Antihypertensive therapy and the benefits of atorvastatin in the Anglo-Scandinavian Cardiac Outcomes Trial: lipid-lowering arm extension

Peter S. Sever[a], Neil R. Poulter[a], Bjorn Dahlof[b] and Hans Wedel[c], on behalf of the ASCOT investigators

Objective **To determine the cardiovascular benefits of atorvastatin stratified by blood pressure-lowering regimen, 2.2 years after closure of the lipid-lowering arm (LLA) of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-LLA).**

Methods **In ASCOT-LLA, 10 305 hypertensive patients randomized to amlodipine-based or atenolol-based therapy and with a total cholesterol 6.5 mmol/l or less were further randomized to atorvastatin or placebo. ASCOT-LLA was terminated after 3.3 years median follow-up. Cardiovascular outcomes in these patients were further evaluated 2.2 years later, at the end of the blood pressure-lowering arm (BPLA).**

Results **By the end of BPLA in both groups originally assigned statin or placebo, approximately 65% were receiving a statin, and lipid levels had equalized. The benefits of atorvastatin observed in LLA were sustained throughout BPLA. At the end of BPLA, in those assigned amlodipine-based therapy, atorvastatin reduced coronary heart disease deaths and nonfatal myocardial infarction (MI) by 46% [hazard ratio 0.54, confidence interval (CI) 0.40–0.72, $P<0.0001$], stroke by 37% [hazard ratio 0.63, CI 0.46–0.87, $P=0.004$] and total cardiovascular events and procedures by 27% [hazard ratio 0.73, CI 0.63–0.86, $P<0.0001$]. In the atenolol-based group, atorvastatin reduced coronary heart disease death and nonfatal MI by 25% [hazard ratio 0.75, CI 0.57–0.97, $P=0.03$], stroke by 10% [hazard ratio 0.90, CI 0.69–1.18, $P=0.43$] and total cardiovascular events and procedures by 13% [hazard ratio 0.87, CI 0.76–1.0, $P=0.05$]. P values for heterogeneity were low, but failed to achieve statistical significance (0.10, 0.10 and 0.11 for chronic heart disease, stroke and total cardiovascular events, respectively).**

Conclusion **Although not statistically significant, the benefits of atorvastatin appeared greater among those on amlodipine-based compared with atenolol-based therapy. These data provide supporting evidence that coassignment to atorvastatin may have generated differential effects on coronary and other cardiovascular outcomes by amlodipine-based and atenolol-based treatment in ASCOT-BPLA.** ***J Hypertens*** **27:947–954 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Journal of Hypertension 2009, **27**:947–954

Keywords: antihypertensive drugs, atorvastatin, cardiovascular outcomes, coronary heart disease

Abbreviations: ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; BPLA, Blood pressure lowering arm; CHD, Coronary heart disease; LLA, Lipid lowering arm

[a]Imperial College London, International Centre for Circulatory Health, London, UK, [b]Department of Medicine, University of Goteborg, Clinical Trial Unit, Ostra Hospital and [c]Nordic School of Public Health, Goteborg, Sweden

Correspondence to Professor Peter Sever, Imperial College London, International Centre for Circulatory Health, 59 North Wharf Road, London W2 1LA, UK
Tel: +44 020 7594 1100; fax: +44 020 7594 1145;
e-mail: p.sever@imperial.ac.uk

Received 27 August 2008 **Revised** 20 November 2008
Accepted 17 December 2008

Introduction

We have previously reported the benefits of lipid lowering with atorvastatin in reducing major cardiovascular events among over 10 000 hypertensive patients in the Anglo-Scandinavian Cardiac Outcomes Trial-lipid-lowering arm (ASCOT-LLA) [1]. In a subsequent report, we conducted a prespecified analysis to determine whether there was any synergy between assignment to atorvastatin and either of the antihypertensive treatment arms. We demonstrated that the reduction in coronary heart disease (CHD) event rates, associated with atorvastatin compared with placebo, appeared to be greater in those assigned amlodipine-based treatment compared with those assigned atenolol-based treatment (53 versus 16%, respectively). This observation was of borderline statistical significance for a tertiary endpoint (P heterogeneity = 0.025) [2].

Following premature termination of ASCOT-LLA after a median follow-up of 3.3 years, patients continued in the blood pressure-lowering arm of the trial (ASCOT-BPLA) until its termination after 5.5 years [3]. During this follow-up period, many of those originally assigned atorvastatin stopped taking it, and of those originally assigned placebo, the majority commenced statin therapy. By the end of the trial, a similar number of patients in each limb were taking a statin (approximately 65%), and lipid levels in the two arms were almost identical. However, despite this, as previously reported, relative risk reductions in event rates for all prespecified endpoints were essentially unchanged [4]. In this analysis, in keeping with our initial report on ASCOT-LLA, we did not subdivide the patients according to their antihypertensive drug assignment.

0263-6352 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI:10.1097/HJH.0b013e328326cb1a

In the current set of analyses, we report additional findings associated with statin use among ASCOT-LLA patients, according to their original allocation to both BP and lipid-lowering treatment groups and a comparison of risk reductions observed at the end of ASCOT-LLA (3.3 years) with those observed at the end of ASCOT-BPLA (5.5 years). It was our intent with this extended and expanded database to seek further evidence for an interaction between lipid-lowering and BP-lowering treatment strategies.

Methods

The detailed ASCOT protocol has been published previously [5], and further information is available at www.ascotstudy.org. In summary, patients were recruited between February 1998 and May 2000, largely from family practices in the UK, Ireland and the Nordic countries. Hypertensive patients, on or off antihypertensive treatment, with three or more other risk factors for cardiovascular disease were eligible for ASCOT-BPLA. These risk factors included male sex, age more than 55 years, a history of smoking, left ventricular hypertrophy or other specified ECG abnormalities, history of early CHD in a first-degree relative, microalbuminuria or proteinuria, noninsulin dependent diabetes, peripheral vascular disease, previous stroke or transient ischemic attack or ratio of plasma total cholesterol to high-density lipoprotein (HDL)-cholesterol of 6 or higher. Exclusion criteria included prior myocardial infarction (MI), currently treated angina, cerebrovascular event within the previous 3 months, fasting serum triglycerides greater than 4.5 mmol/l, heart failure, uncontrolled arrhythmias or any clinically important hematological or biochemical abnormalities.

In ASCOT-BPLA, following a 4-week run-in period, during which eligibility and consent were confirmed, patients were randomized to one of the two BP-lowering strategies, either amlodipine adding perindopril as required (amlodipine-based strategy) or atenolol adding bendroflumethiazide as required (atenolol-based strategy). In ASCOT-LLA, those with a fasting total cholesterol of 6.5 mmol/l or less (250 mg/dl) who were currently untreated with a statin or fibrate were randomized, using a factorial design, to either 10 mg atorvastatin daily or matching placebo. Overall, 19 342 patients were assigned either amlodipine-based or atenolol-based treatment, and 10 305 of these patients were assigned atorvastatin or placebo. Management of those randomized to ASCOT-BPLA is detailed elsewhere [5]. In summary, at each follow-up visit, antihypertensive drug therapy was titrated and additional drugs added (perindopril to amlodipine and bendroflumethiazide-K to atenolol) to achieve target BP levels of less than 140/90 mmHg for nondiabetic patients and less than 130/80 mmHg for diabetic patients.

Following randomization, information was recorded about adverse events and any new cardiovascular event or procedure, including the cause for any hospital admission. Central review of endpoints by the Endpoint Committee was carried out blinded to treatment allocation using criteria for classifying diagnoses that have been reported at www.ascotstudy.org. The primary endpoint of both ASCOT-LLA and ASCOT-BPLA was the composite of nonfatal (including silent) MI and fatal CHD. Secondary endpoints included nonfatal or fatal stroke and a number of additional composite cardiovascular endpoints. Prespecified tertiary objectives included an evaluation of any interaction between the BP-lowering and lipid-lowering regimens.

The number of events during LLA in the current analyses differs slightly from those reported previously [1], because a small number of events that occurred during LLA were not reported until the post-LLA follow-up period. These have now been included and statistical analyses revised accordingly.

Statistical methods

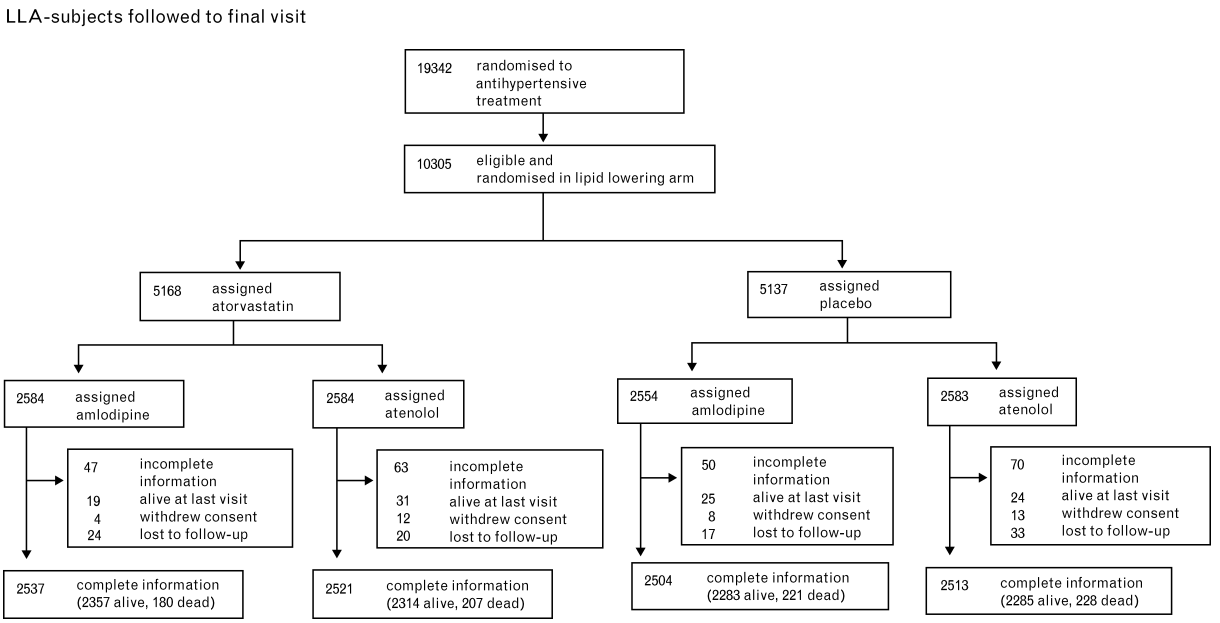
The statistical analysis plan is available at www.ascotstudy.org. Time to first events in the atorvastatin and placebo groups were compared on an intention-to-treat basis until closeout of ASCOT-LLA (median follow-up time 3.3 years) and subsequently at the end of the ASCOT-BPLA (median follow-up time 5.5 years) using the log-rank and Cox proportional hazard models. In order to check the proportional hazard assumption, we have assessed the proportionality by considering the interactions of the treatment indicators and time. The *P* values for time-interaction were larger than 0.30 for all endpoints. Wald's test for interaction between atorvastatin and the two BP-lowering regimens was performed using the full Cox model. All significance tests were two-tailed and conducted at the 0.05 level.

Results

The overall demographics of the ASCOT-LLA population have previously been published [1,2]. Participants were mainly white (95%) and male (81%), with a mean age of 63 years. The patients assigned to the two BP-lowering regimens were comparable as were those assigned atorvastatin or placebo.

Complete information was available on 10 075 patients originally randomized to LLA and followed to the end of BPLA (Fig. 1). However, between the closure of LLA and the subsequent closure of BPLA, there was substantial drop-in and dropout of statin therapy among those originally randomized to placebo and atorvastatin, respectively. Consequently, at the closure of BPLA, of those originally assigned atorvastatin, 63% were still taking it, and of those originally assigned placebo, 56%

Fig. 1



Trial profile. LLA, lipid-lowering arm.

were taking atorvastatin. Adding in other statin use increased these percentages to 67 and 63%, respectively.

At the end of LLA (3.3 years), total cholesterol and low-density lipoprotein (LDL)-cholesterol concentrations among those allocated atorvastatin were around 1 mmol/l lower than those allocated placebo (Fig. 2) in both antihypertensive treatment groups.

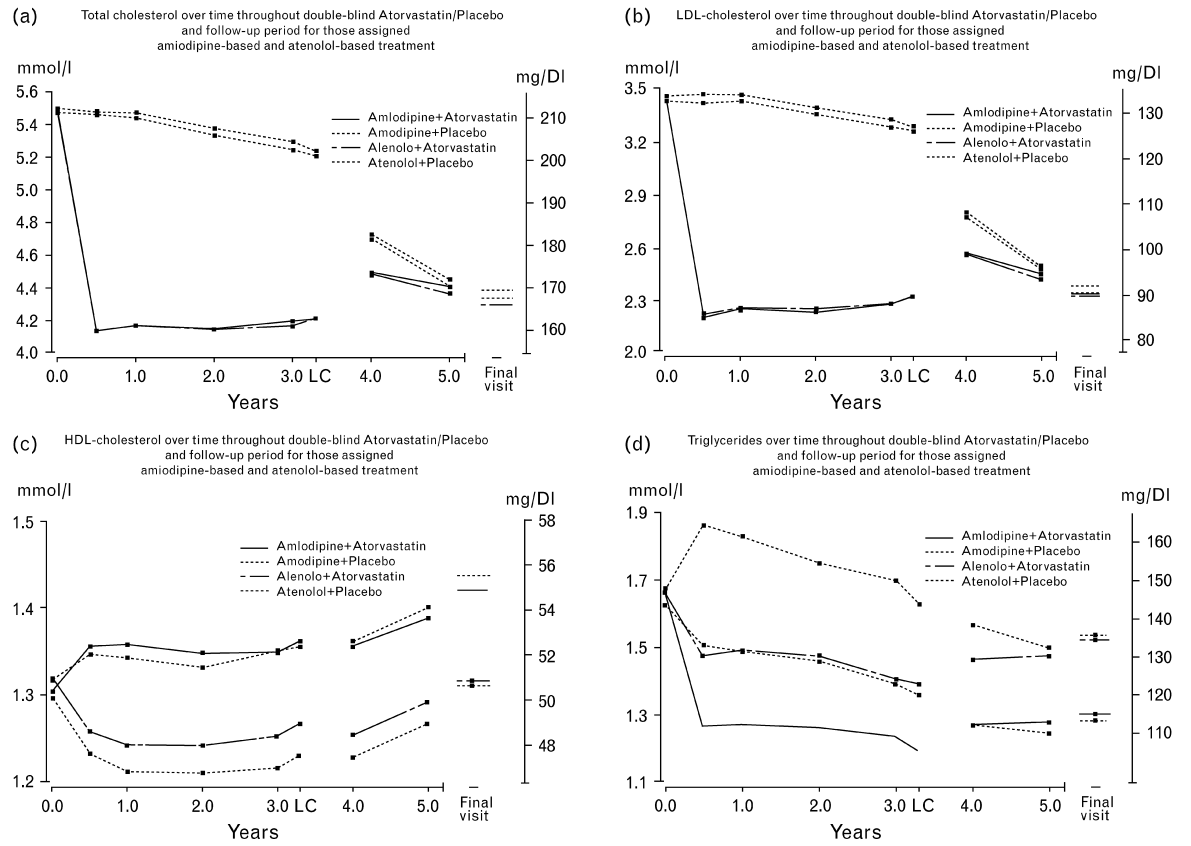
By the end of BPLA, total and LDL-cholesterol concentrations were similar in all four groups (Fig. 2). HDL-cholesterol and triglyceride levels were influenced both by assignment to either amlodipine-based or atenolol-based treatment and by atorvastatin or placebo during LLA (Fig. 2). However, by the end of BPLA, the lower levels of HDL-cholesterol and higher triglyceride levels among those on atenolol-based treatment were only attributable to BP treatment.

BPs were reduced in LLA more rapidly in those assigned amlodipine-based treatment compared with atenolol-based treatment, but by the end of BPLA differed by only about 1 mmHg systolic (Fig. 3). Compared with placebo, assignment to statin had a negligible overall effect on BP values.

By the end of LLA, compared with placebo, allocation to atorvastatin reduced the incidence of the primary endpoint of nonfatal MI and fatal CHD significantly by 53% [hazard ratio 0.47, confidence interval (CI) 0.32–0.68, $P < 0.0001$] among those allocated the amlodipine-based regimen (Fig. 4). Among those allocated atenolol-based treatment, the primary endpoint was reduced by only 14% (hazard ratio 0.86, CI 0.62–1.20, $P = 0.38$) (Fig. 5, test for heterogeneity $P = 0.017$).

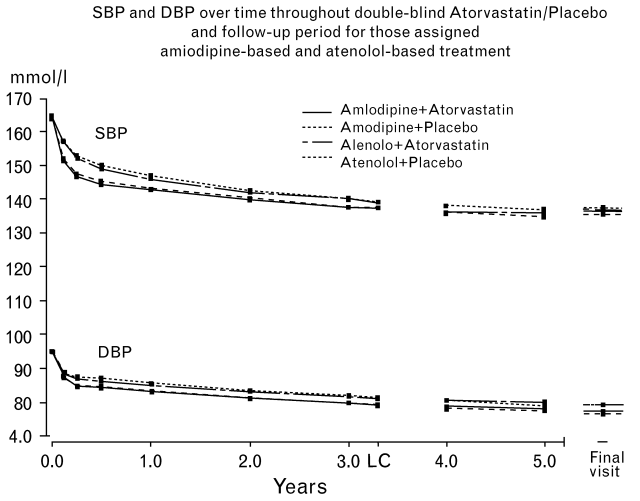
By the end of BPLA, these risk reductions associated with atorvastatin were 46% (hazard ratio 0.54, CI 0.40–0.72, $P < 0.0001$) and 25% (hazard ratio 0.75, CI 0.57–0.97, $P = 0.031$) for amlodipine-based and atenolol-based treatment, respectively (P heterogeneity $= 0.10$). By the end of LLA, compared with placebo, atorvastatin reduced the incidence of stroke by 24% (hazard ratio 0.76, CI 0.52–1.11, $P = 0.15$) in those assigned amlodipine-based treatment (Fig. 4, Table 1) and by 19% (hazard ratio 0.81, CI 0.58–1.13, $P = 0.21$) in those assigned atenolol-based treatment (Fig. 5) (P heterogeneity $=$ 0.81). By the end of BPLA, the risk reduction associated with atorvastatin was 37% (hazard ratio 0.63, CI 0.46–0.87, $P = 0.004$) in those assigned amlodipine-based treatment and 10% (hazard ratio 0.90, CI 0.69–1.18, $P = 0.44$) in those assigned atenolol-based treatment (Figs 4 and 5) (P heterogeneity $= 0.10$). For the combined endpoint of total cardiovascular events and procedures, risk reductions associated with atorvastatin compared with placebo were very similar at the end of LLA and BPLA for both antihypertensive treatment regimens [for amlodipine based, 28%, hazard ratio 0.72, CI 0.59–0.87, $P < 0.001$ at the end of LLA and 27%, hazard ratio 0.73, CI 0.63–0.86, $P < 0.0001$ at the end of BPLA (Fig. 4), and for atenolol based, 17%, hazard ratio 0.83, CI 0.70–0.99, $P = 0.038$ at the end of LLA and 13%, hazard ratio 0.87, CI 0.76–1.0,

Fig. 2



Lipid profiles over time throughout double-blind atorvastatin/placebo and follow-up period for total cholesterol (a), low-density lipoprotein cholesterol (b), high-density lipoprotein cholesterol (c), and triglycerides (d), for those assigned amlodipine-based and atenolol-based treatment. HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Fig. 3



A time course of blood pressure levels throughout lipid-lowering arm and to the end of blood pressure-lowering arm by amlodipine-based and atenolol-based treatment allocation and statin and placebo. DBP, diastolic blood pressure; SBP, systolic blood pressure.

$P = 0.054$ at the end of BPLA (Fig. 5)] (P heterogeneity at the end of BPLA = 0.11). For other prespecified endpoints, risk reductions were also very similar at the two time points (Figs 4 and 5).

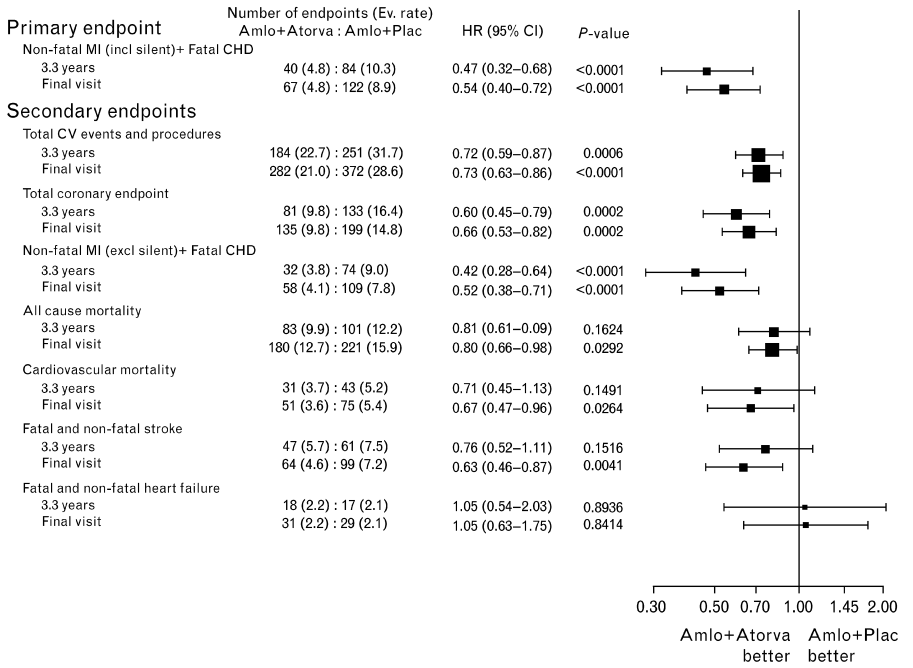
When the effects of amlodipine-based treatment in those assigned atorvastatin are compared with atenolol-based treatment in the absence of atorvastatin, almost all endpoints are significantly reduced among those on statin-based and amlodipine-based therapy at the end of both LLA and BPLA (Fig. 6).

We have previously reported that, overall, the number of serious adverse events and rates of liver enzyme abnormalities did not differ between those assigned either atorvastatin or placebo [1]. The same finding was evident when the two BP-lowering regimens were evaluated separately.

Discussion

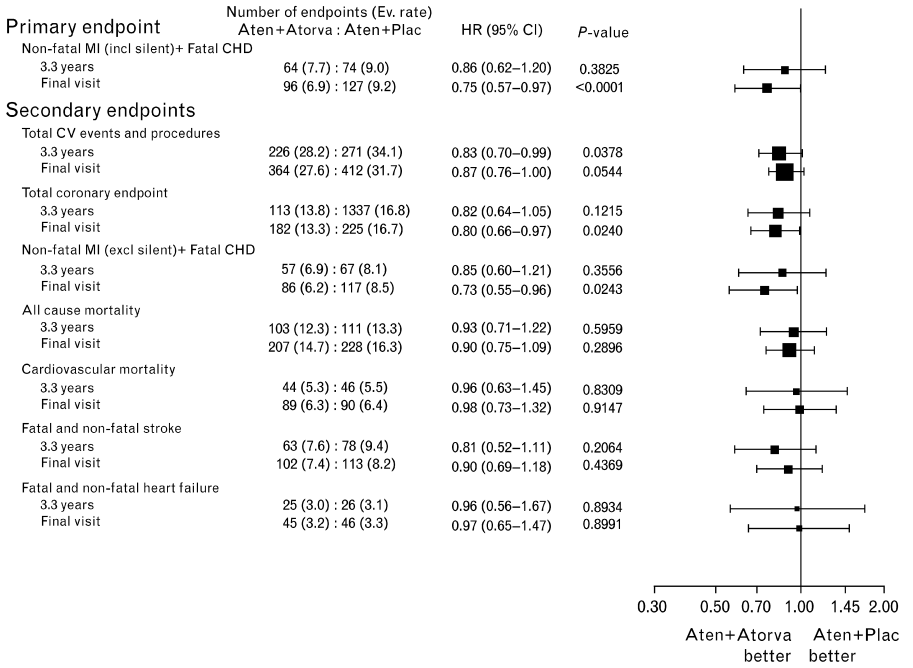
We have now had the opportunity to follow patients initially entered into the LLA for a further 2.2 years

Fig. 4



Effects of atorvastatin versus placebo on prespecified endpoints at the end of lipid-lowering arm (3.3 years) and at the end of blood pressure-lowering arm (5.5 years) in those assigned amlodipine-based treatment. Point estimates are given with 95% CI. Amlo, amlodipine; Atorva, atorvastatin; CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; Ev rate, event rate per 1000 patient–years; HR, hazard ratio; Plac, placebo.

Fig. 5



Effects of atorvastatin versus placebo on prespecified endpoints at the end of lipid-lowering arm (3.3 years) and at the end of blood pressure-lowering arm (5.5 years) in those assigned atenolol-based treatment. Point estimates are given with 95% CI. Aten, atenolol; Atorva, atorvastatin; CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; Ev rate, event rate per 1000 patient–years; HR, hazard ratio; Plac, placebo.

Table 1 Effects of atorvastatin versus placebo on prespecified endpoints at the end of lipid-lowering arm (3.3 years) and at the end of blood pressure-lowering arm (5.5 years) in those assigned amlodipine-based treatment

	LLA**					Followed to final visit**				
	Amlodipine + atorvastatin		Amlodipine + placebo			Amlodipine + atorvastatin		Amlodipine + placebo		
Endpoint	*n* (%)	Rate*	*n* (%)	Rate*	Unadjusted hazard ratio (95% CI) *P*	*n* (%)	Rate*	*n* (%)	Rate*	Unadjusted hazard ratio (95% CI) *P*
Primary endpoint										
Nonfatal MI (including silent) + fatal CHD	40 (1.5)	4.8	84 (3.3)	10.3	0.47 (0.32–0.68) $P = <0.0001$	67 (2.6)	4.8	122 (4.8)	8.9	0.54 (0.40–0.72) $P = <0.0001$
Secondary endpoints										
Total CV events and procedures	184 (7.1)	22.7	251 (9.8)	31.7	0.72 (0.59–0.87) $P = 0.0006$	282 (10.9)	21.0	372 (14.6)	28.6	0.73 (0.63–0.86) $P = <0.0001$
Total coronary events	81 (3.1)	9.8	133 (5.2)	16.4	0.60 (0.45–0.79) $P = 0.0002$	135 (5.2)	9.8	199 (7.8)	14.8	0.66 (0.53–0.82) $P = 0.0002$
Nonfatal MI (excluding silent) + fatal CHD	32 (1.2)	3.8	74 (2.9)	9.0	0.42 (0.28–0.64) $P = <0.0001$	58 (2.2)	4.1	109 (4.3)	7.9	0.52 (0.38–0.71) $P = <0.0001$
All cause mortality	83 (3.2)	9.9	101 (4.0)	12.2	0.81 (0.61–1.09) $P = 0.1624$	180 (7.0)	12.7	221 (8.7)	15.9	0.80 (0.66–0.98) $P = 0.0292$
Cardiovascular mortality	31 (1.2)	3.7	43 (1.7)	5.2	0.71 (0.45–1.13) $P = 0.1491$	51 (2.0)	3.6	75 (2.9)	5.4	0.67 (0.47–0.96) $P = 0.0264$
Fatal and nonfatal stroke	47 (1.8)	5.7	61 (2.4)	7.5	0.76 (0.52–1.11) $P = 0.1516$	64 (2.5)	4.6	99 (3.9)	7.2	0.63 (0.46–0.87) $P = 0.0041$
Fatal and nonfatal heart failure	18 (0.7)	2.2	17 (0.7)	2.1	1.05 (0.54–2.03) $P = 0.8936$	31 (1.2)	2.2	29 (1.1)	2.1	1.05 (0.63–1.75) $P = 0.8414$
Tertiary endpoints										
Silent MI	8 (0.3)	1.0	10 (0.4)	1.2	0.79 (0.31–2.00) $P = 0.6158$	9 (0.3)	0.6	14 (0.5)	1.0	0.63 (0.27–1.46) $P = 0.2792$
Unstable angina	8 (0.3)	1.0	9 (0.4)	1.1	0.88 (0.34–2.28) $P = 0.7886$	17 (0.7)	1.2	15 (0.6)	1.1	1.12 (0.56–2.24) $P = 0.7550$
Chronic stable angina	21 (0.8)	2.5	36 (1.4)	4.4	0.57 (0.34–0.98) $P = 0.0412$	34 (1.3)	2.4	52 (2.0)	3.8	0.64 (0.42–0.99) $P = 0.0419$
Peripheral arterial disease	25 (1.0)	3.0	22 (0.9)	2.7	1.13 (0.64–2.00) $P = 0.6824$	32 (1.2)	2.3	33 (1.3)	2.4	0.96 (0.59–1.56) $P = 0.8576$
Life-threatening arrhythmias	6 (0.2)	0.7	0 (0.0)	0.0	ND	8 (0.3)	0.6	6 (0.2)	0.4	1.31 (0.45–3.78) $P = 0.6153$
Developing diabetes mellitus	112 (5.9)	18.7	107 (5.7)	18.2	1.03 (0.79–1.34) $P = 0.8329$	146 (7.6)	14.6	149 (8.0)	15.4	0.95 (0.76–1.20) $P = 0.6842$
Developing renal impairment	65 (2.5)	7.9	71 (2.8)	8.7	0.91 (0.65–1.27) $P = 0.5661$	104 (4.0)	7.5	112 (4.4)	8.2	0.91 (0.70–1.19) $P = 0.5130$

CHD, coronary artery disease; CI, confidence interval; CV, cardiovascular; LLA, lipid-lowering arm; MI, myocardial infarction; ND, no data. * Per 1000 patient–years. ** Late reported endpoints that occurred during LLA are included as well.

and to ascertain, according to BP treatment, the continuing effect of atorvastatin on all cardiovascular endpoints.

During the LLA extension, statins were offered to those formerly assigned placebo, and some of those originally assigned atorvastatin stopped taking it. Thus, at the end of BPLA, at 5.5 years, statin use was similar amongst those previously assigned atorvastatin and placebo, which explains the virtually identical levels of total cholesterol and LDL-cholesterol in the two groups at the end of the trial.

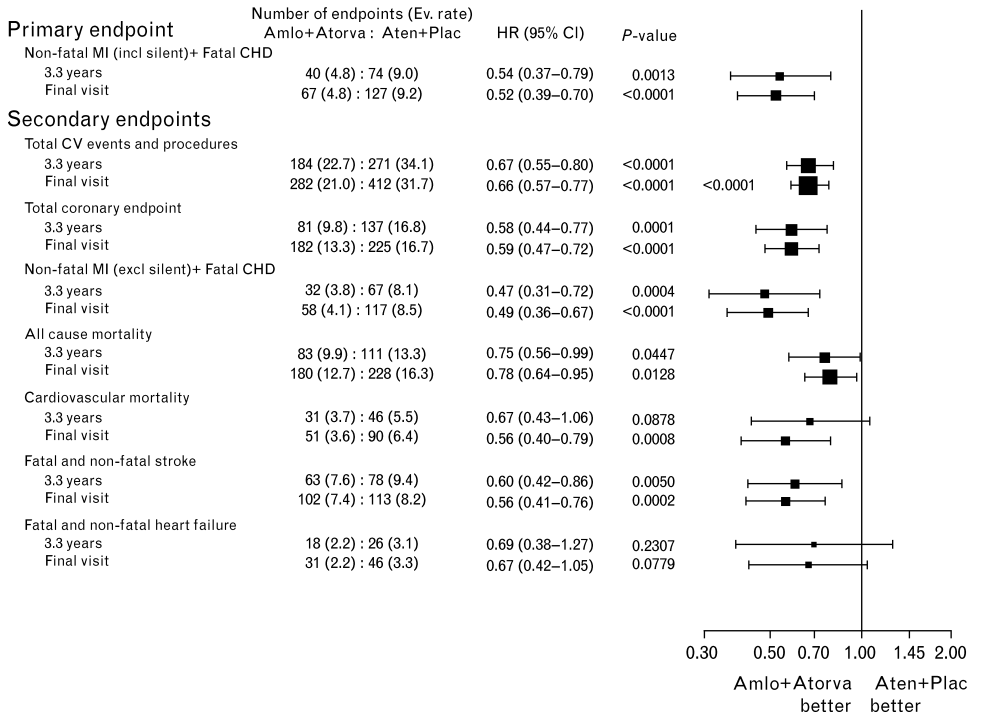
We have previously demonstrated that the overall benefits of atorvastatin are maintained for a further 2.2 years, following the closure of LLA. We now show, however, that the effect on several endpoints is observed in each of the BP-lowering groups, but most notably in those assigned amlodipine-based treatment. In those originally assigned atenolol-based treatment, some of the early, but nonsignificant, benefits of atorvastatin have become significant owing to an increase in the number of events, despite little change in hazard ratios. Possible explanations for these findings included carry-over benefits in those originally assigned atorvastatin, but who stopped taking the drug and some delay in the onset of benefits in those formerly assigned placebo who had started taking statins.

Similar extended benefits following withdrawal of statin treatment have also been reported in three other trials, the Scandinavian Simvastatin Survival Study (4S) [6], the Long Term Intervention with Pravastatin in Ischemic Disease Study (LIPID) [7] and the West of Scotland Coronary Prevention Study (WOSCOPS) [8]. Whether these benefits can be attributed to plaque stabilization or other mechanisms is uncertain.

Although by the end of the trial differences in lipid values attributable to statin use have been minimized, the effects of amlodipine-based and atenolol-based treatment, particularly on HDL-cholesterol and triglycerides, remain extant. We have previously suggested that in-trial differences in HDL-cholesterol might explain some of the differences in CHD outcome between different BP treatments, and these are certainly maintained throughout the trial [9].

We have previously proposed a hypothesis that the BP-lowering regimens used and lipid lowering with statins might interact in either a positive or negative way in relation to cardiovascular disease prevention [2]. We have reported that, for CHD events only, there appeared to be synergy between BP-lowering with amlodipine-based treatment and lipid lowering with atorvastatin, with a relative risk reduction associated with atorvastatin in the primary endpoint of nonfatal MI and fatal CHD of 53% in those assigned amlodipine-based treatment, but only

Fig. 6



Effects of amlodipine-based treatment in those assigned atorvastatin versus atenolol-based treatment without atorvastatin on prespecified endpoints at the end of lipid-lowering arm and at the end of blood pressure-lowering arm. Point estimates are given with 95% CI. Amlo, amlodipine; Aten, atenolol; Atorva, atorvastatin; CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; Ev rate, event rate per 1000 patient–years; HR, hazard ratio; Plac, placebo.

16% in those assigned atenolol-based treatment [2] (revised values in the latest analysis are 53 and 14%, respectively, P heterogeneity = 0.017), and there has been much speculation as to whether this is a real synergistic effect (for which there is a potential molecular mechanism) [10,11] or whether the observations could have been a chance finding. More data from clinical trials are required to confirm or refute this hypothesis.

After a further 2.2 years, by the end of BPLA, there remain substantial benefits of atorvastatin compared with placebo, in those assigned amlodipine-based treatment, not only on coronary end points, but also on stroke and several other cardiovascular endpoints. Rigorous tests of heterogeneity on the comparison of amlodipine-based and atenolol-based treatment in those with and without assignment to atorvastatin failed to reach significance, but P values for heterogeneity for the primary and some secondary endpoints were low ($P = 0.1$), and because of the size of many of the subgroups, the power to detect a significant interaction was low. Moreover, substantial crossover between placebo assignment and atorvastatin and vice versa during follow-up would also reduce the likelihood of demonstrating an interaction between lipid-lowering and particular BP-lowering regimens. Nevertheless, despite these shortcomings, coassignment to the statin appeared to enhance the beneficial effects of amlodipine-based therapy over atenolol-based therapy on some cardiovascular endpoints. Further clinical data are, however, required to confirm these findings.

These results support our previous findings that there are substantial benefits on cardiovascular outcome in hypertensive patients for whom both lipid lowering and BP lowering, particularly with an amlodipine-based regimen, have been combined.

Acknowledgements

Peter S. Sever, Neil R. Poulter, Bjorn Dahlof and Hans Wedel, constituting the ASCOT Executive Committee and members of the Steering Committee designed the study, wrote the protocol, supervised the undertaking of the study, coordinated data collection, wrote the analysis plan, supervised the analyses, interpreted the results, and wrote the reports. Peter S. Sever and Neil R. Poulter are grateful for support from the National Institute for Health Research Biomedical Research Centre Funding Scheme.

Conflict of interest: Peter S. Sever, Neil R. Poulter, Bjorn Dahlof and Hans Wedel have served as consultants to or

Table 2 Effects of atorvastatin versus placebo on prespecified endpoints at the end of lipid-lowering arm (3.3 years) and at the end of blood pressure-lowering arm (5.5 years) in those assigned atenolol-based treatment

	LLA**					Followed to final visit**				
	Atenolol + atorvastatin		Atenolol + placebo		Unadjusted hazard ratio (95% CI) *P*	Atenolol + atorvastatin		Atenolol + placebo		Unadjusted hazard ratio (95% CI) *P*
Endpoint	*n* (%)	Rate*	*n* (%)	Rate*		*n* (%)	Rate*	*n* (%)	Rate*	
Primary endpoint										
Nonfatal MI (including silent) + fatal CHD	64 (2.5)	7.7	74 (2.9)	9.0	0.86 (0.62–1.20) $P=0.3825$	96 (3.7)	6.9	127 (4.9)	9.2	0.75 (0.57–0.97) $P=0.0311$
Secondary endpoints										
Total CV events and procedures	226 (8.7)	28.2	271 (10.5)	34.1	0.83 (0.70–0.99) $P=0.0378$	364 (14.1)	27.6	412 (16.0)	31.7	0.87 (0.76–1.00) $P=0.0544$
Total coronary events	113 (4.4)	13.8	137 (5.3)	16.8	0.82 (0.64–1.05) $P=0.1215$	182 (7.0)	13.3	225 (8.7)	16.7	0.80 (0.66–0.97) $P=0.0240$
Nonfatal MI (excluding silent) + fatal CHD	57 (2.2)	6.9	67 (2.6)	8.1	0.85 (0.60–1.21) $P=0.3556$	86 (3.3)	6.2	117 (4.5)	8.5	0.73 (0.55–0.96) $P=0.0243$
All cause mortality	103 (4.0)	12.3	111 (4.3)	13.3	0.93 (0.71–1.22) $P=0.5959$	207 (8.0)	14.7	228 (8.8)	16.3	0.90 (0.75–1.09) $P=0.2896$
Cardiovascular mortality	44 (1.7)	5.3	46 (1.8)	5.5	0.96 (0.63–1.45) $P=0.8309$	89 (3.4)	6.3	90 (3.5)	6.4	0.98 (0.73–1.32) $P=0.9147$
Fatal and nonfatal stroke	63 (2.4)	7.6	78 (3.0)	9.4	0.81 (0.58–1.13) $P=0.2064$	102 (3.9)	7.4	113 (4.4)	8.2	0.90 (0.69–1.18) $P=0.4369$
Fatal and nonfatal heart failure	25 (1.0)	3.0	26 (1.0)	3.1	0.96 (0.56–1.67) $P=0.8934$	45 (1.7)	3.2	46 (1.8)	3.3	0.97 (0.65–1.47) $P=0.8991$
Tertiary endpoints										
Silent MI	7 (0.3)	0.8	7 (0.3)	0.8	1.01 (0.35–2.87) $P=0.9880$	10 (0.4)	0.7	10 (0.4)	0.7	1.00 (0.41–2.39) $P=0.9921$
Unstable angina	14 (0.5)	1.7	16 (0.6)	1.9	0.88 (0.43–1.80) $P=0.7202$	23 (0.9)	1.6	21 (0.8)	1.5	1.09 (0.60–1.97) $P=0.7709$
Chronic stable angina	21 (0.8)	2.5	34 (1.3)	4.1	0.62 (0.36–1.06) $P=0.0787$	36 (1.4)	2.6	58 (2.2)	4.2	0.61 (0.41–0.93) $P=0.0205$
Peripheral arterial disease	24 (0.9)	2.9	28 (1.1)	3.4	0.86 (0.50–1.48) $P=0.5820$	45 (1.7)	3.2	49 (1.9)	3.5	0.91 (0.61–1.37) $P=0.6575$
Life-threatening arrhythmias	4 (0.2)	0.5	4 (0.2)	0.5	1.01 (0.25–4.02) $P=0.9929$	6 (0.2)	0.4	5 (0.2)	0.4	1.20 (0.37–3.93) $P=0.7637$
Developing diabetes mellitus	167 (8.8)	28.7	144 (7.6)	24.6	1.17 (0.93–1.46) $P=0.1740$	217 (11.5)	22.6	208 (10.9)	21.6	1.05 (0.87–1.27) $P=0.6299$
Developing renal impairment	78 (3.0)	9.5	64 (2.5)	7.8	1.22 (0.88–1.70) $P=0.2289$	134 (5.2)	9.8	114 (4.4)	8.3	1.17 (0.91–1.51) $P=0.2099$

CHD, coronary artery disease; CI, confidence interval; CV, cardiovascular; LLA, lipid-lowering arm; MI, myocardial infarction. *Per 1000 patient–years. **Late reported endpoints that occurred during LLA are included as well.

received travel expenses from or payment for speaking at meetings or funding for research from one or more pharmaceutical companies that market BP-lowering or lipid-lowering drugs, including Pfizer and Servier.

References

1 Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, *et al.*, on behalf of the ASCOT investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003; **361**:1149–1158.

2 Sever P, Dahlöf B, Poulter N, Wedel H, Beevers G, Caulfield M, *et al.*, on behalf of the ASCOT Steering Committee Members. Potential synergy between lipid-lowering and blood-pressure-lowering in the Anglo-Scandinavian Cardiac Outcomes Trial. *Eur Heart J* 2006; **24**:2982–2988.

3 Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, *et al.*, for the ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005; **366**:895–906.

4 Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, *et al.*, the ASCOT Steering Committee Members. The Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm: extended observations 2 years after trial closure. *Euro Heart J* 2008; **29**:499–508.

5 Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, *et al.*, on behalf of the ASCOT investigators. Rationale, design, methods and baseline demography of participants of the Anglo-Scandinavian Cardiac Outcomes Trial. *J Hypertens* 2001; **19**:1139–1147.

6 Pedersen TR, Wilhelmsen L, Faergeman O, Strandberg TE, Thorgeirsson G, Troedsson L, *et al.*, on behalf of the Scandinavian Simvastatin Survival Study Group. Follow-up study of patients randomised in the Scandinavian Simvastatin Survival Study (4S) of cholesterol lowering. *Am J Cardiol* 2000; **86**:257–262.

7 The LIPID Study Group. Long-term effectiveness and safety of pravastatin in 9014 patients with coronary heart disease and average cholesterol concentrations: the LIPID trial follow-up. *Lancet* 2002; **359**:1379–1387.

8 Ford I, Murray H, Packard CJ, Shephard J, Macfarlane PW, Cobbe SM. Long-term follow up of the West of Scotland Coronary Prevention Study. *N Engl J Med* 2007; **357**:1477–1486.

9 Poulter NR, Wedel H, Dahlöf B, Sever PS, Beevers DG, Caulfield M, *et al.*, for the ASCOT Investigators. Role of blood pressure and other variables in the differential cardiovascular event rates noted in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA). *Lancet* 2005; **366**:907–913.

10 Munro E, Patel M, Chan P, Betteridge L, Clunn G, Gallagher K, *et al.* Inhibition of human vascular smooth muscle cell proliferation by lovastatin: the role of isoprenoid intermediates of cholesterol synthesis. *Eur J Clin Invest* 1994; **24**:766–772.

11 Mason RP, Walter MF, Day CA, Jacob RF. Intermolecular differences of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors contribute to distinct pharmacologic and pleiotropic action. *Am J Cardiol* 2005; **96**:11F–23F.