocedural events occurred (1.2%), 1 major (fatal) stroke, 1 T.I.A., 2 arterial thromboses. At follow-up (mean follow-up: 65.8 months ± 33.5), we had 27 restenoses (12%). 13 occurred following angioplasty alone (18.8%) and 14 following angioplasty and stent implantation (8.4%). Primary (PI) and secondary (PII) patencies on an intention to treat basis at 10 year follow-up were 78.1% and 84.5% respectively. In patients without initial stent placement, the rates were 67.5% and 75.5% while in those with stents, the rates rose to 89.7% and 96.9% (P<0.01). PI for all recanalized lesions were 84.6%, 79.1% without stent, 89.7% with stent (P<0.04) and PII 91.6%, 88.5%, 96.9% respectively (P<0.02).
Conclusion: P.T.A. is currently the treatment of choice for subclavian artery lesions. It is a safe and effective procedure associated with low risks and good long-term results. Stents seem to limit the restenosis rate and improve long-term results.

P3415 Simultaneous hybrid revascularisation by carotid stenting and coronary artery bypass grafting

F. Versaci[1], F. Tomai[2], A. Gaspardone[2], I. Proietti[2], P. Nardi[2], A. De Fazio[2], J. Zeitani[2], L. Chiariello[2]. *[1]Rome, Italy; [2]Cardiac Surgery, Tor Vergata University of Rome, Rome, Italy*

Management of simultaneous coronary and carotid disease remains a point of continuing controversy in patients with severe disease in both districts.
Aim: The aim of the present study is to verify both technical feasibility and the safety of a sequential hybrid carotid and coronary revascularization with carotid stent implantation (CAS) and coronary artery bypass grafting (CABG).
Methods: Between April and September 2004, on 500 patients admitted to our hospital for CABG, 32 patients had concomitant coronary and significant carotid artery disease. Of these we selected 10 patients, aged 63-88 (mean age 74) years, for a sequential hybrid carotid and coronary revascularization on the basis of high surgical risk for combined surgery or high risk for deferred one of these interventions. Both sonographic evaluation and subsequent angiography showed in all patients a significant carotid stenosis. Coronary angiography showed in all patients a severe multivessel disease suitable for CABG. All patients underwent carotid stent implantation with distal filter protection under full heparinization. Antiplatelet therapy consisting in the administration of Aspirin at the dosage of 160 mg a day started two days before the procedure. At the end of the procedure, all patients were transferred to the operating room, were the planned CABG interventions were performed. In a 81-year-old patient, the surgical procedure consisted in both CABG and aortic valve replacment. Clopidogrel (300 mg as a loading dose, followed by 75 mg a day for a month) and aspirin (160 mg a day) were initiated in the ICU as well, respectively 6 and 24 hours after the end of the intervention, provided that surgical bleeding from the chest tubes had stopped or when it was less than 50 ml/Hr for three consecutive hours from the sixth hour.
Results: All patients underwent successful carotid stent implantation. There were no major in-hospital adverse events but a brief post-stenting TIA, that had already reverted before to induce general anhestesia for the surgical prcedure. All patients had a uneventful post-operative course and were discharged after a mean in-hospital stay of 7±2 days and after the sonographic demonstration of stent patency and an unchanged Computed Tomographic brain scan.
Conclusions: In the presence of a high surgical risk for both staged and combined surgical operations, a same-day sequential hybrid procedure may be a therapeutic option almost as safe as a single surgical intervention and it warrants further comparison with the conventional strategies.

P3416 Preventing stroke with the PLAATO device: preliminary results of the multicenter registry

Y. Bayard[1], H. Omran[2], P. Neuzil[3], L. Thuesen[4], E. Fischer[1], M. Leetz[1], S. Ostermayer[1], H. Sievert[1] on behalf of PLAATO Investigators. *[1]CardioVascular Center Frankfurt, St. Katharinen, Frankfurt am Main, Germany; [2]St. Marien Krankenhaus Bonn, Bonn, Germany; [3]Na Homolce, Prague, Czech Republic; [4]Skejby Sygehus, Aarhus, Denmark*

Background: The purpose of the PLAATO Registry Study is to determine the feasibility and safety of left atrial appendage (LAA) transcatheter occlusion for stroke prevention. 176 high-risk atrial fibrillation patients unable to take warfarin will be enrolled in the study.
Methods: Inclusion criteria are atrial fibrillation (AF) with inability to take warfarin, prior cerebral ischemia and/or at least two clinical risk factors for stroke. After implantation of the occluder, patients are administered clopidogrel 75 mg for six months and acetylsalicylic acid 300 mg on a continuing basis. Follow up is done with X-ray, TEE and NIH stroke scale in regular intervals.
Results: 99 patients (69% male) with a mean age of 70 ± 10 years were enrolled so far. In 5 patients, the procedure was not attempted due to unsuitable LAA anatomy. All other 94 patients were successfully implanted. The mean procedure time was 73± 34 minutes. Cardiac tamponade was observed in three patients (treated with pericardiocentesis). In one patient, the device embolized but was successfully snared and retrieved; a larger device was successfully implanted in the same procedure.
Thrombus formation on the occluder occurred at the two months follow up in one patient. It was resolved without sequelae with low-molecular heparin.
In a follow up time of 83 patient years, three patients died for reasons not related to the device or the procedure. According to the CHADS2 score, the mean expected annual risk of stroke for the patients enrolled was 6.7%. Of the patients implanted, only one suffered a stroke at 26 days post implant. Thus, the yearly incidence of stroke after implantation is 1.2%. The estimated risk reduction was 82.1%.
The echo corelab analyzed 80 echo tapes at two months. In 75 out of 80 patients (94%), there was a successful occlusion of the LAA.
Conclusion: Catheter closure of the left atrial appendage with the PLAATO device is safe and effective. In comparison to a historical control group, the stroke risk was reduced per follow-up period.

P3417 Transcoronary ablation of septal hypertrophy for HOCM: lower dosages of ethanol reduce the size of the septal defect and lead to the same clinical and haemodynamic improvement

T. Lawrenz, F. Lieder, M. Bartelsmeier-Schmale, G. Beer, C. Leuner, C. Stellbrink, H. Kuhn. *Bielefeld Hospital, Department of Cardiology, Bielefeld, Germany*

Aim of the study: A reduced mortality and arrhythmogeneity after reduction of the amount of ethanol used for transcoronary ablation of septal hypertrophy (TASH) in pts with hypertrophic obstructive cardiomyopathy (HOCM) has been reported by our workgroup previously. Thus we continuously reduced the dosage of ethanol to an average value of 0.7 ml and selected smaller target-vessels or sidebranches of the septal coronary arteries by using the gradient-angiography-guidet technique. The question wether the reduction of the ethanol dosage results in a loss of the clinical benefit is unclear. Therefore we compared the influence of the ethanol-dosage on clinical and hemodynamic parameters (intraventricular gradients, NYHA, CCS, 6 minute walking test, max. creatinin kinase (CK) aktivity) which we assessed before and 6 months after TASH.
Methods: An average dosage of 1.64 $\pm$ 1.3 ml of ethanol was injected in 584 HOCM-pts who were consecutively treated with TASH at our institution. Thus we devided the study group in group A ($<$ 1.6 ml, 345 pts) and group B ($\geq$ 1.6 ml of ethanol, 239 pts).
Results: Group A and Group B showed the same improvement regarding all of the estimated parameters 6 months after TASH (resting gradient 21.7 vs. 21.8 mmHg, provoked gradient 56.6 vs. 49.1 mmHg, NYHA 1.60 vs. 1.60, CCS 1.19 vs. 1.23, 6 minute walking test 517 vs. 411 m; p values n.s.). The improvement rates of all parameters were similar (p values n.s.). In group B we found higher gradients before TASH under resting conditions (53.0 vs. 44.2 mmHg, p=0.0001) and after provokation (120.4 vs. 111.5 mmHg, p=0.061) compared with group A. As expected, in group B the maximal CK- (512.7 vs. 478.8 U/l) and CK-MB-activity (120.4 vs. 111.5 U/l) was higher after TASH (p=0.03). In addition in group B the lokal defect as assessed by the septal diameter in the target-area was greater than in group A (13.4 vs. 16.9 mm, p=0.0001).
Conclusion: The injection of lower dosages of ethanol reduces the size of the septal lesions (lower CK-values, smaller septal notches) after TASH. The low-dose-treatment, however, leads to the same clinical and hemodynamic improvement.

P3418 Percutaneous paravalvular leak closure: a case series

G.E. Pate[1], C.R. Thompson[2], B.I. Munt[2], J.G. Webb[3]. *[1]Saint Paul's Hospital, Interventional Cardiology, Vancouver, Canada; [2]Saint Paul's Hospital, Echocardiography, Vancouver, Canada; [3]Saint Paul's Hospital, Interventional Cardiology, Vancouver, Canada*

Background: Paravalvular leaks (PVLs) are a well-recognised complication of prosthetic valve replacement. Most are asymptomatic and benign but some may cause symptoms as a result of the volume of regurgitation or hemolysis. Re-operation carries significant morbidity and mortality. Medical therapy is palliative (diuretics for heart failure, blood transfusions for haemolysis), and not without complications (e.g. iron overload).
Methods: We reviewed our experience with attempted percutaneous closure of PVLs, using data from medical and procedural records. All were performed under general anaesthesia with trans-oesophageal and radiographic guidance.
Results: Between 2001-2004, 14 procedures were performed in 10 patients (see table) using a variety of devices including atrial septal occluders (ASO), patent ductus arteriosus (PDA) occluders and coils(off label use). Mitral (MVR) and aortic (AVR) valve replacements were involved, both mechanical(mech) and bioprosthetic(bio). Six had a single procedure, which was technically successful in 4: in 2 the PVL could not be crossed. Four underwent a second procedure, in one of which the previously deployed device was dislodged necessitating urgent, but ultimately uneventful, valve replacement. One patient had transient severe hemolysis, which resolved after one week.

Case details

	Age	Sex	Valve	Device	Outcome	Repeat	Device	Outcome
1	75	M	MVR-bio	ASO	Residual leak	Y	Coil	OCCLUDED
2	64	F	MVR-mech		Unable to cross	N		
3	87	F	AVR-bio	PDA	Residual Leak	Y	Coil	OCCLUDED
4	78	M	MVR-bio	PDA	OCCLUDED			
5	77	F	MVR-bio	PDA	Small Residual Leak	N		
6	76	M	MVR-mech	PDA	Residual leak	Y	Coil	Urgent MVR
7	76	M	MVR-mech	ASO	OCCLUDED			
8	50	M	MVR-mech		Unable to cross	N		
9	74	F	MVR-mech		Unable to deliver	Y	PDA	Residual Leak
10	42	M	MVR-mech	PDA	OCCLUDED			

Results: Percutaneous closure of PVLs is time-consuming but feasible in selected patients, with a reasonable degree of technical and clinical success. A second procedure may be necessary and a variety of complications can occur.

P3419 Transcatheter treatment of patients with coarctation and recoarctation of aorta

M. Szkutnik, J. Bialkowski, J. Kusa, J. Baranowski, B. Chodor, S. Regiec, M. Zyla-Frycz. *Silesian Center for Heart Disease, Congenital Heart Dis. & Paediatric Cardiology, Zabrze, Poland*

Introduction: Optimal management of native (CoA) and re-coarctation (ReCoA) of aorta is still controversial. The aim of our study was to present our own experience on the basis of 93 interventional catheterizations.
Material and method: From 1994 to 2005y, 46 patients (pts) with native CoA (aged 14,5 y) and 47 with ReCoA (aged 6,6 y) underwent interventional catheterization in our institution. Balloon angioplasty (BAP) was performed in 71 pts in mean age of 5,5 y and stent implantation in 22 pts in mean age of 28,3y. For stent implantation were qualified older patients, with body weight more than 20 kg, with elastic recoil after previous BAP or longer segment of stenosis. Previous surgery in ReCoA group (gr) was performed 5,3 (0,2 - 30) y earlier. In native CoA gr 31 pts underwent BAP and 15 pts stent implantation (in 1 pt after previous BAP); in ReCoA gr - 40 pts BAP and 7 pts stent implantation (in 3 pts after ineffective BAP). Indications for the procedure were similar in both groups - arterial hypertention (more than 95 percent for BSA), gradient through the isthmus more than 30 mm Hg in ECHO-Doppler and/or 20 mm in hemodynamic examination. In both groups similar technique of catheterization was applied (diameter of balloons equal to diameter of aortic isthmus).
Results: All procedures were terminated without periprocedutral mortality and significant complications. In CoA gr gradient after BAP diminished from 40 to 11 mmHg, and in ReCoA gr - from 38 to 12 mmHg. The procedure was ineffective in 19% of pts in CoA and 20% in ReCoA gr. Small, not progressing aneurysm of aorta after BAP was recognized in 3/31 (9,7%) of CoA pts and 3/40 (7,5%) of ReCoA pts. In follow up (3,1 y and 3,0 y respectively) recurrence of gradient was observed in 9,7% in both groups. After stent implantation mean gradient in CoA gr diminished from 50 to 5 mmHg and in ReCoA - from 54 to 16 mmHg. In the last group in 3 cases with a stiff lesion the procedure was ineffective. In CoA gr migration of stent occurred in 2 pts, however in both cases permanent decrease of gradient was achieved. During 1,5 (0,3 – 5) y of follow–up good result of stent implantation have persisted.
Conclusions: Balloon angioplasty is an effective method of treatment in both – native and recoarctaion of aorta with similar effectiveness and complications rate. In older patient primary stent implantation should be considered. Results of stent implantation are better in native CoA, however the risk of stent migration is higher in this group.

P3420 Carotid artery stenting: does gender matter?

B. Mark[1], R. Zahn[2], T. Ischinger[3], E. Roth[4], K. Hauptmann[5] on behalf of ALKK CAS-Registry. *[1]Herzzentrum Ludwigshafen, Kardiologie, Ludwigshafen, Germany; [2]Herzzentrum Ludwigshafen, Kardiologie, Ludwigshafen, Germany; [3]Städtisches Klinikum, Kardiologie, München-Bogenhausen, Germany; [4]Stadtkrankenhaus, Kardiologie, Worms, Germany; [5]Krankenhaus der Barmherzigen Brüder, Kardiologie, Trier, Germany*

Background: An increasing number of patients (pts.) with carotid artery stenosis is treated by carotid artery stenting (CAS). The influence of patient's gender on clinical characteristics and outcome has not been investigated yet.
Methods: We analysed the data of the prospective CAS-Registry of the ALKK (Arbeitsgemeinschaft der Leitenden Krankenhaus-Kardiologen).
Results: From 1996 to 2004, 1989 consecutive pts. were included. 557 (28%) were women. The pts.' clinical characteristics and outcome until discharge is shown in the table.
In the logistic regression analysis, female gender was not an independent predictor of hospital death or stroke (odds ratio (OR) 1.07; 95% confidence interval 0.64-1.80; p=0.79).

Table 1

	Women n=557 (100%)	Men n=1432 (100%)	p-value	age-adjusted p-value/OR
Age (years)	73 (66-78)	69 (64-75)	<0.001	-
Symptomatic stenosis (%)	56	53	0.24	0.46
CAD (%)	58	71	<0.001	<0.001
Smoker (%)	18	36	<0.001	<0.001
Stenosis pre-CAS (%)	90 (80-95)	90 (80-95)	0.09	0.09
Stenosis post-CAS (%)	5 (1-20)	5 (1-15)	0.22	0.64
Max. balloon diameter (mm)	5 (5-5.5)	5 (5-6)	<0.001	0.03
Duration of CAS (min)	40 (30-60)	40 (30-60)	0.75	0.56
Ipsilateral stroke (%)	3.9	2.9	0.26	1.36 (0.79-2.33)
Death or stroke (%)	4.6	3.6	0.30	1.29 (0.79-2.11)

Clinical characteristics and outcome until discharge depending on gender

Conclusion: 28% of the pts. included in the ALKK CAS-Registry were women. Despite significant differences in pts.' characteristics (age, concomitant coronary artery disease, smoking), interventional characteristics and clinical outcome (hospital death/stroke) were comparable between the genders.

AMI – REPERFUSION MODALITIES

P3421 Looking through the time-window for definitive mechanical repair of the culprit coronary artery after thrombolysis (facilitated angioplasty)

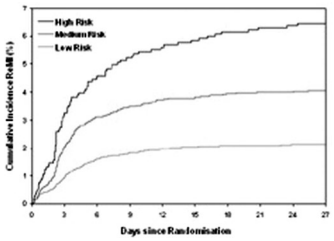
J.H. Alonso-Briales[1], P.L. Sanchez Fernandez[2], J.M. Hernandez[1], M.F. Jimenez-Navarro[1], J.J. Alonso[3], A. Castro-Beiras[4], J. Lopez-Mesa[5], F. Fernandez-Aviles[2] on behalf of Grupo GRACIA. Red Temática de Enfermedades Cardiovasculares, Spain. *[1]Virgen de la Victoria, Cardiology, Málaga, Spain; [2]Hospital Clinico Universitario, ICICOR, Valladolid, Spain; [3]Fuenlabrada, Spain; [4]Hospital Juan Canalejo, Cardiologia, A Coruña, Spain; [5]Hospital Río Carrión, UVI, Palencia, Spain*

Background: The approach to patients with ST elevation acute myocardial infarction consists in achieving early, complete and sustained infarct vessel patency. Facilitated percutaneous coronary intervention (PCI) is defined as planned, early intervention, shortly after initiating fibrinolyis. The concept of facilitated PCI is based on the fact that primary PCI is available world-wide for less than 25% of the patients (pts). With thrombolysis likely to remain a mainstay of reperfusion therapy, pharmacological opening may prolong the time-window for definitive mechanical repair of the culprit coronary artery. We sought to test the optimal time-window for this strategy.
Methods: A total of 334 pts, enrolled in the GRACIA 1 and 2 trials and treated with a facilitated strategy consisting of immediate thrombolysis with tenecteplase followed by adequate PCI within 24 h, were studied. Based on the time for revascularization (after thrombolysis), the pts were divided into 2 groups: early ($<$12 hours, n=149 pts) and delayed ($\geq$12 hours, n=185 pts) revascularization. A composite endpoint of death and reinfarction at one year was evaluated.
Results: Baseline clinical characteristics between both groups were similar. The cumulative incidence of the composite endpoint was similar in the early (6.7%) and delayed (5.4%) groups (odds ratio, 0.78; 95 percent confidence interval, 0.30 to 2.01, p=0.61). Major bleeding rate did not differ between groups with only one episode of intracranial haemorrhage in the early revascularization group.
Conclusions: Definitive mechanical repair of the culprit coronary artery after thrombolysis may be prolonged to 24 hours.

P3422 A simple prognostic score for the re-infarction risk following fibrinolytic therapy for myocardial infarction – data from HERO-2

R.L. O'Connell[1], J.J. Edmond[2], J.K. French[3], P.A. Aylward[4], R.J. Simes[1], H.D. White[5]. *[1]The University of Sydney, NHRMC Clinical Trials Centre, Sydney, Australia; [2]Green Lane Hospital, Cardiology Department, Auckland, New Zealand; [3]Liverpool Hospital, Cardiology Department, Sydney, Australia; [4]Flinders Medical Centre, Cardiology Department, Adelaide, Australia; [5]Green Lane Hospital, Cardiology Department, Auckland, New Zealand*

Early reinfarction (reMI) after fibrynolysis occurs in 2-6% of patients, and is associated with increased mortality. We developed a simple scoring scheme as a prognostic index for reMI, based on data from the 17073 patients enrolled in HERO-2 in 5 regions (Russia, Eastern Europe, Western Countries, Asia, Latin America). 552 patients (3.2%) had reMI adjudicated by the endpoints committee. Various demographic and clinical characteristics, and randomised treatment assignment were considered for inclusion in the risk index. Using backward stepwise logistic regression, all variables entered the initial model and factors remained, if P $<$0.05, as independent predictors of reMI. Simple weights were formed for these variables, which were summed to obtain a total risk score (Table). Of these reMI predictors, CABG and history of angina were associated with a large increased risk, whereas in South America and Eastern Europe the reMI rates were substantially lower; the C statistic was 0.63. Based on the observed reMI rates by prognostic index score, cut points were chosen to delineate patients' risks as low, moderate or high scores ranging from -6 to 3, 4 to 9 and 10 or above (figure 1). These 3 risk categories for reMI were associated with 30 day mortality; 8.3%, 13.2% and 16.4% respectively (p$<$0.01). Though randomisation to receive bivalirudin was associated with reduced reMI risk (p$<$0.01), there were no interactions between treatment assignment, reMI prognostic risk category and either reMI or 30 day mortality (P values $>$0.2).



Risk Factor	Weight
Age	2
Age	0
Pulse	2
Onset	3
Angina	4
Hypertension	2
Female	3
Heparin	2
Previous CABG	6
South America	-5
East Europe	-6
Russia	-3
Asia	0

Figure 1 and Table 1

In conclusion, the prognostic index risk score for reMI was associated with 30-day mortality. Further prospective studies will be required to determine whether this score can be used to 'target' particular patient groups for more intensive treatment.

P3423 Thrombolytic therapy in patients with myocardial infarction after previous revascularisation; 15-years experience

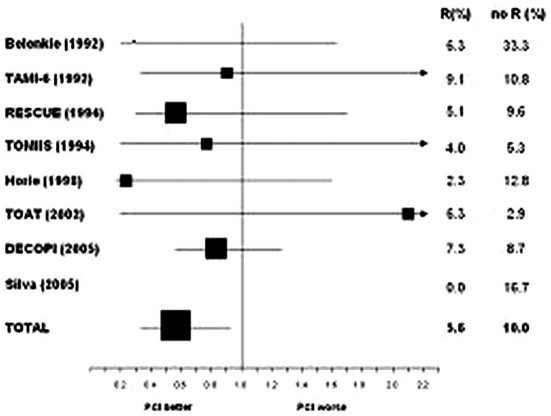
P. Mitrovic[1], B. Stefanovic[2], G. Matic[2], N. Radovanovic[2], M. Radovanovic[2], D. Rajic[2], M. Nedeljkovic[2], Z. Vasiljevic[2]. *[1]Beograd, Serbia and Montenegro; [2]University Clinical Centre, Institute for Cardiovascular Diseases, Belgrade, Serbia and Montenegro*

There is a lack of data about patients (pts) who received thrombolytic therapy (TT) in acute myocardial infarction (AMI) after previous coronary artery bypass surgery (CABS). The aim of this study was to analyze influence of TT after 13-15 years of follow-up period in pts with AMI after previous CABS who were randomized to either treatment with i.c. streptokinase or conventional therapy.
Methods: From April 1988 – January 2005 we studied 720 pts, who developed AMI after CABS, mean age 58.4 $\pm$ 8.0 years, mainly men (80.8%). The pts with early perioperative AMI were excluded from the study. The average time interval from CABS to AMI was 96.2 $\pm$ 16.0 months. The average number of grafts was 3.4 grafts/pts. All pts were divided in two groups: group I - 259/720 (36%) allocated to TT and group II - 461/720 (64%) conventionally treated pts.
Results: Reinfarction and repeated CABS were more frequently after TT. After 15-year approximately 24% of the pts was free of subsequent cardiac events. The cumulative 1, 5, 10 and 15-year survival rates were 93%, 80%, 67% and 51% in pts treated with streptokinase and 86%, 70%, 54% and 44% in the control group, respectively (p$<$0.05). Significant determinants of mortality in multivariate proportional hazards analysis were elderly age, diabetes, previous AMI, indicators of impaired residual left ventricular function and multivessel disease.
Conclusion: Improved survival after TT is maintained beyond the first 15 years. Age, diabetes, previous AMI, left ventricular function and multivessel disease were independent predictors for long-term mortality.

P3424 Long-term mortality after elective recanalisation of occluded arteries after ST elevation myocardial infarction: a systemic review of the randomised trials

F.W.A. Verheugt, M.A. Brouwer. *Radboud University Nijmegen Medical Centre, Department of Cardiology, Heartcenter, Nijmegen, Netherlands*

Background: Although early reperfusion therapy in ST elevation acute coronary syndromes saves up to 80 per 1,000 patients treated, there is still considerable doubt, whether elective recanalisation of occluded infarct arteries after the acute phase may beneficial. Results from randomized trials so far were inconclusive due to small patient numbers and, by the necessarily open design MI and revascularisation/recurrent ischemia are relatively weak endpoints. Since MI is both an entry criterion and an endpoint, it is difficult to evaluate, since it may be induced by intervention and, therefore, its definition in the trials is cumbersome. Thus, long term mortality is the best outcome parameter to evaluate the above strategy.
Methods and Results: The 8 randomized trials were published between 1992 and 2005 and included 684 patients with proven occluded infarct arteries after ST elevation acute coronary syndromes. They were randomized to recanalisation (n = 355, almost exclusively PCI) or a conservative strategy (n = 329) one to 26 (median 8) days after the index event. All cause mortality at a median of 6 months (figure) was 5.3% for elective recanalisation and 10.0% for a conservative strategy (OR 0.56, 95% CI 0.33 - 0.97, p = 0.04). The overall results seem consistent and the test for heterogeneity is not significant.
Conclusion: Although the trials of elective recanalisation of occluded arteries after ST elevation ACS were too small to be conclusive, this meta analysis suggests a nearly 50% reduction of long term mortality. These data strongly support



Long-term mortality

the open artery hypothesis, but definite proof can only be obtained from large ongoing randomized trials, like OAT.

P3425 A prehospital diagnostic strategy reduces time to treatment and mortality in real life STEMI patients treated with primary percutaneous coronary intervention

E. Björklund[1], U. Stenestrand[2], J. Lindback[3], L. Svensson[4], L. Wallentin[1], B. Lindahl[1] on behalf of RIKS-HIA Investigators.
[1]Dept of Cardiology, Uppsala University Hospital, Uppsala, Sweden; [2]Dept of Cardiology, University Hospital Linkoping, Linkoping, Sweden; [3]Uppsala Clinical Research Center, Uppsala University Hospital, Uppsala, Sweden; [4]Division of Cardiology, South Hospital, Stockholm, Sweden

Both randomised trials and registry studies evaluating the impact of time to treatment in primary percutaneus coronary intervention (PCI) in ST-elevation myocardial infarction (STEMI), have yielded conflicting results with respect to mortality. Moreover, the influence on time to treatment and subsequent mortality with a prehospital diagnostic strategy has previously not been evaluated.
Methods: Prospective cohort study using data from the Swedish Register of Cardiac intensive care on patients admitted to the coronary care units of 74 Swedish hospitals in 2002-2003. Only patients younger than age 80 years with the first recorded diagnos of acute myocardial infarction (AMI) treated with primary PCI were included. Out of 2676 patients, 1822 were transported with ambulance out of which 620 had a prehospital electrocardiogram (ECG) sent to hospital. All time delays (minutes) are expressed as medians (with 25th-75th percentile). Mortality data were obtained from the Swedish National Cause of death register.
Results: There were few differences in baseline characteristics according to prehospital ECG or not, only medication with aspirin and beta-blockers were less common in the group with prehospital ECG. In multivariable analyses, after adjusting for risk factors such as age, gender, diabetes, previous MI and medication at entry, a prehospital diagnostic strategy was associated with lower 30-day mortality (OR 0.57; 95% CI, 0.32-1.0).

Table 1

	n/n	Prehosp ECG	No prehosp ECG	p-value
start of symptoms to PCI	600/989	181 (121-330)	240 (144-480)	p<0.001
arrival in CCU to PCI	600/1200	50 (20-138)	55 (22-236)	p=0.02
30-day mortality (%)	620/1202	3.1%	5.1%	p=0.047

Conclusion: Time from symptom onset to primary PCI is reduced by one hour and the adjusted 30-day mortality is decreased with a prehospital diagnostic strategy in this registry study.
A diagnostic strategy with prehospital ECG is important even when treatment is restricted to primary PCI.

P3426 Rescue angioplasty v conservative treatment or repeat thrombolysis for failed lysis: 6 months outcome according to treatment actually received

A.H. Gershlick[1], S.L. Hughes[1], A. Stephens-Lloyd[1], S.E. Stevens[2], S. Redwood[3], M. Malekian[4], F. Alamgir[5], R. Wilcox[6] on behalf of the REACT investigators. *[1]University Hospitals of Leicester, Cardiology Dept., Leicester, United Kingdom; [2]University of Leicester, Leicester, United Kingdom; [3]St Thomas' Hospital, London, United Kingdom; [4]Wishaw General Hospital, Lanarkshire, United Kingdom; [5]Royal Infirmary, Hull, United Kingdom; [6]Queens Medical Centre, Nottingham, United Kingdom*

Up to 40% of patients suffering acute myocardial infarction fail to adequately reperfuse (achieve TIMI Grade 3 patency) following thrombolysis. Subsequent treatment options (percutaneous coronary intervention (RPCI), heparin (Conservative), or repeat thrombolysis (R-Lysis)) have not yet been proven beneficial.
Methods: REACT was a UK-based, randomised comparison of RPCI against R-Lysis (fibrin-specific) or conservative (C) in patients with "failed thrombolysis". Safety, clinical, quality of life and cost-effectiveness outcomes were measured to 1 yr in 427 patients recruited between Dec 1999 and Mar 2004 at 35 UK hospitals. Eligible patients had received lysis and aspirin within 6 hrs of onset of pain but had <50% resolution of ST changes on ECG. Exclusion criteria included cardiogenic shock and measures aimed to reduce excess bleeding risk e.g. age >85 yrs, hypertension and low body weight. Primary endpoint was composite MACCE (death/re-infarction/severe heart failure/CVA) at 6 months.
Demographics: male 79.2%: mean age 61.1 (11) years: 42.5% anterior MI at presentation, 55% inferior: 48% current smokers; 14.1% diabetics; 37.5% hypertensive. Streptokinase was first lytic in 60% of patients. The median time from pain to first lytic was 140 mins (2.3 hrs), with a door to needle time of 27 mins. Randomised (fibrin-specific) R-lysis was administered median 330 mins (5.5 hrs) after onset of pain, and RPCI 414 mins (6.9 hrs), a time difference of 84 mins (1.4 hrs).
Results: ITT analysis showed that R-PCI improved outcome as measured by MACCE, affecting all composites of it at 6 months. Event free survival rates and hazard ratios (HR) significantly favour RPCI: RPCI 84.6% v R-Lysis 68.7% v Conservative 70.1% (p=0.004); RPCI v Conservative HR= 0.47 (95% CI 0.28-0.79)(p=0.004) and v R-Lysis HR = 0.45 (95% CI 0.27-0.75) (p=0.002). However, analysis according to last treatment received within the 12 hrs following randomisation (i.e. 'actual treatment') has been undertaken to account for crossover. Results improved further. Of 142 patients who actually received R-Lysis, 44 (31.0%) suffered at least one component of the composite end-point as did 46 of 154 (29.9%) who were treated conservatively, compared to only 18 (13.7%) of 131 who actually received R-PCI (overall p=0.001). For RPCI vs C the HR improved to 0.42 (95%CI 0.24- 0.72; p=0.0018) with a similar improvement for RPCI vs R-lysis to 0.4 (95%CI 0.23-0.70; p=0.0012).
Conclusions: Rescue PCI improves outcome when used as a treatment strategy in the setting of failed thrombolysis and should be considered the preferred option.

P3427 REscue Angioplasty v Conservative treatment or repeat Thrombolysis for failed thrombolysis in acute MI: the REACT trial one year clinical outcome

A.H. Gershlick[1], A. Stephens-Lloyd[1], S.L. Hughes[1], N. Uren[2], A. de Belder[3], J. Davis[4], S.E. Stevens[5], R. Wilcox[6] on behalf of the REACT investigators. *[1]University Hospitals of Leicester, Cardiology Dept., Leicester, United Kingdom; [2]Royal Infirmary, Edinburgh, United Kingdom; [3]Royal Sussex County Hospital, Brighton, United Kingdom; [4]North Staffordshire Hospital, Stoke-on-Trent, United Kingdom; [5]University of Leicester, Leicester, United Kingdom; [6]Queens Medical Centre, Nottingham, United Kingdom*

Background: Thrombolysis remains the dominant reperfusion therapy following myocardial infarction and has been shown in many trials to save between 20 and 30 lives per thousand treated. However up to 40% of patients suffering acute myocardial infarction fail to achieve adequate reperfusion (i.e. TIMI Grade 3 patency) following thrombolysis. Subsequent treatment options (rescue percutaneous coronary intervention [RPCI], heparin [Conservative], or repeat thrombolysis [R-Lysis]) have until recently been non-evidence-based.
Methods: The REACT trial was a UK-based, British Heart Foundation sponsored, randomised comparison of rescue angioplasty, repeat lysis (fibrin-specific) or conservative therapy in patients with "failed thrombolysis" as defined by lack of ST segment resolution by > 50% at 90 minute ECG. It examined safety, clinical, quality of life and cost-effectiveness outcomes to one year in 427 patients recruited up to March 2004 at 35 UK hospitals. Patients receiving standard treatment (any lysis and aspirin) within 6 hours of onset of pain were eligible. Important exclusion criteria were; age >85 yrs, cardiogenic shock, hypertension and low body weight. Primary endpoint was composite MACCE (death/re-infarction/severe heart failure/CVA) at 6 months.
Demographics: male 79.2%; mean age 61.1 (11) years; 42.5% anterior MI at presentation, 55% inferior; 48% current smokers; 14.1% diabetics; 37.5% hypertensive. Streptokinase was first lytic in 59%. The median time from pain-first lytic was 140 mins (2.3 hrs), with a door-needle time of 27 mins. Randomised (fibrin-specific) R-lysis was administered median 330 mins (5.5 hrs) after onset of pain, and RPCI 414 mins (6.9 hrs), a time difference of 84 mins (1.4 hrs).
Results: The 6-month primary end point analysis has been presented. According to ITT analysis, R-PCI improved outcome as measured by MACCE affecting all composites of it at 6 months; event free survival rates: RPCI 84.6% v R-Lysis 68.7% v Conservative 70.1% (p=0.004). RPCI v Conservative HR= 0.47 (95% CI 0.28- 0.79)(p=0.004) and v R-Lysis HR = 0.45 (95% CI 0.27-0.75) (p=0.002).
12 month follow up data collection will conclude in March 2005, and will be presented for the first time at ESC. It will tell us whether the highly significant results seen at 6 months are maintained out to the longer-term.
Conclusions: Treatment with Rescue PCI has been shown to significantly improve outcome at 6 months in patients with failed thrombolysis. It will be important to see whether benefit is maintained at 12 months.

P3428 Facilitated PCI is superior to primary PCI in AMI pts presenting less than 2 hours after the onset of MI

P. Pillay[1], T. Lefevre[1], P. Garot[2], T. Unterseeh[1], O. Tavolaro[1], P. Dumas[1], Y. Louvard[1], M.C. Morice[1]. *[1]Institut Cardiovasculaire Paris Sud, Massy and Quincy, France; [2]ICPS, ANGIO, Quincy Sous Senart, France*

Background: In AMI-pts, the outcome of thrombolysis is known to be improved after early administration. It remains unknown as to whether a golden hour exists for facilitated PCI.
Methods: Between Jan. 1995 and Dec. 2004, 2139 pts were admitted for <12 hours AMI in the cath-lab of our institution to undergo emergent PCI of the IRA. The present analysis focused on AMI-pts presenting within 2 hours after the onset of chest pain (N=443, 21% of the whole cohort).
Results: Baseline characteristics and PCI outcomes are presented according to the indexed reperfusion strategy consisting of direct PCI or immediate PCI after <2 hours pre-hospital thrombolysis (see Table 1, p. 563).
Conclusion: AMI-pts treated by facilitated PCI had higher TIMI-3 flow on admission, increased ability to direct stent and increased PCI success rates with associated higher EF and decreased in-hospital death rates

Abstract P3428 – Table 1

	Direct PCI (N= 267)	Facilitated PCI (N= 176)	P Value
Age (years)	60±14	59±14	NS
Male	78%	80%	NS
Dyslipideamia	40%	27%	NS
Diabetes	10%	13%	NS
Smoking History	57%	69%	NS
Prior AMI	13%	6%	NS
3 vessel CAD	25.1%	14.2%	NS
Anterior AMI	46%	46%	NS
Shock on admission	10%	0%	<0.001
TIMI 3 on admission	18%	60%	>0;0001
Door to TIMI 3 (Min)	51±14	39±13	<0.01
Direct Stenting	44%	67%	<0.001
No reflow in IRA	5.2%	7;4%	NS
PCI Success	93%	87.5%	<0.05
Ejection Fraction %	53±14	57±0.1	<0.05
Stroke	0.4%	0.4%	NS
Re AMI	0.2%	0.7%	NS
Peak CK (IU/L)	2577±14	2013±1732	NS
In hospital death	8%	3%	<0.01

P3429 High incidence of coronary occlusion in first non-ST-segment elevation myocardial infarction

C. Pena Gil[1], J. Figueras[2], A. Garcia[1], J.M. Garcia-Acuna[1], M. Jaqhet[1], R. Trillo[1], J.R. Gonzalez-Juanatey[1], A. Amaro[1].
[1]Hospital Clinico Universitario, Santiago de Compostela, Spain; [2]Hospital Vall d'Hebron, Cardiology, Barcelona, Spain

Background: Patients with ST-segment elevation myocardial infarction usually have a total coronary thrombotic occlusion and acute reperfusion reduces mortality in this setting. In contrast, patients with non-ST-segment elevation myocardial infarction (NSTEMI) represent a more heterogeneous group in which a non-occlusive thrombus has been suggested as main pathophysiologic mechanism. However, some of these patients may also present a total coronary occlusion but they are no identified as an early reperfusion target.
Methods: Our objective was to analyze the TIMI flow status in 120 consecutive patients with their first NSTEMI. The admission 12 lead ECG and coronary angiographies were reviewed and coronary occlusion was defined as TIMI flow < 3. Patients with Q waves or ST segment elevation with reperfusion criteria were excluded.
Results: Mean age was 64±15, 78 males (65%). In 77 (64%) patients the culprit lesion was identified, in 33 (27%) there were >1 possible culprit lesions and no significant stenosis were found in 10 pts. 51 patients (42%) presented TIMI < 3 (30 TIMI 0, 8 TIMI 1, 13 TIMI 2) in at least one major coronary artery. Collateral flow was found in 20 (17%). 32% patients presented 1 vessel, 35% 2 vessels and 22% 3 vessels disease. 74 patients were treated with Gp IIb/IIIa antagonist and in 74 a PTCA was performed (93%). Two patients died during admission.
Among 77 patients, in which the culprit lesion was identified (44% circumflex (CX), 36% left anterior descending coronary artery (LAD) and 19% right coronary artery (RC)), and coronary occlusion was present in 38 (50%), (60% CX, 29% LAD y 10% RC, p<0.012).
Patients with culprit coronary occlusions were younger (59.5± 13 vs 65±12 p= 0.03), tended to have a higher incidence of smoking and had a larger myocardial necrosis (CK MB mass 108±99 vs 64±60, p=0.02) than those with non occluded culprits.
Conclusion: The presence of a culprit coronary occlusion, in nearly half of the patients with first NSTEMI emphasizes the need to better identify, clinically and electrocardiographically, those that could benefit from early thrombolysis or primary angioplasty.

P3430 Modulation of plasma mediated neutrophil activation by Gp IIb/IIIa inhibitor tirofiban in ACS patients

P. Kalmucki, M. Majewski, W. Rafinski, P. Burchardt, T. Siminiak.
Distric Hospital Poznan, Cardiology, Poznan, Poland

Plaque rupture resulting in platelet and leukocytes are crucial for the pathophysiology of acute coronary syndromes (ACS) and myocardial reperfusion injury. Therefore we conducted a study assessing the influence of platelet receptor IIb/IIIa inhibition on plasma mediated neutrophil activation. We included 39 consecutive patients with ACS without ST elevation, aged 49 to 85 years. We investigated the effects of adjunctive tirofiban administration (19 patients) versus standard antithrombotic therapy (20 patients) including ASA, clopidogrel and enoxaparin on plasma mediated neutrophil expression of CD11b, CD18 and CD62L. Plasma specimens were taken at the time of admission to hospital and 4, 24, 48 hours later as well as on the last day of hospitalization. After incubation of control PMN with plasma specimens antigen expression was assessed by flow cytometry.
We noticed, that in patients treated without tirofiban, incubation of control PMN with plasma specimens taken at 4 hours after admission caused significant increase in CD18 expression (40,42±6,53 vs 44,36±7,199; p=0,0414) vs baseline levels and than significant decrease of CD18 expression (44,36±7,199 vs 40,50±7,059; p=0,0492) after PMN incubation with plasma collected at 24 hours vs levels reached at 4 hours. CD62L expression on the last day of hospitalisation was (61,09±5,856) significantly higher in comparison to CD62L expression at baseline (46,44±3,277 vs 61,09±5,856; p=0,0214), 4 hours (44,62±1,729 vs 61,09±5,856; p=0,0143), and 48 hours after admission (47,60±2,459 vs 61,09±5,856; p=0,0313), suggesting CD62L shedding over 48 hours. No significant differences in CD11b expression levels was observed. In contrast, in patients treated with tirofiban, incubation of control PMN with plasma taken 4 hours after hospital admission inhibited, observed in the first group, increase of CD18 expression. We found that tirofiban inhibited CD62L shedding (no significant differences in expression during hospitalisation). We also noticed that tirofiban caused significant decrease of CD11b expression on PMN incubated with plasma taken at 4 hours (584,9±27,19 vs 659,5±28,05; p= 0,0375) versus baseline levels. In vitro studies showed no significant influence of tirofiban on PMN.
We conclude that in patients with ACS without ST elevation tirofiban infusion modulate PMN activation. We believe that tirofiban acts by modification of PMN-platelet interactions or leads to the inhibition of systemic release of mediators causing PMN activation and subsequent expression of integrins as well as shedding of CD62L.

P3431 The role of aspirin resistance on outcome in patients with acute coronary syndrome and the effect of clopidogrel therapy in the prevention of major cardiovascular events

B. Pamukcu[1], Y. Nisanci[2], H. Oflaz[2], B. Umman[2], I. Onur[2], S. Umman[2] on behalf of -. *[1]Istanbul, Turkey; [2]Istanbul, Turkey*

Aim: Aspirin resistance, clinically, could be defined as having thrombotic and embolic cardiovascular events despite regular aspirin therapy. Major cardiovascular events (MACE) risk is more then threefold in aspirin resistant patients with stable coronary artery disease. The aim of our study was to determine; the prevalence of aspirin resistance in patients with acute coronary syndromes, the role of aspirin resistance on outcome in the follow-up and the effect of clopidogrel therapy in the prevention of MACE in aspirin resistant subjects.
Material and Methods: We detected the prevelance of aspirin resistance in 105 (23 female) consecutive hospitalized patients with acute coronary syndrome. Platelet functions were analyzed in Platelet Function Analyzer (PFA)-100 (Dade Behring,Germany) device with collagen and/or epinephrine (Col/Epi) and collagen and/or ADP (Col/ADP) cartridges. Closure time (CT) = 193 seconds was defined as aspirin resistance with PFA-100. Patients are followed for 14±2 months. Primary end points of the study were myocardial infarction, unstable angina, cardiac death. Comparison of the MACE in aspirin resistant and sensitive patients has been done with chi-square test. P value of =0.05 was considered statistically significant.
Results: 19% (n=20) of patients were aspirin resistant by PFA-100. In the follow-up, MACE occurred in 9 patients (47.3%) in the aspirin resistant patients group and in 10 patients (11.6%) in the aspirin sensitive patients group (p=0.001). Multivariate analysis showed that aspirin resistance was an independant predictor of MACE. The prevalence of MACE in patients who were on clopidogrel treatment for 12 months were lower compared to those who were on a clopidogrel treatment for the first six months (p=0.035). Baseline characteristics of patients were similar. No statistically significant differences in the risk factors of coronary artery disease, involved coronary vessels, biochemical parameters, and blood counts were present between aspirin resistant and sensitive patients.
Conclusions: We determined that the MACE risk in patients with acute coronary syndromes having detected aspirin resistance, is higher at statistically significant levels compared to patients having aspirin sensitive platelet aggregation. Our study results showed that aspirin resistance, was an independant predictor of MACE in patients with acute coronary syndromes. Additional clopidogrel treatment for 12 months to standard aspirin therapy may reduce MACE in patients with aspirin resistance who experienced an acute coronary syndrome recently.

P3432 Does low molecular weight heparin influence outcome in patients With non ST-segment elevation myocardial infarction with or without early revascularisation in a real life setting?

U. Stenestrand[1], L. Wallentin[2] on behalf of the RIKS-HIA registry.
[1]University Hospital, Department of Cardiology, Linkoping, Sweden; [2]University Hospital, Uppsala Clinical Research Center, Uppsala, Sweden

Background: Low Molecular Weight Heparin (LMWH) has been shown to improve outcome in clinical trials when randomizing NSTEMI patients to conservative or early revascularization. We investigated the 30 day outcome in real life setting for NSTEMI patients with or without revascularization within 14 days and the influence of unfractionated heparin (UFH), LMWH, or no type of heparin distributed.
Methods: Prospective cohort study using data from the Register of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKS-HIA) on patients admitted to the coronary care units of 72 Swedish hospitals 1995-2003. 61335 patients with AMI as the final diagnosis and no ST-segment elevation or LBBB on admission ECG were included. 30-day and 1-year mortality data were obtained from the Swedish National Cause of Death Register. Relative risk of mortality was calculated by Cox regression analysis adjusting for 15 confounding variables.

Results: see Table 1.

Table 1

Therapy	Patients	30-day mortality			1-year mortality		
		unadjusted	adj. RR	P*	unadjusted	adj. RR	P*
No revascularisation within 14 days							
No heparin	30213	15.6%	1	1	29.9%	1	1
UFH	4049	11.9%	0.97	0.54	20.7%	0.88	0.001
LMWH	26619	8.7%	0.72	<0.001	19.2%	0.84	<0.001
Revascularisation within 14 days							
No heparin	5441	3.6%	1	1	6.0%	1	1
UFH	1952	4.1%	0.98	0.91	6.5%	0.94	0.58
LMWH	9819	2.2%	0.66	<0.001	4.3%	0.80	0.004

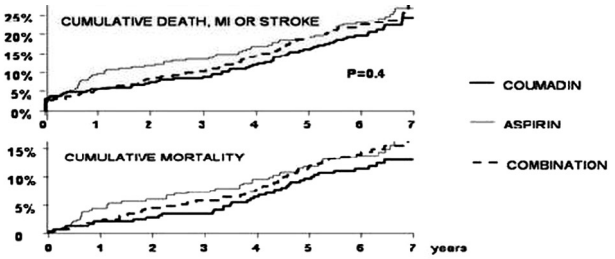
* P-value by Cox regression

Conclusions: In daily clinical practise LMWH but not UFH is associated with significantly improved survival both at 30 days and 1 year in NSTEMI patients revascularized within 14 days. In initially conservatively managed NSTEMI patients both types of heparin are associated with improved long term survival.

P3433 Late clinical outcomes with aspirin, coumadin or both after acute coronary syndromes

R.F. Van Es[1], R.T. Van Domburg[1], M. Vollenbronck[1], J.W. Deckers[1], J.J.C. Jonker[2], F.W.A. Verheugt[3], D.E. Grobbee[4] on behalf of the ASPECT-2 research group. *[1]Erasmus MC, Rotterdam, Netherlands; [2]Andromed, Rotterdam, Netherlands; [3]UMCN, Nijmegen, Netherlands; [4]UMCU, Utrecht, Netherlands*

Background: the role of antithrombotic therapy in secondary prevention of acute coronary syndromes is well established. Coumadin, in combination with aspirin or given alone was superior to aspirin alone in the ASPECT-2 trial. The purpose of this study was to investgate whether the described benefit of coumadin was maintained after a mean observation period of 7 years.
Methods: details of antithrombotic therapy, survival and cardiovascular events were obtained from the civil registry and from patient questionnaires. Mortality and MACE (first occurrence of death, myocardial infarction or stroke)were estimated by Kaplan-Meier curves.
Results: follow-up information was obtained in 988 patients (99%). At follow-up 50 of 333 patients allocated to aspirin, 40 of 323 patients allocated to coumadin ([INR] of 3.0-4.0) and 51 of 332 patients allocated to the combination of aspirin and coumadin ([INR] of 2.0-2.5) were deceased. MACE occurred in 96,87 and 91 patients respectively. Kaplan-Meier curves are shown in the figure. Logrank test of coumadin alone versus aspirin alone showed a p-value of 0.4 for MACE and 0.3 for mortality. Cross-over rate from coumadin to aspirin was 72% and from combination therapy to aspirin was 77%.



MACE

Conclusion: late clinical outcome showed a 20% reduction in mortality and a 7% reduction in MACE of coumadin compared to aspirin, according to intention-to-treat analysis. This difference was not statistically significant. No difference was observed between aspirin and combination therapy. The treatment effect of coumadin may be reduced due to the high cross-over rate to aspirin.

PROGNOSIS AND DIAGNOSIS NON-ST ACS

P3434 Compliance with the guidelines in the management of Non-ST elevation acute coronary syndrome patients in a nationwide representative sample of Spanish hospitals

M. Heras[1], H. Bueno[2], A. Bardaji[3], A. Fernandez-Ortiz[4], H. Marti[5], J. Marrugat[5] on behalf of The DESCARTES Investigators. *[1]Hospital Clinic of Barcelona, Cardiology Department, Barcelone, Spain; [2]Hospital Gregorio Marañón, Cardiology Department, Madrid, Spain; [3]Hospital Joan XXIII, Cardiology Department, Tarragona, Spain; [4]Hospital Clinico San Carlos, Cardiology Department, Madrid, Spain; [5]IMIM, Cardiology Department, Barcelone, Spain*

Objectives: To analyze the effect of treatment appropriateness in patients with Non-ST elevation acute coronary syndrome (NSTEACS) and to determine whether the TIMI risk score predicts outcomes in a nationwide population based study.
Methods: The DESCARTES registry was performed in April and May 2002 in Spain. 45 randomly selected hospitals out of 165 hospitals treating ACS included 1877 patients fully representative of the management of NSTEACS patients in Spain. There was a 6-month follow-up. Patients were classified in seven different risk categories according to the TIMI risk score.
Results: Table 1 shows number of patients and percentage of them who received the guidelines class I recommended treatments for each risk category and 28-day and 6 month (for 28-day survivors) mortality rates.

Table 1

	0	1	2	3	4	5	6	7
n	96	231	347	457	379	249	94	24
Coronar %	31.3	35.3	39.1	42.8	43.9	45.7	46.8	41.7*
Revascu %	14.9	20.1	23.4	26.5	21.8	28.8	28	25+
IIb/IIIa %	3.2	9.9	12.4	10.7	10.6	16.3	21.5	20.8#
ASA %	82.3	84.2	86.1	87.4	88.3	91.5	92.5	91.7*
Clopidogr %	26.3	26.9	31.6	37.4	41.3	47.2	50	41.7#
BBlock %	57.4	57.9	61.9	63	67.7	61.5	64.5	58.3
28d death %	0	0.4	1.4	3.3	2.6	7.6	12.8	16.7#
6m death %	1.1	0.9	1.9	4.3	4.7	6.6	12.5	21.1#

*p=0.001, +p= 0.013, #p<0.001 for trends. Coronar = coronariography. Revascu = percutaneous coronary intervention + CABG.

Conclusions: The TIMI risk score stratified well the risk of acute and 6-month death in this "real world" population. There is a very low invasive approach, especially in the highest risk groups (i.e. TIMI risk score >3) which have the highest mortality. High-risk patients received significantly more clopidogrel and IIb/IIIa receptor blockers but still the utilization is considered low in these groups with high mortality.

P3435 Heart-type fatty acid binding protein is not a useful marker in identifying non-ST elevation myocardial infarction with minor myocardial damage

Y. Cavusoglu, B. Gok, B. Timuralp, A. Birdane, C. Demirustu, A. Unalir, B. Gorenek, N. Ata. *Osmangazi University, Cardiology Department, Eskisehir, Turkey*

Purpose: Cardiac troponins (cTn) are the more sensitive and specific markers of myocardial injury in acute coronary syndromes (ACS). However, an initial rise in cTn is seen after 3 to 6 h of symptom onset. Myoglobin (Mb), the more sensitive but not specific marker of injury, can be detected within 2 h after the onset of infarction. Heart-type fatty acid binding protein (H-FABP) has recently been reported to be a new diagnostic marker of myocyte injury for the early detection (within 2 h after symptom onset) of acute myocardial infarction. There have been no detailed studies evaluating its usefulness for identifying non-ST elevation myocardial infarction (NSTEMI) patients who have only minor myocardial damage. The aim of this study was to evaluate the diagnostic value of H-FABP for the detection of minor myocardial damage in patients presenting with NSTEMI.
Methods: The study consisted of 34 patients with a diagnosis of NSTEMI on the basis of an acute chest pain episode and electrocardiographic changes within 12 h after the onset of symptoms. cTn-I (cTnI), Mb and creatine kinase-MB (CK-MB) were measured at admission, and H-FABP was measured if cTnI level was found to be elevated. H-FABP was determined by a rapid chromatographic immunoassay method that gives result within 15 minutes, and H-FABP levels >7 ng/ml were considered as positive result. Patients were classified as minor myocardial damage group if they had elevated levels of cTnI (>1 ng/ml) without CK-MB elevation (n=23) and as NSTEMI group if they had elevated both cTnI and CK-MB levels (n=11) in 24 h follow-up. The performance of H-FABP test was compared with Mb results.
Results: Mean time from symptom onset to hospital arrival was 5.45±2.1h in minor myocardial damage group in comparison to 4.1±1.44 h in NSTEMI group (p=n.s.) Mean cTnI and CK-MB levels were 3.08±2.7 ng/ml and 19±4.7 U/L in minor myocardial damage group, 5.76±4.3 ng/ml and 53±10 U/L in NSTEMI group, respectively. In minor myocardial damage group, 17 of the 23 patients (73.9%) had elevated Mb levels, but no patient showed positive result of H-FABP test (t= -5.01, sd=42, p< 0.001). In NSTEMI group, Mb levels were elevated in 72.7% of the patients (8/11), H-FABP was found to be positive in 45.4% of the patients (5/11)(t= -1.35, sd= 18, p>0.05).
Conclusions: These results suggest that H-FABP does not appear to represent diagnostic value, and Mb is more sensitive than H-FABP, for identifying NSTEMI patients who have only minor myocardial damage. However, Mb and H-FABP may have similar diagnostic potential in the assessment of patients with NSTEMI.

P3436 The impact of plasma uric acid levels on the long-term cardiovascular mortality in patients with acute coronary syndromes

S.G. Foussas[1], M. Zairis[2], M. Bitza[1], G. Bibis[1], V. Panagiotidis[1], S. Makrygiannis[1], A.J. Manolis[1], D.V. Cokkinos[3] on behalf of the BIAS Study Group. *[1]Tzanio Hospital, Cardiology Dept., Piraeus, Greece; [2]Piraeus, Greece; [3]Onassis Cardiac Surgery Center, Cardiology Dept., Athens, Greece*

Background: Although an elevated plasma uric acid (UrAc) level has been considered as a cardiovascular disease risk factor, its impact on the long term prognosis in patients with acute coronary syndromes has not thoroughly evaluated. We investigated this possible association in the BIAS (Biochemical Indices and outcome in Acute coronary Syndromes) study.
Methods: The BIAS study was designed to evaluate prospectively the impact of several biochemical indices including UrAc on the long term cardiovascular mortality in patients who hospitalised due to either ST elevation myocardial infarction (STEMI) or non-ST elevation acute coronary syndromes (NSTACS). For the purpose of this study 934 consecutive pts with STEMI (458 pts) and NSTACS (476) who were admitted in the first 12 and 24 hrs of index pain respectively, were recruited. All biochemical indices were estimated upon pts' admission and cardiovascular mortality during 5 years of follow up was the primary study endpoint.
Results: Plasma UrAc levels were significantly higher in pts with: diabetes (p=0.01 and p=0.004 for STEMI and NSTACS respectively); hypertension (p=0.04 and p=0.03 for STEMI and NSTACS respectively); age≥75 years (p=0.008 and p<0.001 for STEMI and NSTACS respectively); previously known coronary artery disease (p=0.02 and p<0.001 for STEMI and NSTACS respectively); and history of cerebrovascular or peripheral artery disease (p=0.04 and p=0.006 for STEMI and NSTACS respectively). The incidence of cardiovascular mortality at the end of the follow up was 23.1% and 21.4% in pts with STEMI and NSTACS respectively. By univariate regression analysis high plasma UrAc levels were significantly related with increased risk of 5-year cardiovascular death in pts with either STEMI (RR=2.7; p=0.006) or NSTACS (RR=2.9; p<0.001). However by multivariate regression analysis, in which all univariate predictors of cardiovascular mortality were included, high plasma UrAc levels were not associated with the 5-year outcome in both STEMI (p=0.7) and NSTACS (p=0.9).
Conclusions: The results of the BIAS study have shown that an elevated plasma UrAc level upon admission reflect a more severe baseline risk profile in pts with either STEMI or NSTACS but it is not independently related to long-term mortality in these patients.

P3437 Early invasive treatment benefits patients with mild to moderate renal dysfunction and unstable coronary artery disease

N. Johnston[1], T. Jernberg[2], B. Lagerqvist[3], L. Wallentin[2]. *[1]Akademiska Sjukhuset, Department of cardiology, Uppsala, Sweden; [2]Uppsala Research Center, Uppsala, Sweden; [3]Dept of Cardiology, Uppsala, Sweden*

Background: Renal dysfunction is associated with a worse prognosis in patients with unstable coronary artery disease (CAD). The effects of an early revascularisation in relation to different levels of renal function are unknown.
Methods: The study population consisted of 2457 patients with unstable CAD included in the Fast Revascularisation during Instability in Coronary artery disease trial (FRISC-II). In this trial patients were randomized to an early invasive or non-invasive strategy. The patients were stratified according to levels of estimated creatine clearance (<60 ml/min, 60-90 ml/min, >90 ml/min) and followed for 2 years with regard to death and/or myocardial infarction (MI).
Results: In the non-invasive cohort the rate of MI at 2 years was 19.7% (<60 ml/min), 13.0% (60-90 ml/min) and 8.2% (>90ml/min). In the invasive cohort, there was a reduction in the rate of MI to 12.1% (p=0.023) in patients with creatinine clearance <60ml/min and to 7.3% (p=0.001) in patients with creatinine clearance 60-90ml/min but not in those with creatinine clearance >90ml/min (9.9%). No differences were apparent in mortality rates according to treatment strategy and creatinine clearance stratification. For the combined endpoint of death and MI the findings were similar as with the rate of MI. In a logistic regression analysis including well-known variables associated with prognosis in this patient population, creatinine clearance <60ml/min remained independently associated with the risk for future MI in the non-invasive group (Odds ratio 2.64, 95% CI:1.33-5.21) but not the invasive group (Odds ratio 1.27, 95% CI:0.55-2.94).
Conclusion: An early invasive treatment strategy reduces the long-term risk of future MI in patients with unstable CAD and mild to moderate renal dysfunction.

P3438 Acute coronary syndromes patients ultimately requiring coronary artery bypass surgery remain difficult to predict

D. Chew[1], P. Aylward[2], H.D. White[3], Z. Huang[4], J.W. Hoekstra[5], K.W. Mahaffey[4] on behalf of the SYNERGY Trial Investigators. *[1]Flinders Medical Centre, Cardiovascular Medicine, Adelaide, Australia; [2]Flinders Medical Centre, Adelaide, Australia; [3]Greenlane Hopsital, Auckland, New Zealand; [4]Duke Clinical Research Institute, Durham, United States of America; [5]Wake Forest University Health Sciences, Winston-Salem, United States of America*

Purpose: Current ACC/AHA Guidelines suggest that high-risk acute coronary syndrome (ACS) patients without ST-segment elevation should be treated with antithrombotic therapies and early invasive management with revascularization including coronary artery bypass grafting (CABG). We analysed the SYNERGY database to determine if baseline characteristics can predict which patients would ultimately require CABG.
Methods: 9902 patients from the database (92% undergoing angiography) were studied, including patients requiring CABG at any time after the index angiogram. Logistic regression modelling was used to assess baseline demographics and clinical factors as predictors of need for CABG.
Results: See table. CABG was undertaken in 1793 patients (18.1%). The overall logistic regression model has modest discriminatory ability to predict ACS patients likely to require CABG (c-index 0.68).

	Odds Ratio	95% CI
Interaction: black race/Latin America region	2.35	1.11-4.98
Male sex	2.04	1.79-2.33
Weight less than or equal to 60 by 10 kg	1.57	1.14-2.17
ST depression on baseline ECG	1.35	1.20-1.52
History of diabetes	1.33	1.18-1.50
History of prior angina	1.32	1.17-1.48
History of hypertension	1.18	1.04-1.33
Weight > 60 by 10 kg	0.94	0.91-0.98
Latin America	0.89	0.69
ST elevation on baseline ECG	0.80	0.67-0.95
Clopidogrel prior to admission	0.74	0.57-0.95
Black race	0.70	0.55-0.89
History of prior PCI	0.63	0.54-0.74
Australia/New Zealand	0.55	0.41-0.75
Europe	0.40	0.34-0.48
History of prior CABG	0.25	0.2-0.3

Conclusions: It is difficult to predict which ACS patients with will require CABG. This has potential implications for the initial management with long-acting antithrombotic agents before coronary anatomy is defined.

P3439 Do patients with acute coronary syndromes admitted to non-PCI hospitals have worse short-term outcome? Results from the PL-ACS Registry

M. Gasior[1], L. Polonski[1], M. Gierlotka[1], T. Zebik[1], Z. Kalarus[2], M. Zembala[3], G. Opolski[4]. *[1]Silesian Center for Health Disease, III Cardiology Dept. Silesian School of Med., Zabrze, Poland; [2]Silesian Centre for Heart Disease, I Card. Dep. Silesian School of Med., Zabrze, Poland; [3]Silesian Centre for Heart Disease, Cardiac Surgery Dept., Zabrze, Poland; [4]Warsaw Medical University, Department of Cardiology, Warsaw, Poland*

Background: Guidelines recommend early invasive strategy in unstable angina (UA)/non ST-elevation myocardial infarction (NSTEMI) and primary angioplasty in ST-elevation myocardial infarction (STEMI). We set up a prospective, population-based registry of acute coronary syndromes (ACS) in Poland to assess treatment strategy and determine the outcome in unselected pts.
Methods: Between October 2003 and September 2004 a total of 72 hospitals in Silesia (population of 4,8 million) prospectively collected data of each pt admitted with ACS.
Results: There were 14581 reported admissions of ACS pts in all hospitals. Pts were hospitalised for UA in 44.1%, NSTEMI in 21.2%, and STEMI in 34.7%. Sixty-six hospitals without PCI facilities admitted 63.9% of pts; 15.3% of them were transferred to one of the 6 PCI centres for further treatment within 48 hours. The remaining 36.1% of patients were directly admitted to PCI centres and early angiography was performed in 95.0% of them. The outcomes in relation to treatment strategy and type of ACS are shown in the table.

Table

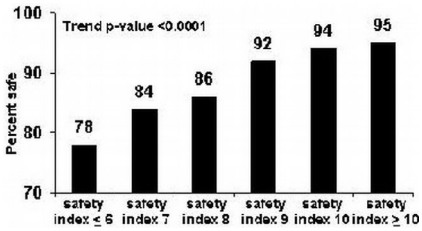
N=14 581	Non-PCI Hospitals		PCI Hospitals	
	Conservative (N=7889)	Transport to PCI hospitals (N=1428)	Conservative (N=265)	Immediate coronary angio (N=4999)
UA (N=6425)	53.9%	5.4%	2.4%	38.3%
In-hospital death or MI	3.1%	1.7%	2.7%	0.7%
30-day mortality	3.0%	2.5%	2.7%	1.1%
NSTEMI (N=3090)	72.7%	10.8%	1.1%	15.4%
In-hospital death or MI	12.2%	5.1%	18.2%	5.7%
30-day mortality	11.2%	7.1%	24.2.%	5.3%
STEMI (N=5066)	43.0%	14.7%	1.6%	40.7%
In-hospital death or MI	20.9%	6.5%	29.6%	5.6%
30-day mortality	24.6%	8.7%	36.4%	7.2%

Conclusion: Patients with acute coronary syndromes benefit most if they are admitted directly to PCI hospitals and had coronary angiography performed. However transport to PCI hospitals noticeably improve the short-term outcome of ACS patients admitted to non-PCI hospitals.

P3440 Deriving a safety index from the GRACE risk score

D. Brieger[1], O. Dabbous[2], K.A. Eagle[3], A. Budaj[4], A. Avezum[5], C.B. Granger[6], B. Costa[7], P.G. Steg[8] on behalf of the GRACE Investigators. *[1]Concord Hospital, Coronary Care Unit, Concord, Australia; [2]University of Massachusetts, Worcester, United States of America; [3]University of Michigan Health System, Ann Arbor, United States of America; [4]Grochowski Hospital, Warsaw, Poland; [5]Dante Pazzanese Inst. of Cardiology, São Paulo, Brazil; [6]Duke University Medical Center, Durham, United States of America; [7]Concord Hospital, Coronary Care Unit, Concord, Australia; [8]Hôpital Bichat, Paris, France*

Background: Acute coronary syndromes (ACS) contribute a significant burden to health care systems yet the majority of these patients experience an uncomplicated clinical course. We sought to develop a model to identify patients that could be managed safely in a less resource intensive environment than the coronary care unit.
Methods: We analysed 7203 patients with non STEMI ACS at presentation in the lowest tertile of risk using the GRACE risk score for in-hospital mortality (c-stat=0.83) to determine predictors of freedom from in-hospital events (MI, dysrhythmia, CHF, major bleeding, stroke or death). A safety index was developed, validated in the higher risk GRACE cohort and in other low risk ACS cohorts identified using the ESC model (no recurrent chest pain, cardiac marker elevation, or ST changes) and TIMI risk score (=2).
Results: The six safety index predictors were: Killip class I (odds ratio (OR, 95%CI) of 3.6, 2.43-5.36), no initial cardiac enzyme elevation (OR 2.0, 1.69-2.44), no prior CHF (OR 2.5, 1.83-3.32), prior PCI (OR 1.5, 1.18-1.80), no prior diabetes (OR 1.4, 1.17-1.70), and initial serum creatinine (OR 1.1, 1.02-1.23 per 1mg/dl decrease). The c-stat of the model was 0.64. This model showed better discrimination when validated in the higher GRACE risk, the TIMI low risk, and in the ESC low risk cohorts (c-stat=0.72, 0.76, and 0.75). Variables from this model were used to derive a 'safety index score' (figure) which can be used to predict freedom from an adverse event in individual patients.



Safety index

Conclusions: The GRACE safety index identifies patients across the entire spectrum of ACS who will have an uncomplicated in hospital course. This index predicts patients who may be considered for immediate triage to step down cardiac or non-cardiac beds.

P3441 Impact of anaemia and mild renal insufficiency in patients undergoing direct percutaneous coronary intervention for acute coronary syndromes

R. Iijima[1], H. Itaya[2], M. Yamamoto[2], R. Nakajima[2], T. Tsunoda[2], M. Nakamura[2]. *[1]Toho University School of Medicine, Third Department of Internal Medicine, Tokyo, Japan; [2]Toho University School of Medicine, Third Dept. of Internal Medicine, Tokyo, Japan*

Background: Anemia and mild renal insufficiency (MRI) are associated with an adverse mortality risk in patients with undergoing elective percutaneous coronary intervention (PCI). However, the impact of anemia and MRI in patients with acute coronary syndromes undergoing direct PCI remains unknown. We sought to investigate whether "Anemia" and "MRI" at the time of PCI predicted In-hospital mortality.
Methods: We analyzed the in-hospital mortality in 418 consecutive patients (age 66 $\pm$ 12 years, 93 women) admitted due to acute coronary syndromes between Jan 2000 and August 2004. Creatinine clearance (CrCl) was determined using Cockroft-Gault equation and MRI was defined as CrCl $<$ 60ml/min at the nearest time point to PCI. Patients on dialysis were excluded. Hematocrit (Ht) $<$ 35% was defined as anemia. These patients were grouped into one of four categories based on CrCl and Ht.
Results: In-hospital death was present in 27 patients (6.5%). Anemia and MRI at baseline were present in 22.7% and 36.4% respectively. In-hospital mortality was 13.8% (21/152) for patient with MRI compared to 2.3% (6/266) for those without MRI ($p < 0.0001$). Similarly a significant rise in mortality was seen with lower Ht (12.6% at Ht $<$ 35%, and 3.7% at Ht $\geq$ 36%, $p = 0.01$). The prevalence of anemia and MRI independently predicted In-hospital mortality (Table 1).

Table 1. In-Hospital Mortality

	CrCl		CrCl $\geq$ 60		p value
	Ht $<$ 35 (n = 64)	Ht $\geq$ 35 (n = 88)	Ht $<$ 35 (n = 31)	Ht $\geq$ 35 (n = 235)	
In-Hospital Mortality, %	15.6	12.5	6.5	1.7	$<$ 0.0001

CrCl: Creatinine clearance (ml/min), Ht: Hematocrit (%)

Conclusion: "Anemia" and "MRI" in patients with acute coronary syndromes undergoing direct PCI is strongly associated with In-hospital mortality. The combined use of these risk indicators is important in identifying patients at high risk for adverse outcomes.

P3442 Very early high-dose Atorvastatin therapy implements outcomes in patients with non ST-segment elevation acute coronary syndromes

A. Conti[1], F. Pieralli[2], L. Sammicheli[2], A. Camaiti[2], S. Raveggi[2], L. Giabbani[2], C. Biagioni[2], G. Bini[2]. *[1]E.D. Careggi Hospital, Emergency Dept., Florence, Italy; [2]Emergency Medicine, Careggi General Hospital, Florence, Italy*

Background: Aspirin, heparin, clopidogrel, and anti-ischemia drugs reduced the risk of coronary events (CE) in patients (pts) recognized as having non ST-segment elevation acute coronary syndromes (NSTEACS), however, a substantial risk of CE still remain in both short and long-term. Atorvastatin added to standard therapy have been shown to reduce CE in patients with NSTEACS; also Tirofiban reduced the incidence of early CE, mainly among patients managed by invasive strategy. Thus, we sought to compare the effects of Atorvastatin or Tirofiban randomly added to the recommended therapy in NSTEACS pts.
Patients and Methods: In the year 2002, 295 consecutive NSTEACS pts (mean age 71 y) with chest pain and ischemic ECG, and/or elevated troponin I (cTnI), and/or new wall motion abnormities at echocardiogram were enrolled into the study. Patients were followed up for in-hospital and 12-month CE (recurrent episodes of ischemia, nonfatal-MI, death, and major bleedings). Within 12 h from admission, pts received 40 mg/day Atorvastatin (group A), or Tirofiban up to 48 h (group B); control patients in Group C.
Results: Baseline characteristics of group A (n=99), group B (n=98), and group C (n=98) were similar. Only 33% of enrolled pts presented mild to moderate hypercholesterolemia. Revascularization procedures performed were similar among groups (>70%). In-hospital major bleeding occurred in 8% of group B pts as compared with 1% and 3% of group A and C, respectively. Overall CE in group A pts were far better as compared with patients of group B and C, both in short-term (-54%: 29% vs 13%, p<.01; and –58%: 29% vs 32%, p<.02, respectively), and long-term (-37%: 25% vs 40%, p<.03; and –44%: 25% vs 44%, p<04, respectively). Of note, reduction of in-hospital CE were mainly driven by recurrent episodes of ischemia (group A versus B: 9% vs 20%, p<.03), and versus group C (9% vs 17%). Also hard events including death, nonfatal MI, and major bleedings were far better in group A (group A versus C: 5% vs 14%, p<.05; and versus group B: 5% vs 10%).
Conclusions: In NSTEACS pts, very early high-dose Atorvastatin independently of hyperlipemia was associated with overall improvement in short and long-term outcomes as compared with Tirofiban and controls (short term:-54%, and –58%, respectively; and long term: -37%, and –44%, respectively). Thus, aggressive lipid lowering could be a cost/effective attractive option among the spectrum of different treatment strategies that can be associated with standard therapy in NSTEACS pts.

P3443 (W) Beneficial effects of platelet glycoprotein IIb/ IIIa inhibitors in non-ST elevation acute coronary syndromes are independent of patient age: a subgroup meta-analysis

A.V. Hernandez Diaz[1], C.M. Westerhout[2], E.W. Steyerberg[1], J.P.A. Ioannidis[3], H. Bueno[4], M.L. Simoons[5], E. Boersma[5]. *[1]Erasmus University Medical Center, Dept. of Public Health, Rotterdam, Netherlands; [2]University of Alberta, Department of Cardiology, Edmonton, Canada; [3]U. of Ioannina School of Medicine, Department of Hygiene and Epidemiology, Ioannina, Greece; [4]Hospital U. Gregorio Maranon, Department of Cardiology, Madrid, Spain; [5]Erasmus University Medical Center, Department of Cardiology, Rotterdam, Netherlands*

Abstract withdrawn.

P3444 Randomised comparison of upstream tirofiban versus downstream high bolus dose tirofiban or abciximab on tissue-level perfusion and troponin release in acute coronary syndromes

L. Bolognese, G. Falsini, F. Liistro, P. Angioli, K. Ducci, T. Taddei, S. Baldassarre, A. Burali. *San Donato Hospital (USL 8), Division of Cardiology, Arezzo, Italy*

Background: Optimal timing and dosage of glycoprotein IIb/IIIa inhibitors for acute coronary syndromes (ACS) remain to be explored.

Methods and Results: We randomized 93 high risk ACS patients undergoing percutaneous coronary intervention (PCI) to receive upstream (in the coronary care unit) tirofiban, downstream (just prior PCI) high dose bolus (HBD) tirofiban; and downstream abciximab. We evaluated the effects of the 3 drug regimens on tissue-level perfusion using the corrected TIMI frame count, TIMI myocardial perfusion grade (TMPG), and myocardial contrast enhancement by intracoronary myocardial contrast echocardiography (MCE) before and immediately after PCI, and postprocedural cardiac Troponin I (cTnI). TMPG 0/1 perfusion was significantly less frequent with upstream tirofiban regimen compared with HBD tirofiban and abciximab both before (28.1% vs 66.7% vs 71%, respectively; p=0.0009) and after PCI (6.2% versus 20% versus 35.5%, respectively; p=0.015). Upstream tirofiban was also associated with a significantly higher MCE score index (0.88±0.18 versus 0.77±0.32 versus 0.71±0.30, respectively; p=0.012). Postprocedural cTnI elevation was significantly less frequent among patients in the upstream tirofiban group compared with HBD Tirofiban and abciximab group (9.4% versus 30% versus 38.7%, respectively; p=0.018). cTnI levels after PCI were significantly lower with upstream Tirofiban regimen compared with HBD Tirofiban (3.8±4.1 versus 7.2±12; p=0.015) and abciximab (3.8±4.1 versus 9±13.8; p=0.0002)
Conclusions: in high risk NSTE-ACS, an early invasive strategy with upstream tirofiban is associated with improved tissue level perfusion and attenuated myocardial damage.

P3445 Combination therapy with angiotensin-converting enzyme inhibitor and angiotensin receptor blocker with early statin administration in patients admitted to a coronary unit for unstable angina

R.S. Gabrielyan[1], A.V. Davtyan[1], A. Gabrielyan[2]. *[1]Yerevan, Armenia; [2]Yerevan, Armenia*

Aims: To evaluate the "synergy" of atorvastatin(At) and combined administration of an perindopril(Pe) and candesartan(Ca) in reducing morbidity and mortality in patients with unstable angina(UA) in hospital period.
Methods: We studied 120 consecutive patients admitted for UA in coronary care unit(CCU)(mean age 58,2±7.4years). Patients were divided into 4 groups according to treatment: Group A (n=30; At 40mg + Pe 4mg + Ca 4mg), group B (n=30; At 40mg + Ca 4mg), group C (n=30; At 40mg + Pe 4mg), group D (n=30; Pe 4mg + Ca 4mg). The value of high-sensivity C reactive protein (hsCRP), low-density lipoprotein-cholesterol(LDL-C) were analysed at baseline and at 21 day. The end point was defined as death, recurrent angina or nonfatal MI, need for coronary intervention, whichever occurred in hospitalization. 21 days after admission patients underwent echocardiography to determine left ventricular end systolic volume (ESV),transmitral velocity E, A and E/A ratio.
Results: Patients in all 4 groups were similar with regard to age, sex, risk factors, ESV, E/A.
During 21 days there were 56 end points; 6 (10,7%) in group A, 11 (19,6%) in group B, 16 in group C (28,5%) and 23 events in group D (41,0%). The relative risk reduction (RRR) in end point in group A was 31% (p=0.01) in comparision to group B, 35% (p=0.001) to group C and 63% (p<0.0001) to group D. Combination of At with Ca and Pe significantly reduces cardiovascular events than At + Ca or At + Pe and considerably more than patients were treated with combination of Ca + Pe. 75% of patiens showed increased levels of (hsCRP) (>2mg/l). Mean (hsCRP) levels were sifnificantly reduced in group A with 36% reduction (p=0.001), and 22% reduction observed in group B (p=0.03), 20% reduction in group C (p=0.02). There was a trend toward reduction of hs-CRP level in patients treated with combination of Pe + Ca (p=0.10). The reduction in LDL-C was similar in group A, B and C compare with baseline levels (p<0.05). After 21 days following treatment, group A patients had smaller ESV than patients in group B and C.Unchanged ESV was seen in patients treated with combination of Pe + Ca. E/A was increased in 20% in group A compare with initial rate and tended to be higher in group A compare with group B, C and D.
Conclusion: The combination of atorvastatin 40mg with candesartan 4mg plus perindopril 4mg demonstrated superioty in reducing hsCRPin UA and it appears that this combination has more effect on ESV, E/A and reduction of endpoints.

P3446 Benefits of intensive drug regimen on six-month mortality in patients with definite non-ST elevation acute coronary syndrome in the nationwide population based study, the DESCARTES registry

M. Heras[1], H. Bueno[2], A. Bardaji[3], A. Fernandez-Ortiz[4], H. Marti[5], J. Marrugat[5] on behalf of The DESCARTES Investigators. *[1]Hospital Clinic of Barcelona, Cardiology Department, Barcelone, Spain; [2]Hospital Gregorio Marañón, Cardiology Department, Madrid, Spain; [3]Hospital Joan XXIII, Cardiology Department, Tarragona, Spain; [4]Hospital Clinico San Carlos, Cardiology Department, Madrid, Spain; [5]IMIM, Cardiology Department, Barcelone, Spain*

Objectives: To analyze the relationship between the intensity of treatment and 6-month mortality of patients diagnosed of Non-ST elevation acute coronary syndrome (NSTEACS) in the DESCARTES registry performed in April and May 2002 in Spain.
Methods: 45 randomly selected hospitals out of 165 hospitals treating ACS included 1606 patients with the definite diagnosis of NSTEACS patients. There was a 6-month follow-up. High-risk patients (n= 478) have been defined as those presenting with troponin positive and ST changes on the admission ECG. An optimization treatment score ranging from 0 to 6 was created according to the following class I recommended treatment strategies: antiplatelet agents, beta blockers, IIb/IIIa receptor blockers, revascularization, ACE inhibitors and statins.
Results: Table 1 shows baseline clinical characteristics and 6-month mortality (for patients discharged alive from hospital) in each treatment score <2,2-3 and ≥ 4. After adjusting for variables shown in the table, the odds ratio (and 95% C.I.) of six-months death for patients with a treatment score of 2-3 compared with those with and score ≥ 4 was 2.29 (1.07-4.88), p=0.032 and 3.42 (1.43-8-18), p=0.006 for those with a score <2.

Table 1

	<2	2-3	≥4	P trends
Age	70.8 (12.4)	67.7 (11.2)	64.9 (11.4%)	<0.001
Diabetes	71 (26.7%)	249 (29.9%)	160 (37%)	0.002
Hypertension	136 (51.5%)	506 (60.9%)	298 (69%)	<0.001
Previous CVD	176 (65.9%)	628 (75.1%)	337 (78%)	0.001
High risk pts	69 (25.7%)	215 (25.6%)	147 (34%)	0.006
6-months death	19 (7.8%)	39 (4.9%)	9 (2.2%)	0.001

Conclusions: Older patients received significantly less optimal treatment. A significant trend to administer more intensive treatment regimens for patients with associated conditions that impact outcome was measured. Patients who received "gold-standard" treatment had significantly lower 6-month mortality. Intensity of treatment was an independent predictor of death after adjusting for age, diabetes, hypertension, previous CVD and troponin positive + ST changes at admission.

P3447 Magnetocardiography predicts coronary artery disease in bundle branch block patients presenting with acute chest pain

J.W. Park[1], P.M. Hill[2], K. Tolstrup[3], M. Hien[1], U. Gerk[4], F. Jung[1]. *[1]Hoyerswerda Hospital, Cardiology, Hoyerswerda, Germany; [2]Johns Hopkins University, Baltimore, United States of America; [3]Cedars-Sinai Hospital, UCLA, Los Angeles, United States of America; [4]Hoyerswerda Hospital, Cardiology Dept., Hoyerswerda, Germany*

Background: 12-lead ECG is non-diagnostic in left and right bundle branch block (BBB) patients with non-ST-elevation acute coronary syndrome (NSTE-ACS). Because of an unique sensitivity for detecting local current disturbance, which early occurs in the cascade of myocardial ischemia, magnetocardiography (MCG) may be useful for ischemia detection in NSTE-ACS patients with BBB.
Methods: Sensitivity and predictivity of admission resting-MCG (CMI 2409, CardioMag Imaging, Inc., Schenectady, USA) for the presence of coronary artery disease (CAD) were prospectively evaluated in 525 consecutive patients presenting with acute chest pain and without ST-segment elevation. Admission MCG findings were compared with admission 12-lead ECG, echocardiography (ECHO), and troponin-I in a head-to-head design. Coronary angiography (CA) performed within 36 hours was used for CAD diagnosis.
A subgroup of 56 patients (11%) presented with BBB (LBBB, n=29; RBBB, n=27; m:35; f:21). Magnetocardiograms were evaluated in a blinded fashion without knowledge of patient's history, troponin I, echocardiographic, and CA findings.
Results: Specificity (SPE), Sensitivity (SEN) as well as Negative (NPV) and Positive (PPV) Predictive Value of the 3 diagnostic tests at admission for the recognition of CAD in BBB-patients with acute chest pain shows the following table.

	Bundle	Branch	Block		LBBB			RBBB	
	MCG	Trop I	Echo	MCG	Trop I	Echo	MCG	Trop I	Echo
	n=56	n=56	n=56	n=29	n=29	n=29	n=27	n=27	n=27
SPE	88%	69%	44%	83%	67%	50%	100%	75%	25%
SEN	87%	45%	64%	88%	53%	75%	87%	39%	57%
NPV	74%	33%	33%	83%	50%	60%	57%	18%	9%
PPV	94%	78%	74%	88%	69%	67%	100%	90%	81%

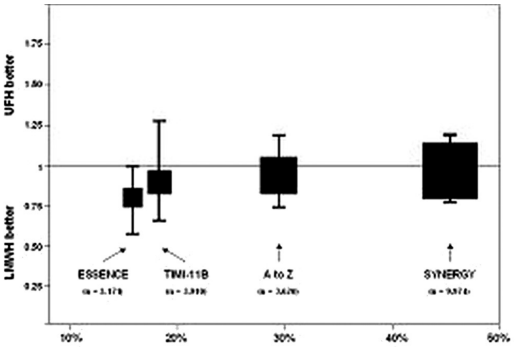
Conclusion: MCG can accurately detect myocardial ischemia in BBB-patients presenting with acute chest pain, a condition, in which ECG is non-diagnostic. For the prediction of CAD in LBBB- as well as in RBBB-patients an admission resting-MCG test was superior to an admission ECHO and troponin-I.

P3448 Benefit of low molecular weight heparin over unfractionated heparin in non ST elevation acute coronary syndromes: role of percutaneous coronary intervention

P.C. Kievit, M.A. Brouwer, F.W.A. Verheugt. *Radboud University Nijmegen Medical Centre, Department of Cardiology, Heartcenter, Nijmegen, Netherlands*

Background: Because of its therapeutic superiority to unfractionated heparin (UFH) and ease of administration low molecular weight heparin (LMWH) has become the standard antithrombin strategy in patients admitted with non ST segment elevation acute coronary syndromes (nSTE ACS) in most facilities. However, in the cath lab UFH is the standard antithrombin agent, and in the recent huge SYNERGY trial LMWH was not superior to UFH in nSTE ACS patients un-

dergoing an early invasive strategy. Therefore, we studied in the previous major LMWH trials with more than 1,000 patients the relationship of LMWH benefit and the proportion of early percutaneous intervention performed.
Methods and Results: The 4 published trials were carried out between 1996 and 2003 and included 20,675 patients with nSTE ACS randomized to LMWH or UFH. Death or myocardial infarction at 30 days were scored on an intention-to-treat basis (95%CI) and correlated to the proportion of percutaneous intervention (figure).



Proportion of PCI

Conclusion: Although the large LMWH trials in nSTE ACS show a reduction in the composite death/MI, a high rate of early percutaneous intervention tends to interfere with the beneficial effect of LMWH as seen in the trials with a more conservative approach. In nSTE ACS patients, in whom early revascularization is intended, routine UFH may be preferable, because of its established role in intervention in general.

P3449 Impact of the ESC/ACC consensus report on re-definition of MI in the Nordic countries

S. Hjortshoj[1], J.E. Otterstad[2], B. Lindahl[3], R. Danielsen[4], K. Pulkki[5], J. Ravkilde[6]. *[1]Cardiovasc. Research Center, Dept. of Cardiology, Aalborg, Denmark; [2]Vestfold Central Hospital, Division of Cardiology, Toensberg, Norway; [3]Uppsala Clinical Research Center (UCR), Dept. of Cardiology, Uppsala, Sweden; [4]Hjartadeild Landspítala Hringbraut, Reykjavik, Iceland; [5]Helsinki University Central Hospital, Laboratory Division, Helsinki, Finland; [6]Skejby Hospital, Dept. of Cardiology, Aarhus, Denmark*

Objective: To evaluate the possible shift in use of cardiac markers in the Nordic countries after the consensus document on diagnosis of myocardial infarction (MI) was published by the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) in year 2000.
Methods and Results: Questionnaires on types of cardiac markers, assays, and cut-off levels for MI were distributed to all relevant departments (N=220) in Denmark, Finland, Iceland, Norway, and Sweden. Of these, 167 (76%) were returned for evaluation. Cardiac troponins I and T (TnI and TnT) and CKMB mass concentration were the predominant markers, covering 93% vs. 65% of all hospitals. Among users of troponins, 34% reported use of TnI vs. 66% using TnT. Older markers such as AST, LD, and CK were only used sporadically (0.6-6%). Myoglobin was used in 3.6% of Nordic hospitals. There was a tendency to lower cut-off levels in Finland and Sweden. Nine different assays of TnI were used as compared to one assay of TnT. For some of these assays, a number of cut-off values were reported. In several cases, cut-off levels were different from the 99th percentile. Also, we identified cut-off values where the coefficients of variability exceeded 10%. Thus, these cut-off values do not meet the recommendations of the ESC/ACC consensus report. Previous national surveys in Denmark (1999), Norway (1995), and Sweden (1998) showed troponin-use in 29%, 3.5%, and 53% of hospitals, respectively. The present survey shows that in year 2004 93% of all Nordic hospitals use troponin testing (Denmark: 96%; Finland: 100%; Iceland: 83%; Norway: 89%; Sweden: 92%). A corresponding decrease was seen in the proportion of hospitals employing CKMB mass concentration and catalytic activity, e.g. Denmark and Sweden, where this proportion decreased from 100% (1999) vs. 82% (2004) and 96% (1998) vs. 77% (2004), respectively.
Conclusions: The Nordic countries approach ESC/ACC consensus on cardiac markers. Compared with national surveys from 1995-1999, there is a clear shift towards the use of troponins. However, differences in cut-off levels for the same assays emphasize the need for harmonization of cut-off values between institutions according to ESC/ACC recommendations.

AMI – ASSESSMENT OF MYOCARDIAL FUNCTION AND PROGNOSIS

P3450 Impact of enhanced platelet reactivity on microvascular reperfusion and left ventricular remodelling in ST-segment elevation myocardial infarction

Z. Huczek[1], J. Kochman[1], K.J. Filipiak[1], R. Piatkowski[1], M. Grabowski[1], G.J. Horszczaruk[1], B. Meier[2], G. Opolski[1]. *[1]Warsaw University Hospital, Ist Chair and Department of Cardiology, Warsaw, Poland; [3]Bern University Hospital, Department of Cardiology, Bern, Switzerland*

Purpose: Platelet reactivity is believed to play an important role in both ischemic and reperfusion phase of myocardial infarction. We tried to determine whether measurement of platelet reactivity on admission may predict impaired microvascular reperfusion and left ventricular remodeling in ST-segment elevation myocardial infarction (STEMI) treated with primary angioplasty (PCI).
Methods: Venous blood samples were collected on admission from 110 patients presenting with STEMI and platelet reactivity (adhesion and aggregation) was estimated with the use of PFA-100 platelet function analyzer (Dade Behring®, Newark, DE) as the time for flowing whole blood to occlude a collagen-adenosine diphosphate ring, with shorter closure times (CADP-CT) indicating greater reactivity. Impaired microvascular reperfusion was defined as myocardial blush grade 0 or 1 (MBG 0/1) on final post-PCI angiogram and the sum of ST-segment resolution $\leq$50% on ECG recorded 30 minutes after PCI relative to the baseline (STR $\leq$50%). An increase of more than 20% in end diastolic volume index (EDVI) at 6-months relative to the baseline value was considered as left ventricular remodeling.
Results: Study population was divided according to median CADP-CT (95 seconds). MBG 0/1 and STR $\leq$50% were significantly more frequent in the inframedian group ($\leq$95 sec.) (55.4% and 48.2%, respectively) compared with supramedian group ($>$95 sec.) (24.1% and 14.8%, $P<0.008$ and $P<0.0002$, respectively). Left ventricular remodeling was present in 56% patients of the inframedian vs. 11.8% of the supramedian group ($P<0.0001$). In multivariate logistic regression model, after adjusting for baseline characteristics including major predictors of abnormal microvascular reperfusion and left ventricular remodeling CADP-CT $\leq$95 seconds remained an independent predictor of MBG 0/1 (odds ratio [OR] 5.3, 95%CI [confidence intervals] 2.1-13.5, P=0.0004), STR$\leq$50% (OR 8.9, 95% CI 2.9-27.3, P=0.0001) and remodeling (OR 7.6, 95% CI 2.2-27, P=0.0016). The performance of multivariate models after incorporation of CADP-CT showed improvement with the concordance (C) index increase from 0.76 to 0.78 for MBG 0/1, 0.78 to 0.84 for STR $\leq$50% and 0.83 to 0.9 for remodeling.
Conclusions: Enhanced platelet reactivity estimated by rapid, point-of-care platelet function analyzer (PFA-100) is a strong and early predictor of impaired microvascular reperfusion and left ventricular remodeling in STEMI treated with primary PCI.

P3451 Early pre-hospital administration of abciximab in patients undergoing PCI for acute myocardial infarction: correlation between periprocedural patency infarct related artery and long-term outcome

M.R. Romano[1], F.B. Buffoli[2], R.R. Rosiello[2], C.L. Lettieri[2], M.A. Aroldi[2], H.K. Kouwornu[2], N.B. Baccaglioni[2], R.Z. Zanini[2]. *[1]Mantova, Italy; [2]C. Poma Hospital, Cardiology, Mantova, Italy*

Introduction: well known is the tight correlation among periprocedural patency of infarct related artery, optimal reperfusion and better long term outcome of patients treated by primary PCI with early pre-hospital admistration of Abciximab.
Material and Methods: Since 1 May 2001 our province has had an operating network for AMI treatment based on the use of primary PCI for all high-risk infarctions. The network provides connection among the following centers: advanced life support ambulances, 7 hospitals, 3 coronary care units, 1 cath lab on call 24 hours a day for primary angioplasty. This program, through its strong telematic platform, allows early assessment of myocardial infarction, and provides primary angioplasty to all high-risk patients, being fibrinolytic treatment reserved only to the low-risk patients admitted in peripheral hospitals. All of the patients undergoing primary PCI are pre-medicated by an abciximab bolus + infusion. The telematic connection relies by LIFEPACK 12 monitor equipped with manual-semiautomatic cadioverter and they are able to convey ECG by GSM located on ambulances. The study sample included 420 consecutive pts treated between 2001 and 2004 of which 46% (194 pts, Group A) reached our cath lab by our first aid and the 28% (120 pts, Group B) by 118 ambulance while the remaining 26% transferred from peripheric hospitals.
Results: The treatment with Abciximab was present in both groups (83%vs81%, p= n.s.), but the patients transferred by 118 presented a flow TIMI 3 pre-procedure of 20% vs 5% in group A (p=0.0003), a flow TIMI 1-2 pre-procedure of 25% vs 15% (p= 0.03) in group A and a flow TIMI 0 of 54% vs 80% (p= 0.04) in group A. Therefore a 46% (55) of pts transferred by 118 in which the IIb/IIIa administration was pre-hospitalizing presented a complete or partial open AMI artery. If we compare this pts which had a mean treatment time of (121$\pm$30 minutes), to a subgroup of A (65 pts) with similiar mean treatment time (132$\pm$38 minutes), (p= n.s), we observed that the incidence of no-reflow was 12% vs 24% in subgroup A,(p=0,003) and the follow up in 21$\pm$12 months cumulative death, re-AMI

and CHF end point in subgroup A was 22% vs 8% in group B (p= 0,0064).Total mortality was 6% (22 pts): 5.6% in group A vs 7,5% in group B (p= n.s.).
Conclusion: Our data shows the importance of an early pre-hospital admistration of Abciximab in patients undergoing to PCI for Acute Myocardial Infarction and the complete or partial patency of infarct related riduces the incidence of no re-flow and improves the long term outcome of these patients.

P3452 Relationship of infarct size measured by delayed contrast enhanced MRI after primary PCI to plasma creatine-kinase, C-Reactive Protein and the time from onset of symptoms to intervention

J. Haase[1], T. Sommer[2], M. Hackenbroch[2], R. Bayar[3], C. Piancatelli[1], J. Thomas[1], H. Stoerger[1], F. Schwarz[1]. [1]*Klinik Rotes Kreuz, Kardiologisches Centrum, Frankfurt am Main, Germany;* [2]*University, Department of Radiology, Bonn, Germany;* [3]*Hospital, MRI Institute, Frankfurt-Hoechst, Germany*

Background: We investigated the relationship between size of myocardial infarctions assessed by delayed contrast-enhanced MRI after primary PCI, elevation of plasma creatine-kinase (CK), c-reactive protein (CRP), and the time from onset of symptoms to intervention.
Methods: Four to 10 days after immediate PCI in 45 acute STEMI patients (<24h) with stenting of the infarct-related artery and treatment with abciximab (i.c. bolus injection of 0.25mg/kg), we performed gadolinium contrast-enhanced 3D inversion recovery gradient-echo MR sequences with complete coverage of the LV-myocardium in short axis slices. The mass of infarcted tissue based on the volume of hyperenhanced myocardium was calculated and linear regression analysis was performed to assess the correlation between absolute size of infarctions (g) as well as relative size (LV%) with peak values of CK (U/l), CRP (U/l), and time to PCI (h).
Results: There was a significant correlation between absolute size of infarctions (g) and peak CK-values (r=0.72; p<0.001) as well as the relative size (LV%) and peak CK (r=0.77; p<0.001). No correlations were found between absolute size (r=0.33) as well as relative size (r=0.27) of infarctions and peak CRP. There was also no correlation between absolute (r=0.29) as well as relative size of infarctions (r=0.27) and the time from onset of symptoms to PCI.
Conclusions: In patients with acute STEMI (<24h) undergoing immediate PCI with stenting and treatment with abciximab, peak CK values correlated well with infarct size as assessed by delayed contrast-enhanced MRI. There were no correlations between infarct size and peak CRP as well as the time to intervention.

P3453 Optimal bypass timing after an acute myocardial infarction: from a surgical view

A. Kiessling[1], F. Isgro[1], R. Zahn[2], U. Weisse[1], R. Besser[1], W. Saggau[1]. [1]*Cardiac Surgery Department,* [2]*Cardiology Department, Klinikum Ludwigshafen, Ludwigshafen, Germany*

Aim: Optimal timing for coronary artery bypass grafting (CABG) after acute myocardial infarction (AMI) remains controversial. The early CABG may result in reperfusion injury; a delay may risk a second ischemic event.
Methods: We retrospectively examined 5561 patients who underwent on pump CABG between 1993 and 2003, after an AMI (minimum 0 days, maximum 23 years). 5 subgroups were sub-divided for the time of surgical intervention. (I. 0-6 day, II. 7-13 day, III. 14-30 day, IV. 30-45 day, V. 45-60 day).
Results: The inhospital mortality is significantly higher in the earliest intervention group. After a waiting period of 7 days, the survival rate is doubled. The demographic data and preoperative ejection fraction is similar in each subgroup.

		0-6 days	7-13 days	14-30 days	30-45 days	45-60 days
Total	(n)	145	78	104	289	211
30-d mortality	(%)	17,5	8,9	7,8	4,2	7,0
Ejection fraction	(%)	49,7±15,9	50,4±15,4	49,9±15,9	49,2±15,9	51,4±15,1
SF-36	(ps)	498±183	453±206	495±189	471±208	476±195
Age	(ys)	65,3±8,7	62,2±9,6	65,3±11,5	64,8±9,5	64,6±9,1

Conclusion: We conclude, that if ischemia or therapy resistant angina is not present after an AMI and clinical improvement is not increasing, the operative intervention should be done after a period of at least 7 days.

P3454 Post-thrombolysis intracerebral haemorrhage. Data from ARIAM, a Spanish register of acute myocardial infarction

M. Ruiz-Bailen[1], F. Rosell-Ortiz[2], F.J. Mellado-Vergel[2], J.F. Brea-Salvago[1], E. Aguayo-Hoyos[3], L. Rucabado-Aguilar[1], A. Morante-Valle[1], J.A. Rodriguez-Puche[1] on behalf of ARIAM investigators. [1]*Complejo Hospitalario Ciudad de Jaen, Intensive Care Unit, Jaen, Spain;* [2]*Empresa Publica de Emergencias sanitar, Almeria, Spain;* [3]*Hospital Universitario Virgen de las N, Intensive Care Unit, Granada, Spain*

Objective: The purpose of this work is to investigate the predisposing factors of patients with acute myocardial infarction (AMI) treated with thrombolysis, complicated by intracranial haemorrhage (ICH), as well as the factors associated with the mortality of patients whose conditions are complicated by ICH.
Methods: A retrospective study including all the AMI patients listed in the Spanish ARIAM register. Period: June-96/Dec-03. The follow-up period was limited to the time spent in ICU/CCU. Univariate analysis for associations with ICH and for evaluating the differences that there were in patients affected by AMI complicated by ICH, between survivors and those who died. Multivariate analyses; to evaluate the factors related to the development of ICH, and to evaluate the factors associated with the mortality of patients with ICH.
Results: 17 111 patients included. ICH occurred in 151 (0.9%) of patients. The variables associated with the development of ICH were non-smoking, OR 1.462 [1.022 - 2.092], oral beta-blockers, OR 0.488 [0.337 - 0.706], angiotensin-converting enzyme (ACE) inhibitors, OR 0.480 [0.340 - 0.678], the presence of arterial hypertension 4.900 [2.758 - 8.705] and age, with an OR of 2.253 [1.117-4.546] for patients aged 55 – 64 years, an OR of 4.240 [2.276 - 7.901] for patients aged 65 – 74 years, an OR of 4.450 [2.319 - 8.539] for patients between 75 – 84 years and an OR of 2.997 [1.039 - 8.647] for patients above 84 years. The mortality rate of the patients with ICH was 48.3% versus 8.3% in the patients who did not have ICH. Among patients with ICH, in the multivariate study the mortality rate was shown to be associated with age with an OR of 1.086 [1.033 - 1.143], arterial hypertension cardiovascular risk factor with an OR 2.773 [1.216 - 6.324] and the need for mechanical ventilation 4.324 [1.665 - 11.230] or cardiopulmonary resuscitation 12.258 [1.268 - 118.523], while the administration of beta-blockers 0.369 [0.136 - 0.997] or ACE inhibitors 0.367 [0.149 - 0.902] was associated with a reduction in the mortality rate.
Conclusions: Factors associated with the development of ICH in our population are age and arterial hypertension, while smoking and the administration of beta-blockers and ACE inhibitors are associated with a reduction in incidence. Among the patients suffering from AMI complicated by ICH, mortality is associated with age, arterial hypertension, cardiopulmonary resuscitation and the use of mechanical ventilation, while the administration of oral beta-blockers and ACE inhibitors could be associated with a reduction in mortality.

P3455 Similar curves of enzymes revealing necrosis in patients with and without electrocardiographic signs of reperfusion after thrombolysis for myocardial infarction – different significance?

G.P. Tatu-Chitoiu, C. Teodorescu, M. Dan, M. Guran, P. Capraru, R. Niculescu, S. Balanescu, M. Dorobantu. *Spitalul Clinic de Urgenta Floreasca, Sectia Cardiologie, Bucharest, Romania*

Background: 1.Rapid reduction of the ST-elevation by more than 50% from the initial value and a CK/CK-MB peak within the first 12 hours are the ECG and biological currently used bed-side criteria for coronary reperfusion (CR) in thrombolysed patients (pts) for ST-elevation myocardial infarction (STEMI). 2. There are poor data regarding the behaviour and clinical significance of the CK/CK-MB curves in pts without ECG signs of CR.
Objective: To compare the curves of CK/CK-MB and prognosis recorded in thrombolysed pts. with and without ECG criteria of CR and in pts. without thrombolytic therapy for STEMI.
Methods: This prospective study enrolled 368 consecutive pts. treated within the first 6 hours after the onset of STEMI either with thrombolytics (284 pts) or without these agents (84 pts). All pts received aspirin, unfractionated heparin or enoxaparin, beta-blockers and converting enzyme inhibitors. In all pts. a 12 lead ECG was recorded at admission and at every 24 hours thereafter. In thrombolysed pts. additional 12-lead ECGs were recorded before the onset of thrombolysis and every 10 min. for the next 180 min. In all pts the CK and CK-MB levels were measured at admission and at 4, 9, 12, 16, 20, 24, 36, 48, 72 and 96 hours thereafter. A coronaroangiography was performed in day 8-12 after admission in thrombolysed pts.
Results: Similar CK/CK-MB curves were seen in pts. with and without ECG criteria for CR. The CK/CK-MB peak was recorded within the first 12 hours in 79.17% of pts. with and in 69.92% of pts. without ECG signs of CR, respectively(non-significantly diference). By contrast,in 78.56% of non-thrombolysed pts. the CK/CK-MB peak was recorded after 16 hours. The 8-12 day coronary angiography showed similar rates of opened coronary artery tree in pts. with (81.39%)and without (79.66%) ECG criteria of CR. The inhospital mortality was 6.69% in pts with ECG signs of CR, significantly lower than that of 26.00% recorded in pts. without ECG criteria and of 25.00% seen in non-thrombolysed pts.
Conclusions: Similar early peak of CK/CK-MB and rates of 8-12 day opened coronary artery can be seen in thrombolysed pts. with/without ECG criteria of CR. These data suggest that early CK/CK-MB peak and more than 50% reduction of the ST-elevation would indicate a complete coronary and myocardial reperfusion announcing an excelent prognosis.On contrary, early peak of CK/CK-MB without ECG signs of CR could indicate only a coronary reperfusion but not a myocardial one and would be a non-invasive sign of the "no-reflow" phenomenon/severe reperfusion injury resulting in a high mortality.

P3456 Time from symptom onset to fibrynolysis initiation influences outcome in patients with ST-elevation acute myocardial infarction undergoing facilitated percutaneous coronary intervention

D. Dudek[1], A. Dziewierz[2], T. Rakowski[1], N. El-Massri[1], Z. Siudak[1], W. Piwowarska[1], K. Zmudka[1], J.S. Dubiel[1]. [1]*Institute of Cardiology, Jagiellonian University, Krakow, Poland;* [2]*Institute of Cardiology, Jagiellonian University, Krakow, Poland*

Background: Time to reperfusion has a direct influence on survival of patients (pts) with ST-elevation Acute Myocardial Infarction (STEMI) subjected especially to thrombolytic therapy. The impact of time to reperfusion on outcomes after facilitated PCI (Percutanueous Coronary Intervention following early combined fibrinolytic therapy) in STEMI is unknown.
Methods and Results: 262 non shock pts with STEMI <12 h, admitted to remote hospitals with anticipated transfer time to cath lab >90 min were enrolled. All pts received iv bolus of 40 U/kg unfractioned heparin, 15 mg alteplase and 0.25 mg/kg abciximab at the remote hospital and were immediately transferred to angiography. Infusion of alteplase (35 mg/60 min) and abciximab (0.125 μg/kg/min) was continued during transfer.
117 pts (44.7%) received combined fibrinolytic therapy <3 h after pain onset, 101 pts (38.5%) at 3-6 h, 44 pts (16.8%) >6 h. Occluded IRA rates (TIMI 0+1) at initial angiography were similar in the study groups. Immediate PCI significantly improved epicardial flow and myocardial perfusion in all 3 groups. At follow-up of 12 months mortality was highest with the longest time to reperfusion (3.4% (<3 h), 4.0% (3-6 h), 13.6% (>6 h), p=0.027). At 6 months left ventricular ejection fraction (LVEF) was significantly improved in two groups of patients with time to initiation of combined fibrinolytic therapy <6 h after pain onset (see table). The independent predictors of lack of LVEF recovery at 6 months in multivariate analysis were: occluded IRA in initial angiography, diabetes mellitus and time from symptom onset to initiation of fibrinolytic therapy.

Table

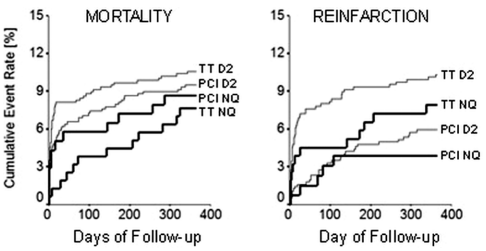
	Total	< 3 h	3-6 h	> 6 h	p=
LVEF at 2-3 days [%]	55.0 ± 9.0	54.5 ± 8.3	55.2 ± 9.7	56.2 ± 10.6	NS
LVEF at 6 months [%]	57.5 ± 11.3	58.6 ± 10.8	58.2 ± 11.2	52.0 ± 12.0	NS
Change in LVEF [%]	2.5 ± 9.0	4.1 ± 8.8	3.0 ± 8.4	- 4.2 ± 8.7	0.006
p=	0.0008	0.0008	0.009	0.078	

Conclusions: Time to initiation of fibrinolytic therapy influences outcome in pts with STEMI undergoing facilitated PCI. In pts with STEMI with time to reperfusion therapy <6 h after pain onset facilitated PCI is associated with low late mortality, and significant improvement of LVEF at 6 months.

P3457 Primary angioplasty is associated with an early hazard but no difference in long-term mortality in patients with the least amount of ST elevation at presentation: results from the DANAMI-2 trial

M. Sejersten[1], G.S. Wagner[2], P. Grande[3], P. Clemmensen[3] on behalf of The DANAMI-2 Investigators. [1]*The Heart Center Rigshospitalet, Copenhagen, Denmark;* [2]*Duke University, Duke Clinical Research Institute, Durham, United States of America;* [3]*Rigshospitalet, The Heart Center, Copenhagen, Denmark*

Introduction: Inclusion criteria for the DANAMI-2 trial were cumulative ST-segment elevation of at least 4 mm in at least 2 of the leads I, aVL, V1-V6 for anterior infarcts and II, III, V5-V6 for inferior infarcts. Nevertheless, some patients not fulfilling these inclusion criteria were included (non-qualifiers).
Hypothesis: Patients meeting the DANAMI-2 inclusion criteria (D2) and non-qualifiers (NQ) have similar long-term benefit with primary percutaneous coronary intervention (PCI) versus fibrinolysis (TT).
Methods: Data analysis was performed in 1445 DANAMI-2 patients with a randomization ECG and corelab ST measurements. The DANAMI-2 inclusion criteria were met by 1149 patients, while 296 patients were NQ. Outcomes were mortality and reinfarction at 30-days and 1-year.
Results: NQ had more prior AMI (15% vs. 10%, p=0.01), more prior PCI (5% vs. 3%, p=0.05), more inferior infarcts (70% vs. 41%, p<0.001), less admission ST elevation (5 mm vs. 14 mm, p<0.001), and lower final QRS score (3.7 vs. 4.3, p=0.02). NQ had a trend towards increased mortality at 30 days in the PCI arm vs. the TT arm (p=0.17, log rank), suggesting an early hazard (figure). This difference disappeared after 1 year (p=0.73, log rank). As expected PCI was associated with fewer reinfarctions compared to TT for both NQ (30-Day: p=0.14, 1-year: p=0.15; log rank), and D2 (30-Day: p<0.0001, 1-year: p=0.005; log rank) (figure).
Conclusions: The results suggest that patients with the smallest ST elevation AMI have an early hazard with PCI compared to treatment with TT, but no increase in 1-year mortality, and fewer reinfarctions.



Kaplan-Meier plots

P3458 TIMI risk score well predicts one year risk of death in patients with ST-elevation myocardial infarction treated with primary PCI

K. Kaminski[1], A. Kozieradzka[1], S. Dobrzycki[1], H. Bachórzewska-Gajewska[2], P. Kralisz[2], W.J. Musial[1]. [1]*Medical University in Bialystok, Department of Cardiology, Bialystok, Poland;* [2]*Medical University, Invasive Cardiology, Bialystok, Poland*

TIMI risk score for ST elevation myocardial infarction (STEMI) was developed in the cohort of patients treated with fibrinolysis. It was though to predict in-hospital and short-term prognosis. Later studies validated this approach in large cohorts of patients, regardless of the applied treatment and presented its good power to predict 30-day mortality. We applied TIMI risk score to our registry of STEMI patients treated with primary percutaneous intervention (pPCI) to validate possibility to predict one year survival.
Our registry comprised consecutive 470 patients (mean age 58.4 ± 11.4 years) with STEMI treated with pPCI who were followed-up for approximately one year (median 430 days). STEMI was diagnosed based on typical criteria: chest pain ECG changes and rise in myocardial necrosis markers. In all patients TIMI risk score for STEMI was calculated and they were divided into three groups: low risk (0-2 points), medium risk (3-5) and high risk (>5 points). Multi-variate logistic regression analysis, Kaplan-Meier survival analysis with Cox and log-rank tests as well as c statistics from receiver-operator curves (ROC) were used for statistical analysis.
TIMI 3 flow was obtained in 94.5% of patients. Average TIMI risk score was (3.67 ± 2.17). During follow-up there were 45 deaths (9.57%). There was statistically significant difference in 30-day survival between both low and medium risk groups and the high risk group (p<0.001 log-rank test). TIMI Risk Score had good power to predict 30-day mortality - C statistics 0.825 (CI 0.748-0.901 p<0.0001). More pronounced differences were noticed in one-year survival: all three groups varied significantly (p<0.001 log-rank test). C statistics for prediction of one year mortality by TIMI Risk Score was 0.802 (CI 0.732-0.871 p<0.0001). Interestingly, when we excluded from analysis all patients who died during first 30 days, TIMI Risk score maintained its very good prognostic value. Both low and medium risk groups had significantly lower mortality than the high-risk group (p<0.001 log-rank test) and the C statistics was 0.744 (CI 0.616-0.872 p<0.0001). In multivariate logistic regression analysis TIMI Risk Score was one of the independent risk factors of death during 1-year follow-up (OR 1.84 CI 1.24-2.74).
TIMI Risk score well defines population of STEMI patients who are at high risk of death not only during first 30 days, but also during long-ter follow-up. This simple score should be included in the discharge letters because it contains very useful information for further care.

P3459 G894T polymorphism on endothelial nitric oxide synthase gene modifies endothelial cells injury and inflammatory response during the acute phase of premature myocardial infarction

C.A. Antoniades[1], D.M. Tousoulis[2], C. Vasiliadou[1], C. Pitsavos[2], K. Marinou[2], D. Panagiotakos[2], N. Koumallos[2], C. Stefanadis[2]. [1]*Athens, Greece;* [2]*Hippokration Hospital, Cardiology, Athens, Greece*

Genetic polymorphism G894T on endothelial nitric oxide synthase (eNOS) has been associated with increased cardiovascular risk. However its role during the acute phase of myocardial infarction (MI) is unknown.
Aim: We evaluated the effect of G894T polymorphism on the risk for premature MI and on the release of von Willebrand factor (vWF), interleukin-6 (IL-6) and oxidised LDL levels (ox-LDL) during the acute phase of premature MI and one year after the event.
Methods: The study population consisted of 228 patients with first event of premature MI (aged 46.96±0.4 yrs old) and 519 age- and sex- matched controls. One year after the event, 61 patients and 205 controls were recalled for the follow-up study. Blood samples were taken from patients during the acute phase of MI and after 1 year. G894T polymorphism was detected by PCR, and levels of vWF, IL-6 and ox-LDL were determined by ELISA.
Results: The frequencies of GG, GT and TT were 97 (42.5%), 99(43.5%) and 32 (14%) in MI and 255(49.1%), 217(41.8%) and 47 (9.1%) in controls. The risk for MI in TT was 1.840 (95%CI: 1.078 to 3.142) p<0.05 compared to GG+GT and 2.01(95%CI:1.118 to 3.606) p<0.05 compared to GG. Carriers of the T allele had higher vWF levels during the acute phase of MI (121.02±5.47%) compared to GG (84.6±7.1%, p<0.01), an effect that persisted after 1 year (90.4±3.8 vs 73.1±4.6%, p<0.01), while there was no difference between carriers of the T-allele and GG in controls (74.3±3.0% vs 77.5±3.2%). During the acute phase of MI, carriers of the T allele had higher ox-LDL and IL-6 (131.2±6.4 ng/ml and 8.5±0.7pg/ml respectively) compared to GG (101.7± 9.64 ng/ml and 6.2± 0.8 pg/ml, p<0.05 for both), but there was no difference at one year (98.9±6.8 ng/ml

and 3.7±0.43 pg/ml vs 84.6±6.7ng/ml and 3.1±0.3 pg/ml respectively, p=NS for both). No difference was observed in ox-LDL or IL-6 levels between carriers of the T allele (72.4±2.7 ng/ml and 2.07±0.2 pg/ml) and GG (70.4±2.6 ng/ml and 2.27±0.23 pg/ml respectively, p=NS for both) among healthy individuals.
Conclusions: The G894T polymorphism on eNOS gene increases the risk for premature MI, and modifies the response of vascular endothelium during the acute phase of MI by affecting the release of vWF, IL-6 and oxidative stress status, an effect diminished one year after the event.

P3460 Early detection of acute myocardial infarction using heart fatty acid binding protein

C.J. McCann[1], I.B.A. Menown[2], C.G. Owens[2], B.M. Glover[1], M.J. Moore[1], H. Gracey[1], I.S. Young[3], A.A.J. Adgey[1]. [1]*Royal Victoria Hospital, Cardiology, Belfast, United Kingdom;* [2]*Craigavon Area Hospital, Cardiology, Craigavon, United Kingdom;* [3]*Queens University, Medicine, Belfast, United Kingdom*

Purpose: Early detection of myocardial infarction (MI) remains suboptimal. We assessed if early detection of MI would be improved by measuring heart fatty acid binding protein (hFABP), (detected 1.5hrs after symptom onset, peak 6hrs, baseline within 24hrs).
Methods: In a multicentre study, patients presenting with chest pain between Aug 03-Aug 04 were recruited prospectively. Patients were assessed on admission for clinical characteristics, ECG features, cTnT, hFABP, haemostatic markers (d-dimer, fibrinogen), and inflammatory markers (myeloperoxidase, white cell count). A 12hr cTnT sample was also obtained. MI was defined as elevated cTnT (>0.09mcg/L) initially or at 12hrs. Evolving MI was defined as initial cTnT normal but elevated at 12hrs. The predictive value of abnormal clinical/ECG features and elevated biomarkers for evolving MI was determined using logistic regression analysis. McNemar's test was used to compare sensitivities.
Results: Initial and 12hr cTnT were obtained in 255 of the 287 patients recruited. MI was confirmed in 113/255 (44%). Initial cTnT was normal in 182/255 (71%), of which 40 (22%) had evolving MI. Median time from pain onset to initial blood sampling for patients with evolving MI was 2.5hrs. Independent predictors of evolving MI were ST elevation >2mm (p<0.001), hFABP >5mcg/L (p=0.004), and white cell count >10,000/μL (p=0.017). Other clinical/ECG characteristics and biomarkers were not of independent predictive value. Of the 94 patients who presented within 4hrs of symptom onset 46 had MI. The sensitivity of hFABP was 80% (37/46), significantly higher than for initial cTnT (35%, [16/46], p<0.001) (Table 1): the specificity of hFABP was 70%.

Table 1. Comparison of the sensitivity of hFABP and initial cTnT for MI detection by time from onset of symptoms

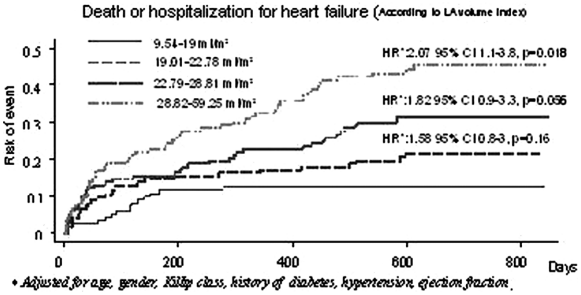
	<4 hrs (n=94)	4-8 hrs (n=65)	8-12 hrs (n=29)	>12 hrs (n=67)
Number with MI	46 (49%)	25 (38%)	9 (31%)	33 (49%)
Sensitivity of hFABP	80%	81%	63%	72%
Sensitivity of initial cTnT	35%	80%	78%	91%
McNemar's test	p<0.001	p=ns	p=ns	p=ns

Conclusions: For patients presenting early after onset of chest pain, hFABP is of significant independent predictive value for detection of evolving MI. Sensitivity of hFABP within the first 4hrs is superior to cTnT for detection of MI.

P3461 Prognostic significance of left atrial volume in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both

M. Amigoni[1], D. Mangalat[1], H. Skali[1], N. Anavekar[1], J.V. McMurray[2], L. Kober[3], J. Ghali[4], S. Solomon[1]. [1]*Brigham and Women's Hospital, Cardiology, Boston, United States of America;* [2]*University of Glasgow, Cardiology, Glasgow, United Kingdom;* [3]*University of Copenhagen Rigshospitale, Cardiology, Copenhagen, Denmark;* [4]*Cardiac Centers of Louisiana, Cardiology, Shreveport, LA, United States of America*

Background: Left atrial (LA) volume is an indirect measure of left ventricular (LV) diastolic function and filling pressure and may be less sensitive to acute hemodynamic changes than Doppler based indices. We assessed the relationship between LA volume index, changes in LV size and function, and cardiovascular (CV) outcomes in patients enrolled in the VALIANT echo substudy.
Methods: VALIANT randomized 14,703 pts with heart failure and/or systolic dysfunction after myocardial infarction (MI) to valsartan, captopril, or both. We studied 496 pts who underwent echocardiography 5.0 ± 2.5 days after MI. LA volume was assessed using the modified biplane Simpson's rule in the apical four-chamber and apical two-chamber views. Measurements were obtained at end systole from the frame preceding mitral
valve opening. Volume was indexed for body surface area and the population was divided into 4 quartiles (LA volume index 9.54-19 ml/m^2; 19.01-22.78 ml/m^2; 22.79-28.81 ml/m^2; 28.82-59.25 ml/m^2). LA volume index was related to LV size, function, and outcomes.
Results: Increased LA volume index was associated with older age, smoking, history of MI, hypertension, diabetes, heart failure and non-Q wave MI (p trend<0.03). LA volume index was significantly greater in patients with increased LV end-diastolic and end-systolic volumes (p for trend <0.001) and lower ejection fraction (p for trend < 0.001). LA volume index was an independent predictor of death or hospitalization for heart failure (LA volume index >28.82 ml/m^2, adjusted HR 2.07, 95% CI 1.13-3.8, p value=0.018).



Kaplan-Meier survival curve

Conclusions: LA enlargment is associated with larger LV volumes, worse LV function, and adverse outcomes in patients with LV dysfunction or heart failure after MI.

P3462 Mean platelet volume predicts impaired angiographic reperfusion and long-term mortality in ST-segment elevation myocardial infarction

Z. Huczek[1], J. Kochman[2], K.J. Filipiak[2], R. Piatkowski[2], G.J. Horszczaruk[2], M. Grabowski[2], B. Meier[3], G. Opolski[2]. [1]*Warsaw University Hospital, Ist Chair and Department of Cardiology, Warsaw, Poland;* [2]*Warsaw University Hospital, Ist Chair and Department of Cardiology, Warsaw, Poland;* [3]*Bern University Hospital, Department of Cardiology, Bern, Switzerland*

Purpose: It has been shown that platelet size, measured as mean platelet volume (MPV), correlates with their reactivity and is predictive of unfavorable outcome among survivors of ST-segment elevation myocardial infarction (STEMI) when measured after the index event. We sought to determine the prognostic value of admission MPV for angiographic reperfusion and 6-month mortality in STEMI treated with primary angioplasty (PCI).
Methods: Blood samples for MPV estimation, obtained on admission in 388 consecutive patients presenting with STEMI were measured before primary PCI. No-reflow was defined as TIMI flow grade <3 on the final angiogram, in spite of residual stenosis <50%, absence of significant dissection, visible thrombus or prolonged spasm in IRA. Additionally, corrected TIMI frame count ≥40 (CTFC≥40) was used to identify patients with impaired reperfusion, as opposed to those with a CTFC<40. The clinical end-point was all-cause mortality at 6 months.
Results: Patients were divided into tertiles based on MPV. The cutoff value for predicting no-reflow (10.3 fL) as identified by receiver operating characteristics (ROC) was identical to the value separating second and third tertile. Thus, the patients were dichotomized (first and second tertile [n=256] vs. third tertile [n=132]) for further analysis. No-reflow was significantly more frequent in patients with high MPV (≥10.3 fL) compared with those with low MPV (<10.3 fL), (21.2% vs. 5.5%, P<0.0001). MPV was correlated strongly with CTFC, (r=0.698, P<0.0001). Kaplan-Meier survival analysis showed 6-month mortality rate of 12.1% in patients with high MPV vs. 5.1% in low MPV group (log rank=6.235, P=0.0125). After adjusting for baseline characteristics in multivariate logistic regression analysis, high MPV remained a strong and independent predictor of no-reflow, CTFC≥40 and mortality (Table 1).

Table 1. Prognostic significance of mean platelet volume (MPV)

	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
No-reflow	4.7 (2.4-9.2)	<0.001	4.9 (2.4-9.9)	<0.0001
CTFC ≥40	8.6 (5.1-14.6)	<0.0001	11.7 (6.5-21.0)	<0.0001
6-month mortality	2.6 (1.2-5.5)	0.015	3.2 (1.4-7.7)	0.0082

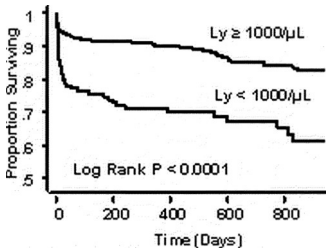
Conclusions: MPV measured on admission, is a strong and independent predictor of impaired angiographic reperfusion and 6-month mortality in patients with STEMI treated with primary PCI.

P3463 Lymphopenia in the early phase of ST-elevation myocardial infarction is a prognostic marker of long-term mortality

R. Dragu[1], D. Aronson[2], R. Zukerman[2], M. Suleiman[2], S. Rispler[2], W. Markievicz[2], M. Kapeliovich[2], H. Hammerman[2]. [1]*Rambam Medical Center, Intensive Cardiac Care Unit, Haifa, Israel;* [2]*Rambam Medical Center, Intensive Cardiac Care Unit, Haifa, Israel*

Introduction: Elevated white blood cell count is associated with adverse prognosis in patients with acute ST-elevation myocardial infarction (STEMI). Myocardial necrosis leads to elevation of polymorphonuclear cell and monocytes. However, a reduction in lymphocyte (Ly) count also accompanies myocardial necrosis. The aim of the present study was to assess the relationship between lymphopenia in the early phase of acute myocardial infarction and long-term prognosis.

Methods: Ly count was obtained within 12-24 h of symptoms onset in a prospective study of 673 patients admitted with ST-elevation infarction (STEMI). Lymphopenia was defined as Ly count < 1000/μL. The relation of Ly count to in-hospital and long-term mortality was evaluated using Cox model, adjusting for age, baseline creatinine, gender, diabetes, hypertension, smoking, prior infarction, Killip class on admission, anterior infarction, and reperfusion therapy.
Results: Lymphopenia was present in 115 patients (17.1%) at admission. During a median follow up of 23 months (range 6-42), 41 patients (35.7%) died in the lymphopenia group, and 75 (13.4%) in the group with normal Ly counts. Kaplan-Meier survival curves indicated that patients with lymphopenia were at increased risk of death (Figure). In a Cox multivariate model, the adjusted RR for death in patients with lymphopenia was 2.2 (95% CI 1.5-3.4, P = 0.005).



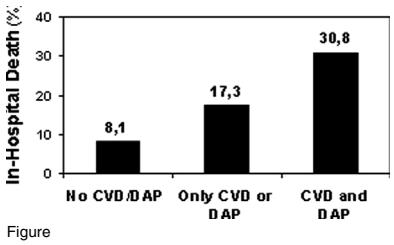
Kaplan-Meier Survival Curve

Conclusion: Lymphopenia in the early phase of STEMI provides prognostic information with regard to long-term risk of death.

P3464 Prior non-coronary atherothrombotic disease has a strong prognostic impact in patients with acute ST elevation myocardial infarction

J.M.S. Ferreira, C. Aguiar, V. Gil on behalf of Investigators of the Portuguese Registry of Acute Coronary Syndromes. *Hospital de Santa Cruz, UNICOR - Servico di Cardiologia, Carnaxide, Portugal*

Background: In patients (Pts) with atherothrombotic disease, the number of involved arterial territories seems to influence the prognosis. We evaluated the prognostic impact of prior history of stroke/transient ischemic attack (CVD) and/or peripheral artery disease (PAD) in Pts presenting with acute ST elevation myocardial infarction (STE-AMI).
Methods: A national registry of acute coronary syndromes collected data from 6121 consecutive Pts with STE-AMI in 2002-2003. The baseline characteristics, treatments, and in-hospital mortality of Pts with prior CVD or PAD were compared to those of Pts without prior CVD and PAD.
Results: Prior CVD was present in 391 Pts (6.4%) and prior PAD in 118 Pts (1.9%). Pts with prior CVD or PAD were older and more likely to have a history of diabetes, hypertension and myocardial infarction. The incidence of heart failure on admission was higher in Pts with prior CVD or PAD. Pts with prior CVD or PAD were less likely to receive reperfusion therapy and beta-blockers and were less frequently submitted to coronariography and revascularization procedures. The in-hospital mortality was 17.4% in Pts with prior CVD, 22.9% in Pts with prior PAD and 8,1% in Pts without prior CVD or PAD. On multivariable analysis, prior CVD (HR 1.45, 1.09-1.98) and prior PAD (HR 2.35, 1.24-4.32) were independently associated with a significantly higher in-hospital mortality. In-hospital mortality increased with the number of involved non-coronary arterial territories (Figure).



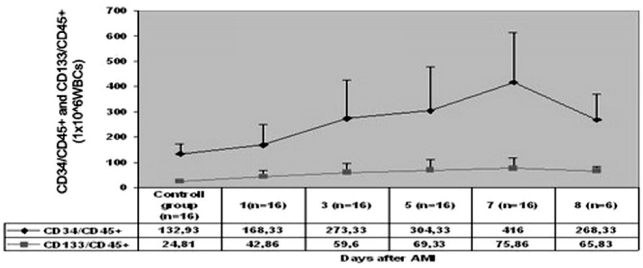
Figure

Conclusions: In Pts who present with STE-AMI the prior history of non-coronary atherothrombotic disesase is a strong independent predictor of in-hospital mortality and is associated with a less aggressive management.

P3465 Kinetic of BM-cEPCs-mobilisation and the correlation with left ventricular function as well as infarct size following acute myocardial infarction

R.G. Turan, M. Brehm, K. Koestering, T. Zeus, T. Bartsch, T. Falke, M. Schannwell, B.E. Strauer. *Heinrich Heine University Duesseldorf, Cardiology, Pneumology and Angiology, Duesseldorf, Germany*

Background: Bone marrow-derived endothelial progenitor cells (BM-cEPCs) are mobilized in adult peripheral blood(PB) and contribute to the regeneration of infarcted myocardium. However, little is known regarding whether the mobilization of BM-derived circulating endothelial precursor cells(CD34+ and CD133+) in to PB depends on left ventricular function and infarct size after acute myocardial infarction(AMI).
Methods: Peripheral blood concentration of CD34/CD45+ and CD133/CD45+ was measured by Flow cytometry in 16 patients on days 1,3,5,7,8 after AMI and in 16 control healthy subjects on day 1 of admission. All AMI patients underwent recanalization of the infarct-related artery by baloon angioplasty. Global EF determined by left ventriculography. Results: Both concentrations of CD34/CD45+ and CD133/CD45+ significantly increased, peaking on day 7. Moreover, the increase of CD133/CD45+ (p=0.019) was earlier significant than the increase of CD34/CD45+ (p=0.29) on day 1 after AMI as compared to the healthy controls. Both concentrations of CD34/CD45+ (p=0.001, r=0.73) and CD133/CD45+ (p=0.04, r=0.51) were significant correlated positively with EF (55±8) and negativly with infarct size (CD34/CD45+: p<0.001 r=-0.81; CD133/45+: p=0.006 r=-0.64) on day 1 after AMI. The peak concentration of CD34/CD45+ on day 7 after AMI was also significantly correlated with EF(p=0.003, r=0.68) as well as infarct size(p=0.007 r=-0.64).



	Control (POD) (n=16)	1(n=16)	3 (n=16)	5 (n=16)	7 (n=16)	8 (n=6)
CD34/CD45+	132,93	168,33	273,33	304,33	416	268,33
CD133/CD45+	24,81	42,86	59,6	69,33	75,86	65,83

Figure 1

Conclusions: Both BM-cEPCs (CD34/CD45+ and CD133/CD45+) are mobilized following acute myocardial infarction in humans and CD133/CD45+ mobilization in response to AMI may be earlier than the mobilization of CD34/CD45+. Moreover, this spontaneus mobilization of BM-cEPCs correlates positively with left ventricular function as well as negatively with infarct size after AMI.

P3466 Absence of preinfarction angina and serum C-reactive protein elevation are predictors of malignant ventricular arrhythmias after acute myocardial infarction

T. Anzai, T. Yoshikawa, Y. Maekawa, Y. Sugano, T. Kohno, K. Mahara, K. Naito, S. Ogawa. *Keio University School of Medicine, Cardiology Department, Tokyo, Japan*

Introduction: Malignant ventricular arrhythmias, such as sustained ventricular tachycardia and ventricular fibrillation (VT/VF), are fatal complications after acute myocardial infarction (AMI). However, VT/VF is not always predictable. The aim of this study is to clarify the determinants of VT/VF after AMI.
Methods: A total of 892 consecutive patients with AMI were examined. Patients' backgrounds, in-hospital complications, coronary angiographic and left ventriculographic findings, peak serum C-reactive protein (CRP) levels and peripheral leukocyte counts, determined by serial measurements (every 24 hours for 4 days), were assessed.
Results: Ninety-two patients (10%) experienced VT/VF during hospitalization. History of prior infarction was more common in patients with VT/VF than those without VT/VF (31 vs 17%, p=0.003). Prevalence of preinfarction angina (53 vs 62%, p=0.008) or use of beta-blockers (47 vs 63%, p=0.01) was less in patients with VT/VF than those without VT/VF. Patients with VT/VF had higher incidence of no-reflow phenomenon (TIMI<3) after primary coronary intervention (p=0.009), pump failure (Killip class≥2 and/or Forrester subset≥II, p<0.0001) and in-hospital cardiac death (p<0.0001) compared with those without VT/VF. Peak CRP level (15.0±10.3 vs 9.2±7.9mg/dl, p<0.0001) and maximum leukocyte count (14155±1913 vs 12084±3747/mm^3, p=0.02) were higher in patients with VT/VF than those without. Predischarge left ventriculography showed lower ejection fraction in patients with VT/VF compared with those without VT/VF (45±16 vs 54±12%, p=0.001). Other patients' backgrounds, such as sex, coronary risk factors, infarct site, number of diseased vessels and pre TIMI flow grade, were not different between the two groups. Multivariate analysis revealed that absence of preinfarction angina (RR=4.07, p=0.002) and peak serum CRP≥10mg/dl (RR=2.42, p=0.04) were independent determinants of VT/VF among variables, including age≥70 years, prior infarction, use of beta-blockers, and post TIMI flow grade<3.
Conclusions: VT/VF after AMI was associated with absence of preinfarction angina, marked serum CRP elevation and worse clinical outcome. Lack of ischemic preconditioning and enhanced inflammatory response might play an important role in occurrence of VT/VF after AMI.

P3467 Can we predict that a patient with an acute coronary syndrome has normal coronary arteries?

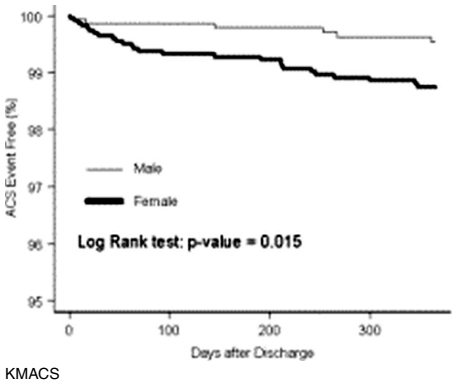
P.F. Monteiro on behalf of the Portuguese Registry of Acute Coronary Syndromes Investigators. *Coimbra University Hospital, Cardiology Dept., Coimbra, Portugal*

Introduction: There is a significant number of patients that underwent coronary angiography during an admission for an acute coronary syndrome (ACS), only to find out that they have normal coronary arteries. Can we predict this result, thus decreasing the number of normal coronary angiographies performed?
Aim: To evaluate, in a population of patients admitted for ACS, independent predictors of a coronary angiography without stenotic lesions.
Population and Methods: Retrospective analysis of a nationwide database containing data from 6992 patients admitted since 2002 in Coronary Care Units or Cardiology wards for ACS and that underwent coronary angiography. This population was subdivided according to the result of that exam: normal (Group A, n=729) or abnormal (Group B, n=6263). Both groups were analyzed regarding demographic, epidemiological and clinical parameters.
Results: Patients from group A were more frequently women than in group B (36.4% vs 25.1%; $p<0.05$) and were also younger (61.3 vs. 64.4 years; $p<0.05$); they had a better risk profile and less previous coronary artery disease (CAD), resulting in a less frequent previous use of cardiovascular therapies. They were less treated with cardiovascular drugs during hospitalization (with the exception of calcium channel antagonists - 20.5% vs. 13.8%; $p<0.05$) and had less frequently severe LV dysfunction (4.2% vs 8.1%; $p<0.05$). The multivariate analysis showed two independent predictors of a normal coronary angiogram: female gender and diastolic blood pressure over 73.5 mm Hg; on the contrary, an age above 48.9 years and the use of glycoprotein IIb/IIIa inhibitors independently predicted significant coronary stenosis.
Conclusion: In patients with ACS that underwent coronary angiography, only two parameters can independently predict a normal coronary angiography: female gender and diastolic blood pressure over 73.5 mm Hg. This means that it is possible, with data from the patient history, to predict the absence of CAD in patients admitted for ACS.

P3468 Angina with normal coronary arteries: sex differences in outcome

K. Humphries[1], C.R. Thompson[2], M. Izadnegahdar[3], C.E. Buller[2], A. Pu[3]. *[1]St Paul's Hospital, Dept. of Cardiology, Vancouver, Canada; [2]St. Paul's Hospital, Medicine/Cardiology, Vancouver, Canada; [3]University of British Columbia, Medicine, Vancovuer, Canada*

Recent evidence from the Women and Ischemic Syndrome Evaluation study demonstrated extensive atheroma by intravascular ultrasound and evidence of myocardial ischemia in women with angiographically normal coronaries. Information on men with normal coronaries is lacking, as is the impact of sex on prognosis. We undertook a population-based analysis of 1-year outcomes in subjects with acute coronary syndrome (ACS), but angiographically normal coronaries.
Methods: All patients in the province of British Columbia (BC) undergoing cardiac catheterization between 2000-2002 for ACS, with angiographically normal coronaries, were included. Those with prior coronary revascularization or non-BC residence were excluded. Demographic, clinical and procedural data were obtained from the BC Cardiac Registry, a registry of all cardiac procedures in BC. Time to hospitalization for ACS was modelled using a Cox model.
Results: Overall, 2198 (23.3%) women and 1449 (7.1%) men had angiographically normal coronaries. Women with normal coronaries were older(median 60 vs 54, $p < 0.001$)had significantly more hypertension (46.8%: 37.8%) prior stroke (4.9%: 3.0%) and COPD (9.4%: 7.3%) than men, respectively. Twenty-six women were hospitalized for ACS within one year of angiography compared with 6 men ($p =0.015$); there were no difference in deaths. After adjustment for baseline differences in age and comorbidities women were still more likely to be hospitalized for ACS (HR 2.67 (95% CI 1.09-6.54).



KMACS

Conclusions: Women with chest pain are 3 times more likely to have angiographically normal coronaries and are 2.8 times more likely to be hospitalized for ACS within 1 year, than men. Further research is required to determine why the prognosis of angiographically normal coronaries differs by sex.

DIAGNOSIS AND PROGNOSIS; CAD

P3469 Prognostic impact of moderate coronary artery disease diagnosed by coronary angiography. A substudy of the MONICA survey

S. Swales[1], J. Duchene[1], G. Wunsch[1], C. Gourdin[1], M. Jeanjean[2], E.S. Schroeder[3]. *[1]Université Catholique de Louvain, Department of Demography, Louvain-La-Neuve, Belgium; [2]Université Catholique de Louvain, Department of Public Health, Bruxelles, Belgium; [3]Cliniques Universitaires de Mont-Godinne, Service de Cardiologie, Yvoir, Belgium*

Non significant coronary artery disease seen at diagnostic coronary angiography is generally considered as a benign expression of atherosclerosis, although there are no large studies to support this thesis.
Aim: To assess the 5-year outcome of patients after diagnostic cardiac catheterization according to the angiographic appearance of coronary arteries.
Methods: The MONICA survey in the Belgian province of Luxemburg allows complete long-term surveillance of a population of 130.000 citizens of this region. In an original substudy of invasive procedures, all coronary angiograms performed on eligible residents of this province (age: 35-74 years) in any Belgian hospital between 1985 and 1996 were analyzed. Fatal and non fatal coronary events were diagnosed according to the WHO MONICA protocol criteria. The following initial diagnoses were made: smooth coronary arteries (group I), moderate (diameter stenosis of less than 50%) disease (group II), single-vessel disease (1 vessel with ? 50% diameter stenosis) not followed by PTCA/CABG (group III). 5-year follow-up is complete with respect to deaths, coronary events and new angiograms. The occurring of following events at 5 years was analyzed: fatal coronary events, non fatal coronary events, PTCA or CABG, worsening of the angiographic appearance of coronary artery stenosis.
Results: The differences on event-free survival at 5 years were highly significant between the 3 groups (table).

Table 1. Event-free survival at 5 years (Kaplan-Meier)

	Group I (smooth) n = 972	Group II (moderate) n = 319	Group III (significant 1-VD) n = 428
Free of fatal coronary events	99.4%	95.3%	93.3%
Free of fatal/non fatal coronary events	98.8%	91.5%	82.3%
Event-free survival	98.2%	87%	79.5%

Conclusion: The angiographic diagnosis of smooth coronary vessels yields excellent prognosis at 5 years. In the presence of moderate coronary artery disease, coronary events will occur in 13% of the patients within 5 years. On the basis of our findings, the general assumption that moderate coronary artery disease bears a benign long-term outcome should therefore be revised.

P3470 Efficacy of an intensive prevention programme in coronary patients in primary care, a randomised clinical trial

J. Marrugat[1], M.A. Munoz[2], J. Sala[3] on behalf of the ICAR Investigators. *[1]Institut Municipal d'Investigacio Medica, Unitat de Lipids I Epidemiologia Cardiov., Barcelona, Spain; [2]Institut Català de la Salut, Barcelona, Spain; [3]Hospital Josep Trueta, Cardiology, Girona, Spain*

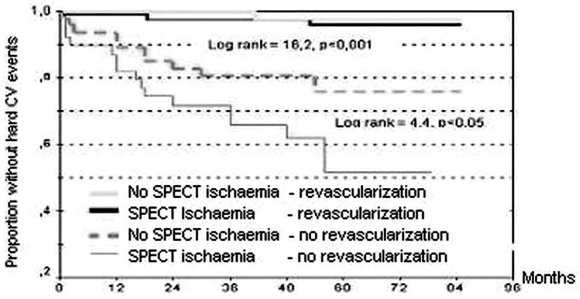
Objectives: To analyse the efficacy of an intensive programme of secondary prevention led by general practitioners to reduce cardiovascular recurrences and mortality and to improve risk factor control, lifestyle, and quality of life for coronary heart disease (CHD) patients.
Design: Three-year follow-up multi-centre randomised controlled clinical trial.
Setting: Twenty-three primary health care facilities in Catalonia, Spain.
Participants: 983 CHD patients age 30-79 without severe mental or physical disability.
Interventions: The 515 patients in the intervention group received a postal reminder to see their general practitioner every three months. At each visit, general practitioner advised about healthy lifestyle, provided informational materials, and adjusted drug therapies. The 468 controls received usual care.
Main outcome measurements: Primary endpoints were cardiovascular events (i.e., myocardial infarction, unstable angina, stroke, coronary revascularisation) and all-cause mortality. Weight, blood pressure, glucose, lipid profile, lifestyle, medications, and quality of life as measured by SF-12 questionnaire were analysed as secondary endpoints.
Results: At three-year follow-up, 67 patients had died and 156 had a non-fatal cardiovascular event. Intervention and control groups did not differ in event rate (3-year Kaplan-Meier 24.0% and 23.5%, respectively) and all-cause mortality (3-year Kaplan-Meier 8.1% and 9.9%, respectively). Improvements in quality of life and number of preventive treatments were similar in both groups. Blood pressure and high-density lipoprotein cholesterol were more frequently within recommended levels in the intervention group than in controls: odds ratio 1.67, 95%

confidence interval 1.08 to 2.57, and odds ratio 2.91, 95% confidence interval 1.44 to 5.88, respectively.
Conclusions: Intensive secondary prevention conducted by general practitioners improved blood pressure control and increased high density lipoprotein cholesterol, but produced no further benefits at three years in other risk factors, quality of life, recurrences, or mortality.

P3471 Revascularisation may improve the patients outcome irrespective of myocardial scintigraphy result

M. Dziuk, A. Kazmierczak, E. Kot, D. Michalkiewicz, M. Cholewa.
Military Institute of Health Services, Internal Medicine and Cardiology, Warsaw, Poland

The impact of myocardial perfusion scintigraphy on coronary artery disease (CAD) treatment in view of long term prognosis has not been investigated.
Aim: to define the preventive or treatment strategies in view of the myocardial perfusion study (SPECT) result in unselected single centre CAD registry patients.
Method: 406 patients with confirmed CAD were examined and prospectively followed-up. Clinical, scintigraphy and angiography data was available and collected in all patients. After the mean of 51±19 months of follow-up the information regarding the outcome and cardiovascular (CV) events were gathered. Kaplan-Meier and multivariate Cox proportional hazards model was used to estimate the risk of CV death, myocardial infarction and brain stroke.
Results: 160 patients (39.4%) experienced the cardiovascular event including 54 deaths. The positive results of myocardial perfusion study we noted in 172 patients. Scintigraphically detected reversible myocardial ischaemia was found to be associated with 2.8-fold (95% confidence interval; 1.5 – 5.2) increased risk of cardiovascular death. The most significant predictive factors for the cardiovascular event were the ejection fraction, positive perfusion scan result and the extent of ischaemia. After 5 years 2/3 of patients with ischaemic scan experienced "hard events" (myocardial infarction, stroke or cardiovascular death), but only 20% of those with negative result had CV complications. In patients with ischaemia the use beta blockers and revascularization reduced the relative risk by 0.4 (0.17-1) and 0,32 (0.12 – 0.52) respectively.



Kaplan-Meier survival curves

Conclusion: The revascularization may improve the outcome even in patients with a negative SPECT result, however it may be most beneficial in subjects with myocardial ischaemia.

P3472 Predicting daily cardiovascular death rate with weather, influenza activity, solar magnetospheric activity, and moon phase in 114164 cases over a 5 year period

P.R. Hunziker[1], R. Osterwalder[2], M. Siegemund[2], M. Pfisterer[3], S. Marsch[2]. *[1]Binningen, Switzerland; [2]Univ.Hospital, Medical Intensive Care Unit, Basel, Switzerland; [3]Univ.Hospital, Cardiology, Basel, Switzerland*

The notion that environmental factors trigger cardiovascular events has only limited scientific support due to problems of statistical power, geographic differences in weather, and sampling problems.
Methods: To yield definitive answers about triggering of cardiovascular deaths, and to explore the possibility of forecasting events, we studied all 114'164 cardiovascular deaths occurring in Switzerland from 1997-2001 by combining
A) the national death registry,
B) the SwissMeteo weather database
C) the Swiss Sentinella influenza data,
D) daily solar activity and magnetosphere data from NASA, and
E) lunar data ("synodic"= moon phase, "anomalistic"=earth moon distance).
Results: Daily cardiovascular death rate was 36 to 114/d (mean 62), a variation not explainable by random variation(Chi-square, $P<0.001$).
In univariate analysis, highly significant associations of daily cardiovascular deaths was found for
– multiple climate variables (e.g., temperature, vapor pressure, barometric changes, snowfall, all $p<0.001$),
– influenza case rate ($p<0.0001$),
– magnetospheric data (sunspot activity, solar flux density; $p<0.001$), and, of borderline significance, for synodic ($p=0.046$) but not for anomalistic moon phase.
Multivariate analysis confirmed an independent impact on deaths of weather, influenza, solar magnetospheric activity, and of marginal importance, moon phase. Correlations of death due to myocardial infarction, heart failure and stroke with environmental data were similar.
In particular, time-shift analysis showed characteristic delays from weather factors to events, with weather conditions 3-7 days before the event of more importance than weather on the event day (except for snowfall and influenza, where no time lag was seen), thus allowing a forecast of expected deaths. A tentative estimation of excess deaths triggered by the environment yielded ~25% on average, but up to 140% excess risk on certain high risk days.
Conclusion: Weather, influenza and solar magnetospheric variables (a new observation) (and to a marginal degree, moon phase) are strongly associated daily cardiovascular death rate. Characteristic time lags from environmental variables to events yield pathophysiologic insights and allow forecasting of risk, thus opening the possibility of climate dependent preventive measures and resource planning.

P3473 Late follow-up after a normal myocardial perfusion scintigraphy

P. Smanio[1], P. Beraldo[2], R. Mello[2], F. Rodrigues[2], A. Thom[2], L. Piegas[2]. *[1]Instituto Dante Pazzanese de Cardiologia, Nuclear Cardiology, Sao Paulo, Brazil; [2]Instituto Dante Pazzanese, Nuclear Cardiology, São Paulo, Brazil*

Background: Studies have already been published, showing a lower risk of cardiovascular events after one year of a normal myocardial perfusion scintigraphy (MPS) in populations without and also with known significant coronary artery disease (CAD).
The aim of this study is to evaluate the follow-up after five years of a normal MPS in high risk of CAD patients (p) with and without known CAD.
Methods: We analyzed a 5 year follow-up of 2.500 p who had performed exercise MPS in 1998. From those 300 studies with normal MPS were selected. Patients were divided in two groups: Group I: 140 p with known CAD, and Group II: 160 p without known CAD. All had achieved at least 85% of the maximal heart rate at the stress. MPS were performed with sestamibi-Tc-99m by tomographic technique. Cardiac death and myocardial infarction were defined as hard events while cardiac bypass surgery, angioplasty/stent implantation and cardiac catheterization were considered soft events. Studies were reported as normal when no perfusion defect after stress was identified.
Results: As summarized in Table I, there was no significant difference (p=0,10) between the 2 groups concerning hard events. In both groups there was a small number of hard events in five years (10/300=3%). Soft events occurred in 35/140 (25%) p of Group I, and in 16/160 (10%) p of Group II ($p<0,05$).

Events rate in pts with and without CAD

	Group I	Group II	
Hard Events	6 (4%)	4 (2,5%)	p=0,10
Soft Events	35 (25%)	16 (10%)	p<0,05

Hard Events: death, IMSoft Events: CABG,PTCAGroup I: pts with CADGroup II: pts without CAD

Conclusion: The results may suggest that even after 5 years, patients with a normal MPS have a low prevalence of hard events. For soft events, our results suggest a higher prevalence in patients with known CAD.

P3474 Incremental predictive value of non-traditional cardiovascular risk factors for severe coronary artery disease

S.C. Seow[1], A.F.H. Low[2], T.C. Yeo[2]. *[1]National University Hospital, Cardiology, Singapore, Singapore; [2]National University Hospital, Cardiology, Singapore, Singapore*

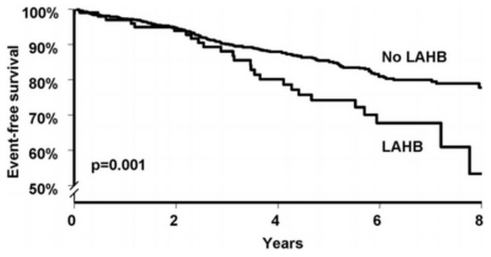
Purpose: The value of non-traditional cardiovascular risk factors like homocysteine, high sensitivity C-reactive protein(hs-CRP) and lipoprotein a (Lpa) in predicting severe coronary artery disease(CAD) is uncertain. We sought to determine if these risk factors have any incremental predictive value compared to traditional cardiovascular risk factors.
Methods: 242 patients presenting for coronary angiography over an 18 month period were recruited. Clinical data as well as serum homocysteine, hs-CRP and Lpa levels were measured. Severe CAD was defined as significant triple vessel or left main coronary artery disease. A traditional cardiovascular risk factor score (TCVRF) was formulated where one point was awarded for the presence of each of the following: male gender, typical angina pectoris, diabetes mellitus, insulin therapy, dyslipdaemia. For each decade above the age of 40 years, one point was added to the score. A separate score (NTRF) was formulated which took into account the non-traditional risk factors. Patients with hs-CRP levels in the uppermost tertile were awarded 2 points. Those in the middle tertile were given one point and the lowest tertile was given 0 points. The same was done for homocysteine and Lpa levels. The NTRF score was the sum of TCVRF and the point scores for hs-CRP, homocysteine and Lpa. Receiver-operator curve (ROC) anal-

ysis was used to assess the accuracy of TCVRF and NTRF in predicting severe CAD.
Results: The study population comprised 61.2% males, mean age 58.4 years. Using a cut-off of 5 points, sensitivity of TCVRF in detecting severe CAD was 80.8% and specificity 54.7%. Negative predictive value was 91.2%. Homocysteine, Lpa and hs-CRP levels did not demonstrate incremental predictive value for severe CAD compared to traditional risk factors (Area under curve 0.726 vs 0.733, p =ns)
Conclusion: Traditional risk factors have a high predictive value for severe CAD. A point score less than 5 had a negative predictive value of 91.2% for severe disease. Novel risk factors like homocysteine, hs-CRP and Lpa did not demonstrate incremental predictive value on top of traditional risk factors. Routine testing for these may result in increased cost with little additional value.

P3475 Prognostic significance of left anterior hemiblock in patients undergoing stress 99mTc-tetrofosmin SPECT for the evaluation of suspected coronary artery disease

A.F.L. Schinkel[1], A. Elhendy[2], S.P. Nelwan[2], R.T. van Domburg[2], A. Huurman[2], E. Biagini[2], J.J. Bax[3], D. Poldermans[2]. *[1]Erasmus Medical Center Rotterdam, Cardiology Dept., Room BA 302, Rotterdam, Netherlands; [2]Erasmus Medical Center Rotterdam, Cardiology Dept., Rotterdam, Netherlands; [3]Leiden University Medical Center, Cardiology, Leiden, Netherlands*

Background: The prognostic implications of isolated left anterior hemiblock (LAHB) in patients with suspected coronary artery disease (CAD) are not clear.
Methods: 1281 patients without previous myocardial infarction underwent resting surface electrocardiography and stress 99mTc-tetrofosmin SPECT for the evaluation of suspected CAD. LAHB was defined as leftward QRS axis of –30 to –90° with rS patterns in lead II, III, aVF, and Q waves in aVL. Follow-up was successful in 1276 (99.6%) patients.
Results: LAHB was present in 221 (17%) patients. Abnormal perfusion was detected in 125 (57%) patients with LAHB, and in 466 (44%) patients without LAHB ($p<0.001$). During the 5.4±2 year follow-up, the cardiac event rate (cardiac death or nonfatal infarction) was significantly higher in patients with LAHB than in patients without (5.4% versus 3.2% per year, P=0.001, see Figure).



Cardiac events according to LAHB

Conclusions: In patients with suspected CAD referred for stress myocardial perfusion imaging, LAHB is associated with an increased risk of cardiac events.

P3476 Multiple inflammatory biomarkers and cardiovascular risk

E. Lubos[1], R. Schnabel[2], H.J. Rupprecht[2], C. Bickel[3], K.J. Lackner[4], T. Muenzel[2], L. Tiret[5], S. Blankenberg[2] on behalf of Blankenberg, S. *[1]Johannes Gutenberg University Clinic, Department of Medicine II, Mainz, Germany; [2]Johannes Gutenberg-University, Departement of Medicine II, Mainz, Germany; [3]Bundeswehrzentralkrankenhaus, Innere Abteilung, Koblenz, Germany; [4]Johannes Gutenberg-University, Clinical Chemistry Medicine, Mainz, Germany; [5]Faculté de Médicine Pitié-Salpétrière, INSERM U525, Paris, France*

Background: Various inflammatory markers have been shown to predict cardiovascular events when considered individually. We hypothesized, that the severity of inflammation reflected by simultaneous elevation of several inflammatory markers might better predict future cardiovascular events than single biomarkers.
Methods: In a prospective study conducted in 1303 patients with coronary artery disease with a mean follow-up of 5.4 (maximum 7.6) years, we assessed the risk of cardiovascular events (n=235) according to baseline levels of inflammatory markers, including acute phase reactants (C-reactive protein, fibrinogen, interleukin-6), proinflammatory cytokines and soluble receptors (interleukin-18, tumor necrosis factor-receptor 1 and 2, interleukin-1 receptor antagonist), soluble adhesion molecules (vascular adhesion molecule-1, intercellular adhesion molecule-1, E-selectin), and matrix metalloproteinase-9.
Results: Among the eleven measured markers, soluble tumor necrosis factor-receptor 2, interleukin-18, soluble vascular adhesion molecule-1, and fibrinogen remained independently associated with cardiovascular outcome. When combining these four markers into a linear score reflecting the number of markers in the top third of the distribution, the score was highly predictive of cardiovascular risk. By comparison to patients having no elevated marker, the hazard ratio of those having one, two, three or four elevated markers was 1.6, 1.8, 3.7 and 7.2 in stable patients ($P<0.00001$), and 1.8, 1.7, 3.5 and 5.1 in patients with acute coronary syndrome (P=0.005) in a fully adjusted model. The score was a better predictor of outcome than any single marker.
Conclusions: Simultaneous assessment of multiple inflammatory markers reflecting different physiological pathways is superior to single marker determinations and adds prognostic information to that conveyed by traditional risk factors.

RISK; NON-CARDIAC SURGERY AND MISCELLANEOUS

P3477 A prognostic risk score to predict outcome after renal transplantation

R. Sharma[1], E. Chemla[2], M. Tome[3], S.J. Brecker[4], R. Chang[2], D. Pellerin[3]. *[1]St George's Hospital, Cardiology, London, United Kingdom; [2]St George's Hospital, Nephrology, London, United Kingdom; [3]The Heart Hospital, Cardiology, London, United Kingdom; [4]St George's Hospital, Cardiology, London, United Kingdom*

Background: Cardiovascular disease is the leading cause of death after renal transplantation. The aim of this prospective observational study was to identify pre - operative non invasive parameters that best predict risk after renal transplantation in a group of patients with end stage renal disease (ESRD).
Methods: 203 patients (mean age 47 ± 12 years, 141 male) with ESRD (mean creatinine 745 ± 382 μmol/L, 183 on dialysis) being assessed for renal transplantation, were prospectively studied over a mean follow - up time period of 3.6 ± 1.8 years. Clinical, biochemical, echocardiography and exercise test data were examined and outcome assessed in a Cox regression model. The primary end point was all - cause mortality.
Results: There were 22 deaths over the follow - up period, 12 of which were cardiac. Survivors were significantly younger (56 ± 8 years vs 46 ± 12 years, $p <= 0.001$), had smaller left ventricular end systolic (LVEDD) diameter ($p = < 0.001$) and left vemtricular end diastolic (LVEDD) diameter ($p = < 0.001$), and higher left ventricular (LV) ejection fraction ($p = < 0.001$) when compared to non survivors. LV mass index (p = 0.001), LV maximal wall thickness (LVMWT, p = 0.006) and the proportion of patients with mitral annular calcification (MAC, p = 0.001) were significantly higher in the non survivors. Standard cardiovascular risk factors, exercise test data, serum haemoglobin and creatinine, the proportion on dialysis were not significantly different in the 2 groups. Multivariate analysis by Cox regression techniques identified 4 independent predictors of adverse outcome after renal transplantation: age > 50 years (p = 0.002), LVESD > 3.5 cm (p = 0.002), LVMWT > 1.4cm (p = 0.014), and MAC (p = 0.036). There was a progressive decrease in survival with an increasing number of prognostic risk factors. Patients with no prognostic factor had an estimated 5-year survival rate of 96% (95% CI 101.9, 90.6). The corresponding 5 - year estimates for 1, 2 and 3 prognostic factors were 86% (95% CI 96.7, 75.5), 68.6% (95% CI 89.4, 185.7), 38.1% (95% CI 77.2,171.1) respectively in patients > 50 years of age.
Conclusions: Pre - operative age > 50 years, LVESD > 3.5 cm, LVMWT > 1.4cm and the presence of MAC all independently predict poor outcome after renal transplantation. A model based on a combination of these risk factors is a better predictor of outcome than any single parameter.

P3478 Effects of balloon occlusion during percutaneous coronary intervention (PCI) on plasma levels of ischaemia modified albumin (IMA) and transmyocardial lactate

M.K. Sinha[1], J.M. Vazquez[2], R. Calvinho[2], D.C. Gaze[3], P.O. Collinson[3], J.C. Kaski[4]. *[1]St George's Hospital Medical School, Cardiological Sciences, London, United Kingdom; [2]Juan Canalejo, Department of Cardiology, La Coruhna, Spain; [3]St George's Hospital, Chemical Pathology, London, United Kingdom; [4]St George's Hospital Medical School, Cardiological Sciences, London, United Kingdom*

Background: Ischemia Modified Albumin has been suggested to be a new marker of myocardial ischemia. An accepted method to objectively detect myocardial ischaemia is the measurement of increased myocardial lactate production from ischaemic myocardium. This study investigated the comparison between IMA levels and myocardial lactate production triggered by balloon inflation during percutaneous coronary intervention (PCI)
Methods: We simultaneously measured arterial and coronary sinus lactate and IMA production in response to balloon inflation group in patients with chronic stable angina undergoing PCI to the proximal left anterior descending artery. Blood was drawn from the coronary guide catheter for arterial samples and a coronary sinus catheter for venous samples at baseline, immediately and 5 minutes post balloon inflation. IMA was measured using the albumin cobalt binding test assay and lactate by enzyme immunoassay.
Results: We studied 10 patients (9 men, mean age 55.5 years±1.6 SD).All patients were stented.Mean balloon inflation time was 120s (± 67s SD). Median arterial IMA at baseline was 101 U/mL, 95% confidence interval (CI) 83-128, which elevated to 114 U/mL (CI 101-139), p=0.04, immediately post balloon inflations and 120 (CI 97-129), p=0.16, at 5 minutes post inflations. Median coronary sinus IMA at baseline was 110 U/mL (CI 98-102), 111 U/mL (CI 94 –142) immediately post, and 111 U/mL (CI 98-124) 5 minutes post. The coronary sinus IMA values

post procedure were not statistically different from baseline (p=0.92, 0.94 respectively). The transmyocardial lactate gradient from baseline to immediately post PCI showed a significant difference, shifting from -0.25 to +0.05, p=0.01, consistent with the development of myocardial ischaemia due to balloon inflation. The transmyocardial lactate gradient at 5 minutes post PCI was slightly but significantly elevated from baseline, p=0.05.
Conclusion: These results show that rise of IMA parallels that of transmyocardial lactate following balloon inflation with PCI. IMA is thus a reliable marker of myocardial ischemia associated to primary reduction in blood flow.

P3479 Pre-procedural statin medication in patients with stenting-related myocardial injury improves long-term survival

M. Haude[1], L. Volbracht[2], T. Konorza[3], I. Kordish[3], H. Wieneke[3], R. Schulz[4], G. Heusch[4], R. Erbel[3]. [1]*Zentrum fur Innere Medizin, Universitatsklinikum Essen, Essen, Germany;* [2]*Institute for Clinical Chemistry, University Hospital Essen, Essen, Germany;* [3]*University Essen, Cardiology Department, Essen, Germany;* [4]*University Hospital Essen, Pathophysiology, Essen, Germany*

Background: Stenting-related myocardial injury is caused by microembolisation of platelet aggregates and plaque debris together with inflammation. HMG-CoA reductase inhibitors (statins) have been shown to limit MI primary because of their pleiotropic effects, but the impact on survival is unclear. Thus, we tested whether pre-procedural statin therapy improves survival especially in patients (pts) with stenting-related MI.
Methods: We stratified 1218 consecutive pts with uncomplicated stenting according to their pre-procedural status of statin therapy (1012 statin-pos. and 206 statin-neg. pts). MI was assessed by analysis of creatine kinase (CK); CK-MB and cardiac troponin I (TI) before, 6, 12, and 24 hours after the intervention. Periprocedural myocardial infarction (MI) was defined as a CK-MB rise three times greater than the upper limit of normal. Pts were followed for 2 years.
Results: Postinterventional maximum CK, CK-MB, and TI elevations were larger in statin-neg. pts (68±62 vs 52±46 IU/L; 24±20 vs 18±18 IU/L; and 0.46±0.48 vs 0.38±0.42mg/L; all p<0.001). Statin pretreated patients with periprocedural MI showed superior survival after 2 years compared to statin-neg. pts with periprocedural MI (Fig. 1).

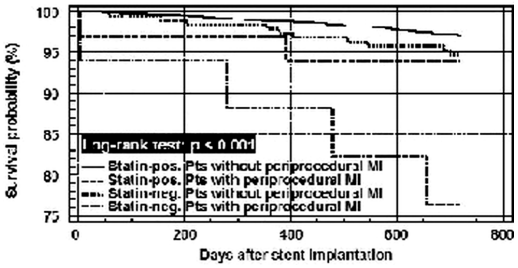


Figure 1. Survival rate

Conclusions: Pre-procedural statin therapy reduces stenting-related MI and improves survival especially in pts with stenting-related MI during 2 years follow-up.

GENETICS

P3480 Influence of mobilised stem cells on clinical symptoms, cardiac perfusion and function in patients with severe chronic ischaemic heart disease

Y. Wang[1], K. Tagil[2], R. Ripa[1], J.C. Nilsson[3], S. Carstensen[1], H.E. Johnsen[4], E. Jorgensen[1], J. Kastrup[1]. [1]*Rigoshospitalet, Department of Cardiology 2014, Copenhagen, Denmark;* [2]*Department of Clinical Physiology, Malmö, Sweden;* [3]*Hvidovre Hospital, Danish Research Centre for MR, Copenhagen, Denmark;* [4]*Herlev University Hospital, Department of Haematology, Herlev, Denmark*

Purpose: A phase I safety and efficacy study with granulocyte colony stimulating factor (G-CSF) mobilization of bone marrow stem cells to induce vasculogenesis in patients with severe ischemic heart disease (IHD) was conducted.
Methods: 29 patients with IHD participated in the study. Thirteen patients were treated in-hospital with one daily subcutaneous injection of 5μgram/kg body weight G-CSF for six days and 16 patients served as controls.
Results: There was a significant increase in leucocytes and in peripheral circulating CD34+ stem cells from the bone marrow during the G-CSF treatment, with normalization after one week. G-CSF treated patients were without any serious adverse events. Four patients were "poor mobilizers" with a maximal increase in CD34+ cells to 5,000±700/mL blood (mean+SD) compared with 28,900±5,100/mL blood in 9 "mobilizers". At the follow-up G-CSF treated had improved in CCS classification, NTG consumption and angina attacks, but the controls only in CCS classification. The decline in NTG consumption tended to be significant in "mobilizers" compared with controls. Myocardial perfusion was unchanged at adenosine stress single photon emission computerized tomography (SPECT) or magnetic resonans images (MRI). Left ventricular ejection fraction decreased from 57 to 52% (P<0.01, MRI) and from 48 to 44% (P=0.07, SPECT) in G-CSF treated patients, but was unchanged measured with echocardiography.
Conclusions: Treatment by G-CSF improved symptoms but not signs of myocardial ischemia in patients with severe IHD. The effects seemed related to mobilization of stem cells. An adverse effect on Left ventricular ejection fraction could not be excluded.

P3481 The reduction in 24-h ambulatory blood pressure after weight loss is increased in obese women with Glu27 β2-adrenoceptor polymorphism

M.U.B. Rondon[1], I.C. Trombetta[1], C.C. Rezk[2], C.L.M. Forjaz[2], M.M.G. Gowdak[1], A. Halpern[3], S.M.F. Villares[3], C.E. Negrao[4]. [1]*Heart Inst (InCor) Univ SPaulo Med Sch, Sao Paulo, Brazil;* [2]*School of Physical Educ and Sports USP, Sao Paulo, Brazil;* [3]*Univ of Sao Paulo, Department of Endocrinology, Sao Paulo, Brazil;* [4]*Sch Phys Educ and Sports USP, Heart Institute (InCor) Univ SPaulo Med Sch, Sao Paulo, Brazil*

Purpose: We have recently reported that obese women who are homozygous for Glu27 of the B2-adrenoceptor polymorphism have augmented muscle vasodilatory response during physiological maneuvers (Trombetta, JAP 98:787-794, 2005). Thus we hypothesized that 24h-ambulatory blood pressure would be lower in obese women encoding Glu27 B2-adrenoceptors polymorphism. In addition, the impact of body weight loss by diet and exercise training on 24h-ambulatory blood pressure would be greater in obese women encoding Glu27 B2-adrenoceptor polymorphism.
Methods: From an initial sampling of 216 volunteers, we studied 42 middle-age normotensive obese women selected to represent two genotypes: 19 with Glu27 B2-adrenoceptors polymorphism and 23 wild type Gln27 (32±1 vs 34±1years, p=0.20; 88±2 vs 86±2kg, p=0.48; and 34±1 vs 33±1kg/m^2, p=0.28, respectively). Hypocaloric diet consisted of a 600kcal/day reduction. Exercise training consisted of three 60-min exercise session/week during 4 months. Twenty-four hour ambulatory blood pressure was evaluated pre and post intervention.
Results: After interventions, body weight, body mass index, 24-hour heart rate, 24-hour pulse pressure, and 24-hour systolic blood pressure were significantly lower in both, Glu27 and Gln27 groups. However, the comparisons between groups showed that the reduction in body weight and body mass index were significantly greater in Glu27 group than in Gln27group (10.7±1 vs 7.4±1kg, p=0.02, and 4.1±0.4 vs 2.8±0.2kg/m^2, p=0.01, respectively). In addition, diet and exercise training provoked a greater reduction in average 24-hour systolic blood pressure (5.1±1 vs 2.2±1mmHg, p=0.05), and average 24-hour pulse pressure (3.6±1 vs 1.5±1mmHg, p=0.01) in Glu27 group when compared to Gln27 group. This reduction insystolic blood pressure and pulse pressure was mainly due to daytime (6.5±1 vs 2.6±1mmHg, p=0.01, and 4.2±1 vs 1.2±1mmHg, p=0.001, respectively). Similarly, diet and exercise training provoked a greater reduction in average 24-hour heart rate in Glu27 group than in Gn27 group (5.5±1 vs 2.3±1bpm, p=0.04). No significant differences in diastolic and mean blood pressure levels were found between groups.
Conclusions: Twenty-four hour ambulatory blood pressure is not lower in obese women with Glu27 B2-adrenoceptors polymorphism. However, diet and exercise training provoke a greater reduction in body weight and 24-hour systolic blood pressure levels in women with Glu27 B2-adrenoceptor. These findings provide evidence for the understanding of the genetic metabolic and cardiovascular regulation of the B2-adrenoceptors in humans.

P3482 Association between a functional polymorphism of CYP4A11 (T8590C) and hypertension but not with left ventricular structure in a population based sample (MONICA-Augsburg LVH Substudy 1994/95)

B. Mayer[1], W. Lieb[1], A. Goetz[1], I. Koenig[2], C. Hengstenberg[3], A. Doehring[4], H. Schunkert[1], J. Erdmann[1]. [1]*Universitaet SH, Campus Luebeck, Medizinische Klinik II, Luebeck, Germany;* [2]*Institut fuer Biometrie und Statistik, Universitaet SH, Campus Luebeck, Luebeck, Germany;* [3]*Universität Regensburg, Klinik für Innere Medizin II, Regensburg, Germany;* [4]*Institut fuer Epidemiologie, GSF Forschungszentrum, Neuherberg, Germany*

Introduction: Recently, a functional variant of CYP4A11 has been associated with hypertension in two independent populations. The aim of the present study was to further investigate the association of the T8590C allele status with hypertension in a large population-based sample and its association with left ventricular structure.
Material and Methods: Individuals who participated in the echocardiographic substudy of the third MONICA (MONitoring trends and determinants in CArdiovascular disease) survey (n=1396) were studied by standardized anthropometric, echocardiographic, and biochemical measurements as well as genotyping for CYP4A11 T8590C allele status.
Results: The 8590TT, 8590CT, and 8590CC genotypes were found in 75.5%, 22.4%, and 2.1% of the study population, the frequencies of the 8590T and 8950C allele were 0.87 and 0.13, respectively. Individuals with the CC genotype had higher systolic (141.4±3.17 mmHg vs. 134.3±0.96 mmHg for CT allele and

134.3±0.53 mmHg for TT allele; p=0.026) and diastolic blood pressure levels (85.4±2.06 mmHg vs. 80.3±0.63 mmHg for CT allele and 80.7±0.34 mmHg for TT allele; p=0.022). The odds ratio (OR) of having hypertension attributable to the CC genotype was 3.30 (95% CI 1.38-7.94; p=0.008) in the entire study population with similar trend in men (4.30 (95% CI 1.08-17.14)) and women (2.92 (95% CI 0.87-9.80)). Echocardiographic parameters were not significantly associated with a specific CYP4A11 genotype.
In conclusion, our data confirm the association between the T8590C polymorphism of CYP4A11 and hypertension. The data are not in favor of a significant contribution of the T8590C polymorphism to the variability of left ventricular mass measurements, suggesting that there is no direct modulatory effect of CYP4A11 in myocardium.

P3483 Evidence for a gene modifying hypertrophy in a large cohort of familial hypertrophic cardiomyopathy

E. Villard[1], L. Duboscq-Bidot[1], P. Charron[2], V. Nicaud[3], L. Tiret[3], K. Schwartz[4], M. Komajda[5]. *[1]INSERM U621, Paris, France; [2]Pitie-Salpetriere hospital, cytogenetics, Paris, France; [3]INSERM U525, Paris, France; [4]INSERM U582, Paris, France; [5]Pitié-Salpêtrière Hospital, Cardiology, Paris, France*

Familial hypertrophic cardiomyopathy (FHC) is an autosomal dominant cardiac disorder with ventricular hypertrophy (LVH) predominantly affecting the interventricular septum. It is a major cause of cardiac death and heart failure. The severity and distribution of LVH is variable among disease mutation carriers, suggesting a potential role for modifier genes. Data suggest that the functional R389 allele of the beta1 adrenergic receptor polymorphism R389G (ADRB1_R389G) is involved in predisposition to heart failure and associated with cardiomyocyte hypertrophy in transgenic mice. We analysed the modifier effect of the candidate ADRB1_R389G polymorphism on the phenotypic expression of LVH in patients with FHC.
Material and method: We recruited 63 unrelated families presenting with hypertrophic cardiomyopathy. Sequencing and genotyping of the MYBPC3, MYH7, MYL2 or TNNT2 genes in these family members identified 232 individuals carrying a disease mutation and 183 non-carriers (controls). We measured left ventricular mass (LVM), interventricular septum (IVS) thickness, maximum thickness of the ventricular wall (MTLV), and the Spirito Marron indicator was calculated. ADRB1_R389G genotypes were determined by PCR-RFLP on genomic DNA. Analysis of variance was conducted with the SAS software package to compare average phenotypic values between genotypes. Phenotypic data were corrected for age, systolic blood pressure and body surface area.
Results:

Table 1. Ventricular mass indices in each group of genotypes at ADRB1_R389G polymorphism

	CC (n=118), Arg alleles	CG (n=86), Arg/Gly alleles	GG (n=28), Gly alleles	p value (recessive model GG vs C+)
LVM (g)	150.7± 5.7	159.15 ± 6.7	133.0 ± 11.9	0.094
IVS (mm)	15.45 ± 0.54	16.12 ± 0.64	12.54 ± 1.12	.0074
MTLV (mm)	16.85 ± 0.56	17.15 ± 0.66	13.63 ± 1.15	.0066
Spirito-Maron	50.63 ± 1.48; n=98	51.58 ± 1.70; n=75	43.35 ± 3.12; n=22	.021

Conclusion: We observed a significant protective effect of the GG genotype of the ADRB1_R389G polymorphism for 3 out of 4 measured hypertrophy indicators (IVS, MTLV, Spirito-Maron) in our FHC population. This effect was not observed in the control group. Our results strongly suggest a modifier effect of the Gly allele of the ADRB 1 gene on left ventricular mass.

P3484 Polymorphisms of the endothelin system as risk factor for coronary artery disease

E. Ciofini, U. Paradossi, C. Prontera, M.G. Andreassi, A. Biagini, M. Colombo. *G. Pasquinucci Hospital, Massa, Italy*

Aim: Endothelin-1 (ET-1) plays an important role in vascular pathophysiology. The aim of the study was to examine whether genetic variations of endothelin-1 (ET-1), a Lys/Asn change at codon 198, and its receptor ETA, C/T in exon 6, H323H, were involved in the susceptibility to coronary artery disease (CAD) in the Italian population.
Methods: Genotyping at these two loci by PCR/restriction fragment analysis was performed 808 subjects who underwent coronary angiography (n=558 with CAD). The severity of CAD was expressed by means of the Duke score. Plasma ET-1 was assayed by Elisa in 93 randomly selected subjects (n=57 with CAD).
Results: The ET-1 Lys198Asn was significantly associated with the occurrence of CAD (p=0.03). The risk of CAD was independently increased among Asn/Asn in comparison to Lys carriers (OR 3.6, p=0.03). Moreover, plasma ET-1 levels significantly correlated with the severity of CAD (r=0.31, p=0.002) and the ET-1 Lys198Asn variation (Lys/Lys:2.0±0.7, Lys/Asn 4.1±1.4, Asn/Asn 16.2±14.7, pg/ml, p=0.007 by Scheffe; Figure 1). In contrast, the ETA receptor H323H was not associated with the disease (p=0.91). However, homozygous carriers of both variants showed a marked increase in the risk of CAD (adjusted OR=11.7, p=0.007, for Asn/Asn and TT vs Lys and C carriers of the ET-1 and ETA polymorphisms, respectively).
Conclusions: The ET-1 Lys198Asn variant seems to be associated with the presence of angiographically assessed CAD by influencing ET-1 plasma levels. Moreover, simultaneously carriers of both ET-1 Lys198Asn and ETA H323H polymorphisms might have a great susceptibility risk to CAD.

P3485 IL-1 gene cluster and incidence of cardiovascular events in patients with stable multi-vessel coronary artery disease

A. Pereira[1], N.H. Lopes[2], P.R. Soares[2], W. Hueb[2], J.E. Krieger[2]. *[1]Heart Institute Sao Paulo, Cardiology, São Paulo, Brazil; [2]Heart Institute Sao Paulo, Cardiology, São Paulo, Brazil*

Introduction: The pro-inflammatory cytokine interleukin (IL)-1 has been suggested to play a role in atherosclerosis. Several genetic polymorphisms have been described in the genes of the IL-1 cluster and associations with coronary artery disease (CAD) and cardiovascular events incidence have been reported, although with contrasting results. The aim of this study was to investigate the possible association between specific genotypes of the IL-1 beta (IL-1B) and IL-1 receptor antagonist (IL-1RA) genes and the incidence of cardiovascular events in a sample of individuals with stable, multi-vessel coronary artery disease prospectively followed in the MASS II trial
Methods: We performed IL-1B(-511), IL-1B(+3954) and a variable number tandem repeat polymorphism in intron 2 of the interleukin 1 receptor antagonist gene (IL-1RN) genotypes in 611 patients with two or three vessel-disease randomized and prospectively followed in the MASS II Trial, a randomized study to compare treatments for multivessel CAD and preserved left ventricle function. Mean follow-up was of 29.4 months. Survival curves were calculated with the Kaplan-Meier method, and evaluated with the log-rank statistic. We assessed the relationship between baseline variables and the composite end-point of death, myocardial infarction and refractory angina using a Cox proportional hazards survival model.
Results: There were no significant differences among individuals within each genotype group for baseline clinical characteristics. Allele and genotype frequencies were in Hardy-Weinberg equilibrium. No significant association was found between the IL-1B(+3954) or IL-1RN polymorphisms and an increased incidence of combined end-points (p=0.71 and p=0.86, respectively). However, a significantly higher incidence of combined end-points was observed in individuals harboring the CC genotype of the IL-1B(-511) polymorphism (p=0.02). Presence of the CC genotype was independently associated with a 1.7 (95%CI – 1.2 – 2.4) increased risk of cardiovascular events in this sample even after adjustment for age, gender, treatment allocation, hypertension, diabetes, obesity and baseline disease severity. No significant interaction was disclosed between the studied polymorphisms.
Conclusions: Patients with stable multi-vessel CAD harboring the IL-1B(-511) CC genotype are at increased risk of cardiovascular events. These data are in accordance with previous studies and may be used to better disease stratification and outcome prediction.

P3486 The effect of genetic polymorphisms C807T and A1648G on platelet glycoprotein Ia, on the risk for premature myocardial infarction in Greece

C. Antoniades[1], D. Tousoulis[2], C. Vasiliadou[1], C. Pitsavos[1], N. Koumallos[1], C. Chrysochoou[1], D. Panagiotakos[1], C. Stefanadis[1]. *[1]Athens University Medical School, Cardiology Department, Athens, Greece; [2]Athens, Greece*

Platelet membrane glycoprotein Ia (GPIa) has an important role in platelet function as a receptor for collagen. Silent genetic polymorphism C807T seems to affect the expression of GPIa, while A1648G polymorphism leads to a Glu/Lys substitution on GPIa.
Aim: we investigated whether C807T and A1648G polymorphisms on GPIa gene, affect the risk for premature myocardial infarction (MI) in young individuals.
Methods: the study population consisted of 704 subjects of the Caucasian race: 203 young patients with premature MI (aged 46.4±5.1 years old) and 501 healthy controls (48.0±12.5 years old). Distributions of the C807T and A1648G polymorphisms were investigated by genotyping DNA by PCR. The allele and genotype frequencies in patients and controls were compared using chi-square test. There was no deviation from Hardy-Weinberg equilibrium for any of the considered polymorphisms.
Results: the prevalence of 807TT homozygotes was significantly higher among MI patients (32 patients, 15.7%) compared to healthy controls (52 subjects, 10.3%, $p<0.05$). The 807CC genotype was present in 68 MI patients (33.6%) and in 182 controls (36.4%, p=NS), while the 807CT genotype was present in 103 MI patients (50.7%) and 267 controls (53.3%, p=NS). The risk for premature MI in 807T homozygotes was 1.616[95%CI:1.006 to 2.596] $p<0.05$) compared to 807CC+CT. However, the risk of 807CT heterozygotes was not significantly different compared to 807CC (1.03[95%CI:0.721-1.479] p=NS). There was no significant difference in the distribution of A1648G genotype between MI patients (AA: 7 (3.4%), AG: 43 (21.2%) and 153 (75.4%)) and controls (AA:10(1.9%), 121 (24.1%), 372 (74.2%) respectively, p=NS for all).
Conclusions: the present study supports that homozygosity for 807T allele on platelet GPIa gene, increases the risk for premature myocardial infarction. However, homozygosity for the 1648A allele in the same gene is rather uncommon in the Greece, and it is unlikely that is plays any significant role in the development of premature myocardial infarction.

P3487 Scal polymorphism of the atrial natriuretic peptide gene is associated with elevated levels of A- and B-type natriuretic peptide concentration in heart failure patients

C. Vassalle, C. Prontera, C. Passino, L. Zyw, M.G. Andreassi, G.C. Zucchelli, M. Emdin. *CNR-National Research Council, Institute of Clinical Physiology, Pisa, Italy*

Background: Plasma natriuretic peptide (ANP, BNP, NTproBNP) levels are elevated in heart failure (HF) with significant diagnostic and prognostic implications, despite of individual heterogeneity.
Methods: To study the possible influence of genetic polymorphism of the natriuretic peptide genes on circulating hormone levels, we sought to assess whether the ScaI mutated allele (A^1) of the ANP gene and the C[-55] variant of the natriuretic peptide clearance receptor gene (NPRC) influence with natriuretic peptide concentration in HF. To address this purpose 96 patients with a diagnosis of ischemic (n= 55) or idiopathic (n= 41) dilated cardiomyopathy (EF: 31±1%, mean±SE).
Results: ANP concentration resulted significantly higher in HF patients who presented the A^1 respect to those with the wild type allele (167±27 and 87±1 pg/ml, p=0.01, with no significant difference in left ventricular ejection fraction or NYHA class). Moreover, patients with the A^1 variant showed a significantly higher BNP and NT-proBNP concentration, when compared to those with the wild type allele (413±113 vs 223±49 pg/ml, p <0.03, 4382±1642 vs 2054±731 pg/ml, respectively, p<0.01). Conversely, no significant association was observed among NPRC variants and ANP, BNP and NT-proBNP circulating levels.
Conclusion: This study suggests that the A^1 allele of the ANP gene, by affecting not only circulating ANP, but even B-type peptide levels may represent an important genetic factor influencing the evolution of heart failure.

P3488 Association of MTRR 66 GA polymorphism with homocysteine and coronary artery disease in a French population

R.M. Gueant-Rodriguez[1], M. Candito[2], Y. Juilliere[1], S. Thirion[3], R. Debard[3], P. Gibelin[4], E. Aliot[1], J.L. Gueant[3]. *[1]CHU Brabois, Cardiology Department, Vandoeuvre Les Nancy, France; [2]University Hospital, Biochemical Department, Nice, France; [3]Medical Faculty and University Hospita, INSERM U-724, Nancy, France; [4]University Hospital, Cardiology Department, Nice, France*

Background: Case control studies evaluating the 677CT polymorphism of methylenetetrahydrofolate reductase (MTHFR) as an independent genetic risk factor of coronary artery disease (CAD) have produced contradictory conclusions, suggesting a limited influence. In contrast the association of other polymorphisms related to homocysteine metabolism needs to be evaluated further. These polymorphisms are the 1298 A>C and 2756 A>G of MTHFR, methionine synthase (MTR) in substitutions and the 66 >A of methionine synthase reductase (MTRR).
Methods and results: We investigated the individual and combined effects of these 4 polymorphisms and of nutritional factors (vitamin B12, folates) relied with the plasma homocysteine (t-Hcys) level in a case control study including 530 CAD patients and 248 health controls. In univariate analysis, plasma t-Hcys was higher in the CAD group than in controls (11.8 vs 10.4 μmol/L, P<0.0001). MTRR AA and MTHFR 677 TT were associated with hyperhomocysteinemia in the whole population (13.8 vs 11.4 μmol/L, P=0.0102 and 12.5 vs 11.0 μmol/L, P=0.0065 respectively). MTTR A allele, but not MTHFR 677 T allele was associated with CAD (0.38 [95% C.I: 0.32-0.44] vs 0.48 [95% C.I: 0.44-0.52] P=0.0081 and 0.35 [95% C.I: 0.31-0.40] vs 0.36 [95% C.I: 0.33-0.39] P=0.7567, respectively). In multivariate analysis, upper quartile of t-Hcys (>14.5 μmol/l) and MTRR AA genotype were two significant independent risks of CAD with respective Odds ratios of 3.3 (95% C.I: 1.7-6.7, P=0.0005) and of 4.3 (95% C.I: 1.5-12.5, P=0.0063).
Conclusion: MTRR AA genotype is an independent predictive of moderated hyperhomocysteinemia and CAD, at least in the French population.

DRUGS

P3489 Effects of perindopril on long-term clinical outcome of patients with coronary artery disease and preserved left ventricular function-The EUROPA study

M.E. Bertrand[1], W.J. Remme[2], K.M. Fox[3], R. Ferrari[4], J. Deckers[5], M.L. Simoons[6]. *[1]Lambersart, France; [2]Sticares Cardiovascular Research Found, Rotterdam, Netherlands; [3]Royal Brompton Hospital, London, United Kingdom; [4]University di Ferrara, Ferrara, Italy; [5]Cardialysis, Rotterdam, Netherlands; [6]Thorax Center, Rotterdam, Netherlands*

Background: The EUROPA trial has demonstrated that perindopril, an ACE inhibitor with high-tissue affinity, significantly decreased the risk of major cardiac events (CV death, non fatal myocardial infarction (MI) and cardiac arrest (CA)) in patients with stable coronary artery disease (CAD) without apparent heart failure (CHF). Since comparable secondary preventive effects have been previously demonstrated in patients with LV dysfunction, with/without CHF, our goal was to assess the long-term clinical outcome in patients with preserved left ventricular function (LV ejection fraction (LVEF) ≥40%) in the EUROPA study.
Methods: Among the 12,218 patients (pts) in EUROPA we retrospectively identified 9,810 (80.3%) pts who had an LVEF assessment. The measurements were obtained by echocardiography in 6723 cases (68.5%) or by angiography in 2622 cases (26.7%). The mean LVEF of the overall population was 57± 10%.
9,478 (96.6%) pts had a LVEF ≥ 40%: 4,730 received 8 mg of perindopril and 4,748 received a placebo. Only 332 pts (3.4%) had an LVEF< 40%, 175 received perindopril and 157 a placebo.In patients (n=332), with impaired LV function (LVEF < 40%), the primary endpoint was also reduced by perindopril ARR=2.5% (HR=0.86 [95% CI: 0.51-1.44]
Results: The baseline characteristics of pts with documented LVEF were not different to the whole EUROPA population in terms of demographics, medical history, physical examination (heart rate, blood pressure), and medications at screening. In pts (n=9,478) with preserved LV function (LVEF ≥ 40%), there was a significant relative risk reduction of 22% of the primary endpoint (CV death, non fatal MI and CA) in the group treated with perindopril: (7.8%) compared to placebo (9.9%). Absolute risk reduction (ARR) = 2.1%, hazard ratio (HR): 0.78 [95% CI: 0.68-0.90]) p<0.001. Similar results were obtained for the first secondary endpoint (total mortality, non-fatal MI, hospital admission for unstable angina, CA): ARR=2.9% HR=0.82 [95% CI: 0.74-0.91] p <0.001, for cardiovascular mortality and non fatal MI: ARR=2% HR= 0.78 [95% CI: 0.69-0.90] p<0.001 as well as for fatal and non fatal MI: ARR:1.7% HR = 0.75 [95% CI: 0.64-0.89] p<0.001.
Conclusions: LVEF was documented in 80.3% of the EUROPA study population and only 3.4% had an impaired LV function, confirming that EUROPA patients did not have asymptomatic LV dysfunction. Results in patients with preserved LV function are consistent with those of the whole EUROPA study population. Perindopril is beneficial in all patients with stable CAD, irrespective of LV function.

P3490 Angiotensin converting enzyme inhbitors improves myocardial adrenergic innervation disturbances in normotensive patients with diabetes type II

M.E. Marketou[1], E.A. Zacharis[1], E. Papadaki[2], M.I. Stathaki[2], G.E. Kochiadakis[1], F. Karageorgou[1], N.S. Karkavitsas[2], P.E. Vardas[1]. *[1]Heraklion University Hospital, Dept. of Cardiology Dept., Heraklion, Crete, Greece; [2]Heraklion University Hospital, Dept. of Nuclear Medicine, Heraklion, Greece*

Purpose: Myocardial sympathetic dysinnervation is frequently observed in patients with diabetes mellitus even in the absence of any heart disease. Cardiac scintigraphy with I 123 -Meta-iodobenzylguanidine (I 123 -MIBG) was used to assess the effect of perindopril - an angiotensin converting enzyme (ACE- I) - on myocardial adrenergic innervation in normotensive patients with diabetes type II.
Methods: We studied 40 normotensive patients (aged 57 ± 8 years, 22 women) with diabetes type II, normal renal function, a fair metabolic control (glycosylated hemoglobin < 7.5%), a normal echocardiogram and single-photon emission computed tomography (SPECT) Thallium201 myocardial perfusion study. None of the participants had any other disease that may have affected myocardial adrenergic innervation. Twenty patients received perindopril 4 mg/day for 6 months, while the rest served as control group. Before entering the study and at 6 months under perindopril therapy, the patients underwent planar and SPECT myocardial imaging of the heart after intravenous infusion of 5mCi I 123-MIBG. Heart to mediastinum ratio (H/M) was used for quantitative assessment of adrenergic innervation, 10 minutes and 4 hours after drug infusion, while SPECT scintigraphy evaluated the regional distribution of adrenergic activity.
Results: No significant changes were observed in systolic blood pressure. At baseline, the H/M ratio at 10 min and 4 hours was 1.62 ± 0.3 and 1.5 ± 0.2 respectively; which significantly improved after the 6-month treatment with perindopril (1.88 ± 0.4 and 1.8 ± 0.2 respectively, p<0.05 for both). During SPECT scintigraphy, 12 patients (80%) revealed severe regional myocardial adrenergic innervation defects. All had defects in the inferior and lateral wall, 8 had additional defects in the anterior wall and 6 in the septal wall. There was a marked improvement after 6 months of therapy, mostly in the anterior and septal walls. No significant changes were observed in the control group.
Conclusions: The administration of ACE- I in normotensive patients with diabetes type II results in a significant improvement of the left ventricular adrenergic innervation abnormalities, independently of its blood pressure effect. Further studies are required to establish the preventative value of ACE- I in cardiovascular complications of diabetes.

P3491 Rosiglitazone improves myocardial glucose uptake in patients with type 2 diabetes and coronary artery disease. A 16 week randomised, double-blind, placebo-controlled study

R. Lautamaki[1], K.E.J. Airaksinen[2], M. Seppanen[3], E. Ball[4], R. Harkonen[5], M. Stewart[4], J. Knuuti[3], P. Nuutila[3]. *[1]University of Turku, Turku PET Centre, Turku, Finland; [2]Turku University Central Hospital, Department of Medicine, Turku, Finland; [3]University of Turku, Turku PET Centre, Turku, Finland; [4]GlaxoSmithKline, London, United Kingdom; [5]Turku University Central Hospital, Department of Nuclear Medicine, Turku, Finland*

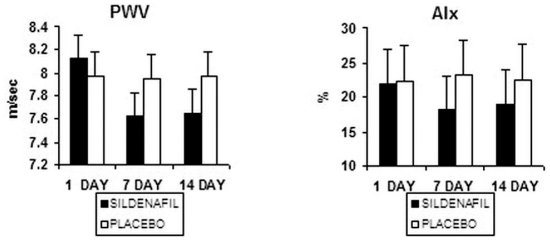
Background: Rosiglitazone therapy has been shown to improve insulin sensitiv-

ity and glucose uptake in patients with uncomplicated type 2 diabetes. In patients with ischemic coronary artery disease, glucose is an important source of energy and preserved myocardial glucose uptake is essential for the viability of the jeopardised myocardium.
Aim: The aim of this study was to test whether rosiglitazone changes myocardial metabolism in type 2 diabetic patients with coronary artery disease.
Methods: We studied 54 patients (38 men, 16 women) with type 2 diabetes (HbA1c 7.2±0.9%) and coronary artery disease in a randomized, double-blind and placebo-controlled trial. Myocardial glucose uptake was measured with [18F]FDG-PET in regions of exercise-induced ischemia evaluated by SPECT and coronary artery stenosis confirmed by coronary angiography, and in non-ischemic regions. Studies were performed during hyperinsulinemic euglycemic clamp before and after 16 week intervention period with rosiglitazone (n=27) or placebo (n=27).
Results: Rosiglitazone significantly improved glycemic control ($P<0.0001$) and whole-body insulin sensitivity ($P<0.0001$). Myocardial glucose uptake was increased from 20.6±11.8μmol/100g/min to 25.5±12.4μmol/100g/min on rosiglitazone (p=0.038 vs baseline; p=0.023 vs placebo) in ischemic regions and from 21.7±12.1μmol/100g/min to 28.0±12.7μmol/100g/min on rosiglitazone (p=0.014 vs baseline; p=0.003 vs placebo) in non-ischemic regions.These increases in MGU were partly explained by the suppression of FFA levels during clamp in the rosiglitazone group.
Conclusion: Rosiglitazone therapy significantly increases insulin sensitivity and improves myocardial glucose uptake in type 2 diabetic patients with coronary artery disease. These results suggest that rosiglitazone therapy may facilitate myocardial glucose storage and utilization in these patients.

P3492 Long-term sildenafil administration improves aortic stiffness and wave reflections in patients with erectile dysfunction of vascular origin

C. Vlachopoulos[1], N. Ioakeimidis[1], K. Rokkas[1], K. Aznaouridis[1], I. Dima[1], E. Tsiamis[1], T. Askitis[2], C. Stefanadis[1]. [1]*Athens Medical School, Hippokration Hospital, 1st Cardiology, Athens, Greece;* [2]*Athens, Greece*

Background: Aortic stiffness and wave reflections are independent prognosticators of cardiovascular risk. We have previously shown that sildenafil, a phosphodiesterase type-5 inhibitor, has an acute beneficial effect on aortic stiffness. Whether sildenafil has a long-term beneficial effect on aortic elastic properties and wave reflections with chronic daily administration has not been determined.
Methods: The effects of a 2-week long treatment with sildenafil on aortic stiffness were studied in 11 men (age 58±15 years) with vasculogenic erectile dysfunction, considered competent to have a safe sexual activity and take phosphodiesterase type 5 inhibitor therapy. The study was carried out on two separate arms, one with sildenafil (100 mg) daily and one with placebo according to a randomized, placebo-controlled, double-blind, cross over design. All measurements were performed 24 hours after the last sildenafil intake. Carotid-femoral pulse wave velocity (PWV) was measured as an index of aortic stiffness using an automated, non-invasive device (Complior®) and augmentation index (AIx) as a measure of wave reflection using a validated system (Sphygmocor®).
Results: Daily sildenafil intake led to a significant sustained decrease in PWV and AIx, indicating a decrease in aortic stiffness and wave reflections ($p<0.05$, figures). There were no significant changes in systolic and diastolic pressure.



Sildenafil therapy and aortic stiffness

Conclusions: This study shows for the first time that chronic treatment with sildenafil has a favourable effect on aortic stiffness and wave reflections in patients with vasculogenic erectile dysfunction. This finding may have important implications for patients receiving sildenafil therapy for erectile dysfunction.

P3493 Impact of beta-blocker therapy at discharge on long-term mortality after primary angioplasty for ST-segment elevation myocardial infarction

G. De Luca[1], J.P. Ottervanger[2], A.W.J. van't Hof[2], M.J. de Boer[2], A.T.M. Gosselink[2], J.C.A. Hoorntje[2], J.H.E. Dambrink[2], H. Suryapranata[2]. [1]*De Weezezenlanden Hospital, Division of Cardiology, Zwolle, Netherlands;* [2]*De Weezenlanden Hospital, Division of Cardiology, Zwolle, Netherlands*

Background: Beta-blockers have been shown to improve outcome in patients with ST-segment elevation myocardial infarction (STEMI) treated with or without thrombolytic therapy. However, few data have been reported in patients with STEMI treated with primary angioplasty.
Methods: Our population is represented by a total of 1513 consecutive in-hospital survivors treated with primary angioplasty for STEMI between April 1997 and October 2001. One year follow-up was available from all patients.
Results: A total of 1325 patients (87.6%) were on beta-blockers at discharge. Patients on beta-blockers had more often normal Killip class at presentation, successful reperfusion, statins at discharge, receiving less often intra-aortic balloon pump. At 1-year follow-up, beta-blocker therapy was associated with a significantly lower mortality (2.9% vs 8.5%, RR [95% CI] = 0.33 (0.18-0.59), $p < 0.0001$). However, when the analysis was performed according to infarct location, beta-blockers emerged as independent correlate of mortality only in patients with anterior infarction (RR [95% CI] = 0.43 [0.21-0.86], p = 0.022).
Conclusions: This study showed that, in patients with STEMI treated with primary angioplasty, beta-blocker therapy is an independent correlate of 1-year mortality only in patients with anterior infarction.

P3494 Pharmacotherapy profile changes after pacemaker implantation in patients with bradycardia-tachycardia syndrome

P. Rucinski[1], A. Kutarski[1], M. Szczasny[2], L. Wdowiak[2]. [1]*Medical University of Lublin, Cardiology Department, Lublin, Poland;* [2]*Medical University of Lublin, Dept. of Health Care Economics, Lublin, Poland*

Bradycardia-tachycardia syndrome (BRTS) is characterized by alternations of paroxysms of atrial tachyarrhythmias and periods of slow atrial and ventricular rates. Patients often require antithrombotic, rate control or rhythm control pharmacotherapy and sometimes pacemaker implantation. Cardiac pacing may influence the need and possibility of different drugs use. The aim of the study was to asses the trends of pharmacotherapy changes after pacemaker implantation in patients with BRTS.
Methods: Data of 125 patients referred to pacemaker implantation due to BRTS were collected. The mean age was 67,9 years and 40,0% were male. Implanted pacemakers were AAI in 66,4% and DDD in 33,6%. We assessed trends in medication use for rate control (beta-blockers, calcium channel blockers and digoxin), sinus rhythm maintenance (Ia, Ic, III), and thromboembolism prevention one year before and after implantation.
Results: Overall rhythm control medication use increased after implantation. The mean quantity of antiarrhythmic drugs was 0,95 per patient before and 1,25 after implantation ($p<0,01$). Among antiarrhythmic medications (quinidine, disopyramide, propafenone, amiodarone, sotalol), use of propafenone was significantly higher after implantation (54,4% vs 41,6%; $p<0,05$). Frequencies of beta-blockers usage increased from 16,0% to 32,0% ($p<0,01$) but calcium channel blockers and digoxin didn't change significantly. Oral anticoagulant use was more spread after implantation too (34,4% vs 46,4%; $p<0,05$). Patients had lower number of hospitalizations due to atrial tachyarrhythmia after implantation than before.
Conclusions: The use of antiarrhythmic drugs as well as beta-blockers was higher after pacemaker implantation than before, in patients with brady-tachy syndrome. It may reflect lower adverse effects rate, especially those associated with bradycardia, in patients with implanted pacemaker. Although oral anticoagulant use increased too, fewer than half of the patients at high risk for stroke were anticoagulated.

P3495 Brain natriuretic peptide levels identify ischaemic patients at high risk for complications during intravenous esmolol infusion

N.I. Nikolaou[1], G. Fournarakis[2], E.A. Andrikou[2], S. Patsilinakos[2], D. Tsigas[2]. [1]*Agia Olga General Hospital, Cardiology, Athens, Greece;* [2]*Agia Olga General Hospital, Cardiology, Athens, Greece*

Purpose: Brain natriuretic peptide (BNP) levels are elevated in patients with latent myocardial dysfunction during acute coronary syndromes (ACS). We assessed the hypothesis that BNP levels might detect patients at high risk for complications during esmolol infusion for the treatment of ACS.
Methods: We studied 52 patients (29 males, age 63±13 years) admitted due to an ACS. In the absence of contraindications, esmolol infusion started at 50 μg/kg/min. Infusion rate was titrated until: 1) a decrease in rate-pressure product by 25%, 2)a dose of 150 μg/kg/min was reached 3)the appearance of complications. Infusion was maintained for 24 h. BNP levels (pg/ml) were measured before esmolol infusion started. End points were: 1) the appearance of complications (systolic blood pressure <90 mmHg, symptomatic bradycardia, pulmonary congestion), and 2) the need to interrupt infusion in order to manage complications.
Results: The median infusion rate was 100 μg/kg/min. Patients were divided in quartiles according to their BNP levels. Complication rates for corresponding BNP quartiles are shown in table. Area under ROC curve for the prediction of any complication was 0.81, (95% CI: 0.68 to 0.91). A BNP value of 222 had a sensitivity of 78%, specificity of 88%, negative predictive value of 88%, and positive predictive value of 78%. Area under curve for the prediction of interruption of infusion was 0.76, (95% CI: 0.62 to 0.87). In this setting a BNP value of 222 had a sensitivity of 82% specificity of 78%, negative predictive value of 94% and positive predictive value of 46%.

BNP (pg/ml)	<50	50-154	155-344	>344	p
No of patients	13	13	14	12	
Hypotension n(%)	1 (7.7)	2 (15.4)	5 (35.7)	4 (33.3)	0.07
Bradycardia n(%)	0 (0)	0 (0)	0 (0)	3 (25)	0.01
Pulmonary edema n(%)	0 (0)	0 (0)	3 (21.4)	4 (33.3)	0.005
Any complication n(%)	1 (7.7)	2 (15.4)	7 (50)	8 (66.7)	0.0005
Infusion stop n(%)	1 (7.7)	1 (7.7)	4 (28.6)	5 (41.7)	0.02

BNP values represent quartile limits; p values indicate the significance of trends for increasing complication rates in quartiles with higher BNP levels.

Conclusion: BNP levels predict patients at high risk for complications during esmolol infusion for the treatment of ACS.

P3496 Absence of rebound phenomenon after abrupt discontinuation of ivabradine, a new selective and specific If inhibitor, in patients with coronary artery disease

J.C. Tardif[1], K. Fox[2], M. Tendera[3], I. Ford[4]. [1]*Montreal Heart Institute, Cardiology Dept., Montreal, Canada;* [2]*Royal Brompton Hospital, Medicine, London, United Kingdom;* [3]*Slaska Akademia Medyczna, Medicine, Katowice, Poland;* [4]*University of Glasgow, Medicine, Glasgow, United Kingdom*

Background: Abrupt withdrawal of beta-blockers may lead to a rebound phenomenon which is characterised in patients with coronary artery disease (CAD) by exacerbation of angina, myocardial infarction (MI), reflex tachycardia and hypertension. The withdrawal symptoms usually begin within 12 to 72 hours after cessation of beta-blockers and may persist for several days. This rebound phenomenon after beta-blocker therapy has been related to over-expression and/or over-affinity of beta-adrenergic receptors after sustained beta-blockade. In contrast, the heart rate reducing agent ivabradine acts directly and selectively on the If current in the sino-atrial node.
Methods: The absence of rebound phenomenon was assessed in 614 patients with CAD and stable angina, in four studies including a double-blind run-out period with an abrupt treatment discontinuation for all ivabradine-treated patients at the end of the study. A one to two-week placebo post-study follow-up in these patients allowed a proper evaluation of any possible rebound phenomenon with ivabradine.
Results: The mean number of angina attacks and mean short acting nitrate consumption per week increased after ivabradine withdrawal but remained markedly lower during the run-out period than at baseline (Table 1). No rebound tachycardia was evidenced and heart rate returned progressively to baseline values (72 bts/min) and similarly no overshoot in blood pressure was measured.

Table 1. Angina attacks and short-acting nitrate consumption per week after abrupt ivabradine withdrawal

		Number of angina attacks/week	Short acting nitrate intake/week
Baseline value	Mean ±SD	3.7 ± 6.3	2.7 ± 6.2
End of run-out period value	Mean ±SD	1.4 ± 3.1	0.9 ± 2.6
Change from end of treatment to end of run-out	Mean ±SD	0.6 ± 2.1	0.4 ± 2.0
Change from baseline to end of run-out	Mean ±SD	-1.4 ± 3.6	-0.9 ± 3.5

In conclusion, unlike beta-blockers, abrupt discontinuation of ivabradine in patients with CAD and stable angina does not cause a rebound phenomenon.

P3497 Cavtratin reduces matrix-metalloproteinase-2 levels and flow-induced outward arterial remodelling

J.A. Rodriguez-Feo[1], G. Pasterkamp[2], C.E. van der Poel[2], B. van Middelaar[2], T. van den Broek[2], D.P.V. de Kleijn[2]. [1]*University Medical Center, Experimental Cardiology Laboratory, Utrecht, Netherlands;* [2]*University Medical Center, Experimental Cardiology, Utrecht, Netherlands*

Background: Cleavage of arterial collagen scaffold by Matrix-metalloproteinases (MMPs) facilitates outward arterial remodelling in the left carotid (LC) artery after ligation of the right carotid (RC) in mice. In cells MMP-2 co-localises with Caveolin-1 (Cav-1), the main coat protein of caveolae. Cav-1 negatively regulates the function of several proteins through interaction via its scaffolding domain (CSD). Biological actions of CSD can be mimicked using a cell permeable peptide named Cavtratin. We hypothesised that Cav-1 is involved in the regulation of vascular MMP-2 levels. In vivo, we studied the effect of Cavtratin administration on flow-induced outward arterial remodelling.
Methods and results: Confocal and cellular fractionation experiments revealed co-localisation of Cav-1 and MMP-2 in human aortic vascular smooth muscle cells (HA-VSMC). Primary aortic smooth muscle cells (SMC) and femoral arteries (FA) harvested from Cav-1 null mice showed an increased level of active MMP-2 (SMC = 3.8; FA= 5.8 fold increase vs wild type). Incubation of HA-VSMC with Cavtratin resulted in a decrease of pro MMP-2 levels in a dose-dependent manner. Moreover, pre-treatment of HA-VSMC cells with Cavtratin inhibited the appearance of active MMP-2 after Concanavalin A stimulation with a 100% inhibitory effect at 10 μM. To study the in vivo effects of Cavtratin, RC artery ligation was performed in Balb/c mice that received either Cavtratin (n=6) (1.5 mg/kg) or scrambled (n=6) or no peptide (n=10) for 30 days using micro-osmotic pumps. Morphometric analysis showed a significant reduction in the external elastic lamina (EEL) area (outward remodelling) in the non ligated LC artery of the Cavtratin-treated group compared to the scrambled-treated group (see table).

Table 1

Animal group (30 days)	Balbc (no peptide)	Balbc + scrambled	Balbc + Cavtratin
Increase in EEL area (μm^2) vs 0 days	23330 ± 5644	19944 ± 13261	735 ± 11612 *

EEL= External elastic lamina, * P<0.05

Conclusions: Our observations demonstrate that Cav-1 acts as an endogenous modulator of arterial MMP-2 levels. Moreover, Cavtratin may well be considered as a novel therapeutic option to prevent MMP-2-dependent outward arterial remodelling.

P3498 Expression of the carnitine transporter OCTN2 (SLC22A5) in human heart: relevance for cardiac drug uptake

M. Grube[1], D. Praeger[1], K. Meissner[1], G. Jedlitschky[1], H.K. Kroemer[2]. [1]*Ernst-Moritz-Arndt University, Department of Pharmacology, Greifswald, Germany;* [2]*University of Greifswald, Pharmacology Dept., Greifswald, Germany*

Background & Aim: Drug therapy of heart disease requires effective local concentrations and therefore cardiac.uptake of compounds. The mechanisms by which drugs enter the human heart are completely unknown. Uptake mechanisms for endogenous compounds such as carnitine may be used by drugs as well. Because myocardial metabolism largely dependents on carnitine as energy source, an adequate uptake is required for cardiac function. The organic cation transporter OCTN2 (SLC22A5) has been identified as high affinity sodium dependent transport protein for carnitine. Consequently genetic variants of the OCTN2 gene can result in heart failure suggesting a physiological role of OCTN2 for cardiac function. Therefore we investigated expression and localization of OCTN2 in human heart. In addition we describe the uptake of cardiovascular drugs by OCTN2 using an expression system.
Methods & Results: mRNA levels of OCTN2 were analyzed in human heart auricular (n = 52) and ventricular samples (n = 15), including samples of dilated (DCM) and ischemic cardiomyopathy (ICM). mRNA levels were analyzed applying TaqMan™ real-time PCR technology, revealing significant expression of OCTN2 in all samples. No significant difference between DCM, ICM and normal samples was observed. Using an antiserum against the 15 C-terminal amino acids of human OCTN2 immunohistochemistry and immunofluorescence microscopy revealed expression of OCTN2 in cardiomyocytes and vascular endothel. For functional studies OCTN2 was expressed in polarized kidney epithelial MDCKII cells. This model system showed the predicted kinetic parameters for carnitine transport (KM = 7.7 μM) and an apical localization of the protein. Using this cell system verapamil, spironolactone and mildronate were characterized as inhibitors for OCTN2 mediated carnitine uptake (EC50 = 25, 26 and 21 μM, respectively) and as substrates for OCTN2.
Conclusion: The carnitine uptake transporter OCTN2 is expressed in human heart indicating a role for cardiac carnitine supply and energy metabolism. Moreover OCTN2 can contribute to cardiac uptake of drugs like verapamil, spironolactone and mildronate.

P3499 Distribution of the polymorphisms of the HMGCR related with the response to statins in the Galician population

R.C. Vidal Perez[1], L. Loidi[2], A. Gesteira[2], F. Barros[2], C. Quinteiro[2], J.R. Gonzalez-Juanatey[3], F. Dominguez[4]. [1]*Santiago de Compostela, Spain;* [2]*Public Foundation of Genomic Medicine, Santiago de Compostela, Spain;* [3]*Cardiology Department, Santiago de Compostela, Spain;* [4]*Physiology Department, Santiago de Compostela, Spain*

Introduction: Statins are currently the cornerstone for dyslipemia pharmacological therapy. Recently was described a correlation between the reduction of cholesterol levels after statins treatment and the polymorphisms 12 (A/T) and 29 (T/G) of the gene of the HMGCR; the carriers of the aleles 12T and 29G had a worse response.
Aim: We analyse the distribution of the polymorphisms 12 and 29 of the gene HMGCR in Galician population for an eventual study of pharmacogenetic of the statins in this population; this included in a pharmacogenetics program on statins effects in this population.
Methods: From DNA of donors, after the firm of the written informed consent, two fragments of the HMGCR gene were amplified, that include the polymorphisms 12 and 29, and subsequently they were secuenced by the dideoxi method.
Results: Up to now 162 chromosomes have been studied: 148 from Galician population and 14 from population from other regions of Spain. The 98.65% of Galician aleles are 12A/29T and 1.35% are 12T/29G, while in the population from other regions the 72,7% are 12A/29T and the 27,3% are 12T/29G.
Conclusions: The haplotype 12T/29G, associate to poor statins responders, has been found in Galician population at a very low frecuency, so the study of pharmacogenetics of statins with these polymorphisms of the gene HMGCR does not

seem indicated in this population. On the other hand in the population from other regions of Spain it might be useful to perform the study. Our results are coincident with the published about the linkage desequilibrium between the polymorphisms 12 and 29.

P3500 Statins Inhibit platelet PAR-1 receptors: the PAR-1 inhibition by statins (PARIS) trial

V.L. Serebruany[1], M. Miller[2], A. Malinin[3], A. Pokov[1], D. Lowry[4], C.H. Hennekens[5]. *[1]HeartDrug, Towson, United States of America; [2]University of Maryland, Baltimore, United States of America; [3]Barnaul, Russian Federation; [4]Midatlantic Cardiovascular Associates, Baltimore, United States of America; [5]Florida Atlantic University, Miami, United States of America*

Background: Recent data from randomized trials of statins support the hypothesis of pleiotropy. We investigated whether statins affect platelet PAR-1 thrombin receptor by performing serial measurements of its activity, and expression level by flow cytometry before and during treatment with statins.
Methods and Results: Seventy patients with metabolic syndrome not taking antiplatelet agents were assigned at random to therapy with one of the six statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin) or to a no statin group. Platelet expression of intact (SPAN-12 antibody), and cleaved (WEDE-15) PAR-1 thrombin receptors were assessed at baseline, Week 4, and Week 6 by flow cytometry. At baseline, there was no difference in receptor expression. However, after 4 weeks of treatment all statins significantly inhibited (46-55%) the activated epitope of PAR-1 expression and following 6 weeks there remained inhibition despite a slight rebound (22-37%). There was also a delayed pattern of inhibition of the intact PAR-1 epitope.
Conclusions: All statins inhibit the activity and antigen level of the platelet PAR-1 thrombin receptor which has a major role in regulating platelet activity and thrombin formation. These data offer one plausible mechanism for the recently demonstrated pleiotropic effects of statins that may contribute to early clinical benefit.

P3501 The effect of pravastatin on microvascular constrictor responses

C.J. Ball[1], J. Kennedy[1], J.F. Beltrame[1], D.A. Saint[2]. *[1]The Queen Elizabeth Hospital, Cardiology, Woodville, Australia; [2]The University of Adelaide, Physiology, Adelaide, Australia*

Background: Pravastatin has been shown to have anti-ischaemic properties in patients with cardiological Syndrome-X undergoing stress ECG testing. The potential mechanisms for this response are likely to be multifactorial and may include alterations in microvascular reactivity. The objective of this study was to determine the effect of pravastatin pre-treatment on vasoconstrictor responses in isolated microvessels.
Methods: Rat mesenteric vessels (200-400μm diameter, n=10 rats) were placed in a Mulvany wire myograph and endothelial integrity assessed with acetylcholine. Concentration-response curves to phenylepherine (PE), serotonin (5HT) and endothelin-1 (Et-1) were determined before and after administration of a therapeutically appropriate pravastatin concentration (50μg). Constrictor responses are expressed relative to the depolarizing potassium solution response.
Results: All microvessels had intact endothelium-dependent vasodilator responses to acetylcholine. Pre-treatment with pravastatin reduced the maximal constrictor response to PE (Baseline = 112 $\pm$ 8%, Pravastatin = 79 $\pm$ 10%, $p < 0.05$) and 5HT (Baseline = 108 $\pm$ 8%, Pravastatin = 85 $\pm$ 12%, $p < 0.05$). Endothelin-1 responses were unaffected by pravastatin pre-treatment.
Conclusions: In rat mesenteric vessels with intact microvascular endothelium-dependent vasodilation, pravastatin reduces constrictor responses to PE and 5HT but not Et-1. This modulation of microvascular constrictor activity may contribute to the beneficial clinical effects of pravastatin.

P3502 Apolipoprotein E polymorphisms influence effect of pravastatin on survival after myocardial infarction in a Mediterranean population: the GISSI-Prevenzione study

B.D. Chiodini[1], M.G. Franzosi[2], C.M. Lewis[1], S. Signorini[3], S. Barlera[2], A. D'Orazio[4], P. Mocarelli[3], G. Tognoni[4] on behalf of GISSI-Investigators. *[1]Guy's Hospital, Division of Genetics and Development, London, United Kingdom; [2]"Mario Negri" Institute, Department of Cardiovascular Research, Milan, Italy; [3]Hospital of Desio, University Department of Laboratory Medicine, Milan, Italy; [4]Consorzio Mario Negri Sud, Santa Maria Imbaro, Italy*

Background: Controversy exists with regard to the influence of APOE polymorphisms on coronary heart disease development and on the efficacy of statin treatment. We investigated the relationship between APO E, mortality and the response to treatment in Mediterranean myocardial infarction (MI) survivors.
Methods and Results: We analyzed 2650 Italian patients who entered the second part of the GISSI-Prevenzione study that randomized patients to pravastatin or no-treatment. Due to premature stopping of this part of the GISSI-Prevenzione study, mean follow-up time was 23.0$\pm$6.7 months, and no significant longer survival was found in patients assigned to pravastatin (p=0.26). Survival curves were calculated using Kaplan-Meier survival analysis, and differences in survival were tested using the log-rank test.
Evidence of interaction between ApoE genotype and treatment was found in a logistic regression model (p=0.06).
In 2220 non-E4 carriers, the survival probabilities were 94.8% in non-treated and 96% in treated patients at the end of the study follow-up and no significant difference in survival was observed (p=0.14). Among the 430 E4 carriers the survival probabilities were 93% in non-treated and 99.2% in treated patients at the end of the follow-up. A significant longer survival was observed in the treated compared to non-treated patients (p=0.02).
Conclusions: We found that E4 allele is a determinant of pravastatin response in terms of survival.
This finding raises the question of whether statins should be considered as an even better, safer, life-saving aspirin for all, or whether patients should be prescribed statins only to be protected from a genetically based risk.

P3503 Rosuvastatin 40 mg versus atorvastatin 80 mg in high-risk patients with hypercholesterolaemia: results of the POLARIS study at 8 and 26 weeks

L.A. Leiter[1], M. Palmer[2], F. Sosef[3] on behalf of the POLARIS study investigators. *[1]University of Toronto, Toronto, Canada; [2]AstraZeneca, Macclesfield, United Kingdom; [3]AstraZeneca, Macclesfield, United Kingdom*

Objective: This 26-week, double-blind, randomised study (4522IL/0106) compared the efficacy of rosuvastatin (RSV) 40 mg with atorvastatin (ATV) 80 mg in high-risk patients (known CHD or CHD-risk equivalent, as defined by NCEP ATP III) with hypercholesterolaemia.
Methods: After a 6-week dietary lead-in period, 871 patients (45-80 years) with LDL-C >4.1 and <6.5 mmol/l and TG <4.5 mmol/l were randomly assigned to treatment with RSV 20 mg or ATV 40 mg daily for 2 weeks, followed by forced titration to RSV 40 mg or ATV 80 mg, respectively, for 6 weeks. Depending on LDL-C level, either the dose was maintained for 18 weeks, the dose reduced, or additional lipid-lowering therapy prescribed. The primary end point was change from baseline in LDL-C at 8 weeks. Secondary end points included lipid goal achievement, effects on other lipids and lipoproteins, and safety at 8 and 26 weeks. Statistical analyses were performed on 8-week data only.
Results: LDL-C reductions were significantly greater in the RSV 40 mg group than the ATV 80 mg group at 8 weeks (56 vs 52%, $p<0.001$). HDL-C and apoB improved significantly more in RSV-treated patients than ATV-treated patients at 8 weeks (Table). At 26 weeks, effects were consistent with those observed at 8 weeks. At 8 weeks, significantly more patients achieved 2003 European LDL-C goals in the RSV 40 mg group than ATV 80 mg group (79 vs 69%, $p<0.001$). At 26 weeks, 81% of RSV-treated patients and 71% of ATV-treated patients achieved goals. Treatments were well tolerated with a similar adverse event profile in each group.

Mean % change from baseline

	RSV 40 mg group: 8 wks (LSM)	ATV 80 mg group: 8 wks (LSM)	RSV group: 26 wks	ATV group: 26 wks
LDL-C	-56***	-52	-57	-53
HDL-C	+9.6***	+4.4	+11.0	+6.2
TC	-40	-39	-41	-39
TG	-22	-27^	-24	-28
apoB	-45*	-42	-45	-43

At 8 wks, *p<0.05 vs ATV, ***p<0.001 vs ATV, ^p<0.05 vs RSV; LSM=least-squares mean

Conclusion: In high-risk patients with hypercholesterolaemia, RSV 40 mg was significantly more effective than ATV 80 mg at improving LDL-C, HDL-C and apoB and enabling patients to achieve 2003 European LDL-C goals after 8 weeks. Results at 26 weeks were consistent with those observed at 8 weeks.

P3504 Safety and tolerability of coadministered amlodipine and atorvastatin in patients with concomitant hypertension and dyslipidemia in the Respond study

J.W. Jukema[1], R.A. Preston[2], F. Sun[3], L. Tarasenko[3]. *[1]Leiden University Medical Center, Cardiology Department C5-P, Leiden, Netherlands; [2]University of Miami School of Medicine, Division of Clinical Pharmacology, Miami, United States of America; [3]Pfizer Inc, New York, United States of America*

Background: Amlodipine/atorvastatin combination therapy has been demonstrated to be an effective approach for the management of concomitant hypertension (HTN) and dyslipidemia (DYS). However, a potential barrier to the use of this treatment might be concerns regarding the occurrence of adverse events (AEs) when coadministering these 2 therapies.
Methods: This randomized, double-blind, multicenter, placebo-controlled, 3x5 factorial study assessed the safety of coadministered amlodipine plus atorvastatin therapy versus either drug alone or placebo. Patients aged 18–75 years with concomitant HTN/DYS were treated for 8 weeks with amlodipine (5 or 10 mg), atorvastatin (10, 20, 40, or 80 mg), 8 combinations of the aforementioned amlodipine plus atorvastatin doses, or placebo. All-causality, treatment-emergent AEs are reported.

Results: A total of 1660 patients with concomitant HTN/DYS (n=110-111 per treatment group) were included in the safety analysis. Overall, 663 (40%) patients reported AEs. Rates of discontinuation due to AEs were similar in the combination (5.6%), amlodipine alone (5.4%), atorvastatin alone (4.1%), and placebo (4.5%) groups. Most AEs were mild or moderate in intensity. Overall, the most common AEs were peripheral edema (overall 7.4%: amlodipine alone 12.2%, atorvastatin alone 1.1%, amlodipine plus atorvastatin 9.9%, placebo 2.7%), headache (6.2%), and respiratory tract infection (4.3%). The incidence of myalgia in combination-treated patients was low (1.6%) and similar to the amlodipine or atorvastatin alone and placebo groups (1.4%, 1.8%, and 1.8%, respectively). No increase in the incidence of AEs was observed with coadministered amlodipine 10 mg plus atorvastatin 80 mg (41.4%) versus amlodipine 10 mg alone (47.7%), and only a small increase versus atorvastatin 80 mg alone (37.3%).
Conclusion: Coadministered amlodipine plus atorvastatin is well tolerated in patients with concomitant HTN/DYS. Furthermore, AEs observed with coadministered amlodipine plus atorvastatin are similar in nature, severity, and frequency to those seen with amlodipine or atorvastatin alone.

P3505 Implementation of a treatment strategy for concomitant hypertension and dyslipidemia with amlodipine and atorvastatin produces significant reduction in Framingham cardiovascular risk

R.A. Preston[1], J.W. Jukema[2], P. Harvey[3], O. Herfert[4], G. Dykstra[5], F. Sun[6], D. Gillen[6]. *[1]University of Miami, Division of Clinical Pharmacology, Miami, United States of America; [2]Leiden University Medical Center, Department of Cardiology, Leiden, Netherlands; [3]Crouch Oak Family Practice, Addlestone, United Kingdom; [4]Linzer Strasse 4, General Practice, Stuttgart, Germany; [5]Bluestem Cardiology, Bartlesville, United States of America; [6]Pfizer Inc, New York, United States of America*

Background: Recent consensus guidelines have uniformly stressed the importance of the simultaneous management of multiple cardiovascular risk factors; however, the actual effects of such strategies have not been adequately tested by clinical trials. The Respond study investigated the efficacy of systematic concurrent treatment of concomitant hypertension and dyslipidemia.
Methods: Respond is a 3x5 factorial, multicenter, double-blind, placebo-controlled trial undertaken in 1660 patients with hypertension and dyslipidemia from 15 countries, randomized to 1 of 15 combinations of amlodipine besylate (placebo, 5, or 10 mg) and atorvastatin calcium (placebo, 10, 20, 40, 80 mg). The main efficacy assessments were mean change in systolic blood pressure (SBP) and low-density lipoprotein cholesterol (LDL-C). A key clinical secondary endpoint was change from baseline to end point in Framingham risk score in patients without coronary heart disease (CHD) or risk equivalent (n = 830).
Results: At 8 weeks, combination-treated patients experienced dose-related and statistically significant reductions in SBP, LDL-C, and Framingham risk score, resulting in 7.7–11.2 mean percentage point reductions at end point (from mean baseline levels of 15.8–18.5%) in the estimated 10-year risk of developing CHD (Table).

Table 1. Mean reduction in estimated 10-year CHD risk (percentage points)

		Amlodipine dose		
		Placebo	5 mg	10 mg
Atorvastatin dose	Placebo	-0.6	-2.9	-4.8
	10 mg	-6.7	-8.8	-7.7
	20 mg	-6.2	-8.0	-9.2
	40 mg	-7.1	-8.2	-9.9
	80 mg	-7.2	-11.2	-11.2

Conclusion: Simultaneous treatment of concomitant hypertension and dyslipidemia with co-administered amlodipine and atorvastatin is a highly effective strategy for reducing SBP, LDL-C, and Framingham risk score.

P3506 The risk of bleeding complications after different doses of aspirin: a post-hoc analysis of 192,036 patients enrolled in 31 randomised controlled trials

V.L. Serebruany[1], A. Malinin[2], S.R. Steinhubl[3], P.B. Berger[4], B. Oshrine[1], J.S. Baggish[5], D.L. Bhatt[6], E.J. Topol[6]. *[1]HeartDrug, Towson, United States of America; [2]Barnaul, Russian Federation; [3]University of Kentucky, Lexington, United States of America; [4]Duke Clinical Research Institute, Durham, United States of America; [5]McNeil Pharmaceuticals, Ft. Washington, United States of America; [6]Cleveland Clinic, Cleveland, United States of America*

Background: Aspirin (ASA) has been a cornerstone for the prevention and treatment of vascular disease. Despite life-saving clinical benefits, ASA therapy is associated with an increased risk of bleeding, especially when associated with higher doses. The objective of this study was to determine and compare the risk of hemorrhage for the low (<100 mg), moderate (100-200mg), and high (>200 mg) doses of ASA. This analysis is specific to ASA and uses dose cutoffs that are well established in the literature and applicable to clopidogrel-aspirin combination therapy, thereby making it more clinically relevant and practical for physicians prescribing antiplatelet agents.
Methods: Data from clinical trials published 1988-2003 in English were retrieved from MEDLINE, OVID, and CARDIOSOURCE. Only those studies in which patients had clinical follow-up for at least one month and in which a detailed description of hemorrhagic complications was reported were included. Information on sample size, study design, duration, ASA dose, patient characteristics and bleeding severity was independently and blindly reviewed. Data from 31 clinical trials with a total of 192,036 patients met the quality criteria, and were analyzed. Bleeding events were classified as major (Mj), minor (Mn), hemorrhagic stroke (HS), gastrointestinal (GI), fatal/life threatening (FLT), and total (T). The rates, variance estimate, and confidence intervals were calculated for each ASA dose dependent on a bleeding type.
Results: Low dose (<100 mg/day) ASA was associated with the lowest risk of bleeding (Mj –1.56%, Mn – 4.9%, HS - 0.24%, GI - 0.97%, FLT – 0.27%, for the T – 3.72%). Moderate daily dose of ASA (100-200mg) was associated with the low risk for Mj (1.54%), GI (0.39%), and FLT (0.46%) bleeding complications, while the rate of Mn (6.75%), and T (11.31%) hemorrhagic events was relatively high. The greatest rate of bleeding complications was associated with the higher (>200 mg) ASA doses, however the HS (0.65%) were significantly (p=0.007) higher in the 100-200mg/daily cohort.
Conclusion: Despite substantial differences in the reporting patterns of bleeding complications, low dose (<100 mg) ASA was associated with the lowest risk, and doses over 200 mg cause the highest bleeding rate. Doses of ASA between 100 - 200 mg also caused a relatively high hemorrhagic event rate, especially with regard to minor or total bleeding, and stroke. These findings should be considered when using combination antiplatelet and/or anticoagulant therapy with ASA, especially with the daily dose over 100 mg.

P3507 Aspirin resistance: a clinical phenomenon or simply a matter of the patients compliance?

M. Marchel[1], M. Postula[2], K.J. Filipiak[2], M. Banas[2], E. Trzepla[2], D. Bobilewicz[3], B. Tarchalska-Krynska[4], G. Opolski[2]. *[1]Warsaw Medical University, 1st Department of Cardiology, Warsaw, Poland; [2]Warsaw Medical University, 1st Department of Cardiology, Warsaw, Poland; [3]Warsaw Medical University, Department of Laborartory Diagnostics, Warsaw, Poland; [4]Warsaw Medical University, Department of Pharmacology, Warsaw, Poland*

Background: Acetylsalicylic acid (aspirin) is widely used in secondary prevention of coronary artery diseases; however, the inhibition of platelet aggregation is variable among individuals. There is abundant research regarding the clinical phenomenon of aspirin resistance. The aim of the present study was to determine to what extend the failure of aspirin to inhibit the platelet function is due to the patient's non-compliance to medical treatment.
Methods: 91 patients with stable coronary artery disease (mean age 67±8,5) taking aspirin (75-160 mg/day, mean dose 83,7±21,3 mg) for at least one month were prospectively studied. Aspirin resistance was measured by the platelet function analyzer (PFA-100). Compliance was assessed by means of a self-report questionnaire designed specifically for the purpose of the present study.
Results: Aspirin resistance was defined as a normal collagen/epinephrine closure time on the PFA-100 (<180 s); the prevalence of aspirin resistance was 47,3% (n = 43). The mean epinephrine closure times for aspirin resistant and aspirin sensitive patients were (125,5±27,2 vs. 280,9±33,1; p<0,0001), respectively. There were no differences in aspirin sensitivity with regard to age, gender, hypertension, diabetes, dyslipidemia, or platelet count. There was a significant difference between the two groups (aspirin resistant and aspirin sensitive) in the number of aspirin pills the patients forgot to take during the previous ten days (2,1±2,3 vs. 1,2±0,8, p<0,02).
Conclusions: In the studied group patients with aspirin resistance were less compliant to medical treatment. Non-compliance may be one of the most important factors responsible for the phenomenon of aspirin resistance.

P3508 Aspirin in the primary prevention of cardiovascular disease – the health economic perspective

M. Lamotte[1], L. Annemans[1], M. Kubin[2], T. Evers[3]. *[1]HEDM, Brussels, Belgium; [2]Bayer Healthcare AG, Health Economics & Outcomes Research, Wuppertal, Germany; [3]Bayer Vital GmbH, Health Economics & Outcomes Research, Leverkusen, Germany*

Purpose: Low-dose aspirin is standard care in patients with a history of cardiovascular disease (CVD). Recent meta-analyses and US and European guidelines support its use in primary prevention in persons at increased CVD risk. This study assessed the health economic consequences of the use of low-dose Aspirin in the primary prevention of CVD in the UK, Germany, Italy and Spain from the healthcare payer perspective.
Methods: Based on two recent meta-analyses, a health economic model was developed to compare the total cost and effectiveness of low-dose aspirin in the primary prevention of CVD over 10 years. The model was applied to patients with a 10-year risk of CHD of 20% (about 5% using the SCORE method) needing low-dose aspirin according the European guidelines. Country-specific costs were determined. Effects are expressed in Quality Adjusted Life Years (QALY).
Results: For patients with a 10-year CHD risk of 20% the model results in significant savings in the four countries (see table). Savings start from the first year on. Sensitivity analyses proved robustness of the results. Based on available epi-

demiological data a conservative estimate on the number of eligible patients and the possible savings was made (see Table 1).

Table 1. Difference in total costs and gains in quality-adjusted life years over 10 years

Country	Strategy	Total cost per patient (€)	Difference in total costs (€)	Qaly gained	Eligible patients (million)	Total savings over 3 years (€)
UK	No Aspirin	1,753				
	Aspirin	1,483	-270	0.05	5.6	340 Million
Germany	No Aspirin	2,095				
	Aspirin	1,708	-386	0.04	7.7	731 Million
Italy	No Aspirin	4,588				
	Aspirin	3,966	-622	0.05	2.6	345 Million
Spain	No Aspirin	7,487				
	Aspirin	6,420	-1,067	0.05	4.3	929 Million

Conclusions: Administering low-dose aspirin to patients with an increased CHD risk according the European guidelines is significantly cost-saving from the health care payer's perspective. Both on clinical and economic grounds, primary prevention with low-dose aspirin seems recommendable in this population.

P3509 Loading with 375 mg dose of clopidogrel after percutaneous coronary intervention in high risk patients results in excellent long-term outcomes, comparable to pretreatment group of CREDO trial

R.S. Kiesz[1], P. Buszman[2], O. Munoz[1], M. Walker[3]. [1]*San Antonio Endovascular & Heart Insti, San Antonio, United States of America;* [2]*Silecian Medical School, Katowice, Poland;* [3]*San Antonio Endovascular & Heart Institute, San Antonio, United States of America*

Background: CREDO trial established cause for pretreatment of patients undergoing percutaneous coronary intervention. However, there is a small but substantial risk of emergent bypass surgery. Patients treated with clopidogrel do have high risk of perioperative and postoperative bleeding. CREDO trial compared 300mg loading dose and pretreatment to maintenance dose 75mg on day of procedure. We hypothesized that delayed loading dose of 375 mg of clopidogrel given at the end of percutaneous coronary intervention, when patients' acute favorable outcome is ensured, will result in favorable and long-term outcomes. This approach would avoid sending patients on clopidogrel therapy for emergent bypass, thus avoiding risk of excessive bleeding.
Methods: 356 patients undergoing 474 PCI procedures for stable angina and acute coronary syndrome, including Q wave MI and cardiogenic shock, received 375 mg of clopidigrel at the end of the procedure, after PCI was complete. Each patient was also treated with 325 mg of aspirin. They were followed postoperatively for a period of one year.
Results: See table.

Follow-up	28 Day Results	1 Year Results	1 Year CREDO Results
MI, Stroke, Death	1.12%	7.5%	8.5%
MI, Death	0.28%	3.9%	7.9%
Death	0.56%	0.56%	1.7%
MI	0.56%	5.6%	6.7%
Stroke	0	1.4%	0.9%
CABG	0.28%	3.6%	

Conclusions: Loading with clopidogrel at the end of PCI in high risk patients results in excellent acute and long-term outcomes thus obviating the need for pretreatment and is comparable to results of pretreatment arm of the CREDO trial. This approach eliminates the risk of increased bleeding complications in case of emergent coronary artery bypass graft.

P3510 Pharmacogenetic modulation of clopidogrel antiplatelet effects: role of gene sequence variations of the CYP3A4 enzyme

D.J. Angiolillo[1], E. Bernardo[2], C. Ramirez[2], U. Cavallari[3], E. Trabetti[3], P.F. Pignatti[3], A. Fernandez-Ortiz[2], C. Macaya[2]. [1]*University of Florida, Cardiology-Shands Jacksonville, Jacksonville, United States of America;* [2]*San Carlos University Hospital, Interventional Cardiology Unit, Madrid, Spain;* [3]*University of Verona, Dept. Mother and Child&Biology-Genetic, Verona, Italy*

Clopidogrel is activated by cytochrome P450 (CYP) 3A4 and the activity of this enzyme contributes to variability in platelet responsiveness to clopidogrel. Since metabolic activity of CYP3A4 is under genetic control, we hypothesized that gene sequence variations of CYP3A4 influences clopidogrel induced antiplatelet effects.
Methods: The CYP3A4*1B, CYP3A4*3 and IVS10+12G>A polymorphisms of the CYP3A4 gene were assessed in 127 patients: 45 receiving a 300 mg clopidogrel loading-dose (Group A) and 82 on long-term (>1 month) clopidogrel (75 mg/d) treatment (Group B). All patients were on aspirin (100 mg/d). Patients were divided into 2 subgroups according to the presence or absence of the mutant allele. Activated GPIIb/IIIa (anti-Fibrinogen-FITC; expressed as % of positive platelets) was assessed by whole blood flow cytometry in ADP (2 μM)-stimulated platelets at baseline, 4 and 24 hours after loading-dose (Group A) and following long-term treatment (Group B).
Results: Only the IVS10+12G>A polymorphism was sufficiently polymorphic (in Hardy-Weinberg equilibrium). Carriers and non-carriers of the mutant allele of this polymorphism were present in 9/45 (20%) and 36/45 (80%) of Group A, and in 14/82 (17%) and 68/82 (83%) of Group B. Patients had similar platelet reactivity at baseline (before clopidogrel front-loading, while patients were only on aspirin). Carriers of the mutant allele had a greater inhibition of the GP IIb/IIIa receptor in group A (4 and 24 hours after clopidogrel and during the overall study time as assessed by MANOVA) and group B (table; mean±SD).

	Non-carriers (GG genotype)	Carriers (AG+GG genotypes)	p
Group A			
Baseline	66.1±21	57.1±31	0.7
4 hours	53.4±29	31.5±24	0.06
24 hours	50.4±25	26.7±27	0.05
MANOVA (Multivariate analysis of variance)			0.025
Group B	50.4±25	27.0±27	0.026

Conclusions: Gene sequence variations of CYP3A4 modulate clopidogrel antiplatelet effects in both the acute and chronic phases of treatment and may therefore contribute to individual variability in platelet responsiveness to clopidogrel.

P3511 Effective inhibition of platelets by low dose tirofiban

A. Aydinalp[1], S. Acikel[2], O. Gulmez[2], I. Atar[2], H. Bozbas[2], H. Muderrisoglu[2]. [1]*Baskent University Tip Fakultesi, Ankara, Turkey;* [2]*Baskent University School of Medicine, Cardiology, Ankara, Turkey*

Background: The body-weight–adjusted standard doses of the glycoprotein IIb/IIIa antagonists recommended today are selected according to previous clinical trials that were based on the inhibition of platelet aggregation using in vitro platelet aggregometry on the basis of small number of patients. We tested the effectiveness of a lower dose of glycoprotein IIb/IIIa antagonists by bedside rapid platelet function assays (RPFA).
Methods: Patients with acute coronary syndromes (ACS) and candidates for elective percutaneous coronary interventions (PCI) received 80% of the standard bolus dose recommended. After receiving 80% of the standard bolus dose, platelet inhibition with RPFA was measured. Patients with 80% inhibition of the platelets received standard infusion for 24 hours and the patients without 80% platelet inhibition received additional doses to complete full bolus dose and standard infusion for 24 hours. We checked the platelet inhibition percentage at baseline, after the reduced bolus dose, and after 8 hours of tirofiban infusion therapy.
Results: Twenty-seven patients, 14 (51.8%) with acute coronary syndrome and 13 (48.1%) undergoing elective angioplasty were randomly assigned to the study. Baseline clinical characteristics were as follows, mean age 60±7, 17 male (63%),19 hypertension (70.4%), 8 diabetes mellitus (29.6%), 20 dyslipidemia (74.1%), 13 family history of heart disease (48.1%), 14 smoker (51.9%). Twenty-four of the 27 patients (88.9%) had effective platelet inhibition with 80% of the standard-dose bolus treatment (P=0.0001). All of the patients with effective platelet inhibition after the reduced-bolus dose maintained effective platelet inhibition 8 hours after the standard-dose tirofiban infusion (table).

Table

Platelet Inhibition %	< 80	>80	p
Reduced bolus (n=27)	3 (11.1%)	24 (88.9%)	0.0001
8.hours (n=24)	0	24 (100%)	

Inhibition of Platelets with Reduced-Dose Tirofiban

Conclusion: Lower doses of tirofiban are effective in most of the patients with ACS and in patients undergoing elective PCI. Bedside platelet inhibition assay devices are useful for measuring effectiveness of the treatment with lower doses of tirofiban.

P3512 Pharmacokinetics and pharmacodynamics of prasugrel (CS-747, LY640315), a novel thienopyridine P2Y12 receptor antagonist, in healthy subjects

C.D. Payne[1], J.A. Jakubowski[2], J.T. Brandt[2], G.J. Weerakkody[2], N.A. Farid[2], M. Jansen[1], D. Salazar[3], K.J. Winters[4]. [1]*Eli Lilly and Company, Lilly Research Centre, Ltd., Windlesham, United Kingdom;* [2]*Eli Lilly and Company, Lilly Research Laboratories, Indianapolis, United States of America;* [3]*Sankyo Co., Ltd., Sankyo Pharma Development, Edison, United States of America;* [4]*Eli Lilly and Company, Indianapolis, United States of America*

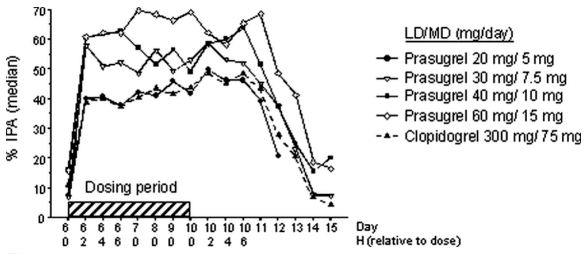
Purpose: Prasugrel (CS-747, LY640315), a novel P2Y12 ADP receptor antagonist, provided more potent inhibition of platelet aggregation (IPA) verses clopidogrel in preclinical studies. This phase 1 study investigated the antiplatelet effects and pharmacokinetics of prasugrel during 21 days of repeat dosing.
Methods: Thirty-two subjects were randomly assigned to 1 of 3 prasugrel oral dosing regimens with a loading dose (LD) on day 1 and a maintenance dose (MD) on days 2-21: 1) prasugrel 40 mg LD/7.5 mg MD, 2) prasugrel 60 mg LD/15 mg MD, 3) placebo LD/placebo MD. IPA was assessed by turbidometric aggregometry using 20 μM ADP as agonist. Pharmacokinetics of 3 inactive metabolites were measured at preselected time points between days 1 and day 26.

Results: Both LDs of prasugrel were effective in rapidly and consistently inhibiting ADP-induced platelet aggregation and achieved substantial levels of IPA (median 65%). The differences in median IPA between both prasugrel groups and placebo were statistically significant within the first hour following the LDs and throughout the MD phase. The prasugrel 15 mg MD regimen was able to maintain the high level of median IPA achieved by the LD; the median IPA with the 7.5 mg MD decreased to approximately 40% by day 14, becoming statistically different to that of the 15 mg MD at day 21. The pharmacokinetics of 3 inactive metabolites of prasugrel were well described by an integrated population pharmacokinetic model. From the pharmacokinetic behavior of these metabolites, it can be inferred that prasugrel was absorbed rapidly, demonstrating only modest intra- and inter-subject variability. The pharmacokinetic parameters for prasugrel metabolites appeared consistent across dose. Among all subjects, the most frequently reported ($\geq$ 10 events) drug-related adverse events were headache, hematoma (procedural related), and dizziness.
Conclusions: In healthy subjects, both prasugrel dosing regimens (60 mg LD/15 mg MD and 40 mg LD/7.5 mg MD) demonstrated consistently high levels of platelet inhibition and were safe and well tolerated. Pharmacokinetics for 3 inactive metabolites of prasugrel indicate that prasugrel was absorbed rapidly and metabolized in all subjects with modest variability.

P3513 Platelet inhibition and pharmacokinetics following prasugrel (CS-747, LY640315), a novel thienopyridine P2Y12 receptor antagonist, or clopidogrel in healthy, aspirin-treated subjects

C.D. Payne[1], J.A. Jakubowski[2], J.T. Brandt[2], G.J. Weerakkody[2], M. Jansen[1], H. Naganuma[3], K.J. Winters[4]. *[1]Eli Lilly and Company, Lilly Research Centre, Ltd., Windlesham, United Kingdom; [2]Eli Lilly and Company, Lilly Research Laboratories, Indianapolis, United States of America; [3]Sankyo Co., Ltd., Tokyo, Japan; [4]Eli Lilly and Company, Indianapolis, United States of America*

Purpose: Prasugrel (CS-747, LY640315, Pras) is a novel, oral, P2Y12 antagonist pro-drug that has demonstrated in preclinical studies more potent inhibition of platelet aggregation (IPA) versus clopidogrel (Clop). This phase 1 study investigated the level of IPA and the pharmacokinetics (PK) of Pras during a dose-ranging study verses Clop in healthy aspirin (ASA)-treated subjects.
Methods: All subjects received ASA (325 mg enteric coated) on days 1-10. Subjects were randomly assigned to 1 of 4 oral Pras-dosing regimens (n=8/group) or a Clop-dosing group (n=12). Subjects received a day 6 loading dose (LD) and a once daily maintenance dose (MD) on days 7-10: Pras with LD/MD of 20 mg/5 mg, 30 mg/7.5 mg, 40 mg/10 mg, 60 mg/15 mg, or Clop 300 mg LD/75 mg MD. IPA to 20 μM ADP was assessed by turbidometric aggregometry. The PK of 3 inactive Pras metabolites were measured at preselected time points.
Results: ADP-induced platelet aggregation was inhibited rapidly following Pras LD. All LD except Pras 20 mg achieved higher IPA compared to Clop 300 mg by 2 hours ($p<.05$) and was maintained until 24 hour post-LD. After 4 days MD, Pras 15 mg maintained a higher level of IPA than Clop 75 mg (69% versus 44%; $p<.05$). Metabolites were formed rapidly in a dose-linear fashion. Pras therapy was well tolerated by all subjects, except for increased rate of bruising events in the Pras 60 mg LD/15 mg MD group. The PK of 3 inactive Pras metabolites fit an integrated population PK model.



Figure

Conclusions: In healthy ASA-treated subjects, Pras at the 30 mg/7.5 mg, 40 mg/10 mg, and 60 mg/15 mg dosing regimens produced greater IPA than Clop at the 300 mg/75 mg dosing regimen and was well tolerated.

P3514 P2Y12 receptor polymorphism and clopidogrel response: is there a link?

D.J. Angiolillo[1], E. Bernardo[2], C. Ramirez[2], U. Cavallari[3], E. Trabetti[3], P.F. Pignatti[3], A. Fernandez-Ortiz[2], C. Macaya[2]. *[1]University of Florida, Cardiology-Shands Jacksonville, Jacksonville, United States of America; [2]San Carlos University Hospital, Interventional Cardiology Unit, Madrid, Spain; [3]University of Verona, Dept. Mother and Child&Biology-Genetic, Verona, Italy*

Clopidogrel (C) inhibits the ADP subtype P2Y12 receptor. Polymorphisms of this receptor have been associated with different degrees of platelet function in healthy volunteers and suggested to modulate individual response to C. However, the modulating role of this polymorphism on C response in patients with coronary artery disease on C therapy is still unknown.
Methods: The T744C polymorphism of the P2Y12 receptor was assessed in 116 pts: Group A (GA), 36 pts undergoing coronary stenting receiving a 300mg C loading-dose; Group B (GB), 80 pts on long-term (>1month) C treatment (75 mg/d). Pts were divided into:TT homozygotes and C carriers. All pts were on aspirin (100 mg/d). Platelet function assessments included: platelet aggregation (PA) in platelet-rich plasma stimulated with ADP 6μM; platelet activation (P-selectin expression and activated GPIIb/IIIa anti-Fibrinogen-FITC using whole blood flow cytometry) in ADP 2μM-stimulated platelets. Platelet function was assessed at baseline, 4 and 24 hours following C loading-dose in GA, and once in GB.
Results: The genotype distribution was:GA 22/36 (61%) TT and 14/36 (39%) C carriers (11 CT and 3 CC); GB: 53/80 (66%) TT and 27/80 (34%) C carriers (24 CT and 3 CC).There were no differences between groups for all platelet function assessments (Table 1).

Table 1

	TT	C carriers	p
GA PA baseline	58.0±18	47.4±14.8	0.7
GA PA 4 hours	43.4±19	37.9±15.2	0.4
GA PA 24 hours	34.1±21	29.7±16.8	0.5
GA GPIIb/IIIa baseline	57.9±26	66.3±1.9	0.4
GA GPIIb/IIIa 4 hours	46.2±30	49.1±31.2	0.8
GA GPIIb/IIIa 24 hours	45.6±23	41.7±32.4	0.7
GA P-selectin baseline	45.4±18	46.5±23	0.8
GA P-selectin 4 hours	30.3±16	25.5±10.4	0.4
GA P-selectin 24 hours	26.4±15	30.0±15.9	0.5
GB PA	33.0±15	30.6±13	0.5
GB GPIIb/IIIa	36.6±24	30.6±24	0.5
GB P-selectin	21.5±15	18.1±16	0.4

Conclusions: The T744C polymorphism of the P2Y12 receptor does not influence individuals' responsiveness to C.

MISCELLANEOUS

P3515 Does risk profile influence management of patients with NonST elevation coronary syndromes?

G. Ambrosio, M. del Pinto, F. Angeli, A. Broccatelli, C. Castellani, S. Notaristefano. *Univ of Perugia School of Medicine, Division of Cardiology, Perugia, Italy*

Background: Current guidelines based on large clinical trials recommend that patients (pts) with Non-ST elevation acute coronary syndromes (NSTE-ACS) be managed by early coronary angiogram (ANGIO) and possible revascularization. However, implementation of this approach in clinical practice seems to lag much behind guidelines.
Objective: To verify adherence to guidelines in pts admitted for NSTE-ACS in the "real world", and to investigate how clinical features influence decision making and ultimate resource utilization.
Design: In NSTE-ACS pts admitted over a 3-mo period at 62 centers (32 with on-site cath lab) we evaluated whether they underwent ANGIO, and how this correlated with indices of high risk.
Results: Data from 2,606 pts were collected. Of these, 1,566 pts (60%) were admitted to centers with cath lab, and 1,040 without (40%). Overall, ANGIO was performed in 33.7% of pts.
Table shows rate of ANGIO according to indices of high risk. While guidelines mandate invasive approach in all pts in whom any high-risk feature is present, only a third of such pts actually received ANGIO. Furthermore, among pts who did get ANGIO, use of invasive strategy was not driven by their high-risk characteristics. In fact, likelihood of undergoing ANGIO was unaffected by TIMI risk score, ECG, or troponin, and it was paradoxically lower in older or diabetic pts. Centers with cath lab showed the expected overall greater use of ANGIO (45% of cases); yet, this was performed only in 42.8% of pts with TIMI risk score ^{3}3, and older pts were treated invasively still less frequently (40.5%) than younger pts (52.1%; $p<0.001$). Interestingly, presence of angina was the major predictor of the decision to proceed with ANGIO (38.1% vs 24.3%; $p<0.01$). GPIIb/IIIa inhibitors were not appropriately used, as 27% of treated pts did not undergo ANGIO.

%	TIMI >3	ST dev >5 mm	Age >65 yr	Diabetes	Troponin +
ANGIO YES	33.7	34.2	30.1	21.0	32.0
ANGIO NO	33.7	32.7	39.3 *	36.0 *	35.0

Conclusion: In this multicenter survey, the majority of high-risk pts with NSTE-ACS did not enjoy early invasive management as recommended. Resource utilization was also suboptimal, as cath lab availability enhanced overall probability to undergo invasive procedures but it did not guarantee proper patient selection.

P3516 Reasons for the gap between guidelines and practice in acute coronary syndromes (ACS). Data from the FACT Nationwide French registry

P.G. Steg[1], G. Montalescot[2], P. Ravaud[3], P. Goldstein[4], G. Jullien[5], J.-J. Dujardin[6], B. Chevalier[7], J. Puel[8] on behalf of FACT registry investigators. *[1]Hopital Bichat-Cl.Bernard, Service de Cardiologie, Paris Cedex 18, France; [2]Hôpital Pitié-Salpétrière, Paris, France; [3]Hôpital Bichat-Claude Bernard, Paris, France; [4]SAMU Régional, Lille, France; [5]Marseille, France; [6]Hôpital de Douai, Douai, France; [7]CCN, Saint-Denis, France; [8]Hôpital Rangueil, Toulouse, France*

Background: "Real-life" patients with ACS are not treated according to guidelines. The magnitude and causes for this gap between evidence and clinical practice remain debated.
Aims: Measuring adherence to evidence-based therapies and querying the reasons for discrepancies between practice and guidelines.
Methods: The FACT registry is a nationwide survey conducted in January 2003 in France. We studied the use of 6 evidence-based therapies (+ one dummy therapy) listed in the Table and collected individually reasons of non-compliance. FACT involved 361 cardiologists who enrolled 3,902 patients with suspected ACS. Distribution of ACS types was 36.8% STEMI, 41.3% NSTEMI and 12.7% unstable angina. The remaining 9.2% were assigned a discharge diagnosis of other disease. The table shows prescription rates of evidence-based therapies for the 3,840 confirmed ACS patients. For all therapies except one, the main reason for lack of use of evidence-based therapies was ineligibility or intolerance. This emphasizes the need for availability of detailed clinical data in order to analyze the causes of "non-compliance" with the guidelines. The "gap" may have been overestimated. Conversely, GP IIb/IIIa inhibitors were used in only a fourth of eligible high-risk patients (TIMI score of 5 or more). The main reasons given for non-prescription were "negative troponins" (52%), "oral antiplatelet treatment sufficient" (37%) or "risk/benefit ratio insufficient" (23%).
Results:

	Compliance	Noncompliance in eligible pts	ineligible
Reperfusion therapy for STEMI < 12h	83.2%	3.4%	13.5%
betablockers in NQWMI	79.9%	2.4%	17.7%
Antiplatelet at discharge	92%	1.7%	6.3%
GpIIb/IIIa blocker if TIMI risk > 5	26.1%	58.3%	15.7%
ACEI in LV dysfunction/CHF	71.5%	5.4%	23.1%
Statin if LDL-C > 1.3 g/l	91.8%	6%	2.3%

Conclusions: 1. Compliance with evidence-based therapies in ACS varies according to agent type.
2. For most therapies except use GP IIb/IIIa blockers in high-risk patients, lack of use is largely explained by ineligibility or intolerance.
3. Efforts to improve use of evidence-based therapies in ACS should focus on GpIIb/IIIa blockers.

P3517 Primary percutaneous coronary interventions (PCI) versus fibrinolytic therapy in acute myocardial infarction: re-evaluating the influence of time delay

C. Asseburg[1], Y. Bravo[1], L. Fenwick[1], S. Palmer[1], K. Abrams[2], M. de Belder[3], M. Sculpher[1]. *[1]The University of York, Centre for Health Economics, York, United Kingdom; [2]University of Leicester, Department of Health Sciences, Leicester, United Kingdom; [3]The James Cook University Hospital, Middlesbrough, United Kingdom*

Background: Time delay - i. e. the additional time it takes to administer PCI rather than fibrinolytic therapy - is thought to have a significant negative impact on the superiority of PCI with regards to deaths at 4-6 weeks in STEMI patients (Nallamothu and Bates, 2003).
Methods: Using a Bayesian framework, we improve this meta-regression by updating the systematic review and analysing secondary endpoint data on non-fatal re-infarctions and strokes. We also extend the time horizon of the model to predict events at 6 months.
Results: Our findings confirm the notion that the mortality benefit associated with PCI in STEMI patients may be negligible when balloon treatment is delayed by more than 1 hour compared to fibrinolytic therapy (see Table 1). However, we show that, in terms of both non-fatal re-infarctions and non-fatal strokes, PCI is the superior treatment even at delays of 80 minutes or more. The assumption that treatment effects after 1 month carry through to the 6-month endpoints is supported by all available data.

Table 1. Treatment effects of PCI compared to fibrinolytic therapy (median and 90%-CI) at assumed delays of 20 or 80 minutes

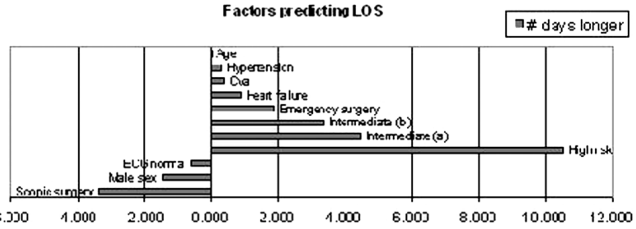
6-month endpoint	Absolute probability difference	Relative risk
death, 20 min delay	-3.7% (-6.9%, -1.3%)	0.49 (0.29, 0.80)
death, 80 min delay	-0.3% (-3.8%, +3.9%)	0.96 (0.57, 1.56)
non-fatal re-infarction, 20 min delay	-4.8% (-7.7%, -2.7%)	0.27 (0.14, 0.53)
non-fatal re-infarction, 80 min delay	-3.5% (-6.4%, -0.7%)	0.47 (0.25, 0.88)
non-fatal stroke, 20 min delay	-1.8% (-4.0%, -0.6%)	0.18 (0.05, 0.59)
non-fatal stroke, 80 min delay	-1.4% (-3.6%, -0.3%)	0.32 (0.11, 0.81)

Discussion: In comparison to a standard (Frequentist) meta-regression model, which cannot easily address the simultaneous modelling of several endpoints measured at multiple times, our Bayesian approach explicitly models correlation between treatment effects, baseline event rates and the different endpoints, and it allows us to model the measurement error in "time delay". Our work shows both the methodological relevance of Bayesian modelling in clinical evidence synthesis and presents a fresh look at the evidence regarding PCI and fibrinolytic treatments in patients with acute myocardial infarction.

P3518 Effect of cardiac risk factors on in-hospital stay after non-cardiac surgery

M.A. van de Pol[1], M. van Houdenhoven[1], E.W. Hans[2], H. Boersma[3], H.H.H. Feringa[4], M. van Sambeek[4], J.J. Bax[5], D. Poldermans[6]. *[1]Erasmus Medical Centre, Anaesthesiolgy, Rotterdam, Netherlands; [2]University of Twente, Operational Methods, Enschede, Netherlands; [3]Erasmus Medical Centre, Cardiology Dept., Rotterdam, Netherlands; [4]Erasmus MC, Vascular Surgery, Rotterdam, Netherlands; [5]University hospital Leiden, Cardiology, Leiden, Netherlands; [6]Erasmus MC - Anesthesiology, Rotterdam, Netherlands*

Background: In this era of increasing health care costs, insurance companies insist that in-hospital length of stay (LOS) is minimized after surgery. Post-operative non-surgical complications are related to underlying cardiac risk factors and prolong LOS.
Objective: To identify risk factors that predict LOS so that a more robust planning of surgery can be made.
Methods: We examined cardiac risk factors for 108.593 pts undergoing surgery in the period 1991-2004 at the ErasmusMC. The following factors were examined: age, gender, history of myocardial infarction, angina pectoris, heart failure, diabetes mellitus, renal dysfunction, hypertension, stroke and pulmonary disease. An ECG was scored as normal or abnormal. Surgery was divided in four groups according to the definition of the American Heart Association: high risk, intermediate (a) risk, intermediate (b) risk and low risk. First, possible significant factors were found using Mann-Whitney test on LOS. Second, significant factors were used to construct a model for LOS using linear regression.
Results: Risk factors that remained significant in determining LOS in the presence of other factors were surgery type (p=0.000), gender (p=0.000), age (p=0.000), scopic surgery (p=0.000), age (p=0.000), abnormal ECG (p=0.000), history of heart failure (p=0.000), emergency surgery (p=0.000), hypertension (p=0.000) and stroke (p=0.004). Together, these factors explained 21,7% of variance in LOS.



Figure

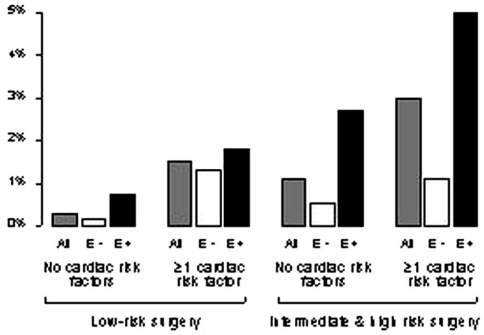
Conclusion: Hospital stay of patients undergoing non-cardiac can be predicted more accurately by cardiac risk factors. These factors should be taken into consideration while planning surgery, in order to get a more accurate and cost-effective schedule.

P3519 Electrocardiography has limited prognostic value for preoperative cardiac risk assessment in patients without cardiac risk factors undergoing low-risk surgery

P. Noordzij[1], O. Schouten[2], E. Boersma[3], J. Bax[4], H. Van Urk[2], J. Klein[1], A. Elhendy[5], D. Poldermans[6]. *[1]Erasmus MC, Anaesthesiolgy, Rotterdam, Netherlands; [2]Erasmus MC, Vascular Surgery, Rotterdam, Netherlands; [3]Erasmus Medical Centre, Cardiology Dept., Rotterdam, Netherlands; [4]University hospital Leiden, Cardiology, Leiden, Netherlands; [5]University of Nebraska, Cardiology, Omaha, United States of America; [6]Erasmus MC - Anesthesiology, Rotterdam, Netherlands*

Background: In non-cardiac surgery, preoperative electrocardiography (ECG) is recommended in pts with one or more cardiac risk factors. We questioned the usefullness of this strategy in low-risk surgery.
Aim: To assess the prognostic value of ECG for 30-day cardiovascular (CV) death in pts undergoing general surgery, stratified by type of surgery.
Methods: At the Erasmus MC between 1990-2000 a total of 28457 pts were screened prior to surgery by cardiac risk factors (history of ischemic heart disease, heart failure, diabetes mellitus, renal dysfunction, and stroke) and ECG. The ECG was scored as: no abnormalities, atrial fibrillation (AF), left or right bundle branch block (BBB), left ventricular hypertrophy (LVH), premature ventricular complexes (PVC), pacemaker, Q-wave, or ST changes. Surgery was stratified as low (N=16106), intermediate (N=12016), and high risk (N=335), representing respectively a pre-test risk of 30-day CV death of <1%, 1-5%, >5%. Logistic regres-

sion was applied to study the relation between ECG abnormalities and outcome, adjusted for cardiac risk factors.
Results: 30-day CV death was 199/28457 (0.7%). All ECG abnormalities were related with 30-day CV death: adjusted odds ratio (95% CI) for AF 4.0 (2.6-6.2), BBB 2.0 (1.2-3.4), LVH 1.8 (1.2-2.6), PVC 2.3 (1.4-3.7), pacemaker 4.4 (1.5-12), Q-wave 2.4 (1.7-3.3), ST changes 2.1 (1.3-3.5). Irrespective of type of surgery, pts with any ECG abnormality had a 4.5-fold increased risk of CV death. However, the absolute risk of CV death remained <1% in the 15382 pts with abnormal ECG, no risk factors, undergoing low-risk surgery.



Conclusion: ECGs have limited prognostic value in pts without cardiac risk factors undergoing low-risk surgery, and seemed to be redundant in over 50% of cases.

P3520 Commercial release of drug eluting stents impacts therapeutic decision making following initial diagnostic catheterisation

R.W. Ligon[1], A. Moore[2], G.J. Mishkel[1]. *[1]Prairie Heart Institute, Springfield, United States of America; [2]Prairie Education & Research Cooperative, Springfield, United States of America*

Purpose: Our objective was to compare revascularization strategies and economics pre- and post- DES commercial release. We hypothesized that subsequent to DES release, CAB rates would fall due to utilization of DES for more complex presentations.
Methods: Clinical, surgical, and economic data from between May 1, 2002 and April 30, 2004 were obtained from hospital databases. This time range was chosen to encompass one year periods before and after U.S. commercial DES release. Patients undergoing a first ever catheterization during the study period were included (n=7199). The demographics of our study group were as follows: females 47%, STEMI 458(6.3%), diabetics 1663(23%), and average age 62.3 (±13.3) years. Bypass interventions with concurrent valve surgery were excluded (n=119).
Results: See table below. From pre- to post-DES release, the number of triple vessel PCI's increased (16.7% to 20.4%); concomitantly the number of single vessel CAB's decreased (7.4% to 4.1%).

		5/1/02-4/30/03 (pre-DES release)	5/1/03-4/30/04 (post-DES release)	p value
	Normal Cath	767 (21%)	778 (22%)	<0.05
Index Procedure	PCI	920 (25%)	965 (28%)	<0.001
(within 30 days of initial cath)	CAB	476 (13%)	316 (9%)	<0.001
	Medical tx	1581 (42%)	1396 (40%)	NS
Cross-Over	PCI (TVR)	32 (3.7%)	12 (1.3%)	<0.05
(revascularization within 6	CAB	11 (2.3%)	8 (2.5%)	NS
months of index procedure)	Medical tx	42 (2.7%)	50 (3.6%)	NS
Economics	PCI	$13,543	$15,558	<0.05
(6 month average U.S. costs	CAB	$26,059	$27,637	NS
adjusted for inflation)	Medical tx	$5,835	$6,514	NS

Conclusions: We conclude that significantly more patients are undergoing PCI as their primary revascularization option, and DES failures occur less frequently than CAB failures. Corrected for inflation, the U.S. cost of PCI in the DES era has increased significantly although it remains a less expensive revascularization strategy than CAB. Bypass volume has declined due to a reduction in restenosis and fewer CAB for single vessel disease. Our results support the hypothesis that PCI is utilized increasingly in a more complex subset of patients in the DES era.

P3521 The climate impacts on myocardial infarction deaths in the Athens territory

P.E. Dilaveris[1], A. Synetos[2], G. Giannopoulos[2], E. Gialafos[2], A. Pantazis[2], C. Stefanadis[2]. *[1]Athens, Greece; [2]Hippokration Hospital, A' University Department of Cardiology, Athens, Greece*

Purpose: Seasonal variations in the development of coronary artery death and associations with low atmospheric temperatures have been reported from mortality data and hospital admission registries. Aim of the present study was to evaluate the impact of meteorological variables on daily and monthly rates of death due to myocardial infarction (MI).
Methods: We analyzed all the death certificate data from the Athens territory, for death caused by MI for the year 2001. Daily mean atmospheric temperature (Celsius), pressure (millibars) and humidity (%) were obtained from the National Meteorological Society for the Athens territory and the same year.
Results: Total number of deaths due to MI in the Athens area was on annual basis 3126 (1953 males/1173 females) from a population of 2,664,776 (0.117%). A significant seasonal variation ($p < 0.0001$) in deaths, with a maximum during winter (December to February, n =890), and a minimum during summer (June to August, n =676), corresponding to a relative difference of 24%, was found. Forward linear regression analysis revealed that only mean daily atmospheric temperature was inversely associated ($R = -0.263$, adjusted$R^2 = 0.067$, $p < 0.0001$) with daily deaths from MI. Considering monthly MI death rates, only mean monthly humidity was strongly associated with total deaths from MI ($R = 0.764$, adjusted$R^2 = 0.541$, $p = 0.004$) (Fig.1).

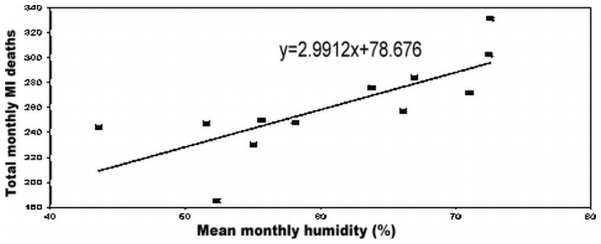


Figure 1

Conclusions: A significant seasonal variability in MI deaths was found in this study, as previously reported. Even in the mild climate of a Mediterranean city like Athens, meteorological variables, such as mean daily atmospheric temperature and particularly mean monthly humidity are significantly associated with MI death rates.

P3522 Local expression of human FGF-1 in the rat skeletal muscle following intramuscular administration of NV1FGF, a plasmid DNA for the treatment of peripheral arterial disease

A. Caron, F. Finiels, A.M. Caron, E. Senechal, O. Tejedor, E. Vigne, P. Delaere. *Centelion SAS, Preclinical Development, Vitry sur Seine, France*

NV1FGF is an expression plasmid encoding human FGF-1 currently in clinical development for the treatment of peripheral arterial disease (PAD). Intramuscular (IM) administration of NV1FGF was shown to promote collateral vessels in a hypercholesterolemic hamster model displaying impaired neoangiogenesis after ischemia. In a phase I clinical trial, IM administration of NV1FGF to the leg of patients with PAD was well tolerated. Kinetics of NV1FGF plasmid distribution and derived expression was investigated in rats to support phase II clinical trials. Rats were subjected to a single IM injection of NV1FGF with doses representing 0.5-25 times the maximal clinical dose (8 mg). Presence of NV1FGF plasmid and derived mRNA was assessed using quantitative real-time PCR and RT-PCR assays. FGF-1 expression in the injected muscle and in serum was assessed using immunohistochemistry and ELISA, respectively. IM administration of NV1FGF (200μg/muscle) led to high local expression of FGF-1 which lasted for 2-3 weeks, and NV1FGF-derived mRNA were still observed in the muscle up to 27 weeks after dosing. IM administration was not associated with quantifiable serum levels of FGF-1. NV1FGF sequences were detected in all distant tissues tested (blood, control muscle, gonads, eyes, bone and liver) after 1 day, while no NV1FGF sequences could be detected 2 weeks post-administration in all tested tissues (including kidney) but bone (4/10 rats). At a higher dose (560μg/muscle), NV1FGF sequences were occasionally detected in bone and kidney up to 3 months after dosing. We hypothesized that the sequences detected in distant tissues were products of plasmid degradation, which was supported by i) rapid degradation of NV1FGF in blood following a 200μg single intravenous administration (1h post injection, the ratio of intact plasmid to degradation products was lower than 1/1000); ii) absence of quantifiable mRNA levels in distant tissues between 1 day and 3 months post-administration (200μg/muscle). In conclusion, the kinetics of FGF-1 expression into the injected skeletal muscle supports multi-site and repeated (2 weeks apart) injections of NV1FGF to achieve optimal spatial and temporal exposure within the leg of patients with PAD. In addition, transient presence of NV1FGF sequences in distant organs was not associated with detectable levels of mRNA and circulating FGF-1, which suggests that the risk of FGF-1 biological activity in non-target organs is minimal after IM administration of NV1FGF.

P3523 (W) Interferon-gamma function blocking regresses and stablizes established atherosclerotic plaques in apoE-knockout mice

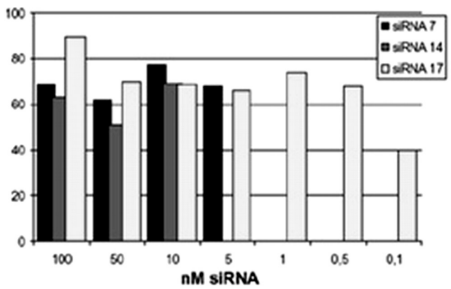
H. Kai, M. Koga, N. Tahara, T. Imaizumi. *Kurume University, Third Department of Internal Medicine, Kurume, Japan*

A triggering role of interferon-gamma is suggested in atherosclerotic plaque formation by activating inflammatory process. Soluble mutant of interferon-gamma receptor (sIFNgR) is known to block interferon-gamma-induced activation of the target cells in vivo. The aim of this study was to determine whether sIFNgR gene therapy attenuates progression of established plaques and stabilizes them. From 8-week old, apoEKO mice were fed daily with Western diet. At 12-week old when oil red-O-stained atherosclerotic plaques are established in the aorta, mice were randomized to 2 groups (n=6/group): sIFNgR-treated mice receiving gene transfer of naked DNA plasmid encoding sIFNgR and mock-treated mice receiving the empty plasmid transfection. sIFNgR or the mock was transfected twice into the bupivacaine-pretreated thigh adductor muscle at 12- and 14-week old. At 16-week old, mock-treated apoEKO mice showed progression of aortic plaques with further increase in the luminal plaque area. They had increased MOMA2-labeled macrophage area, reduced area of alpha-smooth muscle actin-labeled smooth muscle cells (SMCs), and reduced Azan-stained collagen area. These findings demonstrated markedly low plaque stability. sIFNgR gene transfer reduced plaque area by 55% versus mock-treated mice. Moreover, sIFNgR gene transfer stabilized the plaque by decreasing macrophage area and increasing the areas of SMCs and collagen. In mock-treated mice, monocyte attracting protein-1, vascular cell adhesion molecule-1, and interleukin-6 were markedly upregulated in the aortic wall at 16-week old, which were reversed significantly by sIFNgR gene transfer. sIFNgR treatment had no significant effects on the circulating monocyte count and serum cholesterol level. In conclusion, atherosclerotic plaques in apoEKO mice were reduced and stabilized by blocking interferon-gamma function through the anti-inflammatory effects. Targeting interferon-gamma may be a new strategy for treatment of atherosclerosis.

P3524 Short interfering RNA (siRNA) directed against the regulator protein phospholamban for the therapeutic modulation of cardiac calcium

W. Poller[1], H. Fechner[2], J. Kurreck[3], I. Sipo[2], S. Pinkert[2], X. Wang[2], J. Rekittke[3], V. Erdmann[3]. *[1]Universitätsklinikum Benjamin Franklin, Kardiologie & Pneumologie, Berlin, Germany; [2]Charite - Campus Benjamin Franklin, Cardiology and Pneumology, Berlin, Germany; [3]Freie Universität Berlin, Institute of Chemistry (Biochemistry), Berlin, Germany*

Background: a decrease in sarcoplasmic reticulum calcium pump (SERCA2) activity plays a key role in the impairment of diastolic function of the failing heart. The expression ratio of SERCA2-regulatory protein phospholamban (PL) to SERCA2 provides an important target to improve contractile dysfunction. This general approach has been evaluated previously in models of heart failure, by using dominant negative PLmutants or PL-antisense-RNA as regulatory tools. We report here on the employment of RNA interference mediated via short interfering RNAs (siRNAs) to achieve significant PL suppression at low siRNA concentrations, taking advantage of their particularly high intrinsic activity.
Methods and Results: on the basis of a set of theoretical selection criteria 6 siRNA sequences were synthesized for further experimental evaluation. 2 of these were highly efficient,2 had intermediate and 2 others had no efficacy in suppressing PL, although all fulfilled the selection criteria. Most efficient siRNA #17 achieved maximal PL suppression up to 95% in PL expressing cells, as assessed by Western blot analysis. Half-maximal inhibition occurred at an siRNA concentration of only 0.1 nM.



Percent inhibition of phospholamban protein expression as a function of siRNAs concentration.

Conclusions: efficient RNA interference was achieved using a specific siRNAs directed against the cardiac regulatory protein PL. The level of suppression accomplished here at very low siRNA concentrations was sufficient to improve cardiac function in vivo in several previous studies which have used protein or antisense-RNA tools for calcium cycle modification. The specific siRNA identified here provides a new and highly efficient tool for further evaluation in models of heart failure. Employment of AAV vector-based siRNA transcription may further enhance efficacy.

P3525 Local overexpression of decorin induces smooth muscle cells contractile phenotype expression and reduces neointimal hyperplasia after vascular injury in atherosclerotic rabbits

A. Al Haj Zen, E. Durand, C. Brasselet, F. Addad, D. Urbain, P. Bruneval, A. Lafont. *Rene Descartes Medical Shcool, INSERM EMI 0016, Paris, France*

Background: Extracellular matrix remodeling and cell phenotype play an important role in vascular repair after injury. Decorin, a small proteoglycan, is a natural inhibitor of TGF-beta and also regulates cell proliferation and migration. In this study, we investigated the effect of adenovirus-mediated of decorin overexpression on smooth muscle cells phenotype and neointimal hyperplasia in an atherosclerotic rabbit double-injury model.
Methods: Atherosclerotic-like lesions were induced in rabbit iliac arteries by endothelial denudation and high cholesterol diet. Four weeks later, iliac arteries underwent simultaneouly balloon angioplasty and gene transfer of a recombinant adenovirus encoding decorin (Ad-Dcn) ($2.5x10^9$ plaque forming units "pfu", n=12) or empty- adenoviral vector control (Ad-null) ($2.5x10^9$ pfu, n=12) was achieved by balloon infitrator catheter.
Results: One week after gene transfer, decorin overexpression was detected in neointima and media of Ad-Dcn-transfected arteries, but not in Ad-null-transfected arteries by immunochemistry (n=5). one month after angioplasty and gene transfer, the intimal cross-sectional area was significantly reduced in Ad-Dcn-transfected arteries compared to Ad-null-transfected arteries (2.8 ± 1.3 vs 3.8 ± 1.1 ($x10^6$ μm^2), p=0.04). Similarly, the intima/media ratio was barley reduced by (2.5 ± 1.2 vs 3.2 ± 0.8 ($x10^6$ μm^2), p=0.07) in Ad-Dcn-transfected arteries compared to Ad-null-transfected arteries. By immunochemistry, alpha-smooth muscle cells actin positive cells (contractile phenotype) increased significantly and co-localized with decorin expression in Ad-Dcn-transfected arteries compared to Ad-null-transfected arteries.
Conclusions: Local overexpression of decorin reduces the neointimal hyperplasia and enhances contractile phenotype of intimal smooth muscle cells.

P3526 Incidence and progression of cardiac lesions in rheumatoid arthritis

I. Moyssakis[1], D. Papadopoulos[1], E. Gialafos[1], P. Vlahoyannopoulos[2], G. Vayopoulos[2], P. Sfikakis[3], V. Votteas[1]. *[1]Cardiology, [2]Rheumatology, Laiko Hospital, Athens, Greece; [3]University Medical School, 1st Dept. of Propaedeutic Medicine, Athens, Greece*

Purpose: Rheumatoid arthritis (RA) is a systemic disease involving many organ systems and is accompanied by cardiac involvement. The aim of our study was to evaluate echocardiographically the incidence and progression of cardiac involvement in patients (pts) with RA.
Material and Methods: Seventy nine (73 females – 6 males, aged 56 ± 11 years) pts with RA were evaluated with M-mode, 2D and Doppler echocardiogram after a follow-up period of 56 ± 14 months. The left ventricular (LV) fractional shortening (FS) and the velocity of tricuspid jet plus the right atrial pressure served as LV systolic function and pulmonary systolic pressure respectively. Organic valvular involvement was defined as valve thickening and/or regurgitation. Left ventricular (LV) mass index was calculated by the Penn convention formula.
Results: Depressed LV systolic function was present in 7 (8,9%) pts at the beginning and in 11 (13,9%) at the end. Pericardial effusion had 17 (21,5%) at the beginning and 15 (19%) pts at follow-up. Aortic regurgitation had 18 (22,8%) pts in the first study and in 7 it was due to aortic root or ascending aorta dilatation. In the last study aortic regurgitation had 24 (30,4%) pts and in 11 was due to aortic root or ascending aorta dilatation. Particularly in 5 cases the aortic regurgitation deteriorated. Likewise mitral regurgitation had 8 (10,1%) pts in the first study (causing from mitral valve prolapse in 3) and 11 (13,9%) at the end. Pulmonary hypertension also had 9 (11,4%) pts at the beginning and 12 (15,2%) at follow-up. The LV mass index was 109 ± 22 g/m^2 at the beginning and 118 ± 26 at the end of our study ($p<0.05$).
Conclusion: Our results show that cardiac abnormalities in pts with RA are frequently appeared with predominant lesions the aortic regurgitation and pericardial effusion.The most significant changes during the progression of the disease are aortic lesions and increased LV mass index.

P3527 Angiographic evaluation of myocardial perfusion in patients with syndrome-X

Y. Atmaca, A. Ongun, C. Ozdol, D. Oguz, S. Gulec, D. Kumbasar, C. Erol. *Ankara, Turkey*

Objective: to evaluate the tissue level perfusion in patients with syndrome-X by using the myocardial blush grade (MBG) technique.
Method: Study population consisted of prospectively enrolled 55 patients (22 women and 33 men; age, 50.8 + 8.4 years) and 55 control subjects (30 women and 25 men; age, 51.8 + 8.4 years) whose angiographic films were technically adequate for MBG analysis. Microvascular perfusion was graded on CD films at 25 frames by two experienced investigators who were blinded to the study population. After grading, we defined total blush score for both groups. Total blush score was determined as the sum of the blush grades of each coronary territory.

Result: A total of 330 coronary territories in both groups were assessed. Averages of MBG in LAD and RCA territories in patients with syndrome-X were significantly lower than those of control group (2.7 + 0.5 vs 2.9 + 0.2; p=0.01 and 2.7 + 0.4 vs 2.9 + 0.3; p=0.03, respectively). Similarly, average of total blush score (the sum of the blush grades of each coronary territory) was significantly lower in patients with syndrom-X than that of control group (8.2 + 0.7 vs 8.7 + 0.5; p<0.0001). Though, average of MBG in the Cx territory showed a decreased trend when compared with control group, this failed to meet statistical significance (2.7 + 0.4 vs 2.9 + 0.3; p=0.06). Normal tissue perfusion in all coronary territories in patients with syndrome-X was observed in 23 (41.8%) patients, whereas it was observed in 44 (80%) subjects of the control group. Averages of myocardial blush grades of each coronary territory were shown in table 1.

Table 1.MBG of the coronary territories

	Syndrome-X (n=55)	Control (n=55)	p
LAD	2.7 + 0.5	2.9 + 0.2	0.01
Cx	2.7 + 0.4	2.9 + 0.3	0.06
RCA	2.7 + 0.4	2.9 + 0.3	0.03
Total blush score	8.2 + 0.7	8.7 + 0.5	<0.0001

Conclusion: We have demonstrated for the first time that a substantial number of patients with syndrome-X have impaired tissue level perfusion and this might be assumed as a surrogate marker of diseased microvascular network in the catheterisation laboratory.

P3528 12-months outcomes of percutaneous and surgical revascularisation in acute coronary syndromes without ST-segment elevation in patients with multivessel coronary artery disease

B. Szygula-Jurkiewicz[1], K. Wilczek[1], A. Lekston[1], T. Niklewski[1], R. Wojnicz[1], J. Szkodzinski[1], M. Zembala[2], L. Polonski[1]. [1]*Silesian Centre of Heart Diseases, Cardiology Dept., Zabrze, Poland;* [2]*Silesian Centre of Heart Diseases, Department of Cardiosurgery, Zabrze, Poland*

Purpose: Early invasive strategy is believed to be an effective treatment modality of acute coronary syndromes without ST-segment elevation (NSTEACS). We aimed at the assessment of 12-month clinical outcomes including health related quality of life in patients with NSTEACS and multivessel coronary artery disease (CAD) who underwent percutaneous (PCI) or surgical revascularization (CABG).
Methods: We analyzed a group of 412 patients (92%) who were qualified for invasive treatment based on results of coronary angiography performed within 24 hours after admission and whose long-term follow up data were available. The inclusion criteria were: rest angina within 24 hours prior to admission and at least one of the following: ST segment depression (>0,5mm), transient (<20min) ST-segment elevation, negative T-waves in at least 2 contiguous leads, positive serum cardiac markers. Patients with single-vessel CAD or qualified for conservative treatment were excluded from the study. We analyzed adverse cardiac events rate (death, non-fatal myocardial infarction, unstable angina, repeat revascularization, cardiovascular hospitalization) at one year. The quality of life was assessed using Short-Form–36 (SF-36) questionnaire. The patients who were treated with PCI (group I) were compared with the CABG group (group II)
Results: Deaths rate was 5,3% vs 9,3% (NS), myocardial infarction 3,4% vs 0% (p=0,054), unstable angina 20,9% vs 2,8% (p=0,0000), repeated revascularization 12,6% vs 0% (p= 0,0001) and cardiovascular hospitalization 36% vs 22,7% (p= 0,001) in the in group I and II respectively. Physical Component Summary Scores were 38,7±11,6 vs 43,08±9,5, p=0,001 in group I and II respectively. Mental Component Summary Scores were similar in both groups (46,34±13,05 vs 45,97±11,9, NS).
Conclusions: The overall mortality rate was similar in both groups. PCI patients had more frequent rate of unstable angina, rate of hospitalization and repeated revascularization. This study has shown that there is a significant difference in health-related quality of life 12 months after PCI and CABG. This difference arises from better physical function (Physical Component) for CABG surgery patients compared with PCI patients. Despite impairment of the physical health status, the mental health status remained similar in both groups.

P3529 Subclinical coronary artery atherosclerosis in patients with erectile dysfunction

E. Chiurlia[1], M. Menozzi[2], R. D'Amico[3], C. Ratti[1], R. Rossi[1], A. Granata[4], R. Romagnoli[5], M.G. Modena[1]. [1]*University of Modena and Reggio Emilia, Cardiology Department, Modena, Italy;* [2]*University of Modena and Reggio Emilia, Cardiology Department, Modena, Italy;* [3]*University of Modena and Reggio Emilia, Statistic Unit, Modena, Italy;* [4]*University of Modena and Reggio Emilia, Internal Medicine Department, Modena, Italy;* [5]*University of Modena and Reggio Emilia, Institute of Radiology, Modena, Italy*

An association between erectile dysfunction and ischemic heart disease has been suggested.
Aim: To assess the prevalence and extent of coronary artery atherosclerosis in asymptomatic patients with vascular erectile dysfunction.
Methods: We studied 70 consecutive patients with vascular erectile dysfunction, evaluated by penile Doppler, and 73 control subjects with no history of coronary artery disease. All patients underwent ultrasound detection of brachial artery reactivity and multidetector CT to screen for the presence of coronary artery calcification, a marker of coronary atherosclerosis.
Results: The patients and the control group were well-matched for age, race and Framingham risk scores. Patients with erectile dysfunction had significantly higher hs-CRP levels (P<0.0001). Flow-mediated dilation was more impaired in patients with erectile dysfunction than in controls (P<0.001). Coronary artery calcification was more frequent in individuals with erectile dysfunction (75.7%) than in control subjects (54.8%). More patients with erectile dysfunction had a calcium score above the median value compared to controls (P<0.0001). Logistic regression models showed that patients with erectile dysfunction had an overall odds ratios of 2.98 (P=0.004) for having calcium score above the 75th percentile (Table 1).

Table 1

Variables	Patients (N=70)	Controls (N=73)	OR 95% CI	P Value
Coronary Artery Calcification	53 (75.7%)	40 (54.8%)	2.57 (1.26-5.26)	0.01
Calcium Score				
0	17 (24.3%)	33 (45.2%)	1.0	
1 to 64	17 (24.3%)	29 (39.7%)	1.14 (0.49-2.64)	0.76
≥65	36 (51.4%)	11 (15.1%)	6.35 (2.35-17.16)	<0.001
Volume Score >75 percentile	29 (41.4%)	14 (19.1%)	2.98 (1.41-6.32)	0.004

Regarding Calcium Score three classes were created according to the median, which was 65. The first class is 0 that corresponds to absence of calcification and it is used as the reference level in the logistic regression analyses

Conclusions: Coronary atherosclerosis is more severe in patients with vascular erectile dysfunction and is independent of traditional risk factors for cardiovascular disease. Thus, erectile dysfunction may be considered an additional, early warning sign of coronary atherosclerosis.

P3530 Implications of passive cigarette smoking on the severity and prognosis of patients with acute coronary syndromes: the Greek study of ACS (the GREECS)

D.B. Panagiotakos[1], C. Pitsavos[2], A. Antonoulas[2], Y. Mantas[2], Y. Kogias[2], S. Zombolos[2], S. Arapi[2], C. Stefanadis[2]. [1]*Glyfada, Greece;* [2]*University of Athens, Hippokration Hospital, Athens, Greece*

Background: Although smoking increases the risk of a coronary event and accelerates the progression of atherosclerotic disease, the implication of passive cigarette smoking among non-smokers in the prognosis of patients with acute coronary syndromes (ACS) has rarely been investigated.
Methods: From October 2003 to September 2004, 2172 patients from 7 major general hospitals in Greece and with a discharge diagnosis of ACS were enrolled into the study. Of them, 76% were men (65 ± 11 years old) and 24% were women (72 ± 13 years old). Regression analysis and Cox proportional hazard models were applied to evaluate the relationships between exposure to environmental tobacco smoke (i.e. passive smoking > 30 minutes/day for more than 3 days per week), the severity of the disease (using troponin I levels as an bio-index) and the 30-day outcome of cardiovascular events (death or hospitalization due to CVD), after adjusting for several potential confounders.
Results: 39% of patients reported non-smokers, and 29% of them reported exposure to someone else cigarette smoke at least 30 min per day and 3 days per week. Exposure to cigarette smoke was associated with higher Troponin-I levels (beta = 4.23 ± 1.2, p = 0.03), after controlling for age, sex, and clinical characteristics of the patients. Moreover, people exposed to someone else cigarette smoke were 4.6 times more likely to have acute myocardial infarction as compared to unstable angina (p < 0.001). Compared to non-passive smokers, passive smokers experience 25% higher risk (relative risk = 1.25, p = 0.02) of an event during the first 30 days after discharge.
Conclusion: Our findings reveal the association of passive smoking with the severity and the prognosis of patients with ACS.

P3531 Severe depression is associated with an increased risk for myocardial infarction, not explained by lifestyle, lipids, coagulation and inflammation – the SHEEP study

I. Janszky[1], A. Ahlbom[2], J. Hallqvist[3], S. Ahnve[3]. [1]*Karolinska Institute, Stockholm, Sweden;* [2]*Institute of Environmental Medicine,KI, Department of Epidemiology, Stockholm, Sweden;* [3]*Karolinska Institute, Public Health Sciences, Stockholm, Sweden*

Background: Depression has been considered to be a risk factor for coronary heart disease (CHD) in initially CHD free populations. However, subclinical CHD or other somatic causes for depressive symptoms were suggested to possibly account for the observed association.
Aim: To test if severe depression increases the risk for first AMI and to explore the possible explanatory mechanisms.
Methods: In a population-based case-control study we evaluated the history of hospitalization for depression in 1799 cases, 45-70 years, who had a first AMI

and in 2339, age-, sex-, and hospital catchment area matched controls by search through the computerized Swedish hospital discharge registry.
Results: After adjustment for matching criteria and socio-economic position the odds ratio (OR) for AMI was 2.9 (1.8-4.9) for the ever-depressed when compared to the never-depressed. The risk for AMI was associated with the frequency of hospitalizations for depression (OR for a single depressive episode=2.5, 1.2-4.8; OR for 4 or more hospitalisations= 6.8, 1.5-31.3). Patients hospitalised before or after the median time between the first hospitalization for depression and the AMI, i.e. 15 years and 2 months, were at similar risk. Life-style variables, lipid profile, coagulation, and inflammation or other factors could just partly explain the observed relation.
Conclusion: Hospitalisation for depression was associated with increased risk for AMI in a dose dependent manner. Subclinical CHD or other somatic causes are unlikely to account for our findings as (1) we used a relatively long follow up time, (2) hospitalisation for depression implies that non-psychiatric causes of depressive symptoms were probably carefully excluded, and (3) known risk factors for CHD were extensively controlled for.

INFLAMMATION AND ARRHYTHMIAS

P3532 New markers for inflammation and remodelling in chronic atrial fibrillation

B. Candemir[1], O. Akyurek[1], N. Akyurek[2], D. Kumbasar[1], K. Vurgun[1], U.O. Ozcan[1], H. Goksuluk[1], C. Erol[1]. [1]*Ankara University, Cardiology Department, Ankara, Turkey;* [2]*Gazi University, Department of Pathology, Ankara, Turkey*

Purpose: to evaluate expressions of MMP2, MMP9, TIMP2, eNOS, iNOS and COX2 at tissue level by means of semi-quantitative methods and to explain possible pathophysiologic mechanisms for remodeling and inflammation in chronic atrial fibrillation.
Method: A total of 36 patients (12 women and 24 men; age, 53.5 + 11.2 years), 15 of which were with chronic atrial fibrillation were enrolled in the study. After enrollment, detailed echocardiographic examination was performed in each patient. Right atrial appendages were dissected after the aortopulmonary bypass cannulation. The appendages were then stained immunehistochemically for MMP2, MMP9, TIMP2, eNOS, iNOS and COX2 activities. Enzyme expression (none, low, intermediate or high) was determined according to density and extent of staining.
Results: 216 pathologic specimens in both groups were examined. The left atrium diameter was found to be increased in AF group (57 + 8mm in AF, 41 + 8mm in sinus group; p=0.001). MMP2 and MMP9 activities in AF and sinus (SR) groups were found to be similar (60% vs 47,7%; p=0,46 and 80% vs 76.2%; p=0,78 respectively). Similarly, TIMP2 and COX2 activities failed to reach statistical significance in AF and SR groups (73.4% vs 76.3%; p=0,78 and 40% vs 52,3%; p=0,45 respectively). eNOS expression was significantly higher in AF group (86,7% vs 47,7%; p=0,016). Although iNOS expression showed an increased trend in AF group when compared with SR group, this failed to meet statistical significance (66,7% vs 42,9%; p=0,15). MMP9 and COX2 expressions were observed to be localized especially under the epicardium.

High Enzyme Activities in AF&SR groups

	AF (n=15)	SR (n=21)	p
MMP2	60%	47.7%	0.46
MMP9	80%	76.2%	0.78
TIMP2	73.4%	76.3%	0.84
COX2	40%	52.3%	0.45
eNOS	86.7%	47.7%	0.016
iNOS	66.7%	42.9%	0.15

Conclusion: Except for increased eNOS expression in AF group; there was no difference in the expressions of MMP2, MMP9, TIMP2, iNOS and COX-2 activities. We have also demonstrated for the first time that COX2 expression is not increased in AF.

P3533 Effect of C-reactive protein reduction on paroxysmal atrial fibrillation

I. Dernellis[1], M. Panaretou[2]. [1]*Mitilini, Greece;* [2]*Mytilini, Greece*

Background: C-Reactive Protein (CRP) lowering is associated with a reduction in recurrent and permanent atrial fibrillation (AF). This study sought to determine whether CRP lowering also results in a reduction of paroxysmal AF (PAF) during daily life.
Methods and Results: We enrolled 80 patients with proven PAF, CRP between 0.08 and 1.30 mg/dL, and at least one episode of PAF on ambulatory ECG monitoring. Forty patients were randomised to placebo (placebo group) and 40 to atorvastatin (treatment group). Plasma CRP levels and ambulatory monitoring were repeated after 4 to 6 months of therapy. The two groups were comparable with respect to baseline characteristics, number of episodes of PAF, and baseline plasma CRP levels. The treatment group had lower median CRP levels at study end and experienced a significant reduction in the number of episodes of PAF compared with the placebo group. PAF was completely resolved in 26 of 40 patients (65%) in the treatment group versus 4 of 40 (10%) in the placebo group. The treatment group exhibited a highly significant reduction in PAF ($P<0.001$). By logistic regression, treatment with atorvastatin was an independent predictor of PAF resolution.
Conclusions: CRP lowering with atorvastatin appears to be effective in eliminating PAF during daily life in a significant proportion of patients.

P3534 Relationship between atrial fibrillation and inflammation

A. Dogan[1], O. Gedikli[2], G. Acar[2], M. Ozaydin[2], A. Altinbas[2], S.M. Aslan[2]. [1]*Isparta, Turkey;* [2]*Sevket Demirel Heart Center, Cardiology, Isparta, Turkey*

Aim: The failure in preventing the recurrences of atrial fibrillation (AF) has led to new searches in its pathogenesis. Systemic inflammation may be one of the most popular mechanisms of AF. Thus, we investigated the role of systemic inflammation markers in the different categories of AF.
Methods and Results: Consecutive 85 patients with AF were enrolled in the study. Atrial fibrillation was also categorised as new onset, chronic, lone and secondary AF. Control group was consisted of 30 healthy subjects. Blood samples were for the serum level of high-sensitive C-reactive protein (hs-CRP and plasma levels of interleukin-6 (IL-6). The levels of hs-CRP (0.63 ± 0.57 vs 0.23 ± 0.1, mg/dL, p=0.001) and IL-6 (29 ± 36 vs 11.6 ± 9.7, pg/mL, p=0.008) were significantly higher in overall AF group than those of control group. In subgroup analysis, the levels of hs-CRP and IL-6 were significantly higher in both chronic (0.69 ± 0.62 vs 0.23 ± 0.1, mg/dL, p=0.001; 30 ± 39 vs 11.6 ± 9.7, pg/mL, p=0.001, respectively) and new onset AF groups (0.51 ± 0.46 vs 0.23 ± 0.1, mg/dL, p=0.003; 28.4 ± 31 vs 11.6 ± 9.7 pg/mL, p=0.009, respectively) compared with control group. There was no difference in the inflammation markers between new onset and chronic AF subgroups. The level of hs-CRP was significantly higher in secondary AF subgroup than control, whereas hs-CRP level in lone AF subgroup was similar to that of controls. The presence of AF was identified as a significant independent factor affecting the hs-CRP levels in multiple regression analysis (OR:0.35, 95%CI:0.1-0.61, p=0.005).
Conclusion: Our results show that inflammation may have a role in pathogenesis of AF.

P3535 Elevated risk of myocardial infarction associated with COX-2 inhibitor therapy in anticoagulated patients with atrial fibrillation in the SPORTIF III & V trials

M. Gomberg-Maitland[1], J.L. Halperin[2], J. Feyzi[3], D. DeMets[3], N.K. Wenger[4]. [1]*U of Chicago Hospital, Cardiology Department, Chicago, United States of America;* [2]*Mount Sinai Medical Center, New York, NY, United States of America;* [3]*University of Wisconsin - Madison, Madison, WI, United States of America;* [4]*Emory University School of Medicine, Atlanta, GA, United States of America*

Purpose: the Stroke Prevention using an ORal Thrombin Inhibitor in patients with atrial Fibrillation (SPORTIF) program included 2 clinical trials, SPORTIF III (open-label, 259 centres in Europe, Asia, and Australia) and V (double-blind, 409 centres in North America) that compared the efficacy and safety of ximelagatran vs warfarin in patients with atrial fibrillation (AF) at risk for stroke. Concomitant treatment was permitted with aspirin up to 100 mg/day, nonsteroidal anti-inflammatory drugs up to 7 days/month, or cyclo-oxygenase-2 (COX-2) inhibitors ad libitum. Following recent reports of elevated myocardial infarction (MI) risk in patients using COX-2 inhibitors, we assessed MI risk in this anticoagulated cohort.
Methods: based upon pooled data from 7329 enrolled patients in both trials, we analysed COX-2 inhibitor usage at randomization and during follow-up over the period on-treatment with the anticoagulants, and determined event rates and hazard ratios (HR) by Cox proportional hazards modelling. Covariates included randomized treatment, trial, age, gender, prior stroke or transient ischaemic attack, left ventricular dysfunction, blood pressure, diabetes, coronary disease, body mass index, alcohol, and tobacco use.
Results: 480 patients took COX-2 inhibitors at entry, 5% of those enrolled in SPORTIF III and 23% of those in SPORTIF V; 87.8% of these did so at least half the time during the study. Rates of acute MI were 2.05%/year (95% confidence interval [CI], 0.94-3.17%/year) among those on COX-2 inhibitors vs 0.93%/year (95% CI, 0.73-1.13%/year) in those not taking COX-2 inhibitors (n = 6849; adjusted HR 2.00; 95% CI, 1.09-3.67%/year; P = 0.025). For the endpoint of stroke alone and for the combined endpoint of stroke, systemic embolism, MI and all-cause mortality, there was no significant difference in rates based on COX-2 inhibitor use.
Conclusions: despite anticoagulation with warfarin or ximelagatran, patients with AF taking COX-2 inhibitors developed MI at a higher rate than those who did not, with HR in the range reported for populations not treated with anticoagulants. This post hoc observation requires prospective confirmation and may have implications for the mechanism of such events.

P3536 Effects of prednisone on atrial tachycardia remodelling of atrial electrophysiology and nitric oxide synthase in dogs

B.J.J.M. Brundel[1], A. Shiroshita-Takeshita[2], R.H. Henning[3], H.H. Kampinga[1], S. Nattel[2]. [1]*University Groningen, Radiation and Stress Cell Biology, Groningen, Netherlands;* [2]*Montreal Heart Institute, Department of Medicine, Montreal, Canada;* [3]*University, Clinical Pharmacology Dept., Groningen, Netherlands*

Background: there is evidence suggesting the possible involvement of oxidative stress, inflammation, and calcineurin/NFAT pathway in atrial fibrillation (AF). This study was conducted to evaluate the hypothesis that anti-inflammatory agents or calcineurin inhibition may affect atrial tachycardia remodelling and consequent changes in endothelial (eNOS) and cytokine-induced nitric oxide synthase (iNOS).
Methods: dogs were subjected to atrial tachypacing (ATP) at 400 bpm for 7 days. Drugs were started 3 days before ATP onset to ensure steady state at pacing-onset. Electrophysiological studies were performed in dogs subjected to ATP-only (n=8), ATP plus anti-inflammatory drugs prednisone (PDN, n=6) or ibuprofen (IBU, n=4) or the calcineurin inhibitory drug cyclosporine A (CyA, n=4), and non-paced controls (n=10). Left atrial tissue was used to determine the protein levels of eNOS and iNOS by Western-blotting.
Results: seven-day ATP significantly increased mean AF duration (DAF) and reduced atrial effective refractory period (ERP) in dogs (DAF: 962 $\pm$ 339 s, in ATP-only vs 26 $\pm$ 8 s in non-paced controls; ERP at basic cycle length 300 ms: 73 $\pm$ 7 ms in ATP-only vs 119 $\pm$ 5 ms in non-paced controls, $p<0.01$ for each, data are mean $\pm$ SEM). This increase in DAF and decrease in ERP were strongly suppressed in PDN-treated dogs (DAF: 96 $\pm$ 60 s and ERP: 101 $\pm$ 6 ms, $p<0.05$ vs ATP-only), but not affected by IBU or CyA. The protein expression levels of iNOS and eNOS (in optical density units normalised to GAPDH) were significantly increased by 7-day ATP (iNOS: 0.25 $\pm$ 0.06 and eNOS: 0.50 $\pm$ 0.06 in ATP-only vs 0.08 $\pm$ 0.03 and 0.25 $\pm$ 0.06 in non-paced controls, $p<0.05$ for each). The increase in eNOS caused by 7-day ATP was attenuated in PDN treated dogs (0.17 $\pm$ 0.04, $p<0.05$ vs ATP-only), but not significantly affected by IBU (0.38 $\pm$ 0.12) or CyA (0.37 $\pm$ 0.14). The ATP-induced iNOS increases were unaffected by PDN, IBU, and CyA therapy.
Conclusion: Prednisone inhibits the effects of atrial tachycardia on atrial electrophysiology and eNOS, but not iNOS expression. Ibuprofen and cyclosporine A are ineffective. These results point to important protective effects of prednisone on atrial tachycardia remodelling, possibly mediated by interactions with oxidant stress systems, as well as a potential anti-thrombotic effect by preventing endocardial eNOS activation.

P3537 Evaluation of Renin-Angiotensin-Aldosteron System after catheter ablation of atrial fibrillation

F. Sacher[1], A. Georges[2], P. Jais[3], J.B. Corcuff[2], M. Hocini[3], M. Haissaguerre[3], L. Bordenave[2], J. Clementy[3]. [1]*Service Pr CLEMENTY, Bordeaux Pessac, France;* [2]*Service Medecine Nucleaire, Bordeaux- Pessac, France;* [3]*Bordeaux Pessac, France*

Angiotensin-Converting-Enzyme (ACE) inhibitors have recently been proposed to prevent atrial fibrillation (AF). However little is known on Renin-Angiotensin-Aldosterone system (RAAS) changes after AF ablation.
Methods: 92 consecutive patients (84 M, 55 $\pm$10 yrs) underwent AF ablation for paroxysmal (58), persistent (8) or permanent (26) AF. Patients with paroxysmal AF (PAF) had pulmonary vein isolation (PVI) alone (38) or associated with linear ablation (20). Persistent and permanent AF (PerAF) patients had PVI with a combination of lines and/or atrial ablation. Renin Plasmatic Activity (RPA) [0,20-2,50 ng/mL/h] and aldosterone [150-500 pmol/L] were measured before, 24 hours, 3 days and 3 months after ablation as a marker of RAAS. Notably 58 pts had beta-blocker therapy and 6 had ACE inhibitors stopped few days before.
Results: See Table. RPA in PAF pts was high before and till day 3 after ablation. At 3 months RPA was significantly lower (p=0.001) and within normal range. For PerAF pts the trend was the same but without significant value. Concerning aldosterone, level at baseline was lower than normal range for both PAF and PerAF. After a significant decrease between baseline and day 3 after ablation (p=0.05) aldosterone came back to its baseline level at 3 months. Comparing pts with recurrence or not, trends were similar for both RPA and aldosterone with no significant difference depending on the outcome.

RPA and Aldosterone levels

	Before ablation	Day 1	Day 3	At 3 months
Renin Plasmatic Activity (ng/mL/h)				
Paroxysmal AF (n=58)	3.19±8.53	3.26±7.91	2.92±9.2	0.71±0.81
Persistent and Permanent AF (n=34)	1.58±2.07	3.49±5.05	4.20±10.42	0.89±1.72
Total (n=92)	2.57±6.82	3.34±7.04	3.38±9.50	0.76±1.09
Aldosterone (pmol/L)				
Paroxysmal AF (n=58)	130±117	96±79	54±40	168±96
Persistent and Permanent AF (n=34)	179±119	182±189	110±82	113±40
Total (n=92)	149±118	124±130	73±63	153±87

Conclusion: There is no significant difference in RPA and aldosterone level before and 3 months after ablation depending on the AF type or the recurrence of AF. ACE inhibitors efficacy in preventing AF can't be explain by modification of RPA and aldosterone level. Other parameters of RAAS need to be investigate to unsderstand hormonal action of ACE inhibitors in AF.

P3538 Prevention of specific processes in early electrical remodelling by enalapril in an animal model of atrial fibrillation

R.E. Wessel[1], R. Laszlo[2], C. Winkler[2], R.F. Bosch[2]. [1]*Tübingen, Germany;* [2]*Uniklinikum Tuebingen, Cardiology, Tuebingen, Germany*

Background: Atrial tachycardia reduces Kito - and L-type Ca 2+ - current densities. Likewise protein and mRNA expression of L-type Ca 2+ channel subunits are reduced. These are two important steps in electrical remodelling during onset of AF. The underlying cellular mechanisms are not understood.
The purpose of this study was to investigate the effect of preventive treatment with Enalapril on Kito - and L-type Ca 2+ - current densities in rapid atrial pacing (RAP) rabbit model of atrial fibrillation (AF).
Methods: Rapid (600 bpm) atrial pacing was performed in rabbit via an pacemaker for 24 h. Study groups: sham without Enalapril, 24h pacing without Enalapril, Sham with Enalapril and 24h pacing with Enalapril. Dosage was 0,16 mg/kg/KG s.c. once a day.
Ionic currents were measured by patch clamp techniques.
Results: RAP reduced L-type Ca 2+ current density by 48% ($p < 0,005$) in animals without Enalapril treatment. Even with Enalapril pre-treatment there was a reduction in current densities by 41% ($P< 0,05$).
The Kito current density was reduced by 45% ($p < 0,01$) in 24h pacing group without Enalapril. In the group with Enalapril pre-treatment there was no reduction of Kito current density (114%, $p > 0,5$).

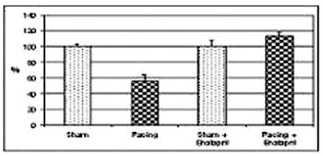


Fig. 1A Current densities of K_{to}-channel in RAP. Sham no drug control group, density is set as 100% pacing no drug, reduction by 45% is significant $P < 0,01$ Sham+ Enalapril group with Enalapril pretreatment, density set as 100%, pacing with Enalapril pretreatment, no statistically significant changes.

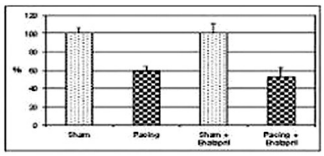


Fig. 1B Current densities of L-type Ca^{2+} channel in RAP. Sham no drug control group, density is set as 100% Pacing no drug, reduction by 48% is significant $P < 0,005$ sham group with Enalapril pretreatment, density set as 100%, pacing with Enalapril pretreatment,. reduction by 41% is significant $P < 0,05$

Conclusion: Our data shows for the first time that a pre-treatment with the ACE inhibitor Enalapril can prevent down regulation of Kito current densities in RAP induced atrial remodelling. These results suggest a modulation of Angiotensin II induced processes by ACE inhibitors can prevent tachycardia induced electrical remodelling related to Kito current densities. These results are in line with other investigations demonstrating the important role AT1 receptor. This is a first hint for potential target of a preventional drug treatment, e.g. in perioperative atrial fibrillation.

P3539 Success of electric cardioversion in persistent atrial fibrillation and markers of fibrosis and remodelling

A. Tello-Montoliu[1], V. Climent[2], F. Marin Ortuno[3], V. Roldan[4], B. Freestone[5], L. Mainar[6], J.G. Martinez[2], G.Y.H. Lip[5]. [1]*Hospital General de Alicante, Servicio de Cardiología, Alicante, Spain;* [2]*Hospital General de Alicante, Servicio de Cardiología, Alicante, Spain;* [3]*Alicante, Spain;* [4]*Hospital San Vicente, Hematology, Alicante, Spain;* [5]*City Hospital, Department of Medicine, Birmingham, United Kingdom;* [6]*Hospital de Requena, Cardiologia, Valencia, Spain*

Structural abnormalities have been described in the atria of patients with atrial fibrillation (AF). Atrial remodelling may be influenced by changes in extracellular matrix turnover. These changes may be related to the maintenance of the arrhythmia. The aim of the present study was to investigate whether success or failure of direct-current cardioversion in patients with persistent AF and posterior permanence in sinus rhythm may be related to markers of fibrosis (assessed by tissue inhibitor of metalloproteinase-1, TIMP-1) and extracellular matrix turnover (carboxy-terminal telopeptide of collagen type I, CITP).
Patients: we recruited 59 patients (66.6 $\pm$ 10.2 years, 74% males) with persistent AF (mean arrhythmia duration 32.1 $\pm$ 42.8 weeks) who underwent elective cardioversion by a standardised step-up protocol with increasing shock strengths (200-300-360-360 J). Forty subjects with similar co-morbidities in sinus rhythm were included as control group. Blood samples were obtain immediately before and one month after cardioversion. Presence of sinus rhythm was also assessed one month after successful cardioversion by ECG. Measurements of TIMP-1 and CITP were performed by ELISA (commercial kits).
Results: the rate of success of cardioversion was 71%. There were no differences in baseline TIMP-1 and CITP (before cardioversion) between patients and controls. Moreover, baseline markers did not show any relation to immediate and 1-month outcome. At 1-month, the rate of relapse of AF was 43%. In samples obtained at one month, CITP levels were higher in patients who suffered a relapse into AF (4.20 $\pm$ 1.46 mcg/L) and patients with unsuccessful cardioversion (3.90

± 1.25 mcg/L) versus those maintaining sinus rhythm at one month (3.04 ± 0.75 mcg/L), both p<0.02.
Conclusions: indexes of fibrosis and remodelling failed to predict initial success cardioversion and long-term outcome. However maintenance of sinus rhythm conditioned a significant reduction on CITP (a marker of extracellular matrix turnover), suggesting that AF may promote atrial remodelling.

P3540 Markers of inflammation in patients with malignant ventricular tachycardia and electrical storming

F. Streitner[1], J. Kuschyk[1], C. Veltmann[1], R. Schimpf[1], M. Brueckmann[1], T. Bertsch[2], M. Borggrefe[1], C. Wolpert[1]. *[1]University Hospital of Mannheim, I. Dept. of Medicine - Cardiology, Mannheim, Germany; [2]Clinic Nuremberg, Dept. of Clinical Chemistry, Nuremberg, Germany*

Background: As recently demonstrated cytokine expression is elevated in patients with coronary artery disease (CAD) and predicts a worse outcome in patients with advanced heart failure. Additionally, Interleukin-6 (IL-6) and the C-reactive protein (CRP) are reported to be elevated in patients with atrial fibrillation. However, little is known about whether markers of inflammation are elevated during spontaneous ventricular tachyarrhythmias (VT/VF). The aim of this prospective study was therefore to compare cytokine serum concentrations in patients without spontaneous VT/VF-episodes, with single VT/VF episodes and with an electrical storming.
Patients and Methods: 57 consecutive patients were enrolled into the study. CRP and IL-6 serum concentrations were determined in the absence of myocardial ischemia or an acute infection. VT/VF-episodes were analysed by stored electrograms of an implanted carioverter defibrillator or during monitoring at intensive care unit. 347 VT/VF-episodes occurred in 10 patients with an electrical storming, 13 patients had single and 34 patients experienced no VT/VF-episode. Patients with an electrical storming had a mean age of 68±7 years and a mean left ventricular ejection fraction of 33±18% (others 66±9 years; 41±16%). Out of all patients, 43/57 (75.4%) suffered from CAD and 14/57 (24.6%) from idiopathic dilated cardiomyopathy.
Results: For CRP, patients with an electrical storming had significantly higher serum concentrations than patients with single VT/VF-episodes (15.6±9.81 vs. 5.85±7.39 mg/l, p=0.029) or without VT/VF-episodes (15.6±9.81 vs. 6.0±6.41 mg/l, p=0.001). No significant difference could be seen when comparing CRP serum concentrations in patients with single or without VT/VF-episodes (p=0.95). For IL-6, patients with an electrical storming (9.05±5.73 vs. 3.42±7.33 pg/ml, p=0.019) or single VT/VF-episodes (7.8±4.88 vs. 3.42±7.33 pg/ml, p=0.024) had significantly higher IL-6 serum concentrations than patients without spontaneous VT/VF-episodes. No significant difference could be seen when comparing IL-6 serum concentrations in patients with electrical storming or single VT/VF-episodes (p=0.25).
Conclusions: 1. Patients with an electrical storming had significantly higher CRP and IL-6 serum concentrations than patients without spontaneous VT/VF-episodes.
2. With regards to IL-6, patients with single spontaneous VT/VF-episodes had significantly higher serum concentrations than patients without VT/VF-episodes.
3. These findings support a possible association of a proinflammatory status and spontaneous VT/VF.

P3541 Eosinophilia associated allergic etiology might be related with early occurrence of amiodarone induced pneumonitis

Y. Yamada[1], T. Shiga[1], H. Sakamaki[2], M. Naganuma[1], N. Matsuda[1], N. Hagiwara[1], H. Kasanuki[1]. *[1]Tokyo Women's Medical University, Department of Cardiology, Tokyo, Japan; [2]Tokyo Saiseikai Central Hospital, Department of Respiratory Medicine, Tokyo, Japan*

Purpose: Amiodarone is highly effective for supra-ventricular and ventricular tachycardia, but its use is often limited by the severity of adverse effects. Especially amiodarone induced pneumonitis (AIP) sometimes can be fatal, therefore the prevention and the risk assessment are significant. But they are not always understood, since the etiologies are unknown. Some reports speculated drug accumulation in lung organs might cause AIP. However, we have experienced two types of AIP. One occurred in the first 9 months (early phase) with eosinophilia and the other occurred in 10 to 120 months (late phase) without eosinophilia. The etiologies may be different between early phase and late phase, for example toxic mechanism or allergic mechanism. The purpose of this study is to investigate the clinical features and speculate the etiologies in both phases.
Methods: 33 cases caused AIP in 520 amiodarone therapy cases in our hospital. AIP was finally diagnosed by abnormal findings in chest computed tomography. The time course until the occurrence, eosinophil counts, ages at diagnosis, loading and maintenance doses were retrospectively investigated in case records. Each variable was compared between the early phase and late phase AIP. Multivariated logistic analysis was used to identify whether eosinophilia was an independent factor for early phase AIP compared with other variables. Early phase AIP was defined as equal or within 9 months from administration, whereas late phase AIP was above 9 months. Eosinophilia was defined above 350 eosinophil counts per milliliter.
Results: In total 33 AIP cases early phase AIP was 11 and late phase AIP was 22. Eosinophilia was found in 7 cases (64 percent) in early phase AIP, whereas 6 cases (27 percent) in late phase AIP. Multi-variated analysis statistically support eosinophilia is an independent factor for early phase AIP.
Conclusions: The etiology of early phase AIP might be different from late phase AIP. Eosinophilia associated allergic etiology might be one of the causes of early phase AIP.

AF CARDIOVERSION AND ATRIAL FUNCTION

P3542 Clinical profile and treatment of patients submitted to electrical cardioversion in 2004: results of REVERSE trial

X. Vinolas Prat[1], J.M. Alegret[2], J. Sagrista[3], A. Hernandez-Madrid[4] on behalf of REVERSE investigators. *[1]H. Sant Pau, Cardiology, Barcelona, Spain; [2]Hospital San Joan, cardiology, Reus, Spain; [3]H valle de Hebron, Barcelona, Spain; [4]H Ramon y Cajal, Madrid, Spain*

Recently AFFIRM and RACE trials have suggested that maintenance of sinus rhythm is not superior to rate control in patients with atrial fibrillation. We do not know if the patients cardioverted in our country are similar and thus if these results can be extrapolated.
Objective: to know clinical profile of patients (P) cardioverted, antiarrhythmics treatments prescibed and antithrombotic regimens used in year 2004 in real life clinical practice in our country.
Material & methods: the REVERSE (REgistro cardioVERSion en Espana) was conducted in 97 spanish hospitals and included prospectively all P (n=1516) with persistent AF (>7days) submitted to electrical cardioversion (EC) from february to june 2004. Clinical and echocardiohraphic data, antiarrhythmic and antithrombotic treatment, methodology and success of EC were prospectively introduced in an online database.
Results: see table. The antithrombotic treatment pericardioversion was:55% coumadine 3 weeks before EC, 31% of P were already chronically anticoagulated, 8% transesophageal echo + coumanide after EC, 4% LMW heparines.

age	63±11	EC effectiveness	91%
male	63%	immediate recurrence	5%
hypertension	55%	Antiarrhythmics	
no cardiopathy	50%	amiodarone	58%
previous EC	20%	IC	15%
AF duration <3m	38%	sotalol	2%
AF duration>6m	24%	no treatment	22%
unknown duration	19%		

Conclusions: P cardioverted in our country are younger and has less cardiopathy compared to recent published trials therefore these results should be extrapolated with caution to clinical practice. Amiodarone is the most frequent prophylactic treatment, and a high proportion of P do not receive any antiarrhythmic treatment. Anticoagulation strategy using tranesophageal echo is very infrequently used in our country.

P3543 A novel rectangular biphasic waveform from a radiofrequency defibrillator compared with a conventional waveform for the transvenous cardioversion of chronic atrial fibrillation in patients

B. Glover[1], C.J. Mccann[2], S.J. Walsh[2], M.J. Moore[2], G. Manoharan[2], M.J. Roberts[2], J.D. Allen[2], A.A.J. Adgey[2]. *[1]Royal Victoria Hospital, Cardiology Department, Belfast, United Kingdom; [2]Royal Victoria Hospital, Cardiology, Belfast, United Kingdom*

Purpose: The optimal waveform for the transvenous direct current cardioversion (DCC) of atrial fibrillation (AF) is unknown. A novel rectangular biphasic waveform (6/6msec duration, phase 2 peak voltage 50% of phase 1) delivered from a radiofrequency (RF) powered defibrillator was compared with a conventional capacitor based exponential biphasic waveform of equivalent duration and voltage.
Method: Patients with chronic AF (fully anticoagulated) were randomised to receive either the RF or a conventional trapezoidal waveform (Ventritex HVS-02). Defibrillation electrodes were positioned in the right atrial appendage (cathode) and distal coronary sinus (anode). All shocks were R-wave synchronised. Phase 1 peak voltage was increased in stepwise progression from 50V-300V. Success was defined as return of sinus rhythm for = 30 seconds. Cardiac troponin and CKMB were checked post procedure.
Results: Patients (n=22, 15 male) received 119 shocks (RF=62, conventional=57). Mean age was 62 (±13.2) years, mean BMI was 30 (±7) and mean duration of AF was 10.2 (±11.1) months. The groups were matched in terms of age, gender, BMI, duration of AF, aetiology, drugs and echocardiographic features.
The RF waveform performed significantly better than the conventional waveform for the cardioversion of chronic AF (9 of 12 patients (75%) versus 2 of 10 patients (20%) success, p = 0.01). The mean leading edge voltage for the RF was 216V (Range 100-300) and for the conventional waveform was 270V. No significant

arrhythmias, sinus pauses or episodes of hypotension occurred. There was no elevation of cardiac enzymes.
Conclusions: The novel biphasic waveform has a superior efficacy at a lower voltage compared with the conventional waveform in the transvenous cardioversion of AF. There were no arrhythmic, haemodynamic complications or elevation of markers of myocardial injury. Use of this waveform may improve the efficacy of implantable devices for the treatment of AF.

P3544 Left atrial appendage Doppler flow as a predictor of restoration of sinus rhythm in patients with persistent atrial fibrillation

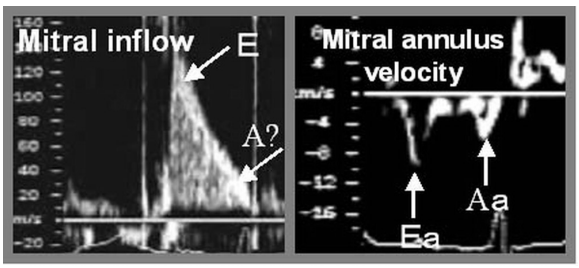
A. Navazio, O. Gaddi, I. Monducci, M. Pantaleoni, M. Calzolari, G. Tortorella, U. Guiducci. *Santa Maria Nuova Hospital, Cardiology Department, Reggio Emilia, Italy*

Background: Echocardiographic parameters for predicting cardioversion outcome in patients with persistent non valvular atrial fibrillation are not accurately defined.
Aim: To evaluate the role of left atrial appendage flow velocity detected by transesophageal echocardiography for prediction of cardioversion outcome in patients with persistent non valvular atrial fibrillation.
Methods: 62 patients (38 males, mean age 68±11 years) with persistent nonvalvular atrial fibrillation lasting more than 4 weeks but less 12 months duration underwent transthoracic and transesophageal echocardiography before electrical cardioversion.
Results: Cardioversion was successful in restorig sinus rhythm in 54 patients (87%). Mean left atrial appendagepeak emptying flow velocity was significantly higher in patients with successful than those with unsuccessful cardioversion (34±16.4 cm/sec vs 24.3±14.7 cm/sec; $p < 0.001$); other independent predictors of cardioversion success at univariate analysis were left end-diastolic diameter $\leq$ 57 mm ($p < 0.05$), ejection fraction $\geq$ 50% ($p < 0.04$) and the pretreatment with antiarrhythmic drugs ($p < 0.04$). At multivariate regression analysis (Cox model) the mean left atrial appendage flow velocity $\geq$ 33 cm/sec (p = 0.0018, OR 3.2, CI 95% = 1.7-5.8), the arrhythmia duration $\leq$ 6 weeks (p = 0.032, OR 5.2, CI 95% = 2.4-14.3), the left atrial diameter (parasternal long axis) $\leq$ 48 mm (p = 0.036, OR 2.3, CI 95% = 1.4-3.9) and pretreatment with antiarrhythmic drugs (p = 0.04, OR 2.4, CI 95% = 1.4-4.1) were independent predictors of cardioversion success.
Conclusions: In patients with persistent nonvalvular atrial fibrillation, measurement of left atrial appendage peak emptying flow velocity by transesophageal echocardiography before electrical cardioversion provides valuable information for prediction of cardioversion outcome. In transesophageal echocardiography guided management of atrial fibrillation, assessment of left atrial appendage velocity profile can be easily incorporated into pre-cardioversion echocardiographic examination.

P3545 Tissue Doppler imaging provides an effective evaluation of left atrial contraction after the maze procedure

T. Yuasa[1], Y. Otsuji[1], B. Yu[1], T. Uemura[1], E. Kuwahara[1], S. Minagoe[1], R. Sakata[2], C. Tei[1]. *[1]Kagoshima University Hospital, First Department of Internal Medicine, Kagoshima, Japan; [2]Kagoshima University Hospital, Second Department of Surgery, Kagoshima, Japan*

Background: Transmitral flow atrial wave in pulsed wave Doppler after the maze procedure is often small and is difficult to detect, especially with concomitant mitral valve plasty or replacement. The purpose of this study is to investigate whether Tissue Doppler Imaging (TDI) allows effective evaluation of left atrial (LA) contraction after the maze procedure or not.
Methods: In 16 patients with maze procedure and mitral valve plasty or replacement, mitral flow velocity by pulsed flow Doppler and lateral annular velocity by TDI was recorded.
Results: 1) Pulsed flow Doppler echo detected LA contraction in only 7 of the 15 (47%) patients, potentially due to prolongation of E deceleration time (225 ± 52 msec) with overlapping of E and A flow wave (figure). 2) In contrast, pulsed annular tissue Doppler echo detected LA contraction in all of the 15 (100%) patients with significantly greater incidence ($p < 0.01$), potentially due to significantly shorter tissue E deceleration time (123 ± 52 msec, $p < 0.01$) without overlapping of E and A wave. 3) Patients with LA contraction both by flow and tissue Doppler and those with LA contraction only by tissue Doppler had similar reverse LA remodeling in the chronic phase (LA volume: minus 36 ± 23 vs. minus 27 ± 24% compared to preoperative volume, n.s.).
Conclusion: Compared to flow Doppler echo, Tissue Doppler Imaging enables better evaluation of LA contraction after the maze procedure.



A wave on flow and tissue Doppler

P3546 Atrial dilatation and atrial fibrillation impair atrial contractility by different mechanisms

H.-R. Neuberger[1], S. De Haan[2], M. Allessie[2], U. Schotten[2]. *[1]University Hospital, Department of Cardiology, Homburg-Saar, Germany; [2]Medizinische Klinik und Poliklinik, Innere Medizin III, Homburg-Saar, Germany*

Both atrial fibrillation (AF) and chronic atrial dilatation (AD) impair atrial contractile function. This is associated with an increased thromboembolic risk. We recently demonstrated, that the loss of atrial contractile function during AF goes hand in hand with a shortening of the atrial refractory period (AERP), indicating that the reduction of the Ca^{2+} inward current underlies this type of "atrial contractile remodeling". However, in dilated atria the mechanisms responsible for atrial contractile dysfunction are not yet known.
Methods: In 8 goats we implanted 2 quadripolar leads in the right atrium. At the tip of each lead sonomicrometer crystals were mounted to measure changes in atrial diameter. AERP and atrial fractional shortening (AFS) were determined at pacing intervals of 400and 300 ms. After 48h of AF maintained by atrial burst pacing, these parameters were measured again. To produce atrial dilatation the His bundle was ablated and a slow idioventricular rhythm occurred. After 3 weeks of AV block (no AF) the right atrium was dilated by 18±2% ($p<0.01$) and the measurements were repeated.
Results: Both 48h AF and 3weeks of AV block (chronic atrial dilatation) impaired atrial contractility. After 48h AF the reduced contractility went along with a shortening of the AERP. In contrast, in AD the AERP was unchanged. After 48h of AF, but not in AD, rapid atrial pacing (300ms) increased the AFS.

n=8; * $p<0.05$ vs. control	Control	After 48h AF	After 3 weeks AV block (AD)
AFS 400ms [%]	18.4±1.7	8.4±1.3***	12.8±1.5*
Difference AFS(300)-AFS(400) [%]	- 2.1±1.0	+ 3.4±1.4**	- 0.8±0.6
AERP [ms]	172±8	132±10**	165±9

Conclusions: In a goat model of chronic atrial dilatation due to complete AV block, atrial contractility is impaired. This does not go along with a shortening of the AERP and shows a frequency response different from the AF-induced contractile dysfunction. This indicates that chronic atrial dilatation and atrial fibrillation impair atrial contractility by different mechanisms.

P3547 Right atrial appendage function in patients with paroxysmal and permanent atrial fibrillation

O. Celebi, A. Agacdiken, T. Sahin, G. Kahraman, A. Vural, G. Kozdag, D. Ural, B. Komsuoglu. *Kocaeli University Medical Faculty, Cardiology, Kocaeli, Turkey*

Depressed right atrial appendage (RAA) function has been reported in patients with chronic atrial fibrillation. However, differences in RAA function between clinical subgroups of atrial fibrillation has not been evaluated. The aim of the study was to assess RAA function and its possible relationship to left atrial appendage (LAA) function in patients with paroxysmal (PAF) and permanent (PeAF) atrial fibrillation. We studied 30 patients with PAF (19 women, 11 men, mean age 60 ± 11 years) and 24 patients with PeAF (10 women, 14 men, mean age 63 ± 10 years). Transesophageal echocardiographic examination was performed in all patients. RA and LA sizes and, RAA and LAA maximal areas were larger and RA ejection fraction (EF) and LA EF were lower in patients with PeAF when compared to patients with PAF. In addition, RAA peak emptying velocity, RAA EF and LAA EF were lower in patients with PeAF. The two groups were not different with respect to the LAA emptying velocity (table).

	Patients with PAF	Patients with PeAF	p
RAA maximal area (mm^2)	29±12	38±16	0.04
LAA maximal area (mm^2)	38±9	48±14	0.004
RAA ejection fraction (%)	64±10	42±15	<0.001
LAA ejection fraction (%)	62±12	28±13	<0.001
RAA emptying velocity (m/s)	0.26±0.06	0.16±0.05	<0.001
LAA emptying velocity (m/s)	0.28±0.11	0.23±0.09	0.06

RAA emptying velocities of the patients with PAF also were lower than the reported normal values. Significant correlations were observed between EFs of RAA and LAA in both groups (for PAF; r=0.68, $p<0.001$, for PeAF; r=0.58, p=0.003). RA EF and LA EF were correlated only in patients with PAF (r=0.51, p=0.005). Despite there were no significant differences in the presence of RAA and RA spontaneous echo contrast (SEC) between the groups, LAA and LA SEC were detected in most of patients with PeAF (both $p<0.001$). AF could affect both atrial appendage functions in patients with PAF and PeAF.

P3548 Impact of atrial tissue structural remodelling on cardiac rhythm after successful mitral surgery

T. Mularek-Kubzdela[1], W. Seniuk[1], A. Marszalek[2], W. Stachowiak[3], M. Prech[1], O. Trojnarska[1], S. Grajek[1], A. Cieslinski[1]. *[1]University School of Medical Sciences, 1-st Cardiology Department, Poznan, Poland; [2]University School of Medical Sciences, Department of Clinical Pathomorphology, Poznan, Poland; [3]University School of Medical Sciences, Department of Cardiosurgery, Poznan, Poland*

The purpose of this study was to investigate which histopathologic abnormalities are predictive for restoration and maintenance of sinus rhythm after mitral surgery. Additionally clinical factors were analyzed. 101 consecutive patients (male 25, female 76) aged 23 to 71 (mean 52) with mitral valvular disease admitted for mitral surgery were enrolled in the study. In all patients electrocardiography, echocardiography and clinical examination were performed before the operation. 36 patients were in sinus rhythm, 65 had atrial fibrillation. Biopsies of the posterior wall of the left atrium were obtained during open heart surgery. Tissue was analyzed for cell size, percent of fibrosis and capillaries density using Leica Q500MC image analyzer. We also semiquantitatively measured the amount of intramyocardial adipose tissue (grade 0 to IV), inflammatory infiltrates (grade 0 to IV), area (percentage of myolytic cells) and degree (A,B,C) of myolysis. 12 months after operation cardiac rhythm was checked. 8 patients died before 12-month - follow-up, 3 patients were lost to follow-up. Remaining 90 patients were divided into two groups according to the rhythm: group I - sinus rhythm (SR, 50 patients), group II - atrial fibrillation (AF, 40 patients).

Results: Univariate analysis revealed a significant difference between I and II group in mean percent of left atrial fibrosis 32,8% vs 39,0% ($p<0,009$), severity of inflammatory infiltrates ($p<0,02$), mean dimension of left atrium 50 vs 56mm ($p<0,00027$), incidence of pure of predominant regurgitation 42% vs 20% ($p<0,040$), incidence of chronic preoperative AF 40% vs 95% ($p<0,0001$), mean duration of chronic preoperative AF 1,4 vs 6,6 ($p<0,00017$), incidence of pitting edema 44%vs 68% ($p<0,02$), NYHA class ($p<0,049$) and cyanosis ($p=0,03$).
Multivariate predictors for rhythm 12 months after successful mitral surgery were: atrial fibrosis ($p=0,003$), incidence of chronic preoperative AF ($p=0,005$) and mean duration of chronic preoperative FA ($p=0,005$).

Conclusion: The amount of left atrial fibrosis was the only histologic independent parameter connected with cardiac rhythm late after successful mitral surgery.

P3549 Echocardiographic assessment of diastolic left ventricular function is a valuable tool for predicting the risk of early recurrence of atrial fibrillation after successful cardioversion

C.M. Schannwell[1], D. Lazica[2], T. Moysidis[2], B.E. Strauer[2]. *[1]Düsseldorf, Germany; [2]Duesseldorf, Germany*

Background: After successful cardioversion early recurrence of atrial fibrillation is documented frequently. The purpose of this study was to investigate whether left ventricular (LV) diastolic parameters are valuable to predict the risk of early atrial fibrillation after successful cardioversion.

Methods: In 58 consecutive patiens with atrial fibrillation (58 $\pm$ 6 years; 61% male; duration of atrial fibrillation $>$ 28 days in 81%) who underwent successful cardioversion (electrical: 85%) to sinus rhythm, we performed an echocardiographic examination 24 hours after successful cardioversion. Following parameters of diastolic function were assessed: peak early (VE) and peak late (VA) diastolic flow velocity; early-to-late flow velocity ratio (VE/VA); acceleration (AT) and deceleration time (DT) of flow velocity in early diastole and isovolumetric relaxation time (IVRT). All patients were treated with anti-arrhythmic agents after cardioversion. Early recurrence was defined as documentation of atrial fibrillation during 30 days after cardioversion. Using multiple logistic regression, clinical and Doppler-echocardiographic parameters were tested for an association with recurrence of atrial fibrillation.

Results: 18 patients had recurrence of atrial fibrillation within 30 days after successful cardioversion. All patients (n = 11) with a restrictive diastolic filling pattern (VE/VA-ratio: 2.1 $\pm$ 0.8, DT: 158 $\pm$ 21 ms, IVRT: 51 $\pm$ 5 ms) and duration of atrial fibrillation $>$ 28 days had early recurrence of atrial fibrillation. In 5 patients with restrictive diastolic filling pattern and atrial fibrillation $<$ 28 days before successful cardioversion and 2 patients without restrictive filling pattern who had atrial fibrillation for more than 28 days also early recurrence of atrial fibrillation was documented. Multivariate analysis adjusted to clinical parameters as age, gender, presence of coronary artery disease and use of different antiarrhythmic agents after cardioversion demonstrated that just parameters of LV diastolic function were significantly associated with the recurrence of atrial fibrillation.

Conclusion: Assessment of LV diastolic function by Doppler-echocardiographic analysis of the diastolic transmitral flow 24 hours after successful cardioversion can predict the risk of early recurrence of atrial fibrillation. A restrictive diastolic filling pattern is associated with significantly increased risk of early recurrence of atrial fibrillation.

P3550 High prevalence of vagal type in idiophatic atrial fibrillation

I. Molina, L. Mont Girbau, D. Tamborero, A. Macias, M. Sitges, B. Vidal, B. Coll-Vinent, J. Brugada. *IMCV Hospital Clinic, Department of Cardiology, Barcelona, Spain*

Vagal atrial fibrillation (AF) is considered an unusual form of atrial fibrillation. The aim of the study was to analyze the prevalence of vagal AF in patients with idiopathic AF.

Methods: A prospective registry of patients attending the emergency room with a documented AF episode and no structural heart disease started in Jan 2001. Echocardiography and 24 hours Holter monitoring were performed. All patients answered a detailed questionnaire about AF episodes. When AF occurred at least 85% of the time during sleep and/or after dinner were classified as vagal AF, whereas AF episodes that took place at least 85% of the time during or shortly after physical exertion or stress were classified as adrenergic AF. Remaining pts were classified as having random AF episodes.

Results: a series of 72 consecutive pts were included in the analysis. There were 74% men, mean age was 48$\pm$12 years, 50% had paroxysmal AF. Left atrial diameter was 38$\pm$5 mm, diastolic and systolic left ventricular diameters were 51$\pm$5 mm and 32$\pm$5 mm respectively, and ejection fraction was 62$\pm$7%. Overall, 75% of the patients had vagal AF, 7% had adrenergic AF and 18% had random AF. The majority of episodes occurred at night during sleep. No clinical differences were found between vagal and non vagal AF patients.

Conclusions: Vagal AF is highly prevalent in patients with idiopathic AF. Whether this presentation reflects a different underlying mechanism of AF remains speculative.

P3551 Vagal and adrenergic atrial fibrillation is found frequently among patients in the Euro Heart Survey

R. Nieuwlaat[1], S.B. Olsson[2], J.Y. Le Heuzey[3], W. Davies[4], A. Capucci[5], S. Levy[6], A.J. Camm[7], H.J.G.M. Crijns[1] on behalf of Expert committee of the Euro Heart Survey on Atrial Fibrillation. *[1]Academic hospital Maastricht, Cardiology, Maastricht, Netherlands; [2]University hospital Lund, Cardiology, Lund, Sweden; [3]Hopital Europeen Georges Pompidou, Cardiology, Paris, France; [4]St. Mary's hospital, Cardiology, London, United Kingdom; [5]Hospital Guglielmo da Saliceto, Cardiology, Piacenza, Italy; [6]Hopital Nord, Cardiology, Marseille, France; [7]St. George's Hospital, Cardiology, London, United Kingdom*

Purpose: How often are triggers for atrial fibrillation being recognised in daily practice, and how are patients with identified triggers being managed?

Methods: In the Euro Heart Survey on Atrial Fibrillation 5333 AF patients were enrolled in 35 ESC countries, in 2003 and 2004. Patients were classified according to trigger pattern as follows: adrenergic (exercise, emotion, daytime only); vagal (postprandial, sleep, nighttime only); mixed (both adrenergic and vagal triggers); indifferent (no triggers found or reported).

Results: Triggers were reported in 1169 patients (22%). Patients with an autonomic trigger pattern were younger and were all symptomatic (table 1). Vagal AF patients were more often male, mostly presented as paroxysmal AF, and less frequently had minimal heart disease. Patients with an autonomic trigger pattern were more often treated with a rhythm control strategy, particularly with catheter ablation. Class IC drugs were mainly applied in vagal AF patients, but beta blocker prescription hardly varied among groups.

Table 1

	Adrenergic (n=586)	Vagal (n=163)	Mixed (n=420)	Indifferent (n=4161)
Age >70 years	33	33	34	48
Female gender	42	36	40	43
Paroxysmal AF	40	58	42	25
Minimal heart disease*	26	40	22	28
Symptoms (ever)	98	99	99	84
Rhythm control	73	76	67	56
Catheter ablation	11	12	11	3
Class IC drugs#	11	24	15	8
Beta blocker$	57	52	53	50

Results are reported as percentage; * None, or hypertension only; # According to Vaughan Williams classification; $ Including sotalol

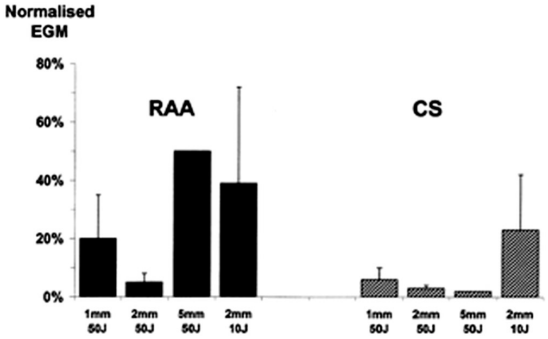
Conclusions: This survey shows that an autonomic trigger pattern for AF may be found in over 20% of patients. These patients are highly symptomatic explaining the more frequent application of rhythm control. Finding a specific trigger pattern is associated with differences in type of treatment. We speculate however that further fine-tuning of treatment may enhance management of this patient group.

P3552 Safety of atrial internal cardioversion with diagnostic electrophysiology catheters

M.C.E.F. Wijffels[1], C. Timmermans[2], R.J. van Suylen[3], S. Philippens[2], M.J. Schalij[4], H. Crijns[2], L.M. Rodriquez[2]. *[1]Leiden University Medical Centre, Cardiology Department, Leiden, Netherlands; [2]University Hospital Maastricht, Cardiology, Maastricht, Netherlands; [3]University Hospital Maastricht, Pathology, Maastricht, Netherlands; [4]Leiden University Medical Centre, Cardiology, Leiden, Netherlands*

Introduction: Internal cardioversion of atrial fibrillation (AF) by specially designed catheters is safe and effective. This study evaluated conventional diagnostic electrophysiology catheters for internal cardioversion.

Methods and Results: In 11 goats (weight 63±11 kg), 2 catheters were positioned in the right atrial appendage (RAA) and coronary sinus (CS). In 4 goats, during sinus rhythm 10 biphasic 50J-shocks were given using diagnostic electrophysiology catheters with 1mm electrodes (Lifewire St Jude Medical, surface area 0.7cm^2). In 6 goats similar catheters with 2mm electrodes were used. In 3 of these 6 goats, 10 shocks of 50J were given, while in the other 3 goats, 10 shocks of 10J were applied. In the remaining goat, 10 shocks of 50J shocks were delivered via custom cardioversion catheters (5mm electrodes, ElecathTM Electro-Catheter Corp, surface area 3.1cm^2). No major adverse effects occurred. However, the amplitude of electrograms at the RAA and CS decreased markedly (see Figure). The amount of amplitude decrease was most pronounced with the diagnostic catheters and the 50J shocks. Goats were sacrificed after 9±1 days. Macro- and microscopic evaluation showed endocardial lesions with thrombus formation and necrosis of atrial and ventricular myocardium and surrounding adipose tissue. These changes were again most marked with the diagnostic catheters and the 50J shocks, whereas they were absent in the goats in which shocks of 10J were used.



Conclusions: Internal cardioversion by diagnostic electrophysiology catheters is safe. However, due to local ablation of myocardium, electrogram amplitude decreased markedly. The amount of amplitude decrease, macro- and microscopic damage was related with energy applied and electrode surface area.

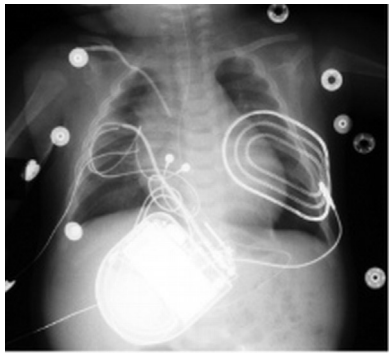
GENETIC ASPECTS

P3553 Syndactyly and long QT syndrome (Ca (v)1.2 missense mutation G406R) is associated with cardiac hypertrophy and ventricular dysfunction

S.M. Lo-A-Njoe[1], A.A.M. Wilde[2], M. Alders[3], R. Bokenkamp[4], L. Erven van[5], M.J. Schalij[5], N.A. Blom[4]. *[1]Emma Child Hospital/Academic Medical Centre, Pediatric Cardiology, Amsterdam, Netherlands; [2]Academic Medical Centre, Cardiology, Amsterdam, Netherlands; [3]Academic Medical Centre, Clinical Genetics, Amsterdam, Netherlands; [4]Leiden University Medical Centre, Pediatric Cardiology, Leiden, Netherlands; [5]Leids University Medical Centre, Cardiology, Leiden, Netherlands*

The combination of syndactyly and long QT syndrome has recently been reported to result from the (de novo) Ca (V) 1.2 missense mutation G406R. The L-type calcium channel dysfunction causes multi-organ dysfunction, including marked QT prolongation, webbing of fingers and toes (syndactyly), recurrent infections, intermittent hypoglycemia, autism and occasionally congenital heart disease. Patients (pts) have a high risk of sudden death early in life due to lethal ventricular arrhythmias.

We describe two boys (pt A, pt B) with syndactyly and long QT syndrome caused by the CACNA1C missense mutation G406R. They presented prenatal with fetal bradycardia and hydrops in pt B. In both pts marked QT prolongation (QTc pt A 630ms, pt B 650 ms), intermittent pseudo 2:1 atrioventricular block and T wave alternans were present. Therapy: cardiac pacing, potassium suppletion and high dosage of beta-blocker. Follow-up echocardiography demonstrated moderate cardiac hypertrophy associated with left ventricular dysfunction in both pts (pt A: SF 25%, pt B SF 20%). Both pts developed clinical heart failure requiring diuretic therapy. Pt A had a small persistent duct. He died suddenly at one month with documentation of ventricular arrhythmias (torsades de pointes). Pt B, born at 34 weeks, birth weight 2 kg, developed frequent torsades des pointes and syncope after 4 weeks. Mexiletin was added to the beta-blocker therapy and a subcutaneous ICD system was placed at the age of three months. During 8 months follow-up Pt B is still alive but has received 8 appropriate shocks.



LQTS PtB

Conclusion: CACNA1C missense mutation G406R appears to have a poor prognosis, our findings expand the clinical spectrum of the Ca (V) 1.2 channel dysfunction to include cardiac hypertrophy and dysfunction.

P3554 A341V, a KCNQ1 mutation, causes LQT1 of unusual clinical severity

P.J. Schwartz[1], L. Crotti[1], P.A. Brink[2], A. Goosen[2], M.J. Heradien[2], S. Bacchini[3], A. Lundquist[4], A.L.J. George[4]. *[1]IRCCS S. Matteo/University of Pavia, Dept. of Cardiology, Pavia, Italy; [2]University of Stellenbosch, Dept. of Internal Medicine, Tygerberg, South Africa; [3]IRCCS S. Matteo/University of Pavia, Dept. of Cardiology, Pavia, Italy; [4]Vanderbilt University, Division of Genetic Medicine, Nashville, TN, United States of America*

Congenital long QT syndrome (LQTS) has considerable clinical and genetic heterogeneity. There are no predominant mutations and no single specific alleles have been associated with unusually severe manifestations. Here, we present data are based on 166 mutation-carriers (54% females) from 24 South African LQTS families, of the LQT1 subtype, caused by a founder mutation, KCNQ1-A341V. Unexpected difficulties in finding asymptomatic patients suggested that A341V might be an unusually severe mutation and prompted a comparison between this South African cohort and the largest published group of LQT1 patients, 355 patients from 104 families (Priori et al – NEJM 2003) including 6 small A341V families. Compared to this inclusive LQT1 population (LQT1), the South African A341V patients have a more severe form of the disease with a greater incidence of a first cardiac event by age 40 (80% vs 30%, $p<0.0001$), they become symptomatic earlier (8 ± 4 vs 13 ± 9 years, $p<0.0001$), have a longer QTc (493 ± 49 vs 466 ± 44 ms, $p<0.0001$) and have a lower prevalence of silent mutation carriers (7% vs 36%, $p<0.0001$). Also, they have a high incidence (14%) of sudden death before age 20. When KCNQ1-A341V is expressed in CHO cells stably expressing wild-type KCNQ1 with KCNE1, we observed a 50% reduction in IKs magnitude compared to co-expression of empty vector, demonstrating that KCNQ1-A341V exerts dominant suppression of IKs. However, the degree of IKs suppression is somewhat less than other LQT1 mutations suggesting that another aspect of the channel malfunction may account for the more severe clinical phenotype. We conclude that A341V is a malignant mutation associated with unusually severe clinical manifestations.

P3555 Phenotypic characterisation of Timothy syndrome, a complex cardiac and multisystem disorder

C. Napolitano[1], K.W. Timothy[2], R. Bloise[3], I. Splawski[4], P.J. Schwartz[5], M.T. Keating[4], S.G. Priori[6]. *[1]IRCCS Fondazione Salvatore Maugeri, Molecular Cardiology, Pavia, Italy; [2]University of Utah, Salt Lake City, United States of America; [3]IRCCS Fondazione Salvatore Maugeri, Molecular Cardiology, Pavia, Italy; [4]Harvard Medical School, Children's Hospital, Boston, United States of America; [5]Policlinico San Matteo-Univ of Pavia, Dept. of Cardiology, Pavia, Italy; [6]Molecular Cardiol. Fond. Maugeri, and University of Pavia, Pavia, Italy*

Timothy syndrome (TS) is a rare variant of Long QT syndrome (LQT8). We have recently reported a mutation in the cardiac voltage-gated calcium channel (Cav1.2) in several TS patients (pts). However, the clinical features and genotype-phenotype correlation of TS remain poorly investigated. Here, we report the phenotypic characterization of the largest series of TS patients studied so far.

Twenty children with TS have been thoroughly phenotyped during a follow up of 12 years. Genetic analysis was performed in all patients with available DNA and showed the same (G406R) Cav1.2 mutation (n=12 probands). All TS pts presented remarkable QTc prolongation (mean 600ms, range: 510-700ms) at birth, often associated with 2:1 functional AV block and macroscopic T wave alternans. Cardiac arrhythmias (polymorphic VT or VF) occurred in 13/17 (77%) pts, while

71% (12/17) had congenital heart disease (patent ductus arteriosus, patent foramen ovale, tetralogy of Fallot) and 29% (5/17) had cardiac hypertrophy. Of note cardiac events were frequently triggered by anesthesia, which caused tachy- or brady-arrhythmias in 80% of cases. The most frequent extracardiac manifestations were: hand/feet syndactyly and facial dysmorphsms (100%), respiratory infections 67% (10/15), language, motor and/or social developmental delays in 80% (12/15).
All patients were treated with beta-blockers. Six patients received an implantable cardioverter defibrillator and 3 underwent left cardiac sympathetic denervation. Despite such aggressive therapy deaths occurred in 50% (10/20) at a mean age of 35±39 months. Survivor's mean age was 10±6years. Interestingly the cause of death was not arrhythmic in three pts: one sepsis and two intractable hypoglycemia.
Our data, based on the largest TS population, allow concluding that TS is a genetic channelopathy with complex clinical presentation and put forth the evidence that clinical management requires prevention of cardiac arrhythmias and also the evaluation and treatment of the life-threatening extracardiac manifestations. The identification of genetic basis of TS has paved the way to possible gene-specific treatments and preventive strategies.

P3556 Truncation of the C-terminal region of Connexin43 leads to QT-prolongation and ST-elevation in neonatal mice

A. Ghanem[1], K. Maass[2], J.W. Schrickel[1], M. Linhart[1], T. Lewalter[1], B. Luderitz[1], K. Willecke[1], K. Tiemann[1]. [1]*University of Bonn, Cardiology Department, Bonn, Germany;* [2]*Institute of Genetics, Univ. of Bonn, Bonn, Germany*

Background: Connexin abnormalities have been found to result in conduction disturbances and arrhythmias. In this study we evaluated whether partly changed Cx43 as induced by truncation of the C-terminus of Cx43 (Cx43K258stop) results in ECG abnormalities.
Methods: 6-lead ECG was performed in neonatal mice (14 wild type (WT), 29 heterozygous (HT), 18 homozygous (HO)) (ADInstruments, Milford, MA, USA). ECG channels were amplified, filtered between 10 and 100 Hz and sampled at a rate of 1 kHz. Serial ECG recordings were obtained from day 1 to day 6 and standard ECG parameters were obtained. The QT-interval was additionally rate corrected (QTc) according to Mitchell.
Results: A total of 144 mouse recordings were performed, in detail 33 of Cx43 WT, 71 of Cx43K258stop HT and 40 of Cx43K258stop HO neonatal mice. Heart rate was 475 ± 61 bpm in WT, 470 ± 60 bpm in HT and 424 ± 71 bpm in HO indicating a significantly lower rate in homozygously mutant mice ($p<0.001$). P-wave duration, PR-interval and QRS duration did not exhibit significant differences among the groups. QTc demonstrated a significantly longer repolarization in HO mice (WT: 19 ± 2 ms, HT: 21 ± 3 ms, HO: 29 ± 17 ms; $p<0.01$). Subgroup analysis revealed that 20% of the HO mice demonstrated QT-prolongation ($p<0.001$) along with significant ST- and T-elevation. The remaining recordings of homozygous mice demonstrated a "normal" mean QTc-interval, ST- and T-wave.
Conclusion: Our results indicate that C-terminally truncated Cx43K258stop can lead to impairment of ventricular repolarisation in neonatal mice. These ECG abnormalities are similar to ST-elevation and QT-prolongation in overlap syndromes (Brugada- and Long-QT-Syndrome) associated with mutations in the SCN5A sodium channel gene.

P3557 Low-voltage ECG and impaired systolic cardiac function in neonatal mice expressing Connexin 31 instead of 43

A. Ghanem[1], Q. Zheng-Fischhofer[2], J.O. Schwab[1], J.S. Kim[3], G. Schwarz[2], B. Luderitz[1], K. Willecke[2], K. Tiemann[1]. [1]*University of Bonn, Cardiology Department, Bonn, Germany;* [2]*Institute of Genetics, Univ. of Bonn, Bonn, Germany;* [3]*University of Ulsan, College of Medicine, Seoul, Korea, Republic of*

Background: Connexin43 (Cx43) deficient mice die shortly after birth due to obstruction of the right ventricular outflow tract. The aim of the study was to determine the impact of its substitution with Cx31 in a Cx43-knock-out Cx31-knock-in mouse model (Cx43KI31).
Methods: 6-lead ECG was performed in 81 neonatal mice (23 wild type (WT), 43 heterozygous (HT), 15 homozygous (HO)) on first postnatal day (P0). ECG channels were amplified, filtered between 10 and 100 Hz and sampled with a rate of 2 kHz. All standard ECG parameters were evaluated off-line in signal-averaged ECG (ADInstruments, Milford, MA, USA). High-resolutional 2-D echocardiography (HDI 5000, Philips Ultrasound, Bothell, WA, USA) was performed in 18 mice (4 WT, 9 HT, 5 HO) on P4.
Results: The offsprings of heterozygous Cx43KI31 mice resulted in Mendelian frequencies, but all homozygous Cx43KI31 mice died before P12. Neonatal homozygous Cx43KI31 hearts showed irregular hypertrophic trabeculae with abnormal pouches in the subpulmonary outlet of the right ventricle similar to general Cx43 deficient mice. Electrocardiography of P0 mice revealed significantly lower heart rates in the HO group (295 bpm ± 25) as compared to WT and HT (362 bpm ± 65, 325 bpm ± 35, $p < 0.05$). Moreover, voltage of the QRS complex - expressed as mean sum of Einthoven's leads I and II - was significantly lower in homozygous Cx43KI31 animals (188 μV ± 77) as compared to WT and HT (1300 μV ± 418, 1096 μV ± 390, $p<0.001$). Echocardiography revealed significantly lower ejection fraction in HO mice (65% ± 10) as compared to WT and HT mice (87% ± 7, 78% ±10, $p<0.01$) indicating reduced systolic function in mice lacking Cx43.
Conclusion: Lack of Cx43 in homozygous Cx43KI31 mice might increase proportion of slow signal progression in the transverse direction, resulting in destruction of cardiac uniform anisotropy. Dispersion of the electrical vector might explain significant low voltage and impaired systolic left-ventricular function.

P3558 A novel mutation in SCN5A, F1344S, leads to fever-triggered Brugada syndrome

D. Keller[1], H. Huang[2], J. Zhao[2], N. Schwick[3], V. Suarez[4], M. Brink[4], S. Osswald[5], M. Chahine[2]. [1]*Basel, Switzerland;* [2]*Laval Hospital, Research Department, Quebec, Canada;* [3]*Swiss Cardiovascular Center, Bern, Switzerland;* [4]*University Hospital Basel, Cardiovascular Research, Basel, Switzerland;* [5]*University Hospital Basel, Department of Cardiology, Basel, Switzerland*

Background: Brugada syndrome (BS) is a primary electrical cardiac disorder defined by right bundle branch block and ST segment elevation in V1 to V3 on the ECG, leading to sudden cardiac death. 20% of patients show a mutation in the SCN5A gene encoding the alpha-subunit of the human cardiac voltage-dependent sodium channel hNav1.5. Fever has shown to unmask or trigger the BS phenotype, but little is known about the molecular mechanisms. Here we screened a 42-year old male patient with the BS phenotype during fever for mutations in SCN5A and studied the effect of the mutation on the channel function in vitro.
Methods: DNA was extracted from whole blood. All coding exons of SCN5A were amplified by polymerase chain reaction and directly sequenced. The hNav1.5/F1344S mutant was constructed in vitro using site directed mutagenesis. Mutant channels were expressed in the tsA201 human cell line and studied using whole cell patch clamp technique.
Results: The patient was hospitalized due to pneumonia with 39°C fever and developed polymorphic ventricular tachycardia degenerating into ventricular fibrillation. He was successfully resuscitated, and the ECG showed a type-1 BS phenotype during fever. The ECG was completely normal in the absence of fever. A heterozygous missense SCN5A mutation, F1344S, was identified in the patient. The mutation is localized in the S5 region of domain DIII. The F1344S mutation exhibit a shift of the activation of about 10 mV, and this may explain the loss of function of sodium channel carrying this particular mutation.
Conclusions: We identified a novel mutation in SCN5A, F1344S, in a patient with the BS phenotype during fever leading to ventricular fibrillation, most probably by loss of function of sodium channels due to the shift of activation. Recent studies have shown a mutation-induced total reduction in INa leading to a loss of channel function in this phenotype (Keller ESC 2004). This indicates a functional heterogeneity in the background of a genetic heterogeneity in BS triggered by fever.

P3559 Right ventricular enlargement and spontaneous ventricular tachycardias in mice with heterozygous plakoglobin deficiency – a molecular cause for ARVC?

P. Kirchhof[1], L. Fabritz[1], M. Zwiener[1], H. Witt[2], M. Schaefers[3], P. Ruiz[2], T. Wichter[1], B. Levkau[4]. [1]*University Hospital Münster, Cardiology and Angiology, Münster, Germany;* [2]*Charite, Ctr for Cardiovascular Research, Berlin, Germany;* [3]*University Hospital Münster, Nuclear Medicine, Münster, Germany;* [4]*University of Essen, Pathophysiology, Essen, Germany*

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited arrhythmogenic disorder characterized by spontaneous ventricular tachycardias and dilatation and dysfunction of the right ventricle. Mutations in proteins that form mechanical connections between myocytes, i.e. in plakophilin, desmoplakin, and plakoglobin, have been associated with ARVC and cause haplo-insufficiency (less functional protein). To date, only homozygous mutations in the plakoglobin gene have been associated with the disease. To study the functional relevance of plakoglobin for ARVC, we studied mice with heterozygous deletion of the plakoglobin gene (plako-/+) and corresponding reduced cardiac plakoglobin expression (JCB 82:8-15,1999) and their wild type littermates (WT).
Forty weeks (wk) old plako-/+ mice had enlarged right ventricles on echocardiography (15 MHz transducer, examination following NIH study on ARVC protocol adapted to mice, RV short axis diameter plako-/+ 1.81±0.15mm vs. WT 1.25±0.06mm, RV short axis area plako-/+ 4.9±0.4mm^2 vs. WT 2.2±0.3mm^2, RV area long axis area plako-/+ 6.6±0.5mm^2 vs. WT 4.4±0.3 mm^2, all $p<0.01$, 11 plako-/+ and n=9 WT) and on mouse 18C-FDG PET. Left ventricular size and function were not altered in plako-/+ mice. AV nodal block provoked spontaneous ventricular tachycardias (VT) in 40wk old isolated, Langendorff-perfused plako-/+ hearts (plako -/+ VT in 9/13 hearts vs. WT 1/7 hearts, $p<0.01$). Programmed ventricular stimulation did not induce more arrhythmias in plako -/+ mice (plako -/+ VT in 9/13 hearts vs. WT 4/7 using a single extra stimulus). At younger age(9-12 wks), right ventricular size and function were not different between genotypes (n=24 per genotype), and ventricular tachycardias could not be provoked in isolated hearts (spontaneous VT 2/11 plako-/+ vs. 2/10 WT). Right ventricular activa-

tion times and monophasic action potential durations were not different between genotypes, neither in old nor in young mice.
Conclusions: Heterozygous plakoglobin deficiency provokes ARVC with selective right ventricular enlargement and spontaneous ventricular tachycardias. Development of the disease is age-dependent. Plakoglobin-deficient mice may be a model to study cellular mechanisms and therapeutic interventions in ARVC.

P3560 Cardiac arrhythmias and conduction disorders in myotonic dystrophy patients: clinical, functional and genetic finds and correlations

M. Martinelli[1], S.A.D. Nishioka[1], M.Z.S. Marie[2], S. Siqueira[1], J.A.F. Ramires[1]. *[1]University of São Paulo Medical School, Heart Institute (InCor), São Paulo, Brazil; [2]University of São Paulo - Bioscience, Biology, São Paulo, Brazil*

Objectives: Myotonic Dystrophy (MD) is an autosomal dominant neurological disorder with cardiac involvement. It causes arrhythmias and conduction dysfunction which have not been extensively studied. The objective of this study was: to evaluate the characteristics of arrhythmic events in MD; to correlate them with clinical, electrophysiological study (EPS) and genetic findings as well as mortality.
Methods: Eighty-three consecutive patients with MD were studied. Forty-five patients (54.22%) were male, mean age=36.77±11.95. Mean follow-up=42±30.63months. Clinical evaluation, EKG, ECHO, Holter monitoring and genetic testing were carried out.
Results: The most prevalent finding was intraventricular block (IVB) in 39%. Left bundle branch block (LBBB) was observed in 23% and right bundle branch block (RBBB) in 16%; first degree atrioventricular block (AVB) in 24 patients (29%), tachyarrhythmia in 24 patients (29%), atrial flutter in 3 (3.61%) and non sustained ventricular tachycardia (NSVT) in 14 (17%). Estimated mortality was 11%; first degree AVB, IVB, left ventricular ejection fraction (LVEF)<60% were predictive factors of death. Genetic defect ranged from 100-2333 repetitions and EPS abnormalities were observed in 34% of the patients.
Conclusions: In a long term follow up of MD patients the incidence of arrhythmias and conduction disorders was 50%; atrial flutter was the most frequent sustained arrhythmia; the genetic defect did not correlate to any arrhythmia or conduction disorder; overall mortally was low (11%) and sudden death was observed in half of the cases; first degree AVB, IVB and LVEF<60% were mortality predictors and LVEF was the independent prognosis predictor; cardiac disease increased as the MD severity and was faster than the neuromuscular disease; EPS identified the risk group for pacemaker implant.

P3561 Minimal limits for the QT interval in children and adolescents. Role of the ethnic distinction

L. Makarov[1], I. Kisileva[2], V. Dolgikh[3], A. Bimbaev[2], T. Bairova[2]. *[1]Moscow, Russian Federation; [2]Childrens hospital of Byriatia, Pediatric Cardiology, Ulan-Ude, Russian Federation; [3]Institute of Pediatry and Reproduction, Pediatry, Irkutsk, Russian Federation*

Short QT syndrome (SQTS) is a new arrhythmogenic primary electrical disease with high risk of sudden death - SD (I.Gussak 2004). In mostly cases SQTS has hereditary nature that determinate necessity for family ECG investigation in each cases suspected on SQTS. Diagnosis of SQTS based on normal values of QT interval in apparently healthy population. Also a number of diseases with risk of SD for which typical ethnic predisposition recently have been described (K.Nademanee 1997). Role SQTS as one of mechanisms SD in these cases is discussed. The aim of study were to determine the minimal normal limits for QT interval in children, find possible ethnic distinctions.
Methods and results: For 1531 children aged 0 to 17 years (8,6 ± 10,2) whithout apparent heart diseases a 12-lead ECG was recorded on speed 25 mm/s and measurement manually in lead II. There were 52,8% boys (B) and 42,7% girls (G); 57,3% Slavs and 42,7% Buryats (Mongolian ethnic type, area of Baikal lake). The QT and QTc (by Bazzet's formula) interval were calculated for 7 age groups. Results were obtained next the medians, lower (2nd percentile) and upper limits (98th percentile) for QTc (ms) interval: 0-1 years old - 400 (333-451) for B and 400 (344-462) for G; 1-2 years old - 420 (349-443) for B and 387 (346-443) for G; 3-4 years old - 390 (347-423) for B and 400 (351-442) for G; 5-7 years old - 383 (326-442) for B and 381 (330-431) for G; 8-11 years old - 340 (345-436) for B and 395 (334-466) for G; 12-15 years old - 390 (337-440) for B and 403 (350-471) for G; 16-17 years old - 380 (331-436) for B and 396 (349-464) for G. Significant differences were not shown to exist, compared with different ethnic groups. QTc less 350 ms (mean 334 ± 27,4 ms) were found in 12 (0,78%) of children (9 boys, 3 girls). 8 (66,7%) children from these had syncope and/or positive family history of sudden death in young age.
Conclusion: Normal minimal limits for the QTc interval in children and adolescents not have distinction from ethnic type. Lowest limit (2 percentile) of the QTc consist 330 ms and has not has distinct in age and sex groups of children 0-17 years. Shortening of the QT interval need in excluding of SQTS and other diseases with high risk of SD.

P3562 Diagnostic yield of additive chest leads in patients with Brugada syndrome

R. Schimpf[1], C. Veltmann[2], L.F. Hsu[3], M. Haissaguerre[4], M. Borggrefe[2], C. Wolpert[2]. *[1]Universitätsklinikum Mannheim, Ist dept. of Medicine, Arrhythmieambulanz, Mannheim, Germany; [2]Ist Department of Medicine, University Hospital Mannheim, Mannheim, Germany; [3]Hopital Cardiologique du Haut-Leveque, Bordeaux-Pessac, France; [4]Hopital Cardiologique du Haut-Leveque, Bordeaux-Pessac, France*

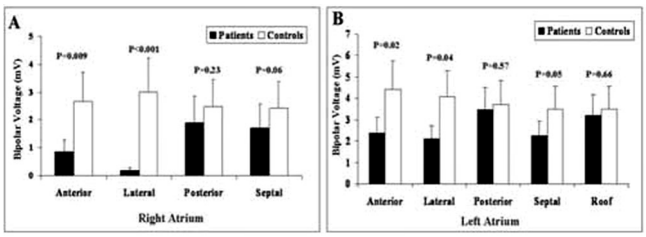
Essential for a correct identification of the patient with a Brugada syndrome is the 12 channel ECG with typical repolarisation abnormalities in the precordial leads V1-V3. The diagnosis is established by documentation of a type I ECG spontaneously or after provocation and unmasking with a intravenous antiarrhythmic drug test according to the criteria of the Brugada consensus conference. Conventionally the ECG electrodes are positioned standardized in the fourth intercostal space parasternally for V1 and V2.
Aim: Aim of the actual study was to examine whether additive electrode positions one and two intercostal spaces above are of additional value in identification of patients with a Brugada syndrome.
Patient and methods: patients with a Brugada syndrome are examined with conventional and additive electrode positions one and two intercostal spaces above either for the resting ECG and for intravenous drug testing (ajmaline).
Results: at all from 16/34 consecutively examined patients with a Brugada syndrome (mean age 47±12 years) presented no diagnostic index ECG. After performing an ajmalin challenge further 11 patients showed a diagnostic Brugada ECG. In the remaining five patients a diagnosis of a Brugada syndrome could only be made together with an analysis of the ECG with the additional higher positioned leads. Out of these five patients four patients had a history of syncopes, one patient had a history of ventricular fibrillation.
Clinical implication: 1. A Brugada syndrome could be potentially overlooked with conventional precordial lead positions during routine ECG recording and intravenous drug testing. 2. Assessment of additional higher precordial leads in 5/16 patients confirmed the diagnosis of a Brugada syndrome. 3. Routine application of additional chest leads should be performed in the examination of patients with history of syncope and suspicion of a Brugada syndrome.

ABLATION OF AF

P3563 Intra-atrial macroreentry associated with spontaneous right atrial scarring: evidence for diffuse atrial cardiomyopathy

L.-F. Hsu[1], P. Sanders[2], C. de Chillou[3], M. Hocini[2], D.C. Shah[4], C. Scavee[2], M. Haissaguerre[2], P. Jais[2]. *[1]National Heart Centre, Department of Cardiology, Singapore, Singapore; [2]Hopital Cardiologique du Haut-Leveque, Bordeaux-Pessac, France; [3]CHU de Nancy, Nancy, France; [4]Hopital Cantonal de Geneve, Division of Cardiology, Geneva, Switzerland*

Background: We sought to characterize right atrial (RA) macroreentrant tachycardia associated with spontaneous atrial scarring.
Methods: Twelve patients without prior cardiac surgery (10 male, age 47±17 years, 2 with coexisting heart disease) who underwent catheter ablation for atypical RA flutter, and 8 controls, were studied. Electroanatomical activation and voltage mapping was performed for both atria.
Results: Compared to controls, the study patients demonstrated biatrial enlargement (RA volume 141 ± 28mL vs 44 ± 4mL, P < 0.001; LA volume 100 ± 15mL vs 45 ± 14mL, P = 0.001), and reduced atrial voltages (mean RA voltage 1.16 ± 0.50mV vs 2.64 ± 0.65mV, P < 0.001; LA voltage 2.73 ± 0.66mV vs 3.79 ± 0.94mV, P = 0.04). Large electrically silent areas or scars (bipolar voltage amplitude <0.05mV and no RA capture when pacing from these areas), localized to the RA free wall and surrounded by large regions of low voltage (<0.5mV), were demonstrated in all study patients. Regionally, the lowest voltages were localized to the anterior and lateral RA, and septal, anterior and lateral LA (Figure). Sixteen reentrant circuits (12 clinical, 4 induced) were demonstrated. Among the 12 clinical tachycardias, single-loop reentry around the scar was demonstrated in 6 and dual-loop reentry in the rest (4 with loops around the scar and tricuspid annulus, and 2 with figure-of-eight reentry utilizing a channel through the scar). After ablation, no recurrence of AFL was observed over 14±6 months, though AF developed in 3 patients and 1 had sinus node dysfunction requiring a pacemaker.



Regional distribution of bipolar voltage

Conclusion: Spontaneous RA scarring associated with intra-atrial macroreentry may be a manifestation of a more diffuse atrial cardiomyopathy, with possible implications in the development of AF and sinus node disease.

P3564 Latrogenic atrial septal defect after pulmonary vein isolation – an underestimated risk?

C. Hammerstingl[1], C. Troatz[2], T. Lewalter[2], B. Luederitz[2], K. Tiemann[2]. [1]*Medizinische Klinik II, Universitv of Bonn, Cardiology, Bonn, Germany;* [2]*University of Bonn, Cardiology, Bonn, Germany*

Background: In selected patients (pts) with paroxysmal atrial fibrillation (AF) pulmonary vein isolation (PVI) is performed to cure AF. PVI is presumed to have a low interventional risk and high treatment feasibility, consequently the number of PVI in pts with AF is increasing in spite of a success rate of 50-80%. During PVI the interatrial septum is punctured to reach the pulmonary veins. The percentage of persistent iatrogenic atrial septal defect (iASD) after PVI during long term follow up (FU) is unknown. Patent foramen ovale and ASD with right-to-left-shunting (RLS) are potent risk factors for the occurrence of cerebral ischemia due to paradoxical embolism. Subject of this study was the incidence and character of iASD after PVI and its impact on pts thromboembolic risk.
Methods: Data of pts with AF who underwent PVI in our department between 2000-2004 were analyzed. Transesophageal echocardiography was performed before and after PVI. Incidence of ASD before and after PVI was documented, shunt volume and RLS were quantified by contrastechocardiography.
Primary endpoint: iASD after PVI.
Secondary endpoints:RLS, onset of pulmonary hypertension (PAH), incidence of thromboembolism, other adverse events after PVI.

Table 1. Results

	n	age [y]	FU time [d]	EPI time [min]	RLS
group A	8 (22.22%)	51.67±10.49	292.5±88.0	200.0±39.02	6 (16.7%)
group B	28 (77.78%)	51.1±22.91	282.0±48.5	256±82.91	0
p		0.99 = ns	0.91 = ns	0.13 = ns	

Results: 59 pts with PVI, 36/59 with complete FU; transseptal puncture sheath diameter 8 [F]. 8 pts with iASD(group A), thereof 6pts with distinct RLS; 28 pts without iASD (group B); echocardiographic and interventional data: Table 1.

P3565 Effects of pulmonary vein beta radiation: an experimental study in pigs

N. Perez Castellano[1], J. Villacastin[1], P. Fantidis[2], P. Aragoncillo[2], M.J. Garcia Torrent[1], M. Sabate[2], C. Prieto[2], C. Macaya[2]. [1]*San Carlos University Hospital, Arrhythmia Unit, Cardiovascular Institute, Madrid, Spain;* [2]*San Carlos University Hospital, Madrid, Spain*

Radiofrequency catheter ablation of pulmonary veins (PVs) is an effective treatment for atrial fibrillation (AF). However, this is usually a long and difficult procedure requiring extensive radiofrequency applications that can have serious potential complications.
Methods: Eight 30 kg female minipigs were used in this study. Under general anesthesia, PVs were approached from the right femoral vein by means of a transeptal puncture aided by intracardiac echocardiography (ICE). PV morphology was studied by selective angiography and ICE. Beta radiation was delivered by means of P-32 encapsulated in a balloon catheter (Galileo® III, Guidant). This catheter was positioned through a guiding catheter at the superior aspect of the right PV and adjacent left atrium (LA). Radiation time was calculated to deliver 60 Gy at a depth of 1 mm from the contacting endocardial surface. Left PVs were not radiated due to their unfavorable anatomy.
Results: One animal died after PV radiation apparently due to mechanically induced ventricular fibrillation, although pathological analysis revealed a severe pulmonary hemorrhage affecting the right superior lobe. All remaining animals were euthanized for pathological analysis at least 1 month after radiation. At gross examination the radiated area displayed a normal appearance. Histological analysis revealed a normal endothelium in 2 cases and a patchy endothelial disruption in the remaining 6 cases. In 3 cases the subendothelial layer, the media and the adventitia were thickened. In 7 cases the elastic lamina was disrupted. All minipigs had sleeves of atrial myocardium entering 3±1 mm into the PVs, which were more prominent at the upper and lower borders of the PVs. LA myocardium and PV sleeves had variable degrees of necrosis (3 cases), inflammatory infiltrates (5 cases), fibrosis (5 cases), and neovascularization (2 cases). These lesions were transmural in 6 pigs (63%). Three PVs had a focal mild stenosis. Laminar platelet-rich white thrombi were identified in 3 cases. Unspecific pericarditis was disclosed in 1 case.
Conclusion: These data support that PV sleeves can be ablated by beta radiation. Additional studies using specific devices and refined technology are required to better define the usefulness of this energy source in the treatment of AF.

P3566 Significance of early recurrences after circular plus linear left atrial ablation for treatment of atrial fibrillation

H. Tanner, G. Hindricks, R. Kobza, C. Piorkowski, A. Dorszewski, J.H. Gerds-Li, U. Backenkohler, H. Kottkamp. *University of Leipzig - Heart Center, Cardiology - Dep. of Electrophysiology, Leipzig, Germany*

Background: In ablation strategies aiming at trigger elimination to cure atrial fibrillation (AF), early AF recurrences are indicative for treatment failure and lead to early re-ablation. In ablation strategies aiming at left atrial substrat modification the role of early recurrences is less clear. The aim of the present study was therefore to analyze the significance of early AF recurrences for mid- and long-term follow-up in patients treated with left atrial linear ablation for treatment of AF.
Methods and Results: In 202 patients (pts) with paroxysmal (n=153) and persistent (n=49) AF, radiofrequency (RF) energy induced circular plus linear lesions were combined and placed around the left and right pulmonary veins (PV) respectively, between the two circles and from the left circle to the mitral annulus using the Carto system. Complete isolation of both right and left PVs was present in 5% of all pts. Follow-up was done using serial continuous 7-day-ECGs. Pts were divided into 2 groups: group A (n=56, 28%) included all pts with stable sinus rhythm during immediate post-ablation 7-day-ECG and group B (n=146, 72%) consisted of all pts with AF recurrences during post-ablation 7-day-ECG. Group A and B did not differ with respect to gender, paroxysmal or chronic AF, duration and number of AF episodes prior to ablation, and left ventricular ejection fraction. Group A was younger than group B, 49±12 vs. 55±9 years ($p<0.0001$), and left atrial diameter was smaller in group A, 38±8 vs. 42±8 mm in parasternal long axis. Freedom from AF in group A vs. group B was present in: 83 vs. 48% after 3 months, 81 vs. 43% after 6 months, and 91 vs. 47% after 12 months, respectively (always $p<0.0001$). In case of AF recurrence after 12 months, mean time spent in AF was significantly shorter in group A vs. group B: 0.07±0.3 h vs. 23±44 h (p=0.02).
Conclusions: In pts without early AF recurrences during 7-day-ECG after placement of circular plus linear left atrial lesions, mid- and long-term freedom from AF is excellent. Early AF recurrences do not necessarily result in long-term failure, since half of these pts were in stable sinus rhythm after one year.

P3567 Rhythm outcome after circular plus linear left atrial lesions for treatment of atrial fibrillation using serial 7-day-ECGs

H. Tanner, H. Kottkamp, R. Kobza, C. Piorkowski, A. Dorszewski, J.H. Gerds-Li, U. Backenkohler, G. Hindricks. *University of Leipzig - Heart Center, Cardiology - Dep. of Electrophysiology, Leipzig, Germany*

Background: Success rates after left atrial ablation for curative treatment of atrial fibrillation (AF) depend on the mode of follow-up, i.e. symptom based, 24-h-Holter ECG or longer ECG recordings. The aim of this study was to report the rhythm outcome after circular plus linear left atrial lesions for treatment of highly symptomatic AF by the means of serial continuous 7-day-ECGs in a large patient population.
Methods and Results: In 213 patients (pts) with paroxysmal (n=163) and persistent (n=50) AF, radiofrequency energy induced circular plus linear lesions were combined and placed around the left and right pulmonary veins (PV), respectively, between the two circles and from the left circle to the mitral annulus using an electroanatomic mapping system. The first 100 procedures were done using a 8-mm tip ablation catheter, thereafter a irrigated tip ablation catheter was used. Follow-up was done using serial continuous 7-day-ECGs and more than 115000 hours of ECG recordings were analyzed. Complete freedom from AF directly after the ablation measured 29% in pts with paroxysmal AF and 22% in pts with persistent AF, 58% and 56% after 3 months, 54% and 52% after 6 months, and 64% and 38% after 12 months, respectively. Fifty-five percent of pts free from AF after 12 months had no antiarrhythmic drug therapy (class Ic and/or III). Freedom from AF did not differ whether 8mm or irrigated tip catheters were used. In pts with AF recurrences, mean time spend in AF per 7-day-ECG decreased significantly over time: 67 h before ablation, 30 h after ablation and 16 h after 12 months, respectively ($p<0.0001$), whereas the number of AF episodes per 7-day-ECG remained unchanged: 7 episodes before ablation, 13 episodes after ablation, and 9 episodes after 12 months, respectively (p=ns).
Conclusions: The results obtained by serial 7-day-ECGs over time in pts with highly symptomatic AF applying the technique of placement of circular plus linear left atrial lesions show better long-term freedom from AF in pts with former paroxysmal AF than in those with former persistent AF. Continuous 7-day-ECG was helpful to detect relatively rare and short AF episodes.

P3568 Transmural pulmonary vein lesions created by using a new ultrasound balloon catheter – an experimental study

H.C. Maia[1], T.N. Seixas[1], L. Leite[2], J. Sobral Neto[1], J.R. Barreto[1], C. Septimio[1], E.M. Oliveira[1], A.K. Peres[1]. [1]*Ritmocardio, Electrophysiology, Brasilia, Brazil;* [2]*Brasilia, Brazil*

Background: Pulmonary vein isolation (PVI) using RF energy has resulted in cure of atrial fibrillation (AF), but may be complicated by PV stenosis. Moreover,

AF recurrences after first procedure are very common, mostly because of re-sumption of conduction from PV to left atrium.
Methods and Results: To evaluate the effects of circumferential ultrasound (US) application at the PV ostium and possible collateral damages associated with this energy, 12 PVs were ablated in 6 in-vivo ovine (60-70 kg). US energy was delivered through a balloon catheter under fluoroscopic guidance (50W, 120 seconds, and 60°C). Pulmonary veins and neighboring tissue were examined for acute lung burns, collateral vascular burns, and other tissue injury. Pulmonary vein lesions were seen in all animals studied. Of a total of 12 PVs, 11 (92%) showed transmural lesions on gross and histological evaluation. Energy deliveries at left and right PV resulted in no left or right lung burn. No evidence of pulmonary artery, aorta, pericardial, or superior vena cava injury was seen. Discrete alveolar hemorrhage was seen bilateral in lower lung segment.
Conclusions: US energy application can create transmural lesion in ovine PVs. Minimal collateral damage was seen with circumferential US energy at the PV ostium. This suggests that US is a safe and possibly effective alternative energy for PVI.

P3569 Pulmonary vein isolation using a new ultrasound balloon catheter for treatment of atrial fibrillation in patients

J.R. Barreto[1], L. Leite[2], T.N. Sixas[3], H.C. Maia[1], J. Sobral Neto[1], E.M. Oliveira[1], J. Rocha[1], A.K. Peres[1]. *[1]Ritmocardio, Electrophysiology, Brasilia, Brazil; [2]Brasilia, Brazil; [3]Hospital Santa Lucia, Electrophysiology, Brasilia, Brazil*

Background: Although RF ablation to isolate pulmonary vein (PV) has been an effective treatment for atrial fibrillation (AF), the high recurrence rate of AF and the incidence of PV stenosis are important limitations. Thus, alternative energy might be an attractive approach to increase long-term results and decrease complications.
Methods and Results: To evaluate the feasibility of a new Ultrasound Balloon Catheter (USBC) for PV isolation, we studied 6 patients (54±20y-o, 4 males) presenting with refractory paroxysmal or persistent AF, despite 2.2 ± 1.1 antiarrhythmic drug trials. US energy was delivered through a new USBC under fluoroscopic guidance (35-50W, 100 seconds, and 60°C). Primary end-point was to eliminate all PV potential with no more than 10 applications per vein. PV angiography was performed before and after ablation, as well as, baseline and 3-month follow-up contrast-enhanced spiral CT scanning. Patients were followed for 6 months with clinical visit and transtelephonic ECG monitoring.
Overall, 23 PVs were ablated. All, but 1 right inferior PV, targeted were accessed with the Balloon Catheter. All PVs were eliminated with a mean of 7±3 US applications per vein. Total fluoroscopic time was 133±41 min, and total procedure time 210±40 min. No acute complication was observed. There was no recurrence of AF, but 1 patient had occurrence of non sustained atrial tachycardia. This patient had also a 40% PV narrowing compared to baseline spiral CT scanning.
Conclusion: This new US balloon catheter showed to be an effective approach to isolate PV, and might be an attractive approach for treatment of AF patients.

P3570 Accuracy of the CARTO map to image the true left atrial anatomy as compared to multislice CT scans

C. Piorkowski[1], G. Hindricks[2], D. Schreiber[2], H. Tanner[2], A. Koch[3], U. Backenkohler[2], J.C. Nielsen[2], H. Kottkamp[2]. *[1]Gross Gaglow, Germany; [2]Heart Center Leipzig, Electrophysiology, Leipzig, Germany; [3]University Leipzig, Heart Center, Radiology, Leipzig, Germany*

Background: Catheter ablation is increasingly used to treat patients (pts) with AF. Current approaches focus on three dimensional mapping systems facilitating three dimensional orientation. The present study compared the left atrial (LA) anatomy resulting from an electroanatomical reconstruction (CARTO) to the gold standard of contrast enhanced multislice CT scans.
Methods: 82 pts were selected for a left atrial ablation procedure. Prior to intervention, all pts received a contrast enhanced 4 row multislice CT scan of the left atrium (LA). The oesophagus (oeso) was contrasted with barium. After transseptal access and before ablation a whole chamber electroanatomical reconstruction of LA was performed. Additionally, the oesophagus was tagged with a CARTO catheter in a conventional gastric tube. The following distances were measured on CARTO and on multiplanar CT reconstructions: RUPV-LUPV, RUPV-oeso, LUPV-oeso, RLPV-LLPV, RLPV-oeso, LLPV-oeso, RUPV-RLPV, LUPV-LLPV, LA-oeso endoluminal surface, LA-oeso contact length, mitral isthmus length.
Results: The distance between the PVs was similar on CARTO and CT (46±9mm vs. 44±8mm for the superior veins; 45±8mm vs 46±7mm for the inferior veins). The position of the oesophagus between the PVs was not significantly different between the 2 methods. On CT 84% of the pts. showed a minimal distance <3 mm between oesophageal and LA endoluminal surface, accurately displayed on CARTO as well, with a high concordance in respect to oesophageal course (83%) and contact (82%). However, the length of contact between LA and oesophagus was underestimated by CARTO (33±9mm vs. 48±12mm; $p<0.05$), mainly at the inferior LA, due to an only limited extension of the LA map beyond the regions of interest around the PV ostia and the mitral annulus.
Conclusions: Electroanatomical reconstruction of the LA can accurately mirror the true 3-D anatomy. The visualisation of the regions of interest for AF ablation (LA roof, posterior LA around the PV ostia and the oesophagus) appears to be reliable, giving confidence to avoid injuries to sensitive structures like the PVs and the oesophagus.

NON-PHARMACOLOGICAL MANAGEMENT OF HF

P3571 The practice of 2 hour observation following dose escalation of beta-blocker therapy is not necessary

S. Lange[1], C. O'Loughlin[1], B. Travers[1], M. Ledwidge[1], K. Mcdonald[2]. *[1]St Vincents University Hospital, Heart Failure Unit, Dublin, Ireland; [2]St. Vincent's University Hospital, Cardiovascular Research Director, Dublin 4, Ireland*

Background: Beta-blockers (BB) are of proven benefit in heart failure (HF). However, prescription practice remains suboptimal. While multifactorial, the complexity of the recommended titration process likely contributes to their underutilisation. The major practical impediment occurs at each dose escalation (DE) when it is advised that patients are observed for a period of two hours to record symptomatic deterioration (SD) or sustained asymptomatic haemodynamic changes (HC: Heart rate (HR) remaining <50bpm and/or systolic BP (SBP)<90mmHg after 2 hours). This consumes a significant amount of specialist nurse time (maximum number of 4 patients/session/nurse) and clinical space. The clinical importance of this advice needs to be addressed.
Aim: The purpose of this report is to assess the frequency of SD and HC in an unselected population of patients undergoing routine BB titration in the setting of a HF clinic.
Methods: All patients were assessed prior to DE to ensure suitability to proceed to the next dose. Following dose escalation HR and BP were assessed every 30 minutes for 2 hours and record was made of any symptom to report.
Results: 287 dose titration visits have been assessed, encompassing both first exposure to BB and subsequent titrations (mean age 62.15 ± 13.86 years, 62% male). No patient was deemed unsuitable for DE. Mean HR and SBP prior to DE were 75 ± 12 bpm and 129/77 ± 17/12 mmHg. Only three visits were complicated by events occurring in different patients (event rate: 1%). One related to fatigue, on related to dizziness and one asymptomatic bradycardia. The BB was not stopped in any of these cases.
Conclusions: These data strongly suggest that patient observation may not be required following DE and that adhering to this practice standard consumes significant resources without major benefit. Consideration of remote titration in the patient's home with access to a help line may be a more practical approach to this issue and aid in more effective use of this important therapy.

P3572 Systematic review of decision models in heart failure treatment

A.G. Goehler[1], R.D. Dietz[1], J.K.O. Osterziel[1], U.S. Siebert[2]. *[1]Charite - Campus Virchow Klinikum, Division of Cadiology, Berlin, Germany; [2]Harvard Medical School, MGH Institute for Tech. Assessment, Boston, United States of America*

Background: Congestive heart failure (CHF) is a major cause of morbidity and mortality in the population and the societal burden of CHF is likely to escalate in the next decades. Several research groups have developed decision-analytic models to investigate the long-term clinical effectiveness and cost-effectiveness of several interventions. We sought to give an overview on published decision-analytic models and methodological approaches evaluating health technologies in CHF and to derive general recommendations for future comprehensive CHF decision models.
Methods: We performed a systematic literature review to identify studies that evaluated diagnostic, therapeutic and disease management procedures for CHF using mathematical decision models. Using a standardized assessment form, information on the study design, methodological framework and data sources were extracted from each publication and systematically reported.
Results: We identified 11 studies that used mathematical models to evaluate different pharmaceutical treatment options in CHF. Models evaluating diagnostic work-up or disease management strategies for CHF were not identified. All identified models included clinical and economical outcomes. Modeling approaches comprised mathematical equations and Markov models with a time horizon ranging from one year to lifetime. Treatment effects were modeled by slowing disease progression, which was either represented by New York Heart Association (NYHA) stages or by the number of repeat hospital admissions. The influence of different etiologies of CHF was not considered in the course of the disease in any model. Only one study included quality-adjusted life years as outcome and no study reported external validation results.
Conclusions: Well-elaborated decision models are available for CHF treatment but neither increasingly implemented disease management programs nor diagnostic patient assessment and management (e.g., with brain-natriuretic peptide) have been modeled. Future comprehensive, generic and flexible decision models should link diagnostic and therapeutic options, allow the evaluation of multiple outcomes and quality-of life, integrate different etiopathologies, and be validated with independent data.

P3573 How the doctors estimates the quality of life of patients with heart failure

A. Frigy, M. Orban, A. Incze, E. Carasca. *Clinica Medicala 4, Cardiology, Targu-Mures, Romania*

The improvement of quality of life (QOL), among with increasing the survival, is a main goal in the management of heart failure. The better knowledge of patients' QOL contributes to the individualisation of treatment and increases the cooperation of patients. In our work we studied how the consultant physicians know and estimate their patients' QOL.

Patients and method: A modified version of the Minnesota Living with Heart Failure questionaire was completed by 25, randomly assigned heart failure patients (17 men, mean age 72±6,3 years) and by their consultant physicians. The questions were grouped in three category - those which assessed the physical (Ph), emotional (E) and socio-economical (SE) status- and a score was calculated for every category. The scores obtained by the patients were compared with the scores reflecting the physicians evaluation (t test, significant p=0,05).

Results: There were no significant differences between the patients' and physicians' evaluation regarding the Ph and E scores (14,3±4,19 vs. 14,4±4,1, p=0,58; and 4,29±1,49 vs. 4,68±2,58, p=0.75), however the E status was significantly worse in the physicians' view (8,1±2,45 vs. 7,0±3,48, p=0,05).

Conclusions: The consultant physicians evaluated correctly the Ph and SE status of the patients, which are relatively objective components of QOL. The more negative appreciation of the emotional status by the doctors could be explained by their understanding of the disease (and its prognosis) and – perhaps – by the deficiencies in the physician-patient communication.

P3574 Self-care behaviour and the European heart failure self-care behaviour scale, is Europe united?

C. Theaker[1], J. Kellock[1], M. Cowie[2], H. Pryse-Hawkins[3], T. Jaarsma[4], C. Shuldham[5]. *[1]Nursing Research Unit, Royal Brompton & Harefield NHS Trust, London, United Kingdom; [2]National Heart & Lung Institute, Department of Clinical Cardiology, London, United Kingdom; [3]Royal Brompton & Harfield NHS Trust, Cardiology Department, London, United Kingdom; [4]University Hospital Gronigen, Department of Cardiology, Groningen, Netherlands; [5]Royal Brompton & Harfield NHS Trust, Nursing and Quality, London, United Kingdom*

There is increasing interest in the self-care behaviour of patients with heart failure. The European Heart Failure Self-care Behaviour Scale (EHFScBS) attempts to quantify the measures patients take to manage their heart failure and improve their quality of life. The scale covers 3 domains: complying with a regime, asking for help, and adapting daily activities. The scale was produced in Dutch and has been translated into Italian and Swedish with good internal consistency results (Cronbach's Alpha 0.81). Although it has been translated into English, its usefulness has not been tested in an English-speaking population within the United Kingdom.

A descriptive study was designed to establish the internal consistency, validity and test-retest reliability of the EHFScBS. Internal consistency results were compared against those generated from the Minnesota Living with Heart Failure Questionnaire and the Self-management of Heart Failure Index. The Minnesota Living with Heart Failure Questionnaire measures patient's perceptions of heart failure. The Self –management of Heart failure Index is a 15-point index that aims to measure the self-care of heart failure patients and was used to assess validity.

Heart-failure patients (NYHA Class I-IV) attending a hospital heart failure outpatient clinic were invited to complete the EHFScBS, the Minnesota Living with Heart Failure Questionnaire, and the Self-management of Heart Failure Index. Internal consistency was measured using Cronbach's Alpha. Results presented here are those of internal consistency only. Data on validity and test-retest reliability will be presented at the conference.

The study set out to recruit 200 patients. 150 patients have been recruited to date (113 Male, Median age 68, 74.8% NYHA Class II or III). Internal consistency was good for the Minnesota Living with Heart Failure Questionnaire (Cronbach's Alpha 0.94) and the Self –management of Heart failure Index (0.85) but less so for the EHFScBS (0.64). An alpha of 0.7 or above is generally considered acceptable.

Conclusion: The EHFScBS demonstrated a lower level of internal consistency in an English speaking population than it has in other populations. The Minnesota Living with Heart Failure Questionnaire & the Self –management of Heart failure Index, both of which were developed in English speaking populations, demonstrated higher internal consistency than the EHFScBS. Self-care behaviours may be culture-specific and may require culture-specific measurement tools.

P3575 Clinical efficacy of therapeutic education and out-patient observation in patients with chronic heart failure III-IV functional class

S.S. Yakushin[1], N.N. Nikulina[2] on behalf of Yakushin S.S.. *[1]Ryazan, Russian Federation; [2]ryazan, Russian Federation*

Aim: To study clinical efficacy of therapeutic education and out-patient observation in patients with III-IV functional class (FC) CHF.

Materials and methods: 78 patients with III-IV FC CHF aged 25 to 72 years (mean age 56,0±1,5 years) were enrolled in the study and randomized to the treatment group #1, the treatment group #2 and the control group at ratio of 1:1:1. Patient of the first treatment group have undegone a course of therapeutic education with subsequent contacts by phone in addition to the standard therapy. Patient of the second treatment group have undegone a course of therapeutic education in addition to the standard therapy without out-patient observation by phone contacts.

The major clinical parameters were comparable between the groups. The disease duration was from 1 year to 17 years (mean duration 7,0±1,5 years). CHF functional class in the patients averaged 3,54±0,051. Among patients coronary artery disease was diagnosed in 80.1%, hypertensive heart in 7.7%, dilated cardiomyopathy in 7.7%, myocarditis in history in 4.5%. Patients' medical history, physical examination were performed for all patients. Six-minute walk test was served as exercise test. Life quality information was obtaned with a spesial questionnaire – "Life With Heart Failure" (LWHF) Minnesota questionnaire. Changes were considered significant with p below 0.05. Values are presented as mean±SD.

Results: In the first group there was a decrease in CHF functional class from 3,5±0,05 to 2,7±0,10 and there was a decrease in number of patients with IV FC by 42% ($p<0.001$). Simultaneously, in the second group there was a decrease in CHF functional class from 3,5±0,05 to 3,3±0,10 and there was a decrease in number of patients with IV FC by 15% ($p>0.05$). The six-minute walk test distance was reduced by 48% ($p<0.001$) and 11% ($p>0.05$) respectively. Life quality increased in patients of both treatment group during period of study, but the most significant increase was seen in patient of group 1 (41% ($p<0.01$) versus 23% ($p>0.05$)).

Conclusions: 1) Positive changes of functional status and life quality were seen in patients with CHF III-IV FC on combination standard therapy with addition of therapeutic education and subsequent out-patient observation by phone contacts for 52 weeks. 2) Using of therapeutic education without out-patient observation do not produce significant results.

P3576 Diastolic and systolic heart failure patients derive similar benefit from a hospital based disease management program: 3 year follow up of 438 patients

R. Martos[1], C. Conlon[2], C. O'Loughlin[1], M. Ledwidge[1], K. McDonald[1]. *[1]St Vincents University Hospital, Heart Failure Unit, Dublin, Ireland; [2]St Vincents University Hospital, Heart Failure Unit, Dublin, Ireland*

Background: Disease management programmes (DMP) have been repeatedly shown to reduce morbidity and mortality in heart failure (HF). However, many reported programmes have excluded HF patients with preserved systolic function (PSF) HF.

Aim: This report compared the long term outcomes of HF patients with PSF and reduced systolic dysfunction (SHF) enrolled into our hospital-based DMP.

Methods: Patients surviving admission with NYHA class IV HF enrolled in a multidisciplinary hospital based DMP are followed up in the clinic 2, 6 and 12 weeks following discharge and are reviewed at least annually thereafter. In addition patients receive weekly phone calls throughout the first 3 months on non-clinic weeks and are instructed to contact the clinic for weight gain or symptomatic deterioration at any stage during follow up. We report on mortality, HF hospitalisations, emergency non-HF hospitalisation and emergency unscheduled visits without hospitalisation (UV) to the HF service for management of clinical deterioration (CD).

Results: Of 438 HF patients enrolled into the DMP, 88 (20.09%) had PSF (average age 73.9 ± 8.7 years, 51.1% male, 58.1% ischaemic) and 350 (79.01%) had SHF (average age 68.3 ± 12.3 years, 66.9% male, 70.3% ischaemic, all $p<0.01$ vs. PSF). HF medication profiles were similar between the groups, although significantly fewer PSF patients received ACE inhibitors (75.0% vs. 89.3%, p=0.001). Kaplan Meier survival analysis showed no difference between PSF and SHF patients over 36 months in terms of probability of death (0.683 vs. 0.671 p=0.877), HF admission (0.770 vs. 0.768, p=0.778) and the combined endpoint of death and/or all cause emergency hospitalisation (0.325 vs. 0.277 p=0.719). Furthermore, a total of 44 (50.6%) PSF patients and 189 (54.1%) SHF patients had UV to the HF service for management of clinical deterioration (p=0.620).

Conclusion: These data highlight similar long-term morbidity and mortality outcome in patients PSF and SHF. The hospitalisation rate and high use of unscheduled emergency visits among patients with PSF HF underlines the need for this group to be included in DMP for HF.

P3577 Predictors of quality of life in symptomatic heart failure patients across the left ventricular ejection fraction spectrum

E. Lewis[1], J.J.V. McMurray[2], C.B. Granger[3], E. Michelson[4], J. Carlsson[5], S. Yusuf[6], K. Swedberg[7], M.A. Pfeffer[1] on behalf of CHARM investigators and committee. *[1]Brigham and Women's Hospital, Cardiovascular Division, Boston, United States of America; [2]University of Glasgow, Glasgow, United Kingdom; [3]Duke University Medical Center, Durham, United States of America; [4]Astra Zeneca, Wilmington, United States of America; [5]Astra Zeneca, Molndal, Sweden; [6]McMaster University, Hamilton, Canada; [7]Sahigrenska University Hospital, Ostra, Goteborg, Sweden*

Background: Quality of life (QOL) responses are quite variable in patients with chronic heart failure (HF). Little is known about the predictors of QOL in HF patients, which may help explain this variability. We utilised the Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity (CHARM) population to determine predictors of QOL across the spectrum of LVEF.
Methods: CHARM enrolled 7599 patients with HF (NYHA Class II-IV) randomised to candesartan or placebo. Patients enrolled in the QOL substudy (all from North America) completed the Minnesota Living with Heart Failure questionnaire (MLWHF). Patients were grouped into quartiles based upon MLWHF scores and independent predictors of QOL were assessed using analysis of covariance (significance p-value$<$0.001).
Results: a total of 2709 of 2744 (98.6%) of eligible patients completed the MLWHF at baseline (mean age 65, 33% women, 59% ischemic, LVEF 38.4%). MLWHF score ranged from 0 to 105 (mean 40.9). There were 8 independent predictors of QOL (Table). Women and younger patients had worse QOL. Other predictors of worse QOL included higher body mass index, lower systolic blood pressure, greater symptom burden, and worse functional status. Ejection fraction (LVEF) was not a significant predictor of QOL.

Table

	0-20	21-39	40-58	≥59
Characteristics	Better QOL			Worse QOL
Gender (% Female)*	25.6	32.3	35.4	39.9
Age (years)*	67.9	67.7	65.5	61.8
Body Mass Index (kg/m^2)*	28.0	28.9	30.2	31.4
Systolic BP (mm Hg)*	130.2	129.4	126.7	125.9
Angina Pectoris (%)*	13.3	18.4	26.1	32.5
New York Heart Association (% Class 3 or 4)*	43.6	60.0	70.9	80.0
Paroxysmal nocturnal dyspnea (%)*	46.5	50.7	57.8	72.8
Rest dyspnea (%)*	48.2	52.3	56.9	67.7
Left ventricular ejection fraction (%)	39	37	39	39

Minnesota Living with Heart Failure Quartiles (* p$<$0.001)

Conclusion: female gender and younger age are independent predictors of worse QOL. HF patients have an impaired QOL irrespective of the presence or absence of low LVEF. These novel findings warrant future studies to better understand these QOL differences.

P3578 Defining a new outlook for survivors of class IV heart failure admission: 3 year follow-up of 477 patients managed in a hospital based disease management programme

C. Conlon[1], C. O'Loughlin[2], C. Traynor[2], C. Ryan[2], R. Martos[2], M. Ledwidge[2], K. McDonald[2]. *[1]St Vincents University Hospital, Heart Failure Unit, Dublin, Ireland; [2]St Vincents University Hospital, Heart Failure Unit, Dublin, Ireland*

Background: Historically the outlook for survivors of class IV heart failure (HF) admission was poor. We previously reported on the short term reduction in emergency admissions in this population within a hospital based HF disease management programme (DMP). However, there are few data on the long term morbidity and mortality of patients managed in such programmes.
Methods: Since the initiation of our programme, patients surviving admission with NYHA class IV HF have been followed in a multidisciplinary hospital-based DMP. To help maintain clinical stability, patients attend for follow up at 2, 6, 12 and 52 weeks following discharge and annually thereafter. In addition, patients receive weekly phone calls throughout the first 3 months on non-clinic weeks and are instructed to contact the clinic for weight gain or symptomatic deterioration at any stage during follow up. We report on mortality, HF hospitalisations, emergency non-HF hospitalisation and unscheduled visits to the HF unit for management of developing clinical deterioration. Results: 477 (age 69.5 $\pm$11.9 years, 64.8% male, 83.2% systolic dysfunction, 67.9% ischaemic, 25% diabetic, 24% chronic obstructive lung disease) managed in the DMP have been followed for a mean of 17.7 months (range 1.0 to 71.2 months). Kaplan Meier survival probabilities at 1, 2 and 3 years are presented in the Table.
Conclusion: These data define a new outlook for survivors of class IV HF admissions reflecting the improvement seen in the care of this patient population within DMPs.

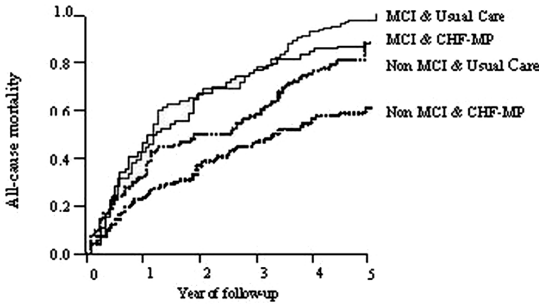
Cumulative Survuval Probability

Type of Event	Year 1	Year 2	Year 3
Death	0.853	0.742	0.679
HF Admission	0.853	0.804	0.726
Non-HF Acute Admission	0.627	0.496	0.403
Death and All-cause Admission	0.530	0.366	0.273
Unscheduled Visits	0.433	0.327	0.240
Total Patients Followed Up	405	349	324

P3579 Health outcomes in chronic heart failure patients with mild cognitive impairment: does specialist disease management make a difference?

S.N. McLennan, S. Stewart. *University of South Australia, School of Nursing and Midwifery, Adelaide, Australia*

Purpose: there is increasing evidence that Mild Cognitive Impairment (MCI) is both prevalent and a poor prognostic marker in patients (pts) with Chronic Heart Failure (CHF). We studied baseline MCI in a typical cohort of CHF pts to determine its overall prognostic significance and to determine the specific impact of a dedicated CHF management program (CHF-MP) on pts with MCI.
Method: consecutive elderly patients admitted to a metropolitan hospital with CHF were randomised to CHF-MP (n = 100) or Usual Care (n = 100). At baseline, patients with MCI were identified using the Mini Mental Status Examination (score $<$ 27). All patients were followed for 5 years. Study endpoints were all-cause mortality and event-free-survival (time to death or readmission).
Results: a total of 27 pts had MCI at baseline. Independent predictors were older age (p $<$ 0.001) and no high-school education (p = 0.003). Overall, pts with MCI were significantly more likely to die (96% vs 68%) (adjusted RR 2.15, 95% CI 1.39 – 3.31, p 0.001), and suffer combined death or readmission (96% vs 87%) (adjusted RR 1.63, 95% CI 1.05 – 2.55, p 0.03). Further examination showed that although the CHF-MP was associated with prolonged survival overall (adjusted RR 0.70, 95% CI 0.50 - 0.99, p 0.03), it had minimal impact on the survival prospects of patients with MCI, which were similar regardless of whether they were randomised to CHF-MP or Usual Care (see figure) (adjusted interaction RR 2.25, 95% CI 1.17 – 4.34, p 0.015). A similar but non-significant pattern was observed in relation to event-free survival.



Figure

Conclusion: these data suggest that CHF pts with MCI do not gain the same benefits from CHF-MPs as cognitively intact pts. Cognitive screening and alternate models of care for pts with MCI are indicated.

P3580 Heart failure in patients with atrial fibrillation: analysis of determinants and proposals for management improvement

A. Martin[1], P. Laguna[2], C. Arco[2], J. Sanchez[2], P. Pinera[2], P. Gargantilla[2], B. Coll-Vinent[2], C. Suero[2] on behalf of the GEFAUR investigators. *[1]Hospital de Mostoles, Emergency Department., Mostoles, Spain; [2]Spanish Society of Emergency Medicine, Arrhythmia Division, Madrid, Spain*

Heart failure (HF) and Atrial Fibrillation (AF) are common causes of cardiovascular disease in clinical practice but limited information concerning its relationship and determinants is available. Purposes: We analysed clinical presentation and management of HF in patients with AF and determined the benefits of the implementation of the guidelines on AF in these patients.
Methods: analysis of the GEFAUR prospective multicenter studies database; GEFAUR 1&2 [observational, July 2000 and Feb-01, 12 emergency departments (ED)] and GEFAUR-3&4 (interventional, April-02 and Dec-03: implementation of the ACC/AHA/ESC guidelines on AF, 20 ED). Conventional treatment of HF was prescribed in both groups. Epidemiological and clinical variables: analysis of the complete GEFAUR database. Management and disposition: analysis of the G-1&2 observational studies and comparison with G-3&4 interventional ones. Interventions: Rate control (RATEC) if HR at rest $>$ 100 bpm (effective if achieved 60-90 bpm), calcium/βblockers (Ca-BB) rather than digoxin (severe systolic dysfunction, disability); cardioversion (CV) in AF$<$48 hours, amiodarone or DC-CV (hemodynamic instability or drug failure); anticoagulation (ACO) if risk factors for stroke.
Results: 4255 patients included, HF in 1096 (25.7%), no differences among study periods. Patients with HF had a higher prevalence of elderly (67vs53% $>$75years, OR=1.7), male gender (61vs57%, OR=1.8), structural HD (71vs50%, OR=2.4),

hypertension (67vs57%, OR=1.4), diabetes (28vs21%, OR=1.4) and disability (26vs21%, OR=1.3) and presented more often with dyspnea (84vs19%, OR=23), rapid HR (47vs41%, OR=1.2) and hemodynamic instability (6vs3%, OR=2); conversely, palpitation (16vs32%, OR=0.4), chest pain (15vs21%, OR=0.7), syncope (0.8vs5%, OR=0.1) and current prophylaxis with antiplatelets were less frequent. In HF, higher proportion of RATEC (40vs32%, OR=1.5) mainly with digoxin (87vs55%, OR=5.3), ACO (28vs23%, OR=1.2) and admission (73vs38%, OR=3). In HF, effectivenes of RATEC and CV was 40% and 33%, and symptom relieving was achieved in only 21% of patients. The implementation of the guidelines increased RATEC (OR 1.3) with higher effectiveness (OR 2.4) and Ca-BB use (OR 1.6), CV (OR 3.9) and its success (OR 1.3), ACO (OR 1.2) and symptom relieving (OR 4.5).

Conclusions: HF is a common clinical feature of AF in the acute setting and associates a severe clinical profile (elderly, structural HD, co-morbidity and highly symptomatic presentation). The implementation of guidelines on AF improves current management and its results in this daily practice setting.

P3581 Establishing the clinical utility of the living with heart failure quality of life measurement instrument in the management of heart failure patients

C. O'Loughlin[1], M. Ledwidge[1], K. Mcdonald[2]. [1]*St Vincents University Hospital, Heart Failure Unit, Dublin, Ireland;* [2]*St. Vincent's University Hospital, Cardiovascular Research Director, Dublin 4, Ireland*

Background: Quality of Life (QOL) measures are increasingly recognised as important prognostic factors in the management and treatment of heart failure (HF) patients. One such measure is the Minnesota Living with Heart Failure questionnaire (LIhFE). This disease specific (QOL) measure has been used to demonstrate treatment effectiveness and has been shown to be reliable and valid within a variety of contexts.

Aim: To establish the clinical utility of this measure in predicting long term mortality and morbidity within a HF patient population as well as demonstrating the benefits of an established multidisciplinary programme (MDP).

Methods: This is a retrospective analysis of HF patients who completed a MDP of 3 months with annual follow-up over a period of 3 years: Endpoints: Time to all acute hospitalisations, HF and Non HF; unscheduled clinic contact (UC), and death. Changes in pre and post MDP QOL scores: Instrument Administration: Immediately pre and post the MDP (0 & 3mths). Statistical Analysis: Baseline demographics: Mean±SD, Frequencies and percentages: Univariable & Multivariable analysis: t-test, Repeated Measures ANCOVA, chi square and Proportional Hazards Model (All: ?=0.05, 2 tailed). Scale reliability: Cronbach's Alpha. Software: SPSS for Windows (V.11).

Results: 230 patients completed the LIhFE at baseline (age 69.5±12.3yrs: median 71.2 yrs): Male 141 (61%): Ishcaemic 144 (63%): EF<45% 171 (74%): NYHA Functional Class I-II=174 (81%), >II=42 (19%)). Internal Consistency measures at baseline and post MDP were, ?=0.91 and ?=0.93 respectively. Average pre and post QOL Total (Range: 0-105), Physical (Range: 0-40): and Emotional (Range: 0-25) dimension scores respectively were (N=85: total: 49.3±26.1, 29.7±19.9, P<0.001; Physical: 23.8±12.4, 14.1±10.3, P<0.001; Emotional: 10.9±7.6, 7.0±5.5, P<0.001). Controlling for Gender, Age, NYHA class and EF levels, baseline LIhFE scores were significant independent predictors of mortality (LIhFE: HR=1.021, CI: 1.004: 1.038, P=0.016; Age: HR=1.689, CI: 1.019:1.101, P=0.004). None of the LIhFE dimensions were significant predictors of acute HF admissions, acute non HF admissions nor UC with the clinic.

Conclusions: The LIhFE QOL instrument demonstrates internal consistency within this HF population. The significant reduction in scores indicates that this instrument is useful in detecting the effectiveness of an intervention. Higher baseline levels of QOL were found to be a significant independent predictor of mortality, demonstrating the potential clinical utility of this measure within a DMP.

P3582 Quality of life in heart failure is related to mood and illness beliefs rather than left ventricular dysfunction

K. Mulligan[1], A. Zaphiriou[2], P. Hargrave[3], D.H.L. Patterson[4], M.R. Cowie[2], S.M.C. Hardman[4], S. Newman[5]. [1]*University College London, Ctre. Behavioural & Social Sci. in Med, London, United Kingdom;* [2]*National Heart and Lung Institute, Cardiac Medicine Dept., London, United Kingdom;* [3]*Whittington Hospital, Cardiology, London, United Kingdom;* [4]*Whittington Hospital & UCL, Academic & Clinical Cardiology, London, United Kingdom;* [5]*University College London, Ctre. Behavioural & Social Sci in Med, London, United Kingdom*

Purpose: People with heart failure have reported poorer quality of life than the general population and those with other chronic illnesses. The extent to which quality of life is impaired appears to be related to New York Heart Association classification (NYHA) but less is known about other potentially important factors, such as mood and illness beliefs. This study explored how clinical indices of heart failure severity, mood, social support and illness beliefs are related to quality of life.

Methods: Patients admitted to hospital with heart failure (ESC criteria) were managed according to local guidelines and recruited to the study when stable, shortly before discharge. Quality of life was assessed using the Short Form 36 (SF-36), a generic measure which gives composite scores for physical (PCS) and mental (MCS) quality of life. Patients also completed measures of social support, mood, and beliefs about their illness. Clinical indices of severity of heart failure included NYHA classification and echocardiographic measures of global left ventricular (LV) function. Data were analysed by means of correlation analysis followed by multiple linear regression.

Results: One hundred and forty-seven patients completed all assessments [median age 74(range 21-94), 60% male, NYHA classification at recruitment I (9%), II (68%), III (22%) and IV (1%), 75% had moderate or severe LV systolic impairment]. Mean scores on PCS were 2 s.d. below population norms and 0.5 sd below on MCS, indicating impaired quality of life. PCS and MCS were not related to LV function. Multiple regression analysis indicated that poorer PCS was significantly associated with patients' beliefs regarding the extent to which their heart failure could be controlled and managed, the number of symptoms that they attributed to heart failure, as well as their level of depressed mood. Although NYHA was associated with PCS in univariate analysis, it was no longer statistically significant in the final equation. Poorer MCS was accounted for by younger age, the number of symptoms attributed to heart failure and less self-confidence in patients' ability to manage their illness.

Conclusion: The quality of life of patients admitted to hospital with heart failure is related to their mood and the beliefs they hold about their illness but not to social support or the extent of the underlying left ventricular damage. Understanding and addressing these issues may be one of the routes to improving the quality of life of people with heart failure.

P3583 Anti-depressive medication in patients with heart failure: effects on vascular endothelium and inflammatory process

A. Drolias, D. Tousoulis, C. Antoniades, C. Tentolouris, C. Vasiliadou, M. Toutouza, C. Pitsavos, C. Stefanadis. *Athens University, Cardiology, Athens, Greece*

Previous studies have shown that depression in patients with heart failure may be associated with higher inflammatory markers such asinterleukin-6 (IL-6), C-reactive protein (CRP) and fibrinogen, affecting the prognosis in these patients. However, the effect of anti-depressive agents on endothelial function and inflammatory process in these patients is unknown.

Aim: We compared the effect of anti-depressive medication with tricyclic antidepressants (TA), serotonin and norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs) on endothelial function and inflammatory process in patients with congestive heart failure.

Methods: The study population consisted of 162 patients with congestive heart failure (aged 68±2 years old), 116 with clinically documented depression (92 treated with SSRIs and 24 treated with SNRI/TA) and 46 without depression. Forearm blood flow was measured by venous occlusion strain-gauge plethysmography. Endothelium dependent dilation (EDD) and endothelium independent dilation (EID) were expressed as the % change of flow from baseline to the maximum flow during reactive hyperemia or after sublingual nitroglycerin administration respectively. Serum levels of CRP, and fibrinogen were evaluated with standard methodology and IL-6 levels with ELISA.

Results: Patients with depression treated with SNRIs/TA had significantly lower levels of IL-6, CRP and fibrinogen (4.8±0.3pg/ml, 6.44±0.91 mg/ml and 333.6±21mg/ml respectively) compared to both patients treated with SSRIs (6.5±0.5pg/ml, 15.37±2.01 mg/ml and 373±16mg/ml respectively, p<0.05 for all) or patients without depression (5.6±0.6pg/ml, 13.5±2.8 mg/ml and 368.5±13mg/ml respectively, p<0.05 for all). There was no significant difference in any of the examined inflammatory markers between patients treated with SSRIs and those without depression. Similarly, there was no difference in EDD and EID between patients treated with SNRIs (43.7±1.6% and 62.2±1.1%), SSRIs (44.8±3.4% and 59.2±1.3%) and untreated patients (44.0±2.5% and 65.2±2.7%), p=NS for all.

Conclusions: Patients with heart failure and depression receiving non-selective serotonin reuptake inhibitors (such as tricyclic antidepressants or serotonin and norepinephrine reuptake inhibitors) have lower levels of IL-6, CRP and fibrinogen compared to those receiving selective serotonin reuptake inhibitors or those receiving no anti-depressive medication. These findings suggest that the type of anti-depressive medication may affect inflammatory process in patients with heart failure.

P3584 Education and outpatient follow up for patients with class III and IV congestive heart failure

O.F. Frolova[1], E.I. Tarlovskaya[2]. [1]*Kirov, Russian Federation;* [2]*Kirov, Russian Federation*

Congestive heart failure (CHF) is a serious public health problem, which demands search of new approaches to optimize of treatment.

Aims: To study influence of education and outpatient follow-up on the rate of readmission, mortality, quality of life, clinical and functional parameters and depression in patients with class III and IV CHF.

Methods: 45 inpatients (mean age 60.5 ± 5.2, 62% male, left ventricular ejection fraction < 40%, NYHA III-IV) with CHF were studied. Patients were randomized into 2 groups – intervention group (n=22) and control group (n=23). Both groups received the same components of basic medication treatment (ACE - inhibitor,

beta-blockers, diuretic, 40%-Digoxin). The intervention included inpatient education by physician and close telephone monitoring. Follow-up was for 12 months.
Results: After 12 months, the patients from the intervention group had fewer CHF readmissions (11 vs 25; p=0.003) and fewer readmissions for any other causes (25 vs 32; p=0,002), as compared with the control group. There was no significant difference between the intervention and control groups for mortality (3 vs 5, p=0.06). Quality of life was significantly improved only for the intervention group (the mean total score of MLHFQ was reduced from 58.8 ± 19.6 to 37.8 ± 16.3, p=0.012). After 12 months, the intervention group showed improved compliance with drug therapy (88.8% vs 53% as compared with the control group). This resulted in improvement of their exercise capacity and functional status (within 12 months the six minute walk distance increased 51.3% vs 17.8% p = 0.043) as compared with the control group. Furthermore, the patients from the intervention group improved left ventricular systolic function (from 26.7 ± 7.74% to 33.0 ± 6.4%, p=0,01). Of the 45 patients, 37.7% had major depressive disorder (Hospital Anxiety and Depression Scale - HADS). After 12 months, the prevalence of major depression in the intervention group decreased 21.5% ($p>0.05$). In the control group, it increased 15% ($p>0.05$). Antidepressants were not prescribed to both groups.
Conclusion: Due to the above management program based on optimal medication treatment, education and outpatient follow-up, the patients with CHF could reduce hospitalization rate, improve functional and clinical status, and quality of life.

DIASTOLIC FUNCTION

P3585 Diastolic heart failure is associated with elevated serum markers of collagen turnover

R. Martos[1], J. Baugh[2], C. O'Loughlin[3], M. Ledwidge[3], S. Donnelly[2], K. McDonald[3]. *[1]St.Vincents Univesity Hospital, Heart Failure Unit, Dublin, Ireland; [2]Conway Institute, University College Dublin, Dublin, Ireland; [3]St Vincents University Hospital, Heart Failure Unit, Dublin, Ireland*

Background: The pathophysiology of diastolic heart failure (DHF) is poorly understood. Reduced ventricular compliance has been demonstrated but the aetiology of this abnormality is unclear. One potential explanation is an active fibrotic process producing increased ventricular stiffness compromising filling.
Methods: To address this hypothesis we measured serum markers of collagen turnover in 31 patients with DHF. DHF was defined by dyspnoea, at least one hospitalisation for heart failure, Doppler indices of diastolic dysfunction with normal left ventricular systolic function (LVEF >45%) and elevated brain natriuretic peptide (BNP; Triage, Biosite). This group was compared with 27 patients with controlled hypertension and LVEF >45% without evidence of DHF. Procollagen III amino terminal (PIIINP) and procollagen I amino terminal (PINP) were measured by radioimmunoassay. Metalloproteinase (MMP I) and its tissue inhibitor (TIMP I) were assayed by ELISA. Patients with DHF were older (72 ±11 vs. 64±10 years, p=0.005). Otherwise the populations were similarly matched with equal numbers on ACEI, ARB and beta blocker therapy.
Results: BNP was higher in DHF (264 ±182 vs. 22 ± 12 pg/ml, p=0.0001). There was no difference between the two groups in measurements of MMP or TIMP. However, PIIINP was significantly greater in DHF (5.8 ±2.3 vs. 3.9 ±1.2 μg/L, p=0.001) and there was also trend towards an increase in PINP in the DHF group (53.1 ±30.4 vs. 40.1±19.9 μg/L, p=0.07). Controlling for the age difference PIIINP remains significantly different between groups [F(1,50)=9.489; p=0.003].
Conclusions: These data demonstrate serological evidence of an active fibrotic process in patients with proven DHF. This observation may help explain the pathophysiology of DHF and may open up new avenues of therapeutic intervention.

P3586 Neurohumoral activation and ventilatory efficiency as markers of severity in diastolic heart failure

A. Schmidt, C. Luers, A. Busse, S. Schmidt-Schweda, S. Andreas, B. Pieske. *University of Gottingen, Kardiologie und Pneumologie, Gottingen, Germany*

Background: Preserved systolic function among heart failure patients is a common finding. However, regarding diagnosis and severity of diastolic function, there is no generally accepted single parameter. The goal of this study was to employ functional, neurohumoral, and echocardiographic markers to assess severity of isolated diastolic dysfunction.
Methods and Result: We studied 70 consecutive patients with symptoms and signs of heart failure and a normal ejection fraction (LVEF 60.9%). Coronary angiograms excluded significant stenotic coronary artery disease in all patients. LVEDP at rest was elevated (>12 mmHg) in 44 patient. Patients were classified as having normal, impaired relaxation, and pseudonormal/restrictive filling patterns by use of Doppler echocardiography according to the Canadian Consensus Guidelines. Exercise testing (Naughton protocol) revealed a significant stage dependent decrease in peak VO2 correlating with an increase in severity of diastolic dysfunction. Furthermore, ventilatory efficiency, VE/VCO2 slope, which has recently been demonstrated to be of prognostic value in systolic heart failure, was robustly increased in patients with a pseudonormalized or restrictive filling pattern. This increase correlated well with a stage dependent increase in B-type natriuretic peptide levels (NT-proBNP;Elecsys, Roche Diagnostics) (Pearson r=0.378; P=0.0014). Interestingly, the ratio of peak mitral velocity to early diastolic velocity of the mitral annulus (E/E') showed a better correlation with ASE-Class than any other Doppler variable (Pearson r=0.661;P<0.000001).

Stages of Diastolic Dysfunction

ASE-Stage	Normal 0	Delayed Relaxation I	Pseudonorm. Restr. Filling II/III
LVEDP (mmHg)	15.5±1.3	14.3±1.0	24.4±2.4*#
Peak VO2 (ml/kg/min)	22.2±1.3	16.6±0.9*	13.1±1.3*#
VE/VCO2 slope	25.2±0.9	28.8±1.0	31.5±1.7*
NT-proBNP (pg/ml)	81.9±16.9	109.3±16.3	411.3±75.6*#
E/E'	7.2±0.7	11.1±0.5*	16.6±1.7*#

Values: mean ± SEM. * p<0.05 vs, Normal; # p<0.05 vs. Delayed.

Conclusion: For the first time, we were able to show that in patients with normal systolic function ventilatory efficiency correlates with both, the severity of diastolic dysfunction and NT-proBNP levels.

P3587 The usefulness of isovolumetric relaxation index for detection of elevated end-diastolic pressure in patients with diastolic dysfunction

R. Rudko[1], T. Przewlocki[2], P. Musialek[2], W. Tracz[2]. *[1]Krakow, Poland; [2]Institute of Cardiology, Dep. of Cardiac and Vascular Diseases, Cracow, Poland*

Objective: Isovolumetric relaxation time (IVRT) measured with continuous wave Doppler imaging depends on the rate of active relaxation and end-diastolic pressure (EDP). It is believed that left ventricular diastolic dysfunction begins with the deterioration of active relaxation which results in prolongation of IVRT. However, an increase in left ventricular stiffness entails shortening of IVRT due to EDP elevation. This IVRT shortening is not seen when it is measured with pulsed-wave Doppler tissue imaging. Then, IVRT prolongs with the progression of diastolic dysfunction independent of EDP. Therefore, we created IVRT index which is the ratio of IVRT measured with pulsed-wave Doppler tissue imaging to IVRT measured with continuous wave Doppler imaging. We tested the hypothesis that the index we developed may correlate with EDP and possibly detect EDP elevation.
Methods: We studied 51 subjects (aged 60 ± 9.3 years) with diastolic dysfunction by echocardiographic criteria including the ratio of early to atrial peak mitral inflow velocity, deceleration time of early mitral filling, IVRT, color M-mode flow propagation velocity, peak early myocardial velocity. IVRT was measured with continuous wave Doppler imaging from aortic valve closure click to the onset of mitral inflow and with pulsed-wave Doppler tissue imaging from the end of S wave to the beginning of E wave. EDP was obtained invasively during diagnostic cardiac catheterization before any contrast application. Patients were divided into two groups: normal EDP =<15 mmHg, 18 pts) and elevated EDP (>15 mmHg, 33 pts). The elevated EDP group was further subdivided into those with highly elevated EDP (≥25 mmHg, 12 pts) and moderately-elevated EDP (16-24 mmHg, 21 pts). IVTR index was compared between the groups. Statistical analysis for any correlation between EDP and IVRT index was performed.
Results: IVRT index was significantly higher in the elevated EDP group (1.12±0.42) as compared to normal EDP group (0.61±0.18) (p = 0.001). IVRT index was also significantly higher in highly-elevated EDP subgroup (1.35±0.3) in comparison with moderately-elevated EDP subgroup (0.99±0.41) (p = 0.007). Moreover, we found a statistically significant correlation between IVRT index and end-diastolic pressure (r=0.66, p=0.001).
Conclusions: Our preliminary data indicate a significant correlation between IVRT index and end-diastolic pressure in patients with diastolic dysfunction. Our findings suggest that IVRT index might be a useful non-invasive tool in detecting normal, moderately-elevated, and highly-elevated end-diastolic pressure.

P3588 Tachycardia exacerbates abnormal left ventricular-arterial coupling in patients with diastolic heart failure

K. Onishi[1], T. Yamanaka[2], M. Tanabe[2], K. Dohi[2], K. Funabiki[2], N. Isaka[2], T. Nakano[2]. *[1]Mie University School of Medicine, Department of Laboratory Medicine, Tsu, Japan; [2]Mie University School of Medicine, The First Dept of Internal Medicine, Tsu, Japan*

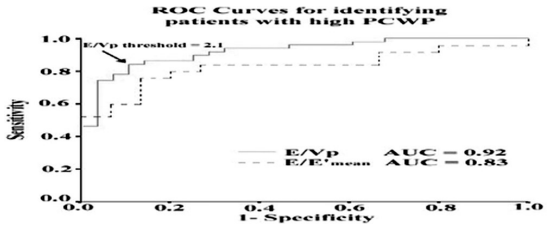
Background: Diastolic heart failure (DHF) is not solely a diastolic disease but is also characterized by left ventricular (LV) and arterial stiffening and, thus, adverse coupling between the systems. Purpose: We hypothesized that such patients show the exacerbation of LV-arterial coupling during tachycardia, which may worsen diastolic function.
Methods and results: LV pressure-volume relations were measured using conductance catheter and micro-tip manometer in patients with DHF (n=10) and systolic heart failure (SHF; n=8). None had significant coronary artery or valvular disease. LV-arterial coupling was quantified as Ees/Ea, where Ees is the slope of end-systolic pressure-volume relation, and Ea is arterial elastance. LV-arterial coupling was 0.33±0.20 in SHF and 0.95±0.18 in DHF before pacing. In patients with SHF, an increase in heart rate by 60 beats/minutes increased Ea but not Ees, thus Ees/Ea fell to 0.21±0.13 ($p< 0.05$). By contrast, an increase in heart rate by 60 beats/minutes significantly enhanced Ees in patients with DHF. How-

ever, Ea increased to the greater extent than Ees, which caused the exacerbation of Ees/Ea to 0.68±0.25 ($p<0.05$).
Conclusions: Tachycardia exacerbated abnormal LV-arterial coupling in patients with DHF as well as SHF. This may play an important pathophysiologocal role by exacerbating systemic load interaction with diastolic function under tachycardia.

P3589 Comparative value of mitral flow propagation velocity and tissue Doppler imaging in assessing left ventricular filling pressure. A Doppler-catheterisation study

B.A. Popescu[1], A.C. Popescu[2], E. Schwammenthal[2], R. Kuperstein[2], S. Rath[2], V. Guetta[2], M.S. Feinberg[2]. [1]*Tel Hashomer, Israel;* [2]*Heart Institute, Sheba Medical Center, Tel Hashomer, Israel*

Background: Both the ratio of transmitral early diastolic velocity E to its propagation velocity Vp (E/Vp) and E to tissue Doppler imaging (TDI) early diastolic velocity of the mitral annulus E' (E/E') have been shown to correlate with left ventricular filling pressure (LVFP), providing incremental information over conventional transmitral Doppler flow parameters alone. However, data about direct comparisons of these two indices against invasively measured LVFP are scarce.
Methods: We studied 78 consecutive patients (pts)(60 men, 53 ± 13 years, LV ejection fraction: 32 ± 17%) referred for right heart catheterization. Pulmonary capillary wedge pressure (PCWP) was used for LVFP assessment. Complete Doppler echocardiographic studies were performed within 2 hours before the invasive study, including measurements of Vp and E' at the septal (E'sep) and lateral (E'lat) mitral annulus level, by pulsed-wave TDI. E'mean (the average of E'sep and E'lat), E/E'sep, E/E'lat, E/E'mean, and E/Vp ratios were calculated.
Results: E/Vp ratio had the best correlation with PCWP (r=0.68, $p<0.001$). An E/Vp ratio ≥2.1 had a sensitivity of 84% and a specificity of 89% in identifying pts with a PCWP >15 mm Hg (area under the ROC curve, AUC=0.92). The best correlation with PCWP by TDI was for the E/E'mean ratio (r=0.49, p=0.001). An E/E'mean ratio ≥11.6 had a sensitivity of 76% and a specificity of 87% in identifying pts with a PCWP >15 mmHg (AUC=0.83).



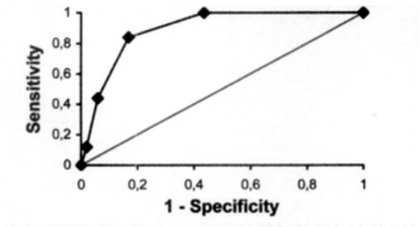
ROC curves

Conclusions: In a population of pts with predominant global LV systolic dysfunction both E/Vp ratio and E/E' ratio correlated significantly with LVFP. However, the single best predictor of LVFP in this setting was the E/Vp ratio. This index should be included in the routine noninvasive assessment of LVFP.

P3590 Doppler assessment of left ventricular diastolic function helps to identify patients with restenosis after coronary stenting

W. Kosmala[1], M. Przewlocka-Kosmala[2], W. Mazurek[2]. [1]*Wroclaw, Poland;* [2]*Medical University, Cardiology, Wroclaw, Poland*

It has been recognized that revascularization ameliorates left ventricular (LV) diastolic dysfunction whereas restenosis after PTCA is accompanied by deterioration of diastolic parameters.
Aim: To investigate whether evaluation of LV diastolic performance can improve non-invasive diagnosis of restenosis after PTCA with stent implantation.
Methods: Studied group consisted of 126 pts aged 63.7±10.5 with stable, single vessel disease referred for elective PTCA. Echo study was performed at baseline and 3 days, 1, 3, 6 and 12 months after the procedure and included estimation of: peak velocity of early (E) and late (A) transmitral flow, deceleration time of E wave (DT), isovolumic relaxation time (IVRT), E (ETT) and A (ATT) wave transit time to the LV outflow tract, flow propagation velocity of E wave (Ep) and A wave (Ap).



ROC curve

Results: Clinically relevant in-stent restenosis was angiographically confirmed in 25 pts. PTCA improved LV diastolic function as expressed by significant increase in Ep and Ep/Ap and decrease in ETT, ETT/ATT and E/Ep, which became evident 1 month after revascularization, whereas subsequent restenosis led to the opposite changes in these parameters. Alteration of >20% in at least 2 of aforementioned indices indicating worsening of LV diastolic function between examination performed 1 month after PTCA and any subsequent examination during the rest of the follow-up enabled identification of restenosis with sensitivity 84%, specificity 83% and accuracy 83%. Diagnostic value of proposed method was additionally confirmed in ROC curve analysis (figure).
Conclusion: Doppler evaluation of LV diastolic function may be helpful in distinguishing patients with restenosis after coronary stenting.

P3591 The echocardiography parameter E/Em index is not superior to Em/Am index in detecting diastolic dysfunction

M. Kasner, R. Gaub, H.-P. Schultheiss, C. Tschoepe. *Charite Campus Benjamin Franklin, Kardiologie Dept., Berlin, Germany*

Introduction: the ratio between early diastolic mitral flow and annular velocity (E/Em Index) is a non-invasive echocardiographic parameter for the determination of LV filling pressure in patients with reduced EF. We examine its effectiveness to detect an isolated diastolic dysfunction (DD) and compared it to other established diastolic indices revealed from echocardiography and right- and left heart catheterisation.
Method: for 111 patients (50F, 61M; 53±14 years) with reduced exercise tolerance despite preserved EF (>50%) we determined E/A ratio, deceleration time (DT), and isovolumic relaxation time (IVRT) by echocardiography, early (Em) and late (Am) diastolic velocity of mitral annulus motion by tissue Doppler (TDI) and LVEDP, dP/dtmin, tau and PCWP from left- and right heart catheterisation. Isolated DD was diagnosed according to the European Study Group criteria for Diastolic Heart Failure. Plasma NT-proBNP level (Elecsys 2010, Roche) was determined simultaneously. The area under the Receiver-Operating-Characteristic (ROC) curve (AUC) was used to establish the accuracy in detection of DD.
Results: 61 patients (33 M, 28 F) with isolated DD had significantly increased E/Em index (11.2±5.1 vs. 6.3±2.3, $p<0.001$). Linear regression analysis revealed a significant correlation with PCWP and LVEDP (LVEDP=8.1+0.58*E/Em and PCWP=4.2+0.61*E/Em, $p<0.01$). Having AUC of 78%, reliability of that non-invasive parameter to detect DD was high and lay between those of LVEDP (86%) and PCWP (77%), but was not better than NT-proBNP (83%) or Em/Am ratio (82%). E/Em index was significantly more accurate than parameters of conventional Doppler echocardiography (AUC 61- 73%). His Cut-off value of 8.5 resulted with an optimal sensitivity/specificity relation (59%/91%). Specificity of 100% is reached at E/Em Index of 11.5
Conclusion: using the echocardiography E/Em index, it is possible to determine filling pressures and consequently to detect an isolated LV diastolic dysfunction. In the same time, that index is proved to be superior to the conventional mitral flow Doppler echocardiography and showed to be an equivalent to the accuracy of TDI alone.

P3592 Relation of left ventricular diastolic function and plasma levels of TNF-alpha, IL-6 and IL-10 in patients with stable angina pectoris and preserved left ventricular systolic performance

W. Kosmala[1], M. Przewlocka-Kosmala[2], W. Mazurek[2]. [1]*Wroclaw, Poland;* [2]*Medical University, Cardiology, Wroclaw, Poland*

Inflammation seems to play a significant role in etiopathogenesis of coronary artery disease (CAD) as well as in progression of systolic heart failure. Whether inflammatory processes also promote left ventricular (LV) diastolic dysfunction has not been evaluated so far.
Aim: To investigate the association of plasma levels of proinflammatory (TNF-alpha, IL-6) and anti-inflammatory (IL-10) cytokines with Doppler indices of LV diastolic function in patients with stable CAD and preserved LV systolic performance.
Material and methods: Studied group consisted of 184 pts aged 64.1±9.3 yrs with stable effort angina and LV ejection fraction >50%. 136 pts had single-vessel disease whereas 58 multivessel disease. Each patient underwent echo study including estimation of: peak velocity of early (E) and late (A) transmitral flow, deceleration time of E wave (DT), isovolumic relaxation time (IVRT), E (ETT) and A (ATT) wave transit time to the LV outflow tract, flow propagation velocity of E wave (Ep) and A wave (Ap). Plasma TNF-alpha, IL-6 and IL-10 levels were evaluated by radioimmunometric method.
Results: Significant correlations were found out for TNF-alpha and: Ep (r = -0.41, $p<0.003$), E/Ep (r = 0.45, $p<0.002$) and ETT (r = 0.38, $p<0.005$). IL-6 correlated with Ep (r = -0.39, $p<0.005$), Ep/Ap (r = -0.34, $p<0.01$) and E/A (r = -0.33, $p<0.002$), whereas IL-10 with ETT (r = 0.37, $p<0.002$), Ep (r = -0.44, $p<0.005$), E/Ep (r = 0.46, $p<0.003$) and Ep/Ap (r = -0.47, $p<0.003$). The independence of aforementioned associations was shown in multivariate analyses including age, gender, type of the disease (single- or multivessel), drug assignment, plasma levels of all evaluated cytokines, LV ejection fraction, smoking habit, body mass index, coexistence of diabetes and hypertension, plasma LDL and HDL.

Conclusions: In pts with stable CAD more profound abnormalities of LV diastolic performance as expressed by the values of echo-doppler diastolic indices are related to higher plasma levels of both proinflammatory and anti-inflammatory cytokines. Whether this association indicates a causative role of immunologic upregulation in the development of LV diastolic dysfunction or only reflects the presence of myocardial ischaemia leading both to LV diastolic disorders and immunoinflammatory activation needs to be further established.

P3593 Cardiopulmonary functional capacity is determinated by diastolic filling pattern and oxidative stress in patients with hypertension

M. Dekleva[1], B. Pencic Popovic[1], V. Celic[1], N. Kostic[1], Z. Caparevic[1], S. Dimkovic[2]. [1]*Clinical and Hospital Centre "Dr D.Misovic", Cardiology Department, Belgrade, Serbia and Montenegro;* [2]*University Clinical Centre Zvezdara, Belgarde, Serbia and Montenegro*

Objective: Oxidative stress, an imbalance between oxidant production and antioxidant defenses contributes to the pathophysiology of heart failure in patients with hypertension. Left ventricular (LV) diastolic dysfunction (LVDD) is, also, an important determinant in heart failure development. Exercise test is well known model of oxidative stress and peak oxygen uptake (pVO2), maximal oxygen consumption (VO2 max), ventilatory response to exercise (VE), and test duration (RER), measured during cardiopulmonary exercise testing are an accepted parameters to assess functional capacity in patients with heart failure.
The aim of the study was to assess incremental prognostic power of diastolic indexes for cardiopulmonal exercise capacity in patients with hypertension. Contribution of oxidative stress during exercise test in those patients was investigated.
Methods: LV function was evaluated by Doppler echocardiography by assessment of mitral flow velocities (E, A), left atrial size (LA) and ejection fraction (EF).The activity of super oxide dismutase (SOD) (U/gHb) and erythrocyte activity of glutathione peroxidase (GSH-Px) (U/g/Hb) was evaluated with commercially available kit. Each subject performed a symptom limited bicycle exercise test with standardized 25 Watt increment stress protocol with breath by breath gas exchange and Spiro metric analysis during and post exercise. Seventy two patients, 42 male, mean age 52.9±9.2 with essential hypertension, without any other disease. were studied.
Results: All patients had preserved systolic function (EF= 54± 15%) and impaired LV relaxation (E/A= 0,79±15) with slightly dilated LA size (45±0,9 mm).
In hypertensive patients reduction of maximal oxygen consumption significantly correlated with degree of LVDD (E/A vs pVO2; r= -0.317, p=0,03). There was also significant negative correlation between A wave velocity and duration time to anaerobic threshold (E/A vs RER r= - 0, 395, p=0,007). SOD values increased with more oxygen uptake (SOD vs pVO2; r=0.412, p=0.05, and with test time duration (SOD vs RER; r=0.407, p=0.05). GSH-Px values positively correlated with oxygen utility (GSH-Px vs pVO2; r=0.533, p=0.04)
Conclusions: This study demonstrated that the degree of impaired LV relaxation predicts maximal functional capacity and could explain lower maximal performance observed in patients with hypertension. These patients undergo an important oxidative stress which contributed to their cardiopulmonal exercise capacity.

P3594 Echocardiographic findings in long-term treated rheumatoid arthritis patients without clinically evident cardiovascular disease

C. Gonzalez Juanatey[1], M.A. Gonzalez-Gay[2], A. Testa-Fernandez[2], A. Garcia-Castelo[2], J. Vidan-Martinez[2]. [1]*Otero de Rei, Spain;* [2]*Complejo Hospitalario Xeral-Calde.Lugo, Cardiología, Lugo, Spain*

Background: Cardiovascular disease is the most common cause of mortality in rheumatoid arthritis (RA) patients. Recent studies showed a high prevalence of congestive heart failure in RA.
Objective: To assess the frequency of echocardiographic and Doppler abnormalities in long-term treated RA patients without clinically evident cardiovascular manifestations.
Methods: Forty-seven patients fulfilling the 1987 ACR classification criteria for RA were recruited from our hospital. Patients were required to have been treated for at least 5 years, including current treatment with one or more disease-modifying antirheumatic drugs. Patients with diabetes mellitus, renal insufficiency, hypertension, cardiovascular or cerebrovascular disease and smokers were excluded. Forty-seven matched controls were also studied. Echocardiographic and Doppler studies were performed in all cases and controls.
Results: Mild aortic regurgitation and moderate tricuspid regurgitation were found in 8 (17%) of the 47 patients. A pulmonary artery systolic pressure of 30 mm Hg was more commonly found in patients (25 [53.2%]) than in controls (6 [12.8%]) ($p < 0.001$). Likewise, when a pulmonary artery systolic pressure >35 mm Hg was used as a cut-off point for pulmonary hypertension similar differences between patients and controls were seen (patients: 10 [21.3%]; controls: 2 [4.3%]; p= 0.027). As a consequence of this, the mean pulmonary artery systolic pressure was higher in RA patients (30.3 mm Hg) than in controls (26.2 mm Hg) (p=0.004). Left ventricular diastolic dysfunction due to impaired relaxation was more common in RA patients (66%) than controls (43%) (p= 0.023). In RA patients with diastolic dysfunction the disease commenced at an older age (mean age 47 years versus 36 years in RA patients without diastolic dysfunction) (p= 0.001). Extra-articular manifestations were more common in RA patients with diastolic dysfunction (p= 0.048). However, no differences in C-reactive protein values between patients with or without diastolic dysfunction were observed.
Conclusions: The present study confirms a high frequency of left ventricular diastolic dysfunction and mild pulmonary hypertension in RA patients without evident cardiovascular disease. Since extra-articular manifestations are generally the best expression of a more severe disease in RA, the presence of an increased risk of left ventricular diastolic dysfunction may indicate that unknown pathogenic mechanisms may be implicated in the development of left ventricular dysfunction and other severe extra-articular manifestations of RA.

P3595 Relationships between diastolic dysfunction and Doppler and laboratory indexes of endothelial function in CAD and syndrome X

K. Mizia-Stec, Z. Gasior, B. Zahorska-Markiewicz, M. Mizia, S. Gomulka, J. Janowska, P. Pysz, M. Holecki. *Silesian University School of Medicine, Department of Cardiology, Katowice, Poland*

Aim: To assess the relationship between left ventricular diastolic dysfunction and endothelial function, metabolic, and inflammatory factors in coronary artery disease (CAD) and syndrome X.
Methods: The study involved 69 patients with stable CAD (CCS II-III; mean age: 57.5±9.5 years): 41 with diastolic dysfunction (39-delayed relaxation, 2-pseudonormal filling), and 18 with normal LV function; and 58 patients with syndrome X (mean age: 54.3±11.1 years): 34 with LV diastolic dysfunction (31-delayed relaxation, 3-pseudo-normal filling) and 24 with normal LV function. 17 healthy subjects were the control group (mean age: 50.6±5.5 years). Flow mediated dilatation was measured as the percent change of brachial artery diameter after a 3-minute occlusion (%FMD), and following the administration of 0.4 mg sl. NTG (%NTG-MD). Laboratory analyses involved assessment of serum IL-18, ghrelin, and IGF-1 (Insulin-like Growth Factor-1) concentrations.
Results: CAD patients and syndrome X patients did not differ as to %FMD (8.6±6.7%, 7.7±4.9%, respectively) and %NTG-MD (14.4±9.6%, 12.4±7.1%, respectively), however, these parameters were significantly decreased ($p<0.05$) as compared to controls (14.0±5.1%, 27.7±15.4%, respectively). In all CAD patients examined serum IL-18 concentration was significantly increased (411.5±202 pg/ml, $p<0.05$), and IGF-1 concentration decreased (136.4±50 ng/ml, $p<0.05$) in comparison to syndrome X patients (218.9±168, 236.0±108, respectively). The appearance of diastolic dysfunction in CAD group did not change the %FMD, as well as laboratory markers assessed. In syndrome X patients with diastolic dysfunction the %FMD was significantly decreased, and serum ghrelin and IL-18 levels were significantly increased in comparison to patients with normal LV function (table).

	%FMD	IGF-1 [ng/ml]	Ghrelin [pg/ml]	IL-18 [pg/ml]
Syndrome X with diastolic dysfunction	7.6±4.6 *	225.6±91.8	61.1±6.4 *	240.8±140.0
Syndrome X with normal LV function	10.4±6.4	248.7±141.6	56.8±6.9	141.9±99.0

* $p<0.05$

Conclusion: The impairment of endothelial function exists in both CAD and syndrome X, however, it results from different haemodynamic, metabolic and inflammatory factors. In syndrome X left ventricular diastolic dysfunction coexists with more exaggerated impairment of endothelial function and increased inflammatory activation.

P3596 Atrial volume changes in anterior myocardial infarction

K. Iltumur, A. Karabulut, A. Karadede, N. Toprak. *Dicle University Faculty of Medicine, Cardiology Department, Diyarbakir, Turkey*

Purpose: Prognostic value of left atrial volume is known after acute myocardial infarction (AMI). This study was planned about to evaluate left atrial volume changes and the effect of these changes on diastollic parameters in patients with anterior miyocardial infarction whose ejection fraction are preserved.
Methods: Consecutive 34 patients with acute anterior myocardial infarction were enrolled in this study along with 20 normal individuals whose age and gender are similar with patient group in this study. In additional to the standard echocardiographic evaluation, left atrial (LA) volume measurements and tissue doppler analysis were done.
Results: Left atrial maximal volume (Volmax) (43.6±8.8 vs 38.7±5.3 ml; $p<0.05$) and volume p (Vol p) (32±7.6 and 24.1±4.9 ml; $p<0.0001$) were significantly higher in AMI group than normals. However, minimal volume (Vmin) (19.5±6.7 vs 16.8±5.6 ml; $p>0.05$) and total emptying volume (TEV) (24.1±4.1 vs 22.1±2.9; $p>0.05$) were not significant between two groups. In AMI group, passive emptying volume (PEV) and its fraction was lower, although active emptying volume (AEV) and its fraction was higher than controls. At the same time pulmonary vein systolic and diastolic flows was lower in AMI group. There was a significant relationship between left ventricular diastolic parameters (mitral E/A and mitral tissue E'/A') and LA active emptying volume in AMI group (r= -0,35 and r=-0,36 $p<0,05$, respectively).
Conclusion: Our study suggested that left atrial volume changes are significant

in the AMI. In addition, these changes are paralel to diastolic dysfunction. Left atrial volume changes may be used confidently compared to mitral valve's diastolic parameters that are changeable.

P3597 Pulmonary venous inflow parameters are sensitive markers of left ventricular diastolic dysfunction in young patients with type 1 diabetes mellitus (IDDM)

K. Kurnicka[1], K. Kurnicka[2], B. Lichodziejewska[2], A. Lipinska[2], K. Grudzka[2], M. Ciurzynski[2], D. Liszewska-Pfejfer[2]. *[1]Warsaw, Poland; [2]Medical University, Internal Medicine and Cardiology, Warsaw, Poland*

The impairment of LV diastolic function (LV-DD) may lead to heart failure and worsens the prognosis in diabetic patients. We studied mitral valve flow (MVF) and pulmonary venous flow (PVF) parameters in young IDDM patients in an aim to evaluate LV-DD using an echocardiographic method.

Material and method: The study group (I) consisted of 100 persons (49 men, 51 women, mean age 30 ± 7,1 years old) with IDDM, without cardiovascular diseases. Mean IDDM duration was 15,7 years.

60 healthy persons (31 men, 29 women, mean age 30,6 ± 6,4 years old) served as a control group (II). In MVF, the ratio of maximal velocity (Vmax) of early phase (E) to Vmax of late phase (A)- E/A, E- deceleration time -DT, isovolumetric relaxation time-IVRT were assessed. In PVF, Vmax of systolic flow (S), Vmax of diastolic flow (D), S/D ratio and Vmax of atrial reversal flow (Ar) were evaluated.

Results: Mean value of E/A ratio was significantly lower in group I than in II (1,3 ± 0,3 vs 1,4 ± 0,3; p=0,02). Mean values of DT and IVRT were significantly higher in group I than in II: 168,7 ± 18,0 vs 158,0 ± 15,6 ms; p- 0,0001 and 60,1 ± 8,1 vs 57,6 ± 6,2 ms, p= 0,03, but these results still remain within the normal range for this age group. Mean value of S/D ratio in group I was abnormal for this age group and higher than in group II (1,2 ± 0,2 vs 0,9 ± 0,1; p< 0,0001). Vmax of diastolic flow (D) was lower in group I with IDDM duration >20 years, than in group I with IDDM duration <20 years (44,5 ± 7,1 vs 48,9 ± 7,7 cm/s; p<0,02). Mean value of Ar was higher in group I than in II (29,5 ± 4,2 vs 27,7 ± 3,8 cm/s; p=0,04).

Conclusions: 1.The assessment of PVF shows an impairment of LV relaxation in young IDDM patients even when MVF remains normal. 2.PVF parameters are especially sensitive markers in detection of preclinical LV-DD and depend on IDDM duration.

P3598 The prevalence of left ventricular diastolic dysfunction assessed by tissue Doppler imaging in patients with ankylosing spondylitis

T. Okan[1], I. Sari[2], O. Goldeli[1], S. Akar[2], B. Akdeniz[1], H. Cece[3], N. Akkoc[2], S. Guneri[1]. *[1]Dokuz Eylul University, Cardiology, Izmir, Turkey; [2]Dokuz Eylul University,Rheumatolgy, Izmir, Turkey; [3]Dokuz Eylul University Radiology, Izmir, Turkey*

Purpose: Cardiac involvement in ankylosing spondylitis (AS) had been reported previously. However, evaluation of ventricular functions using tissue Doppler imaging (TDI) method has not been reported before. We aimed to evaluate left ventricular diastolic function (LVDF), right ventricular diastolic function (RVDF) in patients with AS by TDI.

Methods: Forty- nine patients with AS (25 male; mean age: 38.2±10.8) were included in the study. Control group consisted of 33 age and sex matched healthy subjects. Patients with hypertension, diabetes mellitus, overt heart failure and, left ventricular hypertrophy were not included in the study. LVDF, RVDF and myocardial performance index (MPI) were assessed by TDI. Sample volumes were obtained in lateral ring of mitral valve and tricuspid valve with TDI. The presence of e'< a' was accepted for diastolic dysfunction for both ventricles. Activity indexes (Bath Ankylosing Spondylitis Disease functional index (BASFI), Bath Ankylosing Spondylitis Disease Ativitiy index (BASDAI index) and inflammation status (CRP, sedimentation rate and fibrinogen) of AS were determined.

Results: Left ventricular ejection fraction was normal in all patients. The proportion of subjects with left ventricular diastolic dysfunction (LVDD) was significantly higher in AS group (46.9%) than control group (18.2% p=0.008). However, assessment of RVDF did not show significant difference between groups. MPI were similar between AS and control group for right ventricular examination but were found to be significantly higher in AS group for left ventricle. In univariate analysis; age (OR= 10.8; p< 0.0001), body mass index (BMI) (OR=2. 98; p=0.006) and presence of AS (OR= 3.98 p=0.0008) were associated with LVDD. In multivariate logistic regression analysis, presence of AS was found to be independently associated with LVDD (adjusted OR=5.39; 95% CI =1.5-19.40; p<0.01) adjusted to age and BMI. Activity indexes (BASDAI (p=0.67 and BASFI (p=0.16) and inflammation status (CRP, sedimentation rate and fibrinogen) did not correlated to presence LVDD.

Conclusion: The prevalence of left ventricular diastolic dysfunction is increased in patients with ankylosing spondylitis. Right ventricle seems to be unaffected in AS. Activity index and inflammation status did not seem to influence the development of left ventricular diastolic dysfunction.

P3599 Mitral wave propagation velocity: differentiating normal from pseudonormal filling patterns

L.F. Martins[1], F. Pinto[2], R. Mota Garcia[2], T. Sotto Maior[2], J. Santos Mendes[2]. *[1]Universidade Fernando Pessoa, Faculdade das Ciencias da Saude, Porto, Portugal; [2]Hospital S. Sebastiao, Cardiology Department, Santa Maria da Feira, Portugal*

Objective: Verify if mitral wave propagation velocity (Vp) obtained from M-mode colour Doppler can be a clinical useful tool for studying left ventricular diastolic filling patterns (LVDFP)in hypertensive patients HTs).

Design and Method: In a prospective study, 165 normal individuals (NTs; 92 women; 73 men) and 346 hypertensive patients (HTs; 189 women, 157 men), considered to be well controlled (for at least 1 month) under "office" criteria (BP<160/90 mmHg, evaluated 3 times), were evaluated by Doppler echocardiography. All studies were performed in the morning, at least two hours after antihypertensive drugs were taken. Early (E) and late (A) peak velocities, isovolumic relaxation time (IVRT) and deceleration time of E(DectE) were obtained from pulsed Doppler transmitral tracings; E/A ratio was calculated. To identify "pseudonormal" LVDFP, pulmonary veins (PV) velocity curves were used. The propagation of LV peak early diastolic filling flow was visualised by M-mode colour Doppler mitral flow signals; Vp was measured as the slope of first alliased velocity from mitral valve ring to 4 cm distally into the LV cavity. E/Vp ratio was also calculated. Measurements were made in 5 cardiac consecutive cycles and, for final analysis, averages were used. Statistic analysis: descriptive and Anova with Bonferroni method. A p<0,001 was considered significant.

Results: All data was compared with that of a control group of 165 normotensives (NTs). See Table I.

Table I

	Group I (n=165) NTs; Normal LVDFP	Group II (n=96) HTs; Normal LVDFP	Group III (n=178) HTs; Abormal relaxation	Group IV (n=72) HTs; Pseudonormal
Age (years)	57 ± 12	49 ± 7*	64 ± 10	64 ± 9
mean BP (mmHg)	96 ± 9	115 ± 14	117± 10	118 ± 17
E/A	1,21 ± 0,33	1,29 ± 0,19*	0,69 ± 0,12	1,59 ± 0,58
IVRT (msec)	93 ± 18	91± 17*	109 ± 14	79 ± 18
Vp (cm/sec2)	49,8 ± 9,1	51,4 ± 4,6*	34,3 ± 7,7	32,5 ± 5,6
E/Vp	1,54 ± 0,4	1,69 ± 0,5*	1,75 ± 0,5	3,05 ± 0,7

* p<0,001 Group II vs. Group IV

Conclusion: In clinical setting, Vp obtained from M-mode colour Doppler is a useful index to distinguish normal from "pseudo-normal" LVDFP in HTs. With this index, the study of PV velocity curves to evaluate LV diastolic function is not mandatory.

P3600 Impact of insulin resistance on left ventricular diastolic function in normotensive offspring of subjects with essential hypertension

B. Zizek[1], A. Trojar[2], T. Zeljko[2], P. Poredos[2]. *[1]Zdravstveni dom, Zeleznicarski, Ljubljana, Slovenia; [2]Department of Angiology, University Medical Centre, Ljubljana, Slovenia*

Our previous reports have shown that in young individuals with familial trait (FT) the endothelial function of the peripheral arteries is altered. The aim of the present 9 years follow up study was to evaluate left ventricular diastolic function (LVDF) in subjects with FT. We also investigated relationships between LVDF and some biochemical parameters which thougt to be etiopathogenetic determinants of early functional detorioration of left ventricle, like hyperinsulinaemia/insulin resistance and aldosteron conc.

Methods: Study encompassed 76 reinvited subjects of whom 44 were normotonics with FT aged 28–39 (mean 33) years and 32 age and sex matched controls without FT. LVDF was measured echocardiographicaly by using indices of left ventricular relaxation derived from transmitral and tissue Doppler, and reported as the peak E/A wave ratio, deceleration time DT, isovolumic relaxation time IVRT, and septal mitral annular velocities ratio Em/Am. Late diastole was determined using an index of LV compliance E/Em. Insulin and aldosteron were determined by radio-immunoassay kit.

Results: Subjects with FT had worse diastolic function (lower E/A and Em/Am, and higher IVRT, DT, E/Em than controls, P<0.001). Subjects with FT had higher insulin conc. than control group (P=<0.001). There was no difference in aldosteron conc. between groups. In subjects with FT E/A (r=-0.32, P=0.005), Em/Am (r=-0.57, P=<0.001) were negatively and IVRT (r=0.42, P=<0.001), DT (r=0.40, P<0.001) positively associated with insulin conc.

Conclusions: Our results indicate that subjects with FT have impaired LVDF in the absence of elevated blood pressure. The results also suggest that early detorioration of diastolic function is related to hyperinsulinaemia/insulin resistance, but not to aldosteron conc.

P3601 Effects of intravenous digoxin on global and regional diastolic function in patients with essential hypertension

G. Kahraman[1], A. Agacdiken[2], E. Ural[1], A. Birand[1], G. Kozdag[1], T. Sahin[1], D. Ural[1], B. Komsuoglu[1]. [1]*Kocaeli University Medical Faculty, Cardiology, Kocaeli, Turkey;* [2]*Kocaeli University Medical Faculty, Cardiology, Kocaeli, Turkey*

Increased concentrations of ouabain-like factor (OLF) have been reported in patients with mild to severe hypertension and in patients with asymptomatic left ventricular dysfunction. Increased OLF levels are a risk factor for more severe forms of hypertension associated end organ damage. In experimental studies, digoxin has been reported to prevent ouabain-induced hypertension. Diastolic dysfunction is a frequent end organ damage in essential hypertension. The aim of this study was to investigate acute effects of digoxin on global and regional diastolic function in patients with essential hypertension.

Eighty-seven patients (63 female, 24 male, aged 54±10 years) with essential hypertension and normal systolic function were included to the study. Global and regional diastolic functions were evaluated with PW- and tissue Doppler echocardiography and patients were divided as group I (patients with diastolic dysfunction) and group II (patients without diastolic dysfunction). After 0.5 mg digoxin was given as intravenous bolus injection, echocardiographic examinations were repeated at 5th minute and second hour.

In both groups, E/A ratio decreased (Group I: from 0.77±0.1 to 0.73±0.3; $p<0.001$ and group II: from 1.27±0.2 to 1.14±0.3; $p<0.001$), deceleration time (Group I: from 244±27 to 279±32 ms; $p<0.001$ and group II: from 199±16 to 230±29 ms; $p<0.001$) and isovolumetric relaxation time (Group I: from 113±8 to 124±13 ms; $p<0.001$and group II: from 92±6 to 104±10 ms; $p<0.001$) increased from baseline to 2nd hour significantly. Regional diastolic function evaluated at four sites of mitral annulus showed similar changes, Am velocity increased and Em/Am ratio decreased significantly in both groups. Changes in diastolic parameters were more evident in group I compared to group II patients.

These data suggest that digoxin may have a detrimental effect on left ventricular diastolic filling in hypertensive patients. This effect seems to be more marked in patients with diastolic dysfunction.

P3602 Impact of aortic stiffness contributing to left ventricular diastolic function in hypertensive patients

K. Ito[1], K. Yamamoto[1], Y. Katagiri[1], T. Genda[1], M. Karasawa[1], S. Nakagawa[2], H. Inou[2], T. Kawakami[2]. [1]*Iida Municipal Hospital, Cardiology Department, Iida, Japan;* [2]*Azumi General Hospital, Internal Medicine, Nagano, Japan*

Background: left ventricular diastolic dysfunction is a common abnormality in hypertensive patients. Arterial pulse wave velocity(PWV) has been reported to be a noninvasive method to evaluate aortic stiffness. The role of aortic stiffness in the development of the left ventricular(LV) diastolic dysfunction is unclear. The aim of this study was to assess the effect of aortic stiffness on left ventricular function.

Methods: We studied 242 treated hypertensive patients(69.5±10 yrs). We measured their PWV by VaSera VS-1000 (FUKUDA DENSHI, Japan) and evaluate left ventricular diastolic function by pulse Doppler echocardiography of trasmitral fllow{ the ratio of early (E) to late (A) peak velocities of transmitral flow (E/A)}. LV diastolic dysfunction was defined as E/A <1. We analyzed clinical data regarding body mass index(BMI), a history of diabetes mellitus, hyperlipidemia, smoking, and left ventricular hypertrophy by electrocargiography. Multivariate analysis was performed with logistic regression analysis to assess LV diastolic dysfunction and interactions of the variables (age, sex, BMI, diabetes mellitus, hyperlipidemia, smoking, and LVH)

Results: PWV and age were significantly higher in patients with LV dysfunction than without LV dysfunction in hypertensive patients (PWV: 16.4±2.6 vs 14.6±2.6 m/sec, $P<0.0001$, age: 69.4±9.4 vs 64.3±10 yrs, $P<0.0016$). Multiple logistic regression analysis showed that aortic stiffness was independent risk factor of LV diastolic dysfunction in hypertensive patients (OR=1.30, P=0.034, 95%CI 1.02-1.68).

Conclusions: Our data showed that increased PWV was significantly associated with the presence of LV diastolic dysfunction in hypertensive patients. Patients with increased PWV were likely to have LV diastolic dysfunction. We speculate that aortic stiffness may be the most important contributor to the development of LV diastolic dysfunction.

P3603 Prognosis predictors in heart failure with preserved systolic function

E.P. Gouvea, R. Mourilhe Rocha, D.C. Albuquerque, A.G.M. Ferreira, M.I. Bittencourt, A.P. Oliveira, R. Esporcatte, F.M. Albanesi Filho. *State University of Rio de Janeiro, Cardiology Department, Rio de Janeiro, Brazil*

Background: Heart failure (HF) is a disease that continues to increase prevalence, especially in elderly population. During the last few years, despite several advances in the management of patients with systolic dysfunction, little knowledge is available concerning patients with clinical signs of HF and a preserved left ventricle (LV) systolic function.

Hypothesis: Analyze morbidity and mortality variables of patients with HF and preserved systolic function.

Methods: We prospectively evaluated 371 patients admitted in the HF clinic and identified 49 cases of HF with preserved systolic function (HFwPSF). They were on NYHA functional III (n=40; 81.63%) and IV (n=9; 18.36%). We analyzed at admission if the presence of different variables [age, gender, body mass index (BMI), diabetes, left ventricle hypertrophy (LVH), time until diagnosis, etiology (ischemic and non ischemic), presence of atrial fibrillation, intervention (coronary artery bypass surgery or percutaneous coronary intervention) and functional class] would determine a modification on prognosis.

Results: We observed a group formed by patients with a mean age of 69.69±9.47 y/o, the majority of feminine gender (n=31; 73.46%) with overweight or obesity (mean BMI=27.99±5.30 kg/m^2) and mean ejection fraction of 69.58%. The mean time until the diagnosis was 22.06±19.80 months. The endpoints (except death) were more prevalent in non-ischemic etiology, in ischemic patients in which an intervention was not possible and in patients admitted in functional class III. There were a greater prevalence of death in the group which etiology was ischemic heart disease (p=0.03) and in the proportion of patients that did not improved to the functional class I (p=0.05) during the follow-up period.

Conclusion: The group observed was mostly composed of elderly women with an elevated BMI and that had taken a long time until the diagnosis of HFwPSF. The morbidity predictors were the admission functional class, the performance of coronary intervention and non-ischemic etiology. The ischemic etiology and poor response to medical therapy constituted the predictors of death. These findings suggest the necessity of an aggressive therapeutics strategy in this subgroup of patients.

P3604 Prevalence of isolated left ventricular diastolic dysfunction in hospitalised diabetic patients

S. La Carrubba, A. Puleo, G. Pumilia, F. Arancio, S. Di Rosa. *Azienda Ospedaliera Villa Sofia, Internal Medicine Dept., Palermo, Italy*

Background: Approximately 40% of patients with heart failure have preserved left ventricular systolic function, thus having diastolic heart failure (DHF). Patients with diabetes have an increased risk of heart failure and DHF may be the first stage of diabetic cardiomiopathy.

Objectives: The aim of this study has been to assess the prevalence of global and isolated diastolic dysfunction in diabetic patients hospitalized in a Department of Internal Medicine.

Methods: We studied 496 consecutive patients (mean age 60.8 ± 17.6 years) admitted to the Department of Internal Medicine of Azienda Ospedaliera Villa Sofia, Palermo, from february 2004 to january 2005. Patients were submitted to standard transthoracic Echocardiography and electrocardiography. Data of the clinical history and examination were recorded on a electronic database. Diastolic dysfunction was assessed using conventional Doppler echocardiography (deceleration time, isovolumic relaxation time, early diastolic velocity [E]/peak atrial systolic velocity [A] ratio) at rest and during the Valsalva maneuver. “Isolated diastolic dysfunction” was defined in presence of pattern of diastolic dysfunction and EF = 50% (biplane Simpson’s method).

Results: Of the 496 patients admitted to the study, 121 had diabetes mellitus (age 67.5 ±12 years); 65 (53.7%) had a normal diastolic function, diastolic dysfunction was observed in 44 patients: 28 (23.1%) with a mild diastolic dysfunction (impaired relaxation), 10 (8,3%) with a moderate diastolic dysfunction (pseudonormalization), 4 (3.3%) with a severe diastolic dysfunction (reversible restrictive), 2 (1.7%) with a severe diastolic dysfunction (fixed restrictive). We haven’t been able to assess the degree of diastolic function in 12 patients (9.9%).

The global prevalence of isolated DHF in diabetic patients was 37.2% while in non diabetics was 21.4% (OR 2.18 CI 95% 1.34-3.52; p=0.002).

On a multivariate analysis, diabetes mellitus has been independently related to isolated diastolic dysfunction.

Conclusions: This study confirms an increased prevalence of DHF in diabetic patients as compared to non-diabetics.

Isolated DHF (with preserved systolic function) can be identified in diabetic patients at an early stage of disease and predicts the development of systolic heart failure and ischemic heart disease. Strict ecocardiographic monitoring looking for evidence of diastolic dysfunction in diabetic patients could be useful in identifying subgroups at major risk of severe heart failure and death, who could receive intensive therapeutic regimens.

HYPERTENSION, VASCULAR EFFECTS

P3605 Apelin, a novel biochemical marker of heart failure is elevated in patients with cardiac cachexia

M. Marchel, K.J. Filipiak, P. Stolarz, G. Opolski. *Warsaw Medical University, 1st Department of Cardiology, Warsaw, Poland*

Background: Apelin has been shown to be a cardiac inotrope and is the one of the most potent stimulators of cardiac contractility known. Apelin is expressed in the human heart and secreted by adipocytes. The aim of our study

was to investigate the pathophysiology of apelin in the cachexia associated with chronic heart failure (HF).
Methods: Plasma apelin was measured in 60 patients with HF and 10 control subjects. Patients with HF were divided into two groups, those with cachexia (n=18) and those without cachexia (n=42).
Results: Plasma apelin did not significantly differ between all HF patients and controls (672±248 vs. 565±97 fmol/mL, P=0,059). However, plasma apelin was significantly higher in HF patients with cachexia than in those without cachexia (600±168 vs. 828±201 fmol/mL, P<0,001). NT-proBNP and uric acid were significantly higher and protein plasma levels and cholesterol were significantly lower in patients with cardiac cachexia than in those without cachexia. Aditionaly, plasma apelin correlated positively with uric acid (r=0,47; p<0,05) and weight loss (r=0,23; p<0,01) and negatively with left ventricular ejection fraction (EF)(r=-0,54; p<0,01) and cholesterol levels (r=-0,34; p<0,05). There was no correlation between plasma apelin levels and adipose tissue measured by electrical impedance.
Conclusions: Plasma apelin was markedly higher in patients with cardiac cachexia. Increased apelin levels may represent a compensatory mechanism in cachectic patients with HF and suggest it as an attractive target for pharmacotherapy in the setting of heart failure.

P3606 Long-term levothyroxine treatment impairs exercise capacity in young adults with congenital hypothyroidism

V. Guardasole[1], M.C. Salerno[2], T. Lettiero[2], R. Simeone[2], E. Zarra[1], L. Sacca[1], A. Cittadini[1]. *[1]Univ.Federico II, School of Medicine, Dept. Int. Medicine & Cardiovascular Sciences, Napoli, Italy; [2]University Federico II, Department of Pediatrics, Naples, Italy*

Congenital hypothyroidism is known to significantly impact on cardiovascular function and its treatment requires careful biochemical monitoring. However, little is known with regard to the effects of long-term levothyroxine treatment on physical exercise in patients with congenital hypothyroidism. To this aim, 30 young adults with congenital hypothyroidism (aged 18±.2 yrs) and 30 age- and sex matched normal controls (19±.5 yrs) underwent symptom-limited cardiopulmonary exercise testing. Hypothyroidism was diagnosed by neonatal screening and levothyroxine treatment was initiated within the first month of life. Levothyroxine dosage was carefully adjusted every 3- 6 months in order to maintain TSH levels in the normal range and FT4 in the high-normal range, and at the time of the study was 2.1±0.1 micrograms/kg/day. Compared with controls, exercise capacity was significantly impaired in the hypothyroid patients compared with controls as shown by reduced peak VO2, peak power output and anaerobic threshold (Table 1). Data are expressed as mean±SEM

Tabble 1

	Controls	Hypothyroid Patients
Peak VO2 (ml/kg/min)	37±2	30±1.7*
Peak power output (watt)	272±17	219±17*
Anaerobic threshold (ml/kg/min)	2.4±2	1.8±.1*

*p<0.01

Despite careful monitoring of serum TSH and adjustment of levothyroxine dosage, long-term levothyroxine treatment is associated with impaired exercise capacity in young adults with congenital hypothyroidism.

P3607 Does adiponectin contribute to the adverse cardiovascular prognosis in essential hypertensive subjects with obstructive sleep apnoea?

K. Thomopoulos, C. Tsioufis, A. Amfilochiou, C. Vasiliadou, M. Kokladi, D. Tousoulis, C. Stefanadis, I. Kallikazaros. *Hippokration Hospital, Department of Cardiology, Athens, Greece*

Purpose: Although the pathophysiological role of adiponectin is not yet well established, it seems to suppress almost all processes in atherosclerotic vascular transformation and is related to endothelial dependent vasodilatation. On the other hand, many of the obstructive sleep apnea syndrome (OSAS) cardiovascular effects are mediated by endothelial dysfunction and enhanced inflammatory processes on vessels wall. In this setting, we postulated the hypothesis of decreased plasma adiponectin levels in essential hypertensive subjects with OSAS compared to hypertensives without OSAS.
Methods: We studied 46 consecutive subjects (35 men, aged 49±8 years, BMI of 30.9±3 kg/m^2, 24 smokers) with stage I-II untreated EH [office blood pressure (BP)=150±12/98±9mmHg] and OSAS diagnosed by polysomnography (PSG) [apnea/hypopnea index (AHI)>5] and a control group of 53 untreated essential hypertensive subjects matched for age, sex, BP, smoking status and BMI but with negative PSG. All subjects underwent echocardiography to estimate left ventricular mass index (LVMI) and relative wall thickness (RWT). A venous blood sample was drawn after an overnight fasting for determination of lipids profile, serum glucose and plasma adiponectin and hsCRP levels.
Results: OSAS hypertensive group compared to hypertensive controls demonstrated similar levels of total cholesterol (226±40 vs 228±35 mg/dl, p=NS), triglycerides (161±82 vs 160±62 mg/dl, p=NS) and serum glucose (97±10 vs 94±11 mg/dl, p=NS). In the OSAS hypertensive group compared to control, plasma adiponectin was significantly lower (6.77±3.23 vs 8.73±5.56 ng/ml, p<0.05), while hsCRP was significantly higher (4.84±3.6 vs 3.05±2.43 mg/l, p<0.04). LVMI was similar in the two groups (109±21 vs 103±23 gr/m^2, p=NS), while the OSAS hypertensive subjects compared to controls demonstrated greater value of RWT (0.47±0.06 vs 0.42±0.06, p<0.01). In the OSAS hypertensive group adiponectin was negatively correlated to BMI (r=-0.412, p<0.01) and hsCRP (r=-0.32, p<0.05). No correlation was found between adiponectin or hsCRP levels and OSAS severity.
Conclusions: Essential hypertensive subjects with OSAS are accompanied by increased hsCRP and decreased adiponectin levels. Furthermore, there is an inverse correlation between adiponectin and hsCRP but there is not any correlation with the severity of OSAS. These findings suggest that adiponectin might be a valuable biomarker of increased sub-clinical inflammation and adverse cardiovascular prognosis in essential hypertensive subjects with OSAS.

P3608 Parathyroid hormone related protein mRNA expression after ischaemia and reperfusion in rat ventricular myocardium

A. Halapas[1], P. Lembessis[1], C. Pantos[2], D.V. Cokkinos[3], M. Koutsilieris[1]. *[1]Medical School, Department of Experimental Physiology, Athens, Greece; [2]Onassis Cardiac Surgery Center, 1st Cardiology Dept. and Pharmacology Dept., Athens, Greece; [3]Onassis Cardiac Surgery Center, 1st Cardiology Department, Athens, Greece*

Objective: Cardiac vascular smooth muscle cells, coronary endothelial cells and cardiomyocytes express parathyroid hormone related protein (PTHrP), which possesses positive chronotropic and inotropic activities on myocardium. In addition, hyperthyroidism increases the tolerance of the heart to ischemia/reperfusion. Therefore, we have analyzed the expression of PTHrP and its receptor (PTH.1-R) mRNA in control (C) vs. hyperthyroid (THYR) rats using the Langendorff model for ischemia (I) and reperfusion (R).
Methods: Thirty hearts from THYR. (L-Thyroxine 25μg/100g body wt given once daily for 14 days) and thirty C male Wistar Rats were subjected to I and R by the Langendorff technique. The ventricular myocardium was initially stabilized (STAB) and then subjected to 5, 10, and 20 minutes of zero-flow condition (global ischemia; I) followed by 20 min, 45 min and 60 min of reperfusion (R) [N=5 animals for each time point]. The expression of PTHrP and PTH.1-R mRNA was assessed by quantitative RT- PCR technique, using as an internal standard the 18s ribosomal RNA. Optic density was assessed by the image analyzing system Kodak EDAS 290.
Results: In C myocardium, the expression of PTHrP mRNA did not show any appreciable modulation during I phase (5 up to 20 min), however, PTHrP mRNA expression was found to increase at late R phase (45 min), detecting significantly higher expression of PTHrP mRNA than this of the late I phase (p<0.01). In addition, while PTH.1-R mRNA expression decreased during I phase (5 up to 20 min; p<0.05) as compared to this of STAB it showed significant recovery, thus enhancing PTHrP expression at late R phase (60 min) as compared to late I phase but still decreased as compared to STAB (p<0.05). In THYR rat, the expression of PTHrP mRNA increased during late I phase (20 min; p<0.01); it also increased further during both early (20 min) and late R phases (45 and 60 min; p<0.01). The expression of the PTH.1-R mRNA also showed a significant decrease during late R phase (45 and 60 min), but less than that of C.
Conclusion: The hyperthyroid rat showed a greater and earlier increase of PTHrP m RNA during I/R than that of control and lesser decrease of PTH.1-R mRNA. The protective effects of these substances seem to be upgraded by thyroid hormone administration.

P3609 Low T3 predicts the prognosis of patients with hypertensive heart failure

M. Iida[1], K. Kamiya[2], I. Kodama[2], H. Honjo[2]. *[1]Mitsubishi Nagoya Hospital, Cardiology, Nagoya, Japan; [2]School of Medicine, Nagoya University, Department of Circulation, RIEM, Nagoya, Japan*

[Purpose] Low triiodothyronine (T3) syndrome, increasing the secretions of catecholamines, aldosterone and natriuretic peptides, has been recently reported to predict the cardiovascular deaths of heart failure (Circulation 2003). However the roles of low T3 in deteriorating the prognosis remain unknown. Our aim is to investigate if low T3 is associated with ongoing myocardial damage and can be used as a prognostic factor in hypertensive heart failure. [Methods] TSH, free T3, free T4, serum creatinine, brain natriuretic peptide (BNP), and left ventricular posterior wall thickness corrected for body surface area (LVWT/BSA) were measured in patients with hypertensive heart failure (n=163, HF), and control (n=27). As markers of ongoing myocardial damage, we measured troponin T and heart type fatty acid binding protein (H-FABP). [Results] All participants had normal TSH and troponin T levels, and were free of thyroidal illnesses. BNP levels (pg/ml) were 122±52 in HF and 18±3 in control. Free T3 (pg/ml) significantly (p<0.05) decreased in HF (2.8±0.4) than in control (3.0±0.3). In HF, free T3 were significantly and negatively correlated with BNP (r= -0.38), H-FABP(r= -0.38), LVWT/BSA (r=-0.19) and creatinine (r=-0.36), but not in control. The patients were prospectively followed up for cardiac events for 31±16 months. The events occurred in 42 patients. Free T3(Relative Risk[RR]=0.38, p=0.04), H-FABP(RR=1.1, p=0.01) and LVWT/BSA (RR=1.35, p=0,04) were the independent prognostic factors in a Cox

hazard model entering age, gender and all the variables measured. [Conclusion] Low T3 syndrome is a predictor of poor outcome in patients with hypertensive heart failure, and may participate in the process of ongoing myocardial damage or left ventricular remodeling.

P3610 Human insulin and soluble leptin receptor number in healthy offspring of hypertensive patients

D. Papadopoulos, T. Makris, P. Krespi, E. Sanidas, I. Paizis, M. Daskalaki, A. Hatzizacharias, V. Votteas. *Laiko Hospital, Cardiology Department, Athens, Greece*

Essential hypertension is associated with increased insulin and leptin plasma levels and decreased human insulin and soluble leptin receptor number.
Aim of our study was to determine human insulin receptor (hINR) and soluble leptin receptor (hsLR) number in healthy offspring of hypertensives (HOH) and to compare the findings to those of healthy offspring of healthy parents (HOHP), matched for age, sex and BMI.
Methods: Forty six (24M, 22F) HOH mean age 18±3 yrs and BMI 22,4±1,4 kg/m^2 (Group A) and 50 (28M, 22F) HOHP mean age 18±3,2 yrs and BMI 22,6±1,7 kg/m^2 (Group B) were studied. The hINR and hsLR number (ELISA method) and immunoreactive insulin and leptin plasma levels (RIA method) were determined in the study population. The two groups are matched for age, gender, BMI.
Results: The results and the differences between the two groups are shown in the table:

	Group A (n=46)	Group B (n=50)	p
hINR (receptorX103/red cell)	7±2	9,5±1,4	<0.001
hsLR(IU/ml)	20±7	29±8	<0.001
Insulin (IU/ml)	20±8	14±7	<0.01
Leptin (ng/ml)	10±5	6±3	<0.001

Conclusions: Our findings suggest that offspring of hypertensives have significantly higher insulin and leptin plasma levels and significantly lower hINR and hsLR number. This group of individuals needs a closer follow-up and further examination.

P3611 Thyroxine administration increases the expression of HSP27 and HSP70 and protects the heart against ischaemia-reperfusion injury

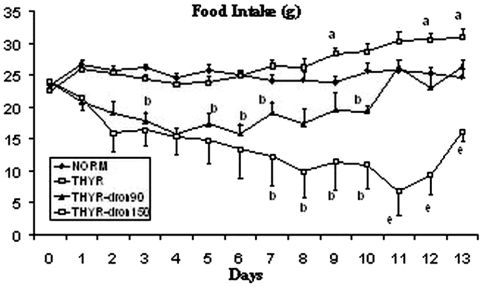
V. Malliopoulou[1], A.D. Cokkinos[1], A. Thempeyioti[1], I. Mourouzis[1], C. Pantos[2], D.V. Cokkinos[3]. *[1]Department of Pharmacology, Goudi, Greece; [2]Onassis Cardiac Surgery Center, 1st Cardiology Dept. and Pharmacology Dept., Athens, Greece; [3]Onassis Cardiac Surgery Center, 1st Cardiology Department, Athens, Greece*

Thyroid hormone, although increasing myocardial energy expenditure, is shown to enhance tolerance of the heart to ischaemic injury. Heat shock proteins are known to protect the myocardium from ischaemia–reperfusion injury. We investigated whether thyroxine induced cardioprotection is accompanied by changes in HSP27 and HSP70 myocardial expression.
Methods: L-thyroxine (T4) (25 μg/100g/day s.c.) was administered to Wistar rats for 2 weeks (THYR, n=5), while normal animals served as controls (NORM, n=5). NORM and THYR isolated hearts were perfused in Langendorff mode and subjected to 20 min of zero-flow global ischaemia followed by 45 min of reperfusion, NORM-I/R, n=8 THYR-I/R n=8. Postischaemic recovery of left ventricular developed pressure at 45 min of reperfusion was expressed as % of the initial value (LVDP%). Baseline expression of total and phosphorylated HSP27 and HSP70 were assessed by western blotting.
Results: Basal total HSP27 and phospho-HSP27 levels were increased in THYR hearts, 1.5 and 1.6 fold respectively as compared to NORM, p<0.05. In addition, HSP70 expression was increased 1.8 fold in THYR vs NORM hearts, p<0.05. LVDP% was 62.4 (4.2) for THYR-I/R vs 45.8 (5.5) for NORM-I/R, p<0.05.
Conclusion: Long-term thyroxine administration increases the expression and phosphorylation of HSP27 and the expression of HSP70 in the myocardium and protects the heart against ischaemia-reperfusion. This effect might be of important therapeutic relevance, since thyroid analogues are now being tested in various cardiovascular diseases.

P3612 Blockade of thyroid hormone receptor alpha 1 suppresses food intake and potentiates thyroxine effect on body weight reduction

C. Pantos[1], I. Mourouzis[2], I. Paizis[2], A.D. Cokkinos[2], N. Katsilambros[2], D.V. Cokkinos[3]. *[1]Onassis Cardiac Surgery Center, 1st.Cardiology Dept. and Pharmacology Dept., Athens, Greece; [2]Department of pharmacology, Goudi, Greece; [3]Onassis Cardiac Surgery Center, 1st Cardiology Department, Athens, Greece*

Obesity is realized to be a risk for cardiovascular disease. Thyroxine has been used for its energy expenditure action for controlling body weight, although the increase in food intake and cardiac side effects limit its use. We investigated whether these undesired effects can be prevented by dronedarone (antagonist of TRa1 that is shown to suppress food intake).
Methods: L-Thyroxine (25 μg/100g/day s.c.) was administered in Wistar rats for two weeks (THYR), while untreated animals served as controls (NORM). Animals were also treated with a combination of thyroxine and dronedarone 90 mg/kg or 150 mg/kg (THYR-dron90, THYR-dron150).
Results: Food intake was increased with thyroxine and suppressed by dronedarone as shown in fig. Change in animal body weight was +33.3 (5.4) g for NORM, +17.5 (6.4) for THYR, p<0.05 and -10.3 (3.7) for THYR-dron90 and –58.8 (18.0) g for THYR-dron150, p<0.05 vs NORM and THYR. Heart rate (HR) was 460 (10) in THYR, 378 (9) in NORM, 340 (13) in THYR-dron90 and 303 (42) in THYR-dron150 hearts, p<0.05 vs NORM.



Food Intake. a p<0.05 vs NORM, b p<0.05 vs THYR, e p<0.05 vs THYR-dron90.

Conclusion: Dronedarone potentiates the effect of thyroxine on body weight loss, while limiting its unwanted effects on food intake and HR. These actions may be of therapeutic importance in the management of obesity.

P3613 The role of urotensin II in etiopathogenesis of essential hypertension – preliminary results

M. Kobusiak-Prokopowicz[1], M. Przewlocka-Kosmala[2], B. Jolda-Mydlowska[1], M. Witkowska[1]. *[1]Medical University, Cardiology, Wroclaw, Poland; [2]Wroclaw, Poland*

Urotensin II is a one of recently discovered vasoactive peptides. Preliminary studies indicate important role of this peptide in blood pressure regulation, in etiopathogenesis of essential hypertension and in hypertensive target-organ damage such as left ventricular (LV) hypertrophy and arterial remodeling.
Aim: To estimate plasma urotensin II level in patients with essential hypertension in comparison with healthy subjects.
Material and methods: Investigations were carried out in 37 patients (11 males, 26 females) aged 53 ± 14 yrs with essential hypertension stage 1 – 5 patients, stage 2 – 22 patients and stage 3 – 10 pts without any comorbidities. 7 patients were free of target-organ damage whereas in 30 patients hypertensive organ involvement was present including LV hypertrophy and/or nephropathy and/or angiopathy. Control group consisted of 7 healthy subjects aged 43 ± 18 yrs. Plasma urotensin II concentration was estimated by radioimmunometric method. Interventricular septum and posterior wall thickness as well as LV dimensions were measured during echocardiographic examination. LV hypertrophy was present in 21 hypertensive patients.
Results: Plasma level of urotensin II in group:
- control - 99.28 ± 19.48 pg/ml
- all hypertensive pts - 105.50 ± 34.62 pg/ml
- pts with stage 1 hypertension - 90.51 ± 25.33 pg/ml
- pts with stage 2 hypertension - 114.86 ± 41.00 pg/ml
- pts with stage 3 hypertension - 93. 36 ± 12.21 pg/ml
- pts without target-organ damage - 97.51 ± 52.95 pg/ml
- pts with target-organ damage - 108.83 ± 29.80 pg/ml
- pts with LV hypertrophy - 112.55 ± 31.46 pg/ml * (p<0.03)
- pts without LV hypertrophy - 96.79 ± 32.37 pg/ml

Correlations: Urotensin II and interventricular septum thickness (r = 0.40, p<0.01) Urotensin II and LV mass index (r = 0.43, p<0.01)
Conclusions: (1) There are no differences in plasma urotensin II level between healthy subjects and pts with hypertension, between pts with subsequent stages of hypertension and between hypertensive pts with and without target-organ damage. (2) Higher plasma urotensin II levels in pts with LV hypertrophy as well as positive correlation between plasma urotensin II level and interventricular septum thickness and LV mass index may suggest urotensin II involvement in development of myocardial hypertrophy or increased urotensin II production in hypertrophied myocardium. The last issue needs further studies to be disclosed.

P3614 The role of ghrelin in etiopathogenesis of essential hypertension – preliminary results

B. Jolda-Mydlowska[1], M. Przewlocka-Kosmala[2], M. Kobusiak-Prokopowicz[1], M. Witkowska[1]. *[1]Medical University, Cardiology, Wroclaw, Poland; [2]Wroclaw, Poland*

Ghrelin is one of neurohormons with endo-, para- and autocrine mode of ac-

tion, which probable antagonizes hypertensive effect of endothelin-1. Experimental studies suggest its role in etiopathogenesis of essential hypertension.
Aim: To estimate plasma ghrelin level in patients with essential hypertension in comparison with healthy subjects.
Material and methods: Investigations were carried out in 37 patients (11 males, 26 females) aged 53 ± 14 yrs with essential hypertension stage 1 - 5 pts, stage 2 – 22 pts and stage 3 – 10 pts without any comorbidities. 7 pts were free of target-organ damage whereas in 30 pts hypertensive organ involvement was present including LV hypertrophy and/or nephropathy and/or angiopathy. Control group consisted of 7 healthy subjects aged 43 ± 18 yrs. Plasma ghrelin concentration was estimated by radioimmunometric method. Interventricular septum and posterior wall thickness as well as LV dimensions were measured during echocardiographic examination. LV hypertrophy was present in 21 hypertensive pts.
Results: Plasma level of ghrelin in group:
- control - 401.03 ± 208.78 pg/ml
- all hypertensive pts - 242.88 ± 131.08 pg/ml
- pts with stage 1 hypertension - 323.34 ± 87.87 pg/ml
- pts with stage 2 hypertension - 222.29 ± 109.47 pg/ml
- pts with stage 3 hypertension - 245.90 ± 179.34 pg/ml
- pts without target-organ damage - 315.45 ± 96.21 pg/ml
- pts with target-organ damage - 225.61 ± 135.03 pg/ml
- pts without LV hypertrophy - 260.59 ± 105.11 pg/ml
- pts with LV hypertrophy - 230.23 ± 148.09 pg/ml

Plasma level of ghrelin in hypertensive pts was significantly lower than in control group ($p<0.01$), whereas in pts with stage 1 hypertension was significantly higher than in pts with stage 2 hypertension ($p<0.04$) and pts with stage 3 hypertension ($p<0.05$). Plasma level of ghrelin in hypertensive pts without target-organ damage was significantly higher compared to pts with target-organ damage ($p<0.04$) as well as in pts without LV hypertrophy in comparison to pts with LV hypertrophy ($p<0.05$).
Conclusion: Plasma level of ghrelin in hypertensive pts is inversely proportional to blood pressure level and cumulative risk of cardiovascular complications.

P3615 The BNP in the crossroads of mechanical and humoral signalling: the paradigm of paroxysmal atrial fibrillation in hypertensive subjects

I. Skiadas, C. Tsioufis, D. Chatzis, P. Stougiannos, E. Taxiarchou, G. Chartzoulakis, C. Stefanadis, I. Kallikazaros. *Hippokration Hospital, Department of Cardiology, Athens, Greece*

Purpose: A growing body of evidence underscores the role of B-natriuretic peptide (BNP) in the management algorithms of various cardiovascular conditions. The present study was conducted in order to reveal the plausible interrelationship between paroxysmal atrial fibrillation (PAF) and mechanical or humoral factors, in the setting of essential hypertension.
Methods: We studied 46 consecutive essential hypertensive subjects (aged 64 years, 22 men, office blood pressure (BP) 144/86mmHg) with a history of PAF and no other evident comorbidity and 49 consecutive essential hypertensives without any evidence of PAF, matched for age, sex and BP. All included subjects were on sinus rhythm without any history of atherosclerotic or valvular heart disease. In addition, all the participants underwent blood sampling for the determination of BNP plasma levels and metabolic profile, according to established methods. Moreover, urinary albumin excretion was expressed as the albumine/creatinine ratio (ACR) from 2 non-consecutive spot urine samples. Lastly, aortic stiffness was evaluated non-invasively by means of carotid – femoral pulse wave velocity measurements with an established device (Complior SP).
Results: The two groups were similar regarding demographics but hypertensives with PAF compared to those without PAF had increased body mass index (28.1 ± 3 vs $26.9\pm3 kg/m^2$, $p<0.05$) and were smokers in a higher percentage (45 vs 31%, $p<0.05$). Moreover, the two groups did not differ with respect to total cholesterol, LDL cholesterol and triglycerides levels (p=NS for all cases). However, BNP levels and carotid-femoral PWV were significantly higher among hypertensives with PAF than in those without PAF (37.6 ± 43 vs 17.2 ± 14 pg/ml, and 9.65 vs 8.44 m/sec, $p<0.05$ for both). In the group of hypertensives with PAF, BNP levels were positively correlated with office pulse pressure ($r=0.35$, $p<0.05$), duration of hypertension ($r=0.32$, $p<0.05$) and the ACR ($r=0.715$, $p<0.05$).
Conclusions: BNP plasma levels are in parallel with PWV increased in hypertensives with PAF and are strongly associated with ACR, an established index of early renal dysunction. However, the underlying pathophysiological mechanisms merit further investigation through properly designed prospective studies.

P3616 Determinants of the structure of subcutaneous small resistance arteries in hypertensive patients

G.E.M. Boari[1], M.L. Muiesan[1], E. Porteri[1], M. Salvetti[1], C. De Ciuceis[1], G.A.M. Tiberio[1], D. Rizzoni[2], E. Agabiti Rosei[1]. *[1]University of Brescia, Dept. of Medical and Surgical Sciences, Brescia, Italy; [2]Brescia, Italy*

Objective: It has been previously demostrated (Rizzoni D et al, Circulation 2003) that structural alterations of subcutaneous small resistance arteries of hypertensive patients (as indicated by an increased media to lumen ratio (M/L)), is the most potent predictor of cardiovascular events. Aim of the present study was to identify the determinants of small resistance artery structure, obtained with non invasive approaches.
Design and Methods: One hundred and ninety-nine subjects were included in the present study. They were 26 normotensive subjects, 103 patients with essential hypertension, 16 patients with pheochromocytoma, 21 patients with primary aldosteronism, 12 patients with renovascular hypertension, and 21 normotensive patients with non-insulin dependent diabetes mellitus (NIDDM). All subjects were submitted to a biopsy of subcutaneous fat from the gluteal or the anterior abdominal region. Small resistance arteries were dissected and mounted on an isometric myograph, and the tunica media to internal lumen ratio was measured. Left ventricular mass was evaluated by echocardiography. Clinic and 24 hour blood pressure (ABPM) values were also measured by sphygmomanometer and automatic devices. In addition, an index of large artery distensibility (pulse pressure/stroke volume: PP/SV) was calculated. Standard biochemistry tests were performed (serum glycemia, creatinine, triglycerides, cholesterol, BUN, etc.). Creatinine clearance was calculated according to validated formulas (Cockroft-Gault equation and MDRD study equation).
Results: The following variables were significanly correlated with M/L: creatinine clearance (MDRD): r=-0.25, p=0.002; creatinine clearance (Cockroft-Gault): r=-0.18, p=0.049; serum creatinine: r=0.29, $p<0.001$; BUN: r=0.27, p=0.003; glycemia: r=0.18, p=0.024; serum sodium: r=0.23, p=0.013; clinic pulse pressure: r=0.23, p=0.001; PP/SV: r=0.21, p=0.019; clinic systolic blood pressure, r=0.29, $p<0.001$; clinic diastolic blood pressure, r=0.22, p=0.002; clinic mean blood pressure: r=0.27, $p<0.001$; pulse pressure during daytime: r=0.21, p=0.003. In a multivariate analysis only serum creatinine was demonstrated to be an independent predictor of small resistance artery structure.
Conclusions: Our results indicate that subcutaneous small resistance artery structure is closely related to renal function, possibly because it reflects microvascular alterations at the glomerular level. Blood pressure and large artery distensibility, although less closely, are also related to microvascular structure.

P3617 Ascending aortic blood pressure-derived indices are not correlated with the extent of coronary artery disease in patients with impaired left ventricular function

P. Jankowski[1], D. Czarnecka[2], M. Brzozowska-Kiszka[2], K. Styczkiewicz[2], L. Bryniarski[2], J. Dragan[2], D. Dudek[3], K. Kawecka-Jaszcz[2]. *[1]Krakow, Poland; [2]Jagiellonian University, I Department of Cardiology, Kraków, Poland; [3]Jagiellonian University, II Department of Cardiology, Kraków, Poland*

Background: Ascending aortic blood pressure-derived indices were shown to be related to the extent of coronary atherosclerosis. Unfortunately, most studies published so far had included only patients with preserved left ventricular function. Therefore, the aim of the present study was to investigate the relation between aortic blood pressure-derived indices and the extent of coronary atherosclerosis in patients with impaired left ventricular systolic function.
Methods: The study group consisted of 480 patients (383 men and 97 women; mean age: 59.3 ± 10.4 years) with angiographically confirmed coronary artery disease (CAD) and EF<55%. Invasive ascending aortic blood pressure during catheterization and conventional sphygmomanometer measurements were taken. The extent of coronary atherosclerosis was assessed using severity and Gensini scores (both scores were validated). Number of stenosed coronary arteries was used as another index of CAD severity.
Results: None of the brachial or aortic blood pressure-derived indices differed between patients with one-, two- and three-vessel CAD in univariate nor in multivariate analysis. None of the studied indices was correlated with Gensini or severity scores. We did not find any significant correlation between blood pressure-derived indices and the extent of coronary atherosclerosis in patients with ejection fraction <25%, 25–40% or >40% (table). Multivariable regression analysis revealed no significant relationship between coronary atherosclerosis and the studied indices.

Table 1. Correlation coefficients of the relation between aortic blood pressure-derived indices and Gensini score according to categories of left ventricular ejection fraction (all coefficients statistically not significant)

Ascending aortic hemodynamic variable	Ejection fraction		
	<25%	25–40%	40–55%
Systolic blood pressure (SBP)	0.14	0.11	0.00
Diastolic blood pressure (DBP)	0.11	0.12	- 0.04
Mean blood pressure (MBP)	0.13	0.13	- 0.02
Pulse pressure (PP)	0.11	0.07	0.03
Pulsatility (PP/MBP)	0.07	0.00	0.06
Pulsatility index (PP/DBP)	0.05	0.01	0.05

Conclusion: Ascending aortic blood pressure-derived indices are not correlated with the extent of coronary atherosclerosis in patients with CAD and impaired left ventricular function.

P3618 Independent prognostic information provided by aortic blood pressure-derived indices. The preliminary results from the aortic blood pressure and survival study

P. Jankowski[1], D. Czarnecka[2], G. Dymek[2], M. Kloch[2], E. Kopacz[2], J. Wilinski[2], A.M. Curylo[2], K. Kawecka-Jaszcz[2]. [1]*Krakow, Poland;* [2]*Jagiellonian University, I Department of Cardiology, Kraków, Poland*

Background: Ascending aortic blood pressure-derived indices were shown to be related to the extent of coronary atherosclerosis. However, their prognostic significance is still unknown. Therefore, the aim of the present study was to evaluate the relationship between baseline aortic blood pressure-derived indices (pulsatility - the ratio of pulse pressure to mean blood pressure; pulsatility index - the ratio of pulse pressure to diastolic blood pressure) and the risk of the major cardiovascular complications.
Methods: The study group consisted of 440 patients (301 men and 139 women; mean age: 57.3 $\pm$ 9.8 years) with preserved left ventricular systolic function (EF $>$ 55%), undergoing coronary angiography. Invasive ascending aortic blood pressure during catheterization was taken at baseline. The mean duration of follow-up was 53.7 $\pm$ 18.4 months. The primary end point was defined as: cardiovascular death, myocardial infarction, stroke or myocardial revascularization. The Cox proportional hazard regression analysis was used to assess the relation between blood pressure-derived indices and long-term event-free survival.
Results: At baseline, aortic systolic blood pressure was 138.8 $\pm$ 22.5, diastolic blood pressure 72.7 $\pm$ 10.7, mean blood pressure 94.8 $\pm$ 13.1, pulse pressure 66.1 $\pm$ 18.2, pulsatility 0.69 $\pm$ 0.15 and pulsatility index 0.92 $\pm$ 0.27. The primary end point occurred in 82 (18.6%) patients over the whole follow-up. The crude and adjusted hazard ratios are given in the table.

Table

Hemodynamic variable	Crude HR (95% CI)	Adjusted HR * (95% CI)
Systolic blood pressure per 10 mmHg	1.18 (1.07-1.30)	1.16 (1.03-1.30)
Diastolic blood pressure per 10 mmHg	1.05 (0.85-1.29)	1.08 (0.86-1.37)
Mean blood pressure per 10 mmHg	1.20 (1.01-1.42)	1.18 (0.98-1.43)
Pulse pressure per 10 mmHg	1.27 (1.13-1.43)	1.23 (1.05-1.42)
Pulsatility per 0.1	1.31 (1.13-1.52)	1.21 (1.01-1.44)
Pulsatility index per 0.1	1.15 (1.07-1.25)	1.10 (1.00-1.21)

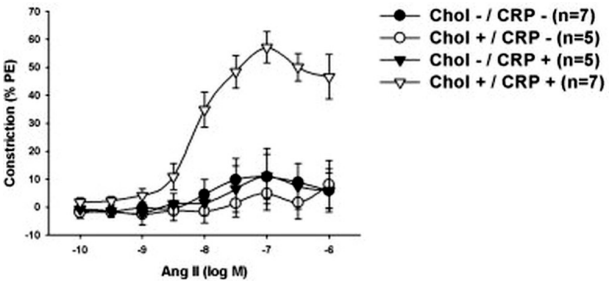
* adjustments were made for age, gender, ejection fraction, extent of coronary atherosclerosis, risk factors and treatment

Conclusion: Ascending aortic pulsatility and pulsatility index are related to the risk of major cardiovascular complications in patients undergoing coronary angiography.

P3619 Synergistic effect of c-reactive protein and LDL-cholesterol on vascular angiotensin II responsiveness

P. Van der Harst[1], F.W. Asselbergs[2], A.A. Voors[1], H. Buikema[3], L.J. Wagenaar[4], T.H. Plokker[4], D.J. Van Veldhuisen[1], W.H. Van Gilst[5]. [1]*University Hospital Groningen, Cardiology, Groningen, Netherlands;* [2]*University Medical Center Groningen, Cardiology, Groningen, Netherlands;* [3]*University Medical Center Groningen, Clinical Pharmacology, Groningen, Netherlands;* [4]*St. Antonius Hospital, Cardiology, Nieuwegein, Netherlands;* [5]*Universital Hospital Groningen, Clinical Pharmacology, Groningen, Netherlands*

Objective: synergistic effects of elevated LDL-cholesterol and increased inflammation in the progression of atherosclerosis might involve angiotensin II (Ang II) type 1 receptor upregulation and, consequently, increased responsiveness to Ang II. We hypothesise that elevated C-reactive Protein (CRP) and LDL-cholesterol may jointly have profound effects on vascular responsiveness to Ang II.
Methods: the study group consists of 24 patients, from whom blood samples and segments of internal thoracic artery were obtained during coronary bypass surgery. Measurements of constriction to cumulative doses of Ang II (0.1nM-1μM) were performed in organ baths and expressed as percentage of response to phenylephrine. Comparisons between the complete concentration-response curves of Ang II were made by multivariate model of repeated measurements of variances. For these analyses, measured variables were treated as binary variables, dichotomised at the median value, and also considered as continuous variables.



Results: median LDL-cholesterol and CRP was 100 mg/dL and 1.12 mg/L, respectively. As shown in the figure, we observed a strong interaction between LDL-cholesterol and CRP when dichotomised ($p<0.001$). Indeed, this finding remained significant ($p<0.01$) when both tested as a continuous variable.
Conclusions: this study provides evidence that combined exposure to increased LDL-cholesterol and increased CRP has detrimental synergistic effects on vascular responsiveness to Ang II.

P3620 Pulse wave velocity and risk of cardiovascular mortality; a population based study

T.W. Hansen[1], J. Jeppesen[2], S. Rasmussen[2], H. Ibsen[2], C. Torp-Pedersen[3]. [1]*Research Center for Prev. and Health, Glostrup, Denmark;* [2]*Glostrup University Hospital, Medical Department M, Copenhagen, Denmark;* [3]*Bispebjerg University Hospital, Department of Cardiology, Copenhagen, Denmark*

Purpose: To study the relationship between pulse wave velocity (PWV) and risk of cardiovascular mortality in a general population.
Methods: Prospective study of a random sample of 2458 men and women, age 41-72 years, without major cardiovascular diseases. At baseline, PWV, office blood pressure, 24-hours ambulatory blood pressure, and other risk factors were recorded.
Results: After a mean period of 9.5 years, 92 cardiovascular deaths were recorded. In a multivariate Cox proportional-hazards model, adjusted for traditional cardiovascular risk factors, including systolic and diastolic office blood pressure, the relative risk (95% confidence interval) pr. SD (3.42 m/s) of PWV was 1.19 (1.02-1.39; p=0.027). In this model neither systolic nor diastolic office blood pressure were significant predictors (p=0.32/0.28; systolic/diastolic). However, when the model was further adjusted for systolic 24-hours ambulatory blood pressure, PWV was no longer a significant predictor (p=0.37), whereas systolic 24-hours ambulatory blood pressure was a significant predictor (p=0.004).
Conclusions: PWV was a significant predictor of cardiovascular mortality in a general population, but the prognostic information was contained within 24-hours ambulatory blood pressure.

P3621 A comparison of the vasodilatory action of testosterone in isolated male and female human pulmonary arteries

A.M. Smith[1], R.D. Jones[2], T.H. Jones[3], K.S. Channer[4]. [1]*Department of Cardiology, Sheffield, United Kingdom;* [2]*University of Sheffield, Hormone and Vascular Biology Group, Sheffield, United Kingdom;* [3]*Barnsley District General Hospital, Centre for Diabetes and Endocrinology, Barnsley, United Kingdom;* [4]*Royal Hallamshire Hopsital, Cardiology, Sheffield, United Kingdom*

Aims: Pulmonary hypertension is a rare disease of the pulmonary vasculature that is more common in females (3:1). Recent therapies are directed at the vascular bed, causing vasodilatation. Testosterone has been shown to be a vasodilator in both the coronary and pulmonary circulations with a mechanism of action involving calcium channel blockade. This study was carried out to see if there was a difference in the response of the pulmonary vascular bed to testosterone in males and females.
Methods: Pulmonary tissue was obtained from patients (7 males, 6 females, mean age 60yrs $\pm$3.8) undergoing elective lung or lobe resection, at Northern General Hospital. 2mm sections of pulmonary artery were then carefully dissected in the laboratory (diameter 546 $\pm$251 μm) and mounted in a wire myograph in physiological saline. The vessels were bubbled with 95% oxygen, 5% carbon dioxide to maintain pH 7.4 and loaded to a tension equivalent to 17.5mmHg. Vessels were contracted with U46619 (1μM) to confirm viability of the smooth muscle and then endothelial integrity was confirmed by dilation to acetylcholine (10nM-100μM). Vessels were washed and then exposed to increasing concentrations of U46619 (1nM-1μM), followed by cumulative additions of ethanol vehicle. Vessels were then washed and the addition of U46619 was repeated (1nM-1μM) followed by increasing concentrations of testosterone (T) (1nM-100μM).
Results (Table 1): Testosterone dilated male and female pulmonary arteries, with the male vessels dilating at significantly lower doses of testosterone.

Table 1. Results shown as percentage relaxation mean (standard error mean)

	T 1μM	T 3μM	T 10μM	T 30μM	T 100μM
Males	-3.28 (1.07)	-3.75 (1.27)	-5.08 (1.54)	-8.17 (2.20) *	-24.7 (3.08) *
Females	-1.14 (1.74)	-1.07 (2.19)	-1.68 (2.39)	-5.06 (2.10)	-25.2 (3.40) *

* $P<0.05$ via Student's t test for independant variables

Conclusion: Testosterone at micromolar concentrations dilates human pulmonary arteries, with a greater efficacy in males compared to females. The influence of the sex hormones in the etiology and treatment of pulmonary hypertension warrants further investigation.

P3622 Vasodilatory effects of testosterone in isolated perfused human lungs

A.M. Smith[1], R.T. Bennett[2], R.D. Jones[3], M.E. Cowen[2], K.S. Channer[4]. *[1]Department of Cardiology, Sheffield, United Kingdom; [2]Castle Hill Hospital, Department of Cardiothoracic surgery, Cottingham, United Kingdom; [3]University of Sheffield, Hormone and Vascular Biology Group, Sheffield, United Kingdom; [4]Royal Hallamshire Hospital, Department of Cardiology, Sheffield, United Kingdom*

Aim: Testosterone has been shown to be a coronary vasodilator, with beneficial effects in angina and chronic heart failure. This study was carried out to research the potential vasodilatory effects of testosterone in the pulmonary circulation, with an aim of being a potential treatment in pulmonary hypertension.
Methods: Lung samples were obtained from 8 patients (4 male, 4 female, mean age 61.1 yrs ± 5.6) undergoing elective lung (n=1) or lobe (n=7) resection, for study as an isolated perfused system (methodology described in (1)). The pulmonary arterial and bronchial systems were cannulated and the lungs were ventilated with room air (Tidal volume 100-300ml/min) and perfused with Krebs bicarbonate buffer (1L, 100-300ml/min). Perfusion pressure (mmHg) was recorded continuously via a pressure transducer. The lungs were preconstricted with potassium chloride, KCL (70mM) to confirm viability followed by cumulative additions of ethanol vehicle (100-700μL). The lungs were then washed and the addition of KCL (70mM) was repeated followed by increasing concentration testosterone (1nM -100μM).
Results (Table 1): A statistically significant relaxation to testosterone was seen, compared to the control vehicle ethanol.

Table 1. Results showed as percentage mean relaxation (standard error mean)

	1μM	3μM	10μM	30μM	100μM
Testosterone	-11.6 (10.7)	-8.7 (19.7)	-12.5 (19.5)	-33.2 (18.4) *	-92.2 (15.8) *
Ethanol	14.6 (14.0)	18.6 (16.4)	22.4 (21.0)	27.8 (22.1)	25.0 (22.4)

* P<0.05 via Wilcoxon signed rank test for paired samples

Conclusion: Testosterone dilates the human pulmonary arterial system at micromolar concentrations. This may be translated into improved pulmonary haemodynamics and symptoms in patients with pulmonary hypertension.
Vasoconstrictive effects of endothelin-1, endothelin-3 and urotensin II in isolated perfused human lungs and isolated human pulmonary arteries. Thorax 2004;59:401-407.

P3623 Noninvasive evaluation of ventriculo-arterial coupling in type 2 diabetes from carotid arterial wave intensity

H. von Bibra, T. Siegmund, U. Pischa, P.-M. Schumm-Draeger. *Stadt. Klinikum Munchen-Bogenhausen, 3. Med. Abt. (Academic Hospital Bogenhausen), Munich, Germany*

Arterial stiffness is important in the prognosis of cardiovascular (CV) disease. CV involvement in type 2 diabetes (DM) with preclinical myocardial disease still awaits clarification and remains a clinically relevant issue. In order to evaluate ventriculo-arterial coupling in preclinical CV disease, we used a wave intensity approach.
Methods: 46 DM patients (HbA1c 6.7±1.2%, 90% on insulin and 50% on OAD therapy) and 33 control individuals (CO), all without evidence of hypertension and coronary artery disease were selected. Groups were comparable with regards to age (57±10 years), CV risk factors, cardiac medication, left atrial and ventricular size and wall thickness. Myocardial velocities were assessed by tissue Doppler and the characteristics of pulse wave intensity noninvasively, using a combined Doppler and echo-tracking system (Aloka SSD-5500, Tokyo). By measuring diameter and flow in the right carotid artery, instantaneous changes were derived in local arterial stiffness (epsilon) and in wave intensity (calculated as the product of pressure and velocity changes with respect to time). From the two characteristic wave intensity peaks resulting from forward travelling waves, the early systolic compression wave (W1) is related to LV inotropism and the late systolic expansion wave (W2) influenced by peripheral resistance.
Results: DM patients had significantly (p<0.01) higher heart rate (71±10 vs 63±10 bpm), systolic blood pressure (139±13 vs 125±15 mmHg), rate pressure product, pulse pressure (56±12 vs 47±12 mmHg) and LV filling pressure (p<0.001). Systolic myocardial velocity was not different from CO but diastolic myocardial velocity was decreased (8,2±2.1 vs 10.0±1.8 cm/s, p<0.0003) and so was the maximal flow velocity in the carotid artery (52±13 vs 64±12 cm/s, p<0.002). Intima-media thickness and epsilon were higher (p<0.02) and so was W1 (12472±549 vs 8634±4536, p<0.05) but not W2.
Conclusion: In patients with type 2 diabetes without evidence of CV disease, a preserved pump function is maintained against increased arterial impedance at expense of increased myocardial oxygen requirements, possibly from enhanced sympathetic drive. Facing the known limitations of mitochondrial energy supply and of myocardial perfusion in diabetes mellitus, this constellation requires therapeutical compensation. The wave intensity approach may have the potential for therapeutic follow up.

P3624 Cardiovascular consequences of hyperthyroidism before, during and after antithyroid treatment

F. Osman[1], J.A. Franklyn[2], M.C. Sheppard[2], M.D. Gammage[3]. *[1]Queen Elizabeth Hospital, Department of Cardiovascular Medicine, Birmingham, United Kingdom; [2]Queen Elizabeth Hospital, Department of Medicine, Birmingham, United Kingdom; [3]Queen Elizabeth Hospital, Cardiovascular Medicine Deptartment, Birmingham, United Kingdom*

Aim: To evaluate the prevalence of cardiovascular symptoms, signs, and haemodynamic changes before, during and after antithyroid therapy.
Methods: 408 consecutive unselected patients with overt hyperthyroidism and 408 age/sex-matched euthyroid controls were recruited. All had full cardiovascular history, examination and standing/lying blood pressure measurements. Patients exhibiting the biochemistry of subclinical hyperthyroidism (normal serum thyroid hormones with suppressed thyrotrophin {TSH}), as well as those rendered biochemically euthyroid at follow-up, were compared with controls.
Results: Median age was 50yrs (IQR 37-65), 320 females/88 males in each; past/family history of vascular disease were no different (20% vs 18% and 68% vs 70%, p=ns). Median serum free thyroxine (T4) and tri-iodothyronine (T3) concentrations in patients were 37.5pmol/L (IQR 27-52) and 11.4pmol/L (IQR 8-18); serum TSH undetectable in all. Serum free T4, T3 and TSH were normal in controls. Patients had a higher prevalence of palpitation (73% vs 20%), chest pain (25% vs 10%), dyspnoea (60% vs 14%), orthopnoea (6% vs 1%), cough (35% vs 11%), peripheral oedema (23% vs 10%), cardiac murmur (17% vs 6%) and abnormal chest sounds (9% vs 2%, p<0.0001 for all) compared with controls. Resting pulse and systolic pressure were higher in patients (82±1bpm vs 73±1bpm and 137±1mmHg vs 129±1mmHg, p<0.0001 for both) but diastolic pressure was no different. Systolic blood pressure on standing dropped in patients but rose in controls (-3±1mmHg vs 2±1mmHg, p<0.0001). 110 patients exhibited the biochemistry of subclinical hyperthyroidism (mean follow-up 27.1±2.1wks) and had greater prevalence of palpitation (45% vs 21%, p<0.0001), dyspnoea (28% vs 14%, p<0.002) and cough (20% vs 11%, p<0.05) than controls. Raised pulse rate and systolic pressure persisted (76±1bpm vs 73±1bpm and 137±2mmHg vs 130±1mmHg, both p<0.01), as did systolic pressure drop on standing (-3±1 mmHg vs 1±1mmHg, p<0.005). 219 patients were rendered biochemically euthyroid (mean follow-up 36.9±1.6wks) and had a higher prevalence of palpitation (34% vs 21%, p<0.0001), dyspnoea (26% vs 14%, p<0.005) and cough (21% vs 11%, p<0.003) compared with controls. Blood pressure and pulse rate were no longer different but systolic pressure drop on standing persisted (-2±1 mmHg vs 1±1mmHg, p<0.009).
Conclusions: Cardiovascular symptoms, signs, and haemodynamic disturbances are common in hyperthyroidism. These persist during and after antithyroid therapy suggesting ongoing cardiovascular effects despite restoration to normal of serum thyroid hormones.

THE HEART IN HYPERTENSION

P3625 Changes in aortic stiffness in intensive treated patients with hypertension and type 2 diabetes

M. Klocek[1], M. Rajzer[2], K. Kawecka-Jaszcz[2]. *[1]Krakow, Poland; [2]Jagiellonian Univ., Medical College, I Cardiac Department, Krakow, Poland*

Objective: The aim of the study was to assess whether intensive blood pressure lowering and/or intensive treatment of diabetes mellitus (DM) influence aortic stiffness in hypertensive patients with type 2 diabetes.
Material and method: Prospective, open study. 110 patients, 52 men and 58 women (mean age 64.2 ± 7.3 years) with DM (mean duration 6.9 ± 2.6 years) and hypertension (H, mean duration 10.6 ± 4.5 years) were enrolled. The patients were randomly divided into two groups: group A (54 patients, mean 63.3 ± 6.5 years) – to obtain BP < 130/80 mmHg and HbA1C < 6.4% or more, and group B (56 patients, mean 65.2 ± 8.5 years) – to obtain at least BP < 140/90 mmHg and HbA1C < 7.0%. The study lasted 24 months. At baseline all patients with DM were treated with oral hypoglycemic drugs. If needed insulin was added at any time. Treatment of H was based on ACE-inhibitors, then during the study other drugs were added when BP goal was not achieved. In all patients measurements of SBP, DBP, HR, BMI, waist/hips (W/H) ratio, lipids, fasting glucose and HbA1C levels were performed at baseline and 24 months. Aortic stiffness was measured at baseline and after 24 months by assessing carotid-femoral pulse wave velocity (PWV) using the Complior® system.
Results: At the end of study 44 patients (81.5%) in group A achieved BP < 130/80 mmHg (mean 126/76 mmHg), and HbA1C < 6.4% (mean 6.15%), among them 34 patients required intensive treatment with insulin. At 24 months in 37 patients SBP was between 131-140 mmHg, and in 29 was over 140 mmHg. Higher HbA1C level (7.52% vs 6.15%, p<0.01) was found in patients treated less intensively. At baseline PWV did not differ between group A and B. After 24 months PWV was significantly lower only in hypertensives with DM in whom both marked reduction in BP and HbA1C was observed (at baseline 14.04 m/s vs 12.58 m/s at 24 months, p<0.01). PWV did not change during the study in patients in whom planned target both for BP and HbA1C was not achieved (PWV at baseline 14.14 m/s vs 13.97 m/s at 24 months, respectively).

Conclusions: Treatment of hypertension and type 2 diabetes mellitus should be intensive and comprehensive because only such approach leads to significant improvement in properties of large arteries in hypertensives with diabetes.

P3626 Indapamide SR versus hydrochlortazide for the treatment of systolic hypertension in older people

I. Marchenco, T. Chalabi, V. Tzoma, U.A. Brel, S. Nedogoda. *Medical University, Volgograd, Russian Federation*

Objective: In older patients, elevated systolic BP, wide pulse pressure and low vascular compliance predict cardiovascular risk better than diastolic BP. This study compared the efficacy and safety of two different diuretics indapamide SR (IND-SR), hydrochlortiazide (HCTZ) and the dihydropyridine calcium antagonist nitrendipine (NTR) on BP in older patients with systolic and/or wide pulse pressure hypertension.
Design and Methods: This was a 24-week, double-blind, titration-to-effect study in patients >65 years (mean age 71.7 years) with systolic hypertension and/or widened pulse pressure (SBP 150 mmHg and <165 mmHg and PP 70 mmHg; or SBP 165 mmHg and <200 mmHg and DBP <95 mmHg). Patients were randomized to receive initially either IND-SR 1.5 mg/day (N=54), HCTZ 12.5 mg/day (N=54) or NTR 12.5 mg/day (N=52) (N=52).There were 2 potential titration steps (100 and 200 mg QD of EPL or 5 and 10 mg QD of AML at 2 and 6 weeks, respectively) as needed to reduce SBP to <140 mmHg. ABPM, changes in arterial compliance, measured by pulse-wave velocity (PWV) with COLSON device, changes in microalbuminuria, safety and tolerance were assessed at baseline and after 24 weeks of therapy.
Results:

Parameter	IND-SR	HCTZ	P-value*	NTR	P-value*
Changes in systolic BP(mmHg)	-28,4±1,5	-19,1±1,6	0,0048	-28,1±1,6	0,091
Changes in Pulse Pressure(mmHg)	-24,2±1,1	-12,9±1,1	0,004	-22,6±1,6	0,089
Changes in carotid-femoral PWV(msec)	-2,4±0,3	-1,1±0,2	0,051	-1,5±1,6	0,049
Microalbuminuria(%)**	-23,3	-8,3	0,002	-11,3	0,046
Edema rates(%)	–	–		9	0,053

*compare to indapamide SR, **only for patients with baseline microalbuminuria (>30 mg/g)

Conclusions: Indapamide reduced systolic BP and pulse pressure more than hydrochlortiazide and similar to nitrendipine. Indapamide SR reduced microalbuminuria and increased and vascular compliance to a greater extent than hydrochlortiazide and was associated with significantly less peripheral edema than nitrendipine.

P3627 Diuretic-AIIRA combination: persistence of differences in AIIRA efficacy. COSIMA study

N. Postel-Vinay, G. Bobrie, C. Moulin, A. Giacomino, R. Asmar. *Paris, France*

Purpose: Compare the antihypertensive efficacy of irbesartan 150 mg vs. valsartan 80 mg, when combined with hydrochlorothiazide (HCTZ) 12.5 mg.
Methods: Untreated or uncontrolled treated hypertensive adults (n=800) were enrolled (V1) in a 5-week open-label lead-in phase in which they received 12.5 mg HCTZ od. Those whose blood pressure remained uncontrolled (office SBP > 140 mm Hg after 4 weeks (V2) and SBP > 135 mm Hg by home blood pressure monitoring [HBPM] at week 5 - at least 12 valid measurements over 5 days) were randomised (n=464) at V3 to either irbesartan/HCTZ (150/12.5 mg) or valsartan/HCTZ (80/12.5 mg) for 8 weeks. HBPM was performed at weeks 5 (before V3) and 13 (before V4) using a validated device (Tensioday™): after 5 minutes rest, 3 measurements were made at 1 minute intervals, in a sitting position in the morning (6-10 am) before treatment intake and in the evening (6-10 pm), for at least 3 days. Data were transferred automatically via teletransmission to an independent core laboratory blinded to treatment allocation.
Results: The intent-to-treat dataset included 449 patients (irbesartan/HCTZ: 222 and valsartan/HCTZ: 227). Baseline characteristics were well matched: mean age 59.3, 56% men; initial home SBP/DBP 148.8/89.5 mm Hg and office SBP/DBP 153.0/90.6 mm Hg. The differences in BP (mm Hg) measured by HBPM (W5-W13) in the morning and in the evening are presented in the table below. The overall safety was similar in the two groups.

COSIMA study

mm Hg	ΔSBP morning	ΔDBP morning	ΔSBP evening	Δ DBP evening
irbesartan/HCTZ	12.4 ±10.7	9.0± 6,7	14.0 ±11,4	10.3 ±7.3
valsartan/HCTZ	9,6 ±10.7	6.7± 6.7	11.9 ±11.4	8.4 ±7.3
delta mean (95% CI)	2,9 (0.8;5.0)	2.3 (1.0;3.5)	2.1(-0.1;4.3)	1.9(0.4;3.3)
p	0,0067	0,006	0,0648	0,0097

All values are expressed as mean±sd/CI: confidence interval

Conclusion: The combination irbesartan/HCTZ 150/12.5 mg is more potent in terms of BP reduction that the combination valsartan/HCTZ 80/12.5 mg. The more pronounced decrease in BP observed in the morning (before treatment intake) with irbesartan/HCTZ is consistent with the longer duration of action of irbesartan 150 mg which is not blunted by the addition of HCTZ 12.5 mg.

P3628 Increased vascular selectivity and prolonged pharmacological efficacy of the L-type Ca^{2+} channel antagonist lercanidipine in human cardiovascular tissue

B. Boelck[1], K. Brixius[1], T. Gross[1], P. Tossios[2], H.-J. Geissler[2], U. Mehlhorn[2], R.H.G. Schwinger[1]. *[1]Clinic III of Internal Medicine,Cologne Univ., Lab. of Muscle Res. & Mol. Cardiology, Cologne (Koln), Germany; [2]University of Cologne, Clinic of Cardiothoracic Surgery, Cologne, Germany*

The present study investigates the vasoselectivity of lercanidipine (LER), a 1,4-dihydropyridine calcium channel blocker (CCB) compared to amlodipine (AML) and nifedipine (NIF) in human cardiovascular tissue. Experiments were performed either in human left ventricular failing myocardium (orthotopic heart transplants) or in isolated right atrial trabeculae and isolated vessel preparations of arteria mammaria obtained from patients undergoing aortocoronary bypass-operation.
The obtained rank order for the L-type Ca^{2+} channel affinity in human tissue was LER > NIF ≥ AML. LER had the lowest negative inotropic efficacy (1 μM, LER: 60.3%basal < AML: 79.1%basal < NIF:92.4 basal) and potency (IC50, NIF: 3.5 nM < AML:48nM < Ler: 127nM) in right atrial trabeculae. The vasorelaxant potency of LER (IC50:0.5 nM) and AML (0.8 nM) was similar and significantly increased compared to NIF (5.9 nM) in A. mammaria preparations of the very same patients. The following rank order was obtained for vasoselectivity: LER (260)< AML(60)< NIF(0.7). The pharmacological effects of LER and AML were still present 2h after drug washout.
Conclusions: lercanidipine is characterised by a high vasoselectivity and a prolonged interaction with the L-type calcium channel in human cardiovascular tissue This may be advantageous especially for the treatment of patients with arterial hypertension.

P3629 Effects of sildenafil on 1-year survival of patients with idiopathic pulmonary arterial hypertension (PAH)

N. Galié[1], G. Burgess[2], T. Parpia[3], L. Rubin[4] on behalf of The SUPER Study Groups. *[1]University of Bologna, Bologna, Italy; [2]Pfizer Ltd, Sandwich, United Kingdom; [3]Pfizer Limited, PGRD, Sandwich, United Kingdom; [4]University of California at San Diego, La Jolla, United States of America*

Purpose: patients with idiopathic PAH (IPAH) had a median survival of 2.8 years prior to the availability of epoprostenol and bosentan, Sildenafil improves exercise capacity in PAH patients. 1-year observed survival of sildenafil-treated IPAH patients is compared with predicted survival.
Methods: 278 PAH patients (idiopathic, 63%) were randomized to placebo or sildenafil (20, 40, or 80 mg) tid in a 12-week double-blind placebo-controlled study. Patients completing this study could enter an extension study to receive sildenafil 20, 40, or 80 mg tid based on tolerability. IPAH patients treated with sildenafil were analyzed on an intention to treat basis. Patients taking prostaglandins (PG) and endothelin receptor antagonists (ERA) were not excluded. Observed survival was estimated using the Kaplan-Meier method. Predicted survival was estimated using the prognostic index based on the NIH registry of IPAH patients utilizing baseline values of cardiac index (CI), mean pulmonary arterial pressure (mPAP) and mean right atrial pressure (mRAP).
Results: survival could be predicted in 141/175 IPAH patients who had baseline values for CI, mPAP and mRAP. Baseline characteristics were: mean (SD) age, 48 (15) years; female, 72%; WHO functional class: I, 1%; II, 38%; III, 59%; IV, 3%; mean (SD) CI, 2.3 (0.7); mean (SD) mPAP, 54 (15) mmHg; mean (SD) mRAP, 9 (5) mmHg. 9 IPAH patients (6%) took PG or ERA within 1 year of treatment.

Table

Number at Risk	141
1-year Observed Survival	96%
1-year Expected Survival	71%

Conclusions: compared with predicted survival, first-line treatment of IPAH with sildenafil (and subsequent additional therapy if necessary) appears to improve survival.

P3630 A health-economic evaluation of the real life long-term consequences of an angiotensin II receptor blocker (ARB) in the management of post-MI patients. Case study on valsartan in Canada

M. Lamotte[1], L. Annemans[2], A. Gnanasakthy[3], Z. Khan[4]. *[1]HEDM-IMS, Brussels, Belgium; [2]Ghent University, Brussels, Belgium; [3]Novartis Pharmaceutical Corporation, East Hanover, New Jersey, United States of America; [4]Novartis Pharma AG, Pharma Affairs Dept., Basel, Switzerland*

Objectives: The VALIANT trial showed that valsartan, an angiotensin II receptor blocker (ARB), was at least as effective as captopril, an ACE inhibitor, at reducing mortality and cardiovascular morbidity in patients who developed heart failure and/or LVSD after surviving an MI. Health-economic analysis of this trial showed slightly higher costs for ARB than ACE inhibitor treatment. However, patients intolerant to ACE inhibitors were excluded from the trial, and observational data show that in real life practice, less than 50% of post MI patients are actually treated with

ACE inhibitors. This economic evaluation therefore aimed to assess the real life cost-effectiveness of valsartan, a representative of the ARB class, in post MI patients through its impact on the number of adequately treated patients. The case country for this study is Canada.
Methods: Based on the outcomes of VALIANT and a meta-analysis of the ACE-inhibitor trials, a Markov state-transition model was built with a 10-year time horizon. A "world with ARBs" was compared to a "world without ARBs" from the health care payer's perspective. As a base case, it was assumed that if ARBs were not available, 50% of the patients now on ARBs would have been on ACE-inhibitors and 50% would not have been on any angiotensin-related drugs (ACE-I nor ARB). Current drug market data was provided by IMS. The costs of events and drugs were based on literature data and official tariffs. Utility data (TTO) were derived from the literature. Results are expressed as cost per QALY (Quality Adjusted Life Years). Discounting of 3% was applied on costs and effects.
Results: In the base case, over 10 years, an additional 0.0298 QALY were gained in the "world with ARB" for an extra cost of €97 (160 CAD). The resulting incremental cost-effectiveness ratio (ICER) was €3,260/QALY gained (5,362 CAD). Sensitivity analyses revealed that the key factor determining cost-effectiveness is the impact of ARBs on the number of adequately treated patients. A 2% increase in the total number of patients treated due to the availability of ARBs is already sufficient to obtain a favorable ICER.
Conclusions: Valsartan, as a representative of the ARB class, is cost-effective in a post-MI population if its availability leads to more patients receiving angiotensin-related drugs. Our results also show the impact of real life treatment patterns on cost-effectiveness of health strategies, and highlight some of the problems that occur in 'head-to-head' active-controlled clinical trials.

P3631 Preterax in hypertensive patients in private practices in Germany: the PRIMUS study

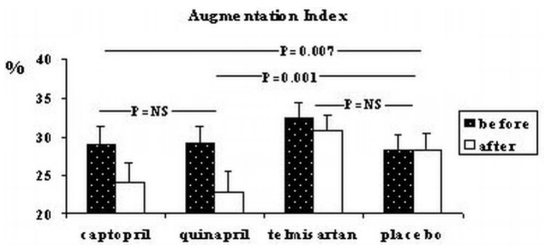
H. Holzgreve. *Munchen, Germany*

Rationale: The newest guidelines (ESH/ESC, German Hypertension League) recommend low-dose combinations (LDC) for initial treatment of hypertension (HT). Preterax®, consisting of ACE-inhibitor perindopril 2 mg and diuretic indapamide 0.625 mg, is the only LDC approved for first-line antihypertensive therapy in several European countries including Germany.
Objective: The objective of PRIMUS was to evaluate the efficacy and tolerability of Preterax® in a large population of hypertensive patients in general practice.
Design and method: For the prospective, open-labelled, multicenter trial, 1892 general practitioners in Germany recruited patients with HT (SBP≥140 mmHg and/or DBP≥90 mmHg). Treatment consisted of 1 tablet daily of Preterax® for 12 weeks. Doubling the dose was possible to reach target BP. SBP, DBP, pulse pressure (PP), normalization rate (SBP/DBP <140/90 mm Hg), responder rate (SBP/DBP <140/90 mm Hg and/or SBP reduction ≥15 mm Hg and/or DBP reduction ≥10 mm Hg), efficacy and tolerability according to physician's judgment (excellent, good, moderate, insufficient) were evaluated. A descriptive statistical analysis was performed on changes between baseline and last observation.
Results: Baseline values in 8023 patients (mean age: 59.6 (±12.1) years, 48% males, BMI: 27.6 (±4.0) kg/m_) were SBP 164.6 (±14.8) mm Hg, DBP 95.8 (±9.1) mm Hg, and PP 68.8 (±14.1) mm Hg. 89% of patients had additional risk factors (RF) (defined according to German Hypertension Guidelines). Main reasons for initiating the LDC were uncontrolled BP (51.6%), newly-diagnosed HT (38%), or side effects with preexisting antihypertensive regimen (11.8%). In 9.5% of patients, dose was doubled. The LDC decreased SBP by −28 mm Hg (±14.4), DBP by −14 mm Hg (±9.4), and PP by −14 mm Hg (±13.4) (7846 completed data sheet). Normalization rates were 50% and 54% and responder rates were 96% and 98% in all patients and newly detected hypertensives, respectively. Efficacy and tolerability of the LDC was evaluated as "excellent/good" in 88% and 90% of patients, respectively. No unexpected adverse effects were observed.
Conclusion: The LDC showed excellent antihypertensive efficacy and tolerability in a large population of hypertensive outpatients, either newly diagnosed or already treated but uncontrolled or with side effects on previous medication, mostly with additional RF. In daily practice, Preterax® is not only a suitable strategy for initiating antihypertensive treatment in newly detected patients, as recommended in recent guidelines, but is also suitable for patients with previous insufficient therapy.

P3632 Effects of acute inhibition of the renin-angiotensin axis on wave reflections in hypertensive patients

K. Aznaouridis[1], J. Lekakis[2], C. Papamichael[2], K. Stamatelopoulos[2], E. Karatzis[2], T. Papaioannou[2], M. Mavrikakis[2]. *[1]Univ. of Athens, Hippokration Hospital, 1st Dept. of Cardiology, Athens, Greece; [2]Alexandra Hospital, Department of Clinical Therapeutics, Athens, Greece*

Purpose: Antihypertensive drugs that inhibit the renin-angiotensin axis, such as angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB), have been shown to exhibit a protective role in cardiovascular performance, beyond BP decrease. Arterial wave reflections (WR) are determinants of cardiovascular function and predictors of the corresponding risk. The acute effect of such drugs on WR has not been fully investigated in a hypertensive population.
Methods: We studied the effect of captopril 25 mg, quinapril 20 mg (a high tissue affinity ACEI), telmisartan 80 mg and placebo, in 100 untreated patients (pts) with mild to moderate essential hypertension (mean age 57.2 years, 48 men), according to a double-blind design. Each treatment arm included 25 age-matched pts, and WR were studied using a validated system (Sphygmocor®) that employs arterial tonometry and pulse wave analysis, before and 2 hours after administration of the drug. Augmentation index (AI) was measured as an estimate of WR.
Results: At baseline, the 4 groups did not differentiate (p=NS) in heart rate, mean BP (109 vs 111 vs 113 vs 109 mmHg for captopril, quinapril, telmisartan and placebo groups respectively) or AI. After 2 hours, all the 3 active drugs decreased mean BP (by 7.4, 10.6 and 5.4 mmHg for captopril, quinapril and telmisartan respectively, p<0.01 for all), but placebo not. AI corrected for heart rate decreased significantly and in the same degree with quinapril and captopril as compared with placebo, but AI did not change with telmisartan (figure).



Changes in AI after treatment

Conclusion: ACEI antihypertensive treatment causes an acute decrease in WR in mild to moderate hypertensives. It seems that this beneficial effect is independent from changes in BP or tissue affinity properties.

P3633 Novel anti-inflammatory and metabolic effects of candesartan in hypertensive patients

K.K. Koh[1], S.H. Han[2], M.J. Quon[3], W.-J. Chung[1], E.K. Shin[1]. *[1]heart center, ghil hospital, cardiology, Incheon, Korea, Republic of; [2]Ghil hospital, Gachon medical school, Cardiology, Incheon, Korea, Republic of; [3]NIH, Diabetes Unit, Bethesda, United States of America*

Background: Angiotensin II type 1 (AT1) receptor blocker therapy prevented the progression of coronary heart disease. The mechanisms of this benefit may relate to the ability of AT1 receptor blockers to reduce inflammation and insulin resistance.
Methods: We administered placebo or candesartan 16 mg daily during 2 months to 45 patients with hypertension. This study was randomized, double-blind, placebo-controlled, crossover in design.
Results: Candasartan therapy significantly lowered blood pressure and improved flow-mediated dilation and decreased plasma malondialdehyde levels. Compared with placebo, candesartan therapy significantly lowered plasma hsCRP levels relative to baseline measurements from 1.10 to 0.70 mg/l (P=0.024) and sCD40L levels by 30±11% (P<0.001) and TNF-alfa by 10±4% (P=0.026) and MCP-1 by 9±3% (P=0.003). There were significant correlations between baseline adiponectin levels and baseline HDL-cholesterol levels (r=0.499, p<0.001), insulin (r=-0.317, p=0.034), or baseline QUICKI (r=0.371, p=0.012). Compared with placebo, candesartan therapy significantly lowered fasting insulin levels (P=0.011) and increased plasma levels of adiponectin by 15±4% (P=0.012) and increased QUICKI by 8±2% (P=0.007). There were significant correlations between percent changes in adiponectin levels and percent changes in HDL-cholesterol (r=0.309, p=0.041), insulin (r=-0.340, p=0.022), or QUICKI (r=0.325, p=0.029).
Conclusions: Candesartan therapy significantly improved the percent flow-mediated dilator response to hyperemia and reduced levels of oxidant stress and inflammation markers and increased adiponectin levels and improved insulin sensitivity in hypertensive patients.

P3634 Microalbuminuria and cardiovascular morbidity: effect of 1-year treatment with Irbesartan in clinical settings

J.R. Gonzalez Juanatey[1], E. Alegria[2], V. Bertomeu[3], J. Honorato[2], J. Zamorano[4], I. Gonzalez-Maqueda[5], M.J. Salvador[6], C. Filozof[7]. *[1]Hospital Clinico, Department of Cardiology, Santiago de Compostela, Spain; [2]Clinica Universitaria Navarra, Cardiology, Pamplona, Spain; [3]Hospital Universitario San Juan, Cardiology, Alicante, Spain; [4]Hospital Clinico, Cardiology, Madrid, Spain; [5]Hospital La Paz, Cardiology, Madrid, Spain; [6]Clinica Dexeus, Cardiology, Barcelona, Spain; [7]BMS Spain, Medical Department, Madrid, Spain*

Microalbuminuria is a marker of cardiovascular risk. Objective. The aim of this study was: 1 - to assess blood pressure (BP) control and cardiovascular morbidity in hypertensive (HT) patients with microalbuminuria (MAU) attending cardiology Units in Spain and to compare these data with HT subjects with normo (NAL) and macroalbuminuria (PROT); 2 - To assess BP control and changes in MAU/PROT after 1-year treatment with Irbesartan.

Design and Method: KORAL-CARDIO is a prospective, open, 1-year follow-up study.
Results: We studied 2267 (age: 63.9± 10.1 y) patients. At baseline, mean (SD) systolic blood pressure (SBP) [163.8 (±16.2)] mmHg was significantly higher ($p<0.01$) in PROT than both MAU and NAL but similar between these two groups [160.0 (±14.4) and 158.8 (±15.7)] mmHg, respectively. Mean (SD) diastolic blood pressure (DBP) was lower ($p<0.01$) in NAL than both MAU and PROT but without difference between these groups. Presence of CV morbidities increases with increasing albuminuria (table 1). DBP correlated positively with Urinary albumin excretion rate (r: 0.12, $p<0.001$). After 1-year treatment with Irbesartan, mean SBP and DBP decreased significantly in the three groups ($p<0.001$) and proportion of patients achieving BP targets (BP targets<130/80 for D and <140/90 for non-D) increased from 18.0% to 72.8%, from 13.0% to 64.9% and from 9.1% to 54.8% in NAL, MAU and PROT, respectively. At the 1-year follow-up, 33% of patients regressed to NAL. Proportion of patients with macro and microalbuminuria diminished significantly not only in patients achieving BP targets but in those who did not, as well ($p<0.001$).

CV morbidities and albuminuria

%	NAL (n:473)	MAU(n: 1535)	PROT (n:259)	p
Diabetes	37.4	44.8	56.4	<0.001
Ischaemic Heart Disease	26.1	28.5	38.2	<0.01
LVH	44.5	60.3	64.1	<0.001
Peripheral Arteriopathy	4.7	7.4	12.4	<0.01

NAL: Normoalbuminuria, MAU: microalbuminuria, PROT: proteinuria

Conclusion: We confirm a parallelism between CV and renal disease in these HT subjects attending cardiology Units in Spain The addition of Irbesartan to the usual treatment improves not only BP control but metabolic profile. Additionally, this treatment is associated with an increased proportion of patients who regressed to NAL, independently of BP control.

P3635 Left atrial volume in hypertension: effect of chronic treatment with a AT2 blocker

A.V. Mattioli, A. Lattanzi, S. Bonatti, L. Bonetti, M. Zennaro, G. Mattioli. *University of Modena & Reggio Emilia, Dept. of Cardiology, Modena, Italy*

The aim of the study was to evaluate the effect of regression of left ventricular (LV) hypertrophy on left atrial (LA) size and function in patients (pts) with mild-moderate hypertension treated with telmisartan. Pts population included 85 pts with mild-moderate LV hypertrophy (64 men and 21 women of mean age 51 ± 10 years, range 43-62). Left atrial size was measured during systole from the parasternal long axis view from M-mode). LA volumes were determined at mitral valve opening (max vol) and at mitral valve closure (min vol). LA volumes were measured from the apical 4-chamber and 2-chamber views by means of the biplane area-length method, and corrected for body surface area. Atrial function was assessed by Doppler echo: transmitral peak A vel (A) and integral (Ai), atrial filling fraction (AFF), and atrial ejection force (AEF).
All pts had an increased LVMI. Results of serial evaluation of LA size and function are shown in Table 1.

Table 1

Parameters	baseline	6 months	12 months	18 months
LA antero-posterior diameter (mm)	39 ± 7	39 ± 7	36 ± 6*	36 ± 5
LA supero-inferior diameter (mm)	42 ± 6	40 ± 5	38 ± 7*	38 ± 6
Maximal volume (cm^3)	35 ± 5	34 ± 4	32 ± 5*	32 ± 6
P atrial volume (cm^3)	18 ± 3	15 ± 5	14 ± 6*	15 ± 2
Minimal volume (cm^3)	14 ± 2	11 ± 2	10 ± 5*	10 ± 4
Conduit volume (cm^3)	34 ± 4	32 ± 2	31 ± 6*	31 ± 6
Passive emptying volume (cm^3)	11 ± 3.2	10 ± 3.1	10 ± 3.3	10 ± 3.2
Active emptying volume (cm^3)	7 ± 2.4	6 ± 2.1	6 ± 2	6 ±1.9

* $p<0.01$ vs baseline

Atrial function was increased during follow-up and atrial performance parameters correlated with regression of LV hypertrophy (AEF and LVMI r= -0.67; peak A vel and LVMI r=-0.53; AFF and LVMI r=-0.61; $p<0.001$). In conclusion regression of hypertrophy induced a reduction of LA size and volumes and a better atrial performance in hypertensive pts treated with telmisartan.

P3636 Prevalence of atrial fibrillation (AF) and mitral regurgitation (MR) in patients with arterial hypertension depending on the diameter of the left atrium

F. Baborski, I. Scuric, N. Lakusic, D. Cerovec, M. Jersek, M. Majsec. *Hospital for med. rehabilitation, Cardiology department, Krapinske Toplice, Croatia*

Aim: To analyze echocardiographic functional and morphological parameters of left ventricle (LV) in patients with hypertension with and without atrial fibrillation (AF) according to left atrium diastolic diameter.
Method: Echocardiographic examination was done (M mode, B mode and CDFI imaging) using Aloka 5500 software. We analysed 4149 patients, average age was 60±12 and 46% were female.
Results: Our results are presented in table 1. AF had total of 450 pts. (10,9%) and 51.4% were female. Patients with AF were significantly older than patients with sinus rhythm (68±9 vs. 60±12, $p<0.001$), and MR was found in 38.7 pts with AF and only 18.0% in SR ($p<0.001$). Diastolic diameter of the LA in that group was 46.5±7.7 mm and was significantly greater ($p<0.001$) than in group with sinus rhythm (39.5±6.4 mm). LVM was increased in both groups, but signifficantly greater in group with AF (333±127 vs. 308±108; $p<0.001$). EF was normal in both groups but signifficantly lower in group with AF ($p<0.001$). There was no significant difference in BMI and LVDd in those two groups.

Table 1. Echocardiographic and functional characteristics of patients with arterial hypertension depending on the diameter of LA

	LA (mm)	N	AF (%)	MR (%)	EF (%)	LVM (g)	LVDd (mm)	E/A*	Age (yrs)	BMI
Group a	≤40 mm	2321	4.4	15,3	72 ±11	280 ±92	51 ±7	0,98 ±0,40	59 ±13	28 ±5
Group b	41-50 mm	1510	14.5	24,0	68 ±14	339 ±109	55 ±8	1,08 ±0,54	62 ±11	31 ±7
Group c	>50 mm	315	41.3	41,6	62 ±17	406 ±143	58 ±9	1,19 ±0,52	66 ±11	1 ±5
p a vs. b			<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
p a vs. c			<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
p b vs. c			<0.001	<0.001	<0.001	<0.001	<0.001	<0.04	<0.001	NS

AF - atrial fibrillation; MR - mitral regurgitation; EF - ejection fraction; LVM - mass of the left ventricle; LVDd - diastolic diameter of the left ventricle; E/A* - E/A index for patients in sinus rhythm.

Conclusion: AF was found in 10.9% pts and MR in 20.4% of pts with hypertension. When LA diameter was greater than 50 mm 41.6 pts had MR and 41.3% had AF. LVM is greater and EF smaller in patients with AF and greater LA. Echocardiography gives a number of important morphological and functional parameters for evaluation and therapy of patients with hypertension.©

P3637 Does hypertrophyregression effect the arrhythmogenety of hypertensive heart disease

C. Perings[1], G. Plehn[2], C. Zuehlke[2], H.-J. Trappe[2]. [1]*Heinrich-Heine-Universität Düsseldorf, Cardiology Dept, Düsseldorf, Germany;* [2]*University-Hospital Ruhr-University Bochum, Herne, Germany*

Arterial hypertension often leads to left ventricular hypertertrophy with a siginificant increase in the incidence of arrhythmias. To what extend this phenomenon is reversible due to hypertrophyregression is not systematically examed yet.
59 patients (pts, 36% female) with a mean age of 58,1 years and a normal coronary angiogram were followed during 61±27 months. The follow-up examinations every 6 months included echocardiography (estimation of muscle-mass-index=MMI), Holter-ECG (ventricular extrasystoles=VES, couplets and non-sustained ventricular tachycardias=nsVT), late potential analysis (LPA with fQRS, RMS and LAS) and measurements of QT-dispersion.
Patients with a significant pharmacological reduction of MMI from 177±70g/m^2 to 154±33g/m^2 ($p<0,05$) over time showed a significant improvement in arrhythmogenety with less ventricular arrhythmias in the Holter-ECG: VES/24h 837±513 vs 219±133, Couplets 27±42 vs 1±2, nsVT 10±3 vs 3±1 ($p<0,05$ each). Furhtermore late potential analysis changes significantly as well as QT-dispersion: fQRS shortens from 126±30ms to 102±12ms, RMS reduces from 45±26μV to 22±16μV as well as QT-dispersion does from 57±22ms to 39±10ms ($p<0,05$ each).
This is one of the first longitudinal studies in hypertensive patients with an invasively proven normal coronary angiogram that could demonstrate an exclusively positive effect of hypertophyregression on the arrhythmogenety of left ventricular hypertrophy measured by non-invasive risk predictors in Holter-ECG, late potential analysis and QT-dispersion

P3638 Left ventricular hypertrophy is accompanied by a state of increased inflammatory process and arterial stiffness in essential hypertensive subjects: a novel insight to target organ damage

K. Dimitriadis, C. Tsioufis, D. Chatzis, M. Toutouza, V. Chatzistamatiou, K. Toutouzas, C. Stefanadis, I. Kallikazaros. *Hippokration Hospital, Department of Cardiology, Athens, Greece*

Purpose: Subclinical inflammation and arterial stiffening are both markers of increased cardiovascular risk, while left ventricular (LV) hypertrophy (LVH) is an independent risk factor. In the present study we investigated the relationship between augmented LV mass and inflammatory markers, such as high sensitivity CRP (hs-CRP), serum amyloid-A (SAA), tumor necrosis factor-a (TNF-a) and arterial stiffness in essential hypertensive subjects.
Methods: 148 newly diagnosed untreated non-diabetic patients with stage I to II essential hypertension [98 men, mean age=49 years, office blood pressure (BP)=150/97 mmHg], underwent a full echocardiographic examination and according to recently established gender-specific criteria were divided into those with LVH (n=72) and those with normal LV mass (n=76). Additionally, arterial stiffness was evaluated on the basis of carotid to femoral pulse wave velocity (PWV), by means of a computerized method (Complior SP), while venous blood samples were drawn for estimation of lipid profile, hs-CRP, SAA and TNF-a concentrations.

Results: Patients with LVH compared to subjects without LVH were older (54±4 vs 45±7 years, p<0.005), had greater 24h systolic BP (138±10 vs 132±15 mmHg, p=0.001), daytime and nighttime systolic BP (141±11 vs 132±18 mmHg and 127±9 vs 122±17 mmHg, respectively; p<0.005 for both cases). In the entire population hs-CRP was associated with body mass index (BMI) (r=0.328, p<0.001), 24-h systolic BP (r=0.140, p<0.05), 24-h diastolic BP (r=0.361, p<0.005), SAA (r=0.425, p<0.0001), TNF-a (r=0.555, p<0.0001) and PWV (r=0.412, p<0.0001). Moreover, PWV was associated with age (r=0.294, p<0.005), BMI (r=0.233, p<0.05), 24h systolic BP (r=0.327, p<0.0001), SAA (r=0.232, p<0.05), and TNF-a (r=0.189, p<0.05). Although the two groups did not differ regarding body mass index, smoking status and lipid levels (p=NS for all cases), hypertensives with LVH as compared to patients without LVH exhibited higher levels of hs-CRP (3.3±0.7 vs 2.1±0.5 mg/l, p<0.05), greater SAA (9.0±4.3 vs 5.8±3.7 mg/dl, p<0.05), TNF-a (2.83±0.5 vs 1.81±0.2 pg/ml, p<0.0001) and more increased PWV values (9.2±0.9 vs 7.9±1.3 m/sec, p<0.05). Analysis of covariance revealed that hs-CRP, SAA, TNF-a and PWV values remained significantly different between groups after adjustment for confounding factors (p<0.05).
Conclusions: LVH in essential hypertensive subjects is accompanied by pronounced inflammatory activation and impaired arterial compliance. These findings may partially explain the augmented cardiovascular risk associated with LVH in this setting.

P3639 Changes in QTc dispersion during seven years follow-up in hypertensive patients with left ventricular hypertrophy

D. Djordjevic[1], B. Lovic[2], I. Tasic[2], M. Deljanin Ilic[2], S. Ilic[2]. *[1]Institute of Cardiology, Clinical Cardiology, Niska Banja, Serbia and Montenegro; [2]Institute of Cardiology, Clinical Cardiology, Niska Banja, Serbia and Montenegro*

Objective: The aim of this study was to examine changes in QTc dispersion during seven years prospective follow-up in patients with treated arterial hypertension and left ventricular hypertrophy.
Method: We examined 28 patients, 15 male and 13 female, mean age 54.3 ± 6.2 years with essential hypertension. All patients were without regular medical treatment at the beginning of the study. The mean follow-up period was 86 ± 5 months. At the beginning of the study the duration of hypertension was 10.5 ± 8.0 years. At baseline and after seven years regular antyhypertensive treatment in all patients clinical and laboratory examination, electrocardiography and echocardiography were done. Bazett's formula was used to obtain rate corrected value of QT interval (QTc). The QTc dispersion was defined as the difference between maximum and minimum QTc interval.
Results: After seven years of treatment systolic blood pressure decreased significantly from 180.5 ± 26.6 to 161.6 ± 21.5 mmHg (p < 0.001) and diastolic from 106.4 ± 11.5 to 92.3 ± 10.3 mmHg (p < 0.0001). The left ventricular mass reduced from 308.8 ± 68.2 to 302.9 ± 80.4 g (n.s.) and left ventricular mass index increased from 162.1 ± 29.3 to 163.7 ± 35.6 g/m^2 (n.s.). The left ventricular mass index regression was achieved in 15 patients (53.6%). The ejection fraction was changed from 67.6 ± 5.0% to 66.9 ± 4.7% (n.s.). The QTc interval decreased from 415.3 ± 18.9 to 403.4 ± 31.2 ms (p < 0.05) and QTc dispersion decreased significantly from 58.9 ± 19.9 to 48.7 ± 14.7 ms (p < 0.01). The reduction in QTc interval dispersion was found only in patients with left ventricular mass regression (from 67.9 ± 21.0 to 51.7 ± 15.9 ms; p < 0.01). There was no correlation between degree of changes in QTc dispersion and left ventricular mass index in whole group during follow-up (r = 0.356; n.s.). There were no new cardiovascular events during seven years of treatment.
Conclusion: In patients with hypertensive left ventricular hypertrophy seven years antyhypertensive treatment led to significant decreased in QTc interval and QTc dispersion and the reduction in QTc dispersion was associated with left ventricular mass regression.

P3640 Structural and functional cardiac adaptations in essential hypertensive subjects with paroxysmal atrial fibrillation

C. Tsioufis. *Hippokration Hospital, Department of Cardiology, Athens, Greece*

Purpose: The role of arterial hypertension in the pathogenesis of paroxysmal atrial fibrillation (PAF) is well established. This study was conducted in order to investigate the structural and functional characteristics of the hypertensive heart with PAF.
Methods: We studied 46 consecutive essential hypertensive subjects (aged 64 years, 22 men, office blood pressure (BP) 144/86 mmHg) with a history of paroxysmal atrial fibrillation and no other evident comorbidity and 49 consecutive essential hypertensives without any evidence of PAF, matched for age, sex and BP. All included subjects were on sinus rhythm without any history of atherosclerotic or valvular heart disease and underwent a complete conventional and tissue doppler imaging (TDI) echocardiographic study. Left Ventricular(LV) diastolic function was estimated by TDI, averaging diastolic mitral annular velocities measurements (Emav, Amav, Emav/Amav ratio) from four separate sites (basal septal, lateral, anterior, and inferior LV wall).
Results: Hypertensives with PAF compared to those without PAF had increased body mass index (28.1±3 vs 26.9±3kg/m^2, p<0.05), were smokers in a higher percentage (45 vs 31%, p<0.05) and had a longer duration of hypertension (5±1.3 vs 2±0.8 years, p<0.05). Hypertensive subjects with PAF compared to those without PAF did not differ regarding LV mass index but they had significantly increased relative wall thickness (0.46 vs 0.44, p<0.05). In addition, hypertensives with PAF had significantly increased left atrial volume indexed for body surface area (LAV index) (23.63±7.88 vs 19.68±3.7 ml/m^2 p<0.05) and lower Emav (7.5±1.6 vs 8.4±1.4 cm, p<0.05) and Emav/Amav values (0.8±0.11 vs 0.9±0.38 p<0.05).
Conclusions: Hypertensive subjects with PAF have significantly higher LAV index and worse TDI-detected LV diastolic dysfunction. Future prospective studies are needed to clarify the pathophysiological substrate of these interrelationships as well as their prognostic implications.

P3641 Increased mast cell number and activity in the hypertrophied heart

R. Tozzi[1], S. Fallarini[2], G. Palladini[1], C. Gatti[1], G. Busca[3], R. Nano[2], A.U. Ferrari[4], S. Perlini[1]. *[1]University of Pavia, Clinica Medica 2, IRCCS San Matteo, Pavia, Italy; [2]University of Pavia, Dept. Biol. Animale, IGM-CNR, Pavia, Italy; [3]IRCCS Osp. Maggiore, Clin.Med. General, Milano, Italy; [4]Ctr Fisiol Clin e Ipertensione, Dip Medicina, Prev e Biotecnol Sanit, Milan, Monza and Pavia, Italy*

Mast cells (MC) are multifunctional cells that can be found in most fibrovascular tissues of the body and that are involved in several types of inflammation and tissue repair processes via extracellular release of several mediators, such as cytokines, growth factors (TNF-alpha, TGF-beta1), histamine, proteases (chymases and tryptases) and leukotriens. Aim of the present study was to quantify the degree of myocardial infiltration by MC in a model of pressure-overload hypertrophy (POH). Moreover, since chronic sympathectomy (Sx) has been shown to have favourable effects on left ventricular (LV) function and on survival in this setting, the effects of chronic abrogation of the sympathetic activity on MC density were also assessed.
Methods: Abdominal aortic banding (B) or sham operation (S) were performed in 8 week-old Sprague-Dawley rats which were then allocated to Sx (6-hydroxydopamine, 150 mg.kg-1 i.p. twice a week) or vehicle (Vh) treatment for 10 weeks. LV and lung weights (LVw and LUNGw, g) were measured at sacrifice. Collagen fraction (%, Syrius Red) and mast cell density and degranulation (cell/mm^2, toluidine blue technique) were quantitatively assessed by computer-aided analysis in myocardial tissue samples.
Results (means±SD; *p<0.05 B vs. corr. S): POH was associated with marked interstitial fibrosis, lung congestion, as well as with a clearcut increase in activated MC density (+30%). In sympathectomized animals degranulating MC density was significantly increased, independently of the presence of POH. However in these animals, POH was not associated with an increase in degranulating MC density and in myocardial fibrosis.

	LVw	LUNGw	Collagen fraction	Total MC density	Degranulating MC density
SVh (n=9)	0.92±0.07	1.49±0.35	0.64±0.35	2.56±0.79	1.35±0.43
BVh (n=10)	1.24±0.018*	1.76±0.18*	3.15±1.15*	2.92±0.82	1.75±0.64*
SSx (n=10)	0.84±0.10	1.45±0.08	0.93±0.26	2.99±0.88	1.93±0.47
BSx (n=15)	1.12±0.19*	1.59±0.16	0.86±0.49	3.11±0.80	1.94±0.39

Conclusions: Intestitial fibrosis caused by POH is associated with an increased activation of myocardial mast cells. Chronic abrogation of sympathetic nerve activity inhibits pressure-overload related myocardial fibrosis and mast cell activation, indicating a role of adrenergic hyperactivity in mast cell biological activity and extracellular matrix remodeling.

P3642 C-reactive protein, metabolic syndrome and target organ damage in the hypertensive patient: three steps on the same way?

V. Venturelli, S. Sciarretta, A. Ferrucci, G.M. Ciavarella, L. De Biase, M. Volpe. *S.Andrea Hospital - University of Rome, Cardiology Department, Rome, Italy*

Background: C-reactive protein, a marker of systemic low-grade inflammation, is frequently elevated in essential hypertension and predict cardiovascular prognosis independent of conventional risk factors. However the links of this marker with the organ damage and the Metabolic Syndrome (MS), diagnosed by the ATP III criteria, have not yet been clearly studied.
Methods and Results: Albuminuria (24-hours urine collection), high-sensitive C-reactive protein (hs-CRP), 24-hours blood pressure, waist circumference, lipids and fasting glucose were evaluated in 26 never treated Hypertensive Patients (HP); each patient underwent standard echocardiography and Pulsed Tissue Doppler evaluation. Albuminuria > 30 micg/min was defined as MicroAlbuminuria (MA), hs-CRP values above and below median (1,3 mg/l) as high and low ones, MS was diagnosed with at least 2 more criteria added to hypertension, according to ATP III criteria, and Left Ventricular Hypertrophy (LVH) was defined for values above 125 g/m^2 BSA or 51 g/height2.7. Diastolic left ventricular function was evaluated considering both indexes derived from Pulsed Doppler LV inflow

and Tissue Doppler with the sample volume placed at level of lateral mitral annulus. HP were divided into two groups, one of 17 patients with high hs-CRP values and the other of 9 patients with low hs-CRP. The group with high hs-CRP values show an higher prevalence of LVH (43,75% vs 33,10%), impaired LV relaxation (66.6% vs 50.0% for mitral inflow and 33.0% vs 58.8% for Tissue Doppler), MA (25% vs 11,10%), association of LVH and MA (18,75% vs 11,1%) and there is an higher prevalence of MS (58% vs 22,2%).
Conclusions: The evidence of subclinical inflammation in HT is a correlate of metabolic syndrome and of target organ damage and identifies a subgroup of patients with higher cardiovascular risk.

P3643 Efficacy of antihypertensive therapy in postmenopausal hypertensive women

K. Nikogosyan, S.V. Gurgenyan, S.K. Vatinyan. *Institute of Cardiology, Department of Arterial Hypertension, Yerevan, Armenia*

Background: nowadays majority of medical practitioners are interested in problem of arterial hypertension (AH) in women of postmenopausal age, when estrogens and progesterone concentrations are decreased. This situation predicts clinical signs and pathogenesis of AH. The purpose of study was comparison of efficacy of different antihypertensive drugs' combination in patients of postmenopausal age with essential hypertension (EH).
Design and methods: 56 women of postmenopausal age with mild to moderate EH from 50 to 66 years old were investigated. The echocardiography was performed to all of them at baseline and after 4 weeks of treatment. End diastolic diameter (EDD), post wall thickness (PWT), inter-ventricular septum thickness (IVST) and left ventricular mass index (LVMI) were determined. Patients of I group (28 women) received Atenolol up to 100 mg and Indapamide 1,5 mg daily, patients of II group (28 women) – Carvedilol 25mg and Indapamide 1,5 mg daily.
Results: significant hypotensive effect received in both groups at the end of 4-week treatment period was accompanied with significant improvement of echocardiographic parameters: EDD decreased by 4,4% in I group and 5,3% in II group. PWT decreased by 4,0% in I group and 4,7% in II group; IVST decreased by 3,9% in I group and 4,5% in II group and LVMI decreased by 5,8% in I group and 7,2% in II group.
Conclusions: despite the similar hypotensive effect the administration of combined therapy with Carvedilol + Indapamide is preferable than combination of Atenolol + Indapamide, so far vasodilatative effect of Carvedilol predicts decrease of high peripheral vessel resistance and finally caused regression of left ventricular hypertrophy and allow correction of heart remodelling.

P3644 The metabolic syndrome at hypertensive patients with left ventricular hypertrophy, after seven years of investigation

I. Tasic[1], B. Lovic[2], V. Stefanovic[3], D. Djordjevic[2], D. Mijalkovic[2], D. Petrovic[2], M. Deljanin Ilic[2], M. Lovic[2]. *[1]Niska Banja, Serbia and Montenegro; [2]Institute for cardiology, Cardiology, Niska Banja, Serbia and Montenegro; [3]Institute for Nephrology and Hemodialy, Nephrology, Nis, Serbia and Montenegro*

Metabolic syndrome (MS) is one of the numerous risk factors for some patients with cardiovascular diseases.
Aim: 1. to prove the presence of MS at patients with hypertension and left ventricular hypertrophy (LVH) analyzing clinical parameters; 2. to estimate the impact of MS on patient prognosis.
Method: There have been analyzed 73 hypertensive patients (43 male), average age 56.3 $\pm$ 8.5 with echocardiographically proved LVH (average LVMI 163.5 $\pm$ 31.8 g/m^2).
Results: 36 patients (55 $\pm$ 8 years) fulfilled the criterion of MS. They had significantly higher glucose level, lower HDL cholesterol, higher triglycerides and higher body mass index (29.6 $\pm$ 3.8 vs. 27.8 $\pm$ 3, $p<0.03$). LVMI was also higher at those patients but not statistically significant (165.5 $\pm$ 29 vs. 159.9 $\pm$ 34, ns.). This group of patients had more frequent complex VA and significantly lower values of HRV. After 12-month treatment this group of patients had significantly higher glucose level, higher double product at physical exercise test, lower daily SDNN and shorter daily and nightly RR interval than the patients from the group without MS. After 7 years of observation, 12 patients in this group had serious cardiovascular incidents (5 CVI – 3 deaths, 1 sudden death, 2 IM, 3 angina pectoris, 1 severely bilateral stenosis a. carotids), while in the second group 3 patients had serious cardiovascular incidents (1 IM, 1 PTCA with inbuilt stent, 1 angina pectoris) ($p<0.05$). At patients with MS without serious cardiovascular incidents there was noticed an increased glucose level (5.9 vs. 8.1; $p<0.02$), an increased LVMI (150.3 vs. 164.7 g/m^2), an increased left atrium (36.9 vs. 41.1 mm), and mean carotid intima media thickness (IMT) was 1.0 mm. Patients with non-metabolic syndrome had a decreased LVMI (172.1 vs. 163.9 g/m^2), decreased posterior wall thickness (11.7 vs 10.8 mm, $p<0.001$), decreased dispersion QTc intervals (59.4 vs. 49.1; $p<0.09$), increased exercise capacity (METs) 6.6 vs 7.7, $p<0.07$, decreased double products 28 vs 24; $p<0.008$, and mean IMT was 1.05 mm.
Conclusion: Metabolic syndrome at hypertensive patients with LVH is connected with significantly higher activity of sympathetic nervous system (expressed in HRV) and increased risk of cardiovascular disease and progression of left ventricular hypertrophy at hypertensive patients.

P3645 The affect of the regression of the left ventricular hypertrophy of the functional capacity in hypertensive patients

I. Tasic[1], B. Lovic[2], D. Djordjevic[2], D. Petrovic[2], D. Mijalkovic[2], M. Deljanin Ilic[2], S. Ilic[2], M. Lovic[2]. *[1]Niska Banja, Serbia and Montenegro; [2]Institute for cardiology, Cardiology, Niska Banja, Serbia and Montenegro*

The objective of our study was to evaluate the effects of long-term antihypertensive treatment (seven years) in left ventricular hypertrophy (LVH), physical working capacity and arrhythmogenic marcers (QTc interval dispersion).
Methods: 44 hypertensive patients were analyzed (27 male and 17 female) who were an antihypertensive treatment, average age 56.3 $\pm$ 8.5 with echocardiographic LVH (left ventricular mass index: 163 $\pm$ 30.3 g/m^2). Each subject underwent two-dimensional and Doppler echocardiography, 12-lead electrocardiogram examination and exercise stress testing (Bruce - protocol).
Results: Decrease of index LVM (I group – regression LVH) was achieved in 24 pts (55% - 173.9 g/m^2 vs 150 g/m^2; $p< 0.005$), while in 20 pts it was increased (II group – progression LVH) (45% - 150 vs 175.8 g/m^2; $p<0.005$). The reduction was due to a decrease in septal (13.75 $\pm$ 2.34 vs 12.9 $\pm$ 1.9 mm; ns) and posterior wall thickness (11.5 $\pm$ 1.4 vs 10.5 $\pm$ 1.2 mm; $p< 0.03$), without changes in LV diameter. In patients of the I group ratio of the velocity time integrals of żE to żA mitral waves increase (E/A before Th 0.85 $\pm$ 0.14 vs 0.92 $\pm$ 0.25, ns). Patients with reduction of the left ventricular mass could be shown a significant reduction of QT dispersion from 64.9 $\pm$ 21.8 to 51.1 $\pm$ 15.9 ms ($p<0.009$), opposite the patients with progression LVH (49.5 $\pm$ 14.5 vs 45 $\pm$ 12.5; ns). After regression LVH (I group), the functional capacity was significantly increase (6.8 vs 8.2 METs; $p < 0.05$), decrease maximum systolic BP (212.5 vs 176.7 mmHg, $p<0.0008$), decrease peak double products (29.4 vs 21.9, $p<0.001$), decrease Ddouble product (peak minus resting) (16.7 vs 12.4, $p<0.02$) and decrease Ddouble product/METs (2.47 vs 1.52, $p<0.005$) while it remained unchanged in pts of the II group.
Conclusion: LVH regression in our patients was achieved by the decrease of wall thickness of the left ventricle and it is followed by the improvement of the functional capacity and by the reduction of QT dispersion.

P3646 Dynamics of plasma leptin and brain natriuretic peptide level in hypertensive and normotensive patients undergoing primary coronary angioplasty for ST-elevation acute myocardial infartion

T.W. Deptuch[1], A. Witkowski[2], Z.T. Bilinska[2], J. Janas[2], A. Januszewicz[2], W. Ruzyllo[2]. *[1]Warszawa, Poland; [2]Institute of Cardiology, Warsaw, Poland*

Objective: Hypertension (HT) is a common preexisting condition among patients with acute myocardial infarction (AMI). It was recently reported that higher leptin level predicts AMI in HT patients (pts). We investigated the leptin serum level changes within first 48 hours after AMI in HT and normotensive (NT) subset and it's relation to changes of brain natriuretic peptide (BNP) which is known to correlate with mortality after AMI.
Design and Method: 94 pts with ST segment elevation AMI referred to our Institute for primary coronary angioplasty were enrolled. 36 pts had previously diagnosed HT; 58 patients were NT. Since leptin is known to correlate with body mass index, the patients were matched for this factor. Blood samples for leptin and BNP were drawn at baseline and then after 6, 24 and 48 hours. Leptin and BNP values were compared within groups (ANOVA) and between groups (Student test). Correlation between BNP and Leptin values was examined with Spearman test.
Results: Pts in the HT and NT group did not differ in terms of demographics and cardiovascular risk factors, except for diabetes mellitus which was more frequent in HT group (OR 5,6). The results of leptin and BNP levels in HT and NT groups are shown in the table as means (SD). In NT group leptin level peaked after 24 hours and than decreased, but in HT group it was raising up to 48 hours after AMI. In the pooled HT and NT group BNP level at 24 hours correlated significantly with leptin level at any time point (Rs 0.23 – 0.26), however this was not the case in HT group alone.

Results of leptin and BNP plasma level

	Baseline	after 6 hours	after 24 hours	after 48 hours
HT leptin [ng/ml]	11.55 (10.29)	13.54 (12.04)	14.92 (12.90)#	16.38 (17.44)#,@
NT leptin [ng/ml]	9.20 (9.57)	10.30 (9.68)	12.27 (12.98)#	10.31 (7.48)#,@
HT BNP [pg/ml]	54.31 (82.62)	131.56 (202.06)	274.18 (418.34)#	181.07 (209.14)#
NT BNP [pg/ml]	74.61 (154.47)	91.84 (92.09)	173.60 (117.60)#	36.86 (112.64)#

- $p<0.05$ within group vs. baseline value; @ - $p<0.05$ between groups

Conclusions: Leptin level tends to be higher in HT than NT on all occassions and this difference reaches statistical significance 48 hours after AMI. The leptin level changes differ between groups - it peaks at 24 hours in NT group while raises up to 48 hours in HT group. BNP at 24 hours correlates with leptin measured at any of four time points in pooled HT and NT group, but not in HT group alone.

P3647 Coronary reserve impairment anticipates a poor outcome in hypertensive heart disease

C. de Carvalho Frimm[1], V.F.A. Pereira[1], A.C.T. Rodrigues[2], M. Cúri[3]. *[1]University of São Paulo Medical School, LIM - 51, São Paulo, Brazil; [2]University of São Paulo Medical School, Heart Insitute, São Paulo, Brazil; [3]Institute of Mathematics/Statistics, University of São Paulo, São Paulo, Brazil*

The prognostic value of coronary reserve impairment has not been determined in hypertension yet. Hypertensive patients with left ventricular dysfunction may potentially represent a feasible target for this investigation, since advanced cardiac disease is expected to be associated with higher rates of cardiovascular events over a shorter period of follow-up.

Aim: To investigate the prognostic value of coronary reserve in a population with hypertension, including patients with left ventricular systolic dysfunction.

Methods: From June 1996 to August 2001, 68 hypertensive patients aged 52±12 years, 43 men, 32 nonwhite, 45 with left ventricular fractional shortening <30%, were consecutively included and followed-up until September 2003. The primary end-point contemplated was total mortality. Exclusion criteria were diabetes mellitus, creatinine >3.0 mg/dL, chronic angina, history or ECG evidence of myocardial infarction, and Chagas' disease. Obstructive coronary disease was additionally examined with coronary angiography in 48 patients, after informed consent. Left ventricular structure and function were evaluated by means of thransthoracic echocardiography and coronary flow velocity by means of transesophageal Doppler of the anterior descendent coronary artery. Coronary reserve was calculated as the ratio of maximal (adenosine 140 mcg/min, i.v.) to baseline diastolic coronary flow velocity. Myocardial perfusion was further assessed by 99mTc-sestamibi scintigraphy. Kaplan-Meier survival curves and Cox regression model were used to assess clinical markers of mortality.

Results: After a mean follow-up of 3.7±1.2 years (range: 0.8 to 7.3; median: 3.6), seven patients died, six of them from cardiovascular causes (heart failure 1, sudden death 3, stroke 1, myocardial infarction 1). Univariate analysis selected coronary reserve (Wald p=0.01), systolic blood pressure (Wald p=0.04), abnormal scintigraphy (log-rank p=0.03), serum creatinine (Wald p=0.02) and potassium (Wald p=0.02) for being related to mortality. Parameters of left ventricular hypertrophy and of systolic and diastolic function did not predict the outcome. Multivariate analysis identified (hazard ratio; p-value) coronary reserve (0.178; 0.01) and creatinine (5.05; 0.03) as independent predictors of mortality.

Conclusion: Microvascular disease affecting the heart, and possibly the kidneys, predicts the long-term clinical prognosis in hypertensive heart disease.