The Anglo-Scandinavian Cardiac Outcomes Trial: blood pressure-lowering limb: effects in patients with type II diabetes

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Objective **To compare the effects of two antihypertensive treatment strategies for the prevention of coronary heart disease and other cardiovascular events in the large subpopulation ($n = 5137$) with diabetes mellitus in the blood pressure-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial.**

Methods **Patients had either untreated hypertension or treated hypertension. For those with type II diabetes mellitus, inclusion criteria required at least two additional risk factors. Patients were randomized to amlodipine with addition of perindopril as required (amlodipine-based) or atenolol with addition of thiazide as required (atenolol-based). Therapy was titrated to achieve a target blood pressure of less than 130/80 mmHg.**

Results **The trial was terminated early due to significant benefits on mortality and stroke associated with the amlodipine-based regimen. In patients with diabetes mellitus, the amlodipine-based treatment reduced the incidence of the composite endpoint – total cardiovascular events and procedures – compared with the atenolol-based regimen (hazard ratio 0.86, confidence interval 0.76–0.98, $P = 0.026$). Fatal and nonfatal strokes were reduced by 25% ($P = 0.017$), peripheral arterial disease by 48% ($P = 0.004$) and noncoronary revascularization procedures by 57% ($P < 0.001$). For the other endpoints included in the composite, the endpoint differences were less clear including coronary heart disease deaths and nonfatal myocardial infarctions (the primary endpoint), which were reduced nonsignificantly by 8% (hazard ratio 0.92, confidence interval 0.74–1.15).**

Conclusion **In the large diabetic subgroup in the blood pressure-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial, the benefits of amlodipine-based treatment, compared with atenolol-based treatment, on the incidence of total cardiovascular events and procedures was significant (14% reduction) and similar to that observed in the total trial population (16% reduction).** ***J Hypertens*** **26:2103–2111 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Keywords: antihypertensive treatment, Anglo-Scandinavian Cardiac Outcomes Trial, blood pressure, cardiovascular mortality, coronary heart disease, diabetes mellitus, hypertension, stroke

Abbreviations: ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; BPLA, Blood pressure-lowering arm; CHD, Coronary heart disease; HDL, High density lipoprotein; LLA, lipid lowering arm; RAAS, renin-angiotensin-aldosterone system; RCTs, randomized clinical trials

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Introduction

Diabetes and hypertension are frequently concomitant conditions. About 15% of hypertensive patients have diabetes [1] and approximately 75% of type II diabetic patients have hypertension [2]. Hypertension enhances the absolute risk of cardiovascular disease more in patients with diabetes than in normoglycemic people [3–5]. There are probably several reasons for this increased risk, including enhanced susceptibility to pressure-induced vascular wall stress. The diabetic myocardium may also be more sensitive to other cardiovascular risk factors, increasing the risk of myocardial hypertrophy, ischemia and heart failure [6]. Furthermore, diabetic nephropathy is incrementally accelerated by a raised blood pressure, creating a vicious cycle once hypertension and nephropathy are present [7].

Few large randomized clinical trials (RCTs) of antihypertensive agents have evaluated major cardiovascular outcomes in patients with both diabetes and hypertension. However, several large placebo-controlled RCTs have reported specifically on cardiovascular outcomes in

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the sizeable subgroups of patients with diabetes in these trials [8–10]. A consistent finding in these subgroup analyses is a marked reduction of the risk of subsequent cardiovascular events among patients on active antihypertensive treatment compared with placebo. This finding is consistent for all different types of antihypertensive drugs that have been studied. More recently, different antihypertensive drugs have been compared with each other. Generally, there have not been any clear differences between the different drug classes in diabetic patients [11,12]. In some of these studies, blockade of the renin–angiotensin–aldosterone system (RAAS) may confer additional benefit when treating hypertension in diabetic patients who are particularly at high risk of cardiovascular disease [13–16]. In the LIFE study, which recruited patients at high risk due to established left ventricular hypertrophy, blood pressure-lowering therapy initiated with the angiotensin receptor blocker, losartan, was more effective in reducing the primary composite cardiovascular endpoint than the β-blocker, atenolol. In that study, the beneficial effect of losartan was especially apparent in the diabetic subpopulation [16].

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) [17–19] was an independent, investigator-initiated and investigator-led, multicenter trial designed to compare two antihypertensive treatment strategies for the prevention of coronary heart disease (CHD) and other vascular events in more than 19 000 hypertensive patients with no prior history of CHD. The main results of the blood pressure-lowering arm (BPLA) of ASCOT have been published [19]. The subject of this report is a detailed analysis of the effects of the blood pressure lowering in the diabetic subpopulation.

Patients and methods

Patients

The study design, organization and main results of the study have been previously published [17–19]. Patients eligible for inclusion in ASCOT were men and women aged between 40 and 79 years, with either untreated hypertension, defined as systolic blood pressure of 160 mmHg or more, and/or diastolic blood pressure of 100 mmHg or more, or treated hypertension with systolic blood pressure of 140 mmHg or more, and/or diastolic blood pressure 90 mmHg or more. In addition, the study population was required to have at least three additional risk factors for cardiovascular disease: type II diabetes, peripheral arterial disease, previous stroke or transient ischemic attack, male sex, age 55 years or older, microalbuminuria or proteinuria, smoking, plasma total cholesterol to high-density lipoprotein (HDL) cholesterol ratio of 6 or higher, or family history of premature CHD. For those with type II diabetes, therefore, at least two of the remaining additional risk factors were required together with hypertension.

The diagnosis of diabetes was based on the WHO criteria at the time of inclusion [20]. The diagnostic criteria were updated during the study when the new WHO criteria were published, that is a fasting venous blood glucose level of 7 mmol/l or more or a 2-h value of 11.1 mmol/l or more following a 75 g glucose load. Patients who had been diagnosed as having diabetes in the past, and who were either on hypoglycemic drugs or treated by diet, were also considered as having type II diabetes. Exclusion criteria included previous myocardial infarction, currently treated angina, a cerebrovascular event within the previous 3 months, fasting triglyceride levels higher than 4.5 mmol/l, heart failure, uncontrolled arrhythmias or any clinically important hematological or biochemical abnormality on routine screening.

Most patients in ASCOT were recruited from family practice. In the Nordic countries, 686 family practices randomized patients, and in the UK and Ireland, 32 regional centers, to which patients were referred by their family physicians, recruited patients. The study conformed to good clinical practice guidelines and was conducted under the guidelines of the Declaration of Helsinki. The protocol and all subsequent amendments to the protocol were reviewed and ratified by central and regional ethics review boards in the UK and by the national ethics and statutory bodies in Ireland and the Nordic countries.

In the UK and Ireland, all data were recorded electronically and transferred to the UK coordinating center. In the Nordic countries, data were entered on paper case-report forms and transferred to the electronic system by study monitors, who sent them to the Scandinavian coordinating center. The Scandinavian coordinating center coordinated central data management and analyses, including data cleaning. Investigators submitted all information on any potential endpoints to the Scandinavian coordinating center for central review of endpoints by the endpoint committee, who were unaware of treatment assignment.

Trial procedure

Patients were recruited between February 1998 and May 2000.

During a 4-week run-in period, patients on antihypertensive medication remained on the same medication, but those on β-blockers had their dose down-titrated. Eligibility and consent for randomization were confirmed. At the randomization visit, recruited patients underwent a physical examination and blood pressures and heart rate were recorded. Fasting blood samples were obtained for total cholesterol, HDL cholesterol, triglycerides, creatinine and glucose. All previous antihypertensive medication was stopped and patients were randomized to an amlodipine-based or atenolol-based

Table 1 Treatment algorithm

	Calcium channel blocker-based regimen	β-Blocker-based regimen
Step 1	Amlodipine 5 mg	Atenolol 50 mg
Step 2	Amlodipine 10 mg	Atenolol 100 mg
Step 3	Amlodipine 10 mg	Atenolol 100 mg
	Perindopril 4 mg	BFZ 1.25 mg + K^+
Step 4	Amlodipine 10 mg	Atenolol 100 mg
	Perindopril 8 mg (2 × 4 mg)	BFZ 2.5 mg + K^+
Step 5	Amlodipine 10 mg	Atenolol 100 mg
	Perindopril 8 mg (2 × 4 mg)	BFZ 2.5 mg + K^+
	Doxazosin GITS 4 mg	Doxazosin GITS 4 mg
Step 6	Amlodipine 10 mg	Atenolol 100 mg
	Perindopril 8 mg (2 × 4 mg)	BFZ 2.5 mg + K^+
	Doxazosin GITS 8 mg	Doxazosin GITS 8 mg

BFZ, bendroflumethiazide; GITS, gastrointestinal transport system.

regimen and treated according to a prespecified algorithm as outlined in Table 1. At each follow-up visit, antihypertensive drug therapy was titrated to achieve target blood pressures (<130/80 mmHg for diabetic patients and <140/90 mmHg for all other patients), and the information about adverse events and any new cardiovascular event or procedure, including the cause for any hospital admission, was recorded.

Patients with a nonfasting total cholesterol of 6.5 mmol/l or less who were not treated with a statin or fibrate at the time of study and whose physicians did not intend to treat them with a statin or fibrate were randomly randomized to atorvastatin 10 mg daily or matching placebo if they consented to participate in the lipid-lowering arm of the study (ASCOT–LLA) [18].

In October 2004, the data safety monitoring board recommended that the BPLA of the trial should be stopped on the grounds that those on the atenolol-based therapy had significantly higher all-cause mortality as well as worse outcomes on several secondary endpoints including stroke compared with those on the amlodipine-based therapy. This recommendation was accepted by the steering committee and, between December 2004 and June 2005, the trial physicians recalled all patients for a final end-of-study visit. All patients were offered non-study antihypertensive therapy at the discretion of the investigator.

Statistical methods

The primary endpoint of ASCOT was fatal CHD and nonfatal myocardial infarction (symptomatic and silent). Because the study was stopped prematurely due to clear effects on all-cause mortality, cardiovascular mortality and stroke, the study power relating to the primary endpoint was reduced. Thus, total cardiovascular events and procedures were considered the most relevant endpoint for analyzing effects in the diabetic subgroup. This composite endpoint included the following diagnoses: cardiovascular mortality and nonfatal myocardial infarction (symptomatic and silent), unstable angina, chronic stable angina, life-threatening arrhythmias, nonfatal heart failure, nonfatal stroke, peripheral arterial disease and revascularization procedures.

Another prespecified composite endpoint was total coronary endpoints, which included the following diagnoses: fatal coronary heart disease and nonfatal myocardial infarction (symptomatic and silent), chronic stable angina, unstable angina, and fatal and nonfatal heart failure. All components of composite endpoints were reviewed by the endpoint committee.

We compared the time to first endpoint event in the different treatment groups on an intention-to-treat basis. For the main analyses, we used the log–rank procedures and the Cox's proportional hazards model to calculate confidence intervals (CIs). Cumulative incidence curves were generated by the Kaplan–Meier method for all cardiovascular events and procedures in the active and placebo groups. Hazard ratios and 95% CIs for all prespecified endpoints were calculated.

Role of the funding source

ASCOT was conceived, designed and coordinated by an independent investigator-led steering committee, members of which represented all the countries where the trial was undertaken. The principal funding source had two nonvoting members on that committee and the trial report was prepared independently of the principal funding source.

Results

Of the 19 342 patients randomized to one of the two antihypertensive regimens, 5137 had a diagnosis of diabetes at baseline. Two thousand five hundred and seventy-two of these patients were randomized to the atenolol-based regimen and 2565 to the amlodipine-based regimen.

The diabetic participants were mainly white (92%) and men (63%) and had a mean age of 63.4 years. Baseline blood pressures and other characteristics of the diabetic participants in the two randomized groups were well matched (Table 2).

At the close of follow-up, complete information was obtained on 98.5% of the 5137 diabetic patients originally randomized. Thirteen patients were lost to follow-up. The frequency of usage of the different medications for lowering blood pressure during the trial is depicted in Table 3.

A majority of patients received combination treatment with either amlodipine and perindopril or atenolol and thiazide. Blood pressure was reduced more by treatment based on amlodipine (Fig. 1). At year 1 of the follow-up, systolic blood pressure was 143 mmHg in the amlodipine

Table 2 Baseline characteristics for patients with diabetes in blood pressure lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial

	Amlodipine ($n = 2565$)	Atenolol ($n = 2572$)
Demographics and clinical characteristics		
Female sex	715 (27.9)	699 (27.2)
Age (years)		
≤60.0	875 (34.1)	876 (34.1)
>60.0	1690 (65.9)	1696 (65.9)
Mean (SD)	63.4 (8.4)	63.4 (8.3)
White [*n* (%)]	2355 (91.8)	2361 (91.8)
Current smoker [*n* (%)]	614 (23.9)	567 (22.0)
Alcohol consumption (units/week) [mean (SD)]	6.8 (10.9)	6.8 (10.9)
Systolic blood pressure (mmHg) [mean (SD)]	164.9 (18.2)	164.8 (17.9)
Diastolic blood pressure (mmHg) [mean (SD)]	92.7 (10.4)	92.3 (10.3)
Heart rate (beats/min) [mean (SD)]	74.2 (12.9)	74.4 (13.1)
BMI (kg/m^2) [mean (SD)]	30.2 (4.8)	30.2 (4.8)
Total cholesterol (mmol/l) [mean (SD)]	5.7 (1.1)	5.7 (1.1)
Low-density lipoprotein cholesterol (mmol/l) [mean (SD)]	3.6 (1.0)	3.5 (0.9)
High-density lipoprotein cholesterol (mmol/l) [mean (SD)]	1.2 (0.3)	1.2 (0.3)
Triglycerides (mmol/l) [mean (SD)]	2.0 (1.1)	2.1 (1.1)
Fasting glucose (mmol/l) [mean (SD)]	8.6 (2.8)	8.6 (2.8)
Creatinine (mmol/l) [mean (SD)]	97.2 (16.8)	98.0 (17.7)
Medical history		
Previous stroke/TIA [*n* (%)]	228 (8.9)	229 (8.9)
LVH (according to ECG or ECHO)[a] [*n* (%)]	485 (18.9)	468 (18.2)
Atrial fibrillation [*n* (%)]	36 (1.4)	37 (1.5)
ECG abnormalities other than LVH[b] [*n* (%)]	629 (24.5)	634 (24.7)
Peripheral vascular disease [*n* (%)]	148 (5.8)	166 (6.5)
Other relevant cardiovascular disease [*n* (%)]	131 (5.1)	139 (5.4)
Number of risk factors [mean (SD)]	4.1 (1.0)	4.1 (1.0)
Drug therapy		
Previous antihypertensive treatments		
None [*n* (%)]	370 (14.4)	399 (15.5)
One [*n* (%)]	1085 (42.3)	1121 (43.6)
Two or more [*n* (%)]	1110 (43.3)	1052 (40.9)
Lipid-lowering therapy [*n* (%)]	396 (15.4)	369 (14.3)
Aspirin use [*n* (%)]	509 (19.8)	519 (20.2)

ECG, electrocardiogram; ECHO, echocardiogram; LVH, left ventricular hypertrophy; TIA, transient ischemic attack. [a] LVH on echocardiography within 2 months. Assessed according to ASE criteria or on ECG using either Cornell voltage duration product (>2440) or Sokolow Lyon criteria (>38). [b] LV strain pattern, abnormal Q-waves, LBBB, ST-T changes compatible with IHD.

group and 148 mmHg in the atenolol group. The corresponding diastolic pressures in the two groups were 81 and 84 mmHg, respectively. By the end of the study, these differences were smaller. Patients on the amlodipine therapy had a blood pressure of 136/75 mmHg and those on the atenolol therapy 137/76 mmHg. The mean systolic and diastolic blood pressures throughout the study were 3.0 and 1.9 mmHg lower among those on treatment with the amlodipine-based regimen.

Blood levels of glucose, creatinine and triglycerides were all significantly ($P < 0.001$) higher and those of HDL cholesterol were lower ($P < 0.001$) among patients receiving atenolol-based treatment compared with those receiving amlodipine-based treatment (Fig. 2).

Events

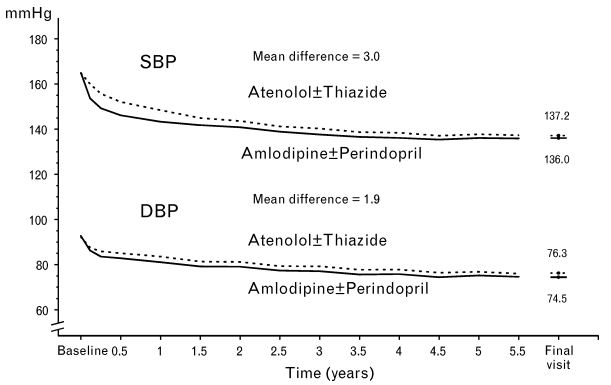
The amlodipine-based regimen was associated with a significantly lower incidence of total cardiovascular events and procedures compared with the atenolol-based regimen (hazard ratio 0.86, CI 0.76–0.98, $P = 0.026$) (Figs 3 and 4, Table 4). The effect was similar to that in nondiabetic patients in ASCOT for almost all of the

Table 3 Mean percentage time during study period (SD) on antihypertensive medication by treatment group and year

	Year						
	1st	2nd	3rd	4th	5th	6th	All study
Randomized to amlodipine							
Amlodipine ± others	88.2 (28.2)	83.6 (35.8)	81.4 (37.9)	80.7 (38.6)	79.7 (39.3)	78.5 (40.5)	82.5 (33.1)
Perindopril ± others	56.1 (38.9)	69.7 (43.9)	72.2 (43.4)	73.6 (43.0)	74.0 (42.9)	72.6 (44.0)	68.3 (37.6)
Amlodipine + perindopril ± others	49.0 (40.2)	60.8 (46.7)	62.6 (46.9)	63.6 (46.9)	63.6 (47.1)	62.4 (47.8)	59.2 (40.5)
Randomized to atenolol							
Atenolol ± others	88.3 (27.9)	82.6 (36.5)	79.9 (39.0)	77.7 (40.5)	76.6 (41.4)	75.4 (42.6)	80.9 (34.0)
BFZ ± others	59.1 (38.5)	69.3 (43.8)	70.0 (43.9)	70.4 (44.2)	69.9 (44.6)	68.3 (45.8)	66.9 (37.3)
Atenolol + BFZ ± others	53.3 (39.7)	61.3 (46.3)	61.0 (46.8)	61.0 (47.3)	59.9 (47.7)	58.3 (48.6)	58.5 (39.6)

The values are percentage (SD). BFZ, bendroflumethiazide.

Fig. 1



Systolic and diastolic blood pressure during the course of the study. DBP, diastolic blood pressure; SBP, systolic blood pressure.

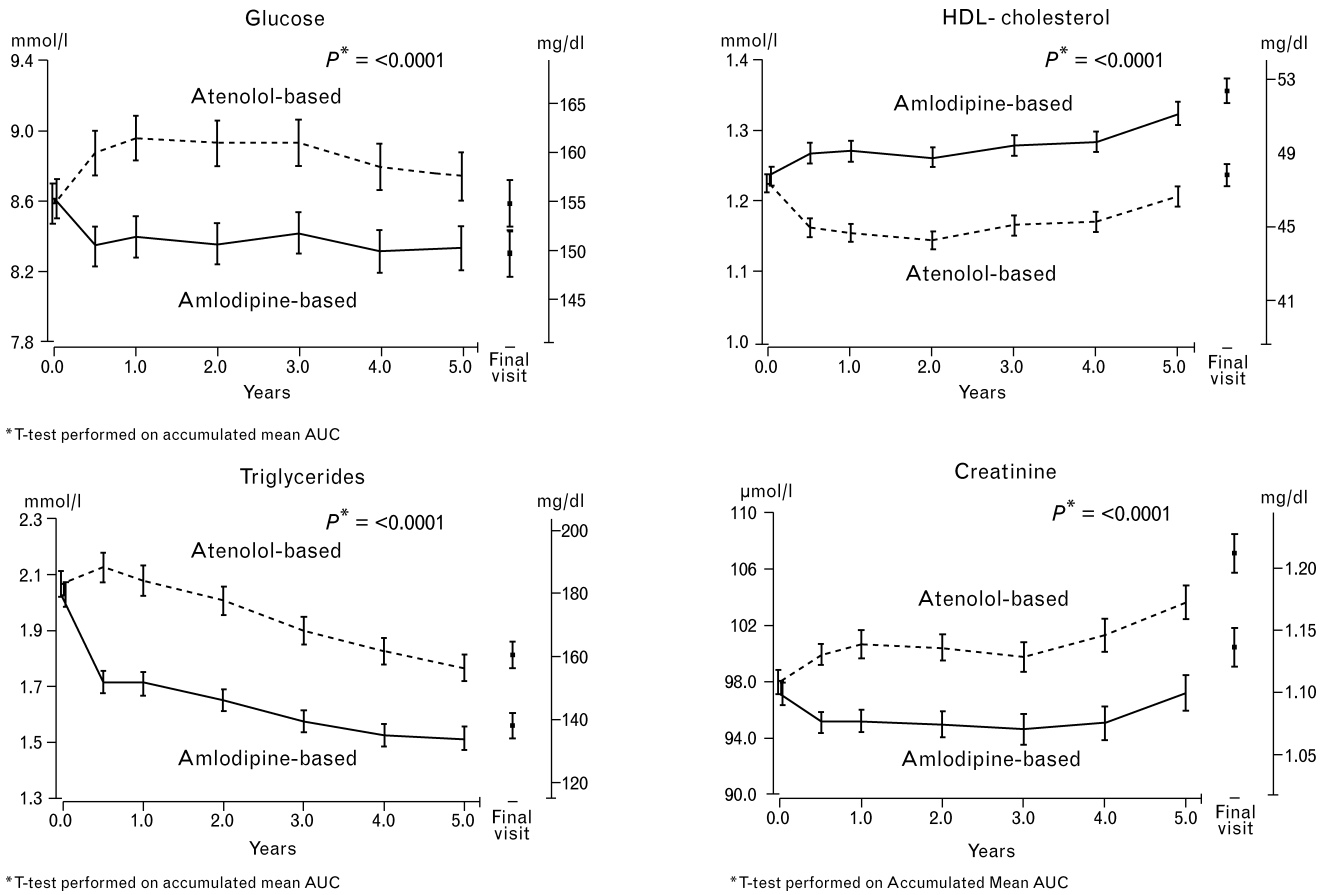
secondary endpoints, with no significant heterogeneity except for strokes (P for heterogeneity = 0.046) and stable angina (P for heterogeneity = 0.004) (Fig. 4). Furthermore, there was no difference in the effect when major subgroups of diabetic patients were compared. Thus, the reduction in events was comparable in men and women, in age groups above and below 60 years and whether or not systolic blood pressure was above or below the median at baseline (P for heterogeneity = 0.41–0.51).

Among individual components of the composite endpoint, fatal and nonfatal strokes were 25% lower ($P = 0.017$), peripheral arterial disease was 48% lower ($P = 0.004$) and noncoronary revascularization procedures were 57% lower ($P < 0.001$) in the amlodipine-based group, but for the other endpoints included in the composite endpoint, the differences were less clear and nonsignificant (Fig. 4). CHD death and nonfatal myocardial infarction (the primary endpoint in ASCOT) were reduced by a nonsignificant 8% (hazard ratio 0.92, CI 0.74–1.15).

Discussion

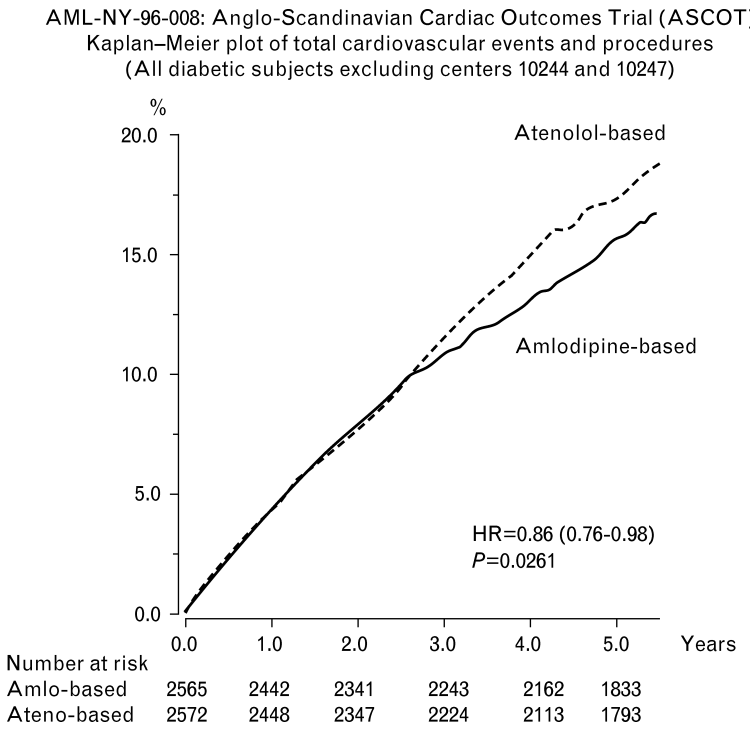
In the diabetic subgroup of patients included in ASCOT, treatment with an amlodipine-based regimen significantly reduced the incidence of cardiovascular events

Fig. 2



Plasma concentrations of *S*-glucose, lipid fractions and *S*-creatinine by visit and treatment. HDL, high-density cholesterol.

Fig. 3



Cumulative incidence curves for total cardiovascular events and procedures. HR, hazard ratio.

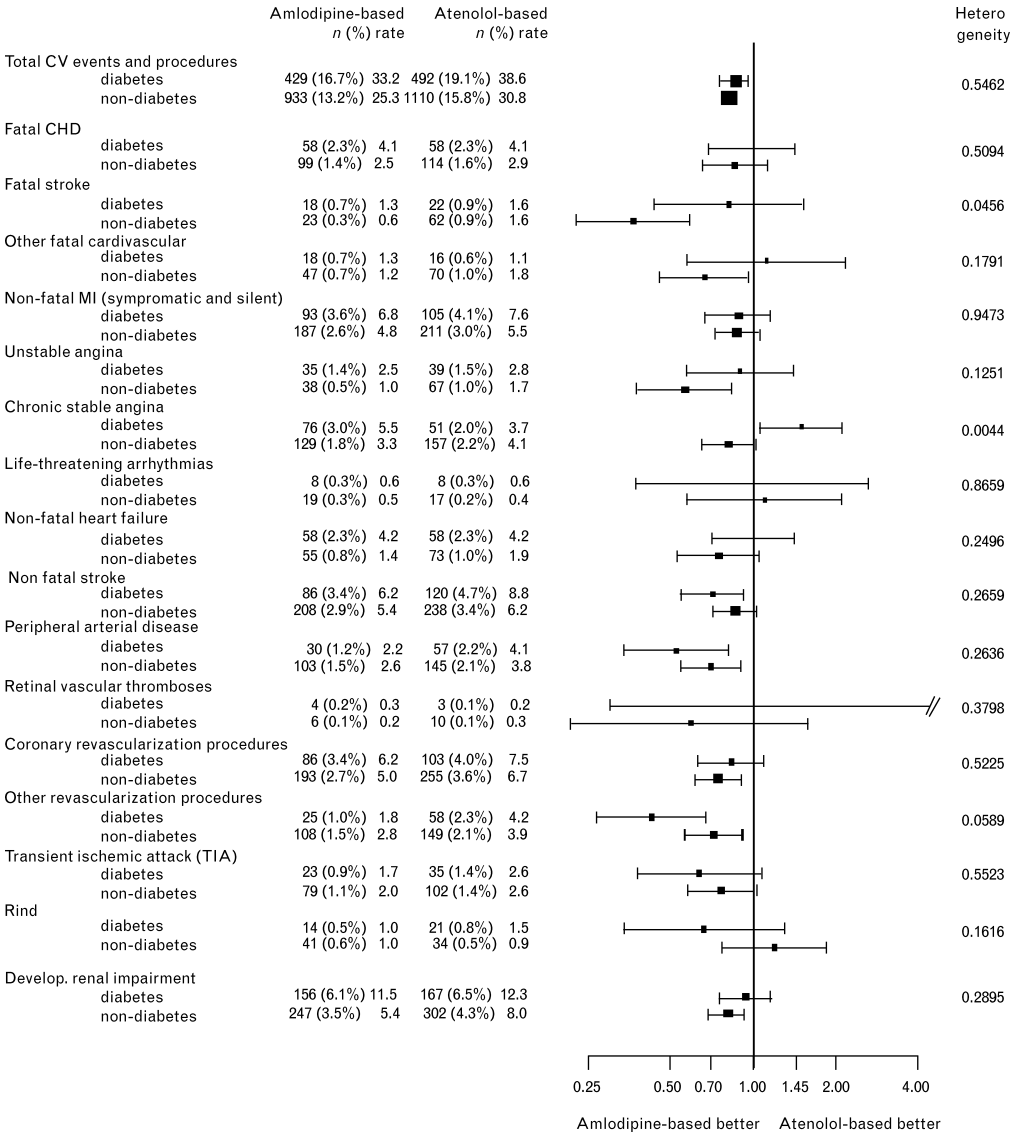
and procedures by 14% during a median follow-up period of 5.5 years compared with treatment with an atenolol-based regimen. Findings in subgroups should always be interpreted with caution, but this finding is consistent with the overall finding of a 16% risk reduction of total cardiovascular events and procedures by treatment based on amlodipine in the total trial population. Although not the primary endpoint of the ASCOT trial, the more extensive endpoint of total cardiovascular events and procedures can be considered to be the most relevant one for analyzing the effects in subgroups because the study was not powered to analyze the effect on the primary endpoint in subgroups. Furthermore, the trial was stopped early due to clear benefits on mortality and stroke in the group randomized to the amlodipine-based therapy, thus diminishing study power to analyze the primary endpoint of nonfatal myocardial infarction and coronary death. The nonsignificant 8% reduction in the primary endpoint associated with amlodipine-based treatment seen in the diabetic subgroup was however not significantly different from the 10% reduction seen in the nondiabetic population of the trial.

The event rates (33.2 and 38.6 per 1000 patient-years in the amlodipine-based and atenolol-based groups, respectively) in the diabetic participants were higher than those in the nondiabetic participants, and the absolute risk reduction in total cardiovascular events and procedures associated with allocation to the amlodipine-based regimen was very similar in the nondiabetic (2.6%) and diabetic (2.4%) subgroups in ASCOT. The findings of this analysis are thus in congruence with the similarity between diabetic and nondiabetic individuals regarding the benefits from lipid-lowering seen in ASCOT–LLA [21].

Overall, blood pressure was radically reduced by both antihypertensive treatment regimens, but more effectively so by the amlodipine-based treatment. This was especially evident during the first year of treatment. At the end of the study, blood pressure differences were reduced to only 1 mmHg. These in-trial blood pressure differences probably influenced the difference in cardiovascular events between the treatment groups to a certain extent [22]. Mean blood pressure at the end of study was still above the target blood pressure of 130/80 mmHg for diabetic patients, reflecting the difficulty of reaching the target blood pressure especially in patients with diabetes, a finding also reported in other studies [12,23].

Treatment with a regimen based on amlodipine with the addition of perindopril as required positively affected metabolic variables in comparison with the atenolol with or without thiazide-based treatment. Thus, triglycerides and glucose levels were significantly lower and HDL

Fig. 4



Hazard ratios for endpoints included in diabetic and nondiabetic patients – the area of the square is proportional to the amount of statistical information. Forest plot with point estimate for hazard ratio and 95% confidence intervals. *P* values for heterogeneity. CHD, coronary heart disease; CV, cardiovascular.

cholesterol level was significantly higher in the amlodipine-based group (all $P < 0.001$). The latter difference may have contributed to the better cardiovascular outcome associated with amlodipine-based treatment and is compatible with the effect emerging after 2–3 years of treatment [22]. A possible positive interaction between amodipine-based treatment and concomitant treatment with atorvastatin may also be of importance [24]. Serum creatinine was significantly lower in patients on amlodipine-based compared with those on atenolol-based treatment, and this may also contribute to the better outcome because renal function is an important predictor of cardiovascular events [25,26].

The recently published ADVANCE trial of over 11 000 patients with type II diabetes showed that a combination of perindopril and indapamide produced an average in-trial blood pressure reduction of 5.6/2.2 mmHg compared with placebo, with which major cardiovascular beneficial effects were associated, irrespective of baseline blood pressure [27]. A similar finding was reported previously with ramipril compared with placebo in the diabetic subpopulation of the HOPE trial [28]. The ACCOMPLISH trial includes a large population of diabetic patients [29]. Preliminary results reported recently from this trial indicate that the combination of an ACE inhibitor and amlodipine was superior to the combination of a

Table 4 Hazard ratio for primary and secondary endpoints in patients with diabetes

	Amlodipine		Atenolol			
Endpoint	*n* (%)	Rate[a]	*n* (%)	Rate[a]	Unadjusted hazard ratio (95% CI)	*P*
Nonfatal MI (including silent) + fatal CHD	148 (5.8)	10.8	161 (6.3)	11.7	0.92 (0.74–1.15)	0.46
Total cardiovascular events and procedures	429 (16.7)	33.2	492 (19.1)	38.6	0.86 (0.76–0.98)	0.026
Total coronary endpoint	275 (10.7)	20.6	284 (11.0)	21.3	0.97 (0.82–1.15)	0.74
Nonfatal MI (excluding silent) + fatal CHD	137 (5.3)	9.9	148 (5.8)	10.7	0.93 (0.73–1.17)	0.52
All-cause mortality	245 (9.6)	17.5	250 (9.7)	17.8	0.98 (0.82–1.17)	0.81
Cardiovascular mortality	94 (3.7)	6.7	96 (3.7)	6.8	0.98 (0.74–1.30)	0.88
Fatal and nonfatal stroke	103 (4.0)	7.5	136 (5.3)	9.9	0.75 (0.58–0.97)	0.031
Fatal and nonfatal heart failure	66 (2.6)	4.8	65 (2.5)	4.7	1.02 (0.72–1.43)	0.92
Development of renal impairment	156 (6.1)	11.5	167 (6.5)	12.3	0.94 (0.75–1.17)	0.56
Fatal CHD	58 (2.3)	4.1	58 (2.3)	4.1	1.00 (0.70–1.44)	0.99
Fatal stroke	18 (0.7)	1.3	22 (0.9)	1.6	0.82 (0.44–1.52)	0.52
Other fatal cardiovascular diseases	18 (0.7)	1.3	16 (0.6)	1.1	1.13 (0.57–2.21)	0.73
Nonfatal MI (symptomatic and silent)	93 (3.6)	6.8	105 (4.1)	7.6	0.89 (0.67–1.17)	0.40
Unstable angina	35 (1.4)	2.5	39 (1.5)	2.8	0.90 (0.57–1.42)	0.64
Chronic stable angina	76 (3.0)	5.5	51 (2.0)	3.7	1.50 (1.05–2.14)	0.023
Life-threatening arrhythmias	8 (0.3)	0.6	8 (0.3)	0.6	1.00 (0.37–2.66)	0.99
Nonfatal heart failure	58 (2.3)	4.2	58 (2.3)	4.2	1.00 (0.70–1.44)	0.99
Nonfatal stroke	86 (3.4)	6.2	120 (4.7)	8.8	0.71 (0.54–0.94)	0.017
Peripheral arterial disease	30 (1.2)	2.2	57 (2.2)	4.1	0.52 (0.34–0.82)	0.004
Retinal vascular thromboses	4 (0.2)	0.3	3 (0.1)	0.2	1.34 (0.30–5.99)	0.70
Coronary revascularization procedures	86 (3.4)	6.2	103 (4.0)	7.5	0.83 (0.63–1.11)	0.21
Other revascularization procedures	25 (1.0)	1.8	58 (2.3)	4.2	0.43 (0.27–0.69)	0.0003
Transient ischemic attack	23 (0.9)	1.7	36 (1.4)	2.6	0.64 (0.38–1.08)	0.09
Reversible ischemic neuro deficit	14 (0.5)	1.0	21 (0.8)	1.5	0.67 (0.34–1.31)	0.23

CHD, coronary heart disease; CI, confidence interval; MI, myocardial infarction. [a]Per 1000 patient-years.

diuretic and an ACE inhibitor (Jamerson, personal communication).

In conclusion, the findings in the diabetic subpopulation of the ASCOT trial are consistent with the results in the total ASCOT population, indicating that a therapy based on amlodipine with addition of perindopril as required is superior for long-term cardiovascular outcomes in hypertensive individuals regardless of the presence of type II diabetes mellitus. To what extent this result is dependent on blood pressure differences, metabolic alterations induced by the treatments or other factors is not clear. In clinical practice, treatment of hypertension is often maintained for longer than 4–5 years, the usual duration of such clinical trials. To what extent differences between various blood pressure-lowering regimens will affect cardiovascular morbidity and mortality over such an extended period is unclear but the difference may be more important than that suggested by relatively short clinical trials.

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