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CLINICAL RESEARCH
Prevention and epidemiology

The Anglo-Scandinavian Cardiac Outcomes Trial lipid lowering arm: extended observations 2 years after trial closure

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Aims To determine the cardiovascular benefits in those originally assigned atorvastatin in the Anglo-Scandinavian Cardiac Outcomes Trial—2.2 years after closure of the lipid-lowering arm of the trial (ASCOT-LLA).

Methods and results The Blood Pressure Lowering Arm of the ASCOT trial (ASCOT-BPLA) compared two different antihypertensive treatment strategies on cardiovascular outcomes. ASCOT-LLA was a double-blind placebo-controlled trial of atorvastatin in those enrolled into ASCOT-BPLA with total cholesterol concentrations at baseline of $\leq$6.5 mmol/L.

A total of 19 342 hypertensive patients were enrolled in ASCOT-BPLA and 10 305 were further assigned either atorvastatin, 10 mg, or placebo. ASCOT-LLA was stopped prematurely after a median 3.3 years follow-up because of substantial cardiovascular benefits in those assigned atorvastatin. Trial physicians were invited to offer atorvastatin to all ASCOT-LLA patients until the end of ASCOT-BPLA.

The primary outcome of ASCOT-LLA was combined fatal coronary heart disease (CHD) or non-fatal myocardial infarction.

Secondary outcomes included all coronary events, all cardiovascular events and procedures, fatal and non-fatal stroke, cardiovascular mortality, all cause mortality, development of chronic stable angina, heart failure, and peripheral arterial disease.

By the end of ASCOT-LLA, there was a 36% relative risk reduction in primary events ($n = 254$) in favour of atorvastatin [hazard ratio (HR) 0.64, 95% CI: 0.50–0.83, $P = 0.0005$]. At the end of ASCOT-BPLA, 2.2 years later, despite extensive crossovers from and to statin usage, the relative risk reduction in primary events ($n = 412$) among those originally assigned atorvastatin remained at 36% (HR 0.64, 95% CI: 0.53–0.78, $P = 0.0001$). For almost all other endpoints, risk reductions also remained essentially unchanged and in the case of all cause mortality, the risk reduction of 15% now achieved borderline statistical significance ($P = 0.02$).

Conclusion Carry-over benefits from those originally assigned atorvastatin but no longer taking the drug may account for unchanged relative risk reductions in most cardiovascular endpoints observed 2 years after ASCOT-LLA closed.

Keywords Coronary and stroke events • Atorvastatin • ASCOT-LLA • Extension

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Introduction

In 2003, we reported the outcome of the lipid-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-LLA),[1] a placebo-controlled randomized trial of the effects of atorvastatin 10 mg daily in the primary prevention of coronary heart disease (CHD) in hypertensive subjects who had a total cholesterol level $\leq$6.5 mmol/L. The trial was stopped prematurely after a median 3.3 years follow-up due to substantial benefits of atorvastatin on the primary endpoint of non-fatal myocardial infarction and fatal CHD, together with significant reductions in several other cardiovascular endpoints. ASCOT-LLA was part of a factorially designed trial in which hypertensive patients with no prior history of CHD were initially randomized to one of two antihypertensive treatment strategies (a beta-blocker adding a thiazide diuretic as required or a dihydropyridine calcium channel blocker (CCB), adding an angiotensin converting enzyme inhibitor as required[2,3] (ASCOT-BPLA).

After the termination of LLA, subjects continued in BPLA for a further 2.2 years when the trial was stopped on the recommendation of the Data Safety Monitoring Board (DSMB), owing to substantial mortality benefits in favour of the CCB-based treatment strategy. The present report evaluates the cardiovascular outcomes of those subjects originally assigned either atorvastatin or placebo in the LLA and followed-up to the end of BPLA (5.5 years).

Methods

The detailed ASCOT protocol, including study design, organization, clinical measurements, power calculations, recruitment rates, and baseline characteristics has been published,[2] and further detailed information is available on the ASCOT website (www.ascotstudy.org). In summary, the trial was an independent, investigator-led, multicentre study with a prospective, randomized parallel group design incorporating by way of a 2 $\times$ 2 factorial approach, a comparison of two antihypertensive treatment regimens and in a large subgroup, atorvastatin with placebo. Patients eligible for inclusion into the LLA had to be eligible for the blood pressure-lowering arm (BPLA) and have total cholesterol concentrations of 6.5 mmol/L or less, and not currently taking a statin or a fibrate. This population consisted of men and women aged between 40 and 79 years at randomization, with either untreated hypertension defined as systolic blood pressure of 160 mmHg or more, diastolic blood pressure 100 mmHg or more, or both, or treated hypertension with systolic blood pressure 140 mmHg or more, diastolic blood pressure 90 mmHg or more, or both.

Trial participants were also required to have at least three of the following risk factors for cardiovascular disease: male sex, aged 55 years or older, smoking, left ventricular hypertrophy, other specified abnormalities on electrocardiogram, type II diabetes, peripheral arterial disease, previous stroke or transient ischaemic attack, microalbuminuria or proteinuria, ratio of plasma total cholesterol to HDL-cholesterol concentration of 6 or higher or family history of premature CHD. Exclusion criteria included (among others): previous myocardial infarction; currently treated angina; a cerebrovascular event within the previous 3 months; fasting triglycerides $\geq$4.5 mmol/L; heart failure; uncontrolled arrhythmias; or any clinically important haematological or biochemical abnormality on routine screening.

The study conformed to good clinical practice guidelines[4] and was carried out in accordance with the Declaration of Helsinki.[5] 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 (Sweden, Denmark, Iceland, Norway, and Finland).

Patients were recruited between February 1998 and May 2000. Eligibility criteria were established and written informed consent was obtained about 4 weeks before randomization. Blood pressure was measured using standard procedures; non-fasting blood samples were collected and 12-lead electrocardiograms were assessed centrally. After the 4-week run-in period, eligible recruits were randomized, and they underwent a physical examination; blood pressure, heart rate, and 12-lead electrocardiogram were again recorded. Fasting blood samples were obtained for total cholesterol, HDL cholesterol, triglyceride, and glucose levels.

Management of the BPLA is detailed elsewhere.[2] Patients were randomly assigned one of two antihypertensive regimens. Of the 19 342 patients randomized to one of the two antihypertensive regimens, 10 305 with a non-fasting cholesterol concentration $\leq$6.5 mmol/L at the initial screening visit, who were untreated with a statin or fibrate were further randomly assigned, by computer (using minimization procedures), to receive atorvastatin 10 mg daily or matching placebo. Baseline characteristics of participants in these two randomized groups were well matched and have previously been reported.[1–3] At each follow-up visit, antihypertensive drug therapy was titrated to achieve target blood pressures ($<$140/90 mmHg for non-diabetic patients and $<$130/80 mmHg for diabetic patients); information was recorded about adverse events and any new cardiovascular events or procedures, including the cause for any hospital admission. Information on potential endpoints was reviewed by a blinded endpoint committee.

Early closure of the lipid-lowering arm

The DSMB 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.[6]

On 2 September 2002, the DSMB recommended that the LLA of the trial be stopped on the grounds that atorvastatin had resulted in a highly significant reduction in the primary endpoint compared with placebo and a significant reduction in the incidence of stroke.[1]

This recommendation was ratified by the Steering Committee, whereupon all patients in LLA were recalled between October and December 2002, for a final end-of-study visit. Trial physicians were invited to offer atorvastatin 10 mg daily to all patients in LLA until the end of BPLA, which was stopped between December 2004 and June 2005 on the recommendation of the DSMB. Neither trial physicians nor patients were aware of whether they had formerly been assigned atorvastatin or placebo.

Statistical methods

We estimated that a total of at least 18 000 patients followed-up for an average of 5 years were required in ASCOT-BPLA. Of these, we estimated about 9,000 patients would be assigned atorvastatin 10 mg or placebo. In LLA, we calculated power to be $\geq$90% ($\beta = 0.10$) to detect a relative effect of 30% on the primary endpoint of atorvastatin 10 mg compared with placebo. This calculation assumed a significance level of 1% ($\alpha = 0.01$) and a yearly endpoint rate in the placebo group of 13 per 1000 for 5 years of treatment. For the extension of 2.2 years after ASCOT-LLA close-out and with 150 more primary endpoints,

statistical power calculation showed that the study had 83% power with a significance level of 5% for a reduction of 36% in hazard. 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 or at death. Analysis of percentage time on statin was restricted to all those subjects who had a date when the patient was last seen or known alive in the study (disposition date), which fell 6 months after the lipid close-out visit or later. Time on statin was calculated as the number of days on statin between 6 months after the lipid close-out and the disposition date or 6 months after 1 October 2002 and the disposition date for those with no lipid close-out visit.

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.

The intent to treat rule was strictly applied. Patients were analysed according to their randomly allocated treatment group, regardless of later treatment. Thus, a non-compliant patient belonged to the initial randomized group. A patient who had switched drug was analysed as if he/she belonged to the original randomized group. A patient who was lost to follow-up is censored at the time of last visit.

For the main analyses, we used log-rank procedures and Cox's proportional hazards model to calculate confidence intervals.[7] The proportionality of hazard ratio (HR) by time was investigated by using an interaction term of time and the indicator of treatment. No such interactions in time or between periods were found for primary and secondary endpoints. For tertiary endpoints, however, the HR seemed to change in the extended period. Thus, for tertiary endpoints, the HRs should be interpreted as mean estimates over the periods.

Cumulative incidence curves were generated by the Kaplan–Meier method for all major endpoints in the active and placebo groups.

Results

The baseline characteristics of trial participants randomized to either atorvastatin 10 mg or placebo were well matched (*Table 1*). Participants were mainly white (95%) and male (81%), with a mean age of 63 years. Baseline blood pressure and lipid subfraction values were identical in the two groups.

LLA was stopped prematurely after 33 041 patient-years of follow-up (median 3.3 years) when complete information was obtained on 10 186 (98.8%) of the 10 305 patients originally randomized. Of the remainder, vital status was obtained on all but 17 patients.

Following closure of LLA and by the end of BPLA, complete information was available on 10 075 patients originally randomized (*Figure 1*). However, between the closure of LLA and the subsequent closure of BPLA there was substantial drop-in and drop-out 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% were taking atorvastatin (*Table 2*). A small percentage of additional patients were receiving other statins (4 and 7%, respectively—*Table 2*). In a further analysis estimating extensive statin use as taking statins >90% of follow-up time, and minimal statin use as <10% of follow-up time, of those originally assigned atorvastatin 50% continued to use statins extensively and 29% minimally. Of those originally assigned placebo, the figures were 49 and 32%, respectively.

Table 1 Baseline characteristics

	Atorvastatin, *n* = 5168	Placebo, *n* = 5137
Demographics and clinical 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 (unit/week)	8.0 (11.3)	8.2 (12.0)
Systolic blood pressure (mmHg)	164.2 (17.7)	164.2 (18.0)
Diastolic blood pressure (mmHg)	95.0 (10.3)	95.0 (10.3)
Heart rate (b.p.m.)	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/transient ischaemic attack (TIA)	485 (9.4%)	516 (10.0%)
Diabetes[a]	1370 (26.5%)	1370 (26.7%)
leftventricular hypertrophy (LVH) (according to ECG or ECHO)[a]	1194 (23.1%)	1192 (23.2%)
ECG abnormalities other than LVH[a]	1206 (23.3%)	1177 (22.9%)
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 therapy		
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 therapy	41 (0.8%)	52 (1.0%)
Aspirin use	929 (18.0%)	902 (17.6%)

[a]Includes information from investigator, ECG and glucose values.

Compared with placebo at the end of LLA (3.3 years), total cholesterol and LDL-cholesterol concentrations among those allocated were around 1.0 mmol/L lower than those allocated placebo (*Table 3*, *Figure 2A*). However, by the end of BPLA, total and LDL-cholesterol concentrations had lowered in those formerly assigned placebo and had slightly increased in those formerly assigned atorvastatin, such that these values were almost identical in the two groups (*Table 3*, *Figures 2A* and *B*).

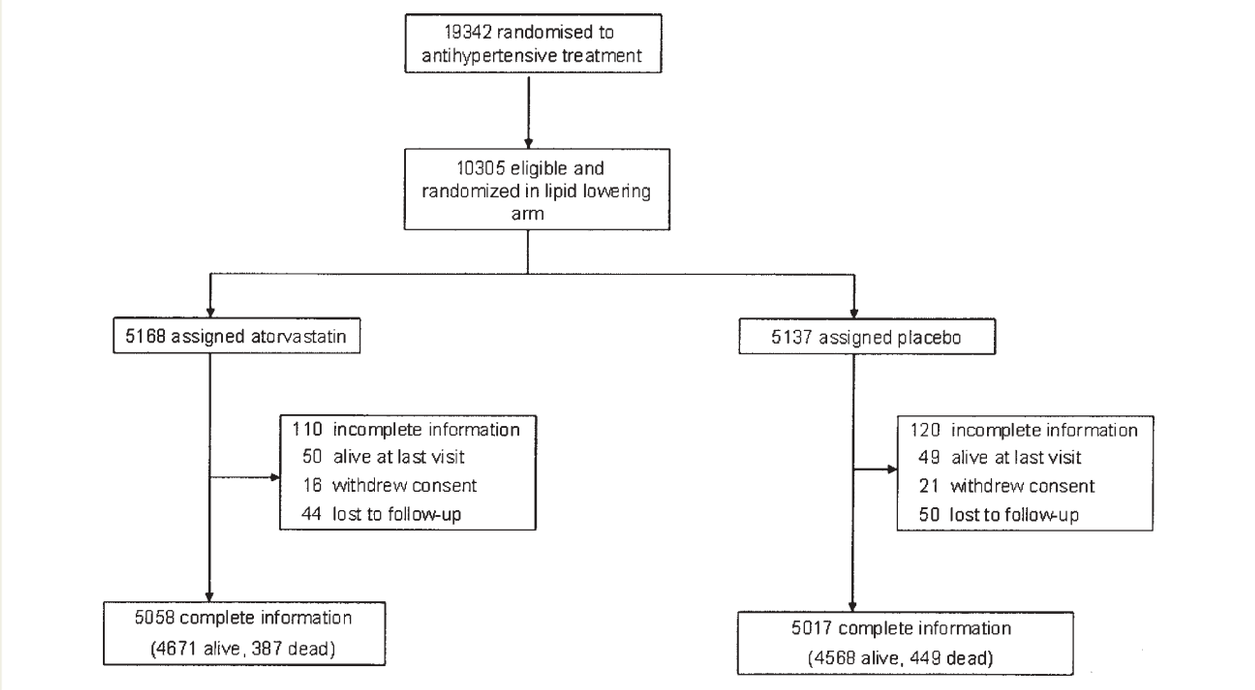

Figure 1 Trial profile

Table 2 Total number of subjects and total per cent of subjects on atorvastatin and other statins respectively at lipid close-out visit and final visit. All LLA subjects by atorvastatin and placebo subgroups

	Atorvastatin, *n* = 4978		**Placebo, *n* = 4916**	
	Atorvastatin, *n* (%)	**Any statins, *n* (%)**	**Atorvastatin, *n* (%)**	**Any statins, *n* (%)**
Lipid close-out visit	4113 (82.6%)	4167 (83.7%)	415 (8.4)	635 (12.9%)
Final visit	3122 (62.7%)	3322 (66.7%)	2752 (56.0%)	3089 (62.8%)

Concentrations of HDL cholesterol were similar in both groups throughout the trial. Compared with placebo, atorvastatin reduced triglycerides by about 0.2 mmol/L at the closure of LLA (*Table 3*, *Figure 2C*), but by the end of BPLA, concentrations were almost identical (*Table 3*, *Figure 2D*) in the two groups. Blood pressures were similar throughout the trial in those assigned atorvastatin and placebo and by the end of the trial had fallen to 137/78 in both treatment groups.

At 3.3 years (the end of ASCOT- LLA), the primary endpoint of non-fatal myocardial infarction and fatal CHD was significantly lower by 35% (HR 0.65 [95% CI: 0.51–0.83], $P = 0.0006$, in the atorvastatin group compared with the placebo group. (*Table 3*, *Figure 3*) Note that late reported endpoints which occurred during LLA are now included. There is a highly significant further divergence during the 2.2 years extension period for the primary outcome despite lipid levels achieving similar valves by the end of 5.5 years of follow-up. After 5.5 years, and with a further 150 primary endpoints, the relative risk reduction of 36% was unchanged (HR 0.64 95% CI: 0.53–0.78, $P < 0.0001$) (*Table 4*, *Figure 3*).

There were also significant reductions in a number of secondary endpoints at the end of LLA which were sustained until the end of BPLA, including total cardiovascular events and procedures (23% vs. 19%); total coronary events (29% vs. 27%), fatal and non-fatal stroke (21% vs. 23%), and all cause mortality (13% vs. 15%), respectively (*Table 4* and *Figures 3* and *4*). Owing to the increase in the number of deaths by the end of the extended period of observation, the risk reduction in all cause mortality associated with assignment to atorvastatin achieved borderline significance ($P = 0.02$).

For the primary endpoint, cumulative event rates continued to fall following the closure of LLA in both those originally assigned atorvastatin and placebo. Similarly, event rates during the follow-up from 3.3 to 5.5 years also fell in both groups of patients (*Table 4*).

The number of serious adverse events and rates of liver enzyme abnormalities between those assigned atorvastatin or placebo did not differ at any stage of the trial.

Table 3 Plasma concentrations of lipid fractions by visit and treatment

	Total cholesterol				LDL cholesterol				HDL cholesterol				Triglycerides			
	Atorvastatin		Placebo		Atorvastatin		Placebo		Atorvastatin		Placebo		Atorvastatin		Placebo	
	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	mean (SD)	*n*	Mean (SD)	*n*
Baseline	5.48 (0.78)	5168	5.48 (0.78)	5137	3.44 (0.72)	4683	3.45 (0.72)	4648	1.31 (0.37)	5168	1.31 (0.36)	5137	1.66 (0.92)	4747	1.65 (0.87)	4708
1 year	4.16 (0.83)	4738	5.45 (0.85)	4670	2.25 (0.69)	4531	3.45 (0.76)	4438	1.30 (0.37)	4738	1.28 (0.35)	4670	1.38 (0.85)	4570	1.65 (0.98)	4520
2 year	4.14 (0.81)	4661	5.35 (0.89)	4589	2.24 (0.68)	4488	3.37 (0.78)	4388	1.30 (0.37)	4661	1.27 (0.36)	4588	1.36 (0.78)	4524	1.60 (0.88)	4442
3 year	4.18 (0.85)	3922	5.27 (0.90)	3904	2.28 (0.71)	3803	3.31 (0.80)	3760	1.30 (0.37)	3922	1.28 (0.36)	3904	1.32 (0.75)	3830	1.54 (0.94)	3812
Lipid close-out	4.21 (0.84)	4517	5.22 (0.91)	4454	2.32 (0.72)	4407	3.27 (0.81)	4324	1.31 (0.37)	4516	1.29 (0.37)	4454	1.29 (0.72)	4429	1.49 (0.87)	4370
4 year	4.48 (1.04)	4408	4.71 (1.04)	4345	2.56 (0.94)	4190	2.79 (0.94)	4128	1.31 (0.38)	4407	1.30 (0.37)	4344	1.36 (0.81)	4222	1.41 (0.85)	4160
5 year	4.39 (1.00)	4204	4.42 (0.98)	4131	2.43 (0.90)	3972	2.48 (0.88)	3938	1.34 (0.38)	4204	1.33 (0.37)	4131	1.37 (0.80)	4003	1.37 (0.77)	3962
Final visit	4.31 (0.96)	4239	4.36 (0.95)	4171	2.33 (0.85)	4000	2.36 (0.84)	3927	1.37 (0.39)	4239	1.37 (0.40)	4171	1.41 (1.01)	4042	1.40 (0.82)	3956

First five rows based are on LLA-locked data, last three rows are based on BPLA-locked data.

Discussion

At the time of the early closure of LLA, it was considered appropriate in the light of the substantial benefits reported with atorvastatin, to recommend to trial physicians that active therapy be offered to all those included in ASCOT-LLA until the end of BPLA. In the event, it was surprising, given the evidence base, that there were physicians and/or patients who chose either not to continue or not to start atorvastatin at the end of LLA. Thus, by the end of BPLA ~60% of the patients originally assigned either placebo or atorvastatin were taking atorvastatin or other statin. This is reflected by the equalization of total and LDL-cholesterol concentrations by the end of the trial. Assuming drop-in to statin therapy occurred at a constant rate throughout the extended follow-up of just over 2 years, it can be predicted that this should have accounted for a relative risk reduction in primary event rates of around 19% in this group from the end of LLA to the end of BPLA. This compared with the observed reduction in this group from the end of the LLA to the end of the BPLA of 15%. Estimates of this type are, however, problematic and potentially confounded by accumulating benefits from reductions in blood pressure. Further analyses taking account of extensive or minimal use of any statins during follow-up, including atorvastatin, do not alter these conclusions.

If there was no carry-over benefit from atorvastatin in those stopping active treatment at the end of LLA, one might have expected a modest rise in event rate in this group during the final phase of the trial. In fact, event rates continued to decline suggesting substantial and important carry-over benefits on cessation of active treatment.

If ASCOT-LLA had proceeded for 5.5 years with continuing assignment to either atorvastatin or placebo, the risk reductions in cardiovascular events associated with atorvastatin would have been expected to continue at the same rates reported at the end of LLA. The cardiovascular event rates reported between the closures of LLA and BPLA were almost identical to those at the termination of LLA, despite substantial changes to active treatment rates after the closure of LLA among those originally allocated to placebo and atorvastatin. Presumably, carry-over benefits from statin among those who dropped out of therapy and continuing benefits of those remaining on statins resulted in similar relative risk benefits at the end of BPLA compared with those at the conclusion of LLA. Also, attrition of susceptibles in the placebo phase of the trial could contribute to reduced benefits on cardiovascular event rates among new-statin users.

One effect of the early termination of LLA was that the study had reduced power to evaluate the effect of atorvastatin on all cause mortality. However, the extended follow-up presented here involves a significantly increased number of deaths and thereby power is restored such that the risk reduction associated with atorvastatin now achieves borderline statistical significance for a secondary endpoint.

Post-trial follow-up observations have been reported from the double blind Scandinavian Simvastatin Survival Study (4S).[8] During an extended 2 year follow-up after the termination of 4S, about 80% of patients originally assigned placebo were given simvastatin and there were fewer coronary and cardiovascular

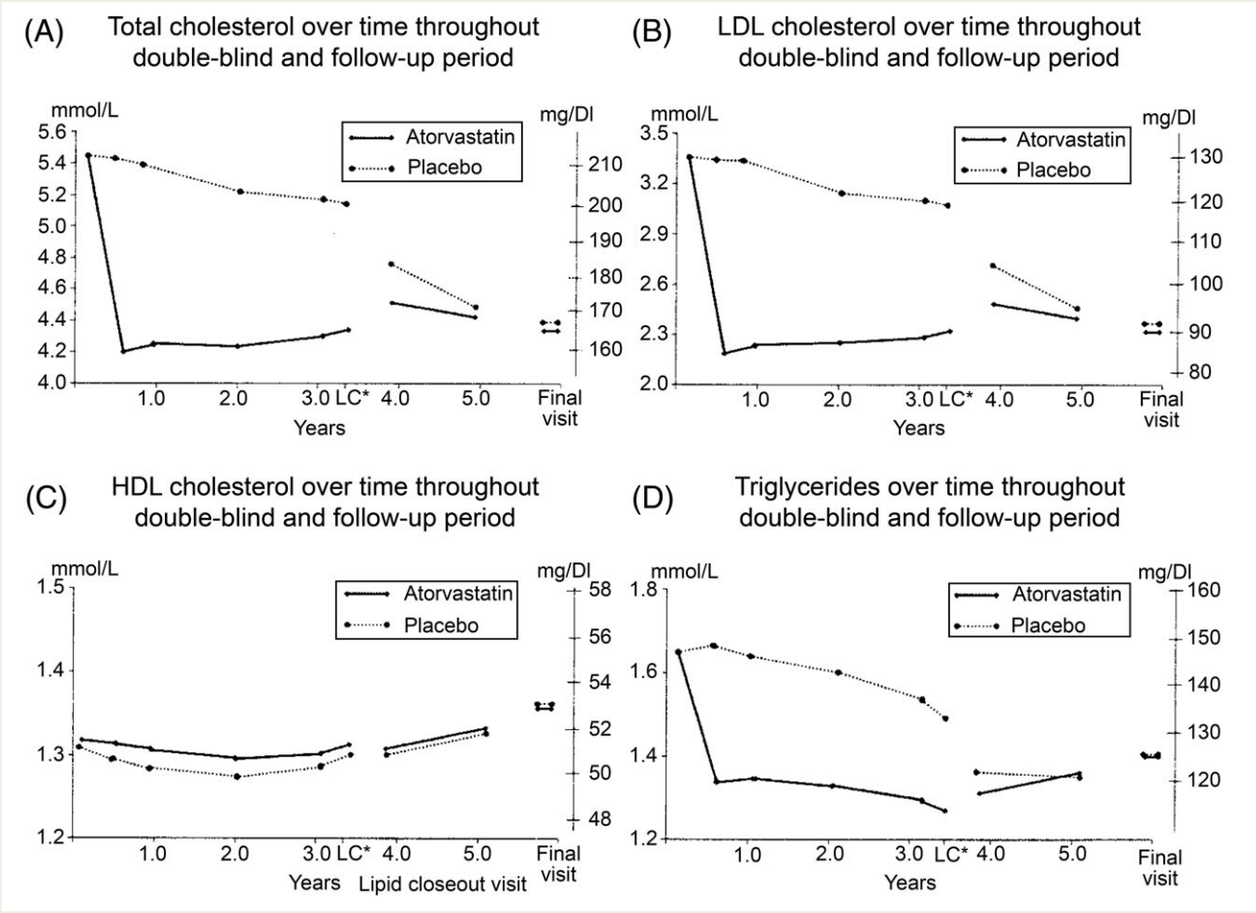

Figure 2 Lipid profiles over time throughout double blind and follow-up period for total cholesterol (*A*), LDL cholesterol (*B*), HDL cholesterol (*C*), and triglycerides (*D*)

deaths in those originally assigned simvastatin, but differences in event rates between those originally assigned statin and placebo were less than those reported at the end of the double blind trial. However, because of relatively small numbers of additional deaths compared with those reported in the double blind trial, overall HRs for coronary and cardiovascular deaths changed little by the end of the extended follow-up (0.57 vs. 0.62 and 0.64 vs. 0.67, respectively). In a subsequent analysis of coronary and cardiovascular deaths during a 5 year extension,[9] the number of deaths between those originally assigned simvastatin and placebo was very similar, probably due to widespread statin use in both groups. The benefits conferred by statin in those originally assigned placebo presumably contributed to the reduction in relative risk between statin and placebo for coronary and cardiovascular deaths between the end of the double blind trial and the end of the 10 year follow-up (0.57 vs. 0.76 and 0.64 vs. 0.83, respectively).

In the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study,[10] patients with previous coronary disease were randomly assigned pravastatin or placebo and were followed-up for 6 years. Most (97%) had 2 years extended follow-up during which 86% of those assigned placebo took open-labelled pravastatin. During this period, patients originally assigned pravastatin, although achieving cholesterol levels almost identical with those originally assigned placebo continued to demonstrate lower events rates for CHD deaths or non-fatal myocardial infarction (25%), stroke (24%), cardiovascular mortality (24%), and all cause mortality (24%). These relative risk reductions during the extended follow-up period are similar to those observed during the double-blind randomized placebo controlled main trial.

A recent report of the 10-year post-trial follow-up of survivors of the West of Scotland Coronary Prevention Study has demonstrated that 5 years in trial treatment with pravastatin was associated with a significant reduction in coronary events for a subsequent 10 years in men with hypercholesterolaemia who had no history of myocardial infarction.[11] Five years after the completion of the trial ~37% of those formerly assigned placebo or pravastatin were being treated with a statin, but there was no information on the comparability of lipid levels at the end of the 10-year follow-up. Nevertheless, it is reasonable to assume that they would be similar in the two groups.

In a further study, 'The Assessment of LEscol in Renal Transplantation', the ALERT trial, fluvastatin was compared with placebo in renal transplant recipients. The primary composite endpoint of cardiac death, non-fatal myocardial infarction and coronary

Table 4 Cardiovascular events during LLA trial (locked data), extension and followed to final visit, atorvastatin vs. placebo

	LLA[a]					LLA extension					Followed to final visit[a]				
	Atorvastatin		Placebo		Unadjusted Hazard ratio (95% CI) P-value	Atorvastatin		Placebo		Unadjusted Hazard ratio (95% CI) P-value	Atorvastatin		Placebo		Unadjusted Hazard ratio (95% CI) P-value
	n (%)	Rate[b]	*n* (%)	Rate[b]		*n* (%)	Rate[b]	*n* (%)	Rate[b]		*n* (%)	Rate[b]	*n* (%)	Rate[b]	
Primary endpoint															
Non-fatal MI (incl silent) + fatal CHD	104 (2.0%)	6.3	158 (3.1%)	9.6	0.65 (0.51–0.83) $P = 0.0006$	59 (1.2%)	5.2	91 (1.9%)	8.3	0.63 (0.45–0.87) $P = 0.0054$	163 (3.2%)	5.8	249 (4.8%)	9.1	0.64 (0.53–0.78) $P = <.0001$
Secondary endpoints															
Total CV events and procedures	410 (7.9%)	25.5	522 (10.2%)	32.9	0.77 (0.68–0.88) $P = 0.0001$	236 (5.1%)	22.4	262 (5.8%)	25.8	0.87 (0.73–1.03) $P = 0.1093$	646 (12.5%)	24.2	784 (15.3%)	30.1	0.81 (0.73–0.89) $P = <.0001$
Total coronary endpoint	194 (3.8%)	11.8	270 (5.3%)	16.6	0.71 (0.59–0.85) $P = 0.0003$	123 (2.5%)	11.1	154 (3.3%)	14.4	0.77 (0.61–0.98) $P = 0.0334$	317 (6.1%)	11.5	424 (8.3%)	15.7	0.73 (0.63–0.85) $P = <.0001$
Non-fatal MI (excl silent) + fatal CHD	89 (1.7%)	5.4	141 (2.7%)	8.6	0.62 (0.48–0.81) $P = 0.0005$	55 (1.1%)	4.8	85 (1.8%)	7.7	0.63 (0.45–0.88) $P = 0.0070$	144 (2.8%)	5.1	226 (4.4%)	8.2	0.63 (0.51–0.77) $P = <.0001$
All cause mortality	186 (3.6%)	11.1	212 (4.1%)	12.7	0.87 (0.72–1.06) $P = 0.1798$	201 (4.0%)	17.4	237 (4.8%)	20.9	0.83 (0.69–1.01) $P = 0.0587$	387 (7.5%)	13.7	449 (8.7%)	16.1	0.85 (0.74–0.98) $P = 0.0219$
Cardiovascular mortality	75 (1.5%)	4.5	89 (1.7%)	5.4	0.84 (0.62–1.14) $P = 0.2621$	65 (1.3%)	5.6	76 (1.5%)	6.7	0.84 (0.60–1.17) $P = 0.3048$	140 (2.7%)	5.0	165 (3.2%)	5.9	0.84 (0.67–1.05) $P = 0.1281$
Fatal and non-fatal stroke	110 (2.1%)	6.6	139 (2.7%)	8.5	0.79 (0.61–1.01) $P = 0.0575$	56 (1.1%)	5.0	73 (1.5%)	6.6	0.75 (0.53–1.06) $P = 0.1047$	166 (3.2%)	6.0	212 (4.1%)	7.7	0.77 (0.63–0.95) $P = 0.0127$
Fatal and non-fatal heart failure	43 (0.8%)	2.6	43 (0.8%)	2.6	1.00 (0.65–1.52) $P = 0.9902$	33 (0.7%)	2.9	32 (0.7%)	2.8	1.01 (0.62–1.65) $P = 0.9531$	76 (1.5%)	2.7	75 (1.5%)	2.7	1.00 (0.73–1.38) $P = 0.9809$
Tertiary endpoints															
Silent MI	15 (0.3%)	0.9	17 (0.3%)	1.0	0.88 (0.44–1.76) $P = 0.7135$	4 (0.1%)	0.3	7 (0.1%)	0.6	0.56 (0.16–1.91) $P = 0.3487$	19 (0.4%)	0.7	24 (0.5%)	0.9	0.78 (0.43–1.43) $P = 0.4261$
Unstable angina	22 (0.4%)	1.3	25 (0.5%)	1.5	0.88 (0.49–1.55) $P = 0.6513$	18 (0.4%)	1.6	11 (0.2%)	1.0	1.61 (0.76–3.41) $P = 0.2088$	40 (0.8%)	1.4	36 (0.7%)	1.3	1.10 (0.70–1.73) $P = 0.6764$
Chronic stable angina	42 (0.8%)	2.5	70 (1.4%)	4.2	0.60 (0.41–0.87) $P = 0.0072$	28 (0.6%)	2.5	40 (0.8%)	3.6	0.68 (0.42–1.11) $P = 0.1213$	70 (1.4%)	2.5	110 (2.1%)	4.0	0.63 (0.46–0.85) $P = 0.0021$
Peripheral arterial disease	49 (0.9%)	2.9	50 (1.0%)	3.0	0.98 (0.66–1.45) $P = 0.9055$	28 (0.6%)	2.5	32 (0.7%)	2.9	0.86 (0.52–1.43) $P = 0.5562$	77 (1.5%)	2.7	82 (1.6%)	3.0	0.93 (0.68–1.27) p = 0.6441
Life threatening arrhythmias	10 (0.2%)	0.6	4 (0.1%)	0.2	2.48 (0.78–7.89) $P = 0.1129$	4 (0.1%)	0.3	7 (0.1%)	0.6	0.56 (0.16–1.92) $P = 0.3503$	14 (0.3%)	0.5	11 (0.2%)	0.4	1.26 (0.57–2.78) $P = 0.5651$
Develop. diabetes mellitus	279 (7.3%)	23.6	251 (6.7%)	21.4	1.10 (0.93–1.31) $P = 0.2524$	84 (2.5%)	10.8	106 (3.2%)	14.0	0.78 (0.58–1.03) $P = 0.0818$	363 (9.6%)	18.5	357 (9.5%)	18.5	1.01 (0.87–1.16) $P = 0.9428$
Develop. renal impairment	143 (2.8%)	8.7	135 (2.6%)	8.2	1.06 (0.84–1.34) $P = 0.6463$	95 (2.0%)	8.6	91 (1.9%)	8.3	1.03 (0.77–1.37) $P = 0.8377$	238 (4.6%)	8.6	226 (4.4%)	8.3	1.04 (0.87–1.25) $P = 0.6392$

[a]Late reported endpoints occurred during LLA are included as well.
[b]Per 1000 patient years.

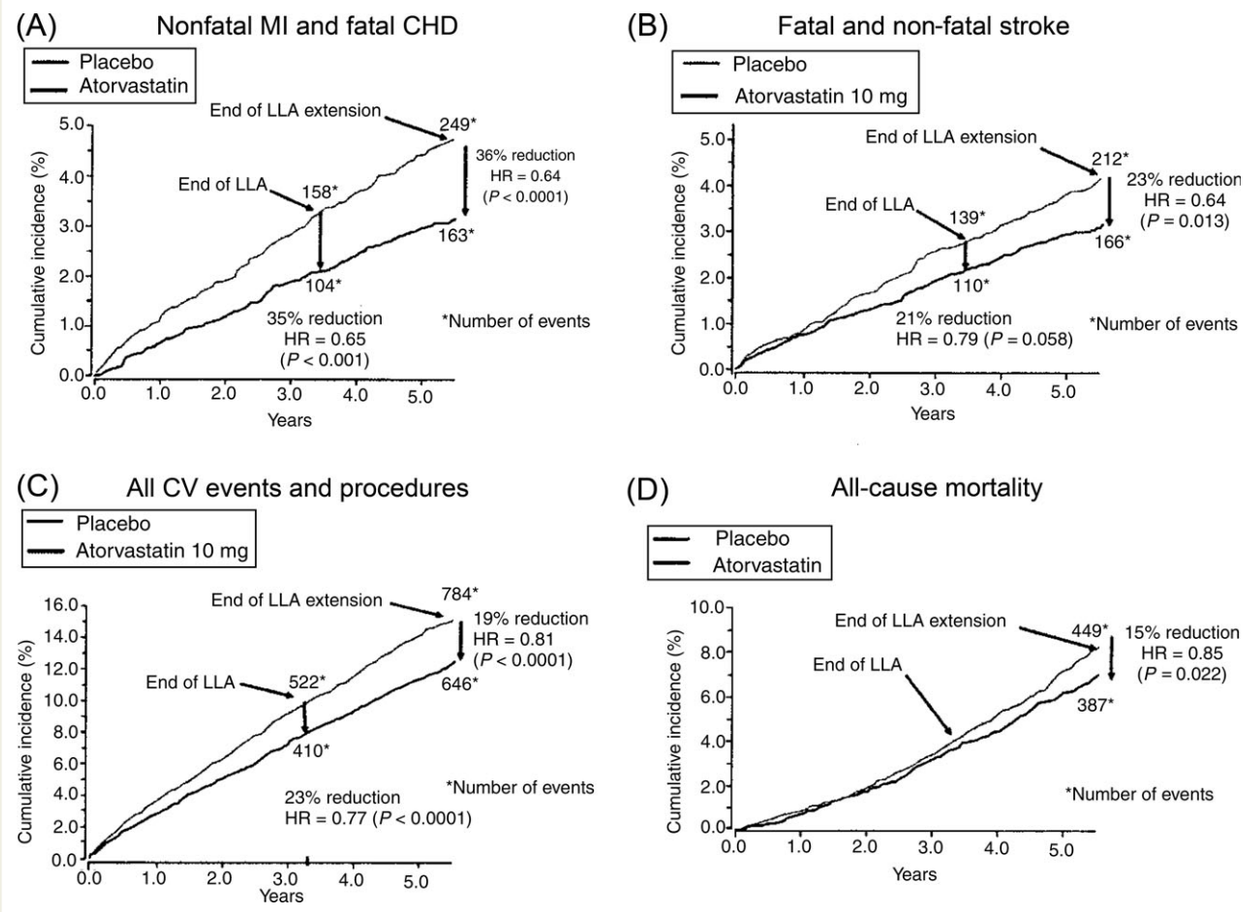

Figure 3 Cumulative incidence of primary endpoint of non-fatal myocardial infarction and fatal coronary heart disease (*A*), fatal and non-fatal stroke (*B*), total cardiovascular events and procedures (*C*), and all cause mortality (*D*). Late reported endpoints occurring during lipid-lowering arm are now included

intervention procedures was non-significantly reduced by 17% at the end of the formal follow-up period of 5.4 years.[12] However, despite widespread use of statins in those formerly assigned placebo during an extended 2 year period of observation and equalization of cholesterol levels, a significant risk reduction of 21% in the primary endpoint in those originally assigned fluvastatin was observed.[13] These observations on extended periods of observation after several trials provide further convincing evidence that withdrawal from active statin treatment is followed by sustained treatment benefits in those with or without prior coronary heart disease events. These observations indicate that the cost-effectiveness of statins will be greater than that previously estimated.[14]

Our findings during short-term extended follow-up of ASCOT-LLA, albeit with substantial numbers of fatal and non-fatal events reported, are similar to those of the 2-year extended follow-up of the 4S trial[8] and the LIPID trial.[10] Although a degree of protective carry-over effect afforded by statins, presumably resulting from plaque stabilization, could reasonably be expected over the short-term, it might be predicted that given sufficient extended follow-up, assuming treatment rates equalize in those originally assigned placebo and statin, that event rates would converge, as witnessed in the longer term follow-up of 4S.

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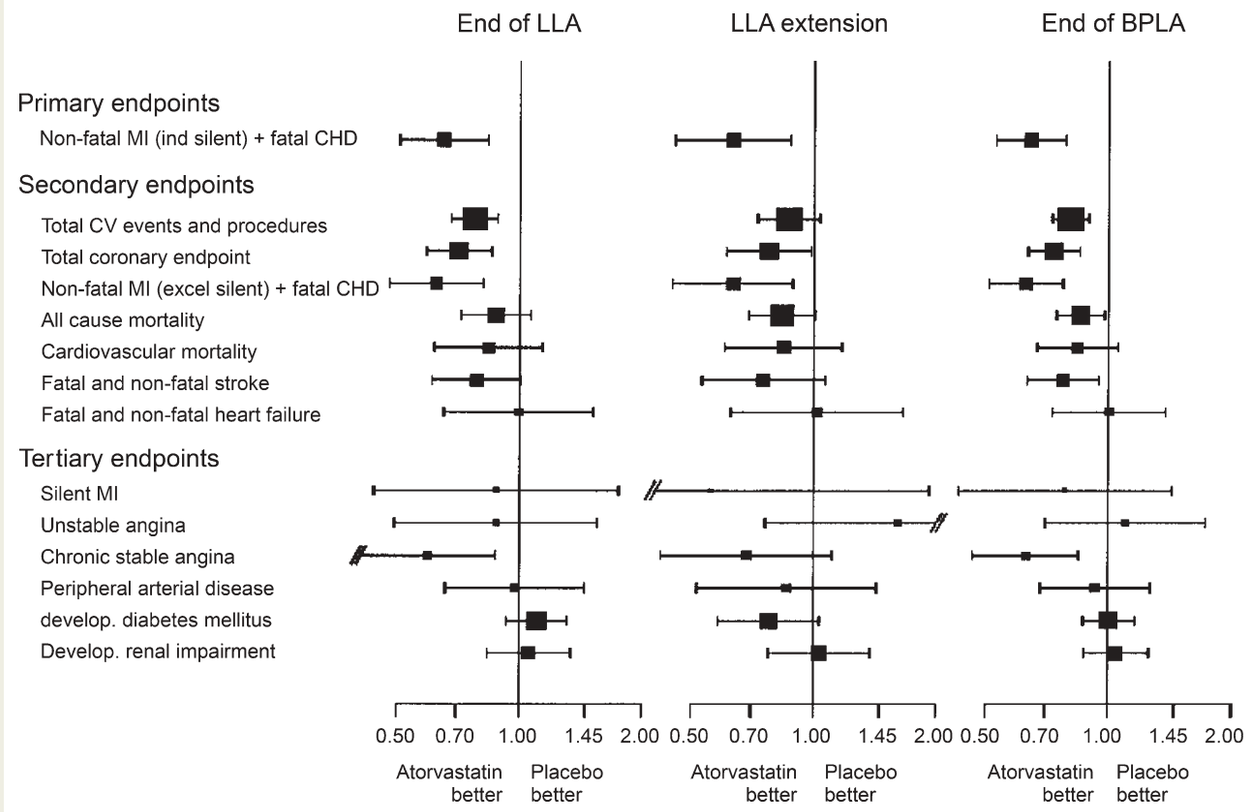

Figure 4 Effects of atorvastatin and placebo on primary, secondary and tertiary endpoints at the end of lipid-lowering arm (3.3 years), during the lipid-lowering arm-extension and at the end of the trial. Area of squares is proportional to amount of statistical information. Point estimates of hazard ratios are given with 95% CI. MI, myocardial infarction; CHD, coronary heart disease

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