Articles

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

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Summary

Background The lowering of cholesterol concentrations in individuals at high risk of cardiovascular disease improves outcome. No study, however, has assessed benefits of cholesterol lowering in the primary prevention of coronary heart disease (CHD) in hypertensive patients who are not conventionally deemed dyslipidaemic.

Methods Of 19 342 hypertensive patients (aged 40–79 years with at least three other cardiovascular risk factors) randomised to one of two antihypertensive regimens in the Anglo-Scandinavian Cardiac Outcomes Trial, 10 305 with non-fasting total cholesterol concentrations 6·5 mmol/L or less were randomly assigned additional atorvastatin 10 mg or placebo. These patients formed the lipid-lowering arm of the study. We planned follow-up for an average of 5 years, the primary endpoint being non-fatal myocardial infarction and fatal CHD. Data were analysed by intention to treat.

Findings Treatment was stopped after a median follow-up of 3·3 years. By that time, 100 primary events had occurred in the atorvastatin group compared with 154 events in the placebo group (hazard ratio 0·64 [95% CI 0·50–0·83], p=0·0005). This benefit emerged in the first year of follow-up. There was no significant heterogeneity among prespecified subgroups. Fatal and non-fatal stroke (89 atorvastatin *vs* 121 placebo, 0·73 [0·56–0·96], p=0·024), total cardiovascular events (389 *vs* 486, 0·79 [0·69–0·90], p=0·0005), and total coronary events (178 *vs* 247, 0·71 [0·59–0·86], p=0·0005) were also significantly lowered. There were 185 deaths in the atorvastatin group and 212 in the placebo group (0·87 [0·71–1·06], p=0·16). Atorvastatin lowered total serum cholesterol by about 1·3 mmol/L compared with placebo at 12 months, and by 1·1 mmol/L after 3 years of follow-up.

Interpretation The reductions in major cardiovascular events with atorvastatin are large, given the short follow-up time. These findings may have implications for future lipid-lowering guidelines.

Lancet 2003; **361:** 1149–58. Published online April 2, 2003 http://image.thelancet.com/extras/03art3046web.pdf
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Introduction

A series of large randomised endpoint trials[1–10] has established the benefits of statins for the prevention of major fatal and non-fatal cardiovascular events. These data are consistent with experimental,[11] observational[12] and other trial data[13,14] in establishing dyslipidaemia as a major independent risk factor for coronary heart disease (CHD). On the basis of observational data, the causal association between dyslipidaemia and increased rates of cerebrovascular disease is unclear,[15] but trial evidence has shown notable reductions in stroke rates associated with statin use.[16]

Intervention studies have confirmed the cardiovascular benefits of statins in primary prevention,[6,7] secondary prevention,[1–5] and acute coronary syndromes,[17] across a wide age range[2,8,9] and among patients with total cholesterol concentrations much lower than average.[8]

The relation between CHD risk plotted on a doubling scale and serum cholesterol in observational studies is roughly linear, such that a long-term cholesterol concentration lowered by about 1·0 mmol/L corresponds to about 50% less CHD, irrespective of cholesterol concentration.[18] In intervention studies, however, the lowering of cholesterol by 1·0 mmol/L maintained over a period of 5 years corresponds to only about 25–35% fewer CHD events.[19]

Observational data indicate that coexistent risk factors, such as raised blood pressure and dyslipidaemia, generally exert a multiplicative effect on the risk of experiencing cardiovascular events,[20] and subgroup analyses of intervention studies[2–4,7,8] suggest that the relative cardiovascular benefits of lipid lowering are similar among hypertensive and normotensive participants.

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However in ALLHAT,[10] the use of pravastatin versus usual care in patients with mild to moderate hypertension produced only non-significant reductions in cardiovascular events.

Most cardiovascular events and deaths attributable to raised blood pressure[21] and dyslipidaemia[18] occur among patients with blood pressure and lipid concentrations deemed normal. Assessment of the effects of lipid lowering is, therefore, important in patients with reasonably controlled blood pressures and normal or only mildly or moderately raised serum cholesterol concentrations.

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) is an independent, investigator-initiated and investigator-led, multicentre, randomised trial[22] designed to compare two antihypertensive treatment strategies for the prevention of CHD events in more than 18 000 hypertensive patients who have no history of CHD. The study uses the Prospective Randomised Open Blinded Endpoints (PROBE) design.[23] In addition, by way of a two-by-two factorial design, ASCOT has included a double-blind randomised comparison of the cardiovascular effects of atorvastatin, a statin, with placebo among patients who have total cholesterol concentrations of 6·5 mmol/L or less. This lipid-lowering arm of ASCOT forms the subject of this report.

The detailed ASCOT protocol, including study design, organisation, clinical measurements, endpoint definitions, rationale for choice of treatment strategies, power calculations, recruitment rates, and some baseline characteristics has previously been published,[22] and further detailed information is available on the ASCOT website.[24] In summary, the primary objective of the lipid-lowering arm was to assess and compare the long-term effects on the combined endpoint of non-fatal myocardial infarction, including so-called silent myocardial infarction, and fatal CHD of a statin (plus antihypertensive treatment) compared with placebo (plus matched antihypertensive treatment) among patients with total cholesterol concentrations of 6·5 mmol/L or less. The secondary endpoints of the lipid-lowering arm were the primary outcome without silent events, all-cause mortality, total cardiovascular mortality, fatal and non-fatal stroke, fatal and non-fatal heart failure, total coronary endpoints, and total cardiovascular events. Tertiary objectives were also prespecified, including the assessment of the effects of statin on the primary endpoint among several subgroups.

Patients and methods

Patients

Patients eligible for inclusion in the lipid-lowering arm of ASCOT were men and women aged between 40 and 79 years at randomisation, with either untreated hypertension, defined as systolic blood pressure of 160 mm Hg or more, diastolic blood pressure of 100 mm Hg or more, or both, or treated hypertension with systolic blood pressure of 140 mm Hg or more, diastolic blood pressure 90 mm Hg or more, or both. Patients had to be eligible for the blood-pressure-lowering arm, have total cholesterol concentrations of 6·5 mmol/L or lower, and not currently be taking a statin or a fibrate.

In addition, the study population was required to have at least three of the following risk factors for cardiovascular disease: left-ventricular hypertrophy, other specified abnormalities on electrocardiogram, type 2 diabetes, peripheral arterial disease, previous stroke or transient ischaemic attack, male sex, age 55 years or older, microalbuminuria or proteinuria, smoking, ratio of plasma total cholesterol to HDL-cholesterol of 6 or higher, or premature family history of CHD.[22]

Exclusion criteria included previous myocardial infarction, currently treated angina, a cerebrovascular event within the previous 3 months, fasting triglycerides higher than 4·5 mmol/L, heart failure, uncontrolled arrhythmias or any clinically important haematological or biochemical abnormality on routine screening.[22]

Most patients in ASCOT were recruited from family practice. In the Nordic countries, 686 family practices randomised patients, and in the UK and Ireland patients were recruited by 32 regional centres, to which patients were referred by their family physicians. The study conformed to good clinical practice guidelines and was done 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 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 centre. 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 centre. Central data management and analyses, including data cleaning, were coordinated by the Scandinavian coordinating centre.

Trial procedure

Patients were recuited between February, 1998, and May, 2000. Around 4 weeks before randomisation, eligibility criteria were established, and we obtained relevant characteristics of patients and written informed consent.[22] We measured blood pressure by standard procedures and collected non-fasting blood samples.[22] Two central laboratories, one for the UK and Ireland, and one for the Nordic countries, analysed blood samples throughout the trial. Recordings from 12-lead electrocardiography were faxed to the Scandinavian coordinating centre for central assessment at the electrocardiography core centre at Sahlgrenska University Hospital/Östra, Sweden.

After the 4-week run-in period, we confirmed eligibility and consent for randomisation. Meanwhile each patient's family physician or investigator had had the opportunity to consider the need for lipid-lowering treatment in light of the results of the screening lipid values. At the randomisation visit, physical examination was done and we recorded blood pressure and heart rate. Fasting blood samples were obtained for total cholesterol, HDL-cholesterol, triglycerides, and glucose, and we recorded another 12-lead electrocardiogram on each patient.

Blood lipid concentrations before randomisation determined whether patients were eligible for randomisation into the lipid group. Patients with a non-fasting total cholesterol of 6·5 mmol/L or less currently untreated with a statin or fibrate, and whose physicians did not intend to treat them with a statin or fibrate were randomly assigned by computer, with use of minimisation procedures at the appropriate coordinating centre, atorvastatin 10 mg daily or matching placebo. More than 90% of eligible patients were randomised. Any lipid-lowering treatment other than a fibrate or a statin, in use before randomisation could be continued during the study. For patients whose dyslipidaemia was subsequently judged by their physician to require additional lipid-lowering therapy, open-label treatment could be added to trial treatment.

Management of the blood-pressure-lowering arm is detailed elsewhere.[22] In summary, 19 342 patients were randomly assigned one of two antihypertensive regimens. At each follow-up visit antihypertensive drug therapy was titrated to achieve target blood pressures

(<140/90 mm Hg for non-diabetic patients and <130/80 mm Hg for diabetic patients), and information was recorded about adverse events and any new cardiovascular event or procedure, including the cause for any hospital admission .

Investigators submitted all information relevant to any potential endpoints to the Scandinavian coordinating centre for central review of endpoints by the endpoint committee, who were unaware of treatment assignment. Criteria defined a priori for classifying diagnoses were used by the endpoint committee.[24] Certified causes of death were sought and, when available, national registries were used to find information on patients who did not return for the final visit. Confirmed endpoints were reported back to the Scandinavian coordinating centre, which forwarded these data to the data safety monitoring board. Events deemed serious adverse events (but that were not endpoints) were reported immediately to the Scandinavian coordinating centre and to the principal funding source of the trial.

Statistical methods

We estimated that a total sample size of at least 18 000 patients followed up for an average of 5 years was required in the hypertension arm of the ASCOT trial. Of these, we estimated about 9000 patients would be assigned atorvastatin 10 mg or placebo. Assuming a relative effect of 30% (equivalent to a hazard ratio of 0·7) on the primary endpoint (non-fatal myocardial infarction and fatal CHD) of atorvastatin 10 mg compared with placebo, under the intention-to-treat principle for analysis, we calculated power to be more than 90% (β=0·90) for the primary endpoint. This calculation assumed a significance level of 1% (α=0·01) and a yearly endpoint rate in the placebo group of 13 per 1000 for 5 years of treatment.

We compared the time to first primary endpoint event in the atorvastatin and placebo groups on an intention-to-treat basis. All analyses excluded endpoints deemed invalid by the endpoint committee, with statistical censoring enforced at the end of the study on Oct 1, 2002, or death before that date. The date used to indicate a silent myocardial infarction was taken as the mean time between the dates of two electrocardiograms, the first of which showed no myocardial infarction, and the second of which did.

For the main analyses we used the log-rank procedure and the Cox's proportional hazards model to calculate CI. Cumulative incidence curves were generated by the Kaplan-Meier method for all major endpoints in the active and placebo groups.

Early closure of the lipid-lowering arm

The data safety monitoring board decided a priori to use the symmetric Haybittle-Peto statistical boundary (critical value Z=3) as a guideline for deciding to recommend early termination of the trial, which has the added advantage that no material adjustment to the final p values is required.[22]

On Sept 2, 2002, the data safety monitoring board recommended that the lipid-lowering arm of the trial be stopped on the grounds that atorvastatin had resulted in a highly significant reduction in the primary endpoint of CHD events compared with placebo and a significant reduction in the incidence of stroke.

This recommendation was ratified by the steering committee, whereupon all patients in the lipid-lowering arm were recalled by their trial physicians between October and December, 2002, for a final end-of-study visit. All patients in the lipid-lowering arm were offered atorvastatin 10 mg daily to be continued to the end of the antihypertensive arm of the trial, which is anticipated to be in early 2005.

Role of the funding source

ASCOT was conceived, designed, and coordinated by an investigator-led independent steering committee, members of which represented all the countries where the trial was undertaken. The principal funding source had two non-voting members on the steering committee. Data analyses and the preparation of the report were done independently of the principal funding source.

Results

Of the 19 342 patients randomised to one of the two antihypertensive regimens 10 305 were further randomly assigned atorvastatin 10 mg daily or placebo (figure 1). Baseline characteristics of participants in these two randomised groups were well matched (table 1).

Participants were mainly white (95%) and male (81%), with a mean age of 63 years. The average number of the additional cardiovascular risk factors required for inclusion in the trial was 3·7. Baseline blood pressure and lipid subfraction values were identical in the two groups.

The study was stopped prematurely after 33 041 patient-years of follow-up (median 3·3 years). At the close of follow-up for the lipid-lowering arm, complete information was obtained on 10 186 (98·8%) of the 10 305 patients originally randomised (figure 1). Of the remainder, vital status was obtained on all but 17 patients. Compared with placebo at 1 year of follow-up, in the atorvastatin group, total cholesterol and calculated LDL-cholesterol were around 1·3 mmol/L and 1·2 mmol/L lower, respectively

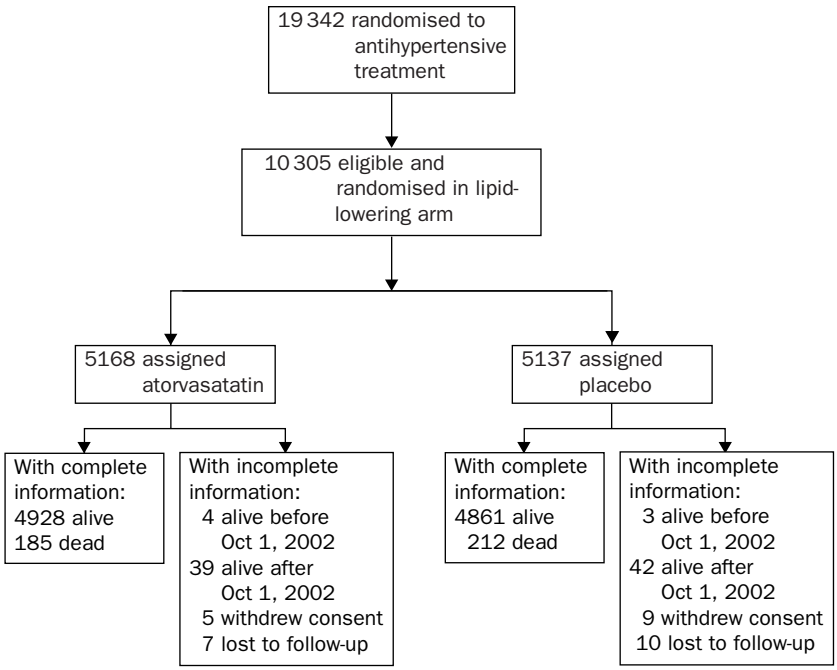


Figure 1: **Trial profile**

	Atorvastatin (n=5168)	Placebo (n=5137)
Patients' characteristics		
Woman	979 (18·9%)	963 (18·7%)
Age (years)		
⩽60·0	1882 (36·4%)	1853 (36·1%)
>60·0	3286 (63·6%)	3284 (63·9%)
Mean (SD)	63·1 (8·5)	63·2 (8·6)
White	4889 (94·6%)	4863 (94·7%)
Current smoker	1718 (33·2%)	1656 (32·2%)
Alcohol consumption (units/week)	8·0 (11·3)	8·2 (12·0)
Systolic blood pressure (mm Hg)	164·2 (17·7)	164·2 (18·0)
Diastolic blood pressure (mm Hg)	95·0 (10·3)	95·0 (10·3)
Heart rate (beats/min)	71·3 (12·8)	71·8 (12·6)
BMI (kg/m^2)	28·6 (4·7)	28·7 (4·6)
Total cholesterol (mmol/L)	5·5 (0·8)	5·5 (0·8)
LDL-cholesterol (mmol/L)	3·4 (0·7)	3·4 (0·7)
HDL-cholesterol (mmol/L)	1·3 (0·4)	1·3 (0·4)
Triglycerides (mmol/L)	1·7 (0·9)	1·6 (0·9)
Glucose (mmol/L)	6·2 (2·1)	6·2 (2·1)
Creatinine (mmol/L)	99·0 (16·9)	99·0 (16·4)
Medical history		
Previous stroke or TIA	485 (9·4%)	516 (10·0%)
Diabetes	1258 (24·3%)	1274 (24·8%)
LVH (on ECG or ECHO)	744 (14·4%)	729 (14·2%)
ECG abnormalities other than LVH	741 (14·3%)	729 (14·2%)
Peripheral vascular disease	261 (5·1%)	253 (4·9%)
Other relevant cardiovascular disease	188 (3·6%)	207 (4·0%)
Mean (SD) number of risk factors	3·7 (0·9)	3·7 (0·9)
Drug treatment		
Previous antihypertensive treatments		
None	1021 (19·8%)	996 (19·4%)
1	2314 (44·8%)	2279 (44·4%)
⩾2	1833 (35·5%)	1862 (36·2%)
Lipid-lowering treatment	41 (0·8%)	51 (1·0%)
Aspirin use	882 (17·1%)	868 (16·9%)

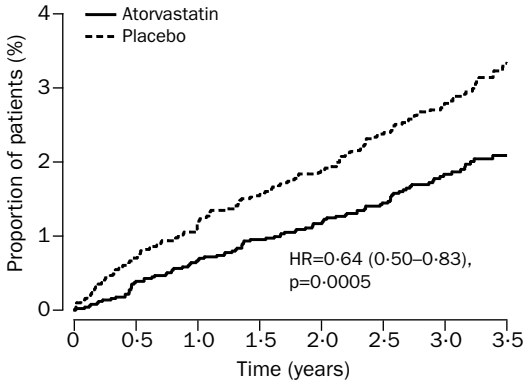
Data not shown as n (%) are mean (SD). BMI=body-mass index. TIA=transient ischaemic attack. LVH=left-ventricular hypertrophy. ECG=electrocardiograph. ECHO=echocardiogram.

Table 1: **Baseline characteristics**

(24% and 35% relative reduction, respectively, table 2). By the end of the study, these differences were 1·0 mmol/L and 1·0 mmol/L (19% and 29%), respectively.

Compared with placebo, atorvastatin reduced triglycerides by about 0·3 mmol/L at 1 year—a relative decrease of 17%, which fell to 14% at study completion. Changes in HDL-cholesterol concentrations were minimal in the two groups. After 3 years of follow-up, 87% of patients originally assigned atorvastatin were still taking a statin, and 9% of those in the placebo group had been prescribed open-label statins.

Blood-pressure control throughout the trial was similar in the patients assigned atorvastatin and placebo, with mean values of 138·3/80·4 mm Hg and 138·4/80·4 mm Hg, respectively, at the end of follow-up.



Number at risk

Placebo	5137	5085	5042	5007	4964	4603	3259	1801
Atorvastatin	5168	5134	5103	5063	5035	4679	3263	1801

Figure 2: **Cumulative incidence for primary endpoint of non-fatal myocardial infarction and fatal coronary heart disease**

The primary endpoint of non-fatal myocardial infarction, including silent myocardial infarction, and fatal CHD was significantly lower by 36% (hazard ratio 0·64 [95% CI 0·50–0·83], p=0·0005) in the atorvastatin group than in the placebo group (figure 2, table 3). To assess the impact of baseline cholesterol on the effect of atorvastatin on the primary endpoint, data were stratified on the basis of the median total cholesterol value among patients who experienced a primary endpoint (⩽5·6 mmol/L *vs* >5·6 mmol/L). The hazard ratios were 0·65 (p=0·015) and 0·63 (p=0·012), respectively in these two groups. Similarly, in a further post-hoc analysis, hazard ratios for patients with baseline total cholesterol concentrations lower than 5·0 mmol/L, 5·0–5·99 mmol/L, and 6·0 mmol/L or higher were 0·63 (p=0·098), 0·62 (p=0·011), and 0·69 (p=0·084), respectively.

There were also significant reductions in four of the seven secondary endpoints, some of which incorporated the primary endpoint: total cardiovascular events including revascularisation procedures (21%); total coronary events (29%); the primary endpoint excluding silent myocardial infarction (38%); and fatal and non-fatal stroke (27%, figures 3 and 4). All-cause mortality was non-significantly reduced by 13%, with non-significantly fewer cardiovascular deaths (figures 3 and 4) and no excess of deaths from cancer (81 assigned statin *vs* 87 assigned placebo) or from other non-cardiovascular causes (111 *vs* 130). Effects of statin on the secondary endpoints of heart failure or cardiovascular mortality, or any tertiary endpoint did not differ significantly from those of placebo, except for chronic stable angina (table 3, figure 5).

	Total cholesterol (mmol/L)				LDL-cholesterol (mmol/L)				HDL-cholesterol (mmol/L)				Triglycerides (mmol/L)			
	Atorvastatin		Placebo		Atorvastatin		Placebo		Atorvastatin		Placebo		Atorvastatin		Placebo	
	n	Conc	n	Conc	n	Conc	n	Conc	n	Conc	n	Conc	n	Conc	n	Conc
Baseline	5168	5·48 (0·78)	5137	5·48 (0·78)	4669	3·44 (0·72)	4627	3·44 (0·72)	5168	1·31 (0·37)	5137	1·31 (0·36)	4733	1·66 (0·92)	4687	1·65 (0·87)
6 months	4802	4·13 (0·80)	4744	5·47 (0·84)	4491	2·21 (0·67)	4395	3·45 (0·75)	4799	1·31 (0·36)	4744	1·29 (0·35)	4527	1·37 (0·81)	4477	1·68 (0·96)
1 year	4736	4·16 (0·82)	4668	5·45 (0·85)	4458	2·25 (0·69)	4384	3·45 (0·76)	4736	1·30 (0·37)	4668	1·28 (0·35)	4496	1·37 (0·85)	4466	1·65 (0·99)
2 years	4659	4·14 (0·81)	4586	5·35 (0·90)	4486	2·24 (0·68)	4386	3·37 (0·78)	4659	1·30 (0·37)	4586	1·27 (0·36)	4522	1·36 (0·78)	4440	1·60 (0·88)
3 years	3880	4·18 (0·85)	3865	5·27 (0·90)	3748	2·28 (0·71)	3713	3·30 (0·80)	3880	1·30 (0·37)	3865	1·28 (0·36)	3775	1·32 (0·76)	3764	1·54 (0·94)
End of follow-up	4415	4·2 1 (0·85)	4348	5·21 (0·91)	4256	2·32 (0·72)	4170	3·27 (0·81)	4415	1·31 (0·37)	4348	1·29 (0·37)	4277	1·29 (0·73)	4215	1·49 (0·87)

Conc=concentration.

Table 2: **Mean (SD) plasma concentrations by visit and treatment**

	Atorvastatin		Placebo		Unadjusted hazard ratio (95% CI)	p
	n (%)	Rate*	n (%)	Rate*		
Primary endpoint†						
Non-fatal MI‡ plus fatal CHD	100 (1·9)	6·0	154 (3·0)	9·4	0·64 (0·50–0·83)	0·0005
Secondary endpoints†						
Total cardiovascular events and procedures	389 (7·5)	24·1	486 (9·5)	30·6	0·79 (0·69–0·90)	0·0005
Total coronary events	178 (3·4)	10·8	247 (4·8)	15·2	0·71 (0·59–0·86)	0·0005
Non-fatal MI§ plus fatal CHD	86 (1·7)	5·2	137 (2·7)	8·3	0·62 (0·47–0·81)	0·0005
All-cause mortality	185 (3·6)	11·1	212 (4·1)	12·8	0·87 (0·71–1·06)	0·1649
Cardiovascular mortality	74 (1·4)	4·4	82 (1·6)	4·9	0·90 (0·66–1·23)	0·5066
Fatal and non-fatal stroke	89 (1·7)	5·4	121 (2·4)	7·4	0·73 (0·56–0·96)	0·0236
Fatal and non-fatal heart failure	41 (0·8)	2·5	36 (0·7)	2·2	1·13 (0·73–1·78)	0·5794
Tertiary endpoints†						
Silent MI	14 (0·3)	0·8	17 (0·3)	1·0	0·82 (0·40–1·66)	0·5813
Unstable angina	21 (0·4)	1·3	24 (0·5)	1·4	0·87 (0·49–1·57)	0·6447
Chronic stable angina	33 (0·6)	2·0	56 (1·1)	3·4	0·59 (0·38–0·90)	0·0135
Peripheral arterial disease	42 (0·8)	2·5	41 (0·8)	2·5	1·02 (0·66–1·57)	0·9254
Life-threatening arrhythmias	10 (0·2)	0·6	3 (0·1)	0·2	3·31 (0·91–12·01)	0·0540
Development of diabetes mellitus	154 (3·0)	9·4	134 (2·6)	8·2	1·15 (0·91–1·44)	0·2493
Development of renal impairment	31 (0·6)	1·9	24 (0·5)	1·4	1·29 (0·76–2·19)	0·3513

MI=myocardial infarction. *Per 1000 patient-years. †Full definition of endpoints provided in reference 24. ‡Includes silent MI. §Excludes silent MI.

Table 3: **Hazard ratio of atorvastatin treatment on primary, secondary, and tertiary endpoints**

The proportional effect of atorvastatin on the primary endpoint did not differ significantly in any prespecified subgroup from that noted overall, although the benefit was not significant in six subgroups, including patients with diabetes, and no benefit was apparent among women (table 4, figure 5). However, we noted no significant interaction between sex and the impact of statin on the primary endpoint, and total cardiovascular and total coronary events were reduced by 20% (p=0·17) and 14% (p=0·56), respectively, among women.

The number of serious adverse events and rates of liver-enzyme abnormalities did not differ between patients assigned atorvastatin or placebo. One non-fatal case of rhabdomyolysis was reported in a man receiving atorvastatin who had had a very high alcohol intake and a recent febrile illness.

Discussion

Our findings in the lipid-lowering arm of ASCOT show that in hypertensive patients, who on average were at moderate risk of developing cardiovascular events, cholesterol lowering with atorvastatin 10 mg conferred a 36% reduction in fatal CHD and non-fatal myocardial infarction compared with placebo. This effect seemed to emerge early, such that the data safety monitoring board recommended early termination of the trial. This decision was also affected by the significant reductions in other major cardiovascular events.

Our results confirm and extend observations from two previous primary prevention trials of the effects of statin treatment on coronary and cerebrovascular events.[6,7] After 1 year of follow-up in ASCOT, total cholesterol and LDL-cholesterol among patients taking atorvastatin were 24% and 35% lower, respectively, than among those taking placebo. By comparison, in an on-treatment analysis of WOSCOPS,[6] 40 mg pravastatin lowered total cholesterol and LDL-cholesterol by 20% and 26%, respectively, which was associated with a reduction in non-fatal myocardial infarction and fatal CHD of 31% after 4·9 years' follow-up. In the AFCAPS/TexCAPS trial,[7] 1-year placebo-corrected reductions in total cholesterol and LDL-cholesterol of 18% and 25% were associated with a 40% reduction in the same endpoint after 5·2 years of follow-up.

The dose of atorvastatin was not titrated in ASCOT from the starting dose of 10 mg daily, although higher doses would have resulted in greater reductions in total cholesterol and LDL-cholesterol concentrations.[4] On the basis of currently available evidence,[10,19] it seems likely that such greater reductions in cholesterol might have produced even larger reductions in cardiovascular events. Had the study continued for an average follow-up of 5 years, as originally planned, the reduction in fatal and non-fatal

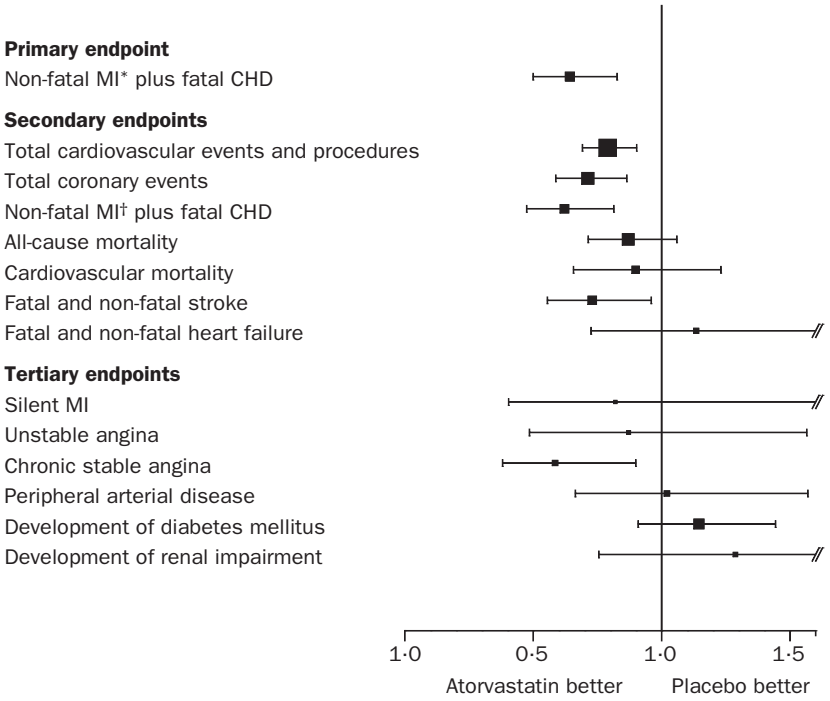


Figure 3: **Effects of atorvastatin and placebo on primary, secondary, and tertiary endpoints**
Area of squares is proportional to amount of statistical information. Point estimates of hazard ratios are given with 95% CI. MI=myocardial infarction. *Includes silent MI. †Excludes silent MI.

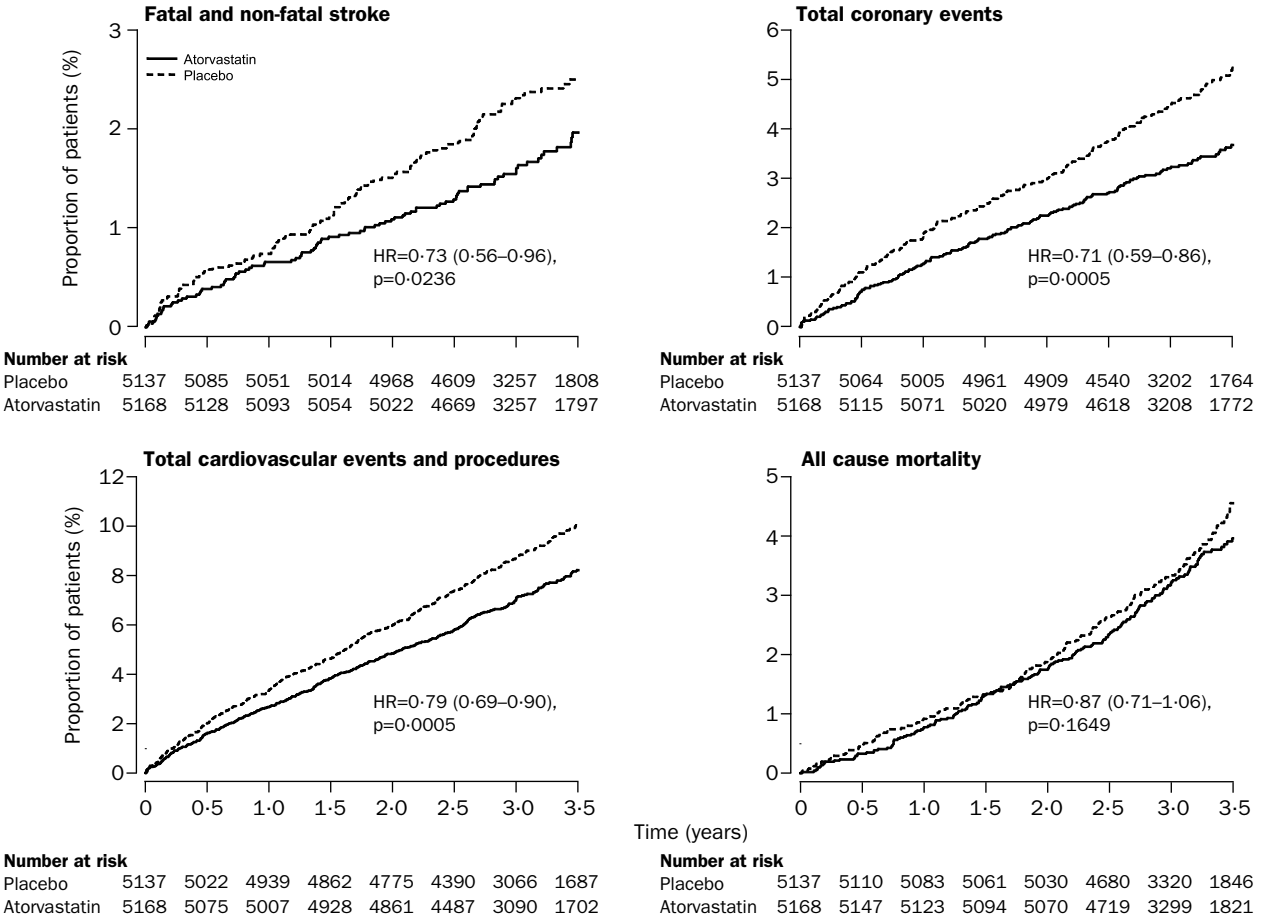


Figure 4: **Cumulative incidence for fatal and non-fatal stroke, total coronary events, total cardiovascular events, and all-cause mortality**

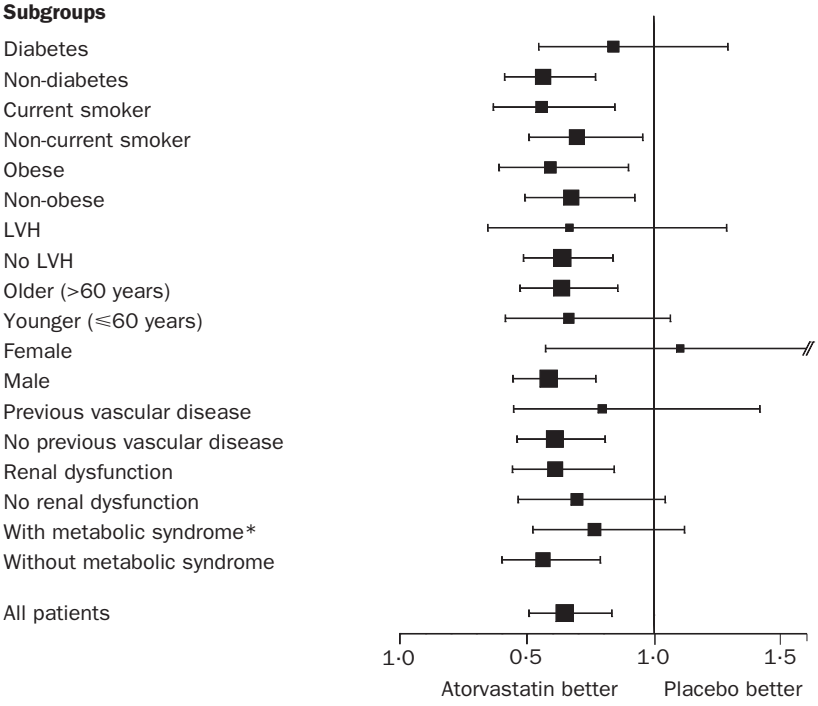


Figure 5: **Effects of atorvastatin and placebo on the primary endpoint in prespecified subgroups**

Area of squares is proportional to amount of statistical information. Point estimates of hazard ratios are given with 95% CI. LVH=left-ventricular hypertrophy. *Definition of metabolic syndrome provided in reference 24.

CHD events may have approached 50%, which, based on observational studies, might be expected from a 1·0 mmol/L reduction in serum cholesterol.[18]

Despite the relatively weak association between serum total cholesterol concentrations and stroke risk derived from observational data,[15] previous randomised trials of statin use have shown, on average, significant reductions in stroke events in both primary and secondary prevention of about 15–30%.[16] Hence the 27% reduction in stroke incidence we noted is easily in keeping with the benefits of statins reported in previous studies. In the PROSPER trial[9] of pravastatin among patients aged 70 years and older, no reduction in strokes was noted. However in a post-hoc analysis of the ASCOT data, stroke prevention was similar among 2416 patients who were older than 70 years and the remainder aged 70 years or younger (31 *vs* 24% reduction).

We noted no significant adverse effects on any of the prespecified secondary or tertiary endpoints[22] in association with the use of atorvastatin. The rates of life-threatening

	Atorvastatin		Placebo		Unadjusted hazard ratio (95% CI)	p
	n (%)	Rate*	n (%)	Rate*		
Diabetes (n=2532)	38 (3·0%)	9·6	46 (3·6%)	11·4	0·84 (0·55-1·29)	0·4253
Non-diabetes (n=7773)	62 (1·6%)	4·9	108 (2·8%)	8·7	0·56 (0·41-0·77)	0·0003
Current smoker (n=3374)	35 (2·0%)	6·2	60 (3·6%)	11·2	0·56 (0·37-0·85)	0·0053
Non-current smoker (n=6931)	65 (1·9%)	5·9	94 (2·7%)	8·5	0·70 (0·51-0·96)	0·0243
Obese (n=3425)†	35 (2·0%)	6·4	59 (3·4%)	10·8	0·59 (0·39-0·90)	0·0130
Non-obese (n=6880)	65 (1·9%)	5·8	95 (2·8%)	8·6	0·67 (0·49-0·92)	0·0137
LVH on ECG or ECHO (n=1473)	15 (2·0%)	6·2	22 (3·0%)	9·3	0·67 (0·35-1·29)	0·2236
No LVH on ECG or ECHO (n=8832)	85 (1·9%)	6·0	132 (3·0%)	9·4	0·64 (0·49-0·84)	0·0011
Older (>60 years, n=6570)	71 (2·2%)	6·8	111 (3·4%)	10·7	0·64 (0·47-0·86)	0·0027
Younger (⩽60 years, n=3735)	29 (1·5%)	4·7	43 (2·3%)	7·1	0·66 (0·41-1·06)	0·0869
Female (n=1942)	19 (1·9%)	5·9	17 (1·8%)	5·3	1·10 (0·57-2·12)	0·7692
Male (n=8363)	81 (1·9%)	6·1	137 (3·3%)	10·3	0·59 (0·44-0·77)	0·0001
Previous vascular disease (n=1471)	21 (2·9%)	9·0	26 (3·5%)	11·2	0·80 (0·45-1·42)	0·4376
No previous vascular disease (n=8834)	79 (1·8%)	5·5	128 (2·9%)	9·1	0·61 (0·46-0·81)	0·0005
Renal dysfunction (n=6517)	60 (1·8%)	5·7	97 (3·0%)	9·3	0·61 (0·44-0·84)	0·0025
No renal dysfunction (n=3788)	40 (2·1%)	6·6	57 (3·0%)	9·5	0·70 (0·47-1·04)	0·0783
With metabolic syndrome (n=3926)‡	47 (2·4%)	7·6	61 (3·1%)	9·9	0·77 (0·52-1·12)	0·1675
Without metabolic syndrome (n=6379)	53 (1·7%)	5·1	93 (2·9%)	9·1	0·56 (0·40-0·79)	0·0007

LVH=left-vetnricular hypertrophy; ECG=electrocardiography; ECHO=echocardiography. *Per 1000 patient-years. †Body-mass index >30 kg/m^2. ‡Definition of metabolic syndrome provided in reference 24.

Table 4: **Hazard ratio of atorvastatin treatment on primary endpoint by subgroup**

arrhythmias, heart failure, renal impairment, and new-onset diabetes were, however, marginally increased among patients receiving atorvastatin, but the differences were based on small numbers of events and are probably the result of chance variation. For example, of the 13 patients who developed a life-threatening arrhythmia in ASCOT, ten were assigned atorvastatin and three placebo, but only six and two patients were taking their respective treatments in the 6 months before these events occurred. In the GREACE trial[4] the use of atorvastatin at a mean dose of 24 mg significantly reduced the heart-failure rate by 50% among patients with established CHD. In the WOSCOPS trial,[25] the rate of new diabetes was reduced by 30% compared with placebo over 4·9 years of follow-up. Furthermore, the rate of development of serious arrhythmias, heart failure, or new diabetes did not differ among the 20 000 high-risk patients assigned simvastatin or placebo in the Heart Protection Study.[8]

The impact of atorvastatin on the primary endpoint of ASCOT was assessed in 18 prespecified subgroups.[22] Given theoretical potential benefits of lipid lowering among patients with diabetes, it was, at first sight, surprising that the relative reduction was less for the primary endpoint among patients with diabetes than among those without. However, the absolute number of events among patients with diabetes was only 84. This finding may well, therefore, reflect inadequate power, especially given the shortened follow-up period, possibly compounded to a small extent by the fact that the drop-in rates of statin use among patients with diabetes assigned placebo was 14% compared with 8% in those without diabetes.

The apparent lack of significant benefit of atorvastatin on the primary endpoint among women may reflect the small number of events they experienced (36 occurrences of the primary endpoint) and these results highlight a potential shortcoming of ASCOT which, in common with most previous large statin studies, included mainly white male participants.

The PROSPER trial reported a tendency to increased cancer diagnoses among patients taking pravastatin.[9] However in neither the Heart Protection Study[8] nor a meta-analysis of earlier statin trials was an adverse effect on non-cardiovascular mortality noted,[26] and in the ASCOT lipid-lowering arm we saw similar numbers with fatal cancer in the two randomised groups. The safety of atorvastatin was further reaffirmed by the lack of differences in raised liver enzymes compared with placebo. Although one case of rhabdomyolysis was reported in the atorvastatin group, the event was potentially confounded by other disorders.

ALLHAT is the only trial other than ASCOT that has been done specifically among hypertensive patients.[10] In that study, the effects of different antihypertensive drugs were compared on fatal and non-fatal CHD events, and a subgroup of 10 355 patients were also randomly assigned pravastatin 40 mg or usual care. The baseline demographics of patients included in the lipid-lowering arm of ALLHAT differ substantially from those of patients in ASCOT, in that ALLHAT included a slightly older cohort, of whom about 14% had a history of CHD, and a notably greater proportion of women and non-white people.

No significant benefits in terms of all cause mortality or coronary and stroke events were apparent with statin use in ALLHAT. However, the potential benefits of pravastatin were compromised by substantial use of statins in the usual-care group, leading to differences in total cholesterol and LDL-cholesterol of only 9% and 17%, respectively, being achieved between the two groups at the end of the trial. By contrast, in ASCOT, only 9% of patients in the placebo group were using statins by 3 years of follow-up, which can probably be explained by the lipid concentrations and risk profiles of patients recruited into the study, being lower than those for most patients for whom statin prescription is currently recommended.[27] In addition, only 13% of patients assigned atorvastatin dropped out of this treatment group at 3 years, thus maintaining the integrity and power of the original study design. Therefore, the apparently disappointing clinical benefits noted in ALLHAT seem merely to be compatible with the dose-response effect on cardiovascular events associated with achieved LDL-cholesterol reduction, and are in keeping with other trial data.[10]

Before publication of the ALLHAT results, analyses of the hypertensive subgroups included in earlier statin trials[2–4,7,8] showed that the relative benefits of lipid lowering among hypertensive patients could be expected to be at least as large as those noted among normotensive patients. These expected benefits have now been confirmed in the ASCOT study.

The relative magnitude of the benefits due to lipid-lowering in the ASCOT study of hypertensive patients with lipid concentrations that were average or lower than average are notably larger for CHD prevention than are the effects

of blood-pressure lowering in randomised placebo-controlled trials, whereas the relative reduction in stroke seems somewhat smaller.[28] The reduction in all-cause mortality in ASCOT (13%) was very similar to that seen in the blood-pressure-lowering trials (12%).[28] The overall benefits in terms of preventing cardiovascular events attributable to one strategy or another in a given population is, however, dependent on the demography of that population and on the rate of CHD and stroke events. For example, in northern Europe and the USA, where CHD events are more common than stroke, greater overall benefits are likely to accrue from lipid lowering than from blood-pressure lowering. However our results show the benefits of statin treatment are additional to those of good blood-pressure control. Consequently, more serious consideration now needs to be given to the most resource-effective way of providing both of these risk factor intervention strategies to hypertensive patients to prevent fatal and non-fatal cardiovascular events.

Current guidelines for the use of lipid-lowering agents vary strikingly around the world.[27,29] Recommendations relating to treatment thresholds have been driven more by cost considerations than by trial evidence of treatment benefits.[30] Our findings add further support to the concept that treatment strategies to reduce cardiovascular disease should depend on global assessment of risk rather than on numerical values of individual risk factors, and that benefits of lipid lowering are apparent across the whole range of serum cholesterol concentrations. The coronary event rate in the placebo group of the AFCAPS/TexCAPS trial[7] was equivalent to a 10-year CHD event rate of 6%. This rate is significantly lower than any treatment threshold currently recommended for lipid-lowering drugs in the context of primary prevention. The placebo group in ASCOT experienced the equivalent of a 9·4% 10-year coronary event rate (non-fatal myocardial infarction and fatal CHD) and a 7·4% 10-year fatal and non-fatal stroke event rate yielding a combined first stroke or CHD event rate in this population of about 16·5%. However, risk estimation used to decide whether to treat such patients should include measurement of blood pressure before treatment.[31] After 3 years of follow-up, mean blood pressure in all ASCOT recruits had fallen by around 25/14 mm Hg (unpublished data) and, therefore, had they not received aggressive blood-pressure lowering treatment, the cardiovascular risk experienced in the placebo group would have been in excess of 20% over 10 years (roughly equivalent to a 15%, 10-year coronary risk), which is increasingly accepted as a reasonable treatment threshold for lipid lowering.[29,31] The ASCOT data, therefore, reinforce the trend to adopt lower lipid-lowering treatment thresholds at least among patients with hypertension.

There has been much speculation as to whether statins reduce blood pressure,[32] a topic that is particularly relevant to patients such as those included in ASCOT. However, no firm conclusions can be drawn from the ASCOT database since, by design, antihypertensive medication was titrated upwards based on achieved blood pressure, thereby potentially masking any impact of statin treatment on blood pressure.

The possible interaction of statin treatment with either of the blood pressure-lowering regimens used in ASCOT is a tertiary objective of the trial. This interaction will be assessed when the blood-pressure-lowering arm of the trial comes to an end.

The impact of our assessment of the benefits of atorvastatin in hypertensive patients with other cardiovascular risk factors on the use of open-label lipid-lowering treatment in the ASCOT cohort overall and among the hypertensive population in general remains to be seen. Reaction to the 36% relative reduction in the primary endpoint and the other benefits observed in ASCOT may need to be tempered by consideration of the absolute risk reduction of a coronary event of 3·4 per 1000 patient-years. Furthermore there are clearly financial implications of statin use among all hypertensive patients with absolute levels of cardiovascular risk as low as those included in ASCOT.

Our findings in the ASCOT lipid-lowering arm show important and large relative reductions in cardiovascular events associated with the use of atorvastatin 10 mg among a population of hypertensive patients who on average were, despite other risk factors, at only moderate cardiovascular risk, and who would not conventionally have been deemed dyslipidaemic. We hope our results will help to close the gap between what is recommended[29,31] and the current suboptimal use of lipid-lowering treatment in clinical practice.[33]

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Conflict of interest statement

DGB, NRP, RC, PS, MC, JM, SEK, AK, JÖ, BD, MSN, EO'B, GMcI, and HW have served as consultants to and received travel expenses, payment for speaking at meetings, or funding for research from pharmaceutical companies marketing lipid-lowering drugs, including Merck Sharp and Dohme, Bristol-Myers Squibb, Astra-Zeneca, Sanofi, Schering, Servier, Pharmacia, Bayer, Novartis, Aventis Pfizer. DGB, NRP, RC, PS, MC, JM, SEK, AK, JÖ, BD, MSN, EO'B, GMcI, and HW received financial support from Pfizer to cover administrative and staffing costs of ASCOT, and travel, accommodation expenses or both incurred by attending relevant meetings.

Acknowledgments

We thank all trial participants, physicians, nurses, and practices in the participating countries for their important contribution to the study. The study was supported by the principal funding source, Pfizer, New York, NY, USA. Funding was also provided by Servier Research Group, Paris, France, and Leo Laboratories, Copenhagen, Denmark. We thank Yvonne Green and Sandra Johnson for their help in typing and collating the report.

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