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[Evidence-Based Review of Stroke Rehabilitation]

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Secondary Prevention of Stroke

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8.2.1 Stroke and TIA as Risk Factors

8.2.1.1 Urgent Assessment and Intervention Post-TIA

Table 8.2.1.1 Urgent Assessment and Management of TIA

Author, Year Country Pedro Score	Methods	Outcomes
Admission to hospital		
Calvet et al. (2007) France No Score	203 consecutive patients, with a diagnosis of possible or probable TIA, were admitted to a stroke unit within 48 hours of symptom onset. Routine assessment included MRI, EKG, prolonged 3-lead cardiac monitoring, standard blood tests, cholesterol, C-reactive protein, hemoglobin A_{1c}, Doppler ultrasound and/or cervical gadolinium-enhanced magnetic resonance angiography and echocardiography. Early risk for stroke was assessed using the ABCD score. Follow-up was conducted by a neurologist at 3 months.	Median interval from TIA onset to first medical management was 180 min – median interval from onset to admission was 12 hours. 100% of patients underwent brain imaging within 48 hrs of TIA onset. Time from symptom onset to initial treatment was ≤6 hrs in 54% of patients. All patients received antithrombotic therapy (either ASA or ASA + clopidogrel), 28% of patients received anticoagulation (including 10 newly identified cases of AF) and 4% underwent specific treatments such as carotid revascularization during admission. Mean admission duration was 6 days (SD=4). Risk of ischemic stroke or TIA was 2.5% (95% CI 0.1-4.6) at 2 days, 5.0% (2.0-8.0) at one week and 9.9% at 90 days (5.6-14.1).
Kehdi et al. (2008) Australia No Score	2535 presentations with TIA to emergency departments within a single healthcare service over a 5-year period were examined for disposition from the ED. Individuals admitted a ward, to critical care or admitted then transferred to another facility were assigned to the "admitted" group for the purposes of analysis (n=1816). Individuals who left at their own risk or were discharged as an outpatient from the ED were considered "discharged" (n=719). TIA or stroke presentations were noted for the periods of 0-28 days and 29 – 365 days following the index TIA event. For individuals treated within a single hospital, $ABCD^2$ scores were calculated retrospectively.	Mean age = 70 (SD 14.1) for the admitted group and 67.9 yrs (SD 15.8) for the discharged group. When admitted, mean length of stay = 6.6 days (SD=6.43). In the first 28 days, there was a greater occurrence of stroke (OR=3.46; 95% CI 1.59, 7.51), recurrent TIA (OR=2.16; 95% CI 1.23, 3.81) and all events (OR=2.54; 95% CI 1.6, 4.01) in the group discharged from the ED compared to the admitted group. However, there were no significant differences in occurrence of events in the 29-365 day follow-up period. In patients who were admitted, 31% of recurrent events happened within the first 28 days vs. 56% of events in those who were discharged. $ABCD^2$ scores were calculated for 383 admitted patients and 102 discharged. There were no between group differences in terms of the proportions of individuals considered to be at low, moderate and high risk in each group. Discharged high risk individuals experienced significantly greater odds for stroke or TIA recurrence than admitted high risk individuals (OR=6.7; 95% CI 2-17.7).
Wu et al. (2009) Canada No Score	189 patients admitted to a rapid evaluation unit following referral from an emergency department March 2002 – April 2003 were compared to a standard care cohort (individuals presenting to an emergency room, and provided with a discharge diagnosis of TIA). A high-risk subgroup was identified within the standard care cohort (defined as individuals who met the admission criteria for the evaluation unit, i.e.	At baseline, patients admitted to the rapid evaluation unit were more frequently male and smokers while there were more individuals with history of congestive heart failure, or dementia in the high-risk standard care group. Based on their initial presentation for TIA, there were more individuals with motor, speech and visual symptoms in the high-risk standard care group. In terms of early management, individuals admitted to the rapid evaluation unit received more MRI and echocardiograms, in addition to MR angiogram and CT angiogram procedures. There were also more likely to

	TIA within 24 hours, a hemispheric event or monocular blindness). Primary study outcome was stroke occurrence following TIA.	receive endarterectomy or angioplasty as well as new (or additional) medications for hypertension or hyperlipidaemia. There were more stroke events in the first 90 days post-TIA in the high-risk standard care cohort vs. those admitted for rapid assessment ($p<0.05$). This may have been associated with the higher rates of carotid procedures received by those in the rapid evaluation unit. Controlling for baseline differences between groups, the major predictor associated with recurrence of TIA was group membership; the rapid evaluation unit was associated with reduced odds for early stroke (OR=0.43, p=0.029 vs. standard care. Costs associated with admission to the rapid evaluation cohort were almost double that of standard care (CDN $8360 vs. $4820, $p<0.001$)
Emergency Department (ED) protocols, observation and/or assessment		
Brown et al. (2007) USA No Score	75 patients in a community ED with TIA received assessment/ intervention following a TIA clinical pathway. TIA tests pre-set according to the pathway included basic lab studies, electrocardiography, CT and CT angiography of the neck. Carotid Doppler ultrasonography, echocardiography, aspirin, aspirin-dipyridamole & clopidogrel were also available in the TIA order set. Patients could also be kept in the ED for a 12 – 24 hour period of observation. Outcomes included adherence to the clinical pathway, use of antithrombotics and vascular imaging and patient safety (defined as 90-day risk for stroke)	Physicians used the clinical pathway for 85.3% of patients. Antithrombotic agents were given to 90.7% and vascular imaging performed for 93.3%. 53.7% of patients were admitted, 25.3% were discharged from the ED, and 21.3% were held for observation in the ED and then discharged. A 90 days, risk for recurrent TIA was 9.3% (95% CI 0.05, 0.18). Risk for stroke was 1.3% (95% CI 0.00, 0.07).
Ross et al. (2007) USA 7 (RCT)	149 emergency department TIA patients (diagnosed by an ER physician) were randomized to receive either TIA-accelerated protocol (n=75) or inpatient admission (control group n=74). Accelerated protocol patients were admitted to the emergency department (ED) observation unit. All pts received antiplatelet therapy in the ED. The protocol consisted of 4 key components: 1) carotid imaging, 2) echocardiography, 3) serial clinical evaluation (every 2 hours for 12 hours, then every 4 hours), 4) for at least 12 hours. Primary outcome = index length of stay. Secondary outcomes = 90-day total costs and clinical outcomes.	Length of stay for most patients was 12 – 24 hours for the accelerated group vs. 48 – 84 hours for the admitted group. Mean length of stay and costs were significantly lower for patients admitted to the accelerated protocol program ($p<0.001$). 15% of patients admitted to the accelerated protocol became inpatients due to events while under ED observation. More ED patients received carotid imaging and echocardiography than inpatients (97% vs 91% & 97% vs. 73% respectively). In both cases, patients received imaging in less time in the accelerated protocol program. Incidence of stroke during 90-days post-discharge was 3.3% for both groups. Total direct costs were significantly lower in the accelerated protocol vs. inpatient group ($p<0.001$).
Stead et al. (2009) USA No Score	Observational study of a 10-bed ED observation unit with an evaluation protocol for TIA that included head CT, electrocardiogram, laboratory tests, carotid Doppler and neurology consult. Patients were followed prospectively for 90 days after the index event in order record subsequent events. 418 patients were evaluated in the	69.6% of patients were admitted to hospital based on the results of their emergency department evaluations; the remainder were discharged from the ED. 4 stroke were recorded within 2 days (0.96%), 5 within 7 days (1.2%), 8 at 30 days (1.9%) and 10 within 90 days (2.4%). There were no significant differences in reported stroke events between individuals who were admitted vs. discharged following ED observation.

	observation unit over a 3-year period.	
Kim et al. (2011) USA No Score	Retrospective examination of patient data from 16 EDs having 24-hour on-call neurology coverage for consultation by telephone or in-person from March 1997 – May 1998. Chart reviews/abstractions were conducted and recorded stroke, TIAs, cardiovascular events and death were collected from available databases. 1707 patients were identified.	28% of identified patients (n=474) received consultations from on-call neurologists; 87% by telephone only. Patients presenting during weekday (non-holiday) hours (8:00 a.m. – 5:00 p.m.), were more likely to see a neurologist in person when compared to "after hours", weekends and holidays (p=0.03). Patients who received a neurology consultation in the ED were significantly more likely to be admitted to hospital (OR=1.36; 95% CI 1.02, 1.81) and were more likely to be discharged on antithrombotic therapy (OR = 1.91; 95% CI 1.22, 2.98), although the use of diagnostic tests (head CT, MRI, carotid ultrasound) was similar for those who did and did not receive a consultation. Cumulative risk for stroke was lower for those individuals who received a neurology consultation (5.3% vs. 7.5% p=0.02). By 90 days, this difference was no longer significant (9.9% vs. 11.0%, p=0.48).
Stead et al. (2011) USA No Score	All consecutive patients reporting to the emergency department of an academic medical centre with possible transient ischemic attack from December 2001 – December 2006 (n=637) were managed via the ED observation unit protocol (see Stead et al. 2009). $ABCD^2$ scores were calculated at presentation. Stroke risk at 7 and 90 days was reported.	15 ischemic strokes occurred in the first 90 days following the index TIA. For low, intermediate and high risk groups, reported rates of stroke were lower than those published for the $ABCD^2$ emergency department cohort at both 7 and 90 days following TIA. At 7 days, the $ABCD^2$ ED cohort rates were 2.0%, 6.0% and 10.9% for low, intermediate and high risk patients. In the present cohort, the corresponding rates of stroke by risk category were 1.1% (95% CI 0.29, 3.78), 0.3% (95% CI 0.05, 1.67) and 2.7% (95% CI 0.92, 7.6).
Torres Macho et al. (2011) Spain No Score	97 patients managed using a diagnostic & therapeutic protocol within a single ED. Study outcomes included presence of ischemic attack (or recurrent TIA) within 90 days. 90-day risk of stroke was compared with the predicted risk based on the $ABCD^2$ score	At 7 days, there were stroke events or recurrent TIAs reported for 9 (9.3%) of patients, but moderate to severe stroke in only 1 individual. At 90 days, there were 5 strokes reported (5.1%) and 23 (23.7%) recurrent TIAs and strokes. Given an average $ABCD^2$ score in the present cohort, and based on the California ED derivation group presented in Johnston et al. (2007), the authors report a lower actual risk for stroke at 7 & 90 days (1% and 5% respectively) compared to predicted risk (6% and 9.9%).
Nahab et al. (2012) USA No Score	Patients evaluated by neurology and admitted from an emergency department (Jan – Nov. 2008; n=57) were compared with those managed via an ED observation unit using a TIA-accelerated diagnostic protocol (ADP) (Nov 2008 – June 2009; n=85). Costs associated with both management processes were evaluated using total direct hospital costs for the index TIA visit. Outcomes included cost, clinical outcomes (TIA/stroke events), and compliance with diagnostic evaluation and secondary prevention measures.	Median LOS for all patients seen using the TIA-ADP was reported to be 20.8 hours shorter than for those seen prior to implementation of the protocol (p<0.01). Median costs were estimated to be lower following ADP implementation by a median of US$1642 (95% CI 1047-2238). Overall stroke rate following ADP was reported to be 1.2% at 90 days. There were no significant differences reported in use of carotid imaging, ECG, diabetes screening, screening & treatment for hypercholesterolemia or antithrombotic therapy before and after the initiation of a TIA-ADP in the ED observation unit.
Expedited/rapid access TIA clinic		
Lavallee et al. SOS-TIA (2007)	From 2003 – 2005, 1085 patients with suspected TIA were admitted to SOS-TIA, a specialized, hospital-based, TIA clinic with 24-	26% of patients were admitted (LOS median = 4 days, IQR = 2 – 7), 74% were discharged home on the day of examination. 59% of patients were diagnosed with definite TIA, 13% had

France No Score	hour access. Assessment (neurological, arterial and cardiac imaging) was performed within 4 hours. Antithrombotic therapy was started in all patients and, where possible, therapy to lower blood pressure and blood lipids was started or modified at time of discharge. Outcomes included risk of stroke at 90 days and risk of stroke, myocardial infarction and vascular death at one year.	possible TIAs and 5% had minor ischaemic strokes. 99% of patients received brain imaging. 98% of patients with definite or possible TIA or minor stroke received antithrombotic medication. 1052 patients were followed for a median of 16 months. Two (2) vascular events occurred within 7 days; 13 strokes within 90 days (2 fatal) and 20 strokes in the first year (2 fatal). In patients with TIA (definite and possible; n=770), there were 13 strokes. Reported 90-day risk of stroke ranged from 0.71% (0.10 – 4.93) in individuals with possible TIA to 4.76% (2.01 – 11.06) in patients with TIA/new lesion. In all patients (n=1052), 90-day risk of stroke was 1.24% (0.72 – 2.12). This was compared to an expected risk (based on the ABCD scores) of 5.96%.
Rothwell et al. EXPRESS (2007) UK No Score	The EXPRESS study was nested within the Oxford Vascular Study) – EXPRESS was a prospective before and after study of a specialized TIA service comparing phase 1 (n=310) to phase 2 (n=281). In phase 1, patients were referred to a TIA and minor stroke clinic (EXPRESS clinic – appointments were scheduled as soon as possible, imaging and ECG were obtained on the same day or shortly thereafter, other imaging (carotid ultrasound) was scheduled for the following week. Results of the initial assessment and recommendations were faxed to the primary care physician, but no treatment was started in the clinic. In phase 2, no appointments were necessary and treatment was initiated immediately upon confirmation of diagnosis. Patients were followed up at 1, 6, 12 and 24 months. Primary study outcome was proportion of patients with recurrent stroke within 90 days.	Of patients referred to the EXPRESS clinic, 23.4% experienced a delay of ≤ 24 hours between first medical attention and assessment in the clinic in phase 1. In phase 2, 59.1% of patients were seen in 24 hours or less ($p<0.0001$). 32/310 (10.3%) phase 1 patients experienced stroke in the first 90 days following presentation vs. 6/281 (2.1%) in phase 2 (Adj HR = 0.20, 95% CI 0.08-0.49, $p=0.0001$). Reduction in risk for recurrent stroke from phase 1 to 2 was present for patients with TIA, with stroke, both sexes, and all ages. Median time to first prescription of treatment was significantly shorter in phase 2 vs. phase 1 (20 days vs. 1 day, $p<0.0001$). At one-month follow-up, all patients in phase 1 and 2 were on an antiplatelet or anticoagulant; however, in phase 2 significantly more patients were on ASA + 30-day course of clopidogrel, a statin, or one or more blood pressure lowering drugs ($p<0.0001$).
Banerjee et al. (2009) UK No Score	Patients attending the nurse-led, anterior circulation, FASTER-TIA clinic from November 2003 – Deember 2006 (n=282). Referrals were made from primary care, emergency depts., in-patient medicine and neurology via telephone or fax. Assessments included "stroke screen" blood tests, 23-lead ECG, head CT, carotid duplex and chest X-ray. Secondary prevention measures included education & antiplatelet medication(s). Patients with symptomatic carotid stenosis of 70-99% were admitted to hospital, as were individuals with a history of recurrent events. Patients were followed in one-week at a neurovascular clinic and then again (at the clinic) in 3 months to assess compliance with advice and history of recurrent events.	Median time from referral to assessment was 3 days and 7 days from event to assessment. Addition of $ABCD^2$ risk stratification has facilitated earlier screening (within 24-hours) of high risk patients. Unfortunately, the data presented in the present study were gathered prior to the change in protocol (although the authors reported that 1/3 of patients were seen within 24 hours). A vascular event was diagnosed in 242 (86%) of patients and a TIA in 133 of these. 81% of patients were started on (or had already been prescribed) medications for the purpose of secondary prevention at the time of the nurse-led clinic visit. A head CT was performed on 278 patients, carotid duplex on 282 and 12-lead ECG on 282.
Luengo-	*See the previous trial description provided for*	Use of the Phase 2 clinic was associated with reduction in

Fernandez et al. EXPRESS (2009) UK No Score	*Rothwell et al. 2007.* Further analyses were conducted to examine the impact of phase 2 on hospital admissions (within 90 days), hospital bed days, hospital costs and new disability at 6 months (progression from no pre-event disability) or death vs. phase 1 of the study.	number recurrent fatal strokes (p=0.027), number of disabling strokes (p=0.007) and number of fatal or disabling strokes overall (p=0.0005) vs. phase 1. Participation in phase 2 was found to be protective for progression to disability or death (OR=0.51, 95% CI 0.30, 0.85, p=0.022). 18% of patients in both groups were admitted to hospital during the 90-day follow-up period. There were no significant differences in reasons for admission between groups with the exception of recurrent stroke. 8% of patients in phase 1 were admitted with recurrent stroke vs. 2% in phase 2 (OR = 0.21, 95% CI 0.88, -0.55, p=0.001). In addition, phase 2 patients used significantly fewer bed days (p=0.02) with a mean reduction of 4 bed-days per patient. This difference was attributable to days in hospital due to recurrent stroke. Hospital costs were significantly reduced in phase 2 (p=0.03) due to substantial cost reductions associated with fewer recurrent strokes.
Wasserman et al. (2010) Canada No Score	Identified and followed patients diagnosed with TIA (following presentation at 1 or 2 EDs) and referred to a stroke prevention clinic (between Jan 2007 and April 2009). Emergency protocols included blood work, electrocardiogram and head CT. Outpatient assessments that included lipid levels, carotid Dopplers and Holter monitoring were scheduled. Patients referred to the stroke clinic were triaged according to risk stratification based on the $ABCD^2$ score derived during their ED visit. High, moderate and low risk patients were scheduled to see a neurologist ≤7 days, 7-14 days and >14 days, respectively. All outpatient assessments were obtained prior to their clinic visit. Primary study outcome was stroke at 90 days.	1,091 patients were diagnosed with TIA in the ED; 1002 were referred to the Stroke Clinic. 982 patients were included in this study. 90% of patients with TIA were prescribed an antiplatelet agent prior to discharge. Mean time from ED visit to completion of outpatient assessments ranged from 12.5 (SD 14.1) days for carotid doppler to 30.7 (SD 18.2) for Holter monitor. Stroke risk at 90 days was reported to be 3.2% ($ABCD^2$ predicted rate = 9.1%). For low risk individuals, the actual 90 stroke rate was 0.9 (95% CI 0, 1.98) vs. the $ABCD^2$ predicted rate of 3.1%, for moderate risk 3.8% (95% CI; 2.1, 5.58) vs. 9.8% and for high risk 5.2% (95% CI; 2.07, 8.35).
Horer et al. (2011) Germany No Score	123 patients with suspected TIA referred to an outpatient TIA clinic. Median time from symptom onset to clinic presentation = 48 hours. Median duration of symptoms = 30 minutes (range: 10 sec – 24 hours). Assessments included $ABCD^2$ scores, medical history, neurological exam, MRI (DWI), angiography, CT, echocardiography, sonography, screening for PFO, ancle-brachial index, routine blood tests (lipids and glucose). Patients with ABCD2 scores ≥4 and TIA within 72 hours OR symptomatic high-grade extra or intracranial stenosis OR newly detected atrial fibrillation OR recurrent TIA were admitted to the hospital stroke unit.	TIA was diagnosed in 48% of patients referred to the outpatient clinic (minor stroke in 8.1%). MRI was performed in 78% of TIA patients. 82 patients were assigned to a low-risk group based on $ABCD^2$ scores of 0-3; 25 patients were considered to be at intermediate risk and 6 patients were high risk. Based on $ABCD^2$ scores, 90-day predicted risk of stroke = 5.7%. There were no strokes recorded within 2 weeks of clinic presentation. At 3-month telephone follow-up, 2 stroke were recorded (3-month stroke rate = 2.9% in the group of patients with TIA or minor stroke).
Von Weitzel-Mudersbach et al. (2011) Denmark	306 patients referred to an acute TIA team in which in and outpatient care was integrated. 65% of patients were admitted following the index TIA event (median length of stay =1	Time from the index TIA event to assessment by the acute TIA team was ≤24 hours for 58.5% of patients. 70.3% of patients were seen within 24 hours of the referral to the acute team. There were no strokes recorded within 7 days of referral to

No Score	day); 35% were seen as outpatients only. Patients received a diagnostic work-up that included, CT/MRI, ECG, blood work, duplex sonography (extra and intracranial), ankle-brachial index and completion of $ABCD^2$. Treatment included initiation of a program of secondary prevention, including antiplatelet, antihypertensive and cholesterol-lowering therapies in addition to counselling regarding lifestyle changes, health diet and exercise. Follow-up was conducted via telephone at 7 days, and 90 days. A clinical assessment was completed at 1 year. Primary study outcome was combined stroke, MI or death from vascular causes at 1 year.	the acute TIA team. Mean $ABCD^2$ score was 3.6 – 56.9% of patients received an $ABCD^2$ score ≥4. Based on the ABCD2 scores, expected stroke risks was 4.5% at 7 days and 7.5% at 90 days. Actual cumulated risk of stroke was 1.6% after 7 days and 2.0% at 90 days. Cumulated risk of stroke at 1 year was 4.2% while risk for mortality was 2.9%. $ABCD^2$ at baseline was significantly associated with risk for the primary study outcome (RR=12.2, 95% CI 1.6, 94.8) as well as for stroke recurrence at 1 year (RR=9.8 95% CI 1.3, 76.3).

8.2.1.1.1 Pre-Hospital Delay in Pursuit of Care

Table 8.2.1.1.1 Pre-hospital Access to Specialized Care

Author, Year Country Pedro Score	Methods	Outcomes
Kerr et al. (2010) UK No Score	A telephone hotline service providing 24/7 access to a consulting stroke specialist re: diagnosis, investigation emergency treatment and management post TIA/stroke was made available to all GPs. Practice audits of the regional TIA/stroke clinic were conducted for the period from Jan. 2005 – Sept. 2009. The hotline service was introduced in May 2007. Additional data was gathered for a 3-month period including perception of value of the telephone call to patients, consultant activity during the call and management plans agreed upon during consulting calls. Electronic hospital records were also accessed to determine use of secondary healthcare services.	Introduction of the hotline was associated with an increase in numbers of patients accessing the TIA/stroke clinic (by approximately 4 per week; 63 vs. 81 patients per month before and after the hotline began). Delays from the TIA or stroke event to clinic assessment and carotid surgery were significantly reduced (median 58 days to 21.5 days, $p<0.01$). Commencement of secondary prevention measures (e.g. antiplatelet, anticoagulants and statins) were not adversely affected by the initiation of the hotline. Overall, the proportion of individuals prescribed a statin increased following implementation of the hotline (40% to 60%; $p<0.01$). Additional data collected for a 3-month period demonstrated that most calls originated from GPs (81%) and that management plans agreed to during these calls were adhered to in 88% of all cases. Patients referred to the clinic via the hotline represented approximately 80% of all cases seen in the clinic during that 3 month period. Of these patients, 67% were seen by a specialist, in clinic, within 24 hours (94% were seen within 96 hours of the hotline call).
Kim et al. (2012) USA No Score	Feasibility study that identified individuals searching for information on TIA/stroke symptoms online, and evaluated the performance of a self-reported risk score to identify subjects with true TIA or stroke. English-speaking adults who responded to an online advertisement completed an online questionnaire and were telephoned	Over 122 days, 251 (1%) of 25, 292 website visitors completed the online questionnaire and 175 were contacted by telephone for follow-up (mean age 58.5 years; 63% women). 37 (21%) had symptoms within 24 hours and 68 (39%) had TIA/stroke. A modified ABCD2 score was applied and yielded a c-statistic of 0.66, but 2 of 12 with a zero score had a TIA/stroke. Those with new symptoms were more likely to have TIA/stroke (OR 4.90, 95% CI 2.56-

	by a vascular neurologist to assess the likelihood of TIA/stroke.	9.09). A simple self-reported risk score was unable to identify a low-risk population in this selected group.

8.2.1.2 Prediction of Risk for Recurrent Stroke Following TIA

Table 8.2.1.2 Validation of the ABCD^2 Clinical Risk Scores

Author, Year Country	Description and Result	Results
Coutts et al. (2008) Canada	180 patients were enrolled in the study including 87 patients with TIA. Patients received a follow-up neurological assessment at 24 hours, 30 days and 90 days post presentation to the emergency department. Multimodal MRI was performed within 24 hours of symptom onset.	For the prediction of stroke, 8 factors were found to be significant – the 5 clinical factors included on the ABCD^2 and 3 factors from diffusion weighted imaging (DWI lesion status, presence of mismatch and intracranial vessel occlusion). AUC for the ABCD^2 was 0.78 – this increased to 0.88 when presence of lesion and evidence of intracranial vessel occlusion were added to the ABCD^2. While use of DWI may add supplementary information to the clinical risk score, the individual components of risk scores (i.e. age, duration of symptoms, hypertension and diabetes mellitus) do not appear to be associated with positive DWI (Purroy et al. 2009).
Asimos et al. (2010) USA	1,667 nonconsecutive patients admitted over a 35-month period to one of 16 hospitals with TIA within 24 hours of presentation and having no history of previous stroke). ABCD^2 scores were calculated on first assessment and risk dichotomized as scores ≤3 = low risk and >3 = moderate/high risk. Study outcome = stroke within 7 days as determined by patient chart review. Stroke events were classified as disabling vs. non-disabling (Modified Rankin scores >2 vs. ≤2).	A recorded diagnosis of ischemic stroke was identified within 7 days of TIA in 23% of enrolled patients (n=373). 91% of these occurred within 2 days of the index event. 18% were designated as disabling. AUC for the prediction of stroke within 7 days was 0.59 and 0.71 for the prediction of disabling strokes. For low risk patients, there was a reported negative likelihood ratio of 0.54 (95% CI 0.39-0.74) and 0.16 (95% CI 0.04-0.06) for ischemic stroke and disabling stroke only within 7 days of TIA.
Chandratheva et al. (2010) UK	500 patients with TIA identified as part of the OXVASC population-based study. ABCD^2 scores were calculated prospectively. All patients received face-to-face follow-up at 30 days post TIA.	Of the 500 patients, 11% had recurrent TIA and 10% had recurrent stroke within 7 days of the index event. AUC = 0.71 for prediction of 7-day risk ($p<0.001$). However, when stratified for severity of stroke, AUC for major stroke was 0.80 and for minor stroke was 0.57. ABCD^2 scores were inversely related to the risk for recurrent TIA and when the outcomes of TIA and stroke were combined, overall predictive value for any recurrent event was 0.54. For individuals with ABCD^2 scores ≥5, 7-day risk was 18.7%. This was significantly different than the 4.6% risk in patients with scores <5 ($p<0.001$).
Nguyen et al. (2010) Australia	ABCD^2, ABCD and California scores were calculated retrospectively from chart review (n=326) of patients with emergency department discharge diagnosis of TIA. Telephone follow-up was conducted. Study outcome of interest was new stroke occurrence within 2, 7 and 30 days of the initial diagnosis.	Rate of recurrent stroke was 3.1% at 2 days, 4.3% at 7 days and 5.2% at 30 days. ROC analysis revealed AUC = 0.69 at 2 and 7 days and 0.73 at 30 days post TIA. Using a cut-off score of <4 to define low risk, sensitivity of the ABCD^2 was 94.1%, and specificity was 29.1%. Performance of the ABCD^2 was similar to the ABCD and California scores.

Sheehan et al. (2010) Ireland	As part of the North Dublin Population Stroke Study, 700 non-specialist referrals for suspected TIA were seen at a 5-day minor stroke/TIA clinic. Carotid imaging was performed usually on the day of clinic assessment. Follow-up assessments were conducted 2, 7, 28 and 90 days following event onset. Low, intermediate and high-risk were defined as $ABCD^2$ scores of 0-3, 4-5 and 6-7, respectively.	In patients with specialist confirmed TIA (n=443) and recurrent stroke, low $ABCD^2$ scores were reported for 33% of patients with stroke at 7 days, 29.2% with stroke at 28 days and 24.2% of patients with stroke at 90 days. On ROC analysis within this group, the AUC was 0.46 for 7-day stroke, 0.55 for 28-day stroke and 0.55 for 90-day stroke. There was a trend toward higher 90-day stroke risk associated with higher risk categories (score ≥4) on the $ABCD^2$ (p= 0.07). In the group referred by non-specialist physicians (n=700) that included 257 cases given a non-CVD diagnosis, AUC = 0.56 for 7-day stroke, 0.61 for 28-day stroke and 0.61 for 90-day stroke. Greater 90-day risk was seen in those with intermediate to high risk (classified using the $ABCD^2$ score) than those in the low risk group (p=0.056).
Tsivgoulis et al. (2010) Singapore	Calculated an $ABCD^2$ score for 148 TIA patients in 3 tertiary care neurology departments following presentation at emergency services. All hospitalized patients received a CT and the ABCDI score (Sciolla et al. 2008) was also calculated. All TIA patients were followed up 3 months post symptom onset.	Increasing $ABCD^2$ scores were associated with a significant and linear increase in risk for stroke for both 7-day and 90-day risk (p=0.007 and p<0.0001, respectively). On ROC analysis, AUC was 0.72 for 7-day risk and 0.75 for 90-day risk of recurrent stroke. ABCDI results were similar. When a score of 3 was used to dichotomize risk (i.e. 0-3 = low risk & 4-7 = intermediate/high risk), sensitivity = 88% and specificity = 55%. 90-day risk for stroke was 7-times higher in patients with $ABCD^2$>3, than patients with scores ≤3.
Perry et al. (2011) Canada	Enrolled 2056 patients receiving a diagnosis of TIA/minor stroke from 8 participating emergency departments. $ABCD^2$ scores were derived for each patient by a physician, a trained research nurse and where possible, a second, independent physician. Patients with $ABCD^2$ scores >5 were categorized as "high risk". Patients were contacted by telephone at 7 and 30 days post index event to confirm absence of outcomes (TIA or stroke). Primary study outcome was stroke within 7 days of the index visit to the emergency department.	Initially, patients with $ABCD^2$ scores >5 received more intensive care at the time of the index visit to the emergency department. They were more likely to have a CT (p=0.01), receive a consultation with a neurologist (p=0.001) and/or be admitted to hospital (p=0.001). Using the cut-off point of >5, sensitivity and specificity of the $ABCD^2$ as a predictor of stroke was 31.6 and 86.9 at 7 days and 29.2 and 79.7 at 90 days. Using the cut-off point of >4 resulted in sensitivity and specificity of 65.8 and 57.2 at 7 days and 63.1 and 57.4 at 90 days, respectively. Based on the scores derived by the research nurse, AUC = 0.65 at 7 days (0.56 for treating physician) and 0.65 at 90 days (0.6 for treating physician). Physician scores tended to be lower than those derived by the research nurse (ICC=0.76) – the most common physician error was failure to score unilateral weakness if it was reported in the history but had resolved prior to the physical examination. Agreement between treating physician and independent physician scores was adequate (n=39; ICC=0.61).
Walker et al. (2012) UK	Study included 843 patients referred to a rapid access TIA clinic and for whom ABCD2 scores and carotid duplex ultrasound studies were available. Association between ABCD2 scores (0-3 and 4-7) and presence of ≥50% stenosis or carotid occlusion was examined.	12.9% of patients had significant carotid artery disease overall. In patients with $ABCD^2$ scores 0-3, 14.7% had ≥50% stenosis. The prevalence of significant stenosis was 11.8% in individuals with $ABCD^2$ scores of 4-7. There was no significant difference in scores derived by stroke physicians vs. family or emergency physicians. ABCD2 scores were not predictive of the presence of significant

		carotid stenosis (AUC = 0.50 for family or emergency physicians and 0.51 for stroke physicians). There was no association demonstrated between ABCD^2 score and severity of stenosis.
Sandset et al. (2014) Germany Observational No Score TPS_{mean}=NA $TPS_{control}$=NA TPS_{exper}=NA N_{Start}=3014 N_{End}=3014	**Population:** Mean age= 67.3±8.3yr; Gender: Males= 1857, Females=1157. **Intervention:** Patients with previous stroke or transient ischemic attack (TIA) randomized to a previous RCT (The Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial) were selected for further analysis. Participant's heart rate was assessed from electrocardiogram recordings obtained at baseline. **Outcomes:** Heart rate; body mass index (BMI); age; gender; race; systolic blood pressure (SBP); Fasting glucose; total cholesterol; diabetes before randomization; smoker; left ventricular hypertrophy; atrial fibrillation; treatment with diuretics; treatment with beta blockers; valsartan treatment.	Descriptive Statistics: 1. Diabetes mellitus and heart rate at baseline were significantly associated with an increased risk of recurrent stroke in both the univariate (p=0.01; p=0.03) and multivariate (p=0.02, p=0.03) analyses. 2. There was no other significant association found regarding any of the other outcome measures/predictors.

8.2.2 Risk Factor Management

8.2.2.1 Programs for Risk Management Following Stroke

Table 8.2.2.1 Risk Management Programs in Secondary Prevention

Author, Year Country Pedro Score	Methods	Outcomes
Allen et al. (2002) USA 6 (RCT)	96 stroke or TIA patients were randomized to receive either a post-discharge program of care management including management of risk factors (n=47) or usual post-discharge care(n=46). Intervention included telephone contact 3 – 7 days post-discharge, a biopsychosocial assessment by a nurse care manager within 1 month, and development of a personalized care plan (by an interdisciplinary team). The care plan was provided to the primary care physician to implement with support from the nurse manager. Outcomes assessed at 3 months post-discharge included management of risk (an average of adequacy of blood pressure control, depressive symptomatology, number of falls and medication appropriateness) and stroke knowledge.	Complete data was available for 73 patients at 3 months. Management of risk and knowledge of stroke were both significantly better in intervention vs. control group participants (ES = 0.63 95% CI 0.27,0.99 and 0.98 95%CI 0.59,1.4, respectively).
Ovbiagele et al. (2004) PROTECT USA No Score	130 patients were enrolled in the PROTECT-target (ischemic stroke or TIA via large vessel atherosclerosis or small vessel disease) or PROTECT-ACS (patients with ischemic stroke or TIA via other underlying mechanisms – e.g. cardioembolism,	At discharge, adherence rates to medication goals were 100% for both antithrombotics and statins, 94% for ACE/ARBs & 93% for thiazide diuretics. At 3 months rates were 100% for antithrombotics, 91% for statins, 84% for ACE/ARB and 64% for diuretics. Rates

	dissection, etc). The PROTECT program (Preventing Recurrence of Thromboembolic Events through Coordinated Treatment) set both medication (initiation of anti-thrombotic, statin, ACE or ARB and thiazide diuretic therapies) and behavioural modification (diet, exercise, smoking cessation and risk factor/signs of stroke education) for each patient. Maintenance of program goals was examined at a clinic visit 3 months post-discharge.	of adherence for behavioural modifications ranged from 70% (exercise) to 97% (smoking cessation), although awareness ranged from 92% (exercise) to 100% (smoking cessation). At 3 months, 88% of patients/caregivers were aware of the need to call 911 in the event of stroke-like symptoms, 70% were aware of warning signs for stroke and 83% were aware of personal risk factors for recurrent stroke. One-year follow-up data has been published for 128 patients. Medication treatment rates were 98% for antithrombotics, 99% for statins, 89% for ACE/ARBs and 82% or thiazide diuretics. Adherence to behavioural modification goals were 94% for smoking cessation, 68% for diet & 53% for exercise (Ovbiagele et al. 2005).
Ellis et al. (2005) UK 7 (RCT)	205 stroke patients were recruited from a TIA clinic or geriatric day hospital and allocated to receive either usual care (n=105) or intervention (n=100) conditions. Usual care included generic risk factor information and advice from medical staff and a stroke nurse specialist in an outpatient setting. Participants assigned to the treatment condition received additional support, individualized information and advice regarding behavioural change and medication compliance from the nurse specialist who saw them once per month over a three month period. Outcomes were assessed at 5 months. The primary outcome was percentage of patients whose modifiable risk factors were considered to be within the recommended range.	There was no significant between group difference for systolic BP, when adjusted for baseline levels (p=0.126). In addition, there were no significant differences for diastolic BP, smoking, cholesterol levels, random blood glucose and HbA1c. There were no significant between group differences for HRQOL (assessed with the EuroQol) or depression (Geriatric Depression Scale). A follow-up study (McManus et al. 2009) that included 105 members of the original study (49 had been allocated to receive the intervention) demonstrated no significant between-group differences in control of risk factors (p=0.53). Mean follow-up = 3.6 years. Additionally, there were no significant differences in perceived health status, satisfaction with care, or depressive symptomatology.
Goessens et al. (2006) Netherlands VENUS 7 (RCT)	236 individuals with history of TIA, stroke, aortic abdominal aneurysm or peripheral artery disease and 2 or more modifiable risk factors were randomly assigned to intervention vs. control (usual care) groups. Of those randomized, informed consent was obtained for 95 patients assigned to intervention and 80 in the control group. Participants in the intervention were invited to attend a risk factor management clinic where a nurse practitioner & patients set realistic goals and developed personalised action plans for lifestyle changes. Treatment goals were based on current, international guidelines for management of vascular risk factors. After the first visit, patients were seen by the nurse practitioner according to individual need who provided ongoing encouragement and support. Control group participants received usual care provided by their GP and the treating vascular specialist. Follow-up evaluations were conducted at 6 months and 1 year post-randomization. Primary study outcome was change in risk factors and medication usage.	There were a mean of 4 visits per patient (range 1-15) during the follow-up period. There were greater mean reductions in total cholesterol and systolic blood pressure in the intervention vs. the control group; however, these did not reach significance. Participation in the intervention was associated with an increased risk for achieving treatment goals for systolic blood pressure (OR=2.7, 95% CI 1.3=5.4), total cholesterol (OR=3.3, 1.5-7.3), LDL-cholesterol (OR=3.5, 1.5-8.6), and BMI (OR 4.0, 1.2-13.1) when compared to usual care. Both groups used more medications at follow-up than at baseline. The prevalence of smoking was greater at 1 year in both groups than at baseline.

Chiu et al. (2008) Taiwan 4 (RCT)	160 stroke patients who were regular attendees at hospital outpatient clinics were randomly assigned to receive either a pharmacist led intervention for risk factor management (n=80) or usual care (n=80). Pharmacists provided monthly 1-hour education programs to discuss drug effects, lifestyle modification, treatment goals, benefits of therapies, importance of compliance, drug interactions and adverse effects. The intervention continued for a period of 6 months. Outcomes were evaluated at baseline at post-intervention. Study outcomes included blood pressure, lipid levels and fasting blood glucose.	At the end of the intervention period, greater reductions in blood pressure were reported in the intervention group, but not for controls (p<0.001). In the intervention group, 39.7% demonstrated adequate BP control at baseline. This increased to 83.3% by the end of the study (p<0.001). At study end, 43.4% of control patients demonstrated adequate control of hypertension. Comparisons of total cholesterol and LDL levels suggest that greater reductions were experienced by individuals in the intervention vs. control group (p<0.001). Adequate lipid levels were noted in 12.5% of patients at baseline, and in 39.6% of patients at study end (p<0.01), whereas there was no significant change within the control group over time. There were no between group differences reported for fasting blood glucose. Both groups showed modest increases in control of blood glucose levels over time.
Rahiman et al. (2008) PROTECT USA No Score	224 stroke patients in a hospital using the PROTECT program were compared with 98 stroke patients in a non-PROTECT facility (control group). Outcomes were assessed at 3 months post discharge and included adherence rates and vascular event frequency (stroke, TIA or MI). Data from 78 patients in the PROTECT program and 65 patients in the control hospital were available for analysis.	The PROTECT group was younger, had less atrial fibrillation and more smokers. At discharge, patients in the PROTECT program were more likely to be on a statin (p<0.0001), but no more likely to be on either antithrombotic or antihypertensive medication than controls. At follow-up, pts from the PROTECT program were more likely to be taking statins (p=0.01) and antihypertensive medications (p<0.02). On adjusted analysis, the PROTECT program was associated with fewer vascular events than the control condition (p=0.036); however, when each event type was examined the only significant difference was for myocardial infarction (p=0.03). Note: analysis of individual event types was unadjusted.
Joubert et al. (2009) Australia No Score	186 patients, returned to their GPs for ongoing care management, were assigned to receive either integrated care (IC, n=91) or usual care (n=86) over a period of 12 months. Integrated care patients received in-hospital initiation of risk management practices including prescription of appropriate medications, education and promotion of lifestyle changes. Further management post discharge was provided via shared care through GPs. Visits were pre-arranged for 2 weeks, 3 months, 6 months, 9 months and 1 year. GPs received information detailing the shared care process, patient discharge summaries, and a patient risk factor management flow chart. Patients were contacted prior to each GP visit for a semi-structured interview regarding current status, problems and lifestyle. Following the visit, they were contacted to review changes/advice received from the GP. GPs were contacted if best practice was not met consistently. All patients (both	At 12 months, patients receiving IC were more successful than usual care patients in reducing systolic blood pressure (p=0.04, adjusted for age, sex and disability at baseline). 75% of the IC group met target SBP (<140mgHg) vs. 58% of usual care patients (p=0.015). In addition, IC patients were more successful in reducing BMI and increasing physical activity (vs. control; p=0.007, p<0.001, respectively). Although more individuals in the IC group were able to meet total cholesterol targets (64% vs. 55%), the between group difference for change was not significant. Similarly, more patients with AF were taking warfarin in the IC group vs. control (83% vs, 65%), but this difference was not significant. There were no between-group differences noted for smoking or alcohol consumption. More IC patients recalled receiving advice/information than usual care patients for the following topics: blood pressure management, cholesterol management, alcohol

	groups) were evaluated at 12 months. Primary outcome was blood pressure. Secondary outcomes included cholesterol levels, atrial fibrillation, smoking, alcohol intake, weight and physical activity (taking deliberate exercise walks).	intake, physical activity, blood glucose/diabetes, signs & symptoms of TIA, what to do in case of TIA and regular blood tests.
Schwamm et al. (2009) GWTG-stroke USA No Score	The Get-With-The-Guidelines (GWTG) program was a national quality of care improvement initiative involving 790 hospitals and 322, 847 patients over 5 years. GTWG components included organizational stakeholder and opinion leader meetings, hospital recruitment, collaborative workshops for hospital teams, tool kits and hospital recognition. Primary study outcomes included seven, predefined, quality performance measures and one safety measure. These included 4 discharge measures specific to secondary prevention; antithrombotic medication, anticoagulation for atrial fibrillation (AF), cholesterol treatment if LDL>100mg/dL or LDL not documented, and counselling and/or medication for smoking cessation.	Significant improvements were reported for all 7 individual performance measures from baseline to 5-year follow-up (p<0.0001). Use of discharge antithrombotics increased from 95.68% to 96.88%, anticoagulation for AF from 95.03% to 98.39%, lipid-lowering from 73.63% to 88.29% and smoking cessation interventions from 65.21% to 93.61%. Improvements were not equally distributed among all participating hospitals. The greatest rates of improvement were seen in larger hospitals with more bed capacity, institutions with the highest annual stroke discharge rates and hospitals identified as teaching facilities. Further analysis has demonstrated that women were significantly less likely than men to receive the discharge interventions targeted by the GWTG-stroke initiative. This was true for all age groups (Reeves et al. 2009)
Ireland et al. (2010) Canada No Score	A convenience sample of 20 patients was recruited for a 6-month intervention that included an initial consultation with a physician and nurse case manager (NCM) and a minimum of 6 (once per month) follow-up telephone calls from a nurse case manager to provide ongoing counseling and support for risk factor management and adherence to prevention strategies in addition to regular visits to the secondary prevention clinic. Motivational interviewing techniques and self-managed care approaches were implemented in discussions with participants. Primary study outcome was the potential feasibility of the care management model (based on hours spent in providing counseling and consultation). Secondary outcomes included blood pressure, medication self-efficacy and medication adherence.	The NCM spent an average of 4.8 hours with each participant over the 6-month period. Overall, the program required approximately 4 hours per week in calls and visits. There was a significant reduction reported in mean systolic (p<0.001) and diastolic (p=0.004) blood pressure over the 6-month period. There was significant improvement in self-reported medication adherence (p=0.003). Adherence rates reported by community pharmacists suggested that the majority of participants exceeded 80% adherence, although prescription renewals for statin and antihypertensive medications did not demonstrate significant improvements in adherence over time.
Johnston et al. (2010) USA 6 (RCT)	12 hospitals were randomly assigned to either continue usual discharge care following stroke or develop & implement standardized discharge orders. Standardized orders incorporated 3 specific interventions; 1) statin prescription, 2) antihypertensive medications for hypertensive individuals and 3) warfarin for individuals with atrial fibrillation and no contraindication for warfarin use. Hospitals randomized to the intervention received support to implement the orders, as championed by 2 onsite physicians. Educational presentations were provided at each site. Primary outcome was optimal secondary prevention treatment at 6	Comparison of intervention to non-intervention hospitals revealed no significant difference in the composite outcome of improved secondary prevention treatment (OR = 1.39, 95% CI 0.71-2.76, p=0.27). When each component of optimal treatment was examined individually, there was a non-significant improvement favouring the intervention hospitals: statin use OR = 1.26 (95% CI 0.7-2.30, p=0.36), control of hypertension OR =1.18 (95%CI 0.77-1.79, p=0.37l warfarin use OR = 1.79 (95% CI 0.63-5.06, p=0.21). When outcomes were examined at the patient level within intervention and control hospitals, rates of optimal treatment increased from 37% to 45.3%

	months (i.e. compliance on all eligible measures – filled statin prescription covering 6 months post discharge, achievement of controlled blood pressure assess 4 – 8 months post discharge and documentation of filled warfarin prescription or INR results 6 months post discharge). Primary results were analysed at the hospital level.	(p<0.001) in intervention hospitals, but only from 38.6% to 40.2% in non-intervention hospitals (p=0.27). Improvements were attributed to use of statins (OR=1.29, p=0.02) and better control of blood pressure (OR=1.27, p=0.03).
Wolfe et al. (2010) UK 7 (RCT)	136 general practices were allocated to either treatment or control groups – from these practices 523 individuals with stroke were identified. In the intervention, an individually-tailored prevention program (keeping well plan) based on personal risk profiles was produced for all patients and their caregivers (n=274), while participants in the control condition received usual care (n=249). In addition, the GPs of individuals in the intervention condition received a risk profile, personalized prevention plan and relevant UK guidelines for each patient. Primary study outcome was management of key modifiable risk factors for stroke at follow-up (1 years and 18 months post stroke). Primary study endpoints were treatment of hypertension for those diagnosed with hypertension at baseline, treatment with antiplatelet therapy for those with ischemic stroke at baseline and smoking cessation.	Participation in the intervention was not associated improved chance of appropriate risk factor management. ARR for treatment of hypertension was -3.7% (95% CI -13% to 5.6%), 2.25% for treatment with antiplatelets (95% CI -11.97 to 7.59) and -0.58 (95% CI -14.52 to 13.46) for smoking cessation. In addition, participation in the intervention was not associated with improved risk factor management in terms of treatment with statins, hypoglycemic, anticoagulants, appropriate levels of alcohol consumption. Analysis of the primary outcomes adjusted for age, sex, occupation, ethnicity and stroke severity revealed an insignificant trend in favour of the control group.
Brotons et al. (2011) Spain PREseAP Study 6 (RCT)	1224 patients in 42 health centres received either routine care (n=600) or care at a specialized secondary prevention clinic (n=624) following diagnosis of existing cardiovascular disease (including previous stroke; n=414). Patients assigned to health centres providing the specialized clinics received information about their specific condition, counselling regarding lifestyle changes, individually tailored interventions and supervision of treatment in addition to routine care. Visits were scheduled once every 4 months. Individuals assigned to usual care were evaluated at the beginning and end of the study period only. Total study period = 2 years, 9 months. The primary study endpoint = combined mortality and hospital readmissions for cardiovascular reasons. Secondary outcomes included HRQOL, anxiety and depression.	There were no significant between-group differences in terms of mortality or hospital admission, number of individuals with well-controlled blood pressure, chronic renal failure or glycemic level, although there were somewhat fewer smokers and possibly greater reductions in abdominal circumference in the intervention condition (p=0.07). Individuals assigned to care in the specialized secondary prevention clinic experienced less anxiety and depression at the end of the study period than those in the usual care condition (0=0.05 and 0.02, respectively). Examination of treatments indicated greater use of anti-depressant and anti-anxiety medications in the intervention group compared to the control group. There were no significant differences in HRQOL assessed via the SF-36.
Bushnell et al. (2011) USA AVAIL No Score	1-year follow-up of 2,457 patients discharged from 106 hospitals participating in the Get With the Guidelines (GWTG)-Stroke program. Participants were surveyed at 3 and 12 months post-discharge to determine medication usage. Proxy respondents were used if patients could not provide data due to illness, speech/language deficits or death. Persistence (continuation of all secondary prevention medications prescribed at discharge) and adherence (continuation of prescribed	65.6% of participants reported persistence with prescribed medication regimens. Persistence was greatest for antihypertensive medications (87.9%), followed by antiplatelets (87.1%), diabetes (82.3%), lipid-lowering drugs (77.6%) and warfarin (68.2%). On multiple regression, persistence was significantly associated with fewer medications prescribed, attending inpatient rehabilitation, household income adequate to one's needs, MRS score ≤3, history of hypertension, less than college education, older age,

	medications except those terminated by a healthcare provider) were assessed by comparing hospital discharge medications with current medications reported by the patient or proxy.	history of dyslipidemia, appointments with GP, being seen by a neurologist and being seen in a non-academic hospital. 86.6% of participants were classified as adherent. Adherence ranged from 94.8% for antiplatelets to 90.7% for lipid-lowering drugs. On regression, better adherence was associated with fewer drugs prescribed, adequate income, MRS ≤3, appointments with GP, use of pillbox for medications, having insurance, receiving medical instructions, being married and being discharged home. Healthcare provider discontinuation was the most common reason for non-persistence.
Menard et al. (2011) USA No Score	358 individuals with stroke were recruited from an acute care hospital, enrolled in a stroke prevention program and followed for a period of one year. Secondary prevention interventions were all initiated during the acute care stay and focused on hypertension, dyslipidemia, diabetes, cardiac disease, atrial fibrillation, peripheral artery disease, carotid stenosis, obesity, sleep apnea and behavioural risk factors such as smoking alcohol consumption , physical inactivity and poor diet. All patients received both verbal bedside education and written materials regarding stroke etiology, signs and symptoms, and personal risk factors. Upon discharge telephone contact was maintained (calls at 2 and 6 weeks, 3 months and 1 year) to collect clinical information and provide information and support. Primary care physicians were informed of the program and patients were encouraged to visit them at 6 weeks, 3 months and 1 year for ongoing management. All patients were invited to return to a neurology clinic at 6 months post stroke. In addition, participants received mailings periodically that contained a personalized risk factor packet, program timetable, a "health hints" newsletter, prompts to return for follow-up, invitations to the neurology clinic, program satisfaction survey. Live educational sessions were also available on a monthly basis.	80% of participants had experienced stroke as the index event; the remainder were diagnosed with TIA. The majority of patients reported existing hypertension (77.5%) and hyperlipidemia (70.1%). By 6 weeks, there were significant ($p<0.05$) increases in the number of individuals taking antihypertensive, antiplatelet and lipid lower medications; these changes were maintained through the 1-year follow-up assessment. At baseline 74.6% of participants were non-smokers. At one year, this had increased to 85.5%. By 6 weeks, there were significant decreases in the average systolic and diastolic blood pressure readings, as well as improvements in glucose and both HDL and LDL cholesterol. Although these improvements remain significant (when compared to baseline) at 1 year, gains appeared to be lost over time (from 3 months to one year). The observed rate of recurrent stroke over one year was 5.6%. Based on a survey of the literature, the authors suggest that the anticipated rate for stroke recurrence could be 9% (95% CI 7, 11).
Nornnes et al. 2011 Denmark 9 (RCT)	349 patients with stroke or TIA were randomly assigned to receive either usual care (n=177) or 4 home visits by a nurse (n=172). In addition to usual care (advice from the multidisciplinary stroke unit team regarding healthy lifestyle), those assigned to the intervention group received home visits during which the nurse assessed blood pressure, provided feedback and information regarding blood pressure and medications, and individually-tailored counselling with regard to lifestyle changes. Primary outcome was change in BP from baseline to 1-year follow-up. Medication compliance was	There was no difference between groups in change of BP from baseline for either systolic or diastolic pressures. At follow-up, the mean SBP (p=ns) and DBP were both lower in the intervention than in the control group (p=0.007); however, this could be accounted for by a significant increase in DBP in the control group. On linear regression, blood pressure at baseline and age were significant predictors of blood pressure at one-year follow-up.

	explored by interview. Patients were considered compliant if they had taken approximately 80% of prescribed doses during the previous 2 weeks.	
Ogedegbe et al. (2012) USA 6 (RCT)	256 African-American individuals (11% of whom had history of stroke) were randomly assigned to receive either a "culturally tailored educational workbook" about hypertension, self-management and goal-setting or the same workbook + a positive affect intervention. The positive affect intervention consisted of: 1) an additional chapter in the workbook addressing the benefits of "positive moments" relative to medication adherence 2) during phone calls, participants were asked to identify small things that invoked positive feelings and instructed to use these positive feelings in their daily routine 3) participants received unexpected, small gifts in the mail just prior to each phone call and 4) participants were directed to focus on core values and moments in which they felt pride and to recall these whenever they felt they were in a situation that made adherence to medications difficult. Both groups received phone calls from the research team every other month over the period of 1 year (6 calls). Primary study outcome was mean medication adherence at 12 months (assessed using electronic pill monitors).	87% of all randomized patients completed the study. Two-thirds of all study participants reported non-adherences. 96% of patients in the positive affirmation arm of the study reported using the techniques provided. On intention to treat analysis, medication adherence at 12 months was higher in the positive affirmation group than in the workbook only group (42% vs. 36%, p=0.049). NNT for adherence = 16. However, individuals in both conditions did not experience statistically significant reductions in either systolic or diastolic blood pressure.
Hohmann et al. (2013) Germany Prospective No Score TPS=NA N_{Start}=310 N_{End}=281	**Population:** Intervention group (N=155): Mean age: 72.3±11.1yr; Gender: Males=86, Females=69. Control group (N=155): Mean age=70.7±12.0yr; Gender: Males=83, Females=72. **Intervention:** Patients with transient ischemic attacks (TIA) or ischemic stroke were prospectively recruited and allocated to either the intervention group or the control group. In the control group, a discharge letter is given to the patient to inform the primary care physician of main diagnosis, diagnostic findings, lab tests, complications and current medication. Upon discharge, the neurologist included the medication list in the discharge letter as before. In the intervention group, the clinical pharmacist listed the medication at admission and at discharge in the discharge letter and provided detailed information regarding the changes during the hospital stay. The primary care physician was followed-up at 3mo to evaluate adherence to medication in the discharge letter. **Outcomes**: Adherence to medication.	Descriptive Statistics: 1. Adherence to discharge regimen after 3mo was significantly higher in the intervention group compared to the control group (90.9% versus 83.3%; p=0.01). 2. Significant differences between the control group and the intervention group were found with respect to adherence to both antithrombotic drugs (83% in control group versus 91.9% in intervention group; p=0.033) and to statin therapy (69.8% in control group versus 87.7% in intervention group; p<0.001).
Kamel et al. (2013) USA RCT PEDro=3	**Population:** Cardiac Monitoring device group (N=20): Mean age= 65±15yr; Gender: Males=8, Females=12. No monitoring group (N=20): Mean age=69±9yr; Gender: Males=9, Females=11. **Intervention:** Patients with cryptogenic ischemic	Descriptive Statistics: 1. No serious event occurred that was attributable to the monitoring intervention since no patient in either study received a diagnosis of arterial fibrillation or stoke related diagnosis.

TPS=NA N_{Start}=40 N_{End}=40	stroke or high-risk transient ischemic attack were randomized to the intervention group and received a Cardionet mobile cardiac outpatient telemetry monitor for 21d, or to the control group and received routine follow-up alone. Participants were assessed at 3mo and at 1yr follow-up. **Outcomes:** Occurrence of adverse cardiac events according to monitoring device; Recurrent stroke or transient ischemic attack; New diagnosis of atrial fibrillation (AF) within 3mo and 1yr.	2. The current study lacked power and thus failed to examine clinical outcomes.
Dregan et al. (2014) UK RCT PEDro=5 TPS=NA N_{Start}=106 N_{End}=104	**Population:** Intervention group (N practices=53, N participants=5875): Mean age: 72.9±14.1yr; Gender: Males= 2997, Females= 2878. Control group (N practices=51, N participants=5516): Mean age= 72.2±1.9yr; Gender: Males= 2904, Females= 2612. **Intervention:** Family practices were allocated in equal proportions to 2 trial arms. Practices randomized to the intervention group involved using electronic decision support tools (i.e. the DXS Point-of-Care system) to record stroke-related events. In the control arm, patients of the corresponding practices were send letters and reminded to record all adverse events and stroke-related consultations. The intervention was carried out for 12mo. Participants from each study group were assessed at 15mo after the intervention start date. **Primary Outcomes:** Last measure of systolic blood pressure (BP); Diastolic BP, total cholesterol, and prescribing of antihypertensive, cholesterol-lowering, and antiplatelet drugs.	Descriptive Statistics: 1. The systolic BP did not differ between the two groups during the intervention period. The adjusted mean difference in BP between the two groups was –0.56 (-1.38 to 0.26 mmHg; p=0.183). 2. There was also no difference in the total cholesterol values between the 2 groups. The adjusted mean difference in the values between the two groups was -0.02 (-0.06 to 0.01; p=0.194). 3. There was also no difference between the two groups with respect to the number of classes of antihypertensive drugs prescribed. There was no evidence of a trend in outcomes according to the level of intervention utilization.
Estol et al. (2014) Argentina Observational No Score TPS=NA N_{Start}=23332 N_{End}=20332	**Population:** Hispanic group (N=990); Mean age= 67.0±9.4yr; Gender: Males=61.1%, Females= 38.9%. Asian group (N=6660); Mean age=64.8±8.3yr; Gender: Males=65.6%, Females= 34.4%. Euro/Caucasian group (N= 1697); Mean age= 67.0±8.6yr; Gender: Males= 64.1%, Females= 35.9%. Black African group (N=816); Mean age= 64.4±8.6yr; Gender: Male=52%, Females= 48%. **Intervention:** Data was analyzed from patients included in the Prevention Regimen for Effectively Avoiding Secondary Strokes (PRoFESS) trial. This study investigated the correlation between blood pressure values and the different racial-ethnic groups, and the recurrence rate of hemorrhagic and ischemic events. All patients were grouped based on their ethnicity: European-Caucasian, Black African, Caribbean Hispanic, Native Latin, South Asian, Chinese, Japanese, Malays, Other Asian, Arab, Persian, and other.	Descriptive statistics: 1. A significant difference was found among ethnicities for MI and symptomatic intracerebral hemorrhage (p=0.0004, and p=0.006). MI was more frequent among European-Caucasians and Black African groups, while the symptomatic intracerebral hemorrhage was more frequent among Latin Hispanics and Asians. 2. Out of the 3 BP groups analyzed (<135, 135-150, >150 mmHg), the <135 mmHg group appeared to have a lower stroke hemorrhage incidence compared with the other two groups (Pr>chi-square 0.0014 for ischemic stroke, and Pr>chi-square 0.002 for hemorrhage) in Asians. 3. For the Asian group, there was a 28% greater risk of ischemic stroke with a BP>150 mmHg and a 14% greater stroke risk with BP between 135-150 mmHg.

	Outcomes: Number of vascular events; Blood pressure (BP).	
Jonsson et al. (2014) Sweden RCT PEDro=4 TPS=NA N_{Start}=549 N_{End}=391	**Population:** Intervention group (N=194): Mean age=74.3yr; Gender: Males=116, Females=116. Control group (N=197): Mean age= 74.3yr; Gender: Males= 114, Females= 113. **Intervention:** Patients (one month after stroke survivors) were randomized either to the intervention group and were followed up by a specialist nurse (SN) after 3mo, or to the control group and received standard care. All patients were followed-up at 1yr after stroke. **Outcomes:** Health status one year after stroke; Blood Pressure (BP); EuroQol-5.	Descriptive statistics: 1. From baseline to 1yr follow-up, the intervention group demonstrated significant improvement in the EQ-5D subscales pertaining to mobility (p=0.001), self-care (p=0.001) usual activities (p=0.001), and anxiety/depression (p<0.001). 2. The control group only improved from baseline to 1yr follow-up on the anxiety/depression 5Q-5D subscale (p=0.04). 3. The intervention group demonstrated a negative trend in the systolic BP from 3 months (N=142) to 1yr (N=38) (p=0.05), driven by a significantly higher proportion of participants (46% vs. 53%) showing a decrease in systolic BP of ≤139 (p=0.001). Similarly, the diastolic BP also significantly decreased from 3 months (N=81) to 1yr (N=80) in the intervention group (p=0.03). 4. The control group showed no significant difference in systolic BP from baseline to 1yr follow-up, only a decreasing trend in the proportion of participants with systolic BP of 156-209 (p=0.05). 5. In the control group, 75% of patients had health problems that were referred to a physician compared to 62% in the intervention group at 1yr follow-up (p=0.009). The number of health problems referred for further follow-up was significantly lower in the intervention group compared to the control group (p=0.02).
Kronish et al. (2014) USA RCT PEDro=8 TPS=NA N_{Start}=600 N_{End}=600	**Population:** Intervention group (N=301): Mean age= 63±11yr; Gender: Males=40%, Females= 60%. Control group (N=299): Mean age= 64±11yr; Gender: Males= 41%, Females=59%. **Intervention:** Participants with previous transient ischemic attacks from low-income communities were randomized to either an intervention group and received a 6wk (1 session/wk), peer-led, community-based, stroke prevention self-management group workshop, or to the control group which were waitlisted for the workshop. All participants were assessed at baseline and at 6mo. **Outcomes:** Blood pressure (BP); low-density lipoprotein cholesterol (LDL); use of antithrombotic medications at 6 months.	Descriptive statistics: 1. There was no difference in the proportion of intervention and control participants who at 6mo had attained all 3 stroke prevention measures. 2. There was also no difference in the proportion of intervention and control participants who at 6mo had controlled LDL cholesterol or who took an antithrombotic medication. A higher proportion of participants randomized to the intervention had controlled blood pressure at 6mo compared to the control group (p=0.02).
McAlister et al. (2014) Canada RCT PEDro=8 TPS=NA	**Population:** Experimental group (EG; N=143): Mean age= 68.6±11.1yr; Gender: Males= 87, Females= 56. Control group (N=136): Mean age= 66.3±11.3yr; Gender: Males= 75, Females= 61. **Intervention:** Patients were randomized and allocated to the active prescribing pharmacist-led	Descriptive statistics: 1. Significantly more participants in the pharmacist-led group (43.4%) met both the systolic blood pressure and LDL goals by 6 months, compared to the control group (30.9%) (p=0.03). 2. Significantly higher proportions of participants in

N_{Start}=279 N_{End} =279	case manager group (intervention) or to the screening and delegating to primary care physicians nurse-led case management group (control). The intervention lasted 6mo, during which the participants were followed-up with on a monthly basis. **Outcomes:** Mortality; self-reported adherence; body mass index (BMI); smoking status.	the pharmacist-led management program met their LDL cholesterol targets (51.1%) compared to those in the nurse-led group (33.8%) (p=0.003). There were no significant differences in any other outcome measures between the 2 groups.
McAlister et al. (2014) Canada Secondary analysis on RCT No Score TPS=NA N_{Start}=275 N_{End}=275/164	**Population:** Pharmacist-led group (N=139): Mean age= 68.9±11.1yr; Gender: Males=84, Females=55. Nurse-led group (N=136): Mean age= 66.3±11.3yr; Gender: Males=75, Females=59. **Intervention:** Patients with recent stroke/TIA who received usual care were randomized to additional monthly visits with either nurse case managers (who counseled patients, monitored risk factors, and communicated results to primary care physicians) or pharmacist care managers (who were able to prescribe independently according to treatment algorithms). Patients were assessed at baseline, after the 6mo (trial conclusion), and at 12mo (6mo after the last visit). **Outcomes:** Cardiovascular Disease Life Expectancy Model (CDLEM); Framingham Risk Score (FRS).	Descriptive statistics: 1. In both groups of participants there was a similar decline in the CDLEM and FRS scores that differed significantly from baseline (at 6 months) to 12mo (p<0.001). 2. There was no statistical difference between the groups at 6 or 12mo. 3. Out of 275 participants, 111 did not complete all 6 visits at follow-up. Those who attended all visits (N=164) with the pharmacist exhibited larger reductions in FRS and CDLEM than those who attended less pharmacy visits (1-5 visits) (p=0.01 for both). This effect was not observed in the nurse-led group.
Fukuoka et al. (2015) Japan RCT PEDro=3 TPS=NA N_{Start}=321 N_{End} =321	**Population:** Intervention group (DMP; N=156): Mean age= 61.7±7.6yr; Gender: Males=106, Females=50. Control group (CG; N=165): Mean age= 67.5±9.3yr; Gender: Males=119, Females= 46. **Intervention:** Patients were randomized to either the intervention group and received disease management programs (DMPs) aimed at preventing the recurrence of ischemic stroke, or to the control group which received usual outpatient care. After the completion of the 6mo program, the participants were followed-up for 24mo for stroke recurrence. Outcomes were assessed every 3mo. **Outcomes:** Responses to self-efficacy; quality of life; depression scales; blood pressure; body weight; blood tests.	There was no statistical difference between the two groups with respect to any of the outcomes.

8.3 Hypertension

8.3.2 Treatment of Hypertension

Table 8.3.2 Comparative Studies Evaluating Relative Efficacy of Anti-Hypertensive therapy and Stroke Risk

Author, Year Country Pedro Score	*Methods*	Outcomes
SHEP Cooperative	4,736 persons with systolic blood pressures	The average 5-year systolic blood pressures were

Research Group (1991) USA 8 (RCT)	from 160-219 mmHg were randomized to receive active drug treatment or placebo. Patients were followed monthly until goal blood pressure or maximum level of stepped care was reached. Primary study end point was stroke.	155 and 143 mmHg for the placebo and treatment groups, respectively. The incidence of nonfatal and fatal stroke was 5.2/100 for those receiving active treatment and 8.2/100 for those on placebo. The relative risk, based on proportional hazards regression analysis was 0.64 (95% CI 0.50-0.82, p=0.0003).
Systolic Hypertension in Europe (Syst-Eur) Trial Investigators (1997) International 8 (RCT)	4,695 patients with primary systolic hypertension were randomized to receive either nitrendipine (a calcium-channel blocker) 10 – 40 mg/day with the possible addition of enalapril 5 – 20 mg/day and hydrocholorothiazide 12.5 mg – 25 mg/day (n=2,398) or matching placebos (n=2,297).	Patients were followed for a median of 2 years. Antihypertensive drug treatment starting with nitrendipine reduced the total rate of stroke by 42%. Sitting SBP & DBP were reduced by 23 mmHg & 7 mmHg in the treatment group as opposed to 13mmHg & 2 mmHg in the placebo group.
Hypertension Optimal Treatment (HOT) Trial (1998) International 7 (RCT)	A total of 18,790 patients, aged 50 – 80 years with hypertension and systolic blood pressure between 100 & 115 mmHg were randomly allocated to 1 of 3 target groups based on DBP; $\leq$ 90 mmHg (n=6,264), $\leq$ 85 mmHg (n=6,264) and $\leq$ 80 mmHg (n=6,262). Each target group included 1.2% of patients with previous stroke. All patients received a 5-step treatment regimen beginning with felodipine 5 mg/day followed by the addition of ACE inhibitors or β-blockers, increased felodipine, increased ACE-inhibitors or β-blockers and, lastly, an optional diuretic. Additional steps were applied as deemed necessary to achieve the targeted diastolic blood pressure. All patients were then randomized to receive 75 mg of ASA/day (n=9,399) or matching placebo (n=9,391).	Lowest risk of cardiovascular events occurred at a mean achieved diastolic blood pressure of 82.6 mmHg; for stroke, the lowest risk was achieved below 80 mmHg. Average DBP reductions were 20.3, 22.3 & 24.3 mmHg in the 3 target groups. There was no difference between target groups in number of stroke events (p=0.74). In patients with pre-existing ischaemic heart disease, stroke events declined between groups such that the lowest targeted blood pressure was associated with the fewest stroke events (p=0.046). The addition of ASA to the treatment regimen had no effect on the number of stroke events compared to placebo (p=0.88).
UK Prospective Diabetes Study (1998) UK 6 (RCT)	A total of 1,148 hypertensive patients with Type II diabetes (mean age = 56 years) were randomized to tight control vs. less tight control of blood pressure groups. Tight control patients received either captopril 25 – 50 mg twice daily (n=400) or atenolol 50 – 100 mg/day (n=358) to achieve a blood pressure of <150/<85 mmHg. Less tight control patients (n=390) were treated to achieve a blood pressure of <180/<105 without the use of an ACE-inhibitor or β-blocker.	Patients were followed for up to 9 years. Patients allocated to receive captopril or atenolol had similarly reduced blood pressures (14/8 mmHg change vs. 14/7 mmHg). For patients receiving neither drug, mean change was 16/7 mmHg over nine years. Comparing captopril to atenolol, there were fewer strokes among patients receiving atenolol, but this was not significant (RR=1.12, p=0.74). Both agents appeared equally effective in lowering blood pressure in patients with Type II diabetes.
CAPPP Study Group (1999) Sweden, Finland 7 (RCT)	Patients aged 25 – 66 with 2 or more measurements of DBP in excess of 100 mmHg (n=10,985) were randomized to receive either captopril 50 mg/day (n=5,492) or conventional therapy consisting of β-blockers and/or diuretics (n=5,493).	Mean follow-up of 6.1 years. There was no reported difference in the primary combined outcome of fatal & nonfatal MI, stroke and other cardiovascular deaths between the two treatment groups (RR=1.05; p=0.52). However, strokes, fatal & nonfatal, were more common in the captopril treatment group when compared to the

		conventional therapy group (RR=1.25, p=0.044).
Syst-Eur Investigators (1999) Finland, Belgium 8(RCT)	4,695 patients (aged ≥ 60 and having systolic hypertension) were randomized to receive either active treatment with nitrendipine 10 – 40 mg/day with the possible addition of enalapril or hydrochlorothiazide or both (n=252 diabetic & 2,146 non-diabetic patients) or matching placebo (n=240 diabetic & 2,057 non-diabetic patients). Patients with diabetes were included if blood glucose concentrations were controlled.	After 2 years, systolic & diastolic blood pressures in the treatment and active placebo groups differed by 8.6 mmHg & 3.9 mmHg among diabetic patients and 10.3 & 4.5 mmHg among non-diabetic patients. Active treatment was found to reduce the rate of fatal and nonfatal stroke by 73% among diabetic patients and 38% among non-diabetic patients. Reduction in overall mortality, mortality from cardiovascular disease and all cardiovascular events was greater among diabetic patients than among the non-diabetic patients (p=0.04, 0.02 & 0.01).
HOPE Study Investigators (2000) International 8 (RCT)	Population studied was diabetic stroke patients. 1,808 patients received 10 mg Ramipril and 400 IU vitamin E, while 1,769 received a placebo daily.	The study stopped 6 months early because of the consistent benefit of Ramipril compared to placebo. Ramipril lowered risk of combined primary outcome by 25% (p=.0004), myocardial infarction by 22%, stroke by 33%, cardiovascular death by 37%, total mortality by 24%, revascularization by 17%, and overt nephropathy by 24%.
NORDIL Study Group (2000) Sweden, Norway 7 (RCT)	10,881 patients, aged 50 – 69, with previously untreated hypertension (DBP >100mmHg) were randomly assigned to receive treatment regime based on diltiazam (n=5,410) or therapy including β-blockers and/or diuretics (n=5,471). All patients could receive additional treatment in several prescribed steps including the addition of an ACE inhibitor or α-blocker and diuretic to lower diastolic blood pressure to <90mmHg. Patients with previous stroke or TIA were included in the study group.	Mean follow-up was 4.5 years. In that time, fewer strokes occurred among patients receiving the diltiazam-based treatment (p=0.04; RR=0.80). This difference continued to be significant with the addition of TIA events (RR=0.86, p=0.07), but not for fatal stroke events alone (RR=0.96, p=0.89). More episodes of congestive heart failure and cardiovascular deaths were recorded among the patients receiving diltiazam, but this trend was not significant (p=0.42 & 0.41, respectively).
ALLHAT Collaborative Research Group (2000) USA/Canada 9 (RCT)	24,335 patients over the age of 55 with hypertension and at least one other coronary heart disease risk factor were randomly allocated to receive either a diuretic, chlorthalidone 12.5 mg – 25 mg/day (n=15,268), or an α-adrenergic blocker, doxazosin 2 mg – 8 mg/day (n=9,067) for 4 – 8 years.	Median follow-up was 3.3 years. Patients receiving doxazosin had a higher risk of stroke (RR=1.19, p=0.04) and combined CVD (RR=1.25, p<0.001) than patients receiving chlorthalidone.
PROGRESS Collaborative Group (2001) International 8 (RCT)	Population studied was hypertensive and non-hypertensive patients with a history of stroke or TIA within the past 5 years. A total of 6105 patients were studied. 3501 received active treatment flexible regimen based on ACE inhibitor perindopril (4mg daily) with addition of diuretic indapamide at discretion of the treating physicians while 3054 received a placebo.	After a mean follow-up time of 4 years, more patients in the placebo condition were disabled (BI ≤ 99/100) than in the treatment condition (OR=0.76; p<0.001) and a higher percentage of patients in the placebo group were dependent, i.e., required daily assistance (OR=0.84; p=0.04).
ALLHAT Collaborative	33,357 hypertensive patients over the age of	Mean follow-up was 4.9 years. When comparing

Research Group (2002) USA/Canada 9 (RCT)	55 with at least one coronary heart disease (CHD) risk factor were randomly allocated to receive either chlorthalidone (diuretic) 12.5 – 25 mg/day, amlodipine (calcium-channel blocker) 2.5 – 10 mg/day or lisinopril (ACE-inhibitor) 10 – 40 mg/day.	the calcium-channel blocker to the diuretic group, there was no significant difference in primary outcome (fatal CHD or non-fatal MI) or in secondary outcomes including stroke. Five-year systolic blood pressures were higher in the groups receiving amlodipine and lisinopril when compared to the group receiving the diuretic (p=0.03 and p<0.001, respectively). A comparison of results following treatment with the ACE-inhibitor versus the diuretic revealed no significant difference in primary outcome. However, the group treated with the ACE-inhibitor has a higher risk for stroke (p=0.02), combined CVD (p<0.001), heart failure (p<0.001) and hospitalized/treated angina (p=0.01).
LIFE study (2002) Sweden/ International 8 (RCT)	Patients with essential hypertension and left ventricular hypertrophy were randomized to receive either a losartan-based (n=4,605) or atenolol-based (n=4,588) antihypertensive regimen for 4 years until 1,040 patients suffered a major cardiovascular event (death, MI or stroke)	Losartan prevented more cardiovascular events and deaths than atenolol, (508 vs. 588 primary events, p=0.21) for similar reductions in blood pressure.
CONVINCE (2003) International 10 (RCT)	16,602 patients with hypertension and at least one other established risk factor (including previous stroke) were randomly assigned to receive either controlled-onset extended release (COER) verapamil (n=8,241) or active control (atenolol or hydrochlorothiazide (HCTZ; n=8,361). Pre-selection of possible active control condition was performed prior to randomization. Patients received 180 mg of COER-verapamil + matching placebo OR one of either 50 mg atenolol or 12.5 mg HCTZ + matching placebo. Other drugs could be added, in a prescribed sequence, to achieve blood pressure targets. Primary outcomes were first occurrence of stroke, MI or cardiovascular death.	Mean follow up was 3 years. By the end of the trial, 39.4% of the intervention and 39.7% of the active control group had stopped taking the blinded study medication. Participants in the COER verapamil condition discontinued treatment more often than those in the control group for reasons associated with adverse reactions (p=0.02). However, fewer individuals in the treatment condition discontinued treatment due to poor blood pressure control than in the active control group (p<0.001). Blood pressure was reduced significantly within both conditions. For the primary composite outcome, there was no significant between group difference in risk HR=1.02 (95% CI 0.88-1.18, p=0.77). For fatal or non-fatal stroke alone HR=1.15 (95% CO 0.90-1.48, p=0.26). Based on *a priori* limits for the upper boundary of the CI for the primary outcome (1.16) to determine equivalence, COER-verapamil was found not equivalent to atenolol and HCTZ.
ACCESS Study Group (2003) Germany 7 (RCT)	342 stroke patients (mean age 68.3 treatment & 67.8 placebo group) were randomized to receive either 4 mg/day candesartan cilexetil (n=175) or a placebo (n=167) on day one post-stroke. On day 2, dosages in the treatment group were increased targeting a blood pressure reduction of 10 – 15% in 24 hours. After 7 days, patients exhibiting a hypertensive profile were given either more candesartan	Follow-up examinations were undertaken at 3, 6 and 12 months. At outset, during the first 7 days (placebo-controlled phase) and throughout the subsequent 12 months, there was no significant difference in blood pressure between the two groups. However, the number of deaths and the number of vascular events were fewer in the group that had received candesartan cilexetil in the first 7 days post-stroke (p=0.07 & p=0.026, OR=0.475). There were 13 cerebrovascular events

	or an additional hypertensive drug. Members of the placebo group exhibiting hypertension were given candesartan targeted to lower blood pressure to <140/90 beginning on day 7 following admission.	in the treatment group vs. 19 in the placebo group.
Second Australian National Blood Pressure Study (2003) Australia 7 (RCT)	Patients with average SBP of ≥ 160 mmHg or average DBP of ≥90 mmHg, aged 65 – 84 and having no CVD events within the past 6 months were included. Patients were randomly allocated to receive either an ACE-inhibitor (n=3,044), or diuretic (n=3,039). Each patient's family practitioner was responsible for determining the specific agent and dosage used in order to meet the treatment goal of blood pressure reduction by at least 20mmHg systolic & 10 mmHg diastolic.	Blood pressure reduction was the same in both groups (26/12mmHg) after 5 years. There were fewer cardiovascular events or deaths in the ACE-inhibitor treatment group (hazard ratio = 0.89; p=0.05). However, when comparing male to female patients, the hazard ratio was only significant among male patients. There were a similar number of nonfatal strokes in both groups (hazard ratio = 0.93, p=0.65); however, there were significantly more fatal strokes among patients in the ACE-inhibitor treatment condition than the diuretic condition (hazard ratio = 1.91, p=0.04).
VALUE trial group (2004) International 9 (RCT)	15,245 patients over the age of 50 with hypertension (treated or untreated) and at risk for cardiovascular events due to presence of cardiovascular risk factors or disease. Patients were randomized to receive a valsartan-based or amlodipine-based treatment regimen. HCTZ and/or other hypertension drugs could be added to either regimen in a prescribed manner in steps 3, 4 or 5 of the treatment regimens.	Mean follow-up duration was 4.2 years. Reductions in blood pressure were reported in both treatment groups, but blood pressure lowering effects were more pronounced in patients receiving treatment with amlodipine (p<0.001), particularly during early phases of treatment. Primary endpoints included first cardiac events while stroke (fatal & nonfatal) were among secondary study outcomes. In the valsartan condition, there were 322 strokes (fatal and nonfatal) while in the amlodipine condition, there were 281 strokes (hazard ratio = 1.15; p<0.08) representing a trend in favour of the amlodipine treatment regimen.
SCOPE study group (2004) International 8 (RCT)	1,518 elderly patients between the ages of 70 and 89 with isolated systolic hypertension (ISO) were randomized to receive either 8 mg candesartan (n=754) or matching placebo tablet (n=764) once daily. At study entry, hypertension treatment was standardized to 12.5 mg hydrochlorothiazide daily. Patients in either group who had SBP >160, a decrease in SBP <10%, or DBP >85 mmHg could have additional antihypertensive treatments added starting with the standardized treatment – other medications could be added as necessary with the exception of Angiotensin Receptor Blockers or ACE inhibitors.	Blood pressure was reduced significantly in both groups (p<0.001). The average difference in blood pressure decline between groups was 2.0 mmHg for SBP (p=0.64) and 1.2 mmHg for DBP (p=0.64) in favour of the treatment group. Risk of first stroke either fatal or non-fatal was reduced by 42% in the treatment group (p=0.05). This reduction became significant when the greater proportion of higher risk subjects in the treatment was taken into account (p=0.049). The absolute risk reduction was 1.9 per 100 patients, 53 patients would need to receive treatment with candesartan based therapy rather than control therapy to prevent one stroke.
PROGRESS Collaborative Group (Arima et al. 2005; Chapman et al. 2004; PROGRESS Collaborative	Population studied were hypertensive and non-hypertensive patients with a history of stroke or transient ischaemic attack. A total of 6,105 patients were studied. 3,501 received active treatment flexible regimen	During a mean 3.9 years of follow-up – active treatment reduced blood pressure by 9/4 mmHg. Of the active treatment patients, 10% suffered stroke compared to 14% of placebo (28% risk reduction, p<.0001). Active treatment also

Group 2001) International 8 (RCT)	based on ACE inhibitor perindopril (4mg daily) with addition of diuretic indapamide at discretion of the treating physicians while 3,054 received a placebo.	reduced risk of total major vascular events. With treatment, relative risk reduction for ischaemic stroke was 24% and 50% for intracerebral haemorrhage. Relative risk of any stroke was reduced by 26% in patients with a baseline history of ischaemic stroke and 49% in patients whose history included an intracerebral haemorrhage. Treatment effects were not modified by antiplatelet or antihypertensive therapy, AF, residual neurological signs, or time since historical cerebrovascular event. Additional analysis revealed that blood pressure reduction benefits were seen across all age groups for both men and women and for Asian and Western subjects, although blood pressure differences were greater among Asian subjects than among Western subjects. Reductions in stroke risk were greater in participants aged < 65 – each decade of age increase was associated with ¼ less relative risk reduction.
ASCOT-BPLA (2005) International 8 (RCT)	19,257 patients, aged 40 – 79 and either untreated hypertension (SBP ≥160 mmHg or DBP ≥ 100 mmHg or both) or treated hypertension (SBP ≥ 140 mmHg or DBP ≥90 mmHg or both). Patients were excluded if they reported history of stroke within the past 3 months. 11% of participants had previous stroke or TIA (more than 3 months prior to study inclusion). Patients were randomized to receive either amlodipine 5 – 10 mg (and adding perindopril 4 – 8 mg as required to meet target blood pressure; n=9,369) or atenolol 50 – 100 mg (and adding bendroflumethiazide 1.25 – 2.5 mg as required to meet target blood pressure; n= 9,618). Primary study outcomes were nonfatal Myocardial infarction (MI) and fatal coronary heart disease (CHD). Secondary outcomes included fatal and nonfatal strokes.	Median follow-up was 5.5 years. At the end of the trial 78% of patients were being treated with at least 2 anti-hypertensive agents. 5% of patients in both groups had experienced the primary study outcome (HR = 0.90, 95% CI 0.79 – 1.02). Fatal & nonfatal strokes had occurred in 3% of the amlodipine group and 4% in the atenolol group (HR = 0.77, 95% CI 0.66 – 0.89) suggesting a protective effect associated with amlodipine-based treatment. Analysis of individuals with previous vascular disease revealed a protective effect for "total cardiovascular events" associated with amlodipine-based treatment (HR=0.80, 95% CI 0.70 – 0.92). This was slightly smaller than the effect noted for individuals with no previous vascular disease (HR = 0.85, 95% CI 0.78 – 0.92). 25% of patients stopped treatment due to adverse events; though there were no between group differences. More patients receiving atenolol withdrew due to serious adverse events (p<0.0001). It should be noted that, for its primary endpoint, the study was underpowered due to low event rates.
Nazir et al. (2005) UK 7 (RCT)	25 patients with normal blood pressure days following mild stroke or TIA (4-8 days) were randomized to receive either 2 – 4 mg Perindopril daily (n=12) or matching placebo (n=13) for 14 days.	Mean arterial blood pressure was significantly reduced 1 – 10 h following perindopril dose, returning to baseline at 24 hours, compared to placebo group (maximum corrected fall of 12.5mmHg at 10 hours; p=0.005). No differences were observed in internal carotid artery flow, middle cerebral artery velocity, cerebral blood flow or glomerular filtration rate.
MOSES study	1,352 individuals with hypertension and	Mean follow-up time was 2.5 years. Mean target

(2005) Germany/Austria 8 (RCT)	history of TIA, ischaemic stroke or cerebral haemorrhage were randomly assigned to receive either nitrendipine (10 mg o.d., n=671) or eprosartan (600 mg o.d., n=681). Target blood pressures were 140/90 mmHg. Appropriate combination therapy with diuretics, β-blockers or α-blockers was permitted as necessary to reach target pressure. Primary study end points were mortality and number of cardiovascular and cerebrovascular events. Assessment of functional capacity including cognitive function was also undertaken.	blood pressures were achieved in both groups by 3 months and remained stable throughout. Combination therapy was necessary to achieve target blood pressure in 65.6% of eprosartan patients and in 66.9% of nitrendipine patients. 206 fatal & nonfatal events occurred in the eprosartan group vs. 255 in the nitrendipine group (IDR = 0.79, CI=0.66 – 0.96, p=0.014). 206 cerebrovascular events occurred in all; 102 in the eprosartan group and 134 in the nitrendipine group (IDR=0.75, CI = 0.58 to 0.97, p=0.026). There were more cardiovascular events in the nitriendpiine group (p=0.061), but there was no between group difference in mortality in any category (cardiovascular, cerebrovascular and nonvascular). It should be noted that TIA's made up 67% of all cerebrovascular end points. Adverse events included dizziness/hypotension, pneumonia and metabolic disorder. Frequency of adverse events was comparable in both groups. There were no significant differences in cognition or functional ability.
ONTARGET (ONTARGET Investigators et al. 2008) International 10 (RCT)	25,620 patients, following a 3-week single-blind run-in period, were randomized to receive either an ACE-inhibitor (ramipril 10 mg/day, n=8576), an angiotensin receptor blockers (ARB) telmisartan 80 mg/day, n=8542) or a combination of both (n=8502). Patients had a history of coronary, peripheral or cerebrovascular disease or diabetes with end-organ damage. Primary study outcome was death from cardiovascular causes, MI, stroke or hospitalization for heart failure. Follow-up was at 6 weeks, 6 months and every following 6 months until primary event or end of study.	The mean follow-up was 56 months. Relative risk for stoke in the ramipril group compared to the telmisartan group was 1.02 (95% CI 0.94-1.09). Relative risk for stroke in patients assigned to combination therapy was 0.99 vs. ramipril (95% CI 0.91-1.07). Number of deaths was not significantly different between the two monotherapy groups. There was a slightly greater risk for death in combination therapy though this was not significant (RR = 1.07, 95% CI 0.98-1.16). Use of telmisartan was associated with lower rates of cough (p<0.001) and angio-edema (p-0.01) but higher incidence of hypotensive symptoms (p<0.001) than treatment with ramipril. Combination therapy was associated with increased risk of hypotensive symptoms (p<0.001), syncope (p=0.03) and renal dysfunction (p<0.001) when compared to ramipril.
PRoFESS (Bath et al. 2009; Yusuf, Diener, et al. 2008) International 10 (RCT)	20,332 patients with ischemic stroke within 90 days of trial entry were randomly assigned to treatment (80 mg/day telmisartan, n=10,146) or matching placebo (n=10,186). All patients received open-label treatment for hypertension as necessary at the discretion of the investigators. Patients were evaluated at time of discharge from hospital or at a clinic visit, and then at 1, 3 and 6 months and at clinic visits every 6 months thereafter. Telephone follow-up as scheduled between clinic visits. Mean	By study end, use of non-study drugs was more frequent in the placebo than telmisartan condition: 28.2% vs. 22.6% for diuretics, 33.9% vs. 28.4% for ACE inhibitors, 30.9% vs. 26.5% for calcium-channel blockers and 25.4% vs. 22.3% for beta-blockers. Recurrent stroke occurred in 880 patients in the telmisartan group vs. 934 patients in the placebo group (HR=0.95, 95% CI 0.86 to 1.04). No significant difference was reported for any given subtype of stroke. There were no significant between group differences for any secondary outcomes. *Post hoc* analyses

	duration of follow-up was 30 months. Primary study outcome was recurrent stroke of any type. Primary analysis was time to recurrent stroke.	suggested the impact of telmisartan may be time-dependent. Prior to 6 months, use of telmisartan was associated with a non-significant increase in the risk for recurrent stroke (HR = 1.07, 95% CI 0.92 to 1.25), while after 6 months the use of telmisartan reduced stroke risk (HR = 0.88, 95% CI 0.78 to 0.99). Difference in effect between time periods was significant (p=0.04). *Post hoc* analysis demonstrated that use of telmisartan within 72 hours of stroke in a group of patients with mild ischemic stroke and mildly elevated blood pressure was safe and did not result in excess adverse events.
ACCOMPLISH (2008) International 10 (RCT)	11,506 high-risk patients (including history of stroke) with hypertension were randomly assigned to receive treatment with either 20 mg benazepril + 5 mg amlodipine once daily or 20 mg benazepril + 12.5 mg hydrochlorothiazide (HCTZ) once daily. Benazepril was increased to 40 mg after one month in both groups. Investigators could increase amlodipine to 10 mg or HCTZ to 25 mg to meet target blood pressure <140/90 mmHg (130/80 mmHg for patients with diabetes or kidney disease). Addition of other antihypertensives (though not of the same class as the study drugs) was permitted. The primary end point was time to the first event composite of cardiovascular event and death from cardiovascular causes.	Mean follow-up was 35.7 and 35.6 months for the benazepril-amlodipine and benazepril-HCTZ groups respectively. Reduction in blood pressure was similar in both groups over the course of the study. Primary study outcome was recorded in 552 patients in the benazepril-amlodipine group vs. 679 patients in the benazepril-HCTZ group (HR = 0.80, 95% CI 0.72-0.90, p<0.001). Examination of the components of the composite outcome revealed no between group difference in terms of risk for fatal or nonfatal stroke (HR=0.84, 95% CI 0.65 – 1.08); however, there were significantly fewer fatal or nonfatal myocardial infarctions recorded in the group receiving benazepril-amlodipine (HR = 0.78, 95% CI 0.62-0.99).
PRoFESS Study Group (2008) International 10 (RCT)	20,332 patients with ischemic stroke within 90 days of within trial entry were randomly assigned to treatment (80 mg/day telmisartan, n=10,146) or matching placebo (n=10,186). All patients received open-label treatment for hypertension as necessary at the discretion of the investigators. 880 patients in the telmisartan condition and 934 patients in the placebo condition experienced recurrent stroke. Functional outcome was assessed at 3 months after recurrent stroke using the modified Rankin scale and the Barthel Index.	In individuals with recurrent stroke, there was no significant difference in mRS scores between treatment groups (p=0.61). BI scores were dichotomized (<95 or ≥95). Analysis of between group differences demonstrated no significant change in risk for reduced functional deficit following the recurrent stroke event (RR=1.02, 95%CI 0.93-1.11).
TRANSCEND (2008) International 10 (RCT)	Using the protocol from the ONTARGET study, 5,926 high-risk patients who were intolerant to ACE-inhibitors were enrolled. Following a 3-week run-in period (1 week placebo daily, 2 weeks 80 mg telmisartan), patients were randomized to receive either telmisartan (80mg/day, n=2,954) or placebo (n=2,972). All patients received treatment	Mean follow-up was 56 months. Non-study agents (diuretics, calcium channel blockers, β-blockers and α-blockers) were used significantly more frequently in the placebo condition than the telmisartan group. For the primary study outcome, there were no significant differences between groups for either the combined outcome or its components. There was a significant trend

	for hypertension with proven therapies as required. Primary outcome was the composite of cardiovascular death, MI, stroke or hospitalization for heart failure. Patients were assessed at follow-up visits at 6 weeks, 6 months and then every 6 months thereafter.	toward more treatment discontinuations in the telmisartan group (p=0.055). Hypotensive symptoms were reported more frequently in the telmisartan group (p=0.049).
PRoFESS Study Group (2009) International 10 (RCT) N=1360	In a non-prespecified subgroup analysis, functional outcome at 30 days was examined. Patients included in this analysis were those enrolled within 72 hours of acute ischemic stroke event – 647 of whom received telmisartan and 713 received placebo.	There was no significant difference between groups for the outcome of death or dependency (OR=1.03, 95% CI 0.84 – 1.26, p=0.81). There was also no difference when the mRS was dichotomized (0-1 vs. 2-6) (OR=1.0, 95% CI 0.11-1,29). There was also no between group difference noted on the MMSE at 30 days (OR=1.02, 95% CI 0.80-1.31).
COPE (2011) Japan 6 (RCT)	During a run-in period, potential participants with hypertension were treated with 4 mg benidipine once daily. Individuals whose blood pressure did not meet the target level of 140/90 mmHg, were randomly assigned to receive either an angiotensin receptor blockers (ARB) (n=1,167), β-blocker (n=1,166) or half daily dose of thiazide diuretic (n=1168) in addition to the benidipine. Participants were randomized to drug class only – specific drug administered was at the discretion of the investigator. After 4 weeks, if target blood pressure was still not met, other antihypertensive drugs (except from within the classes of the other conditions) could be administered. Duration of treatment was 3 years, with the avg. follow-up being 3.6 years. Primary study outcome was a composite of cardiovascular events and achievement of the target blood pressure.	Analyses were conducted on data from 1110, 1089, and 1094 patients in the ARB, β-blocker and diuretic conditions, respectively. There were approximately 11-13% of patients in each condition who reported a previous history of stroke or MI. There were 21.7%, 26.3% and 29.8% of patients in the ARB, β=blocker and thiazide conditions who were treated with additional anti-hypertensive drugs in addition to benidipine (calcium channel blocker). There was no significant difference reported between groups in terms of the proportion of patients who achieved the target blood pressure. The primary study outcome was reported in 3.7% of patients in the ARB + benidipine condition, 4.4% in the β-blocker+benidipine condition and 2.9% of patients in the diuretic + benidipine condition. Although none of the statistical comparisons were significant, the HR for the composite end point associated with the β-blocker combination approached significance (HR=1.54, 95% CI 0.98-2.41; p=0.056). In terms of the secondary outcome that included fatal and non-fatal stroke, use of the benidipine + thiazide diuretic was associated with improved outcome when compared to the beta-blocker combination (HR=2.13, 95% CI 1.12-4.02; p=0.02)
ALLHAT Extension Study (2012) No Score	Surveillance of participants via access to administrative databases continued for a total of 8 – 13 years from discontinuation of study therapy. Data regarding mortality outcomes and nonfatal events were available for 98% and 65% of study participants, respectively. Primary outcomes were mortality only endpoints including all-cause mortality, CV mortality and mortality from CHD, stroke, heart failure	There were no significant between group differences in terms of 10-year mortality rates for all-cause mortality. However, there were higher 10-year mortality rates among individuals who had been assigned to receive Lisinopril during the the ALLHAT trial vs. the chlorthalidone group (3.1 vs. 2.6; HR=1.20, 95% CI 1.01 -1.41). This difference was not significant for the combined outcome of fatal/nonfatal hospitalized stroke. When comparing in-trial and post-trial events,

	and other CVD. Secondary outcomes included fatal/nonfatal hospitalized events (including stroke).	there were no significant between group differences (amlodipine vs. diuretic and lisinopril vs. diuretic) in terms of all-cause mortality or mortality attributable to stroke. However, there was a reduced risk of fatal/nonfatal CVD events post-trial in individuals who had received lisinopril rather than chlorthalidone (HR=1.05, 95% CI 0.98-1.14 vs. HR=0.92, 95% CI 0.85-1.0; p=0.02). A similar result was reported for fatal/nonfatal stroke alone (HR=1.17, 95% CI 1.02-1.35 vs. HR=0.94, 95% CI 0.82-1.07; p=0.03).
Kerry et al. (2013) UK RCT PEDro=7 TPS=NA N_{Start}=381 N_{End}=338	**Population:** Intervention group (N=187): Mean age=71.1±12.6yr; Gender: Males=111, Females=76. Control group (N=194): Mean age=72.6±11.4yr; Gender: Males=108, Female= 86. **Intervention:** Participants with a history of stroke or transient ischemic attacks (TIA) within the 9mo and had hypertension, were randomized to the intervention or to the control group. The intervention group received a personal blood pressure monitor (Omron M6) and were followed-up by a nurse which reviewed the participant's readings and provided telephone support to the participant. The control participant did not receive a blood pressure machine, but received usual care from their physician and no advice on blood pressure was given. All participants were followed up after 3 and 9mo to check on well-being. **Outcomes:** Change in Systolic Blood Pressure; Mean systolic BP after 6mo; Change in mean diastolic blood pressure; Number of antihypertensive drugs; treatment changes and primary care consultations; Change in Euro-Qol 5-dimension (EQ-5D and frequency of anxiety, Enduring nature of anxiety, Alcohol or sedative use, Restlessness or fidgeting (FEAR scores).	No significant difference between the intervention and the control groups in the mean fall in systolic blood pressure after 12mo was found.
Morrow et al. (2013) USA RCT PEDro=7 TPS=2wk-12mo N_{Start}=4883 N_{End}=4883	**Population:** Experimental (N=2435): Mean Age=64yr; Gender: Male=1661, Female=774. Control (N=2448): Mean Age=65yr; Gender: Male=1625, Female=823. **Intervention:** All patients received concomitant medical therapy including antiplatelet drugs during the intervention period of 2yr. Experimental-received 2.5mg vorapaxar daily for 2yr. Control-received a daily placebo (description not available). **Outcomes:** Composite of cardiovascular	No significant difference between groups in regards to the 3yr incidence of cardiovascular death, myocardial infarction or stroke (exp=13.0%, control=11.7%, p=0.75, hazard ratio=1.03). No significant difference between groups in regards to the recurrence of stroke (exp=10.1%, control=7.5%, p=0.30, hazard ratio=1.13) or any of the other efficacy endpoints measured. Significantly worse GUSTO outcomes in the experimental group compared to the control

	death, myocardial infarction or stroke and bleeding.	group seen by a higher GUSTO moderate or severe bleeding (exp=4.2%, control=2.4%, p<0.001) and increased intracranial hemorrhage (exp=2.5%, control=1.0%, p<0.001).
ALLHAT Study Results by Sex (2013) USA No Score	The results of the ALLHAT study (2002), explained above were analyzed to determine the interaction between sex and the treatments on all-cause mortality, fatal/non-fatal stroke, and combined CVD (CHD, stroke, other treated angina, heart failure, and peripheral arterial disease).	Women accounted for 47% of the study population. Six-year event rates of all-cause mortality, combined CVD, and stroke were lower in women. No significant differences were found between treatment groups for all-cause mortality. No significant gender-treatment interactions were found (p>0.36). Combined CVD significantly increased, in both genders, in the lisinopril vs. chlorthalidone groups. Further, in that comparison, stroke was significantly increased in women. There were no significant gender-treatment interactions.
Arima et al. (2014) Australia Observational No Score TPS=NA N=6105	**Population:** No demographic information specified in the current study. **Intervention:** The current study uses data obtained from the PROGRESS trial to determine whether larger reductions in systolic BP (SBP) was associated with treatment increases in the risk of recurrent stroke among patients with cerebrovascular disease. In the PROGRESS trial, patients with a history of stroke or transient ischemic attack (TIA) within 5yr were randomly assigned to active treatment (2-4 mg perindopril±2-2.5mg indapamide) or matching placebo. Participants were grouped based on SBP reductions of ≥20, 10-19, 0-9, and <0 mmHg. **Outcomes:** Annual rates of recurrent stroke events.	Based on the SBP groupings, the number of stroke events/person-years produced 2.08%, 2.10%, 2.31% and 2.96% annual incidence rates of recurrent stroke (p=0.0006) for trend. The intracerebral hemorrhage and the ischaemic stroke also showed significant trends with increases in annual rates and increased SBP (p=0.0002; p=0.04).

8.4 Managing Diabetes

8.4.2 Management of Diabetes and Associated Macrovascular Complications

8.4.2.1 Glycemic Control

Table 8.4.2.1 Interventions for Glycemic Control and Risk of Stroke

Author, Year Country Pedro Score	Methods	Outcomes
PROactive (2005) International 10 (RCT)	5,238 patients with Type 2 DM and evidence of macrovascular disease were assigned to treatment with pioglitazone (15mg to 45 mg, n=2,605) or matching placebo (n=2,633) in addition to their established medication	Nine-teen percent of participants in each group had a history of previous stroke. Treatment with pioglitazone was associated with a significant reduction in risk for the secondary composite endpoint (HR=0.84, 95% CI 0.72-0.98, p=0.027), after

	regimen. Primary endpoint was the composite of mortality, non-fatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention (coronary or leg arteries), and amputation above the ankle. Secondary endpoint was the included composite of mortality, non-fatal MI and stroke. Mean follow-up of 34.5 months.	adjustment for baseline variables including use of other treatments for glycemic control (insulin, metformin and sulphonylurea). Results for the primary endpoint were non-significant (HR = 0.90, 0.80-1.02, p=0.095). There was a non-significant trend toward reduction in risk for stroke (HR=0.81, 0.61-1.07). Treatment compliance was in excess of 95% in both groups. Increased rates of edema and heart failure were reported in the pioglitazone group, but there were no significant differences in mortality and fewer hospital admissions.
PROactive subgroup analysis (2007)	Evaluated risk for stroke and cardiovascular endpoints in participants with (n=984) and without (n=4254) prior stroke.	In the subgroup of patients with previous stroke, treatment with pioglitazone was associated with significantly reduced risk of the composite endpoint of cardiovascular death, nonfatal stroke or nonfatal MI (HR=0.72. 95% CI 0.5-1.00, p=0.047). This benefit was driven primarily by reduced risk for fatal or non-fatal stroke. Stroke event rates in the pioglitazone group were 5.6% vs. 10.2% in the placebo group (HR=0.53, 0.35-0.85,p=0.009). In patients with no history of previous stroke, there were no significant benefits noted for any endpoints including fatal or nonfatal stroke (HR = 0.86, 0.71 – 1.04). From a multivariate analysis, only pioglitazone use (p=0.0076) and treatment with statins (p=0.0126) had significant effects on reduction in stroke risk among patients with previous stroke.
ACCORD Study Group (2008) International 8 (RCT)	10,251 patients with type 2 diabetes and either a previous history of, or increased risk for, a cardiovascular event were randomly assigned to receive either intensive (HbA_{1c} to <6.0%) or standard (HbA_{1c} to 7.0– 7.9%) glucose-lowering treatment strategies. Treatment formularies/ algorithms were provided. Primary study outcome was the composite of nonfatal MI, nonfatal stroke or death from cardiovascular causes. Mean length of follow-up was 3.5 years. Early study termination occurred based on mortality trends suggesting increased rate of death from any cause associated with intensive therapy. 35% of participants had a history of previous cardiovascular events at the time of study enrolment.	Stable HbA_{1c} levels were obtained in each group by one year (6.4% & 7.5% in the intensive and standard therapy groups, respectively). Fewer primary events were recorded in the intensive therapy group (352 vs. 371), but this difference was not significant (HR = 0.90, 95% CI 0.78 – 1/04, p=0.16). More nonfatal strokes were recorded in the intensive therapy group than in standard therapy (67 vs 61, HR = 1.06, 95% CI 0.75–1.50, p=0.74). Increased mortality from any cause was associated with intensive therapy (HR = 1.22, 95% CI 1.01-1.46, p=0.04); however, the number of deaths from stroke was not significantly different between groups. Intensive therapy was also associated with higher rates of hypoglycaemia, weight gain and fluid retention (p<0.001). A subgroup analysis showed patients with a history of previous cardiovascular events (including stroke) had more events when treated with intensive therapy. Additional *post hoc* analyses demonstrated that intensive therapy in individuals reporting aspirin (ASA) use at baseline was associated with elevated risk for mortality when compared to non-ASA-users (HR = 1.45 vs. 0.96, p=0.03). Other factors identifying patients at higher risk for mortality associated with intensive therapy were history of neuropathy and

		higher A1C (>8.5%) (Calles-Escandon et al. 2010).
ADVANCE Collaborative Group (2008) International 10 (RCT)	11,140 patients with type 2 diabetes were randomly assigned to receive either intensive glucose control (gliclazide + other drugs as necessary to achieve HbA_{1C} ≤6.5%) or standard glucose control. Primary study outcome was a composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke and major microvascular events. Median follow-up was 5 years. 32% of participants reported a history of major macrovascular events including stroke (approximately 9%).	Compared to standard therapy, intensive glucose control was associated with a significant reduction in microvascular (HR = 0.86, 95% CI 0.77–0.97, p=0.01) but not macrovascular events (HR = 0.94, 95% CI 0.84–1.06), p=0.32). More nonfatal strokes (as well as cerebrovascular events in general) were reported for patients receiving intensive therapy, although it did not represent a significant increase in risk. There was no significant effect associated with intensive vs. standard therapy in the subgroup of participants with previous macrovascular events. Severe hypoglycaemia was significantly more frequent in the intensive treatment group (HR=1.86, 95%CI 1.42-2.40, p<0.001).
VADT (2009) USA 8 (RCT)	In an open label study, 1,791 veterans with Type 2 diabetes (and suboptimal response to previous therapy) were randomly assigned to either intensive (maximum doses, n=892) or standard therapy (1/2 maximum doses, n=899). Therapy was determined by BMI (BMI ≥27, metformin + rosiglitazone; BMI <27, glimepiride + rosiglitazone). Primary outcome was time to first cardiovascular event. 40% of participants reported history of previous cardiovascular event. Median length of follow-up was 5.6 years.	Median glycated hemoglobin levels were 6.9% and 8.4% in the intensive and standard therapy groups, respectively. There were no significant differences reported for the primary outcome for intensive vs. standard therapy (HR = 0.88, 95% CI 0.74-1.05; p=0.14) or for any of the individual components of the primary outcome including stroke events (28 vs. 36, HR=0.78, 95% CI 0.48 – 1.28; p=0.32). More adverse events (most frequently hypoglycemia) were reported among individuals receiving intensive therapy (24.1% vs. 17.6%; p<0.001).
Zinman et al. (2015) Canada RCT (6) TPS=NA N_{Start}=7028 N_{End}=7020	**Population:** Experimental Group (EG; n=4687): Mean age=63.1±8.6yr; Gender: Males=3336, Females=1351. Control Group (CG; n=1270): Mean age=63.2±8.8yr; Gender: Males=1680, Females=653. **Intervention:** The EG was treated with 10 or 25mg of empagliflozin. The CG received a placebo. The treatment was provided 1/d for 2wk in addition to standard care. This study was conducted in 590 centres across 42 countries. Assessments were conducted at 30d follow-up then every 6mo up to 48mo post-treatment. **Outcomes:** Incidence of stroke; Mortality rate.	There was no significant difference between groups for the risk of fatal and non-fatal stroke (HR 1.18, 95% CI 0.89-1.56, p=0.26). Non-fatal stroke alone also did not differ significantly between groups (HR 1.24, 95% CI 0.92-1.67, p=0.16). Risk of mortality from all causes (cardiovascular, non-fatal stroke, non-fatal myocardial infarction) was significantly lower in the EG compared to the CG (HR 0.86, 95% CI 0.74 to 0.99, p=0.04). Risk of mortality from cardiovascular causes only was significantly lower in the EG compared to the CG (HR 0.62, 95% CI 0.49 to 0.77, p<0.001).

8.4.2.2 Hypertension Control

Table 8.4.2.2 Studies Assessing Control of Blood Pressure and Stroke Risk in Diabetic Patients

Author, Year Country Pedro Score	Methods	Outcomes
ABCD (1998) USA	470 patients with hypertension and non-insulin-dependent DM were randomly assigned to	At 67 months, nisoldipine therapy in hypertensive patients was discontinued as significant differences in

8 (RCT)	receive treatment with either nisoldipine or enalapril. In addition, patients received either intensive treatment (target diastolic BP = 75 mmHg) or moderate treatment (target diastolic BP = 80–89 mmHg). Open label antihypertensive medications were used if target BP could not be reached with study medications (with the exceptions of other calcium-channel blockers or ACE-inhibitors). Primary study outcome was effect of BP control on change in 24-hour creatinine clearance, assessed every 6 months. Secondary end points included fatal & nonfatal cardiovascular events. Follow-up was 5 years.	the rate of cardiovascular events was found. No significant differences were seen between medication groups in terms of level of BP control. There were more deaths from cardiovascular causes associated with nisoldipine therapy vs. enalapril (10 vs 5, adj. RR = 1.4, 95% CI 0.4 – 5.1). Similarly, there was a greater risk for stroke associated with nisoldipine therapy (Adj. RR = 2.2, 95% CI 0.7 – 7.1).There was a significantly lower rate of myocardial infarctions among patients receiving ACE-inhibitors vs. the calcium-channel blocker. Headaches were a more frequent cause of discontinuation in the nisoldipine group (p=0.009) while fatigue and uncontrolled hypertension were more common in patients treated with enalapril (p=0.04).
UK Prospective Diabetes Study Group (UKPDS 39) (1998a) UK 7 (RCT)	A total of 1,148 hypertensive patients with Type II diabetes (mean age was 56 years) were randomly assigned to tight control vs. less tight control of blood pressure groups. Tight control patients received either captopril 25 – 50 mg twice daily (n=400) or atenolol 50–100 mg/day (n=358) to achieve a BP of <150/<85 mmHg. Less tight control patients (n=390) were treated to achieve a BP of <180/<105 without the use of an ACE-inhibitor or β-blocker.	Patients were followed for up to 9 years. Patients allocated to receive captopril or atenolol had similarly reduced blood pressures (14/8 mmHg change vs. 14/7 mmHg). For patients receiving neither drug, mean change was 16/7 mmHg over nine years. Comparing captopril to atenolol, there were fewer strokes among patients receiving atenolol, but this was not significant (RR=1.12, p=0.74). Both agents appeared equally effective in lowering blood pressure in patients with Type II diabetes.
UK Prospective Diabetes Study Group (UKPDS 38) (1998b) UK 7 (RCT)	A total of 1,148 hypertensive patients with Type II diabetes (mean age was 56 years) were randomly assigned to tight control vs. less tight control of blood pressure (BP) groups. Tight control patients received either captopril 25–50 mg twice daily (n=400) or atenolol 50–100 mg/day (n=358) to achieve a BP of <150/<85 mmHg. Less tight control patients (n=390) were treated to achieve a BP of <180/<105 without the use of an ACE-inhibitor or β-blocker. Patients were stratified according to previous treatment (yes/no) for hypertension.	Mean blood pressure during follow-up was significantly lower in the tight control vs. the less tight group (p<0.0001). Tight BP control resulted in a risk reduction for stroke of 44% (p=0.013). In addition, diabetes related events were reduced in the tight BP control group compared to the less tightly controlled group (24%; p=0.046) as were deaths related to diabetes (32%, p=0.19). After nine years of follow-up, 29% of patients in the tight control group required 3 or more agents to maintain target BP.
FACET (1998) International 7 (RCT)	380 participants with diabetes and hypertension, but no previous stroke, were randomly assigned to receive open-label fosinopril (20 mg/day) or amlodipine (10 mg/day). If BP control was not achieved using the assigned monotherapy, the other study medication could be added to achieve necessary targets. Prospectively defined study outcomes included combined major vascular events (stroke, MI, hospitalized angina) as well as fatal & non-fatal stroke.	By the end of the study, amlodipine had been added to the fosinopril monotherapy group for 30.7% of participants. Similarly, 26.2% of participants assigned to amlodipine monotherapy were also administered fosinopril. Both conditions experienced significant reductions in systolic and diastolic BP. Greater reductions in systolic BP were experienced by participants in the amlodipine group (p<0.01). Use of fosinopril rather than amlodipine was associated with reduced risk for the combined outcome of any major vascular events (HR = 0.49, 95% CI 0.32-0.97). However, there was no significant difference in risk for fatal & non-fatal stroke between groups (HR=0.39, 95% CI 0.12-1.23).

Syst-Eur Investigators (1999) Finland, Belgium 8 (RCT)	4,695 patients (aged ≥ 60 and having systolic hypertension) were randomized to receive either active treatment with nitrendipine 10–40 mg/day with the possible addition of enalapril, hydrochlorothiazide or both (n=252 diabetic & n=2,146 non-diabetic patients) or matching placebo (n=240 diabetic & n=2,057 non-diabetic patients). Patients with diabetes were included if blood glucose concentrations were controlled.	After 2 years, systolic & diastolic blood pressures in the active treatment vs. placebo groups differed by 8.6 mmHg & 3.9 mmHg for diabetic patients and 10.3 mmHg & 4.5 mmHg for non-diabetic patients. Active treatment was found to reduce the rate of fatal & nonfatal stroke by 73% among diabetic patients and 38% among non-diabetic patients. Reduction in overall mortality, mortality from CVD and all cardiovascular events was greater among diabetic patients than among non-diabetic patients (p=0.04).
ALLHAT Collaborative Research Group (2000) USA/Canada 9 (RCT)	31,512 adults aged 55 and over with hypertension were stratified into 3 groups; those with diabetes mellitus (n=13,101), those with impaired fasting glucose levels (IFG; n=1,399) and normoglycemics (NG; n=17,012). Participants were randomly assigned to receive chlorthalidone (2.5-10 mg/ day), amlodipine desylate (2.5–10 mg/ day) or lisinopril (10–40 mg/ day). Reduction in BP was achieved by titrating study drug dose, then adding one of atenolol, clonidine hydrochloride or reserpine and hydralazine hydrochloride as needed. Primary outcomes included fatal CHD or nonfatal MI. Secondary outcomes included all-cause mortality, fatal and nonfatal stroke, combined CHD and combined CVD.	Overall, there were few significant treatment and glycemic interactions identified. In DM and NG participants assigned to receive amlodipine and lisinopril, there was no significant difference in risk for the primary outcome when compared to chlorthalidone. There was a significant reduction in risk for primary outcome in IFG patients assigned to receive amlodipine vs. chlorthalidone. When stroke and CVD were considered, both outcomes were found to be more common in NG patients receiving lisinopril than chlorthalidone (RR=1.31 & RR=1.13 respectively). There was little evidence to support the superiority of treatment with either lisinopril or amlodipine when compared to chlorthalidone.
HOPE Study (2000) 8 (RCT)	Population studied was diabetic stroke patients who received 10mg Ramipril and 400 IU vitamin E (n=1,808) or a placebo daily (n=1,769).	The study stopped 6 months early because of the consistent benefit of Ramipril compared to placebo. Ramipril lowered risk of combined primary outcome by 25% (p=.0004), myocardial infarction by 22%, stroke by 33%, cardiovascular death by 37%, total mortality by 24%, revascularization by 17%, and overt nephropathy by 24%.
STOP-2 (2000) Sweden 7 (RCT)	719 of the 6,614 participants in the STOP-2 trial had diabetes mellitus as well as hypertension at baseline. Random allocation resulted in 253, 235 and 231 patients receiving conventional, ACE inhibitor and calcium antagonist-based therapies for the treatment of hypertension, respectively. Primary study outcome was fatal cardiovascular disease (including MI and stroke).	The impact of treatment on BP was similar in all treatment groups. There were no significant differences in risk for fatal cardiovascular events between groups. There were also no significant differences between the three antihypertensive regimens in terms of combined fatal & nonfatal stroke. For Ca-antagonists vs. conventional therapy the adjusted RR for all stroke was 0.80 (95% CI 0.49 – 1.29), for ACE inhibitors vs conventional therapy RR = 0.88 (95% CI 0.56 – 1.40) and for ACE inhibitors vs. Ca-antagonists RR=1.16 (95% CI 0.71 – 1.91). ACE inhibitor treatment was associated with significantly fewer MIs when compared to Ca-antagonist therapy (RR=0.51, 95% CI 0.28 – 0.92).
ADVANCE trial (2007) International 10 (RCT)	11,140 patients with type 2 diabetes (9% with previous stroke) were randomized to receive a fixed combination of perindopril (2 mg) and indapamide (0.625 mg) (n=5,569) or matching placebo (n=5,571) following a 6-week run-in	A reduction in relative risk for the combined outcome of macro or microvascular disease event was associated with treatment (=0.91, 95% CI 0.83-1.00, p=0.04). However, when considering only macrovascular events, no significant difference was

	period. After 3 months, treatment doses were doubled (4 mg/1.24 mg vs. matching placebo). Patients were not necessarily hypertensive and mean BP at baseline was 145/81 mmHg in both groups. Mean follow-up was 4.3years. Primary endpoints were composites of major macro and microvascular events.	noted between groups (HR=0.92, -4.0 to 20). Similarly, there was no significant reduction reported in risk for major cerebrovascular events (HR=0.98, (-18 to 19).
ACCORD trial (2010) International 8 (RCT)	4,733 hypertensive patients with type 2 diabetes and either a previous history of cardiovascular events or evidence of increased risk for cardiovascular events, were randomly assigned to receive either intensive therapy (target = SBP <120mmHg; n=2,362) or standard therapy (target SBP = 140mmHg; n=2,371). Treatment strategies in current clinical practice were used as required to meet target BPs. The primary study outcome was a composite of first nonfatal MI, nonfatal stroke or cardiovascular death. Fatal or nonfatal stroke and nonfatal stroke alone were included as secondary outcomes. Mean patient follow-up was 4.7 years.	Intensive therapy resulted in greater reduction in BPs that were achieved more quickly than standard therapy. Overall, average BP in all groups was approximately 139/76 mmHg. After the first year, average systolic BP was 199.3mmHg in the intensive therapy vs. 133.5 mmHg in the standard group. Diastolic blood pressure was 64.4 mmHg in the intensive vs. 70.5 mmHg in the standard group. There was no significant difference between groups in terms of the composite primary outcome. However, individuals in the intensive therapy group experienced less risk for all stroke (HR=0.59, 95% CI 0.39-0.89) and for non-fatal stroke (HR=0.62 95% CI 0.41-0.96) than standard therapy. Individuals in the intensive therapy group were exposed to a greater number of antihypertensive drugs and had significantly more adverse events caused by the antihypertensive therapy (p<0.001), including hypotension (p<0.001), bradycardia or arrhythmia (p=0.02) and hyperkalemia (p=0.01).
NAGOYA HEART Study (2012) Japan 7 (RCT)	1,150 patients (82% with diabetes mellitus, remainder with glucose intolerance) were randomly assigned to receive either 80 mg valsartan (n=575) or 5 mg amlodipine (n=575) once per day. All ACE/ARB and CCB antihypertensives were discontinued at study entry. Doses of the assigned study drugs could be titrated to reduce BP to meet study target of 130/80 mmHg. If target BP was not met within 8 weeks, diuretics, β-blockers or α-blockers could be added as necessary. Primary study outcome was a composite of MI, stroke, admission due to heart failure, coronary revascularization and sudden cardiac death. Secondary outcome was all-cause mortality. Median follow-up was 3.2 years (study terminated).	A power calculation estimated 1,500 participants per group to demonstrate a significant treatment effect; however, enrollment was terminated early. In all, there were 56 events recorded in the group receiving valsartan-based therapy, and 64 events in the group receiving amlodipine-based therapy (9.4% vs. 9.7%; HR=0.97, 95% CI 0.66, 1.4; p=0.85). There were 13 reported strokes in the valsartan group vs. 16 in the amlodipine group (2.3% vs. 2.8%; HR = 0.81 95% CI 0.39, 1.68; p=0.57). There were no significant between group differences for any of the components of the composite outcome, with the exception of hospitalization due to heart failure for which there was a significantly smaller risk associated with the use of valsartan-based therapy (HR=0.2, 95% CI 0.06, 0.69; p=0.012). There was no between-group difference for the secondary outcome of all-cause mortality.
Redon et al. (2012) *Post hoc analysis* of ONTARGET (2008) 10 (RCT)	The 25,584 participants in the ONTARGET trial were randomly allocated to 3 treatment groups: 1) ramipril, 2) telmisartan 3) combination therapy ramipril+temisartan. This analysis collapsed treatment groups in order to examine the relationship between reduction in BP and stroke risk in individuals with vs. without	Risk for the primary outcome was elevated in individuals with diabetes compared to those without (HR=1.48 95% CI 1.38, 1.57) and for stroke (HR=1.39 95% CI 1.23, 1.56). When separated into quartiles according to baseline SBP (≤130, 131-142, 143-154 and >154), diabetic participants had a higher risk of stroke in each quartile. In addition, when compared

	diabetes. There were 9,603 participants with diabetes and 15,981 without who were followed for a mean of 4.6 years. 21% of individuals without diabetes reported a history of previous stroke vs. 16.4% of diabetic individuals. The primary study outcome was a composite of cardiovascular death, nonfatal MI or stroke, or hospitalization due to heart failure.	to participants (non-diabetic or diabetic) with baseline SBP ≤130 mmHg, there were significant differences in risk for stroke such that both nondiabetic and diabetic participants with baseline SBP in the 3rd (HR=1.47 95% 1.23, 1.75 and HR=1.95 95% CI 1.59, 2.4, respectively) and 4th quartiles (HR= 1.83 95% CI 1.54, 2.16 and HR= 2.43 95% CI 2.0, 2.96, respectively) had significantly greater risk. Regardless of change in SBP over treatment, individuals with diabetes experienced elevated risk when compared to those without; however, in both groups greater SBP reduction was associated with a reduction in risk for the primary study outcome for participants with baseline SBP of 143-155mmHg.

8.4.2.3 Treatment of Dyslipidemia

8.4.2.3 Studies Assessing Use of Statins for Secondary Prevention in Individuals with Diabetes

Author, Year Country Pedro Score	Methods	Outcomes
Scandinavian Simvastatin Survival Study (4S) (1997) Sweden 8 (RCT)	A *post hoc*, subgroup analysis of 202 diabetic and 4,242 non diabetic patients with previous MI or angina who participated in the 4S study. Patients were assigned to treatment with simvastatin, 20 mg/day titrated to 40 mg (n=105 diabetic patients), or placebo (n=97). Study endpoints included mortality, major CHD events, other acute atherosclerotic events and myocardial revascularization procedures. Median follow-up was 5.4 years.	In diabetic patients assigned to treatment with simvastatin, risk of cerebrovascular disease events was not significantly reduced compared to those receiving placebo (RR = 0.38, p=0.71). However, treatment with simvastatin was associated with a significant reduction in risk for major CHD events (RR = 0.45, p=0.002), any CHD events (RR=0.61, p=0.015) or any atherosclerotic events (RR-0.63, p=0.018). Risk reductions associated with treatment were not dependent on baseline levels of total, LDL, HDL cholesterol or triglycerides.
CARE trial (1998) USA 8 (RCT)	Subgroup analysis of the Cholesterol and Recurrent Events (CARE) trial. 586 (14.1%) of patients enrolled in CARE had a clinical diagnosis of diabetes at baseline. 6% of these had a history of previous stroke. The primary study endpoint was the composite of death from CHD and nonfatal MI. Mean follow-up was 5 years.	Pravastatin treatment was associated with a non-significant reduction in relative risk of 13% for the primary study endpoint in patients with diabetes. For the endpoint of stroke, treatment was associated with a non-significant reduction of 14%. However, treatment was associated with a 25% reduction of risk for coronary events (CHD death, nonfatal MI, CABG and PTCA) (p=0.004). Expressed in absolute terms, this represents an 8.1% risk reduction for coronary events.
PROSPER Study Group (2002) International 8 (RCT)	5,804 patients, aged 70–82, with pre-existing vascular disease (coronary, cerebral or peripheral) or increased risk (smoking, HTN or diabetes) were randomized to receive pravastatin 40 mg/day or matching placebo. 11% of patients in the placebo groups & 1.5% in the treatment group had a history of diabetes. The proportion of these who also had a history	Pravastatin lowered LDL by 34%, overall. For all participants, risk for the combined primary study outcome of coronary death, non-fatal MI, and fatal or non-fatal stroke was significantly reduced (HR = 0.85, p=0.014). When considered alone, risk of stroke appeared unaffected by the intervention (hazard ratio = 1.03). For patients with diabetes, risk of the primary outcome was increased, though non-significantly, in

	of vascular disease or stroke is not known. Mean length of follow-up was 3.2 years.	the treatment group (hazard ratio = 0.1.27, 95% CI 0.90-1.80).
GREACE (2003) International 6 (RCT)	Of 1,600 patients eligible for the GREACE study, 313 had DM and a history of CHD. These patients were randomized to receive either structured care or usual care for hyperlipidemia. Patients in the structured care group received atorvastatin titrated up to a maximum dose of 80 mg/day to reach the National Cholesterol Education Program goal of LDL-C <2.6 mmol/L and were followed by the university clinic. Usual care was according to own physician's standard. Follow-up was conducted by the healthcare professional of the patient's choice outside of the hospital. Primary study endpoints were all-cause and coronary mortality, coronary morbidity and stroke. Mean follow-up was 3 years.	In structured care, 97% of patients took atorvastatin daily and lipid level targets were achieved by 93% of patients. In the usual care group, 17% were receiving long-term treatment with a lipid lowering drug and only 4% reached guideline targets. Fewer patients receiving structured vs. standard care experienced primary outcome events (RRR = 58%, p<0.0001). A relative risk reduction of 68% was reported for stroke (p<0.002).
MRC/BHF Heart Protection Study (2003) UK 8 (RCT)	5,963 adults with diabetes and an additional 14,573 adults with no diabetes but having occlusive arterial disease were randomly assigned to receive 40 mg/day Simvastatin or matching placebo. 19% of participants with diabetes reported a history of MI, 14% of other CHD and 18% of other occlusive arterial disease. Mean duration of follow-up was 4.8 years.	Overall, there was a 24% reduction in first non-fatal or fatal stroke among diabetic patients (p<0.0001). For patients with no previous occlusive arterial disease, risk reduction associated with treatment was 33% (p=0.002). Absolute risk reduction for individual with diabetes and occlusive arterial disease was 18.4% (p=0.002). 66 major vascular events/1000 patients treated could be avoided in a 5 year period. For diabetic patients with LDL levels <3 mmol/L, the vascular event rate was reduced by 27%. The results suggest that therapy with Simvastatin is beneficial for diabetic patients with/without previous occlusive arterial disease and with/without elevated LDL.
LIPID Trial (Keech et al. 2003; H. D. White et al. 2000) New Zealand 9 (RCT)	9,014 patients with previous MI or unstable angina during the previous 3 months to 3 years, with hyperlipidemia were randomized to receive either 40 mg of Pravastatin (n=4,512) or placebo (n=4,502). 1,077 had a history of diabetes (542 received pravastatin), 940 had impaired fasting glucose (IFG; 474 received pravastatin). The remainder were classified as normal fasting glucose (NFG). 6% of patients with diabetes had a previous history of stroke at baseline. The primary study end point was death due to coronary artery disease. Mean follow-up was six years.	The response of lipids to treatment was similar in all 3 groups (diabetes, IFG & NFG), but level of triglycerides fell most in the diabetic group. In the placebo group, absolute excess risk in patients with diabetes (vs NFG) for death or nonfatal MI was 8.9%, and 6.3% for stroke. In patients with diabetes, treatment with pravastatin was associated with a 19% reduction in risk for the primary study outcome (p=0.11). However, treatment with pravastatin reduced the risk for stroke from 9.9 to 6.3% (RRR = 39%, p=0.02; NNT = 53) in patients with diabetes and 5.3% to 3.4% (RRR=42%, p=0.09; NNT = 97) in patients with IFG.

ASCOT–LLA (2005) International 8 (RCT)	A subgroup analysis of the 2,532 patients with Type 2 diabetes enrolled in the Anglo-Scandiavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA). Patients were randomly allocated to a treatment group (10 mg Atorvastatin daily) or placebo group. 7.4% and 7.7% of patients with diabetes in the treatment and control groups, respectively, had a history of previous stroke or TIA. Median follow-up was 3.3 years.	Treatment with atorvastatin was associated with a significant reduction in risk (HR = 0.77, p=0.036) for total cardiovascular events and procedures among individuals with diabetes. However, there was no significant reduction in risk for fatal or non-fatal stroke (HR = 0.67, 95% CI 0.41- 1.09). However, effective comparisons may have been limited by early termination of the trial, thereby reducing the number of endpoint events and limiting the power of tests to compare treatment effect.
ASPEN Study (2006) International 9 (RCT)	2,410 patients with Type 2 diabetes were randomly assigned to treatment with 10 mg/day atorvastatin or matching placebo. 252 patients in the treatment group and 253 in the placebo group were considered "secondary prevention" patients. Of these 9% & 12% of the treatment & placebo groups, respectively, had a history of CVD. Primary study endpoint was a clinical composite that included fatal and non-fatal stroke. Median follow-up was 4 years.	Risk for the composite primary endpoint was not significantly reduced in treatment vs. placebo (HR=0.90, p=0.34). When elements of the primary endpoint were examined individually, treatment with atorvastatin was not associated with a significant reduction in risk for fatal or non-fatal stroke in either primary or secondary prevention patients.
Callahan et al. (2011) *Post hoc analysis* Of SPARCL trial (2006) International 9 (RCT)	Of the 4,731 participants (all with previous stroke or TIA) in the SPARCL trial, 794 were classified as having type 2 DM. The authors of the present analysis examined the impact of the presence of diabetes on the effectiveness of statin therapy vs. individuals with no diabetes or metabolic syndrome at study baseline (reference group). Primary outcome was risk for fatal/nonfatal stroke. Secondary endpoints included major coronary events, major cardiovascular events, any heart disease event and any revascularization procedure. Mean follow-up for the study was 4.9 years.	Risk for stroke was 18.1% in individuals with type 2 diabetes vs. 11% among individuals with neither diabetes nor metabolic syndrome (HR=1.62, 95% CI 1.33, 1.98; p<0.001). Individuals with diabetes also experienced significantly increased risk, when compared to the reference group, for major cardiovascular events and revascularization procedures. In participants with type 2 diabetes, use of atorvastatin was associated with a significant reduction of risk for ischemic stroke (p=0.04) vs. placebo. However, there were no significant treatment X group interactions which suggests that statin therapy may as effective for individuals with diabetes as without.
Sheng et al. (2012) United Kingdom No Score	A population based cohort study with individuals who had at least 2 measurements of total cholesterol over a 14 year span (1993-2007). The use of statins was studied with the main outcomes being total cholesterol (TC) change from baseline, cardiovascular events and all-cause mortality. Both primary and secondary prevention were looked at.	For patients with diabetes, statins were more effective compared to the rest of the study population. Changes in total cholesterol with statins did not appear to correlate with the changes in cardiovascular events and all-cause mortality. TC reduced by 28% with statins in secondary prevention from baseline measurements. A reduction in TC predicted variable reductions in recurrent cardiovascular events by 19% for those with diabetes mellitus. Risk reductions for all-cause mortality varied from 18% to 40% in secondary prevention.
Wang et al. (2012) Taiwan No score	Longitudinal data from 1997 until 2009 was looked at from the National Health Insurance Research Database. A subgroup of 19,925 subjects fit the criteria for secondary prevention. A small subset of these subjects had previously had a stroke, with the remaining experiencing coronary heart disease or a major adverse	Compared with the control group, the benefit of statin use in preventing in-hospital fatalities out-weighed the risk in secondary prevention subjects. Further, the outcomes of those who developed diabetes after statin use are favourable in this subgroup. After accounting for background risk, incident diabetes after statin therapy was associated with an increased risk

	cardiovascular event. This portion of the study looked at statin use and outcomes in diabetics for secondary prevention. A risk-benefit analysis was done for secondary prevention for non-diabetic participants with and without prior statin use and for diabetic patients with and without previous statin use.	for in-hospital death overall, but not in the secondary prevention cohorts compared with the non-diabetic controls.

8.4.2.4 Fibrates and Stroke Prevention in Patients with Diabetes

Table 8.4.2.4. Use of Fibrates in Hyperlipidemia and Stroke Prevention in Diabetic Patients

Author, Year Country Pedro Score	Methods	Outcomes
VA-HIT Study Group (1999) USA 9 (RCT)	2,531 men under the age of 74 (mean age of 64) with a history of coronary heart disease and an LDL of less than 3.6 mmol/L were randomly allocated to either treatment (1 slow-release gemfibrozil 1200 mg/day) or placebo. Median duration of follow-up was 5.1 years. Primary outcome was nonfatal myocardial infarction or death from coronary causes.	After one year, HDL levels were 6% higher in the treatment group relative to the placebo, triglyceride levels were 31% lower, but LDL levels did not differ significantly between groups. Comparing the treatment group to placebo, there was a reduction of 22% for the primary outcome (p=0.006), 25% for stroke (p=0.10) and 59% for TIA (p<0.001).
BIP Study Group (2000) Israel 7 (RCT)	3,090 patients with previous MI or stable angina, total cholesterol of 180 – 250 mg/dL, HDL-C ≤45 mg/dL, triglycerides ≤300 mg/dL, LDL ≤180 mg/dL and who had been placed on a lipid-lowering diet were randomly assigned to either treatment (400 mg bezafibrate/day) or placebo. Primary study outcomes were fatal/nonfatal MI or sudden death. A secondary outcome, for patients free of primary outcomes included stroke. Mean follow-up was 6.2 years.	0.9 % and 1.4% of patients in the treatment and placebo conditions, respectively, had a history of previous stroke. For the primary study endpoint, treatment with bezafibrate was associated with a 9.4% reduction in risk (p=0.26). For stroke, there was no significant between group differences reported for total stroke (p=0.66) or ischemic stroke (p=0.36).
VA-HIT Study Group (2001) USA 9 (RCT)	Men with a history of coronary heart disease and having low levels of HDL (mean = 0.83 mmol/L) and low levels of LDL (mean = 2.88 mmol/L) were randomly allocated to receive either gemfibrozil 1200 mg/day (n=1,264) or matching placebo (n=1,267).	With gemfibrozil, levels of HDL were increased in the treatment group compared to placebo (p<0.001) and triglycerides were lowered (p<0.001) while LDL concentrations remained the same. CHD events were reduced by 11% in the treatment condition for every 0.13 mmol/L increase in HDL cholesterol (p=0.02). However, lipid concentrations achieved within the gemfibrozil group could account for only 23% of the treatment benefit.
FIELD Study (2005) International 9 (RCT)	9,795 patients between the ages of 50 –75 years with type 2 diabetes and an initial plasma total cholesterol of 3.0 – 6.5 mmol/L, plus total cholesterol to HDL ratio of 4.0 or more, or plasma triglyceride concentration of 1.0 mmol/L to 5.0 mmol/L participated in a 16-week study run-in (4 weeks dietary modification, 6 weeks single blind placebo and 6 weeks single blind fenofibrate therapy). After the run-in phase, participants	4% and 3% of patients allocated to treatment and control conditions, respectively, had a history of prior stroke. Relative to placebo, treatment with fenofibrate was associated with an 11% reduction in total-cholesterol concentration, 12% for LDL cholesterol – triglyceride concentration increased by 29% and HDL by 5% by 4 months. Differences were maintained for total cholesterol, LDL and triglycerides over the course of the study. Treatment was associated with a non-significant

	were randomly assigned to receive either micronized fenofibrate (200 mg/day) or matching placebo. Primary study outcome was coronary events. Secondary outcomes included stroke. Study duration was 5 years.	reduction in risk for the primary study outcome (HR = 0.89, 95% CI 0.75 – 1.05). 175 strokes were recorded in the treatment group and 158 in the placebo group. This represented a non-significant reduction in risk for stroke associated with treatment (HR = 0.90 95% CI 0.73 – 1.12).
ACCORD Lipid Study (2010) International 10 (RCT)	5,518 participants with Type 2 DM and had a previous history of, or increased risk for, cardiovascular events who were also being treated with simvastatin were randomly assigned to receive either fenofibrate (160 mg/day to start, adjusted according to the glomerular filtration rate – GFR) or matching placebo. Primary study outcome was the composite of major cardiovascular event (nonfatal MI, nonfatal stroke) or death from cardiovascular causes. 36.5% of participants had a history of cardiovascular events. Mean follow-up was 4.7 years.	Average dose of simvastatin was 22.3 mg/day in the fenofibrate group and 22.4 mg in the placebo group. Adherence to trial medications was 80% at the end of trial. There was no between group difference in risk for the combined primary outcome associated with combination vs. statin monotherapy (HR = 0.92, 95% CI 0.79-1.08, p=0.32). In addition, there were no significant between group differences in risk of fatal & non-fatal stroke (HR = 1.05, 95% CI 0.71-1.56) or non-fatal stroke (HR=1.17, 95% CI 0.76-1.78) when fenofibrate combination therapy was compared to simvastatin monotherapy.

8.5 Hyperlipidemia

8.5.2 Treatment of Hyperlipidemia and the Risk of Stroke

Table 8.5.2 Treatment of Hyperlipidemia with Statins and Risk of Stroke

Author, Year Country Pedro Score	Methods	Outcomes
CARE Study (Plehn et al. 1999; Sacks et al. 1996) USA/Canada 8 (RCT)	4,159 patients, aged 40 – 80 years, with history of myocardial infarction and normal serum cholesterol of <6.2mmol/L and LDL of 3.0 – 4.5 mmol/L were randomized to receive either Pravastatin 40 mg, once per day or a matching placebo.	1996 – There was a reported 24% reduction in the primary outcome of fatal coronary event or nonfatal myocardial infarction group receiving Pravastatin when compared to the placebo group (p=0.003). The frequency of stroke was reduced by 31% (p=0.03). 1999 – pravastatin lowered total serum cholesterol by 20% & LDL by 32%. There was a 32% reduction of total stroke in the treatment group compared to placebo (p=0.03) and 27% reduction of TIA & non-fatal stroke (p=0.02). Pravastatin significantly reduced stroke and stroke/TIA incidence in patients with higher lipid levels but not in patients with lower baseline levels.
GREACE (2002) Greece 6 (RCT)	1,600 patients with history of MI or >70% stenosis of at least 1 coronary artery, LDL-C>100mg/dl, triglycerides <400 mg/dl and age <75 were randomized to receive either structured care (n=800) or usual care (n=800) for hyperlipidemia. Patients in the structured care group received atorvastatin, starting dose 10 mg/day and titrated up to a maximum dose of 80 mg/day to reach the National Cholesterol Education Program goal of	Mean follow-up was 3 years. In the structured care group, 100% of patients received treatment with atorvastatin. After titration doses ranged from 10mg/day to 80 mg/day (mean = 24 mg/day). 95% of structured care patients had recorded LDL-C levels <100mg/dl (2.6 mmol/l). In the usual care group, 26% received lipid-lowering drugs and only 3% reached guideline treatment goals. Patients in the structured care group had a significantly reduced risk for the

	LDL-C <2.6 mmol/L and were followed by the university clinic. Evaluations were conducted every 6 weeks to assess and modify drug treatment as required. Usual care was physician's standard and may have included lifestyle change (diet, exercise, weight loss) and any drug treatments, as necessary. Follow-up was conducted by the healthcare professional of the patient's choice outside of the hospital. Primary study endpoints were all-cause and coronary mortality, coronary morbidity and stroke.	combined study end point (RR = 0.49, p<0.0001). There were 43% fewer deaths from all causes in the structured care group (p=0.0021) and 47% fewer stroke events (p=0.034) when compared to usual care.
MRC/BHF Heart Protection Study (2002) UK 8 (RCT)	20,536 adults with coronary disease, or diabetes were randomly assigned to receive 40 mg of Simvastatin daily or matching placebo. Treatment period was 5 years.	There was a significant reduction in the number of fatal or nonfatal strokes associated with active treatment (444 or 4.3% vs. 585 or 5.7%, p<0.0001).
PROSPER Study Group (2002) Scotland 8 (RCT)	40 mg/day of pravastatin or matching placebo.	Mean length of follow-up was 3.2 years. Pravastatin lowered LDL by 34%. Risk of the combined primary outcome of coronary death, non-fatal MI and fatal or non-fatal stroke was reduced in the treatment group compared to the placebo (hazard ratio = 0.85, p=0.014). When considered alone, risk of stroke appeared unaffected by the intervention (hazard ratio = 1.03).
LIPID Trial (2000) New Zealand 9 (RCT)	9,014 patients with previous MI or unstable angina during the previous 3 months to 3 years, with hyperlipidemia were randomized to receive either 40 mg of Pravastatin or placebo. The primary end point was death due to coronary artery disease.	Mean follow-up period was six years. The risk of stroke among patients given placebo was 4.5%, compared to 3.7% for patients receiving Pravastatin. The associated relative risk reduction was 19% (95% CI 0-34%, p=0.05). Post hoc analysis (2004) revealed treatment with pravastatin in patients with low LDL and low HDL-C significantly reduced major coronary events, stroke and mortality (all causes) (RRR=51%).
CARDS (2004) UK 8 (RCT)	2,838 patients with Type 2 diabetes aged 40 – 75 years (with no prior CAD, LDL ≤4.14 mmol/L, fasting triglyceride ≤ 6.78 mmol/L and one of retinopathy, albuminuria, smoking or hypertension) were randomized to receive 10 mg daily of Atorvastatin (n=1,428) or matching placebo (n=1,410).	Mean duration of follow-up was 3.9 years. Treatment with Atorvastatin was associated with a 37% reduction in major cardiovascular events when compared to the control group (p=0.001). A 48% reduction in stroke was reported. Incidence of first or subsequent major cardiovascular events was 19.5 per 1000 person years in the treatment groups vs. 31.8 per 1000 person years in the control group. Allocation to 10 mg Atorvastatin daily would result in 50 fewer first or secondary major cardiovascular events over a period of 4 years. Overall frequency of adverse reactions or events did not differ between treatments. 10% of the treatment group discontinued the study drug due to an adverse event, and 9% in the placebo group.

ASCOT–LLA (2005) UK, Ireland, Scandinavia 8 (RCT)	10,305 patients with hypertension (controlled via concurrent participation in assessment of antihypertensive regimens) and total serum cholesterol concentration of ≤ 6.5 mmol/L were randomly allocated to a treatment group (10 mg Atorvastatin daily) or placebo group.	Treatment was stopped after 3.3 years. Significantly fewer primary events (non-fatal MI & fatal CHD) had occurred in the treatment group than the placebo (hazard ratio = 0.64, p=0.0005). Risk of fatal & non-fatal stroke was also lower in the treatment group (hazard ratio = 0.75, p=0.024).
SPARCL Study Investigators (2006) International 9 (RCT)	4,732 individuals with previous stroke/TIA 1 – 6 months prior to enrolment, and with LDL between 2.6-4.9 mmoL/L and no known history of coronary heart disease, were randomly assigned to receive either 80 mg/day Atorvastatin or matching placebo. Patients were assessed at 1, 3, and 6 months, then every 6 months thereafter. Primary study outcome was fatal or non-fatal stroke event. Secondary composite outcomes included stroke or TIA, major coronary event, major cardiovascular event, acute coronary event, any coronary event, revascularization procedure, or any cardiovascular event.	Mean follow-up was 4.9 years. In patients assigned to treatment with Atorvastatin, mean LDL level during the trial period was 1.9 mmoL/L vs 3.3 mmoL/L in patients assigned to the placebo. Significantly fewer fatal/nonfatal strokes occurred in the treatment group vs. placebo (p=0.05). Treatment was associated with a 16% relative risk reduction for the primary outcome (adjusted HR=0.84 95% CI 0.71 – 0.99, p=0.03). Similarly, for the combined outcome of stroke and TIA, treatment with atorvastatin was associated with a significant reduction in risk (HR = 0.77 95% CI 0.67-0.88, p<0.001). When examined by stroke type, the HR for ischemic stroke was 0.78 (95% CI 0.66-0.94) and 1.66 (95% CI 1.08-2.55) for haemorrhagic stroke. There were no significant between group differences for serious adverse events.
CORONA Study Investigators (2007) International 9 (RCT)	5,011 patients >60 years of age with systolic heart failure were randomly assigned to receive either 10 mg/day rosuvastatin (n=2,497) or matching placebo (n=2,514). 12% of patients in the treatment and 13% in the control condition reported history of previous stroke. Primary study outcome was the composite of death from cardiovascular causes, nonfatal MI and nonfatal stroke. Assessments were conducted at 6 weeks and 3 months following randomization and then every 3 months thereafter.	Median follow-up was 3.2 years. There were no significant between group differences reported for the pre-specified combined study outcome (HR=0.92, 95% CI 0.83-1.02, p=0.12). There were also no between group differences for death from cardiovascular causes (HR=0.97, 95% CI 0.87-1.09, p=0.60). There was a significant reduction in the combined outcome of fatal or nonfatal MI or stroke associated with treatment with rosuvastatin (HR=0.84, 95%CI 0.70-1.00, p=0.05).
GISSI-HF Investigators (2008) Italy (RCT)	4,574 patients (>age 18) with symptomatic heart failure were randomly allocated to treatment with 10 mg/day rosuvastatin (n=2,285) or matching placebo (n=2,289). 4.3% of participants in the treatment condition and 4.8% in the placebo condition reported a history of previous stroke. Primary study outcomes were time to death and time to death or hospital admission for cardiovascular reasons. Secondary outcomes included stroke. Patients were assessed at 1, 3, 6 and 12 months, and every 6 months thereafter.	Median follow-up was 3.9 years. There were no between group differences for either of the study outcomes. In addition, there were no significant between group differences in rates of either myocardial infarction or stroke (fatal or non-fatal). Over the course of follow-up, LDL-C concentrations decreased in the treatment group by 27%, whereas there was no significant change in LDL-C in the control group (p<0.0001 for time X treatment interaction).

8.5.2.1 Statins and Functional Outcome

Table 8.5.2.1 Pre-Stroke Statin Treatment and Stroke Outcome

Author, Year	Methods	Outcomes

Country Pedro Score		
Marti-Fabregas et al. (2004) Spain No Score	167 patients with first-ever, acute stroke (within 24 hours) were assessed prospectively re: statin use, stroke severity using the National Institute of Health Stroke Scale (NIHSS) and functional outcome at 3 months with the modified Rankin Scale (mRS) and Barthel Index (BI). Good outcome was defined as mRS = 0-1 or BI score of 95-100.	30 patients (18%) were being treated with statins at the time of admission. While NIHSS scores were lower in the statin group, the difference was not significant (p=0.76). There was also no significant between-group difference in terms of proportion of patients demonstrating neurological progression. However, the proportion of patients with a "good outcome" on the BI at 3-months was significantly higher in the group that was pre-treated with statins (76.7% vs. 51.8%, p=0.015). The mRS ratings at three months demonstrated a similar trend (p=0.059). Independent predictive factors for good outcome on the BI were NIHSS score at admission (OR=0.72, 95% CI 0.65-0.80), age (OR=0.96, 95% CI 0.92-0.99) and statin group (OR=5.55, 95% CI 1.42-17.8).
Yoon et al. (2004) USA No Score	Data on statin use, risk factors and stroke severity were recorded on admission for 433 stroke patients. Stroke outcome was assessed at discharge using the modified Rankin Scale (mRS). Good outcome was defined as a discharge mRS score <2.	22% (n=95) of patients were taking statins at the time of admission. 27% of patients in the statin group and 24% of patients in the non-statin group reported a history of previous stroke. There was a greater proportion of patients in the statin group with a good outcome than in the non-statin group (51.2% vs. 38.2%, p=0.03). On multivariate analysis, significant predictors of good outcome were age OR=2.7, 95% CI 1.7-4.3), NIHSS score (OR=7.2, 95% CI 3.5-14.8), WBC count (OR=3.5, 95% CI 1.2-10.1) and statin use (OR=2.9, 95% CI 1.2-6.7).
Elkind et al. (2005) USA No Score	A retrospective analysis of data collected from 650 patients with first-ever ischemic stroke, enrolled in the Northern Manhattan Study. NIHSS was used to assess severity of stroke and the Barthel Index at 6 months was used to assess functional outcome. BI scores were categorized as poor (<60) or excellent (≥95) in separate analyses. Mortality was assessed at 30 and 90 days post stroke.	8.8% of patients were identified as taking lipid-lowering agents at the time of stroke. 90.9% of these were taking statins. While in hospital significantly more of the individuals not using a lipid lowering medication experienced worsening (6.3% vs. 18.2%, p=0.04)and at 90 days, there were fewer deaths among individuals using a lipid-lowering agent at the time of the stroke admission (1.8% vs. 10.6%; p=0.03). However, there was no significant difference in initial NIHSS scores between groups (lipid-lowering vs. non-lipid-lowering). There was also no between group differences for either poor (p=0.51) or excellent (p=0.95) 6-month outcome.
Moonis et al. (2005) USA No Score	In a retrospective study, data was collected from case report forms and used to divide patients into 3 groups: i) pre-treated (n=129) ii) started on statin within 4 weeks following stroke (n=123) and iii) no statin use (n=600). Primary outcome was favourable functional outcome defined as ≤2 on the NIHSS and mRS score ≤2 at 12 weeks.	55/129, 50/123 and 176/600 individuals in the pre-treatment, after stroke and never used statin groups, respectively, had history of previous stroke. There was a significant difference in outcome between groups. More individuals in the statin after stroke group experienced a good outcome than in either of the other two groups (p=0.002), although there was a positive trend toward favourable outcome noted in the pre-treated group. On multivariate analysis, statin use within 4 weeks following stroke (p=0.03), treatment with citicoline (p=0.028) and small vessel stroke (p=0.008) were significant, independent predictors of mRS≤2. Again, pre-treatment with statins approached

		significance (p=0.08).
Blanco et al. (2007) Spain 6 (RCT)	89 patients on statin treatment at the time of acute admission (≤24 hours) for ischemic stroke were randomly assigned to either continued treatment with immediate atorvastatin (20 mg/day; n=43) or withdrawal of statin for 3 days (n=46). On day 4, patients randomized to the withdrawal condition began atorvastatin therapy (20 mg/day). Primary study outcome was death or dependency at 3 months. Dependency was defined as mRS>2. Secondary outcomes included early neurologic deterioration (END) at days 4 – 7 and infarct volume.	There was a greater frequency of dependency at 3 months (60% vs. 39%, p=0.04), END (65.2% vs. 20.9%, p<0.0001) and larger infarct volume (p=0.002) in the patients randomized to statin withdrawal vs. the non-withdrawal group. There was an elevated risk for death and dependency associated with statin withdrawal vs. continued therapy (OR=4.66, 95% CI 1.46-14.91 – adjusted for age and NIHSS at admission) in addition to an increased risk for END (adj. OR = 8.67, 95% CI 3.05-24.63).
Reeves et al. (2008) USA No Score	Over a 6-month period, 1,360 admissions for acute stroke were identified as part of the Michigan Acute Stroke Care Overview and Treatment Surveillance System. Data abstraction included information on pre-admission medication use. Functional status was determined by the mRS score at discharge from hospital. Poor stroke outcome was defined as mRS ≥4.	22.7% of patients were taking statins prior to admission. 37.7% of the total sample had experienced a previous stroke. Pre-treatment with statins was associated with a non-significant reduction in the odds for poor functional outcome (OR=0.74, 95% CI 0.52-1.02). There was a significant interaction between statin use and race such that pre-treatment with statins were associated with reduced risk for poor outcome in whites, but a non-significant increase in risk for blacks.
Goldstein et al. (2009) from the SPARCL Study (Amarenco et al. 2006) 9 (RCT)	Ischemic and/or haemorrhagic strokes were recorded in 576 patients from the SPARCL trial; 265 randomized to receive atorvastatin (80 mg/day) and 311 to the placebo-condition. A secondary analysis was performed for all first outcomes events, ischemic stroke (IS) and haemorrhagic stroke separately. Stroke severity (NIHSS and mRS where mRS 4-5 = severe, mRS 2-3 = moderate and mRS 0-1 = mild stroke) and functional outcome (BI) were also examined. BI scores were categorized as <60, 60 – 95 and >95. Index strokes (previous stroke at time of randomization) were also evaluated for severity and outcome.	There was no significant difference in severity of outcome IS associated with statin treatment based on the mRS, NIHSS or BI. When the analysis was restricted to individuals with ischemic stroke outcome events only, there was a non-significant trend toward reduction in severity of outcome associated with use of atorvastatin (p=0.065). There were also proportional reductions in fatal, severe, moderate, mild stroke and TIAs and an increase in event-free participants randomized to receive atorvastatin (p<0.001). Treatment with statins had no effect on outcome severity for haemorrhagic stroke.
Yu et al. (2009) Canada No Score	Retrospective chart review of 553 patients with acute ischemic stroke. Outcomes of interest were initial stroke severity (Canadian Neurological Scale) and early functional outcome (mRS). Severe stroke was defined as CNS score ≤7 and poor functional outcome as mRS score >3, 10 days after the stroke event.	38.7% of patients had experienced previous stroke or TIA. Multivariate logistic regression (adjusted for age, DM, CAD, hypertension, AF, hyperlipidemia, BP and initial stroke severity) demonstrated that pre-stroke use of statins (adj. OR = 0.50, 95% CI 0.25-1.00), as well as the combination of pre-stroke statins, antihypertensives and antiplatelets (adj. OR = 0.37, 95% CI 0.16-0.87) were associated with favourable functional outcome at 10 days. Neither pre-treatment with statins nor the combination of the 3 agents was associated with initial stroke severity.
Ni Chroinin et al. (2011) Ireland No Score	As part of the North Dublin Population Stroke Study (in which patients with stroke and/or TIA were recruited within 72 hours of qualifying event), 448 adult patients with new ischemic stroke were identified. Patients who had	Both pre-treatment and acute treatment with statin therapy were associated with reductions in early (7-day OR= 0.08; 95% CI 0.02-0.38 for pre-stroke; OR=0.09, 95% CI 0.03-0.32 for acute treatment) and later risk (1-year OR=0.45, 95% CI 0.26-0.78 for pre-stroke

	received a pre-stroke statin were compared to those who were prescribed a statin within 72 hours following the qualifying stroke event and those who received no statin therapy in terms of mortality and functional outcome (mRS). Good functional outcome was defined as mRS scores of 0-2. Follow-up assessments were performed at 7,28, 90 days and 1 year.	treatment; OR=0.23, 95% CI 0.13-0.40 for acute treatment) for mortality when compared to untreated patients. Logistic regression analysis demonstrated that both PRE stroke statin use and new acute treatment were independently associated with mortality at 7 days, 90 days and 1 year. Similarly, both pre-treatment and new acute treatments were associated with good functional outcome [pre-stroke statin therapy (vs. no statin therapy) OR = 1.68 (95% CI 0.97-2.9, p=0.06) at 7 days, OR=1.8 (95% CI 1.08-3.01): acutely prescribed therapy, OR = OR for good functional outcome = 2.23 (95% CI 1.35-3.71) at 7 days, 2.20 (95% CI 1.36-3.56) at 90 days]. On logistic regression, prestroke statin use was significantly associated with good function only at 90 days. At all other time points, for both pre-stroke and acute statin use, the authors identified a trend toward a significant association between statins and good functional outcome.
Dowlatshahi et al. (2012) Canada No score	From the Registry of the Canadian Stroke Network, 2,466 individuals with Intracerebral Hemorrhage (ICH) were identified. The impact of pre-statin use on stroke severity was explored based on the Canadian Neurological Scale (CNS), the individual's modified Rankin score at discharge, and mortality rates at 30 days and 6 months.	Pre-ICH statin users were less likely to have a severe stroke (CNS ≤7) compared to non-statin users (55% vs. 63%, p=0.0003). Statin users and non-statin users shared more similar outcomes in terms of poor discharge outcomes (70% vs. 67%, p=0.16), 30-day mortality (36% vs. 37%, p=0.76), and 6-month mortality (43% vs. 43%, p=0.97). A post-hoc analysis removing stroke severity and intraventricular hemorrhage found no changes in association with the exception of pre-statin use being associated with decreased 6-month mortality (adjusted OR, 0.74; 95% CI, 0.59-0.93;P=0.009).
Hjalmarrson et al. (2012) Sweden No score	This study examined pre-stroke statin use on stroke severity (NIHSS), functional outcomes (mRS) and survival in older patients (mean age 78 years). Functional outcomes and survival were measured at 12-months post-stroke. Patients included were not receiving thrombolytic therapy. A total of 799 patients were included; of which, 183 were pre-stroke statin users. At 12-months 67.1% of participants were reached for follow-up.	Using a binary logistic regression, adjusting for age, sex, and associated pathology, statin treatment had no effect on stroke severity (OR=0.76; 95% CI, 0.46-1.25; P=0.28). Acute survival, 30-day all-cause mortality, did not improve with pre-statin use (HR=1.80; 95% CI, 0.75-4.29; P=0.19) adjusting again for age, sex, stroke severity and associated pathology. In terms of secondary outcomes, those treated with statins had better 12-month survival, and improved functional outcome at both 90 days and 12-months. Of note, on hospital admission premorbid statin users had significantly lower mean serum levels of total cholesterol (P<0.001), LDL cholesterol (P<0.001), and high density lipoprotein cholesterol (P=0.002); however, serum level of triglycerides was higher (P=0.011). Statin use pre-stroke was also strongly associated with cardiovascular conditions and diabetes mellitus.
Phipps et al. (2013) USA No score	A secondary analysis was conducted using data obtained from the Stroke Center at Hartford Hospital Database. Included patients were a minimum of 80 years old and had acute ischemic stroke; however those with intracerebral or	804 subjects, with a mean age of 86 met inclusion criteria. The bivariate analysis between statin and non-statin users, showed no significant differences in terms of stroke severity (p=0.23), or in-hospital mortality or discharge to hospice (p<0.12).

	subarachnoid hemorrhage or with TIA were excluded. The impact of pre-statin use on admission NIHSS, and in-hospital mortality or discharge to hospice were examined.	

8.6 Infection

8.6.1 Pneumonia

Table 8.6.1 Macrolide Antibiotics and the Prevention of Cardiovascular Events and Infection

Author, Year, Country Pedro Score	Methods	Outcomes
ACADEMIC trial (Anderson & Muhlestein 2000; Anderson et al. 1999; Muhlestein et al. 2000) USA 8 (RCT)	302 patients were randomized to receive 500 mg/day azithromycin for 3 days and then 300 mg/week for 3 months (n=150) or a matched placebo (n=152). Patient inclusion criteria: seropositive reaction to C. pneumoniae, coronary artery disease (CAD), over 18 years of age and life expectancy of >2 years Endpoint events were cardiovascular death, resuscitated cardiac arrest, nonfatal MI or stroke, unstable angina requiring hospitalization & unplanned coronary interventions.	At 6 months, the global inflammatory marker scores were lower in the treatment group (p=0.03) as were the change scores over time (p=0.01). However, there was no difference between 2 groups for combined cardiovascular events (p=0.60). The number of strokes were the same in each group (1/ group) and the distribution of events was the same. At 24 months, there was no significant difference in the combined primary event end point between groups (hazard ratio for azithromycin = 0.89, p=0.74). Of 63 events, there were 4 strokes in 24 months which represented a small non-significant reduction in total events noticed in the treatment group (p=0.35; p=0.31 for stroke).
ACES (2005) USA 9 (RCT)	4012 patients with stable coronary artery disease (CAD) were randomly allocated to receive treatment with Azithromycin (600 mg tablet) or matching placebo, once per week for one year. Mean follow-up was 3.9 years.	There were no significant differences between groups on the primary, composite endpoint (death from CAD, nonfatal MI, revascularization procedure or hospitalization for unstable angina). There were no significant differences demonstrated between groups for any secondary study endpoints including stroke. Significantly more patients in the treatment group reported symptoms of nausea, abdominal pain and diarrhea than in the control group.
SPACE (2005) Netherlands 8 (RCT)	509 patients with peripheral arterial disease (PAD) were randomized to receive a 3-day course of azithromycin (500 mg/day; n=257) or matching placebo (n=252). Patients were followed for 2 years.	38% of patients in the treatment group experienced clinical endpoints (coronary, cerebral peripheral events or death) compared to 33% in the control group (p=0.26). There was no significant difference reported between groups for cerebral events (any stroke or TIA; p=0.76), coronary events (p=0.40) or peripheral arterial events (p=0.45). There was no difference in mean seropositivity between groups, although in subjects who reached a cardiovascular or peripheral arterial endpoint, there was a higher average IgA-titre than for subjects who did not experience either endpoint (p=0.02 and p=0.01, respectively).
Joensen et al. (2008) International 8 (RCT)	507 patients with PAD were randomly assigned to treatment with roxithromycin (300mg/day for 28 days) or a matching	There was a non-significant reduction in primary study outcomes (adj. HR = 0.86, 95% CI 0.62-1.19). There were no between group differences in incidence of MI, strokes

	placebo. Mean follow-up was 2.1 years with assessments performed every 6 months. Primary study outcome was peripheral revascularization, death, and major lower limb amputation. Secondary outcomes included thrombosis, stroke, TIA and MI.	or thrombotic events. There were fewer strokes in the treatment group, but this did not represent a significant reduction in risk (HR=0.82 95% CI 0.25 – 2.68).
Dogra (2012) International No Score	40 patients with documented evidence of CAD were screened for immunoglobulin G titers against C. pneumonia and grouped into either the study group (patients with positive titer, n=32) or control group (patients with negative titer, n=8). The study group received oral azithromycin (500mg once daily for 5 days which was repeated after a gap of 10 days). Those in the control group did not have azithromycin added to the standard CAD treatment. Primary outcomes were: death by any cause, recurrent myocardial infarction, coronary revascularization procedure or hospitalization for angina.	30 of 32 patients receiving azithromycin, in addition to regular CAD treatment, completed the 1-year trial period. The remaining 2 patients had to undergo percutaneous coronary intervention in the first quarter of the study. In the control group, one participant died, one had to undergo coronary artery bypass graft surgery, and one had a percutaneous coronary intervention. Administration of azithromycin was associated with a decreased risk of CAD ($\chi^2 = 7.006$, $p<0.01$).
Kalra et al. (2015) United Kingdom RCT (9) TPS=NA N_{Start}=1224 N_{End}=1217	**Population:** Experimental Group (EG; n=615): Mean age=77.7±11.9yr; Gender: Males=265, Females=347. Control Group (CG; n=602): Mean age=78.0±12.2yr; Gender: Males=258, Females=343. **Intervention:** The EG was treated with antibiotics although choice was determined by local antibiotic policy. When no such policy was in place, amoxicillin combined with clarithromycin was recommended. The CG received standard care only. The treatment was provided for 7d within 48hr of stroke onset. Assessments were conducted at 2, 7, 10, 14 and 90d. **Outcomes:** Incidence of stroke extension; Incidence of neurological events; Mortality rate; National Institutes of Stroke Scale (NIHSS); Modified Rankin Scale (mRS); Incidence of pneumonia.	There was no significant difference between the EG and CG regarding the incidence of stroke extension over the course of the study (OR 1.03, 95% CI 0.54-1.96, p=0.98). There was no significant difference between the EG and CG regarding the incidence of neurological events (which included intracerebral hemorrhages) over the course of the study (OR 1.15, 95% CI 0.49-2.78, p=0.84). All-cause mortality did not differ between the EG and CG at 14d (OR 0.95, 95% CI 0.62-1.44, p=0.796) or at 90d (OR 1.22, 95% CI 0.9-1.64, p=0.204) NIHSS score was significantly higher for the EG compared to the CG at 14d (OR 1.3, 95% CI 0.6-2.01, p=0.001). There was no significant difference between groups in the number of patients who scored 0-2 on the mRS at 90d (OR 0.87, 95% CI 0.6-1.24, p=0.448). Incidence of pneumonia did not differ between groups according to the algorithm-defined diagnosis (OR 1.21, 95% CI 0.71-2.08, p=0.489) nor the physician-defined diagnosis (OR 1.01, 95% CI 0.61-1.68, p=0.957).

8.7 Lifestyle Modification

8.7.1 Physical Activity

8.7.1.4 Interventions to Promote Physical Activity Following Stroke

Table 8.7.1.4 Interventions to Promote Physical Activity Following Stroke

Author, Year Country Pedro Score	Methods	Outcomes
ExStroke Pilot Trial Boysen et al. (2009) International 8 (RCT)	314 patients with stroke within 90 days, (aged ≥40 years and able to ambulate independently with/without assistive device use) were randomly allocated to either treatment (n=157) or control (n=157) conditions. While still in hospital, those in the treatment condition received instructions for a detailed, individualized training programme to be followed post discharge. At follow-up visits (once every 3 months for one year and then every 6 months until the end of the study) at a physiotherapist reviewed the programme and made adjustments as necessary. Telephone calls were made between visits to ask about activity and encourage participation. Individuals in the control condition received information regarding physical activity, but no specific, personalized instruction or telephone calls. They were seen in clinic visits with the same frequency as the intervention group. Primary outcome was level of physical activity as assessed on the Physical Activity Scale for the Elderly (PASE).	In the treatment group, there was a non-significant increase in PASE scores over time. There was no change in PASE scores over time in the control group. There were no significant between group differences in PASE scores (p=0.36) even when controlling for pre-stroke PASE. There were no significant between-group differences in terms of recurrent events (p=0.51), number of first falls (p=0.70) or functional outcome as assessed on the mRS at any of the follow-up visits (p = 0.10, 0.25, 0.66 and 0.98 at 3, 6, 12 and 24 months, respectively).

8.7.2 Diet

Table 8.7.2 Dietary Interventions in Secondary Prevention

Author, Year Country Pedro Score	Methods	Outcomes
DASH Research Group Appel et al. (1997) USA 8 (RCT)	Patients were randomized to receive a control diet (n=151), a diet rich in fruits and vegetable (n=154) or a diet rich in fruits and vegetables and low in saturated fat/low in dairy products-DASH diet) (n=151) for 8 weeks.	For systolic and diastolic blood pressures, there was a gradient across diet types. The greatest reductions were observed among subjects receiving the DASH diet, followed by those consuming the diet high in fruits and vegetables, and finally, the control diet.
Lyon Diet Heart Study De Lorgeril et al. (1999) France 7 (RCT)	423 individuals, age ≤70, with a history of first myocardial infarction were randomized to either a low-fat, low cholesterol Mediterranean-type diet or to a control group who were maintained on a "prudent western-type" diet. Three composite outcomes were assessed: CO1=cardiac death and nonfatal myocardial infarction; CO2=CO1 + unstable angina, stroke heart failure, pulmonary or peripheral embolism; CO3 = CO2 + minor events requiring hospital admission.	CO1 was reduced in the experimental (Mediterranean diet) group as compared to the control (prudent Western diet) group (p=0.0001). The combined primary & secondary end points (CO2; p=0.0001, adjusted risk = 0.33 & CO3 ; p=0.0002; adjusted risk ratio = 0.53) were also reduced. Traditional risk factors, high serum cholesterol and blood pressure, were independent and joint predictors of recurrent myocardial infarction.
Sacks et al. (2001) USA 8 (RCT)	Patients with hypertension and without were randomized to receive the DASH diet (n=208) or a control diet (n=204). Within the assigned diet participants ate foods with high, intermediate and low sodium levels. Patients consumed each	DASH diet was associated with significant reductions in systolic blood pressure at each sodium level, compared to control diet. The DASH diet was associated with significant reductions in diastolic blood pressure at both high and intermediate sodium levels.

	of these diets for 30 days, assigned by crossover design.	
Indo-Mediterranean Diet Heart Study Singh et al. (2002) India 8 (RCT)	1000 patients with a history of angina pectoris, MI, or CAD risk factors (hypercholesterolemia, hypertension, diabetes mellitus) were randomized to receive either a diet rich in whole grains, fruits, vegetables, walnuts and almonds (n=499) or a control diet similar to the national cholesterol education program prudent diet (n=500). Two-thirds of patients in both groups were vegetarians. Length of follow-up was 2 years.	Intervention was associated with a significantly increased consumption of vegetables, legumes, walnuts and almonds ($p<0.001$). Mean intake of α-linolenic acid was greater in the intervention group ($p<0.001$). At 2 years, both groups demonstrated significant reductions in total cholesterol, LDL cholesterol and triglycerides. This effect was larger in the intervention group. Fasting blood glucose, body mass index, and blood pressure were significantly reduced ($p<0.0001$) in the intervention group when compared to the control group. The intervention group experienced significantly fewer cardiac endpoints. Stroke events were not an outcome of interest, however, there was no significant difference demonstrated between groups in the few stroke events or stroke deaths ($p=0.17$ & $p=0.65$ respectively) recorded.
Dehghan et al. (2012) Canada No Score	31 546 participants enrolled in 2 randomized trials, the ONTARGET and TRANSCEND trials were studied. Participants were older individuals at risk of CVD and receiving effective drugs for secondary prevention. The modified Alternative Healthy Eating Index and the Diet Risk Score were used. The association between diet quality and the primary composite outcome of CV death, myocardial infarction, stroke or congestive heart failure were assessed.	Patients in the healthier quintiles of modified Alternative Healthy Eating Index scores had a significantly lower risk of CVD (hazard ratio, 0.78; 95% confidence interval, 0.71-0.87, top versus lowest quintile of modified Alternative Healthy Eating Index). The reductions in risk for CV death, myocardial infarction, and stroke were 35%, 14% and 19% respectively. The protective association was consistent regardless of whether patients were receiving proven drugs. Higher-quality diet was associated with lower risk of recurrent CVD events among older individuals.

8.7.2.1 Vitamins/Antioxidants

8.7.2.1.1 Antioxidant Vitamins on Atherosclerotic Progression

Table 8.7.2.1.1 Supplementation with Antioxidant Vitamins on Atherosclerotic Progression

Author, Year Country Pedro Score	Methods	Outcomes
ASAP Study Salonen et al. (2000; 2003) Denmark 6 (RCT)	520 smoking & non-smoking men & postmenopausal women aged 45 – 69 with elevated serum cholesterol randomized to 1 of 4 conditions: twice daily vitamin E (136 IU), twice daily vitamin C (250 mg slow-release), a combination of both (CellaVie) given twice daily or matched placebo. Primary outcome was atherosclerotic progression assessed by measurements of intima-media thickness (IMT) of the common carotid artery. The study continued for an additional 3 years, where placebo groups	At 3-year follow-up, atherosclerotic progression was significantly less in men randomized to receive a combination of both vitamins compared to all other men ($p=0.009$) or to the placebo ($p=0.008$). No significant effect was seen among women. Among men receiving combined treatment, the proportion that experienced progression was reduced by 74% when compared to placebo (OR =0.26; $p=0.003$). The probability of progression was similar in all groups of female subjects. Treatment effects were larger among smoking than non-smoking men. Among smokers, progression was reduced by 64% compared to 30% among nonsmokers.

	continued unsupplemented, but all treatment groups received the combined supplement. 440 participants completed the 6-year study.	At 6 years, there was a significant difference in IMT measurements comparing supplemented (combination treatment) participant to placebo groups from baseline (p=0.34) as well as a difference in slope across the years of study (p=0.014). As at 3 years, treatment effects were significant among men only.
SECURE Lonn et al. for the SECURE investigators (2001) Canada 8 (RCT)	732 patients 55 years of age or older who had vascular disease or diabetes & one other risk factor. The study was randomized in a 3X2 factorial design (ramipril 10 mg, ramipril 2.5 mg each with & without vitamin E 400IU, vitamin E alone or double placebo) Patients were followed for an average of 4.5 years. Atherosclerotic progression was determined by carotid intimal medial thickness (IMT).	After an average length of follow-up of 4.5 years, there was a reduced atherosclerosis progression rate for ramipril overall vs. ramipril placebo (p=0.033). In the 10 mg/day group vs. placebo (p=0.28); relative reduction in mean maximum IMT for the ramipril 10 mg group was 37% vs. placebo. Vitamin E had a neutral effect on reduction in atherosclerotic progression as well as on clinical events recorded during period of follow-up. Long-term ACE inhibitor therapy retarded the progression of atherosclerosis while vitamin E had a neutral effect.

8.7.2.1.2 Antioxidant Vitamins on Clinical Event Rates

Table 8.7.2.1.2 Supplementation with Antioxidant Vitamins on Clinical Event Rates

Author, Year Country Pedro Score	Methods	Outcomes
Steiner et al. (1995) USA 6 (RCT)	100 patient with TIA, previous minor stroke or residual neurologic deficits randomized to receive ASA (325 mg/day) or ASA (325 mg/day) + vitamin E (400IU/day) Follow-up continued for 2 years or until an endpoint was reached.	Vitamin E + aspirin groups reported significantly fewer strokes and TIA events than the group prescribed ASA alone ($p<0.05$) suggesting a beneficial effect arising from the addition of vitamin E to customary aspirin based therapy. Platelet adhesion was reduced in the vitamin E + ASA group by almost 40% over the ASA group ($p<0.0001$).
CHAOS Study Stephens et al. (1996) UK 8 (RCT)	2002 patients with coronary atherosclerosis were randomly assigned to one of two treatment conditions (800 IU vitamin E daily vs. 400 IU daily) or matching placebo condition.	Treatment with vitamin E was associated with a reduction in CV death and nonfatal MI compared to the placebo group (RR= 0.53; p=0.005). However, most of this effect could be explained by the significant effect of treatment on the risk of non-fatal MI alone (RR=0.23; p=0.005).
GISSI-Prevenzione Investigators (1999) Italy 7 (RCT)	11, 324 patients with recent MI randomized to receive n-3 Polyunsaturated Fatty Acid – PUFA - (1 g/day), vitamin E (300 mg/day), both or nothing. Mean follow-up = 3.5 years.	Treatment with n-PUFA compared to controls resulted in a relative risk reduction of 10% for the primary combined endpoint (death, nonfatal MI, stroke). All benefit was attributable to decrease in risk for overall, and cardiovascular death. When the outcome of fatal & nonfatal stroke was examined alone, however, RR=1.21 (two-way, factorial, analysis) and 1.30 (4-way, treatment group, analysis). Patients receiving vitamin E did not differ significantly from controls. In terms of fatal and nonfatal stroke outcome, RR= 0.87 (two way analysis) and 0.95 (4-way).
Heart Outcomes Prevention Evaluation (HOPE)	2,545 women & 6,996 men aged 55+ with CVD or DM and at least one other cardiovascular risk factor. Patients were	No significant differences were found in the number of deaths between those in the Vitamin E groups and those receiving a placebo (relative risk reduction = 1.05).

Study Investigators (2000) Canada 8 (RCT)	randomized in 2X2 design to receive either 400IU vitamin E/day from natural sources or matching placebo OR either Ramipril or matching placebo (ramipril results are reported elsewhere). Mean follow-up = 4.5 years.	Similar results were recorded for MI (RR=1.02) and stroke (RR=1.17). Use of vitamin E did not decrease the incidence of cardiovascular events during a follow-up period of 4 – 6 years.
Leppala et al. (2000) Finland 7 (RCT)	28,519 male smokers with no history of previous stroke were randomly allocated to 1 of 4 treatment groups; 50 mg/d vitamin E, 20 mg/d beta carotene, both or placebo. Mean length of follow-up = 6 years.	Supplementation with vitamin E was associated with a decreased risk of cerebral infarction (RR=0.70) and an increased risk of SAH (RR=2.45) among men with high blood pressure. In hypertensive men with diabetes, it lowered the risk of cerebral infarction (RR=0.33) without increasing the risk of SAH. Supplementation had no effect among men with normal blood pressure. Among men with greater alcohol consumption, beta carotene supplementation was associated with increased risk for intracerebral hemorrhage (RR=3.16) and a modest decrease in risk for cerebral infarction (RR=0.82).
Brown et al. (2001) USA 8 (RCT)	In a 3-year study, 160 patients with CAD, low LDL's and normal LDL levels were randomly assigned to 1 of 4 conditions: 1) simvastatin + niacin, 2) antioxidant vitamins (vitamins C, E, β-carotene, selenium), 3) simvastatin/niacin + antioxidants 4) placebos. The composite clinical event end point consisted of coronary stenosis, first CV event – stroke, MI, revascularization – or death.	Stenosis progressed 3.9% in placebos, 1.8% in antioxidant group, 0.7% in the simvastatin/niacin + antioxidant group. In the simvastatin + niacin group, stenosis regressed by 0.4% ($p<0.001$, vs. placebo). Risk of composite clinical event end point was 90% lower in the simvastatin + niacin group than the placebo group ($p=0.03$). Risk did not differ significantly between the placebo group and any of the remaining treatment groups. Overall, no significant benefits of antioxidant use were reported. There was a nonsignificant trend toward slowing progression of stenosis compared to placebo ($p=0.16$) and a minimal reduction in clinical event rates. When antioxidants were combined with the most effective treatment (simvastatin + niacin), clinical and arterial benefits were diminished ($p=0.02$).
MRC/BHF Heart Protection Study Heart Protection Study (2002) UK 8 (RCT)	20,536 adults (aged 40 – 80) with existing coronary disease, occlusive arterial disease or diabetes were randomized to receive antioxidant vitamins supplementation or matching placebo daily. Vitamin supplementation consisted of 600 mg. Vit. E, 200 mg. Vit. C & 20 mg. beta-carotene. Length of follow-up = 5 years.	While vitamins appeared to be safe to use within this population and their use resulted in increased blood concentrations of the vitamins, they did not produce any significant reductions in 5-year mortality or incidence of primary outcome events. There was no clear indication of either benefit or harm. There were no significant differences between groups in the number of combined fatal and nonfatal stroke events (RR= 0.99; $p=0.8$) , nor were there significant differences based on type or severity of stroke
HOPE & HOPE-TOO Bosch et al. (2005) Canada 9 (RCT)	16,571 patients with vascular disease or diabetes mellitus were randomized to receive either a daily dose of 400 IU of vitamin E (n=8281) or matching placebo (n=8290). Mean duration of follow-up = 7.0 years.	There were no significant differences in risk for any cardiovascular events or death (RR=1.04, $p=0.34$) or for stroke alone (RR=1.10, $p=0.27$) between treatment and placebo conditions in the HOPE trial. Similar findings were reported among patients enrolled in the extended HOPE-TOO trial where RR=1.05 ($p=0.31$) for any cardiovascular events or death and RR=1.09 for stroke ($p=0.39$) when comparing treatment with placebo groups. Higher rates of heart failure and hospitalization for heart failure were noted among patients allocated to

		the treatment condition (RR= 1.13 & 1.21, p<0.05 for HOPE and RR=1.19 & 1.40, p<0.01 for HOPE-TOO)
WACS Study Cook et al. (2007) USA 9 (RCT)	8,171 female patients with previous history of CVD (including stroke) or ≥3 risk factors for CVD were randomized to receive ascorbic acid (500mg/day), vitamin E (600 IU every other day) or beta carotene (50 mg every other day) either alone or in combination in a 2X2X2 factorial design. Matching placebos were provided for non-active agents. Primary study outcome was combined CVD morbidity and mortality (including MI, stroke & coronary revascularization procedures). Individual components were assessed as secondary outcomes. Mean follow=up = 9.4 years.	There was no significant effect of treatment with ascorbic acid (vitamin C), vitamin E or beta carotene on the primary study outcome. In addition, there was no significant effect noted on any of the individual secondary outcomes, including stroke. However, on compliance-adjusted analysis, there was a 27% reduction in stroke associated with active vitamin E treatment (RR=0.73, 95% CI 0.54-0.98, p=0.04) and in patients with previous CVD events, there were significantly fewer major CVD events (RR=0.89, 95% CI 0.79-1.00, p=0.04). There were no significant 2 or 3-way interactions between agents for the primary study endpoint. However, for stroke, there was a significant 2-way interaction between vitamin C and vitamin E, such that patients receiving both agents experienced fewer strokes (p=0.04).

8.7.2.2 Homocysteine

8.7.2.2.1 B-Vitamins on Atherosclerotic Progression

Table 8.7.2.2.1 Effect of Supplementation with B-Vitamins on Atherosclerotic Progression

Author, Year Country Pedro Score	Methods	Outcomes
Till et al. (2005) Germany (RCT)	50 individuals with carotid intima-medial thickness (CIMT) ≥1 mm (predictive of cardiovascular events) were randomly assigned to receive either vitamin supplementation (2.5 mg folic acid, 25 mg vitamin B_6 and 0.5 mg vitamin B_{12}) or matching placebo for one year.	At one year, plasma homocysteine (Hcy) decreased significantly in the treatment group but remained unchanged in the control condition (between group comparison (p<0.001). CIMT decreased significantly following vitamin therapy while there was a non-significant increase noted in the placebo group (between groups, p=0.019). On multiple regression, change in CIMT was dependent upon treatment assignment (p=0.009) and vitamin B_{12} level at baseline (p=0.043). Hcy level at baseline and differences in Hcy at follow-up were not significant predictors of change in CIMT.
Fernandez-Miranda et al. (2007) Spain 6 (RCT)	137 patients with coronary disease and homocysteine < 9 µmol/L were randomly assigned to receive either open-label treatment with folic acid (2.5mg/day) or no treatment for a period of 3 years. Carotid intima-medial thickness (CIMT) measurements were performed at randomization and 3 years. Presence of Methylenetetra-hydrofolate reductase (MTHFR) 677TT polymorphism was assessed at baseline.	Folate levels increased and homocysteine levels decreased in the treatment group, but not in the control group. CIMT did not progress in either group. In a subgroup analysis restricted to those receiving folic acid therapy, 12 patients with MTHFR 677TT were compared to 49 patients without MTHFR 677TT. Patients with the polymorphism experienced a significant decrease in CIMT over the 3 year period (-0.11±0.14mm) vs. no change in the group without the polymorphism (p<0.05 for the between group comparison).On multiple regression, the association

		between MTHFR 677TT and CIMT did not reach significance (p=0.051)
VITATOPS (substudy) Potter et al. (2008) International 10 (RCT)	Carotid intima-medial thickness (CIMT) & flow-mediated dilation (FMD) were assessed for 162 participants a mean of 3.9 years after randomization. Participants in this substudy who had been allocated to the treatment group (n=83) received 2 mg folic acid, 25 mg vitamin B_6 and 0.5 mg vitamin B_{12}. Participants in the control condition (n=79) received matching placebo.	The mean CIMT in the treatment condition did not differ significantly from the mean CIMT in the control condition (mean difference = 0.01mm, 95% CI =-0.04 - 0.06mm). Similarly, there was no significant between-group difference in FMD (mean difference = 0.5%, 95% CI -0.73% - 1.73%). No significant between group differences in CIMT or FMD were found for different types of stroke.

8.7.2.2.2 Folic Acid, Vitamin B3, B6 and Vitamin B12 in Secondary Prevention

Table 8.7.2.2.2 Folic Acid, Vitamin B3, B6 and Vitamin B12 in Secondary Prevention

Author, Year Country Pedro Score	Methods	Outcomes
Goes Trial Liem et al. (2003, 2005) Netherlands 6 (RCT)	593 patients with stable coronary artery disease were randomly assigned to either the treatment (n=300) or control (n=293) conditions. All patients were treated with statins prior to study entry and throughout the study. Treatment participants received open-label folic acid (0.5 mg/day to start) while participants in the control condition received standard care. All patients received the same follow-up and treatment of risk factors. All were encouraged to implement dietary restrictions and quit smoking. The primary study endpoint was a composite of all vascular events (vascular death, noncardiovascular death, recurrent MI, invasive coronary procedures, stroke, TIA or any other vascular surgery).	6% and 7% of individuals in the treatment and control conditions, respectively had a history of stroke/TIA at baseline. Cardiovascular events were evenly distributed between treatment groups. In terms of the study endpoint, there was no significant difference between groups (p=0.85). 4 individuals in the treatment condition and 3 in the control group experienced CVA/TIA in 2 years of follow-up. Additional follow-up (5 years) continued to demonstrate no significant benefit associated with folic acid therapy. At 5 years, 8 individuals in the treatment group and 5 in the control group reported either a stroke/TIA (Liem et al. 2005).
VISP Trial Toole et al. (2004) USA/Canada/ Scotland 8 (RCT)	N=3680 subjects with nondisabling cerebral infarction. All patients received best medical & surgical care and, in addition, were randomly assigned to receive either daily high-dose supplementation of folic acid (2.5 mg.), vitamin B_6 (25 mg) and vitamin B_{12} (0.4 mg) or daily low-dose supplementation of the same vitamins (200µg, 6µg and 20µg respectively. Outcomes included recurrent cerebral infarction (primary), coronary heart disease (secondary) and death (secondary). Follow-up=2 years.	There was no treatment effect on any endpoint. RR for any of the outcomes (unadjusted) was 1.0. Chances of an outcome event within the 2-year follow-up period were 18% in high dose and 18.6% in the low dose group. There was, however, an association between baseline homocysteine levels and outcomes such that a 3µmol/L lower level was associated with a 10% risk reduction for stroke (p=0.05) in the low-dosage group and a non-significant trend to lowered risk (2%) in the high-dosage group.
VITATOPS (Interim report)	285 patients with previous stroke or TIA were randomly allocated to treatment	In the treatment group, homocysteine levels were significantly lower than in the control group at 6 months

Hankey et al. (2005) International 10 (RCT)	(n=143) with folic acid (2.0 mg/day), pyridoxine (25 mg/day) & (cobalamin 0.5 mg/day) or to a control group (matching placebo, n=142). Outcomes assessed at baseline, 3 & 6 months included, blood levels of fasting plasma total homocysteine, red cell folate, serum cobalamin and serum pyrixidone.	(p<0.001). Rise in baseline mean red cell folate over time (from 1998 – 2002) was not associated with reduction in homocysteine levels over the same period. Voluntary supplementation with folic acid has resulted in an increase in baseline folate, however, the homocysteine-lowering effect of treatment has not attenuated.
NORVIT Trial Bonaa et al. (2006) Norway 10 (RCT)	3749 individuals with recent MI (within the past 7 days) were randomly assigned to 1 of 4 treatment conditions: i) 0.8mg folic acid+0.4mg. vit. B_{12}=40 mg vit. B_6, ii) 0.8 mg. folic acid+0.4 mg vit. B_{12}, iii) 40 mg vit. B_6 or iv) placebo. Composite primary study endpoint was a composite of recurrent MI, stroke or sudden death attributable to coronary artery disease. Stroke was evaluated independently as a secondary endpoint. Mean follow-up was 3 years.	There was a significant reduction in homocysteine levels in individuals receiving folic acid; however, treatment with folic acid + vitamin B12 either alone or with the addition of vitamin B6 was not associated with a significant reduction in the primary study outcome. For stroke events alone, the rate ratio for treatment with folic acid + both B vitamins vs. placebo was 0.83 (95% CI 0.47 – 1.47). For those who received vitamin B_6 (groups i and iii) vs. no B_6 (groups ii and iv), the rate ratio for stroke was 0.81 (95% CI 0.54 – 1.20). On subgroup analysis, there was no significant effect of treatment on the primary endpoint for individuals with existing cardiovascular disease (including stroke) or diabetes. Overall, 5%, 4%, 4% and 3% of individuals in groups 1 through 4 reported history of stroke at baseline.
Grace et al. (2006) China 10 (RCT)	In this substudy of VITATOPS, 443 patients (with ischemic stroke within the past 7 months) were randomized to receive either treatment with 2.5 mg folic acid, 0.5 mg vitamin B_{12}, and 25 mg vitamin B_6, or matching placebo. Mean plasma total homocysteine (tHcy) levels were measured at baseline and 1-year follow-up.	Plasma total homocysteine levels were significantly lower in stroke patients receiving treatment with folate and B-vitamins at one year than in stroke patients allocated to the control condition (p<0.0001). This reduction approaches the estimated reduction projected for the VITATOPS trial.
HOPE-2 Lonn et al. (2006) International 9 (RCT)	5522 patients (aged ≥ 55 years) and with existing vascular disease or diabetes were randomly assigned to treatment (2.5 mg folic acid, 50 mg vitamin B_6 & 1 mg vitamin B_{12} per day; n=2758) or control groups (n=2764). Approximately 12% of patients in each group reported a history of stroke or TIA. Average length of follow-up was 5 years.	While, at baseline, there were no significant differences between groups, there were regional differences detected in folate and homocysteine levels. Participants from regions not requiring folate fortification had lower folate and higher homocysteine levels than participants from regions with mandatory fortification. At follow-up, treatment was not associated with reduced risk for the primary composite outcome of death from cardiovascular causes, MI or stroke (RR = 0.95 p=0.41). For stroke, treatment was associated with a reduced risk when compared to the control condition (RR= 0.75 p=0.03). When subgroup analysis was undertaken, no significant beneficial treatment effect could be determined. This included a group of individuals with prior stroke.
WAFACS Trial Albert et al. (2008) USA 9 (RCT)	In this extension of the WACS study, 5,442 women were randomized to receive either a combination pill (2.5 mg folic acid, 50 mg vitamin B6 and 1 mg vitamin B12; n=2,721) or matching placebo (n=2,721) daily. Primary study outcome was a composite of	There were no significant between-group differences on the primary study outcome at by time during follow-up. Relative risk for the composite endpoint associated with treatment vs. placebo was 1.03 (95% CI 0.90-1.19, p=0.65). For the secondary endpoint of total stroke, the RR = 1.14 (95% CI 0.82-1.57), 1.10 (95% CI 0.78-1.56,

	cardiovascular morbidity and mortality. Individual components of the composite outcome were examined as pre-specified secondary endpoints. Follow-up = 7.3 years. 64.8% and 63.5% of participants in the active and control groups reported a history of cardiovascular disease at baseline (MI, stroke, coronary revascularization, angina pectoris, TIA, carotid endarterectomy or peripheral artery surgery).	p=0.57) for ischemic stroke and 1.65 (95% CI 0.60-4.53, p=0.33) for haemorrhagic stroke. On subgroup analysis, there was no significant benefit associated with treatment (vs. placebo) for individuals with existing cerebrovascular disease in terms of the primary composite outcome (RR= 1.03, 95% CI 0.89 – 1.21, p=0.93).
SU.FOL.OM3 Galan et al. (2010) France 10 (RCT)	2,501 participants with previous history of cardiovascular disease (including stroke) were randomly assigned to 1 of 4 groups: supplementation with i) B vitamins (560µg 5-methyltetrahydrofolate, 3 mg B_6, 20µg B_{12}), ii) omega-3 fatty acids (600 mg), iii) both active treatments or iv) matching placebo. For all patients, study treatment consists of 2 capsules taken once daily. Follow-up assessments were conducted via self-report questionnaire at 6, 12 and 24 months. Median follow-up time was 4.7 years. Primary study endpoint was first major cardiovascular event (nonfatal MI, ischaemic stroke or death from cardiovascular causes). Secondary endpoints included stroke.	Approximately one-quarter of participants in each study condition reported history of previous stroke. Compared to the placebo condition, treatment with B-vitamins was not associated with reduction in risk for cardiovascular events overall (HR=0.90, 95% CI 0.66-1.23). However, there was a significant reduction in risk for stroke associated with B-vitamin therapy vs. placebo (HR=0.57, 95% CI 0.33-0.97, p=0.04). Treatment with omega-3 fatty acids was not associated with reduced risk for either cardiovascular events overall, or stroke in particular, when compared to treatment with a placebo. There were no results reported for the combined condition.
VITATOPS Hankey et al. (2010) International 10 (RCT)	8,164 participants (in 20 countries) with previous stroke or TIA were randomly assigned to receive either B-vitamin therapy (2 mg. folic acid, 25 mg. vitamin B_6, 0.5 mg vitamin B_{12}) or matching placebo. Follow-up assessments were conducted every 6 months; median duration of follow-up was 3.4 years. Primary study outcome was composite of non-fatal stroke, non-fatal MI or death from vascular causes. Secondary outcomes included stroke (fatal or nonfatal).	There reduction in risk for the composite primary study outcome associated with B-vitamin therapy when compared to placebo of marginal significance (RR=0.91, 95% CI 0.82-1.00). Analysis of secondary outcomes demonstrated no significant reduction in stroke risk associated with treatment vs. placebo (RR-0.92, 95% CI 0.81-1.06). When the authors added VITATOPS data to a meta-analysis of results from 5 previous studies comparing B-vitamin therapy to placebo, there was no significant benefit associated with therapy for reduction of risk for the composite outcome of non-fatal stroke, non-fatal MI or death due to vascular causes (RR=0.99 (95% CI 0.94-1.03). There were no serious adverse events associated with treatment.
AIM-HIGH Boden et al. (2011) USA 10 (RCT)	3414 patients were randomly assigned patients to receive extended-release niacin, 1500 to 2000 mg/day (n=1718), or matching placebo (n=1696). All patients received simvastatin, 40 to 80 mg/day, plus ezetimibe, 10 mg/day, if needed, to maintain an LDL cholesterol level of 40 to 80 mg per deciliter (1.03 to 2.07 mmol per liter). The primary end point was the first event of the composite of death from coronary heart disease, nonfatal myocardial	20.8% of patients assigned to receive niacin and 21.3% in the placebo condition had a previous history of stroke or cerebrovascular disease at baseline. Primary composite endpoint was recorded in 16.2% of patient in the placebo condition vs. 16.4% in patients receiving extended release niacin (p=0.80). In terms of risk for ischemic stroke, there was no significant between group difference reported (HR=1.61, 95% CI 0.89, 2.90) – although, there was a trend toward increased risk for all strokes associated with the use of extended release niacin (HR=1.67, 95% CI 0.93, 2.99; p=0.09).

	infarction, ischemic stroke, hospitalization for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization. Patients attended clinic visits at 6-month intervals and were contacted by telephone in alternate quarterly intervals. Mean follow-up = 3 years.	
VITATOPS Hankey et al. (2012) International 10 (RCT) *Post hoc analysis*	A *post hoc* analysis was conducted to examine possible associations between antiplatelet therapy and the impact of the folic-acid therapy provided to individuals with previous stroke or TIA on risk for study outcomes. 6,609 participants were identified as taking antiplatelet therapy at study baseline; 3306 assigned to b-vitamin therapy and 3303 assigned to placebo.	For those individuals receiving antiplatelet therapy, treatment with B-vitamins had no effect on the primary study composite outcome (HR=0.98, 95% CI 0.86, 1.11). However, for individuals not treated with antiplatelet drugs at baseline, there was a significant beneficial effect associated with B-vitamin therapy relative to the primary study outcome (HR=0.71, 95% CI 0.55, 0.90) (analyses adjusted for significant baseline imbalance in age, sex, ethnic origin, history of stroke, MI, hypertension, IHD, PAD, diabetes, cholesterol, smoking status, Oxford handicap score, pathology and cause of stroke or TIA). In addition, for those individuals not receiving antiplatelet therapy, B-vitamins were associated with a significant reduction in risk for stroke when compared to placebo (HR=0.65 95% CI 0.46, 0.91).
Arshi et al. (2015) USA RCT PEDro=6 TPS_{Mean}<120d N_{Start} =3680 N_{End}=3649	**Population:** Concurrent Antiplatelet Use: Low Dose (N=961): Mean Age=66.7yr; Gender: Male=63.8%, Female=36.2%. High Dose (N=946): Mean Age=66.6yr; Gender: Male=64.6%, Female=25.4%. No Antiplatelet Use: Low Dose (N=892): Mean Age=65.7yr; Gender: Male=61.7%, Female=38.3%. High Dose (N=881): Mean Age=66.1yr; Gender: Male=59.8%, Female=40.2%. **Intervention:** All patients received a daily dose of either a low or high dose vitamin. Low dose=200µg pyridoxine, 6µg cobalamin, 20µg folic acid. High dose=25mg pyridoxine, 0.4mg cobalamin, 2.5mg folic acid. Pills were indistinguishable, having the same colour, weight and dissolution in water. Patients were contacted every 3mo for the 2yr intervention period. Patients also received treatment to prevent recurrent strokes including risk factor control education and usually aspirin (325mg/d). Patients who were taking antiplatelet drugs concurrently with the vitamin therapy were placed in the concurrent group. **Outcomes:** Number of recurrent stroke; Number of myocardial infarction; Number of deaths from vascular causes.	Concurrent antiplatelet: High dose therapy was associated with a higher risk of stroke compared to low dose therapy (hazard ratio=1.43). No antiplatelet use: High dose therapy showed a trend towards a lower risk of stroke compared to low dose therapy (hazard ratio=0.86). The odds of a stroke, myocardial infarction or vascular death were not affected by high dose therapy. The highest cumulative incidence of recurrent stroke was observed in low dose patients without concurrent antiplatelet use. *No values given, results from figure.

8.7.2.2.3 Homocysteine-Lowering Therapy and Functional Outcome

Table 8.7.2.2.3 Homocysteine-Lowering Therapy and Functional Outcome Post-Stroke

Author, Year Country Pedro Score	Methods	Outcomes
HOPE-2 Saposnik et al. (2009) (additional analysis) International 9 (RCT)	5522 patients (aged ≥ 55 years) and with existing vascular disease or diabetes were randomly assigned to treatment (2.5 mg folic acid, 50 mg vitamin B_6 & 1 mg vitamin B_{12} per day; n=2758) or control groups (n=2764). Approximately 12% of patients in each group reported a history of stroke or TIA. Average length of follow-up was 5 years.	Overall, there was a reduced risk for stroke associated with vitamin therapy (HR=0.75, 95% CI 0.59 – 0.97). There was a higher absolute risk for stroke among the following groups: patients younger than age 70, those with history of stroke/TIA, those from regions without folic acid food fortification, history of hypertension, higher baseline cholesterol and homocysteine and those not receiving antiplatelet and lipid-lowering therapies at baseline. Vitamin therapy was most effective in patients with the highest levels of homocysteine (>13.8 ɥmol/L; HR- 0.57, 95% CI 0.33-0.97, absolute risk reduction 4.1%). The risk of disabling stroke was lower in the treatment group, though this was not significant (HR=0.64, 95% CI 0.39-1.04). More individuals with stroke recovered by day 7 or hospital discharge (15.7% vs. 9.6%) this difference was not significant (p=0.62). There was no significant between group difference in risk for poor function (MRS 3 – 6) after stroke (OR = 0.95, 95% CI 0.57 – 1.56).
Towfighi et al. (2014) USA Post-hoc analysis on RCT No Score TPS=NA N_{Start}=3680 N_{End}=2993	**Population:** Low-dose treatment group (N=1537): Median age <67yr; Gender: Males= 480, Females=243. Median age ≥67yr; Gender: Males= 508, Females= 306. High-dose treatment group (N=1456): Median age <67yr; Gender: Males= 458, Females= 246. Median age ≥67yr; Gender: Males= 473, Females= 279. **Intervention:** In a previous RCT, participants with non-disabling ischemic stroke were randomized to a high-dose treatment group and received 25 mg of pyridoxine, 0.4 mg of cobalamin, and 2.5 mg of folic acid, or to a low dose treatment group which received 200 µg of pyridoxine, 6 µg of cobalamin, and 20 µg of folic acid. Participants were assessed at one month after randomization, at 6mo, and every 6mo thereafter for 24mo. **Outcomes:** Stroke occurrence; Myocardial infarction (MI); Death.	Individuals with median age ≥67, treatment with high-dose therapy was associated with a lower risk of stroke, MI or death (HR 0.77, 95% CI 0.59-1.00). Individuals with median age <67, high-dose therapy was not associated with reduced stroke, MI, or death.

8.7.3 Smoking

8.7.3.1 Smoking Cessation Interventions

Table 8.7.3.1 Non-Pharmacological Smoking Cessation Interventions

Author, Year Country Pedro Score	Methods	Outcomes
Frandsen et al. (2012) Denmark 7 (RCT)	94 inpatients with stroke or TIA who were also smokers <age 76, were randomized to receive either a minimal smoking cessation intervention or intensive smoking cessation intervention. All patients attended a 30-min individual counseling session provided by the study nurse. Patients randomized to intensive smoking cessation intervention also participated in a 5-session outpatient smoking cessation program by an authorized smoking cessation instructor, a 30-min outpatient visit after 6 weeks, and 5 telephone counseling sessions by the study nurse. Free samples of nicotine replacement therapy were offered as part of the intensive smoking cessation program. Smoking cessation rates at 6 months were determined by self-report and verified by measurement of exhaled carbon monoxide (CO).	The 6-month cessation rate was 37.8% in the minimal intervention group vs. 42.9% in the intensive intervention group. Smoking cessation rates verified by exhaled CO levels were 28.9% in the minimal intervention group and 32.7% in the intensive intervention group. Between group differences did not reach statistical significance and participation in the intensive intervention was not associated with improved risk of smoking cessation (OR=1.19 95%CI 0.45, 3.17).

8.7.5 Behavioural Change

Table 8.7.5 Multi-factorial Behavioural Intervention on Secondary Prevention

Author, Year Country Pedro Score	Methods	Outcomes
Risk Factor Intervention Study (RIS) Fagerberg et al. (1998) (Sweden) 7 (RCT)	High-risk male patients, aged 50 – 72 with treated hypertension, were randomized to receive a multifactoral, behavioural intervention (n=253) or usual care (n=255). The behavioural intervention consisted of a program designed to change eating habits and a smoking cessation program. Patients were followed for a mean of 6.6 years.	Overall risk for cardiovascular events (both fatal and nonfatal) was 29% lower in the intervention group (p=0.041). Risk of stroke was lower in the intervention group (RR=0.53). Relative to the usual care group, the intervention group demonstrated lowered serum cholesterol (p<0.0001) and higher adjusted smoking quit rates (p=0.012) after 3 years of follow-up.
Prior et al. (2011) Canada No Score	This study tested feasibility and effectiveness of 6-month outpatient comprehensive cardiac rehabilitation (CCR) program. 110 individuals with mild disabling stroke or TIA within the preceding 12 months and ≥ 1 additional vascular risk factor were recruited from a stroke prevention clinic. All patients were assessed at baseline and participated in a 2-hour group orientation session. Smokers were encouraged to participate in the onsite group smoking cessation program. All participants were enrolled in the exercise and nutrition programs as part of the comprehensive rehabilitation program. The exercise program offered 2 options; a standard onsite program or a home-based option. Nutrition counselling emphasized a Mediterranean diet. Referrals to a psychologist were made if HADS-D ≥8. Outcomes were assessed at 6-months.	80 subjects completed CCR. There were improvements from intake to exit from program recorded for the following: aerobic capacity (+31.4%; P<0.001), total cholesterol (-0.30 mmol/L; p=0.008), total cholesterol/high-density lipoprotein (-11.6%; p<0.001), triglycerides (-0.27 mmol/L; p=0.003), waist circumference (-2.44 cm; p<0.001), body mass index (-0.53 kg/m(2); p=0.003), and body weight (-1.43 kg; p=0.001). There were non-significant, though still favourable changes reported for low-density lipoprotein (-0.24 mmol/L), high-density lipoprotein (+0.06 mmol/L), systolic (-3.21 mm Hg) and diastolic (-2.34 mm Hg) blood pressure. One half of the individuals identified as smokers at intake to CCR (n=14) reported quitting at the time of exit from the program (n=7, p=0.008).

Evans-Hudnall et al. (2012) USA 4 (RCT)	52 primarily African American and Hispanic, low socioeconomic status, first ever stroke patients were randomly allocated to a Secondary Stroke Prevention (STOP) program or usual care (UC) group. The STOP program consisted of three 30-45min cognitive behavioural therapy sessions (first session in person during acute care, second and third session biweekly over the phone). STOP program session targeted stroke knowledge and five health behaviours (exercise, fruit/vegetable intake, tobacco use, alcohol use, and medication adherence). Participants were all assessed at baseline and 4-weeks post (end of intervention).	There was no differences in demographic characteristics or health status between groups at the start of the intervention. At the 4-week follow-up, individuals in the STOP program demonstrated greater improvement in stroke knowledge compared to UC group. In addition, 4-weeks post (end of intervention) individuals in the STOP program demonstrated statistically significant differences in tobacco cessation and alcohol use compared to individual in the UC group. A higher percentage of individuals in the STOP program reported abstaining from tobacco and alcohol use.
Nolan et al. (2012) Canada 5 (RCT)	387 individuals with stage 1 or 2 hypertension were randomly assigned to a 4-month protocol of e-counselling or to a waitlisted control group. The e-counselling intervention consisted of proactively delivered emails from the Blood Pressure Action Plan (Heart and Stroke Foundation) which promoted blood pressure control through self-directed lifestyle changes, based on individual priorities, in the areas of diet, exercise and smoke-free living. Participants assigned to the waitlist control received healthline e-newsletters from the Heart and Stroke Foundation. Outcomes were systolic, diastolic, and pulse pressures, and total lipoprotein cholesterol after treatment.	No significant between group differences were demonstrated using intention to treat analysis. However, randomization was contaminated and per protocol analysis conducted. On per protocol analysis, receipt of ≥ 8 e-counselling messages (a priori therapeutic dose) was associated with a significantly greater mean reduction in systolic BP than 0 e-counselling messages (control) (p=0.03). Similar between group difference in change over time was reported for mean reduction in pulse pressure (p=0.02) and mean reduction in total cholesterol (p=0.03). No significant comparisons were reported for the group of e-counselling participants receiving 1-7 emails vs. control group.
White et al., (2013) England No Score	A pilot program, called Masterstroke, targeting secondary stroke prevention in 22 (mean age = 65.76 years) stroke survivors. The Masterstroke program was conducted over a 9-week period during which participants attended four sessions, each lasting 2 hours. At each session, one hour was allocated to exercise training (a combination of moderate intensity aerobic, strength, mobility, and balance activities), and the second hour was dedicated to stroke education (stroke risk factors, nutrition, diet and managing stroke complications). Participants were assessed at baseline, at the end of the program, and 3-months post. Measures included physical assessments, quality of life, diet, smoking, and alcohol habits.	At the end of the program, with respect to dietary changes, a significant positive change was observed for fat and fibre intake (assessed via the Fat and Fibre Barometer) and a significant reduction in self-reported salt intake. In terms of physical function, participants demonstrated a statistically significant improvement in function balance (assessed via the Timed Up & Go) at the end of program. Furthermore, at the end of the Masterstroke program, participants' stroke knowledge and quality of life score (collected via the Stroke and Aphasia Quality of Life Scale) improved significantly.

8.8 Atherosclerosis and Non-cardiac Embolism

8.8.1 Antiplatelet Therapy

8.8.1.1 Monotherapies

8.8.1.1.1 Aspirin (ASA)

Table 8.8.1.1.1 Details of Studies Evaluating ASA Monotherapy

Author, Year Country Pedro Score	Methods	Outcomes
UK-TIA (1991) UK 8 (RCT)	2435 patients with TIA or minor stroke were randomly assigned to receive long-term treatment in 1 of 3 groups; 1) 600mg ASA twice daily, 2) 300mg once daily, 3) placebo.	OR of major stroke, MI or vascular death was reduced by 15% in the combined ASA treatment groups. There was no significant difference in the efficacy of treatment with 1200mg versus 300mg/day ASA. However, the lower dose was less gastro-toxic.
Dutch TIA Trial Study Group (1991) Netherlands 7 (RCT)	3131 patients with previous TIA or minor stroke were randomly allocated to treatment with 30mg of water-soluble ASA versus 283mg water-soluble ASA. Mean follow-up was 2.6 years.	Age and sex adjusted hazard ratio for the group receiving the lower dose ASA treatment was 0.91. There was a trend toward fewer major bleeding events in the low-dose group and significantly fewer minor bleeding reports (49 versus 84). In addition, patients receiving low-dose ASA reported fewer gastrointestinal symptoms.
SALT Swedish ASA Low-dose Trial (1991) Sweden 8 (RCT)	1360 patients with prior TIA or minor stroke were randomly assigned to receive treatment with ASA (75mg/day) or a placebo. Mean duration of follow-up was 32 months.	Compared to placebo, treatment with ASA was associated with an 18% reduction in the risk for stroke or death (p=0.02). Adverse reactions were more common in the ASA group and patients treated with ASA reported a significantly greater number of "bleeding episodes" (p=0.04).
CAST Chinese Acute Stroke Trial Collaborative Group (1997) China 8 (RCT)	21106 patients with acute ischaemic stroke were assigned to receive either ASA 160mg/day (within 48 hours of onset and for up to 4 weeks during hospital admission) or placebo.	At the end of 4 weeks, there was a 12% reduction for risk of non-fatal stroke or death among patient assigned to receive ASA versus placebo (p=0.03). There were significantly fewer ischaemic strokes among patients receiving ASA, but only slightly more haemorrhagic strokes.
IST International Stroke Trial Collaborative Group (1997) International 5 (RCT)	19435 patients with acute stroke were assigned to receive 14 days therapy with either subcutaneous heparin or ASA as soon as possible post stroke. In a factorial design, patients were further randomised to "receive heparin" (5000 or 12500 IU bd) or "avoid heparin" and to "receive ASA" (300mg/day) or "avoid ASA."	At 6 months post-stroke, neither heparin condition resulted in any benefit. Heparin treatment was associated with a significant increase in major extracranial bleeds (requiring transfusion or causing death) – especially in the case of 12500 IU doses. In the first 14 days post-stroke, patients allocated to receive heparin had fewer nonfatal ischaemic strokes than "avoid heparin" patients; however, this was offset by an increase in haemorrhagic stroke. At 6 months, there was a trend toward fewer deaths and less dependency in the group who had "received ASA" versus "avoid ASA." Within the first 14 days, there were significantly fewer ischaemic strokes and no significant increase in haemorrhagic stroke.
Brighton et al. (2013) USA	**Population:** Intervention group (N=411): Mean age= 55yr; Gender: NA. Placebo group (N=411): Mean age= 54yr; Gender: NA.	The recurrence of VTEs was not statistically different between the intervention and the placebo treatment groups.

RCT PEDro=3 TPS=NA N_{Start}=109 N_{End}=109	**Intervention:** Patients were randomized to the intervention group and received 100 mg of aspirin, or to a control group which received a placebo. Patients were instructed to take the medication for at least 2yr and were followed for up to 4yr after randomization. **Outcomes:** Recurrence of venous thromboembolism (VTE); Composite of vascular events (myocardial infarction, stroke, cardiovascular death).	The subjects randomized to receive aspirin did have lower recurrent VTEs than the placebo group when they were taking the study drug (p=0.03). The composite outcome of vascular events was significantly lower in the aspirin group compared to the placebo group (p=0.01).
Georgiadis et al. (2013) USA Quasi-experimental No Score TPS=NA N_{Start}=1899 N_{End}=1899	**Population:** Trial of ORG 10172 in Acute Stroke Treatment (TOAST): Patients taking aspirin (N=509); Mean age= 67±10yr; Gender: Males=320, Females=189. Patients not taking aspirin (N=766); Mean age= 64±12yr; Gender: Males=453, Females=313. National Institute of Neurological Disorders and Stroke (NINDS) recombinant tissue plasminogen activator (rt-PA) trial: Patients taking aspirin (N=216); Mean age=69±11yr; Gender: Males=131, Females=85. Patients not taking aspirin (N=408); Mean age=66±12yr; Gender: Males=231, Females=177. **Intervention:** Data from 2 prospective RCTs were obtained to examine whether aspirin treatment failure among ischemic stroke patients is associated with increased risk of recurrent ischemic stroke and death. The number of patients taking aspirin before treatment, and patients not taking aspirin were extracted from the two RCTs. In the TOAST study, patients were followed-up at 3mo, while those in the NINDS study were followed-up at 1yr. **Outcomes:** Rate of ischemic events; death	No difference in the risk of stroke between aspirin treatment failure and patients not taking aspirin in either the TOAST (p=0.55) or the NINDS rt-PA (p=0.93) trial was found. The association between aspirin treatment failure and stroke and/or death was not significant among most TOAST patients (p=0.67) or among the NINDS rt-PA patients (p=0.42). Aspirin treatment was not found to be associated with stroke or the combined stroke and death endpoint in any of the stroke subtypes, including large artery atherosclerosis, in either trial.

8.8.1.1.2 Thienopyridines (Ticlopidine and Clopidogrel)

Table 8.8.1.1.2 Details of Studies Evaluating Thienopyridines

Author, Year Country Pedro Score	Methods	Outcomes
CATS Gent et al. (1989) Canada/USA 8 (RCT)	1072 patients with previous history of stroke (1-4 months prior to study) were randomly allocated to receive either ticlopidine (250mg twice per day) or placebo. Treatment and follow-up continued for up to 3 years.	Intention-to-treat analysis revealed a risk reduction for stroke, MI or vascular death of 23.3% (p=0.020). Adverse events included severe neutropenia (1%), severe skin rash and diarrhea (2%). All severe adverse events were reversible with termination of treatment.
TASS Study Hass et al. (1989)	3069 patients with recent TIA or mild, persistent focal retinal or cerebral ischemia were	Three-year event rate for nonfatal stroke or death from any cause was 17% in the ticlopidine group and

USA 8 (RCT)	randomized to receive either ticlopidine hydrochloride (500mg/day) or ASA (1300mg/day). Follow-up lasted 2-6 years.	19% in the ASA group. This represented a risk reduction of 12% (p=0.048) with ticlopidine treatment. Three-year event rate for nonfatal or fatal stroke was 10% in the ticlopidine group and 13% in the ASA group. This represented a risk reduction of 21% (p=0.024) with ticlopidine treatment. Risk of side effects with ticlopidine included severe but reversible neutropenia (<1%), diarrhea (20%) and skin rash (14%). ASA side effects included diarrhea (10%), rash (5.5%), peptic ulceration (3%), gastritis (2%) and gastrointestinal bleeding (1%).
TISS Bergamasco et al. (1997) Italy 6 (RCT)	1632 patients (aged 32-80 years) with a history of TIA, amaurosis fugax or minor stroke within one month of trial entry, were randomly allocated to receive 250mg/day ticlopidine or 200mg indobufen (1x-2x/day). Median duration of treatment=1 year.	Ticlopidine therapy was significantly better than indobufen in preventing fatal and non-fatal stroke (49.6% relative risk reduction). The two groups had similar rates of adverse events (5.5% versus 6.4%). Gastrointestinal disorders were more frequent with indobufen treatment. Skin rashes and abnormal liver function were more frequent among patients treated with ticlopidine.
AAASPS Gorelick et al. (2003) USA 9 (RCT)	1809 black men and women with a recent history of noncardioembolic, ischaemic stroke were randomized to receive either 500mg/day ticlopidine or 650mg/day ASA. Duration of follow-up was 2 years	Study was halted prematurely when futility analysis showed <1% likelihood that ticlopidine would be superior to ASA in prevention of recurrent stroke, MI or vascular death. Kaplan-Meier curves for time to fatal or nonfatal stroke approached a statistically significant reduction in favour of ASA over ticlopidine (p=0.08). Frequency of serious neutropenia among patients receiving ticlopidine was 3.4% versus 2.2% for ASA treatment.

8.8.1.1.3 Clopidogrel

Table 8.8.1.1.3 Details of Studies Evaluating Clopidogrel Monotherapy

Author, Year Country Pedro Score	Methods	Outcomes
CAPRIE Steering Committee (1996) Canada/ International 8 (RCT)	Patients with a history of recent cardiovascular events were randomized to receive 75mg clopidogrel + ASA placebo (n=9553) or 325mg ASA + clopidogrel placebo (n=9546) for 1-3 years.	Patients treated with clopidogrel had a 5.32% annual risk of ischaemic stroke, MI or vascular death compared with 5.83% with ASA. The difference in rates was statistically significant and reflects a relative risk reduction of 8.7% in favour of clopidogrel. There were no differences in terms of safety.
Fukuuchi et al. (2008) Japan 7 (RCT)	Patients with previous stroke were randomly assigned to receive clopidogrel 75mg + placebo or ticlopidine 200mg once daily + placebo for 52 weeks. Primary outcomes were safety endpoints (e.g. hematologic changes, hepatic dysfunction, and non-traumatic hemorrhage). Secondary outcomes were combined incidence of fatal/nonfatal stroke, fatal/nonfatal MI or death from vascular causes.	Patients assigned to clopidogrel treatment were significantly less likely to experience adverse events than those assigned to ticlopidine (HR=0.40, 95% CI 0.276-0.583). There was less hepatic dysfunction with clopidogrel (4.2%) than with ticlopidine (11.9%; HR=0.305, 95% CI 0.192-0.486, p ≤ 0.001). There was no significant difference between groups in terms of incidence of vascular events (HR=0.977, 95% CI 0.488-1.957).

Uchiyama et al. (2009) Japan 7 (RCT)	The authors present data from the previous study (2008) with another, earlier trial. In the earlier trial, patients were randomly assigned to receive the same treatments, but for a period of only 26 weeks. The present analysis included 939 patients assigned to receive clopidogrel 75mg/day and 923 patients assigned to receive 200mg/day ticlopidine. The primary endpoint of the combined analysis was safety of each treatment. Secondary analysis was combined incidence of vascular events (stroke, MI or vascular death).	At 12 months, treatment with clopidogrel was associated with less risk for primary safety events versus ticlopidine treatment (HR=0.610, 95% CI 0.529-0.703). Clopidogrel treatment was associated with reduced risk for hepatic dysfunction when compared to ticlopidine (HR=0.455, 95% CI 0.367-0.565). There was no difference in incidence of combined vascular events or death (HR=0.918, 95% CI 0.518-1.626).
Davidai et al. (2014) Germany Retrospective No Score TPS=NA N_{Start}=11705 N_{End}=11705	**Population:** ASA+ER-DP discontinued group (N= 647): PRoFESS group (N=518): Mean age=66.4±8.4yr; Gender: Males=49%, Females=51%. ESPS2 group (N=129): Mean age= 64.9±10.8yr; Gender: Males=45.7%, Females=54.3. ASA+ER-DP not discontinued group (N=11058): PRoFESS group (N=9537): Mean age= 66±8.6yr; Gender: Males=65.1%, Females=34.9%. ESPS2 (N=1521): Mean age=37.0±11.3yr; Gender: Males=59%, Females=41%. **Intervention:** Data from patients that have participated in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial and the European Stroke Prevention Study (ESPS2), was further analyzed. Patients in the PRoFESS trial were given either ASA+ER-DP or clopidrogrel, while those in the ESPS2 study were given ASA+ER-DP or ASA or ER-DP alone. **Outcomes:** Recurrent stroke rates; deaths.	The risk of stroke in PRoFESS patients taking ASA+ER-PD and discontinued treatment due to headaches was significantly lower than those who did not discontinue treatment (p=0.001). In patients taking clopidogrel, the risk of stroke was not different between individuals that experienced headaches and discontinued use compared to those that continued use. The death rates in patients taking ASA+ER-DP who discontinued treatment due to headache were lower than those who did not discontinue use (p<0.001). In the ESPS2 patients, the risk of recurrent stroke did not differ in patients taking ASA+ER-DP or ER-DP and discontinued treatment compared to those that did not discontinue treatment. In patients that received ER-DP, the death rates were lower in those that discontinued treatment compared to those that did not discontinue treatment (p=0.03).

8.8.1.1.4 Cilostazol

Table 8.8.1.1.4 Details of Studies Evaluating Cilostazol and the Prevention of Recurrent Stroke

Author, Year Country Pedro Score	Methods	Outcomes
CSPS Gotoh et al. (2000) Japan 9 (RCT) N_{Start}=1095 N_{End}=1052	Patients with recent (<6 mo) ischemic stroke and aged <80 years were randomly assigned to receive either cilostazol (100mg twice daily; n=544) or matching placebo (n=548). Patients were followed at 12 week interval from baseline to study end. The primary study outcome was recurrence of stroke. Mean duration of follow-up was 651.8 days in the treatment group and 569.7 days in the control condition.	There was a significant reduction in risk for the primary outcome of stroke associated with cilostazol therapy when compared to the placebo condition (RR=41.7, 95% CI 9.2-62.5, p=0.015; NNT=18, see Shinohara et al. 2005). There was a significant reduction in risk for the combined secondary outcome of ischemic stroke, intracranial haemorrhage or TIA versus placebo (RR=40.9, 95% CI 11.9-60.4, p=0.009). There was no significant increase in bleeding events, allergic reactions or gastrointestinal disorders associated with cilostazol; however, cilostazol was associated with a significant increase in reported symptoms of headache (p<0.001) and heart palpitations

		(p<0.001).
CASISP Investigators Huang et al. (2008) China 9 (RCT)	720 patients with sub-acute stroke (1-6 mo) were randomly assigned to receive either cilostazol therapy (n=360) 200mg twice daily or ASA monotherapy (n=360) 100mg once daily. Treatment lasted one year. Primary study endpoint was any recurrent stroke event (ischemic stroke, cerebral haemorrhage or subarachnoid haemorrhage).	Cilostazol therapy was associated with a non-significant reduction in risk for the primary study outcome when compared to ASA monotherapy (HR=0.62, 95% CI 0.30-1.26, p=0.185). Incidence of reported cerebral bleeding events was higher in the ASA group than in the cilostazol group (p=0.038). Minor adverse effects including headache, dizziness, tachycardia and palpitations were reported more frequently by participants assigned to receive cilostazol therapy.
Shinohara et al. (2008) Japan Subgroup analysis of CSPS Gotoh et al. (2000)	*Post hoc* analyses examining the benefit of therapy on individuals at high risk for stroke; that is, individuals with/without the established risk factors (known hypertension, ischemic heart disease, diabetes and high cholesterol as well as in individuals who were/were not being treated for underlying diseases (e.g. cerebral enhancers or vasodilators, statins, ACE-inhibitors, Ca antagonists and anti-diabetes medications).	There was no significant association between the presence of identified risk factors or associated treatments (e.g. statins, antihypertensive agents) and the reduction of risk associated with cilostazol therapy.
CSPS-2 Shinohara et al. (2010) Japan 7 (RCT)	2757 patients with subacute (<6 mo) non-cardioembolic stroke were randomly allocated to either treatment with cilostazol 100mg twice daily (n=1379) or ASA 80mg once daily (n=1378). Treatment was continued for 1-5 years. Primary study endpoint was first occurrence of stroke (recurrent ischemic or first haemorrhage or SAH). Mean duration of follow-up was 29 months.	Treatment with cilostazol was associated with a significant reduction in stroke events when compared to ASA alone (HR 0.75, 95% CI 0.57-0.99, p=0.04). On per protocol analysis of secondary endpoints, the authors reported that use of cilostazol was associated with a significant reduction in risk for haemorrhagic events (HR=0.46, 95% CI 0.3-0.71, p=0.0004) when compared to placebo, as well as for the combined endpoint of stroke, TIA, angina pectoris, MI, heart failure or any haemorrhage requiring hospitalization (HR=0.799, 95% CI 0.64-0.99; p=0.044). Headache, diarrhea, palpitations, dizziness and tachycardia were all reported more frequently by individuals receiving cilostazol.
Shimizu et al. (2013) Japan RCT PEDro=5 TPS<24hr N=507	**Population:** Experimental group (EG; N=251); Mean age=66.2±9.4yr; Gender: Males=165, Females=95. Control group (CG; N=256); Mean age=66.6±8.9yr; Gender: Males=175, Females=81. **Intervention:** Participants with acute noncardioembolic ischemic stroke were randomly allocated either to an experimental group which received cilostazol (200mg/d) or to the control group did not receive any medication. The therapy was conducted over 3 months. Evaluation occurred at day 1, day 3, 5, and 14, and at 1 and 3 months after enrollment. **Outcomes:** Primary endpoints: rate of progression of stroke (defined as aggravation of the NIHSS score by ≥4 points on day 3, and or day 5 after enrollment, and a modified Rankin Scale (mRS) score of 0 to 1 at 3mo	There was no significant difference in the progression of mRS score from 0 to 1 or 0 to 2 at 1 or 3mo between the two groups. There was no significant difference between the two groups with regards to the NIHSS scores and the progression in scores at day 3, or day 5 however, the NIHSS sores at 14d were significantly higher in the CG than the EG. No significant difference was found between the two groups regarding the number of cerebrovascular events.

	after enrollment); Secondary endpoints: cardiovascular events within the brain, heart and peripheral arteries during 3mo of therapy, the rate of mRS scores of 0 to 1 at 1mo after enrollment, and the rate of mRS score 0 to 2 at 1 and 3mo after enrollment.	

8.8.1.1.5 Glycoprotein IIb/IIIa Inhibitor

Table 8.8.1.1.5 Details of Studies Evaluating Glycoprotein IIb/IIa Inhibitors

Author, Year Country Pedro Score	Methods	Outcomes
APLAUD Study Investigators Harrington et al. (2000) USA 7 (RCT)	451 patients with recent cardiovascular or cerebrovascular acute ischaemic events were randomized to one of five dosing regimens for 12 weeks: 1) placebo; 2) 5mg lotrafiban; 3) 20mg lotrafiban; 4) 50mg lotrafiban; 5) 100mg lotrafiban. All dosing regimens were given twice daily with 300-325mg ASA.	The 5mg treatment group had a rate of bleeding complications similar to the placebo group. The 100mg group was terminated early due to excessive major bleeding events. Thrombocytopenia (<100 000 platelets/μL) occurred in 5 patients treated with lotrafiban. Lotrafiban produced dose-dependent inhibition of platelet aggregation; that is, the 5mg group did not differ from placebo, whereas the 100mg group produced nearly 100% inhibition of platelet aggregation.
AbESTT Study Investigators Adams et al. (2005) Multicentre RCT PEDro=7 TPS_{Exp}=4.5±0.9hr TPS_{Con}=4.5±1hr N_{Start}=400 N_{End}=385	**Population:** Experimental group (EG; N=200): Mean age=67±13.6yr; Gender: Males=120, Females=80. Control group (CG; N=200): Mean age=68±12.8yr; Gender: Males=105, Females=95. **Intervention:** The experimental group received intravenous Abciximab (0.25mg/kg bolus) followed by 0.125mg/kg/min infusion for 12 hours. The control group received intravenous placebo. Assessments were conducted at baseline, at 5 days, and at 3 months. **Outcomes:** Mortality; Fatal and non-fatal major intracranial hemorrhage; Asymptomatic intracranial hemorrhage; Extracranial hemorrhage; Thrombocytopenia; National Institute of Stroke Scale (NIHSS); Modified Rankin Scale (mRS).	No significant difference in mortality was found between the two groups. Symptomatic intracranial hemorrhage at 5 days occurred in 3.6% of EG and 1% in CG. No significant difference between the two groups was found. No significant difference in stroke progression was found between the two groups. Treatment with abciximab showed a non-significant trend in favourable outcome (i.e. mRS scores) at 3 months.

8.8.1.2 Dual Therapies

8.8.1.2.1 Clopidogrel plus ASA

Table 8.8.1.3.1 Details of Trials Assessing ASA in Combination with Clopidogrel

Author, Year Country Pedro Score	Methods	Outcomes
CURE	Patients with unstable angina hospitalized	Significant reduction in primary outcome (composite of

Collaborative Group Yusuf et al. (2001) Canada/ International 8 (RCT)	within 24 hours of onset of symptoms were randomized to receive clopidogrel 75mg/day (n=6259) or placebo, in addition to ASA (n=6303) for 3-12 months.	death from cardiovascular disease, nonfatal MI or stroke) among patients in the treatment group. Relative risk reduction of 0.08. However, there were significantly more major bleeding episodes in the clopidogrel group.
MATCH Investigators Diener et al. (2004) International 8 (RCT)	7599 patients who had an ischaemic stroke or TIA within 3 months. Patients also had at least one of previous ischaemic stroke, previous myocardial infarction, angina pectoris, diabetes mellitus or symptomatic peripheral artery disease (PAD). Participants were randomly assigned to the ASA treatment group (clopidogrel 75mg/day plus ASA 75mg/day; n=3797) or the placebo condition (75mg/day clopidogrel plus matching placebo). Treatment continued for 18 months. Follow-up occurred at 1, 3, 6, 12 and 18 months after randomization.	With regard to the primary outcome (composite of ischaemic stroke, myocardial infarction, vascular death or re-hospitalization for any acute ischaemic event), there was a small, non-significant trend favouring the combination of clopidogrel and ASA versus clopidogrel alone (relative risk reduction=6.4%; p=0.244). With regard to the secondary endpoint of ischaemic stroke, either fatal or non-fatal, there was a relative risk reduction of 7.1% in favour of combined therapy. However, this trend was not significant (p=0.353). In the combined therapy group, there were significantly more incidents of life-threatening bleeding (p<0.0001) as well as more incidents of major bleeding (p<0.0001) and minor bleeding (p<0.0001). Gastro-intestinal bleeding was the most common cause of both life-threatening and major bleeding events in the clopidogrel plus ASA treatment group.
Markus et al. (2005) UK 8 (RCT)	107 patients with recently symptomatic carotid stenosis of ≥50% and recent ipsilateral TIA or stroke were randomly assigned to treatment with either clopidogrel (300mg on day one followed by 75mg 1x/day for 7 days) plus 75mg ASA 1x/day or 75mg ASA plus matching placebo 1x/day. Asymptomatic microembolic signals (MES), markers of risk for stroke or TIA, were used to evaluate antiplatelet efficacy. Primary study endpoint was proportion of patients who were MES positive on day 7.	43.8% of patients in the dual therapy condition were MES positive compared with 72.7% of patients receiving ASA monotherapy. MES frequency was reduced by 61.6% in the combination therapy group at day 7 compared to baseline (p=0.013) while in the ASA group, MES frequency was reduced by 61.4% by day 2 (p=0.0005). Among patients in the ASA group, there were four recurrent strokes and seven TIAs, while there were no strokes and four TIAs in the treatment group. Two TIAs occurred prior to the initiation of treatment protocols.
Serebruany et al. (2005) USA 5(RCT)	70 patients with recent ischemic stroke were randomly assigned to receive 81mg ASA or 81mg ASA plus 75mg clopidogrel per day. All patients were treated with 81mg ASA for at least one month prior to trial commencement. Platelet function was assessed at baseline and then at 30 days post-randomization.	With ASA monotherapy, collagen-induced platelet aggregation was reduced at 30 days (p=0.001). Addition of clopidogrel resulted in reductions of platelet activity assessed by ADP- (p=0.00001), reduction of PAU (p=0.001), decreased expression of PECAM-1 (p=0.005) and GPIIb/IIIa activity with PAC-1(p=0.27). Collagen-induced aggregation was also reduced (p=0.012). Reduced formation of platelet-leukocyte micro particles (p=0.01) was demonstrated in patients assigned to combination therapy.
CHARISMA Investigators Bhatt et al. (2006) International 9 (RCT)	15603 patients with either established cardiovascular disease or multiple risk factors were randomly assigned to receive either 75mg/day clopidogrel + 75-162mg/day ASA (n=7802) or matching placebo + 75-162mg/day ASA (n=7801). Primary study outcome was a composite of MI, stroke or death from cardiovascular causes. Median length of follow-up was 28	For the primary study endpoint, there was no significant between-group difference reported (RR=0.93, p=0.22), although fewer events were recorded in the treatment condition. For nonfatal stroke, there were significantly fewer events reported in the clopidogrel/ASA group than in the ASA alone control condition (150 versus 189; RR=0.79; p=0.03). On subgroup analysis, for patients with symptomatic cardiovascular disease, treatment with clopidogrel/ASA was associated with a reduction in risk for

	months.	the primary study outcome when compared to the placebo/ASA condition (RR=0.88, p=0.046). However, there was a trend toward increased rates of severe bleeding associated with clopidogrel/ASA treatment for both symptomatic and asymptomatic patients. Moderate bleeding was also more frequent in the treatment condition for both asymptomatic (p=0.08) and symptomatic patients (p<0.001).
FASTER Investigators Kennedy et al. (2007) International 10 (RCT)	392 patients within 24 hours of TIA or minor stroke were randomized in a 2X2 factorial fashion to receive clopidogrel (300mg loading dose, 75mg daily), simvastatin (40mg daily) or matching placebo(s). All patients in all conditions were given 80mg/day ASA. The primary study outcome was 90-day risk for total stroke while the secondary outcome was combined 90-day risk for MI, stroke, and vascular death. Follow-up was 90 days.	Patients treated with clopidogrel + ASA did not have a reduced risk for stroke when compared to the placebo + ASA condition (risk ratio=0.5, 95% CI 0.2-1.5, p=0.24). Similar results were obtained for the secondary outcome. Similar non-significant results were reported for treatment with simvastatin +ASA versus placebo +ASA comparisons for both the primary and secondary study outcomes. There was no evidence of a significant interaction between clopidogrel and simvastatin for any of the study outcomes. There was a significant 3% increase in risk (p=0.03) for symptomatic bleeding events in the groups allocated to active clopidogrel +ASA treatment.
CLAIR Study Investigators Wong et al. (2010) International 8 (RCT)	100 patients were randomly allocated (within 7 days of symptom onset) to either treatment with clopidogrel + ASA (300mg on the first day, 75mg thereafter + 75-160mg ASA; n=47) or ASA monotherapy (75-160mg daily) for 7 days. Microembolic signals (transcranial Doppler) were monitored on days 2 and 7. Primary study outcome was proportion of patients with microembolic signals on day 2. Secondary outcomes included signals at day 7 and number of new infarctions on diffusion-weighted MRI.	There were significantly fewer patients with at least one microembolic signal on transcranial Doppler on day 2 in the group treated with combination therapy (31% versus 54%; relative risk reduction=42.4%, p=0.025). This was also true at day 7 (23% versus 51%, relative risk reduction=54.5%, p=0.006). There was no significant between-group difference in terms of number of new infarctions on MRI (p=0.26). There were no significant differences in adverse events; however, two patients in the combined therapy group (versus none in the ASA group) reported minor bleeding events.
CHANCE Trial Wang et al. (2013) International 10 (RCT)	Within 114 centers in China 5170 patients were randomly assigned to combination therapy with clopidogrel + ASA or to placebo + ASA. Patients were randomly assigned within 24 hours after the onset of minor ischemic stroke of high-risk TIA. Patients in the combination group received clopidogrel at an initial dose of 300mg, followed by 75mg per day for 90 days, plus ASA at a dose of 75mg per day for the first 21 days. The ASA group received placebo plus ASA at a dose of 75mg per day for 90 days. The primary outcome was stroke (ischemic or hemorrhagic) during 90 days of follow-up in an intention to treat analysis.	Stroke occurred in 8.2% of patients in the clopidogrel- ASA group as compared to 11.7% of those in the ASA group (hazard ratio, 0.68; 95% confidence interval, 0.57 to 0.81; P<0.001). Moderate or severe hemorrhage occurred in 0.3% in both the clopidogrel- ASA group as well as in the ASA group.
Cote et al. (2014) North America, Latin America, Spain RCT PEDro=6	**Population:** Intervention group (N=427): Mean age= 66±10.6yr; Gender: Males= 265, Females= 162. Placebo group (N=411): Mean age= 66±10.2yr; Gender: Males= 284, Females= 127.	There is no significant difference in the risk of recurrent stroke between the intervention and the placebo group. There was also no difference in the rate of recurrent ischemic stroke, intracranial hemorrhage, and other major vascular events between the two groups.

TPS =NA N_{Start}=838 N_{End}=838	**Intervention:** Patients with recent lacunar stroke receiving (325 mg/d) aspirin were randomized to receive clopidogrel (75 mg/d) or placebo. All patients were followed for a mean period of 3.5yr. **Outcomes:** Stroke recurrence (ischemic and intracranial hemorrhage); Major extracranial hemorrhage.	The risk of all-cause mortality among the intervention group was significantly higher than for those randomized to the placebo (p=0.004).
Seadon et al. (2015) China RCT PEDro=4 TPS=NA N_{Start}=5170 N_{End}=5170	**Population:** Intervention group (N=2584); Control group (N=2586). No additional demographic data provided in the current article. **Intervention:** Patients with acute minor stroke or TIA were randomized to either the intervention group and received clopidogrel and aspirin, or to the control group and received aspirin alone. **Outcomes:** Frequency of ischemic or hemorrhagic stroke at 90 days of follow-up (primary end point); Frequency of cardiovascular events at follow up; All-cause deaths.	There was a significant reduction in the primary end point in the intervention group (p<0.001). The intervention group also showed significant decreases compared to the control group in the incidence of ischemic stroke (p<0.001), and vascular events (p<0.001). All other outcomes show no significant differences between the 2 groups.

8.8.1.2.2 Dipyridamole plus ASA

Table 8.8.1.2.2 Details of Trials Assessing ASA in Combination with Dipyridamole

Author, Year Country Pedro Score	Methods	Outcomes
ESPS Group (1990) Belgium 8 (RCT)	2500 patients with a recent history of cerebrovascular disorders of atherothrombotic origin (TIA, RINDs or complete stroke). Patients were randomly allocated to receive either 75mg dipyridamole + 330mg ASA or matching placebo. Patients were followed for 2 years with assessments occurring every 3 months.	There was a 33.5% reduction (p<0.001) the combined endpoint of all-cause death and stroke and a 38.1% reduction (p<0.001) in all strokes associated with treatment. The reduction death and stroke did not differ by gender, age, nature of cerebrovascular event used to qualify for study participation, site of lesion or diastolic blood pressure.
ESPS-2 Diener et al. (1996) Belgium 8 (RCT)	6602 patients with prior TIA or stroke were randomized to receive 50mg ASA daily, dipyridamole, the both agents in combination or placebo. The primary end points were stroke, death or stroke and death combined.	After 24 months of follow-up, the risk of stroke or death was reduced by 18% with ASA alone, 16% with dipyridamole alone, and 24% with combination therapy when compared to placebo. In the combination group the risk for stroke was reduced by 36% versus placebo. There was no statistically significant effect on the overall death rate.
AGATE Serebruany et al. (2004) International 6 (RCT)	40 patients who had suffered an ischaemic stroke in the previous 2-6 months and had not taken ASA for at least one month were randomized to receive either 81mg ASA per day or Aggrenox twice daily. Treatment continued for 30 days. Blood samples and	Both treatments were associated with rapid and sustained platelet inhibition. At individual time points, Aggrenox was superior to ASA on 25/90 measures (including inhibition of protease activated receptors) while ASA was superior to Aggrenox on only 4/90 comparisons. In 61/90 comparisons, ASA and Aggrenox were equivalent. The stronger

	testing were conducted at baseline, day 1, 3, 7, 15 and day 30. Platelet characteristics were assessed via conventional aggregometry, rapid cartridge-based platelet function analyzers and whole blood flow cytometry.	antiplatelet properties of Aggrenox were apparent later in the trial and differences favouring Aggrenox were clear only after two weeks of therapy.
ESPRIT Halkes et al. (2006) International 8 (RCT)	The ESPRIT study randomized 1363 patients with stroke or TIA to receive treatment with ASA, 30 to 325mg/d (mean dose, 75mg), and 1376 patients to receive ASA at the same dosages combined with 200mg extended-release dipyridamole twice daily. Mean follow-up was 3.5 years. Primary outcome was composite of vascular death, nonfatal stroke, nonfatal myocardial infarction, or major bleeding complication.	The primary outcome event occurred in 173 patients in the combination group (ASA + dipyridamole group) compared to 216 patients in the ASA-alone group. The overall risk ratio was reduced to 0.82 with combination therapy (95% CI 0.66-0.98) and the absolute risk reduction was 1.0% (95% CI 0.1-1.8). Use of combination therapy versus ASA monotherapy was not associated with a significant reduction of risk for ischemic events (HR=0.81, 95% CI 0.65 – 1.01). More patients withdrew from the combination therapy group (470) than the ASA-alone group (184), mainly due to headache.
JASAP Study Uchiyama et al. (2011) Japan 9 (RCT)	1294 patients (aged ≥50 years) with a history of previous ischemic stroke were enrolled from 157 participating medical centres. Patients were randomly assigned to receive either extended release dipyridamole 200mg + 25mg ASA twice daily (n=655) or ASA 81mg once daily (n=640) for a minimum period of one year (including a 1-week run-in period). The primary study outcome was recurrent fatal or nonfatal ischemic stroke.	Mean treatment duration was 447 days in the therapy group and 471 days in the ASA monotherapy group. Based on the primary outcome non-inferiority of combination therapy was not demonstrated. Use of extended release dipyridamole + ASA was not associated with reduced risk of recurrent stroke when compared with ASA monotherapy (HR=1.47, 95% CI 0.93-2.31). Both therapies were well tolerated; although, there was a greater total number of adverse events reported in the combination therapy group (p=0.04). Headache (p<0.0001) and diarrhea (p=0.0016) were reported more often by patients assigned to combination therapy and more participants continued therapy due to headache in the combination therapy versus the monotherapy group (p=0.06). Bleeding events (major and clinically minor events) were comparable between groups.

8.8.1.2.3 Cilostazol plus ASA

Table 8.8.1.2.2 Details of Trials Assessing ASA in Combination with Cilostazol

Author, Year Country Pedro Score	Methods	Outcomes
TOSS Trial Kwon et al. (2005) Korea 6 (RCT)	Patients with recent (within 2 weeks) stroke and symptomatic MCA (M1 segment) stenosis were randomly assigned to receive either 100mg cilostazol twice daily (n=67) or matching placebo (n=68). All patients also received 100mg ASA once daily for the duration of the study period. The primary study outcome was the progression of symptomatic stenosis demonstrated on magnetic resonance angiography (MRA) at 6	There were no recorded stroke events in either group during the study period. Progression of symptomatic stenosis was detected in 6.7% of participants assigned to cilostazol therapy and 28.8% of individuals in the control condition. Regression was demonstrated by 24.4% in the cilostazol group and 15.4% in the placebo group. Progression was identified significantly less frequently in individuals assigned to received cilostazol (p=0.008). Progression rates of asymptomatic stenoses did not differ between groups. There were no significant between group

	months.	differences in terms of serious adverse events. Individuals treated with cilostazol reported skin rash and dizziness more frequently than those in the control condition (p<0.05).
Nakamura et al. (2012) Japan 5 (RCT)	76 individuals with ischemic stroke were randomly assigned to receive cilostazol 100mg twice/day + ASA 300mg once/day or ASA 300mg once daily. ASA dosage was reduced to 100mg on day 4 in both groups. Study baseline was within 48 hours of stroke onset and therapy initiated immediately following baseline assessment. Primary study outcome was neurological deterioration (increased NIHSS scores) or stroke recurrence at 14 days. The reported secondary endpoint was the same, but assessed at 6 months post stroke. Functional status was also assessed 6 months post stroke via the modified Rankin Scale (mRS).	After 14 days, there was a reduction in risk for the primary study endpoint associated with assignment to therapy with cilostazol + ASA versus ASA alone (RR=0.21, 95% CI 0.05-0.87, p=0.013). Improvement in NIHSS scores over the first 14 days tended to be greater in individuals receiving dual therapy, but this did not reach significance (p=0.07). At 6 months, more participants were considered to have "favorable functional status" (mRS of 1-2) in the ASA + cilostazol group than in the ASA monotherapy group (96% vs 65%; RR=1.48, 95% CI 1.07-2.06, p=0.005).
CATHARSIS Trial Uchiyama et al. (2015) Japan RCT PEDro=5 TPS=2wk-6mo N_{Start}=165 N_{End}=122	**Population:** Experimental group (EG; N=83): Median age (range)=68.3 (45-84)yr; Gender: Males=65, Females=18. Control group (CG; N=80): Median age (range)=68.3 (50-82)yr; Gender: Males=43, Females=37. **Intervention:** Participants with ischemic strokes were randomly allocated to receive either dual therapy consisting of cilostazol (200mg/d) and aspirin (100mg/d), or to a control therapy consisting of only aspirin (100mg/d). Assessments were conduted at baseline, at 3 and 6 months, and at 1 and 2 years after randomization. **Outcomes:** Primary endpoints: progression of intracranial arterial stenosis (IAS) at 2yrs; Secondary endpoints: all vascular events (ischemic stroke, MI, other vascular events), death (due to stroke, non-stroke, non-vascular), serious adverse events, recurrent brain infarct, worsening of modified Rankin Scale (mRS).	No significant difference between the two groups was found for the primary endpoint (i.e., progression of IAS), and secondary endpoints which included all vascular events, stroke, ischemic stroke, new silent brain infarcts, and ischemic stroke with new silent brain infarcts. The EG had significantly lower number of events than the CG group regarding all vascular events with new silent brain infarcts, stroke with new silent brain infarcts, and worsening of mRS (p=0.04; p=0.04; p=0.03).

8.8.1.2.4 Clopidogrel versus Dipyridamole-Based Combination Therapies

Table 8.8.1.2.4 Details of Trials Assessing Clopidogrel versus Dipyridamole-Based Combination Therapies

Author, Year Country Pedro Score	Methods	Outcomes
Caplain (2005) France 5 (RCT)	In a randomized, 3X2 crossover design, healthy men aged 18-45 (n=26) were allocated to one of six possible sequences	ASA treatment reduced collagen-induced platelet aggregation in whole blood by a mean of 26.8%, whereas clopidogrel + ASA reduced collagen-induced platelet

	of treatment with ASA, clopidogrel + ASA (75mg ASA, 75mg clopidogrel) and dipyridamole + ASA (25mg ASA, 200mg dipyridamole). Each treatment period lasted 10 days with a 14-day washout period between treatments.	aggregation by a mean of 44.9% and dipyridamole + ASA by a mean of 16.5%. The difference between clopidogrel and dipyridamole based treatments was significant (p=0.0009). Clopidogrel + ASA was more effective than the other treatments in inhibiting collagen-induced platelet aggregation in platelet rich plasma (PRP) (p<0.0001). Clopidogrel + ASA treatment was also significantly more effective than either of the other treatments in inhibiting ADP-induced aggregation in whole blood and PRP (p≤0.0001). Both ASA and clopidogrel + ASA were more effective than dipyridamole in the inhibition of arachidonic acid-induced platelet aggregation (p<0.0001) in whole blood. In PRP, all three treatments produced 100% arachidonic acid-induced platelet aggregation.
ProFESS Study Group Sacco et al. (2008) International 10 (RCT)	In a 2X2 factorial design, high risk patients including those with previous stroke and TIA were randomly assigned to receive either 25mg ASA + 200mg extended release dipyridamole (n=10,181) or 75mg clopidogrel (n=10,151) daily. Mean follow-up was 2.5 years. Primary study outcome was recurrent stroke (any type). Secondary outcome was a composite of stroke, MI or death from vascular causes. Prior to conventional assessment of superiority via testing of the null hypothesis (no difference between treatments) a non-inferiority test was planned (ASA+ dipyridamole versus clopidogrel).	More patients discontinued the study drug prematurely if assigned to combination therapy versus clopidogrel (p<0.001). The risk for major bleeding events was greater with combination therapy versus clopidogrel monotherapy (HR=1.15, 95%CI 1.0–1.32). In terms of the primary study outcome, there was no significant between group difference demonstrated (HR=1.01, 95%CI 0.92-1.11). The upper limit of the CI exceeds the predetermined non-inferiority limit of 1.075; therefore the statistical criteria for non-inferiority were not met despite similar risk for events. In a subgroup analysis of individuals with previous stroke or TIA (approximately 18% and 8%, respectively), there was no significant between group difference for the primary outcome; however, there were fewer events reported in the ASA + dipyridamole treatment group.
King et al. (2011) UK 5 (RCT)	Consecutive patient with symptomatic carotid stenosis were assigned to receive either 200mg dipyridamole MR twice per day (n=30) or clopidogrel 75mg once a day (following a loading dose of 300mg) (n=30). All patients also received 75mg ASA daily. Patients remained on randomized treatment for 1 month and were followed for recurrent stroke for 1 month or until they received carotid endarterectomy. The primary outcome measure was change in embolic signals (ES) between baseline assessment and 48 hours.	78.6% of patients were ES-positive at baseline in the dipyridamole group versus 51% in the clopidogrel group. The primary study endpoint did not differ between groups. When examining only patients who were ES-negative at baseline, there was also no significant between group differences reported. Although there no baseline differences between groups in rate of platelet aggregation, the ADP-aggregation rate was lower with clopidogrel than dipyridamole (p<0.001).

8.8.1.3 Triple Therapies

Table 8.8.1.3 Triple Antiplatelet Therapy

Author, Year Country Pedro Score	Methods	Outcomes
Sprigg et al. (2008)	Patients with previous TIA or stroke (within	The trial was stopped prematurely. Of the 17 patients

UK 6 (RCT) N_{Start}=17 N_{End}=16	the past 5 years) were randomly assigned to receive either triple therapy [open-label ASA (75mg) + clopidogrel (75mg) + dipyridamole (200mg)] or ASA monotherapy (75mg/day). Primary outcomes were tolerability of treatment, safety (mortality), serious adverse events, stroke recurrence and extracranial bleeding.	randomized, 9 went to triple therapy and 8 went to ASA monotherapy. Assignment to triple therapy was associated with a trend toward discontinuation of therapy (44% in the triple therapy group versus 0% in the ASA group). Three of the four patients who discontinued medication did so because of bleeding or bruising. There were significant increases in bleeding (p<0.01) and adverse events (p<0.01) in the triple therapy group compared to ASA alone. Unfortunately, all comparisons are limited by the very small sample size. Stroke recurrence was not reported.
Han et al. (2009) China RCT PEDro=4 N=1212	**Population:** Triple therapy (TT; N=608): Mean age=59.6±10.8yr; Gender: Males=446, Females=162. Dual therapy (DT; N=604): Mean age=60.2±11.1yr; Gender: Male=443, Females=161. **Intervention:** Patients with acute coronary syndromes were randomly allocated either to triple therapy consisting of aspirin (300mg/d for 1mo then 100mg/d indefinitely), clopidogrel (loading dose of 300-600mg/d followed by 75mg/d for 3 to 12mo based on the type of implanted stent), and cilostazol (100mg twice/d), or to dual therapy consisting of aspirin (300mg/d for 1mo then 100mg/d indefinitely), and clopidogrel (loading dose of 300-600mg/d followed by 75mg/d for 3 to 12mo based on the type of implanted stent). The therapy was conducted over the course of 6 months after percutaneous coronary intervention (PCI). Assessments were conducted at 30 days and at 1 year. **Outcomes:** Primary endpoint: major adverse cardiac or cerebral event (MACCE) which consists of a composite of cardiac death, non-fatal MI, stroke, or target vessel revascularization (TVR) at 1yr. Secondary endpoint: TVR and bleeding events at 1yr.	30d outcomes show that dual therapy reported significantly more incidence of all-cause death (p=0.012), cardiovascular death (p=0.033), composite of cardiac death + stroke + MI (p=0.018), MACCE (p=0.025) compared to triple therapy. At 1 year follow-up, only the cardiac death, MI, and stroke composite (p=0.027) and the MACCE (p=0.011) were significantly greater in the dual therapy compared to the triple therapy.

8.8.1.4 Combination Therapy and Functional Outcome

Table 8.8.1.4 Combination Antiplatelet Therapy and Functional Outcome

Author, Year Country Pedro Score	Methods	Outcomes
PRoFESS Study Bath et al. (2010) International 10 (RCT) *Post hoc analysis*	1360 patients in the PRoFESS trial were randomized to treatment with combined extended release dipyridamole + ASA (200mg + 25mg BID) or clopidogrel (75mg o.d.) within 72 hours of the index stroke event. For this post hoc analysis, primary	Functional outcome (combined death and dependency) at 30 days did not differ between treatment groups at 30 days on ordinal logistic regression (OR=0.97, 95% CI 0.79-1.19, p=0.75).

	outcome was functional outcome assessed on the mRS, 30 days after randomization.	
CHARISMA Trial Hankey et al. (2010) International 9 (RCT) *Post hoc analysis*	202 patients assigned to the clopidogrel + ASA condition and 234 patients in the ASA + placebo condition were recorded as having a stroke and a follow-up assessment on the modified Rankin Scale (mRS) at 3 months post adjudicated stroke.	There was no significant difference between groups in the severity of outcome as measured on the mRS at 3 months following adjudicated stroke (p=0.15). When the mRS scores were dichotomized to represent good versus poor outcome there was also no significant differences noted between groups. Dichotomizing mRS at several time points made no difference to the outcome. When considering only those individuals who were included in the study because of previous stroke or TIA, there were 233 stroke events recorded (103 in the combination therapy group and 130 in the ASA group). There was no significant between treatment difference in mRS ratings for this subgroup of patients (p=0.48).
EARLY Trial Dengler et al. (2010) Germany 8 (RCT)	543 patients with acute stroke were randomly assigned to receive either 25mg ASA + 200mg extended release dipyridamole twice per day or ASA monotherapy (100mg once per day) for 7 days. At the end of 7 days, all patients received combination therapy for up to 90 days. The primary study endpoint was mRS scores at 90 days. Favourable outcome was defined as mRS score of 0 or 1.	There was no significant difference between groups in terms of functional outcome at day 90 (p=0.45). In terms of distribution of mRS scores, there was no significant difference noted between groups (p=0.68). At day 8 (immediately following provision of combination therapy to both groups), there was no significant between group difference noted for mRS scores (p=0.89). In the first 7 days, early initiation of combination therapy was associated with more frequent headache (p<0.0001), nausea (p=0.0002) and vomiting (p=0.007). There was a trend toward more frequent headache remaining from day 8 to 90 (p=0.08). There were no significant differences in serious adverse events between groups from either 0-7 days or 8-90 days.
Lau et al. (2014) China RCT PEDro=6 TPS_{Exp}=2.3d $TPS_{Control}$=3.2d N_{Start}=65 N_{End}=39	**Population:** Dual Therapy (N=30): Mean Age=57.6yr; Gender: Male=8, Female=7. Monotherapy (N=35): Mean Age=56.4yr; Gender: Male=7, Female=7. **Intervention:** Dual-received 75-160mg of aspirin daily for 7d in addition to 300mg clopidogrel on the first day followed by 75mg for the remaining days. Monotherapy-received only 75-160mg aspirin daily for 7d. **Outcomes:** Proportion of patients with detectable microembolic signals (MES) on day 2; Proportion of patients with MES on day 7 and the number of MES on days 2 and 7; Magnetic resonance imaging (MRI) of the brain.	No significant difference between groups in regards to proportion of patients with MES on day 2 (dual=38%, mono=55%, p=0.213). No significant difference between groups in regards to proportion of patients with MES on day 7 (dual=31%, mono=53%, p=0.125). Significantly higher median of MES on day 7 in the mono therapy group compared to the dual therapy (dual=0, mono=1, p=0.046). No significant differences between groups in regards to the number of MES on day 2 (median: dual=0, mono=1, p=0.095).
CATHARSIS Trial Uchiyama et al. (2015) Japan RCT PEDro=5 TPS=2wk-6mo N_{Start}=165 N_{End}=122	**Population:** Experimental group (EG; N=83): Median age (range)=68.3 (45-84)yr; Gender: Males=65, Females=18. Control group (CG; N=80): Median age (range)=68.3 (50-82)yr; Gender: Males=43, Females=37. **Intervention:** Participants with ischemic strokes were randomly allocated to receive either dual therapy consisting of cilostazol (200mg/d) and aspirin (100mg/d), or to a	No significant difference between the two groups was found for the primary endpoint (i.e., progression of IAS), and secondary endpoints which included all vascular events, stroke, ischemic stroke, new silent brain infarcts, and ischemic stroke with new silent brain infarcts. The EG had significantly lower number of events than the CG group regarding all vascular events with new silent brain infarcts, stroke with new silent brain infarcts, and worsening of mRS (p=0.04; p=0.04; p=0.03).

	control therapy consisting of only aspirin (100mg/d). Assessments were conduted at baseline, at 3 and 6 months, and at 1 and 2 years after randomization. **Outcomes:** Primary endpoints: progression of intracranial arterial stenosis (IAS) at 2yrs; Secondary endpoints: all vascular events (ischemic stroke, MI, other vascular events), death (due to stroke, non-stroke, non-vascular), serious adverse events, recurrent brain infarct, worsening of modified Rankin Scale (mRS).	

8.8.2 Anticoagulants

Table 8.8.2 Anticoagulants in the Prevention of Noncardioembolic Stroke

Author, Year Country Pedro Score	Methods	Outcomes
SPIRIT The Stroke Prevention in Reversible Ischemia Trial (SPIRIT) Study Group (1997) 7 (RCT)	1316 patients with previous ischaemic stroke of noncardiac origin were randomly allocated to receive either 30mg ASA daily or dose-adjusted oral anticoagulation (INR=3.0-4.5). Mean follow-up was 14 months. The primary combined outcome was death from all vascular causes, nonfatal stroke, nonfatal MI or nonfatal bleeding complication.	Patients in the anti-coagulant groups were more likely to experience a primary outcome (HR=2.3) than patients in the ASA group. This could be attributed to the excess of bleeding complications experienced by patients in the anticoagulant condition (53 versus 6 on ASA therapy). Bleeding incidence increased by a factor of 1.43 for every 0.5 unit increase in INR above 3.0.
WARSS Warfarin- ASA Recurrent Study Stroke Group Mohr et al. (2001) USA 8 (RCT)	Patients with prior noncardioembolic stroke were randomly assigned to receive either ASA 325mg/day (n=1103) or adjusted dose warfarin to INR=1.4 to 2.8 (n=1103). Follow-up was two years. Primary study outcomes were recurrent ischaemic stroke or death from any cause.	No significant differences were found between treatment conditions with regard to primary study outcomes. HR comparing warfarin to ASA=1.13. Rates of major haemorrhage were 2.22/100 patient years in the warfarin group versus 1.49/100 patient years in the ASA group.
WASID Trial Chimowitz et al. (2005) USA/Canada 9 (RCT)	569 patients with history of TIA or non-disabling stroke (<90 days) associated with major cranial artery stenosis of 50-99% were randomized to receive either warfarin (5mg daily) or ASA (650mg twice daily). If side effects developed from high dose ASA, the dosage could be lowered to 325mg twice daily. Mean follow-up was 1.8 years.	The study was stopped early due to concerns about the safety of patients assigned to the warfarin condition. During the follow-up period, study medication was discontinued in 22.5% of patients; significantly more individuals had been allocated to the warfarin treatment ($p<0.001$). There was no significant difference in the primary endpoint (ischaemic stroke, brain haemorrhage or death from vascular causes other than stroke) between treatment conditions (HR=1.04; ns). There were no differences between groups on any secondary endpoint. There were fewer major cardiac events among patients allocated to the ASA group than in the warfarin group (HR=0.40, p=0.02) although this was not initially specified as a study endpoint. The rate of death was significantly lower in the ASA group (HR=0.46, p=0.02) and fewer major haemorrhages were reported in this group (HR=0.39, p=0.01). In the warfarin treatment condition,

		INR<2.0 was associated with greater risk of ischaemic stroke (p<0.001) and with major cardiac events (p<0.001). Higher risk of haemorrhage was associated with INR>3.0.
WARSS Warfarin- ASA Recurrent Study Stroke Group Sacco et al. (2006) USA 8 (RCT)	Patients with prior noncardioembolic stroke were randomized to receive either ASA 325mg/day (n=1103) or adjusted dose warfarin to INR=1.4 to 2.8 (n=1103). Follow-up was two years. Treatment protocol was compared to sociodemographic and vascular risk factors, stroke subtype, arterial territory, and infarct topography.	No treatment differences were found between warfarin and ASA groups across multiple pre-specified subgroups. In *post-hoc* analyses of the subgroups, warfarin was associated with worse outcomes among patients with moderate stroke severity (HR 1.63, 95% CI 1.005-2.64; p=0.047) and better outcomes among those without baseline hypertension or with posterior circulation infarcts sparing the brainstem (HR 0.54, 95% CI 0.33-0.88, p=0.013).
ESPRIT Study Group Halkes et al. (2007) International 8 (RCT)	Patients with noncardioembolic stroke or TIA (<6 mo) were randomized to receive anticoagulation with phenprocoumon, acenocoumarol or warfarin (INR 2.0-3.0, n=536) or ASA (30-325mg, n=532). Primary study outcomes were the composite of vascular-cause mortality, non-fatal stroke, nonfatal MI and bleeding complication. Major ischemic events were included as secondary outcomes. Mean follow-up was 4.6 years.	Oral anticoagulation did not differ significantly from ASA therapy in terms of risk for the primary study outcome (HR=1.02, 95% CI 0.77-1.35) or for all major ischemic events (HR=0.73, 95% CI 0.52-1.01). However, there was a greater risk for bleeding complications associated with oral anticoagulation therapy (HR=2.56, 85% CI 148-4.43). The comparison of anticoagulation versus ASA alone was terminated early based on an earlier ESPRIT report demonstrating greater efficacy of dipyridamole + ASA versus ASA alone. *Post hoc* comparisons demonstrated that, in the ESPRIT trial, risk for primary events was not significantly greater with anticoagulation therapy versus combination therapy (HR=1.31, 95% CI 0.98-1.75). Similarly, there was no significant between-group difference demonstrated for major ischemic events (HR=0.94, 95% CI 0.67-1.31), but there was a significantly increased risk for major bleeding events associated with anticoagulation (HR=4.37, 95% CI 2.27-8.43).

Note. INR = International Normalization Ratio

8.9 Cardiac Abnormalities

8.9.2 Anticoagulant Therapy

8.9.2.1 Warfarin (Coumadin)

Table 8.9.2.1 Warfarin and ASA Therapy In Atrial Fibrillation

Author, Year Country Pedro Score	Methods	Outcomes
AFASAK I Petersen et al. (1989) Denmark 6 (RCT)	A total of 1,007 patients with chronic, non-rheumatic AF were randomly allocated to receive adjusted dose warfarin (INR target range = 2.8 – 4.2), 75 mg ASA once daily, or a placebo (matched to ASA). Follow-up was over a period of 2 years. Thromboembolic complications were defined as (TIA, minor stroke, non-disabling stroke, disabling stroke, fatal stroke, embolism to viscera or extremities).	Annual incidence of thromboembolic complications was 2.0% on warfarin and 5.5% on aspirin and placebo (p<0.05). 21 patients who withdrew due to side effects of warfarin treatment experienced bleeding complications. Two bleeding events were noted with ASA treatment and none in the placebo group.

BAATAF Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators (1990) USA 7 (RCT)	420 adults with chronic atrial fibrillation with no evidence of mitral stenosis were randomly assigned to receive either adjusted dose warfarin (INR 1.5 – 2.7) or nothing. Patients were advised regarding therapy they received. Patients who received no warfarin therapy were allowed to take ASA – doses and frequencies were recorded.	The risk of stroke was reduced in the warfarin therapy group compared to the no therapy group by 86% (p=0.0022). Mortality was also significantly lower in the treatment group (p=0.005). The frequency of major haemorrhage was similar in both groups. Minor haemorrhages were higher within the warfarin group.
CAFA Connolly et al. (1991) Canada 8 (RCT)	187 patients with non-rheumatic AF were randomized to receive adjusted dose warfarin, 191 to receive a matching placebo. The study was stopped early (prior to completing projected recruitment of 630 patients) subsequent to publication of results of SPAF. Targeted INR was 2 – 3. INR was within range for 43.7% of study days.	Combined primary outcome event cluster was comprised of non-lacunar stroke, non-central nervous system embolism and fatal or intracranial haemorrhage. Annual rate of the combined outcome was 3.5% in patients receiving warfarin vs. 5.2% in the placebo group. Relative risk reduction with warfarin was 37% (p=0.17). The annual rate for fatal or major bleeding was increased in the warfarin group (2.5% vs. 0.5%), as was minor bleeding (16% vs. 9%).
SPAF I Stroke Prevention in Atrial Fibrillation Investigators (1991) USA 7 (RCT)	1,330 patients with constant or intermittent, non-valvular atrial fibrillation were separated into two groups based on their eligibility to receive warfarin. Warfarin eligible patients were randomized to receive either dose-adjusted warfarin - INR target range 2.0 – 4.5 - (n=210), enteric-coated aspirin 325 mg/day (n=206) or placebo (n=211). Patients not eligible to receive warfarin were randomized to receive either ASA (n=346) or placebo (n=357). Mean follow-up time was 1.3 years.	Rate of primary events (ischaemic stroke and systemic embolism) was 6.3% per annum in patients assigned to placebo. This rate was reduced by 42% in patients receiving ASA and by 67% in warfarin-eligible patients assigned to receive adjusted dose warfarin. Primary events & death were reduced by 58% with warfarin (p=0.01) and 32% by ASA (p=0.02).
Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators Ezekowitz (1992) USA 8 (RCT)	571 men with chronic nonrheumatic atrial fibrillation were randomly allocated to a treatment condition receiving adjusted dose, low intensity warfarin (INR 1.5 – 2.7) or to a matching placebo condition. Mean follow-up was 1.7 years.	Among patients with no history of stroke, the reduction in risk for stroke associated with warfarin therapy was 0.79 (p=0.001). The annual event rate in patients over age 70 was 4.8%/annum in the placebo group and 0.9%/annum in the warfarin therapy group. Stroke was more common among patients with a history of previous cerebral infarction (9.3%/annum in the placebo group vs. 6.1%/annum in the warfarin group). Major haemorrhages occurred at the rate of 1.3% per annum with warfarin therapy.
EAFT European Atrial Fibrillation Trial Study Group (1993) Netherlands 7 (RCT)	1,007 non-rheumatic atrial fibrillation patients with a recent TIA or minor ischaemic stroke were grouped by eligibility to receive anti-coagulation therapy. Anti-coagulation eligible patients (group 1) were randomized to receive adjusted dose anticoagulation (INR 2.5 – 4.0), aspirin (300 mg/day) or placebo. Those not eligible for anti-coagulation therapy (group 2) were randomized to receive either ASA or placebo. Mean duration of follow-up was 2.3 years.	Among group 1 patients, risk of stroke was reduced from 12% per year to 4% per year when anti-coagulation therapy was compared to placebo (HR = 0.34). Among all patients receiving ASA, the rate of events was 15% compared to 19% for those patients receiving placebo (HR=0.83). Anticoagulation therapy was significantly more effective in preventing stroke than ASA (HR=0.60). The rate of major bleeding events while on anti-coagulation therapy was 2.8% and 0.9% while taking ASA.
SPAF II Stroke Prevention in Atrial Fibrillation Investigators (1994)	715 patients ≤ 75 years of age and 385 patients over the age of 75 were randomly allocated to receive adjusted dose warfarin (INR 2.0 – 4.5) or enteric-coated ASA 325 mg/day. Primary events	In younger patients, rate of primary events was reduced by 0.7% per year among those receiving warfarin therapy vs. ASA therapy (RR= 0.67; p=0.24). By comparison, rate of primary events was reduced

USA 6 (RCT)	were ischaemic stroke and systemic embolism.	by 1.2% per year with warfarin therapy vs. ASA (RR=0.73; p=0.39). In the older group the rate of all stroke (ischaemic & haemorrhagic, with & without residual deficits) was 4.3% in the ASA group vs. 4.6% in the warfarin group. Among older patients, there was a significantly greater risk of major haemorrhage with warfarin than with ASA therapy (4.2% vs. 1.6%; p=0.04).
SPAFIII Cowburn & Cleland (1996) USA 7 (RCT)	1044 patients with atrial fibrillation and one other risk factor for thromboembolism were randomly assigned to receive either adjusted dose warfarin (INR 2.0 – 3.0) or low-intensity, fixed dose warfarin (initial dose adjusted to INR 1.2 – 1.5) and ASA (325 mg/day). Mean follow-up = 1.1 years.	Rate of ischaemic stroke and systemic embolism was significantly higher among patients receiving combination therapy than those given adjusted-dose warfarin (7.9% per year vs. 1.9% per year; p<0.0001). Annual rates of disabling stroke and of primary event/vascular death were also significantly higher in the lower intensity group.
Second Copenhagen Atrial Fibrillation, Aspirin & Anticoagulation Study Gullov et al. (1998) Denmark 6 (RCT)	677 patients with atrial fibrillation (mean age= 74) were randomized to received either; 1) warfarin 1.25 mg/day or 2) warfarin 1.25 mg/day and ASA 300 mg/day or 3) ASA 300 mg/day. These were compared with 4) a group receiving adjusted dose warfarin therapy (INR 2.0 – 3.0).	Cumulative primary event rate (stroke or systemic embolic event) after one year was 5.8% in low-dose warfarin group, 7.2% in the warfarin + ASA group, 3.6% in the ASA group and 2.8% in the group receiving adjusted dose warfarin. Major bleeding events were rare. Though difference between groups was not significant (p=0.67), results favour adjusted dose warfarin over minidose or minidose + aspirin.
Li-Saw-Hee et al. (2000) UK 5 (RCT)	61 patients with non-valvular AF were randomized to one of three treatment groups: warfarin 2mg (n=23), 1 mg warfarin + 300 mg ASA or 2 mg warfarin + 300 mg ASA. Blood samples were taken at 2 weeks and 8 weeks (phase 1). Subsequent to this (phase 2), all patients were offered adjusted-dose warfarin therapy (INR 2.0 – 3.0). An additional blood sample was taken 6 weeks after the start of phase 2. Blood samples were analysed for the normalization of haemostatic markers in individuals with AF.	At baseline, AF patients had significantly elevated levels of fibrinogen (p=0.025), von Willebrand factor (p<0.0001) and fibrin D-dimer (p<0.0001) compared to a group of healthy, age, BP and sex-matched controls. At 2 and 8 weeks (phase 1), there were no significant changes in levels in all three groups, except for an increase in PAI-1 level in the 2mg warfarin+300 mg ASA group (p=0.024). At the end of phase 2 (treatment with adjusted-dose warfarin), there were significant reductions in plasma fibrinogen (p=0.023) and fibrin D-dimer (p=0.0067).
Japanese Nonvalvular Atrial Fibrillation-Embolism Prevention Cooperative Study Group Yamaguchi (2000) Japan 5 (RCT)	115 patients with non-valvular atrial fibrillation less than 80 years of age with a history of previous ischaemic stroke or TIA were randomly allocated to receive either conventional intensity warfarin therapy (INR 2.2 – 3.5) or low-intensity warfarin therapy (INR 1.5 – 2.1). The trial was stopped following major haemorrhage in 6 patients.	Frequency of major haemorrhage was 6.6% per annum in the conventional therapy group compared with 0% in the low intensity group (p=0.01). The mean INR in patients experiencing major haemorrhage was 2.8 and their mean age was 74 years. The annual rate of stroke was not significantly different between groups (1.1% with conventional therapy vs. 1.7% with low intensity therapy).
BAFTA Mant et al. (2007) UK 8 (RCT)	973 patients aged ≥75 years with atrial fibrillation were recruited from 260 general medicine practices over a 3 year period. Patients were randomly assigned to receive either 75 mg. ASA daily or dose-adjusted warfarin therapy to a target INR of 2.5. Protocol for INR testing was not controlled by the study, as it was the intent to test therapy under "real life" conditions. Patients	Patients on warfarin therapy had recorded INR values in the therapeutic range 67% of time. Median INR = 2.3 (IQR 2.0-2.8). 67% of patients assigned to warfarin remained on warfarin throughout the study, while 76% of patients assigned to the ASA condition remained on ASA. Overall, use of warfarin therapy was associated with a significant reduction in risk for stroke (RR=0.46 95% CI 0.26-0.79, p=0.003). Warfarin

	remained in the study for an average of 2.7 years. Patients were reviewed every 6 months following treatment allocation. Primary study outcome was first occurrence of fatal or non-fatal disabling stroke (ischaemic or haemorrhagic), other intracranial haemorrhage or clinically significant arterial embolism.	therapy was significantly associated with the prevention of disabling, non-fatal (RR=0.33, 95% CI 0.13-0.77) and ischemic stroke (RR=0.30, 95% CI 0.13-0.63) when compared to ASA monotherapy. In addition, there was no evidence of increased risk for haemorrhage associated with the use of warfarin (RR=0.96, 95% CI 0.53-1.75). In addition, the effectiveness of warfarin did not differ across age groups (75-79, 80-84 and ≥85).
Pullicino et al. (Pullicino et al. 2014) UK Post-hoc No Score TPS=NA N_{Start}=144 N_{End}=144	**Population:** Incident ischemic stroke (IIS) group (N=84): Age (≥60)=46; Gender: Males= 66, Females= 18.No IIS group (N=2221): Age (≥60)=1229; Gender: Males= 1774, Females= 447. **Intervention:** Baseline data from patients involved in a previous RCT (Warfafin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF)) was further analyzed to identify risk factors for incident ischemic stroke (IIS) and the rate of IIS in patients with prior stroke in the WARCEF trial. **Outcomes:** Onset of IIS; Age; gender; race; systolic BP ≥119.5; Ejection fraction (EF) <15%, NYHA class III or IV; alcohol consumption; smoking status; already on warfarin; atrial fibrillation; diabetes mellitus; hypertension; ischemic cardiomyopathy; myocardial infarction; peripheral vascular disease; baseline stroke.	An EF of 15% was the highest associated with a significant increase in IIS rate (p=0.009). Only baseline stroke and EF 15% were found to be significant risk factors for IIS (p<0.001; p=0.023). The IIS rate between individuals with EF >15% and those with EF <15% was significantly different in patients without baseline stroke (p=0.021). The warfarin versus aspirin effect was significantly different in patients without baseline stroke (p=0.008) compared to those with baseline stroke, and between patients with EF >15% (p=0.001) compared to those with EF <15%.

8.9.3 Antiplatelet Therapy

8.9.3.1 ASA Monotherapy

Table 8.9.3.1 ASA Monotherapy in Patients with AF

Author, Year Country Pedro Score	Methods	Outcomes
SPAF I Stroke Prevention in Atrial Fibrillation Investigators (1991) USA 7 (RCT)	1,330 patients with constant or intermittent, non-valvular atrial fibrillation were separated into two groups based on their eligibility to receive warfarin. Warfarin eligible patients were randomized to receive either dose-adjusted warfarin - INR target range 2.0 – 4.5 - (n=210), enteric-coated aspirin 325 mg/day (n=206) or placebo (n=211). Patients not eligible to receive warfarin were randomized to receive either ASA (n=346) or placebo (n=357). Mean follow-up time was 1.3 years.	Rate of primary events (ischaemic stroke and systemic embolism) was 6.3% per annum in patients assigned to placebo. This rate was reduced by 42% in patients receiving ASA and by 67% in warfarin-eligible patients assigned to receive adjusted dose warfarin. Primary events & death were reduced by 58% with warfarin (p=0.01) and 32% by ASA (p=0.02).
EAFT European Atrial Fibrillation Trial Study Group	1,007 non-rheumatic atrial fibrillation patients with a recent TIA or minor ischaemic stroke were grouped by eligibility to receive anti-coagulation therapy. Anti-coagulation eligible patients (group 1) were	Among group 1 patients, risk of stroke was reduced from 12% per year to 4% per year when anti-coagulation therapy was compared to placebo (HR = 0.34). Among all patients receiving ASA, the rate

(1993) Netherlands 7 (RCT)	randomized to receive adjusted dose anticoagulation (INR 2.5 – 4.0), aspirin (300 mg/day) or placebo. Those not eligible for anti-coagulation therapy (group 2) were randomized to receive either ASA or placebo. Mean duration of follow-up was 2.3 years.	of events was 15% compared to 19% for those patients receiving placebo (HR=0.83). Anticoagulation therapy was significantly more effective in preventing stroke than ASA (HR=0.60). The rate of major bleeding events while on anti-coagulation therapy was 2.8% and 0.9% while taking ASA.
JAST Sato et al. (2006) Japan 7 (RCT)	In this open-label study, 871 patients with non-valvular atrial fibrillation were randomly allocated to treatment (n=426) or control (n=445) groups. Treatment consisted of daily ASA therapy (150 – 200 mg) or no treatment. Primary study outcomes were cardiovascular death, symptomatic brain infarction or TIA.	The trial was stopped early due to higher risk of major bleeding associated with ASA therapy. It was also determined that ASA was unlikely to be associated with superior prevention of study endpoints. Data collected revealed no difference between groups on any of the primary end points including stroke (p=0.967). 7 patients in the treatment group and 2 patients in the control group experienced major bleeding (p=0.1).

8.9.3.2 ASA Combination Therapy

Table 8.9.3.2 ASA + Clopidogrel in Patients with AF

Author, Year Country Pedro Score	Methods	Outcomes
ACTIVE-W Connolly et al. (2006) International 8 (RCT)	6,706 patients with AF and at least one additional risk factor for stroke (including previous stroke or TIA) were randomly assigned to receive open-label therapy with either oral anticoagulation therapy (vitamin K antagonist, INR 2.0–3.0) or dual antiplatelet therapy (clopidogrel 75 mg + ASA 75–100 mg). Primary study outcome was first occurrence stroke, non-CNS systemic embolism, myocardial infarction or vascular death. 15% of enrolled patients had previous stroke or TIA. Median length of follow-up was 1.28 years.	Although designed as a non-inferiority trial, the study was halted prematurely when significant evidence emerged to support the superiority of oral anticoagulation over dual antiplatelet therapy. Patients receiving antiplatelet therapy had a significantly greater risk for stroke than those in the anticoagulation group (RR=1.17, 95% CI 1.24-2.37). This was most evident for ischemic stroke in particular (RR=2.17 95% CI 1.51-3.13). In terms of major bleeding events, there was no significant between group differences noted. There was, however, a significantly greater number of minor bleeding events reported in the group receiving dual antiplatelet therapy (RR=1.23, 95% CI 1.09-1.39).
ACTIVE-A Connolly et al. (2009) International 10 (RCT)	7,554 patients with atrial fibrillation who were not eligible for oral anticoagulation were randomly assigned to receive either clopidogrel (75 mg/day) or a matching placebo. All patients also received ASA (75-100 mg/day was recommended). Primary study outcome was any major vascular event (stroke, non-CNS embolism, MI or death from vascular causes). Median duration of follow-up was 3.6 years.	For the combined primary outcome, fewer events were experienced by participants receiving clopidogrel + ASA than those receiving ASA alone (RR=0.89, 95% CI 0.81-0.98, p=0.01). For stroke alone, the risk for any stroke was lower in the combined treatment group vs. ASA alone (RR=0.72, 96% CI 0.62-0.83, p<0.001). When examined by type of stroke, it was determined that while there was a significant decrease in risk for ischemic stroke (RR=0.68 95% CI 0.57-0.80), there was a nonsignificant increase in risk for haemorrhagic stroke associated with combined treatment (RR=1.37, 95% CI 0.79-2.37). There were significantly more major and minor bleeding events associated with ASA + clopidogrel treatment than ASA alone (RR = 1.57, 95% CI 1.29-1.92,

		p<0.001 and RR=2.42 95% CI 1.52-1.85, respectively).

8.9.4 Alternative Therapies

8.9.4.1 Indobufen

Table 8.9.4.1 Indobufen Therapy in Patients with Atrial Fibrillation

Author, Year Country Pedro Score	Methods	Outcomes
Fornaro et al. (1993) Italy 7 (RCT)	196 patients with history of heart disease and at risk for cardioembolism (90 patients with AF, 106 patients in sinus rhythm with one additional risk factor for cardioembolism) were randomized to treatment with indobufen (100 mg twice daily, n=98) or placebo groups (n=98). Study duration = 3 years. Patients were examined every 3 months.	Age, sex and risk factor adjusted relative risk reduction for primary study endpoints (TIA & fatal or non-fatal stroke) was reported for the group treated with indobufen (RR=0.35, p<0.05, 95% CI = 0.14 – 0.89). Overall, 6 primary events (2 fatal) were reported in the treatment group while there were 17 events reported in the placebo group (7 fatal).
SIFA Investigators Morocutti et al. (1997) Italy 7 (RCT)	916 patients with nonrheumatic AF were randomly assigned to receive either indobufen (100 or 200 mg p.o. o.d.) or adjusted dose warfarin (INR 2.0 – 3.5) for 12 months.	Incidence of primary outcome events (nonfatal stroke, systemic embolism, nonfatal MI and vascular death) was not significantly different between groups (10.6% in the indobufen group vs. 9.0% in the warfarin treatment group). A low frequency of noncerebral bleeding events was observed – there were 4 GI bleed events recorded; all within the warfarin treatment group.

8.9.4.2 Ximelagatran

Table 8.9.4.2 Ximelagatran Therapy in Patients with Atrial Fibrillation

Author, Year Country Pedro Score	Methods	Outcomes
SPORTIF III Olsson (2003) Europe 7 (RCT)	3410 patients with atrial fibrillation and at least one risk factor for stroke, including previous stroke or TIA, were randomly allocated to receive open-label treatment with either ximelagatran (36 mg/day) or adjusted-dose warfarin (INR 2.0 – 3.0). Mean follow-up = 17.4 months.	The rate of stroke or systemic embolism was 2.3% per year in the warfarin group vs. 1.6% per year in the ximelagatran group (relative risk reduction associated with ximelagatran = 29%; p=0.1). Major and minor bleeding events were fewer in the group receiving ximelagatran (relative risk reduction = 14% for major or minor bleeds, p=0.007). Treatment with ximelagatran was associated with more cases of elevated alanine aminotransferase (6.1% of patients).
SPORTIF II Petersen et al. (2003) International 6 (RCT)	A 12-week phase II study in which 254 patients were randomized to one of 4 groups: ximelagatran 20 mg bid (n=66), ximelagatran 40 mg bid (n=62), ximelagatran 60 mg bid (n=59) or open-label dose-adjusted warfarin (INR 2.0 – 3.0) (n=67).	One TIA and one stroke occurred in patients receiving ximelagatran. 2 TIAs were reported among patients treated with warfarin. No major bleeding events were reported among patients receiving ximelagatran. One major bleeding event was reported in the warfarin condition. Minor bleeding was reported in 4, 5 & 7 patients in the 20, 40 & 60 mg ximelagatran groups respectively. Minor bleeding was reported for 6 patients

		in the warfarin group. 4.3% (8) of patients treated with ximelagatran experienced elevations of the liver enzyme S-alanine aminotransferase greater than 3X the upper limit of normal. These resolved with either continued treatment (5 patients) or discontinuation of ximelagatran therapy (3 patients).
SPORTIF V Albers et al. (2005) USA/Canada 9 (RCT)	3922 patients with nonvalvular AF and at least one risk factor for stroke were randomized to receive therapy with either dose-adjusted warfarin (INR 2.0 – 3.0) or ximelagatran 36 mg bid. Mean length of follow-up = 20 months in both treatment groups.	For the primary study endpoint of all strokes and systemic embolic events, the incidence was 1.16% in the warfarin treatment group and 1.61% in the ximelagatran group (p=0.13). By intention to treat analysis, no significant differences were reported for nonfatal or fatal stroke of any type or for all cause mortality. While there were fewer major extracerebral bleeds reported in the ximelagatran group than in the warfarin group, this difference was not significant. When considering major and minor bleeding episodes combined, treatment with ximelagatran represented a relative reduction in bleeding risk of 21% (p<0.001). 6.0% of patients experienced elevated serum ALT levels > 3 times the upper limit of normal. For most, this resolved either spontaneously or following treatment cessation.

8.9.4.3 Dabigatran

Table 8.9.4.3 Dabigatran Therapy in Patients with Atrial Fibrillation

Author, Year Country Pedro Score	Methods	Outcomes
PETRO Study Ezekowitz et al. (2007) International 5 (RCT)	502 patients with history of coronary artery disease, atrial fibrillation and one additional risk factor (HTN, diabetes, heart failure or left ventricular dysfunction, previous stroke/TIA or age >75 years) were randomly assigned to a treatment group receiving a blinded dose of dabigatran (50 mg, 150 mg or 300 mg) b.i.d. either with or without ASA (81 mg or 325 mg o.d.) or to a comparator group that received dose-adjusted warfarin (target INR 2 – 3) for 12 weeks. There were 10 treatment groups in total. Primary study outcome was incidence of bleeding events. Major bleeding was defined as fatal or life-threatening, or requiring surgery or transfusion of ≥units or associated with a decrease in haemoglobin of ≥2 g/L. Minor bleeding was subdivided into clinically relevant vs. nuisance bleeding episodes.	Major bleeding events occurred only in the groups treated with 300 mg b.i.d. + ASA. Groups at the highest dose of dabigatran who also received ASA experienced more clinically relevant and total bleeding events than those not receiving ASA (p=0.03 and p=0.0003) at this dose. Irrespective of ASA condition, there were more bleeding episodes associated with 300 mg b.i.d. doses than 150 mg b.i.d. doses (p=0.002) and more in the 150 mg group than in the 50 mg group (p=0.01). There were fewer clinically relevant bleeding events in the group receiving 50 mg b.i.d. dabigatran than in the warfarin group. However, this was not the case at either the 150 mg or 300 mg levels. The addition of aspirin was associated with more bleeding events. Adverse effects were more frequent in the dabigatran groups than in the warfarin group. Most commonly reported events were gastrointestinal complaints. Use of dabigatran was associated with a paradoxical platelet activation effect in the absence of ASA.
RE-LY Study Connolly et al. (2009) International	In a non-inferiority trial, 18,113 patients with AF and risk of stroke (i.e. one of previous stroke/TIA, left ventricular ejection fraction	Both doses of dabigatran were found to be noninferior to warfarin therapy in terms of risk for stroke or systemic embolism. The fixed dose of 150 mg. b.i.d.

9 (RCT)	<40%, hear failure within 6 months, age ≥75 year or 65-75 with diabetes, HTN or coronary artery disease) were randomly assigned to receive either a fixed dose of dabigatran (110 mg or 150 mg. b.i.d.) or dose-adjusted warfarin. Concurrent ASA (or other antiplatelet) use was permitted. Enrollment was balanced for previous therapy with a vitamin K antagonist (e.g. warfarin naive vs. previously treated for more than 60 days). Median duration of follow-up was 2 years. Primary study outcome was stroke or systemic embolism. Net clinical benefit outcome was estimated using the composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death or major bleeding.	was found to be superior to warfarin therapy in terms of risk for stroke/embolism overall (RR=0.66, 95% CI 0.53 – 0.82, p<0.001). However, when the subgroup of patients with previous TIA/stroke were analysed separately, neither the 110 mg dose of dabigatran nor the 150 mg dose was associated with significant reductions in risk for recurrent events when compared with warfarin (p=0.65 and 0.34, respectively). The risk for major bleeding events were reduced (vs. warfarin) in the 110 mg group only (RR=0.80, 95% CI 0.69-0.93, p = 0.003). However, when life threatening bleeding events and intracranial bleeding were considered separately, both doses of dabigatran were associated with reduced risks for these outcomes when compared to warfarin therapy. For life threatening bleeding RR= 0.68 (95% CI 0.55-0.83, p<0.001) and 0.81 (95% CI 0.66-0.99, p=0.04) for 110 and 150 mg doses respectively, while for intracranial bleeding RR=0.31 (95% CI 0.20 – 0.47, p<0.001) and 0.40 (95% CI 0.27 – 0.60, p<0.001). It should be noted that use of dabigatran 150 mg b.i.d. was also associated with increased risk for gastrointestinal bleeding (both life threatening and non-life threatening) (RR=1.50, 95% CI 1.19 – 1.89, p<0.001). When examining the net clinical benefit outcome there was a small reduction in risk associated with dabigatran 150 mg/b.i.d. vs. warfarin (RR=0.91, 95% CI 0.82-1.0, p=0.04).
RE-LY Subgroup analysis Diener et al. (2010)	Examined the effects of dabigatran etexilate vs. warfarin in individuals with previous history of stroke or TIA. There were 1995 patients with previous stroke in the dabigatran 110 mg. twice daily group, 1233 in the dabigatran 150 twice daily group and 1195 in the warfarin therapy group. The primary study endpoint was stroke or systemic embolism. Other endpoints examined included stroke, haemorrhagic strike, ischaemic or unknown stroke, disabling or fatal stroke, myocardial infarction, vascular death and death from any cause.	Neither dose of dabigatran was associated with a significant reduction in the risk for stroke when compared to warfarin therapy for the group of individuals with previous history of stroke/TIA (RR=0.84, 95% CI 0.58-1.0 for 110 mg; RR=0.75, 95% CI 0.52-1.08). There was a significant reduction in primary outcome noted in individuals with no previous stroke who received dabigatran 150 mg twice daily vs. warfarin (RR=0.60, 95% CI 0.45-0.78). For dabigatran 100 mg, there were significant reductions in risk for haemorrhagic stroke for individuals with and without previous stroke (RR=0.11, 95% CI 0.03-0.47 and RR=0.44, 95% CI 0.22-0.86, respectively). There were also reductions in risk vs. warfarin for individuals with previous stroke for both vascular death (RR=0.63 95% CI 0.43-0.92) and death from any cause (RR=0.70, 95% 0.53-0.94), but these significant benefits were not seen in individuals with no previous stroke. At 150 mg, dabigatran use was associated with reduced risk for haemorrhagic stroke in individuals with and without previous stroke when compared to warfarin (RR=0.27, 95% CI 0.10-0.72 & RR= 0.25, 95% CI 0.11-0.59). There were significant reductions in risk for ischemic stroke, disabling or fatal stroke vascular death or death from any cause for individuals with no previous history of

		stroke, but these significant benefits were not demonstrated in the subgroup of individuals with previous stroke. In all groups, use of dabigatran at either dose was associated with non-significant increases in risk for myocardial infarction when compared to warfarin therapy.
RE-LY Substudy Ezekowitz et al. (2010)	Warfarin and 2 doses of dabigatran (100 mg twice daily and 150 mg twice daily) as per the RE-LY trial (above) were compared in individuals who were vitamin K antagonist (VKA)-naive vs. individuals who were VKA-experienced (where VKA-naive = ≤62 days of lifetime exposure to VKA). Primary study outcomes were as for the RE-LY trial.	There were no significant differences in risk for combined stroke and systemic embolism in the dabigatran 110 mg group for VKA naive vs. experienced participants when compared to warfarin (p for interaction = 0.65). Similarly, for individuals receiving dabigatran 150 mg, there was no difference in reduction in risk vs. warfarin (p for interaction = 0.84). Rates of major bleeding events were lower in VKA-experienced individuals receiving dabigatran 110 mg when compared to warfarin (RR=0.74, 95% CI 0.60-0.90, p=0.003), but not for VKA-naive patients at this dose (RR=0.87, 95% CI 0.72-1.07). In the 150 mg dose, there was no significant difference in rates of bleeding events vs. warfarin in VKA groups. Intracranial bleeding rates were lower in all groups receiving dabigatran vs. warfarin. Rates were similar in VKA-naive vs. VKA-experienced patients.
RE-LY Subgroup analysis Ferreira et al. (2013) Multicentre RCT PEDro=9 TPS=NA N_{Start}=18113 N_{End}=4904	**Population:** Experimental group I (EG1; N=1641); Mean age=68.5±10.3yr; Gender: Males=1142, Females=499. Experimental group II (EG2; N=1640); Mean age=68.0±10.5yr; Gender: Males=1061, Females=579. Control group (CG; N=1623); Mean age=68.4±9.9yr; Gender: Males=1079, Females=544. **Intervention:** This is a subgroup analysis of the RE-LY study. This analysis was conducted in patients with previous heart failure. The EG1 received Dabigatran 110mg b.i.d, the EG2 received Dibigatran 150mg b.i.d, and the CG received warfarin. **Outcomes:** time to first occurrence of stroke or systemic embolism (SE); time to first occurrence of major bleeding; vascular death; hospitalization; intracranial bleeding; total bleeding.	The incidence of stroke or SE was 1.90%/yr in EG1, 1.44%/yr in EG2, and 1.92%/yr in CG. Vascular death and hospitalization was not significantly different between the three treatment groups. The annual rate of major bleeding in CG was 3.90%, 3.26% in EG1, and 3.10% in EG2. Intracranial bleeding occurred significantly more in the CG (0.65%/yr) than in the EG1 (0.22%/yr) and the EG2 (0.26%/yr).
RE-LY Subgroup analysis Hori et al. (2013) Multicentre RCT PEDro=9 TPS=NA N_{Start}=18119 N_{End}=19113	**Population:** Asian (N=2782); Mean age=68.0±9.8yr; Gender: Males=1775, Females=1007. Non-Asian (N=13551); Mean age=72.1±8.3yr; Gender: Males=9739, Females=3812. **Intervention:** This is a subgroup analysis of the RE-LY trial which looked at outcomes based on Asian descent which included the following countries: China, Hong Kong, Japan, South Korea, Taiwan, India, Malaysia,	The rates of strokes in Asian patients were 3.06%/yr in the warfarin group, 2.50%/yr in the DE 110mg group, 1.39%/yr in the DE 150mg group. The rate was significantly lower in the DE 150mg groups compared to the warfarin group. The rates of stroke in non-Asian patients were 1.48%/yr in the warfarin group, 1.37%/yr in the DE 110mg group, and 1.06%/yr in the DE 150mg group. The rate was significantly lower in the DE 150mg group compared to the warfarin group.

	Philippines, Singapore and Thailand. Participants were randomized to receive either dabigatran 110mg b.i.d, or dabigatran 150mg b.i.d, or warfarin. **Outcomes:** occurrence of stroke or systemic embolism (SE); major bleeding events; net benefit defined as a composite of stroke, SE, pulmonary embolism, myocardial infarction, death, or major bleeding.	There was no significant difference between Asians and non-Asians with regards to the incidence of stroke, MI, or bleeding. The rates of major bleeding in Asian patients were 3.82%/yr in the warfarin group, 2.22%/yr in the DE 110mg group, and 2.17/yr in the DE 150mg group. The rates were significantly lower in the DE groups compared to the warfarin group. The rates of major bleeding in Asian patients were 3.53%/yr in the warfarin group, 2.99%/yr in the DE 110mg group, and 3.52/yr in the DE 150mg group. There was significant interaction between ethnicity and treatment (ie. DE 150mg vs warfarin) in Asians with non-Asians however this interaction was no longer significant when the analysis was adjusted for age. The rate of hemorrhagic stroke in warfarin-treated patients was 0.75%/yr in Asian patients and 0.32%/yr in non-Asian parents (p=0.007). There was a significant interaction between treatment (i.e. DE 150mg vs warfarin) and ethnicity for major gastrointestinal bleeding (p=0.009). The interaction remained significant after adjusting for age (p=0.04). For both DE doses, there was a significant interaction between treatment and ethnicity for total bleeding (p<0.0001). Net clinical benefit was consistently in favour of DE for both doses compared with warfarin in both Asians and non-asians.
RELY-ABLE (Extension of RE-LY trial) Connolly et al. (2013) Multicentre Observational No Score TPS=NA N_{Start}=5851 N_{End}=2188	**Population:** Dibigatran 110mg (N=2937); Mean age=71±8yr; Gender: Males=1911, Females=1026. Dibigatran 150mg (N=2914); Mean age=71±8yr; Gender: Males=1914, Females=1000. **Intervention:** The long-term multicentre extension of dabigatran treatment in patients with atrial fibrillation (RELY-ABLE) study was designed to provide additional information on the long-term effects of the 2 doses of dabigatran in patients completing RE-LY by extending the follow-up of patients on dabigatran from a mean of 2 years at the end of the RE-LY by an additional 2.25yrs. In the RE-LY trial, participants were either randomized to 110mg b.i.d. of dabigatran, or 150mg b.i.d of dabigatran, or warfarin. The RELY-ABLE did not include patients receiving warfarin. The RELY-ABLE study visits occurred at 4, 8, 18, 23, and 28 months. **Outcomes:** Stroke or systemic embolism (SE); myocardial infarction; pulmonary embolism; vascular death; total mortality; net benefit (composite of stroke, SE, myocardial	During the RELY-ABLE, there were temporary interruptions of study medication in 43% of patients receiving dabigatran 110mg and in 44% of patients receiving dabigatran 150mg. The most common reasons included surgery and hospitalization. During RELY-ABLE, the annual rates of stroke or SE were 1.46% and 1.60% on dabigatran 150mg and 110mg. Annual rates of ischemic stroke were 1.15% and 1.24% in dabigatran 150m and 110mg. Annual rates of hemorrhagic stroke were 0.13% and 0.14 for dabigatran 150mg and 110mg. Annual rates of myocardial infarction were 0.69% and 0.72% in dabigatran 150mg and 110mg. Annual rates of major bleeding events were 3.74% and 2.99% in dabigatran 150mg and 110mg. Annual rates of gastrointestinal bleeding events were 1.54% and 1.56% in dabigatran 150mg and 110mg. Annual rates of mortality were 3.02% and 3.10% in dabigatran 150mg and 110mg.

	infarction, pulmonary embolism, death, major bleeding).	

8.9.4.4 Rivaroxaban

Table 8.9.4.4 Use of Rivaroxaban in Atrial Fibrillation

Author, Year Country Pedro Score	Methods	Outcomes
ROCKET-AF Patel et al. (2011) International 10 (RCT)	14,264 patients with AF and elevated risk for stroke ($CHADS_2 \geq 2$) were randomly allocated to treatment with either rivaroxaban (20 mg o.d.) or dose-adjusted warfarin (INR target 2.0 – 3.0). Both groups received a placebo tablet in addition to active medication in order to preserve blinding and patients in the rivaroxaban group received sham INR reports. Primary study outcome was the composite of stroke and systemic embolism. Median length of treatment = 590 days. INR values for patients assigned to treatment with dose-adjusted warfarin were within the therapeutic range a mean of 55% of the time over the course of the study.	On intention to treat analysis, there were 269 primary events recorded in individuals assigned to treatment with rivaroxaban vs. 306 patients treated with dose-adjusted warfarin (HR = 0.88, 95% CI 0.74, 1.03; p<0.001 for non-inferiority, p=0.12 for superiority). There were no significant between group differences reported for major or clinically relevant bleeding events (HR=1.03, 95% CI 0.96, 1.11; p=0.44). Rates of major bleeding events were similar between groups (p=0.58), though there were fewer instances of intracranial haemorrhage in the rivaroxaban group than the warfarin group (HR=0.67, 95% CI 0.47, 0.93; p=0.02).
ROCKET-AF Hankey et al. (2012) Sub-group analysis	In this subgroup analysis, investigators examined differential treatment effects in individuals with and without previous history of stroke/TIA. 52% of all participants had previous stroke (n=3754 rivaroxaban; n=3714 warfarin).	Overall, primary outcome events (per 100 person years of randomised patients) was higher among individuals with previous stroke than among those with no previous history of stroke (HR=1.7, 95% CI 1.44-2.02; p<0.0001). However, the efficacy of treatment (rivaroxaban or warfarin) was the same for individuals with vs. without previous stroke (significance of interaction of treatment with history, p=0.23). There were no significant treatment and history interactions for any stroke, haemorrhagic stroke, ischaemic or unknown stroke, non-disabling or disabling/fatal stroke). In terms of adverse events, there were no between group (previous stroke vs. no previous stroke) differences in number of adverse events per 100 person years. Similar to treatment, there were no significant interactions identified between treatment and history of stroke for the outcome of bleeding events (p=0.36).
Mega et al. (2012) United States 9 (RCT)	In a double-blind, placebo-controlled trial, 15 526 patients with a recent acute coronary syndrome were randomly assigned to receive twice-daily doses of either 2.5mg or 5mg rivaroxaban or placebo for a mean of 13 months, up to 31 months. The primary end point of the study was a composite death from cardiovascular causes, myocardial infarction or stroke.	As compared to placebo, rivaroxaban significantly reduced the primary efficacy end point with respective rates of 10.7% and 8.9% with significant improvement for both the twice-daily 2.5mg dose (9.1% vs 10.7%, P=0.02) and the twice-daily 5mg dose (8.8% vs. 10.7%, P=0.03). The twice daily 2.5mg dose of rivaroxaban reduced the rates of death from cardiovascular causes (2.7% vs. 4.1%, P=0.02) and from any cause (2.9% vs 4.5%, P=0.002). In comparison to placebo, rivaroxaban increased the rates of major bleeding

		not related to coronary-artery bypass grafting (2.1% vs. 0.6%, P<0.001) and intracranial hemorrhage (0.6% vs 0.2%, P=0.009), without a significant increase in fatal bleeding (0.3% vs. 0.2%, P=0.66).
Tanahashi et al. (2013) Japan Secondary analysis on RCT TPS=NA N_{Start}=1278 N_{End} =1278	**Population:** Primary prevention group (N=465): Rivaroxaban (N=231): Mean age=72.2±8.28yr; Gender: Males=185, Females=46. Warfarin (N=234): Mean age= 72.6±8.46yr; Gender: Males=173, Females=61. Secondary prevention group (N=813): Rivaroxaban (N=408): Mean age=70.3±8.24yr; Gender: Males=345, Females=63. Warfarin (N=405): Mean age=70.4±7.50yr; Gender: Males=327, Females=78. **Intervention:** Data from participants randomized in a Japanese atrial fibrillation trial (J-ROCKET AF), was analyzed to determine the consistency of safety and efficacy profile of rivaroxaban versus warfarin among the subgroups of participants with previous stroke, TIA, or non-CNS systemic embolisms (secondary prevention group) and those without (primary prevention group). Participants were grouped based on the presence or absence of previous stroke, TIA, or non-CNS systemic embolism, and the safety outcomes and the rate of the efficacy endpoints were compared among groups. **Primary Outcomes:** Rate of principal safety outcome; Major bleeding events.	There was no significant interaction in the primary safety outcome of rivaroxaban compared to warfarin between patients in the primary prevention group and those in the secondary prevention group (p=0.09). No significant interaction was found for the major bleeding of rivaroxaban compared with warfarin between patients in the primary prevention group and those in the secondary prevention group. There was no significant interaction between warfarin and rivaroxaban and the presence or absence of stroke/TIA/non-CNS systemic embolisms. The rates of secondary efficacy endpoints (all cause stroke, hemorrhagic stroke, and ischemic stroke) were comparable between rivaroxaban and warfarin-treated patients in both primary and secondary prevention groups.

8.9.4.5 Apixaban

Table 8.9.4.5 Use of Apixaban in Atrial Fibrillation

Author, Year Country Pedro Score	Methods	Outcomes
AVERROES Connolly et al. (2011) International 10 (RCT)	5599 participants, for whom therapy with a vitamin K antagonist was unsuitable, with atrial fibrillation and at least one other risk factor for stroke were randomly assigned to receive either ASA (81 mg – 324 mg p.o. daily) or apixaban (5 mg p.o. b.i.d). The primary study outcome was a composite of stroke (both haemorrhagic and ischemic) and systemic embolism. Median length of study follow-up was 1.1 years.	There were significantly fewer primary outcome events recorded in the apixaban condition than in the ASA condition (113 vs. 51, HR=0.45, 95% CI 0.32, 0.62; p<0.001). For stroke events, in particular, there were significantly fewer ischemic events in individuals treated with apixaban vs ASA (HR=0.37, 95% CI 0.25, 0.55; p<0.001), although there were no significant between group differences in haemorrhagic stroke (p=0.45). There were also fewer deaths from any cause reported in the group receiving treatment with apixaban vs. ASA (111 vs 140), although this difference did not reach statistical significance (p=0.07). There were no significant between condition differences in terms of major bleeding events (p=0.69). The trial was

		terminated early given the clear benefit demonstrated in favour of apixiban.
ARISTOTLE Granger et al. (2011) International 10 (RCT)	18,201 participants with AF and at least one other risk factor for stroke were randomly assigned to treatment with apixaban (5 mg b.i.d) or dose-adjusted warfarin (INR 2.0-3.0). The primary study outcome was a composite of stroke (haemorrhagic and ischemic) and systemic embolism. The trial was designed to demonstrate non-inferiority; however, superiority was also evaluated on intention to treat analysis. Median duration of study follow-up = 1.8 years. Patients assigned to treatment with dose-adjusted warfarin were within the therapeutic range for INR a median of 66% of the time over the course of the study.	Approximately 19% of individuals assigned to each condition had a history of previous stroke or TIA. In terms of the primary study outcome, there were 212 patients with events in the apixaban condition vs. 265 in the warfarin condition (HR=0.79, 95% CI = 0.66, 0.95; p=0.01). There was no between group difference for ischemic stroke alone (p=0.42); however, treatment with apixaban was associated with a significant reduction in risk for haemorrhagic stroke when compared to warfarin (HR=0.51, 95% CI 0.35, 0.75; p<0.001). There was a significant reduction in risk for death from any cause associated with apixaban (HR=0.89, 95% CI 0.80, 0.99; p=0.047). Major bleeding events occurred less often among patients assigned to treatment with apixaban vs warfarin (HR=0.69, 95% CI 0.6, 0.8, p<0.001). Intracranial bleeding occurred more often in individuals assigned to treatment with warfarin (HR=0.42, 95% CI 0.3,0.58; p<0.001); there were no between group differences in bleeding from gastrointestinal sites (p=0.37). Subgroup analysis demonstrated no significant interaction between treatment and whether or not the participant had a history of previous stroke or TIA (p=0.71).
AVERROES Diener et al. (2012) Subgroup analysis	Of the 5599 participants in the AVERROES study, 764 reported having a previous stroke at study baseline. This subgroup analysis examined whether individuals AF and previous stroke would experience different treatment effects compared to the group of individuals with no previous stroke.	Overall, individuals with previous stroke experienced a greater number of primary study outcomes (HR=2.38, 95% CI 1.66, 3.34, p<0.0001) when compared to individuals with no history of stroke/TIA. However, there was no significant interaction reported between treatment type and history of previous stroke for any of the specified study endpoints. Risk for major bleeding was also greater among individuals with previous stroke (HR = 2.88 95% CI 1.77, 4.55; p<0.0001). However, there were no significant interactions reported between treatment assignment and previous history of stroke in terms of study safety outcomes.
ARISTOTLE Easton et al. (2012) Subgroup analysis	In this subgroup analysis, investigators examined differential treatment effects in individuals with and without previous history of stroke/TIA. Overall, 19% (n=3,436) of trial participants reported having previous stroke or TIA.	Overall, individuals with previous stroke were more likely to experience a primary study outcome event (HR=2.52, 95% CI 2.09, 3.04). However, the interaction between treatment group assignment and history of previous stroke was not significant for the primary study outcome (p=0.71) or for any stroke haemorrhagic stroke, ischaemic or unknown stroke, non-disabling or disabling/fatal stroke. Similarly, there were no significant interactions identified between treatment assignment and history of stroke for the outcome of total bleeding events (p=0.36) or for major, intracranial, gastrointestinal or major bleeding events.

8.9.5 Drug Management

8.9.5.1 Patient Decision Aids

Table 8.9.5.1 Patient Decision Aids and Anti-thrombotic Therapy

Author, Year Country Pedro Score	Methods	Outcomes
Man-Song-Hing et al. (1999) International 6 (RCT)	Centres participating in the SPAF III aspirin cohort study were eligible for participation. Patients at high risk were excluded. In addition to usual study end counselling, 287 non high risk patients from 14 centers were randomized to receive the audiobooklet decision aid (n=139) or not (n=148). The decision aid was designed to help patients with the initial post-study decision of appropriate antithrombotic therapy.	More patients in the decision aid group were able to make decisions regarding anti-thrombotic therapy than in the usual care group (p=0.02). Most patients in the decision aid group were inclined to take ASA (91%). Following a meeting with their primary care physician, most took the medication for which they expressed a preference. Patients in the decision aid group were more knowledgeable aspirin (p<0.001) and warfarin (p<0.001). There were no between group differences in satisfaction or decisional conflict.
McAlister et al. (2005) Canada 8 (RCT)	446 community dwelling patients with atrial fibrillation seen in 102 primary care practices were randomly allocated to receive either usual care or a self-administered booklet and audiotape decision aid tailored to their own risk profile for stroke. The aid contained information regarding the consequences of stroke or TIA, personalized estimates of stroke risk, recommendations for anti-thrombotic therapy and the potential for benefit and risks associated with warfarin & ASA therapy (based on the patient's personal risk profile). Primary study outcome was change in the proportion of patients taking appropriate antithrombotic therapy at 3 months.	At baseline, 31.5% and 39.5% of patients allocated to the decision aid and to the usual care group were receiving antithrombotic therapy appropriate to their stroke risk according to the American College of Chest Physicians (ACCP) Guidelines. Two weeks following the initiation of the intervention, patients in the decision aid group were better informed and reported less conflict in decision-making. At 3 months, there was a 9% increase in patients receiving appropriate therapy in the decision aid group compared to a 3% decline in number of patients receiving appropriate therapy in the usual care group (12% absolute difference, 34% relative improvement, p=0.03). However, by 12 months, care regressed toward baseline levels in both groups. At 12 months, the strongest predictor of appropriate anti-thrombotic therapy was being on that therapy at baseline.
Mazor et al. (2007) USA 5 (RCT)	600 patients receiving anticoagulation therapy were selected for inclusion by clinic staff – of these 317 were enrolled and completed the study. Patients were randomly assigned to receive 1 of three video-based interventions to communicate key information about safe warfarin use (narrative/patient anecdote –base evidence, statistical evidence and a combination narrative/statistical approach) vs. usual care (no video). Warfarin-related knowledge, beliefs and adherence were tested at baseline and post-intervention using a mailed questionnaire developed for the present study. Adherence was also monitored via recorded attendance at lab appointments.	Watching any video was associated with greater knowledge gains when compared to the control condition (p<0.001). In addition, individuals who watched a video demonstrated greater positive shifts in their beliefs regarding the importance of testing (p=0.01) and the benefits associated with warfarin therapy (p=0.012) vs. the control group. Based on clinical records, there was a non-significant trend toward better attendance for lab testing associated with receiving a video (p=0.07). When types of videotaped information were compared, narrative information appeared to result in stronger reported beliefs in the importance of lab testing when compared to statistical information alone (p=0.05). In addition, when adjusted for baseline knowledge, viewing narrative/anecdotally presented information resulted in greater knowledge gains (p=0.006). There were no between group differences for those who received only narrative vs. narrative/statistical information.
Thomson et al.	109 patients aged ≥ 60 years with atrial fibrillation	At the post-intervention assessment, there was

(2007) UK 5 (RCT)	were assigned to either a computerized decision aid/shared decision-making condition (n=53) or evidence-based paper guidelines/physician recommendation condition (n=56). In the decision-aid condition, participants were guided through an individualized presentation of potential harm and benefits and encouraged to consider the advantages and disadvantages of warfarin therapy before meeting with a physician to participate in shared decision-making. In the evidence-based condition, participants received treatment recommendations were derived from the application of evidence-based guidelines to the individual's risk profile. Primary study outcome was decision conflict. Assessments were conducted pre and post intervention and at 3-month follow-up.	significantly less decision conflict among individuals assigned to the decision aid intervention vs. the evidence guidelines condition (p=0.036). This may be been attributable to improved scores on the "informed" (i.e. participants felt more informed) and "values" (i.e. clearer about personal values in terms of risk and benefits) subscales of the decision conflict scale. These between group differences were not present at 3 months. Although knowledge improved for all patients between the pre and post intervention assessment, there were no significant between group differences in knowledge and improvements in knowledge were not sustained over time. For individuals not already on warfarin therapy at the time of the intervention, those in the decision aide group were much less likely than those in the evidence-based group to start warfarin (RR=0.27 (95% CI 0.11-0.63).
Evans-Hudnall et al. (2014) USA RCT PEDro=6 TPS=NA N_{Start}=60 N_{End}=52	**Population:** Intervention STOP group (N=27): Mean age= 56.03±9.9yr; Gender: Males=58%, Females=42%. Control Usual care group (N=25): Mean age= 49.65±10.74yr; Gender: Males=65%, Females=45%. **Intervention:** Participants were randomized to the intervention group and took part in a secondary stroke prevention (STOP) program which consisted of culturally tailored information sessions and goal-setting activities that were delivered in person by a research assistant, or to usual care. Patients were assessed at baseline and at 4wk follow-up. **Outcomes:** Stroke knowledge; self-reported exercise; fruit and vegetable consumption; tobacco and alcohol use; and medication adherence; Depression and anxiety.	At 4wk follow-up, the STOP group demonstrated greater improvement in stroke knowledge post-intervention compared to the control group (p=0.01). At post-treatment, 84% of participants in the STOP group compared to 45% in the control group reported abstaining from smoking any cigarettes over the past 4wk (p=0.01). Participants with greater baseline scores of anxiety had lower quit rates in the STOP group (p=0.04). Neither anxiety nor depression were found to be moderators of treatment group differences fruit/vegetable consumption, physical activity, and medical adherence at 4wk follow-up.

8.9.5.3 Guideline Adherence and Inpatient Anticoagulation

Table 8.9.5.3 Guideline Adherence and Inpatient Anticoagulation

Author, Year Country Pedro Score	Methods	Outcomes
Lewis et al. (2009) USA No Score	Data was included from 562 hospitals participating in the GWTG-stroke program. Pre-printed orders, an online patient management tool, educational conferences and quality improvement review were used to improve guideline adherence. 11% of all patients presenting with stroke were identified with AF (n=17,501) 7,635 of these were diagnosed based on ECG at admission (group	10.5% of all patients had AF with no contraindications to warfarin therapy. Overall, 63.9% of patients with AF without contraindications were prescribed treatment with warfarin. Administration of warfarin was more frequent among patients whose AF was documented during the current hospitalization (group 1) vs. medical history only (group 2) (78.7% vs. 49.4%, p<0.0001). Improvement in participation in warfarin therapy was reported for patients with ECG-documented AF over time (p<0.0001), but not

	1), the remainder via medical history only (group 2). 38% of patients with AF via medical history also had previous stroke vs. 32% with ECG diagnosis.	for patients with AF based on history only. In addition, women and individuals over the age of 65 were less likely to be treated with warfarin.
Duff and Walker (2010) Australia No Score	To increase percentage of patients receiving warfarin education prior to discharge, the percentage of patient whose loading dose is consistent with approved protocol and keep adverse outcomes below the standardized benchmark values, a multidisciplinary team developed interventions targeting physician compliance with guidelines: 1) two decision support tools – one directed at physicians to facilitate prescribing practices that promote therapeutic warfarin levels and one directed at nursing staff (clinical care pathway for patients on warfarin) 2) patient and staff specific education initiatives including a warfarin patient education checklist and self-paced online information package for staff. Process indicators were monitored throughout the project.	Prescriber compliance with loading protocol increased by 12% over the course of the project. Patient education prior to discharge increased by 54% (from 31% to 85%). The percentage of patients with INR >5 fell from 3.7% to 1.1% and the rate of abnormal bleeding events fell from 1.2% to 0%.
Peng et al. (2014) China RCT PEDro=4 TPS=NA N_{Start}=3821 N_{End}=3821	**Population:** Intervention SMART group (N=1795): Mean age= 61.48±11.47yr; Gender: Males=67%, Females= 33%. Control usual care group (N=2026): Mean age= 60.36±11.66yr; Gender: Males=69%, Females=31%. **Intervention:** Hospitals were randomized either to the intervention group and provided the Standard Medical Management in Secondary Prevention of Ischemic Stroke in Chine (SMART) program which is a specialist-based pharmaceutical care program coupled with internet-based lifestyle education to stroke patients, or to the control group and provided usual care where patients received only the interventions chosen by their attending neurologist-clinician. Patient assessments were conducted at baseline and at 6 and at 12mo follow-up. **Outcomes:** Proportion of patients who adhered to recommended measures; Number of new-onset ischemic stroke; Number of new-onset hemorrhagic stroke; Number of Acute coronary syndrome cases; All-cause death.	At 6 and 12mo, the adherence to the Statin treatment only was found to be significantly higher in the SMART group compared to the control group (p=0.005, p=0.006). Adherence to other drugs (i.e. antiplatelet, antihypertensive, antidiabetic) was not found to be significantly different between groups at 6 and at 12mo. There was also no significant decrease in secondary outcomes in the SMART group compared with the control group.

8.9.6 Other Cardiac Diseases

Table 8.9.6 Other Cardiac Diseases

Author, Year Country Pedro Score	Methods	Outcomes
ASPECT-2 Research Group Van Es et al. (2002) Netherlands 7 (RCT)	999 patients with previous MI were randomly allocated to treatment with low-dose ASA, high intensity anti-coagulation therapy or low-dose ASA in addition to moderate intensity oral anti-coagulation therapy. Maximum follow-up was 26 months.	Treatment with high intensity anti-coagulant therapy (HR=0.55) or combination therapy (HR= 0.50) was more effective than ASA alone in reducing the risk of ischaemic events following myocardial infarction. Frequency of minor bleeding was 5% in the ASA group, 8% in the anti-coagulant group and 15% in the combination therapy group. Rate of major bleeding was 1% in each of the ASA and anti-coagulant groups and 2% in the group receiving combination therapy.
Carroll et al. (2013) US, Canada RCT PEDro=6 TPS=NA N_{Start}=980 N_{End}=851	**Population:** Closure group (N=499): Mean age= 45.7±9.7yr; Gender: Males=268, Females=230. Medical group (N=481): Mean age=46.2±10.0yr; Gender: Males=268, Females=213. **Intervention:** Patients were randomly assigned to medical therapy alone or to closure of the patent fragment ovale. The closure group underwent the procedure within 21d after randomization and continued their prerandomization antithrombotic regimen until placement of the device. The medical therapy group received one or more antiplatelet medications (aspirin, clopidogrel, or aspirin combined with extended-release dipyridamole) or warfarin. All patients were evaluated at 1, 6, 12, 18 and 24mos. **Outcomes:** Rate of recurrent stroke.	In the pre-specified per-protocol and as-treated analyses, there was a significant difference in the rate of recurrent stroke (6 events in the closure group versus 14 events in the medical therapy group) (p=0.03, p=0.007). In the intention to treat analyses, there was no significant difference in benefit of foramen ovale closure over the medical therapy alone (p=0.08).
Furlan et al. (2012) CLOSURE I trial Multicentre RCT PEDro=6 TPS=NA N_{Start}=909 N_{End}=909	**Population:** Experimental group (EG; N=447): Mean age=46.3±9.6yr; Gender: Males=233, Females=214. Control group (CG; N=462): Mean age=45.7±9.1yr; Gender: Males=238, Females=224. **Intervention:** Young patients between the ages of 18 and 60 who presented with a cryptogenic stroke or a TIA and had a patent foramen ovale were randomized to a percutaneous device (STARFlex septal closure system) or to medical therapy alone (warfarin, aspirin, or both). Assessments of clinical end points and adverse events were planned at 1mo, 6mo, 12mo, and at 24mo. **Outcomes:** Primary end point: composite of stroke or TIA during the first 2yr of follow-up, death from any cause at 30d, and death from neurologic causes between 31d and 2yr. Secondary end points: major bleeding, death from any cause, stroke, TIA, and transient neurologic events of uncertain cause.	No deaths occurred within 30d in either group or death from neurological causes within 2yrs No significant differences were found between the two groups regarding the rate of recurrent stroke or TIA or a composite of both stroke and TIA.
Hornung et al.	**Population:** Intervention Amplatzer group	The primary endpoint differed significantly between the

(2013) Germany RCT PEDro=6 TPS=NA N_{Start}=660 N_{End}=587	(N=196). Intervention Helex group (N=195). Intervention CardioSEAL-STARflex group (N=196). Additional demographic information for each intervention group not specified in the current article. **Intervention:** Participants were randomized to 3 different patent foramen ovale (PFO) closure devices: the Amplatzer PFO/ASD occluder, the Helex septal occluder, and the CardioSEAL-STARflex device. All patients were followed-up over 5yrs. **Outcomes:** Recurrent cerebral ischemia (stroke, transient ischaemic attacks (TIA), or Amaurosis fugax); Death from neurological cause or any other paradoxical embolism within 5yrs of the index procedure.	three groups, where the Amplatzer group had significantly fewer events (3) compared to the CardioSEAL-STARflex group (13) and the Helex group (5) (p=0.042). Survival analysis revealed superiority of the Amplatzer device over the CardioSEAL-STARflex device (p=0.01), but not over the Helex device. There was no significant difference between the 3 groups regarding the stroke rates, transient ischemic attack rates, and cerebral death rates.
Meier et al. (2013) PT trial Multicentre RCT PEDro=6 $TPS_{Exp\text{-}med(range)}$=4.3 (1.1-8.2)mo $TPS_{Con\text{-}med(range)}$=4.5 (1.3 -8.9)mo N_{Start}=414 N_{End}=341	**Population:** Experimental group (EG; N=204): Mean age=44.3±10.2yr; Gender: Males=92, Females=112. Control group (CG; N=210): Mean age=44.6 ±10.1yr; Gender: Males=114, Females=96. **Intervention:** A total of 29 centres took part in this trial. Patients with patent foramen ovale and ischemic stroke, transient ischemic attack or peripheral thromboembolic events were randomly allocated either to the experimental group to receive an Amplatzer patent formane ovale occlude, or to the control group to receive medical therapy with either antiplatelet therapy or anticoagulation therapy. **Outcomes:** The primary end point: composite of death, nonfatal stroke, TIA, or peripheral embolism. Secondary end point: cardiovascular death, new arrhythmias, myocardial infarction, hospitalization due to patent foramen ovale, device problems, bleeding.	No significant difference was observed between the groups with regards to the primary composite outcome (death, stroke, TIA, or peripheral embolism), death (Cardiovascular or noncardiovascular), thromboembolic event (stroke, TIA, or peripheral embolism), or secondary outcome measures.
Elmariah et al. (2014) USA Observational No Score TPS=NA N_{Start}=909 N_{End} =909	**Population:** No recurrent neurologic event group (N=857): Mean age =45.9±9.4yr; Gender: Males=449, Females=408. Recurrent neurologic event group (N=52): Mean age= 47.1±9.2yr; Gender: Males= 22, Females= 30. **Intervention:** Data from patients recruited for a previous RCT (Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale (CLOSURE I) trial) was further analyzed to identify risk factors for the development of recurrent neurologic events	Patients with recurrent neurologic events had higher BMI (p=0.03), and more prevalent diabetes (p=0.0016), hypertension (p=0.015), and ischemic heart disease (p=0.05). Univariable analyses identified BMI (p = 0.03), history of diabetes (p=0.0027), hypertension (p=0.02), ischemic heart disease (p=0.04), and index TIA (p=0.02) as predictors of recurrent neurologic events. Multivariable analyses identified history of diabetes (p=0.0007), index TIA (p=0.01), and the detection of arterial fibrillation (AF) (p=0.0003) independently predicted recurrent ischemic neurologic events. History of diabetes (p=0.0002) and detection of AF

	in patients with previous cryptogenic stroke or TIA and PFO). Patient medical information was obtained and analyzed for potential risk factors. **Primary Outcomes:** Predictors of recurrent TIA and stroke (Age; Gender; race; cigarette smoking; mean BP; BMI; diabetes mellitus; hypertension; hypercholesterolemia; family history of CVD; ischemic heart disease); Valvular dysfunction; Arrhythmia; Peripheral vascular disease; Pulmonary embolism; Migraine.	(p=0.0003) independently predicted recurrent ischemic strokes, while index TIA (p=0.0001) was associated with recurrent TIA. RoPE scores were found to be associated with rates of recurrent neurologic events. Patients with scores of ≤5 suffered a recurrent event compared with those with a RoPE score of >5 (p<0.0001).

8.10 Carotid Artery Occlusion and Reperfusion Interventions

8.10.1 Carotid Endarterectomy (CEA)

8.10.1.1 Carotid Endarterectomy (CEA) and Symptomatic Carotid Artery Stenosis

Table 8.10.1.1 Details of NASCET and ECST Trials

Author, Year Country Pedro Score	Methods	Outcomes
NASCET Trial Collaborators Barnett (1991) Canada/USA 8 (RCT)	Patients in two predetermined strata based on severity of carotid stenosis (30-69% and 70-99%) were randomized to receive medical treatment or CEA. All patients received optimal medical care, including antiplatelet therapy. The results of 659 patients in the severe stenosis stratum (70 to 99%) were reported.	The absolute risk reduction of any ipsilateral stroke and for a major or fatal ipsilateral stroke at two years was significantly greater in the surgical patients (n=328) than in the medical patients (n=331).
ECST Trial Collaborative Group Ferro et al. (1991) UK 7 (RCT)	2518 patients with a history of post carotid territory, non-disabling ischaemic stroke, TIA or retinal infarct in the past 6 months and with stenotic lesion in the ipsilateral artery were randomized to surgical intervention (carotid endarterectomy) versus nonsurgical intervention (ASA, treatment of HTN and advice to stop smoking). Patients were further stratified on the basis of degree of stenosis (mild 0-29%, severe 70-99%). Mean follow-up was 3 years.	At three years, in patients with mild stenosis (n=374), there was no difference in risk for stroke in either treatment group. For patients with severe stenosis (n=778) the total risk of surgical death, surgical stroke, ipsilateral stroke or any other stroke was 12.3% in the surgical group and 21.9% in the control group (difference of 9.6%, p<0.01) by three years. Among severe stenosis patients, the total 3-year risk of any disabling or fatal stroke was 6.0% versus 11.0% in the control group (p<0.05). However, risks for disabling or fatal stroke in the control group diminish after the first year, so this difference may eventually become nonsignificant.
NASCET Trial Collaborators Barnett et al. (1998) Canada/USA 8 (RCT)	Patients with moderate carotid stenosis were stratified to degree of stenosis and randomized to receive medical treatment (n=1118) or surgical intervention (n=1108) and followed for an average of 5 years.	Among patients with 50-69% stenosis treated surgically, there was a significant reduction in the failure rate (fatal or nonfatal ipsilateral stroke). Among patients with less than 50% stenosis treated surgically, there was not a statistically significant reduction in the failure rate.
ECST Trial	3024 patients with recently symptomatic carotid	Major stroke or death occurred in 37% of surgery

Collaborative Group (1998) UK 7 (RCT)	stenosis (ie. a carotid-territory ischaemic event in the brain or eye within the past 6 months) were randomly assigned to surgery (n=1811) or control (n=1213) conditions. Those in the surgery group underwent CEA + medical treatment while the control group received routine medical care (avoiding surgery as long as possible). Mean follow-up was 6.1 years.	group patients and 36.5% control patients. Risk of major ischaemic stroke ipsilateral to the symptomatic carotid artery increased with the severity of stenosis, especially when stenosis was ≥80%. At this point, risk of surgery outweighed the benefits; at 3 years the frequency of major stroke or death was 26.5% in the control group and 14.9% in the surgical group.
ECST Trial Collaborative Group Rothwell et al. (2003) UK 7 (RCT)	3018 patients with recently symptomatic carotid artery stenosis were randomized to receive immediate carotid endarterectomy + medical treatment (n=1807) or medical treatment alone (n=1211). Mean follow-up was 73 months. All ECST stenosis data was re-calculated using measurements done by the NASCET method. Outcome events were re-defined to coincide with NASCET.	Re-analysis was stratified by degree of stenosis as per the NASCET trial. Surgery reduced the 5-year risk of any stroke or surgical death by 5.7% in patients with 50-69% stenosis (p<0.05). In patients with severe stenosis (70-99%) without near occlusion, risk for stroke or surgical death was reduced by 21.2% (p<0.001). Benefits were maintained at 10-year follow-up. Surgery was of no benefit to patients with near occlusion or with stenosis of 30-49%. In patients with stenosis of less than 30%, surgery was harmful (p<0.007).

8.10.1.2 CEA and Asymptomatic Carotid Artery Stenosis

Table 8.10.1.2 Details of Studies Examining CEA and Asymptomatic Carotid Artery Stenosis

Author, Year Country Pedro Score	Methods	Outcomes
Veterans Affairs Cooperative Study Group Hobson et al. (1993) USA 7 (RCT)	444 adult men with asymptomatic carotid stenosis were randomized to receive carotid endarterectomy with medical management including antiplatelet therapy (ASA 325-650mg/day) or medical management and antiplatelet therapy without endarterectomy. Mean follow-up was 47.9 months.	Incidence of ipsilateral neurologic events (stroke, TIA or transient monocular blindness) was 8.0% in the surgical group and 20.6% in the medical management group (p<0.001). Relative risk for surgery versus medical management=0.38. Incidence of ipsilateral stroke was 4.7% in the surgical group and 9.4% in the medical group. There were no significant differences in the combined outcome of stroke and death within the first 30 days following the procedure.
Asymptomatic Carotid Artery Study (ACAS) Group (1995) USA 6 (RCT)	1662 patients with asymptomatic carotid artery stenosis ≥60% were randomized to receive medical management including ASA therapy and carotid endarterectomy or medical management and ASA therapy alone. All patients received counselling with regard to risk factor reduction. Mean follow-up was 2.7 years.	The aggregate risk over 5 years (based on Kaplan-Meier estimates) for ipsilateral stroke and any perioperative stroke or death was 5.1% for patients in the surgical group and 11.0% for patients who received medical management and ASA therapy alone (p<0.004). For surgical patients, the risk for complications in the perioperative period (stroke, MI, death) was 2.3% (included risk associated with mandatory arteriography of approximately 1.2%). Authors recommend that CEA should be performed with less than 3% perioperative morbidity and mortality.
MRC-ACST Trial Collaborative Group Halliday et al. (2004) International	3120 patients with severe but asymptomatic carotid artery stenosis were randomized to immediate CEA (n=1560) or deferred CEA (n=1560), that is, until a definite condition for CEA arose. Patients were followed for up	Of the immediate CEA group, 88% had undergone the procedure by one year following randomization. In the deferred group, 4%/year underwent CEA. Hence, 5 year analysis is a comparison of the effects of CEA in 90% of patients versus CEA in 10% of patients. The 30-day

8 (RCT)	to 5 years.	perioperative risk of stroke or death was 3.1%. Approximately ½ of perioperative strokes were fatal. The incident stroke rate among individuals in the deferred group was 2% per year. Immediate CEA was associated with a 5-year risk for all strokes of 6.4% compared to 11.8% in the deferred group (p<0.0001). Absolute risk reduction at 5 years was 5.4%. The risk of carotid artery territory stroke was 2.5% in the CEA group, versus 9.5% in the deferred group (ARR=6.8%; p<0.0001). Results were separately significant for men and women, for individuals under age 65 years, aged 65-74 years, and 70% or more narrowing of the carotid artery on ultrasound. There was no significant benefit demonstrated in individuals ≥75 years. The necessity for low surgical risk, adequate surgical audits and appropriate patient selection was stressed.
ASCT Trial Collaborative Group Halliday et al. (2010) 8 (RCT)	10-year follow-up results for the ACST trial. Median length of follow-up among surviving participants was 9.0 years (IQR 6-11). Primary outcomes were perioperative mortality and morbidity (death or stroke within 30 days) and non-perioperative stroke events.	Patients assigned to the immediate CEA condition underwent surgery within a median of one month (IQR 0.3-2.5) of randomization. Patients assigned to the deferral condition 26% received CEA over the 10-year follow-up period. Perioperative risk did not differ between those receiving immediate intervention and those whose intervention was deferred. Overall perioperative risk was reported as 3.0%. There was a 4.1% difference in risk for perioperative stroke or death in favour of immediate intervention, an advantage that was sustained at 10 years (4.6%). Rate of non-perioperative stroke was 4.1% (events/person years) for individuals in the intermediate intervention condition versus 10% in the deferred condition at 5 years. At 10 years, the rate of non-perioperative stroke was 10.8% for individuals receiving immediate CEA and 16.9% in individuals for whom intervention was deferred. Significant benefits, both perioperative and non-perioperative, were reported for both men and women up to age 75 years.

8.10.1.4 Timing for Carotid Endarterectomy

Table 8.10.1.4 Timing of CEA Following Ischemic Stroke

Author, Year Country Pedro Score	Methods	Outcomes
Ballotta et al. (2002) Italy 5 (RCT)	Over a period of 4 years, 86 patients with minor, non-disabling stroke were randomly assigned to receive either early (<30 days post ischemic event) or delayed (≥30 days) CEA. Study outcomes included perioperative death and stroke. In addition, long-term follow-up (mean=23 months) was obtained for	There were no perioperative deaths recorded in either group. There were comparable rates of stroke in both groups (2%) during the perioperative period. On Kaplan-Meier analysis, survival rates were found to be similar over the 1, 2 and 3 years following CEA in both groups (96%, 88% and 66% in the early group versus 95%, 95% and 79%, in the delayed group, p=0.78).

	all patients. Procedures were all performed at a single centre, by the same surgeon.	
Ballotta et al. (2008) Italy No Score	A prospective study of 102 individuals who underwent CEA within 2 weeks of a minor (non-disabling) ischemic stroke in the years 2000-2005. Study endpoints were 30-day stroke and mortality rates as well as long-term stroke recurrence or cerebral hemorrhage.	In this series of patients, there were no strokes or deaths reported in the perioperative period. There were reports of transient neurological deficits in 2.9% of patients, all of which resolved within 24 hours of the procedure. On long-term follow-up (mean=34 months, range 1-66 months), there were no reports of recurrent stroke or cerebral hemorrhage related to revascularization. Using Kaplan-Meier life table, survival rates were 99%, 93.7% and 79.4% at 1, 3 and 5 years respectively.

8.10.1.5 Coordinated Care Following CEA

Table 8.10.1.5 Coordinated Nursing-Led Care Post CEA

Author, Year Country Pedro Score	Methods	Outcomes
Middleton et al. (2005) Australia 7 (RCT)	133 patients scheduled for CEA were recruited during pre-operative visits. Patients were randomly allocated to receive either a coordinated care intervention (n=66) or usual care (n=67). The coordinated care intervention consisted of telephone calls made by a nurse to the patient at 2, 6 and 12 weeks post discharge. Telephone calls focused on patient efforts to amend life style to enhance secondary prevention and the delivery of information. Written materials were mailed to the patient after the 2- and 6-week calls. In addition, at 2 weeks, the nurse contacted the patient's general practitioner by phone and fax. Patients in the usual care group received no contact from the nurse and the general practitioner was contacted briefly at 2 weeks to give information regarding the patient's procedure and recovery.	Participants were assessed by mailed questionnaire at baseline and at 3 months following discharge. Non-responders were assessed by telephone. In both groups, there were significant improvements in ratings of health status, time spent in physical activity per week, as well as in knowledge about having a recurrent stroke and the perceived risk of recurrent stroke. There were no significant differences between groups on these outcomes. There were no significant differences found between groups for changes over time in blood pressure, cholesterol or smoking behaviours. However, patients in the coordinated care group reported significantly making more lifestyle changes ($p=0.006$) and dietary changes ($p<0.001$) than patients in the usual care group. While knowledge about stroke risk and how to respond in the event of stroke increased in both groups, there were no significant between group differences. Knowledge about the warning signs of stroke increased significantly more in the coordinated care group than in the usual care group ($p=0.002$).

8.10.2 Carotid Artery Angioplasty and Stenting (CAS)

Table 8.10.2 Trials Assessing Carotid Angioplasty and Stenting

Author, Year Country Pedro Score	Methods	Outcomes
CAVATAS Investigators (2001)	504 patients with carotid stenosis suitable for both endovascular treatment and CEA. 90% of patients had experienced symptoms within 6	Rate of death within 30 days of procedure did not differ significantly between CEA and endovascular treatment (10.0% versus 9.9% respectively). Cranial neuropathy was

UK 7 (RCT)	months of enrollment, 7% had experience symptoms more than 6 months prior to enrollment and only 3% of patients included for randomization had experienced no symptoms. Patients were randomly assigned to undergo either carotid endarterectomy or balloon angioplasty with or without stents. Mean length of follow-up was 1.95 yrs in the endovascular group and 1.98 years in the surgical group.	more common following surgery (8.7%) than endovascular treatment (0%; p<0.0001). Likewise, major groin or neck haematoma occurred more often following surgery (6.7% versus 1.2%; p<0.0015). At one year following treatment, ipsilateral carotid stenosis was more common post-CAS (14% versus 4%; p<0.001). However, there was no significant difference in rate of stroke following either treatment based on survival analysis up to 3 years post-randomization (adjusted hazard ratio=1.04),
Brooks et al. (2001) USA 5 (RCT)	104 patients with symptomatic carotid stenosis >70% were randomized to undergo either CEA (n=51) or CAS (n=53). Patients were followed for 2 years.	No significant difference was observed between groups in terms of perioperative or postoperative complications, perceptions of procedurally related discomfort and pain, return to activity, length of hospital stay or associated hospital costs. There was a tendency for shorter hospital stays and shorter periods of convalescence for those people undergoing CAS compared to CEA.
Brooks et al. (2004) USA 5 (RCT)	85 patients with asymptomatic carotid artery stenosis >80% were randomly assigned to CEA or CAS (without protection devices). Treatment was completed within 4 weeks of randomization. Follow-up was for 48 months.	No procedurally-related TIAs, strokes or deaths were reported in either group. However, five patients in the CAS group required treatment for bradycardia and hypotension. Length of hospital stay was similar in both groups as were hospital expenditures. No significant differences were reported between groups in terms of pain or time to return to full activity. Post-procedure stenosis was approximately 5% in both groups, and patency at 48 months was satisfactory regardless of interventional technique.
CAVATAS Investigators (2007) UK 7 (RCT)	This study investigated the long-term outcome from the CAVATAS trial, in which 16 patients with symptomatic vertebral artery stenosis were randomized in equal proportions to receive endovascular therapy (balloon angioplasty or stenting) or best medical treatment alone. Patients were followed up at 1 month after treatment and then at 6 months, 12 months, and yearly thereafter by an independent neurologist. The primary outcome was risk of fatal and nonfatal vertebrobasilar territory strokes. Secondary end points included risk of vertebrobasilar TIA, fatal and nonfatal carotid territory stroke, and fatal MI.	Endovascular intervention was technically successful in all eight patients, but two patients experienced transient ischemic attack at the time of endovascular treatment. There was no significant difference in the 30-day risk of cerebrovascular symptoms between the groups. No deaths or strokes in any arterial territory occurred within the first 30 days. During a mean follow-up of 4.7 years, no patient in either treatment group experienced a vertebrobasilar territory stroke, but three patients in each treatment arm died of MI or carotid territory stroke, and one endovascular patient had a nonfatal carotid territory stroke. Overall, there were significantly more secondary end points for patients who received endovascular therapy as compared to best medical treatment alone (p=0.035).
Steinbauer et al. (2008) Germany 5 (RCT)	87 patients with symptomatic, severe (>70%) carotid artery stenosis were randomly allocated to intervention with CEA (n=44) or CAS (n=43) without protection. Follow-up examinations were conducted at 6 months and 1 year. Randomization was stopped prematurely upon initialization of the SPACE trial.	There was a significantly higher rate of ipsilateral stroke following CAS than CEA (4 strokes versus none, p=0.041), but there was no significant difference between groups for all neurological events (all stroke and TIA). There was a significantly higher rate of re-stenosis following CAS when compared to CEA (p=0.023); however, the rate of re-intervention was greater following CEA (p=0.027).
CAVATAS Investigators (2009)	Individuals assigned to receive carotid angioplasty with or without stenting (n=251) versus CEA (n=253) were followed yearly for	Including perioperative events, the 8-year cumulative incidence of stroke was 54.4% in the angioplasty group and 52.9% in the CEA group. Although there were more strokes

UK 7 (RCT) Long-term follow-up	as long as possible following treatment. Median follow-up was 5 years. All major outcome events were recorded (TIA, non-disabling, disabling and fatal stroke, MI, death from any other cause).	in the endovascular treatment group, the difference in risk was not significant (HR=1.08, 95% CI 0.85-1.38). Similarly, there were more non-perioperative strokes and TIAs in the endovascular group than the CEA group (8-year cumulative incidence=36.9% versus 30.2%), but the difference in risk was not significant (HR=1.37, 95% CI 0.95-1.97).
CAVATAS Investigators (2009) UK 7 (RCT) Subgroup Analysis and long-term follow-up	Rates of restenosis were examined in 413 patients; 200 assigned to receive endovascular treatment and 213 assigned to CEA. In addition, investigators examined the effect of use of stents on restenosis. In CAVATAS only 50 patients in the endovascular treatment arm received stents.	Stenosis of ≥70% occurred more often in patients receiving endovascular treatment than CEA (adj. HR=3.17, 95% CI 1.89-5.32, p<0.0001). When individuals who received balloon angioplasty alone were compared with those treated with a stent, risk for recurrent stenosis (≥70%) was significantly lower in individuals who received a stent (adj. HR=0.43, 95% CI 0.19-0.97, p=0.04). When stenosis of ≥50% was examined, the risk reduction was more significant (adj. HR=0.37, 95% CI 0.21-0.62, p=0.0003).
Fanelli et al. (2012) Italy No Score	672 patients underwent CAS at a hospital between 1999 and 2011. 636 of these patients were available for 6 month follow up. 59.9% of patients were symptomatic, 47 patients had staged bilateral CAS procedures. All patients underwent a baseline evaluation with duplex ultrasound and either computed tomographic angiography or magnetic resonance angiography. Outcomes included technical success, minor or major strokes and transient ischemic attacks.	Technical success was achieved in all cases. Neurological events that occurred within 30 days of the procuedure included major strokes 0.4%, minor strokes 1.2% and in 11% of patients transient ischemia attacks. These events occurred in 2% of asymptomatic patients and 4.5% of symptomatic patients (p=0.001). Neurological events proved to be high in patients >80 years and those with complex plaque morphology.
CREST Investigators Lal et al. (2012) RCT PEDro=4 TPS=NA N_{Start}=2191 N_{End}=385	**Population:** Carotid artery stenting (N=1086): Mean age=68.6±8.7yr; Gender: Males=700, Females=386. Carotid endarterectomy (N=1105): Mean age=69.1±8.7yr; Gender: Males=745, Females=360. **Intervention:** Patients with stenosis of the carotid artery who were asymptomatic or had a stroke were randomized to receive either carotid artery stenting or to carotid endarterectomy. Assessments for restenosis or occlusion were conducted at 1, 6, 12, 24, and 48 months. Restenosis was defined as a reduction in diameter of the target artery of at least 70%. **Outcomes:** Restenosis or occlusion.	The frequency of the restenosis or occlusion in 2yr was 6.0% in the carotid artery stenting group and 6.3% in the carotid endarterectomy group (HR=0.90, 95% CI 0.63-1.29, p=0.58). No significant difference in restenosis rates between the two treatment types was found.

8.10.2.1 Cerebral Protection

Table 8.10.2.1 Efficacy of Cerebral Protection

Author, Year Country Pedro Score	Methods	Outcomes
EVA-3S Trial	As part of a larger, ongoing trial, 80 patients	Unprotected CAS was stopped. Results showed 30-day rate

Mas et al. (2004) France 5 (RCT)	with recently symptomatic, severe carotid stenosis already randomized to receive CAS were further randomized to receive CAS with or without cerebral protection (any device approved by the EVA-3S technical committee)	of stroke among patients receiving CAS without the use of a cerebral protection device was approximately four times greater than that among patients receiving CAS with cerebral protection.
Barbato et al. (2008) USA 7 (RCT)	36 carotid stenting procedures (in 35 patients) were randomly allocated to stenting with embolic protection (distal CP filters) versus stenting without embolic protection. Primary outcome was the percentage of patients showing evidence of new ischemic injury on diffusion-weighted MRI following CAS. Secondary endpoints included major adverse events (stroke and death) before discharge and at 30 days.	The study was terminated early due to difficulties in recruitment. New lesions were noted in 72% of the cerebral protection group but only 44% of the unprotected CAS group (p=0.09). Number of lesions per patient and average lesion size did not differ between groups. Only 4 strokes occurred, two in each group. One major stroke was recorded-in the no protection group. Therefore, use of filters was not associated with reduction in microemboli as evidenced by new lesions on DWI.
Jansen et al. (2009) Subgroup analysis SPACE trial International 7 (RCT)	Data from 563 patients randomized to treatment with CAS was used for a subgroup analysis examining outcomes in patients who received interventions with (n=145) versus without (n=418) protection devices. Primary outcome for this analysis was 30-day ipsilateral stroke or death from ipsilateral stroke.	The 30-day rate of the primary outcome was 8.3% in patients receiving CAS with protection and 6.5% in patients received CAS without a protective device (p=0.40). The design of the stent had a greater impact on outcome than the presence versus absence of a protective device.

8.10.2.2 Carotid Endarterectomy (CEA) Versus Carotid Artery Stenting (CAS)

Table 8.10.2.2 Carotid Endarterectomy (CEA) Versus Carotid Artery Stenting (CAS)

Author, Year Country Pedro Score	Methods	Outcomes
SAPPHIRE Investigators Yadav (2004) USA 7 (RCT)	334 patients with symptomatic coronary artery stenosis of at least 50% or asymptomatic stenosis of 80% and coexisting conditions that would increase risk associated with CEA. Patients were randomized to receive either CEA (n=167) or CAS with the use of an emboli protection device (n=167). Patients received acetyl salicylicacid and were treated with therapeutic heparin during the intervention. Primary study endpoint was the cumulative incidence of death, stroke or MI within 30 days of the procedure or death from neurologic causes or ipsilateral stroke between 31 days and one year.	The 30-day incidence of stroke, MI or death was 4.8% in the stenting group versus 9.8% among the CEA patients (p=0.09). The mean length of hospital stay was 1.84 days for patients receiving a stent versus 2.85 days for patients undergoing surgery (p=0.002). At one year, the cumulative incidence of adverse events (stroke or death at 30 days plus ipsilateral stroke or death from neurologic causes) was 5.5% among the stent patient group versus 8.4% among the CEA group (p=0.36). If MI is included in the one-year composite endpoint, incidence rates rise to 12.2% versus 20.1% (p=0.05).
CaRESS Steering Committee CaRESS Steering Committee (2005)	397 patients were enrolled. 32% symptomatic and 68% asymptomatic. Patients were assigned to treatment conditions (CEA or CAS with protection)	Of the CAS patients, 33% were symptomatic and 87% were considered high risk. Of the CEA patients, 31% were symptomatic and 84% were high risk. At baseline, the average stenosis was 80-89% for patients in the CEA groups

USA No Score	based on physician and patient preference. Patients undergoing CAS (n=143) were placed on aspirin and clopidogrel or ticlopidine prior to the procedure, and then heparinized during the procedure. Following CAS, patients were maintained on ASA (325mg once daily indefinitely) and either clopidogrel or ticlopidine (4 weeks). Patients in the CEA condition (n=254) were treated with acetyl salicylic acid prior to the procedure. Additional medications were given as per the instructions of treating physicians. Primary study end points were all cause mortality or stroke 30 days and one year following the procedure.	versus 70-79% in the CAS group. Kaplan Meier estimate of event rates at 30 days and at one year revealed no significant differences between groups for all cause mortality, stroke, acute MI or the combined outcome of death and stroke. Age and a history of previous carotid intervention were significant predictors of outcome (combined death/stroke/MI at one year). Although higher rates of restenosis, residual stenosis, repeat intervention and carotid revascularization were associated with CAS treatment, none of these differences reached significance. There were no significant between-group differences reported in quality of life at one year.
EVA-3S Mas et al. (2006) France 7 (RCT)	527 patients with symptomatic carotid stenosis of at least 60% were randomized to receive either carotid artery stenting (with protection) or endarterectomy. The primary endpoint was incidence of any stroke or death within 30 days after treatment.	The trial was stopped prematurely after the inclusion of 527 patients for reasons of both safety and futility. The relative risk of any stroke or death within 30 days after stenting as compared with endarterectomy was 2.5 (95% CI 1.2-5.1). At 6 months, the incidence of any stroke or death was 6.1% after endarterectomy and 11.7% after stenting (p=0.02). More major local complications occurred after stenting, whereas more systemic complications (mainly pulmonary) occurred after endarterectomy. However, differences were not significant. Cranial nerve injury was more common after endarterectomy than after stenting.
SPACE Collaborative Group Ringleb et al. (2006) International 7 (RCT)	1200 patients with symptomatic carotid artery stenosis (TIA or moderate stroke within 180 days) were randomly assigned to receive either CEA (n=595) or CAS (n=605). Patients treated with CAS were given 100mg ASA +75mg clopidogrel daily for at least 3 days before and 30 days post intervention. Use of embolic protection devices was at the discretion of the interventionalist. Non-inferiority limit for the difference in event rates was defined as <2.5%, based on enrolment of 1900 patients (80% power). Primary outcome=30-day ipsilateral stroke or death. Clinical examinations were scheduled at 7 and 30 days, 6, 12 and 24 months. The trial was stopped prematurely, due to funding and recruitment considerations.	27% of patients receiving CAS were treated using an embolic protection device. No significant difference in primary study events was found between individuals treated with and without the use of protection devices (OR=1.09, 95% CI 0.53-2.25). Rate of primary event in the CAS group=6.84% and in the CEA group=6.34%. The absolute difference between groups was 0.51 (90% CI -1.89-2.91). Therefore, the non-inferiority criterium was not met. Although results tended toward better results in the CEA group, there were no significant differences between groups in terms of risk for primary endpoint events (OR=1.09, 0.69-1.72), or predefined secondary endpoints such as the rate of disabling stroke or death (OR=1.25, 0.71-2.22) or any stroke (OR=1.24, 0.79-1.95).
SPACE Collaborative Group Eckstein et al. (2008) International 7(RCT)	Long-term results of the SPACE trial (2 years). 14 additional patients were randomized before the trial was stopped; therefore, this follow-up study included more patients than the 2006 report (above). Two-year endpoints included rates of ipsilateral stroke (including 30-day stroke/death), ipsilateral strokes/death	Rates of ipsilateral stroke within 2 years (including 30 days post procedure) were not significantly different between groups (9.5% CAS vs 8.8% CEA; HR=1.1, 95% CI 0.75-1.61) nor were combined rates of ipsilateral stroke/death (10.5% versus 9.7%; HR=1.11, 95% CI 0.77-1.60). Rates of ipsilateral stroke from 31 days to 2 years were also not significantly different between groups (2.2% CAS versus 1.9% CEA; HR=1.17, 95% CI 0.51=2.70). Recurrent stenosis (≥70%) was

	before and after day 30, mortality (all-cause) between randomization and 2-years and incidence of re-stenosis (≥70%).	more frequent among patients who had received CAS (10.7% versus 4.6%, p=0.0009).
SAPPHIRE Investigators Gurm et al. (2008) USA 7 (RCT)	Long-term results of the SAPPHIRE trial (3 years). The prespecified 3-year endpoint was the composite of death or ipsilateral stroke between 31 days and 1080 days.	At 3 years, 24.6% of patients in the CAS groups versus 26.9% of patients in the CEA group had experienced the major secondary trial endpoint (absolute difference=-2.3% for CAS, 95% CI-11.8-7.0, p=0.71). For stroke alone, the absolute difference=0 (-6.1-6.1, p=0.99)
EVA-3S Mas et al. (2008) France 7 (RCT)	Long-term results of the EVA-3S trial (up to 4 years). The primary study outcome of EVA-3S was 30-day stroke or death. Pre-specified outcome for long-term follow-up was any periprocedural (30-day) stroke or death and any non-procedural ipsilateral stroke during the follow-up period.	4-year cumulative probability of stroke or death was 6.2% in patients assigned to CEA versus 11.1% in patients assigned to CAS (HR for CAS vs, CEA=1.97, 95% CI 1.06-3.67, p=0.03). However, most strokes occurred within the first 30 days of the procedure; after 30 days, there were few "nonprocedural" strokes recorded in either treatment group. After 30 days, the risk for ipsilateral stroke was similar in both groups (1.26% CAS versus 1.97% CEA; ns). The 4-year rate for a "nonprocedural" stroke was 4.49% in the CAS group versus 4.94% in the CEA group (HR=1.02, 95% CI 0.42-2.44).
CaRESS Investigators Zarins et al. (2009) USA No Score	4-year outcomes from the CaRESS trial. Primary study outcomes were all-cause mortality, any stroke, MI and a series of composite outcomes including stroke/death. Subgroup analyses were performed for both sexes and octogenarians.	At 4 years, the stroke rate was 9.6% for CEA and 8.6% for CAS (p=0.44). Rates for the combined outcome of death and nonfatal stroke were 26.5% for CEA and 21.8% for CAS (p=0.36). For individuals with symptomatic stenosis, the 4-year rate of stroke was 17.8% in the CEA condition and 7.2% in the CAS condition (p=0.12), whereas the in individuals with asymptomatic stenosis had a 4-year stroke rate of 5.7% and 9.2% for CEA and CAS respectively (p=0.65). There was no significant between group difference in 4-year rates of the combined outcome death/nonfatal stroke in individuals with either symptomatic or asymptomatic stenosis. For individuals over the age of 80 years, there were 7 stroke in the CEA condition and 6 in the CAS condition (17.2% versus 31.3%; p=0.5). Similarly, there was no significant difference between the treatment conditions for the combined outcome of stroke/death (p=0.2).
CREST Investigators Brott et al. (2010) International 8 (RCT)	2502 patients with asymptomatic or symptomatic carotid artery stenosis were randomly assigned to treatment with carotid artery stenting or carotid endarterectomy. Treatment protocol for CAS specified the use of the RX Acculink stent and, wherever feasible, the RX Accunet embolic protection device. Primary study outcome was a composite of 30-day stroke, MI, and death from any cause or any ipsilateral stroke within 4 years of study entry. 96.1% of patients were treated using embolic protection. Median length of follow-up was 2.5 years.	There were no significant between group differences in the estimated 4-year rates of the primary endpoint (7.2% versus 6.8%, HR=1.11, 95% CI 0.81-1.51, p=0.51). During the periprocedural period, there was no difference in risk for the primary endpoint between treatment conditions (HR=1.18, 95% CI 0.82-1.68, p=0.38). However, CAS was associated with a significantly greater risk for periprocedural stroke (HR=1.79, 95% CI 1.14-2.82, p=0.01) and a significantly reduced risk for periprocedural MI when compared to CEA (HR=0.50, 95% CIC 0.26-0.94, p=0.03). After the 30-day, periprocedural period, incidence of ipsilateral stroke was similarly low in both groups (2.0 versus 2.4% in CAS and CEA, p=0.85). Treatment effect was not modified by either symptomatic status or sex. A treatment effect by age (p=0.02) was demonstrated such that CAS was more efficacious in individuals <70 years of

		age while CEA was more efficacious in individuals >70 years.
ICSS International Carotid Stenting Study Investigators Ederle et al. (2010) International (RCT)	1713 patients with symptomatic carotid artery stenosis ≥50% as per the NASCET criteria and who were deemed suitable for both surgery and stenting were randomly assigned to receive either CAS (with or without protection at the discretion of the interventionalist) or CEA. Patients were assessed at study entry, 30 days post procedure, at 6 months after randomization and then once a year thereafter. Primary study endpoint was any stroke, death or procedural MI and the primary a priori analysis was between group differences in long-term rates of fatal or disabling stroke in any territory. This report represents interim data up to 120 days post randomization.	Protection devices were used in 72% of CAS procedures. ITT analysis demonstrated no significant between group difference in the rate of disabling stroke or death from randomization to 120 days (4.0% vs 3.2% in the CAS and CEA groups, respectively; HR=1.28, 95% CI 0.22-2.11, p=0.34). The incidence of the combined outcome of stroke/death/procedural MI was 8.5% in the CAS group versus 5.2% in the group treated via CEA (HR=1.69, 95% CI 1.16-2.45, p=0.006). For any stroke, the results at 120 days were also in favour of surgical intervention (7.7% versus 4.1%, HR=1.92, 85% CI 1.27-2.89, p=0.002). 30 day event rates were examined on per-protocol analyses. For the combined, primary study outcome there was an increased risk of events associated with CAS treatment (7.4% versus 4.0%; HR=1.83, 95% CI 1.21-2.77, p=0.003) as there was for the outcome of any stroke (HR=2.13, 95% CI 1.36-3.33) and any stroke or death (HR=2.16, 95% CI 1.4-3.34). The risk for disabling stroke or death was not significantly different between groups (HR=1.43, 95% CI 0.79-2.59).
SPACE-1 collaborative group Demirel et al. (2012) International (no score)	Outcomes of 563 patients within the surgical randomization arm of the Stent-Protected Angioplasty versus Carotid Endarterectomy in Symptomatic Patients (SPACE-1) trial were analyzed by surgical technique subgroups: eversion endarterectomy versus conventional endarterectomy with patch angioplasty.	Primary outcomes were ipsilateral stroke or death within 30 days after surgery. Secondary outcome events included perioperative adverse events and the 2-year risk of restenosis, stroke or death. The risk of ipsilateral stroke or death within 30 days after surgery was significantly greater with eversion CEA (9% versus 3%; p=0.005). No statistically significant differences were found in the rate of perioperative secondary outcome events with the exception of a significantly higher risk of intraoperative ipsilateral stroke rate in the eversion CEA group (4% versus 0.3%; p=0.0035). The 2-year risk of ipsilateral stroke occurring after 30 days was significantly higher in the conventional CEA group (2.9% versus 0%; p=0.017).
Carotid Stenting Trialists' Collaboration Rantner et al. (2013) International (no score)	An investigation of the association of time between the qualifying ischemic event and treatment (0-7 days, 8-14 days, and >14 days) with the risk of stroke or death within 30 dyas after CAS or CEA in a pooled analysis of data from individual patients randomized in the EVA-3S trial, the SPACE trial, and the ICSS trial. Data were analyzed with a fixed-effect binomial regression model adjusted for source trial.	In the first 30 days after intervention, any stroke or death occurred significantly more often in the CAS group (110/1434 [7.7%]) compared with the CEA group (54/1405 [3.8%]; crude risk ratio, 2.0; 95% confidence interval, 1.5-2.7). Patients undergoing CEA within the first 7 days of the qualifying event had the lowest periprocedural stroke or death rate (3/106 [2.8%]). Patients treated with CAS in the same period had a 9.4% risk of periprocedural stroke or death (13/138; risk ratio CAS vs CEA: 3.4; 95% confidence 1interval, 1.01-11.8; adjusted for age, sex, and type of qualifying event). Patients treated 8-14 days showed a periprocedural stroke or death rate of 3.4% (7/208) and 8.1% (19/234), respectively, for CEA and CAS.

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