

The Anglo-Scandinavian Cardiac Outcomes Trial: 11-year mortality follow-up of the lipid-lowering arm in the UK

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Aims

The aim of this study was to determine the outcome benefits in those originally assigned atorvastatin in the Anglo-Scandinavian Cardiac Outcomes Trial—8 years after closure of the lipid-lowering arm (LLA) of the trial (ASCOT-LLA) among the UK population.

Methods and results

ASCOT-LLA was a factorially designed double-blind placebo-controlled trial of atorvastatin in 10 305 hypertensive patients enrolled into the ASCOT-Blood Pressure Lowering Arm (BPLA) of the trial and with total cholesterol concentrations, at baseline, of <6.5 mmol/L. ASCOT-LLA was stopped prematurely after a median 3.3-year follow-up because of a 36% relative risk reduction (RRR) in non-fatal myocardial infarction and fatal coronary heart disease (CHD) (the primary outcome) in favour of atorvastatin and a non-significant reduction in CV deaths (16%) and all-cause mortality (13%). After a further 2.2 years at the end of ASCOT-BPLA, despite extensive crossovers from and to statin usage, the RRR in all endpoints remained essentially unchanged. A median 11 years after initial randomization and ~ 8 years after closure of LLA, all-cause mortality ($n = 520$ and 460 in placebo and atorvastatin, respectively) remained significantly lower in those originally assigned atorvastatin (HR 0.86, CI 0.76–0.98, $P = 0.02$). CV deaths were fewer, but not significant (HR 0.89, CI 0.72–1.11, $P = 0.32$) and non-CV deaths were significantly lower (HR 0.85, CI 0.73–0.99, $P = 0.03$) in those formerly assigned atorvastatin attributed to a reduction in deaths due to infection and respiratory illness.

Conclusion

Legacy effects of those originally assigned atorvastatin may contribute to long-term benefits on all-cause mortality. An explanation for long-term benefits on non-CV deaths has not been established.

Keywords

Cardiovascular deaths • All-cause mortality • Atorvastatin • ASCOT-LLA 11-year follow-up

Introduction

In 2003, we reported the outcome of the lipid-lowering arm (LLA) 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 of ≤ 6.5 mmol/L. The trial was stopped prematurely after a median 3.3-year 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 (CV) 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 the two anti-hypertensive 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 owing to substantial

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mortality benefits in favour of the CCB-based treatment strategy. At this time, the relative risk reductions (RRRs) in CV outcomes for those originally assigned atorvastatin were essentially unchanged despite extensive crossover to and from statin usage, and all-cause mortality was significantly reduced in those formerly assigned atorvastatin. At the end of BPLA, of those originally assigned atorvastatin, 69% were still taking atorvastatin or other statin compared with 63% of those formerly assigned placebo. The present report evaluates the mortality outcomes of those subjects originally assigned either atorvastatin or placebo in the LLA and followed-up for a median 11 years after initial randomization. The analyses are restricted to those subjects recruited to the trial in the UK as information on mortality and cause of death were not available for patients originally followed up in the Nordic countries.

Methods

The detailed ASCOT protocol, including study design, organization, clinical measurements, power calculations, recruitment rates, and baseline characteristics, has been published² 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 × 2 factorial approach, a comparison of two antihypertensive treatment regimens and in a large subgroup, atorvastatin with placebo. Patients eligible for inclusion into LLA had to be eligible for 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 hypertensive men and women aged between 40 and 79 years at randomization, with at least three additional risk factors for CV disease. Exclusion criteria included (among others): previous myocardial infarction; currently treated angina or a cerebrovascular event within the previous 3 months; patients were originally recruited between February 1998 and May 2000.

Early closure of the lipid-lowering arm

During the trial, atorvastatin lowered total cholesterol and LDL cholesterol by an average of 1.1 mmol/L. In 2002, the LLA was stopped on the grounds that atorvastatin had resulted in a highly significant reduction of 36% in the primary endpoint compared with placebo and a significant reduction in the incidence of stroke.¹

Trial physicians were invited to offer atorvastatin 10 mg daily to all patients in LLA until the end of BPLA which was stopped in 2005 (LLA-extension).

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.⁴ 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. A small percentage of additional patients were receiving other statins (4 and 7%, respectively).

Consequently, 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.⁴

Mortality data

In the UK, subjects who were alive at the end of BPLA were flagged for death with the Office for National Statistics and the General

Register Office for Scotland. Post-trial mortality data were sent to us every 2–3 months.

The primary cause of death reported in the death certificates was used to identify the main cause of death. The deaths included in the analyses are death from any cause, death from CV or non-CV disease, and death from cancer. We included three additional *post hoc* outcomes: death from infection, respiratory illness, and infection/respiratory combined. In no case was a cause of death unable to be ascertained.

Death due to infection was defined as death from infectious or parasitic diseases; deaths from respiratory illness were defined as disease of the respiratory system which included pneumonia, chronic obstructive airways disease, and acute respiratory diseases.

The cut-off date for mortality used in this report was 31 December 2010. All deaths occurring before or on this date were included in the analyses.

Statistical analysis

All analyses were performed by the principle of intention-to-treat, and thus follow-up also included trial dropouts who were alive at the beginning of the post-trial follow-up. In all analyses, censoring was assumed to be independent of the outcome. Censoring was defined as death or end of follow-up, 31 December 2010. However, two sites (Crosby, $n = 169$, 7 deaths, and Sunderland, $n = 3$, 1 death) were not flagged and those who were alive at the end of BPLA were censored at the time of their last visit. In-trial period was defined as that from randomization to early termination of the trial in October 2002. The two randomized treatment groups were compared for each mortality outcome in a Cox regression analysis.⁵ Analyses were unadjusted and adjusted for prespecified baseline risk factors. The assumption of proportionality was tested with Schoenfeld's residuals. Tests for interaction between atorvastatin treatment and trial period (in- or post-trial) and between atorvastatin and randomized blood pressure (BP) treatment were conducted. Tests for interactions were also performed to determine whether the atorvastatin effects differed between subgroups such as age, sex, ethnic, or diabetes status.

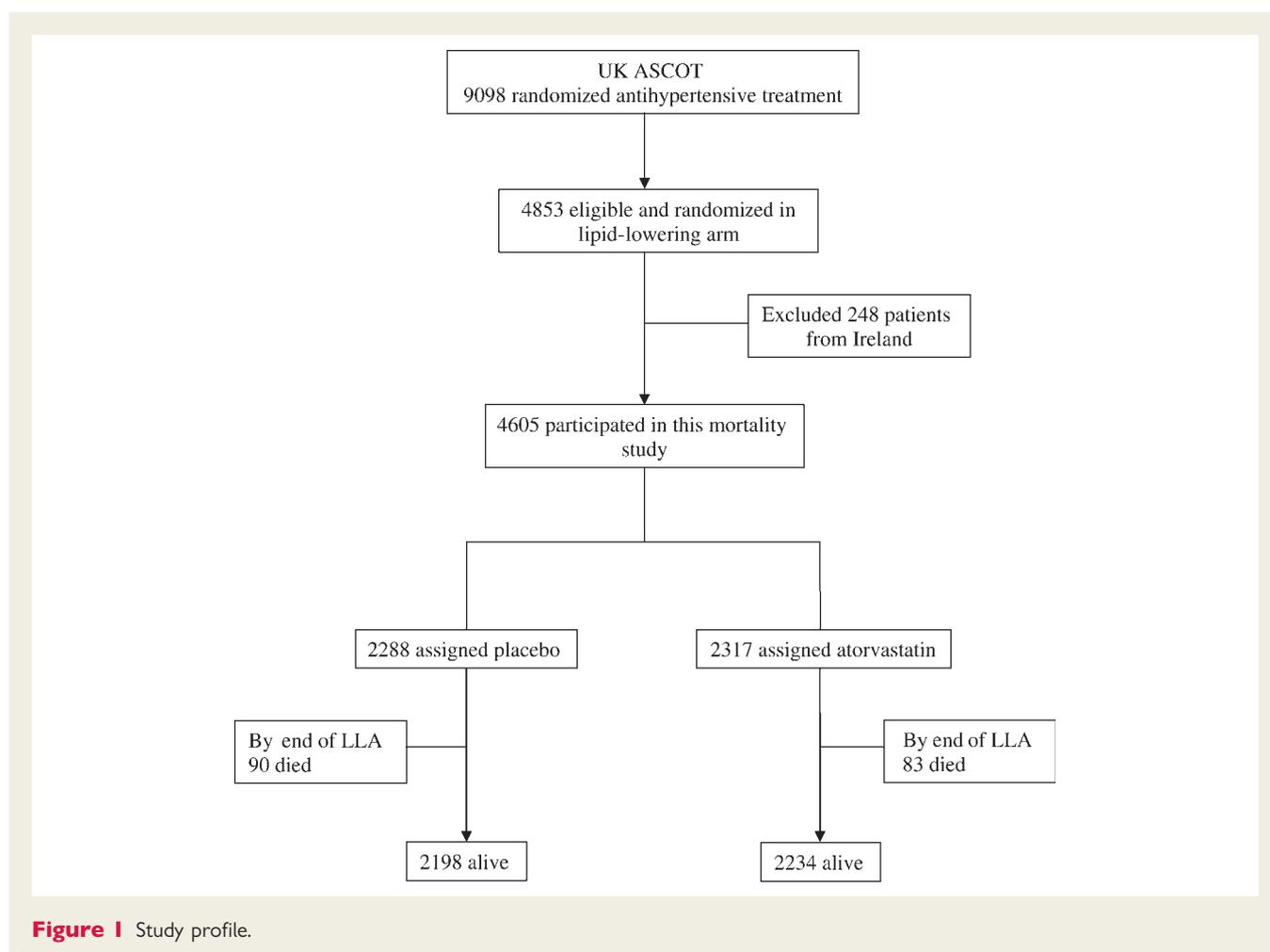
Hazard ratios were estimated after adjusting for baseline risk factors (age, sex, systolic blood pressure, body mass index, total cholesterol, diabetes, current smokers, ethnicity, randomized BP treatment, and age at completion of education). However, the adjusted results were materially unaffected and therefore subsequent analyses were performed using unadjusted models. Statistical tests were two-sided and a P -value of <0.05 was considered to be of statistical significance.

All statistical analyses were performed with SAS V9.1 (SAS Institute, Cary, NC, USA) and STATA 11 (STATA Corporation, College Station, TX, USA).

Results

Baseline characteristics among the surviving patients at the end of LLA are shown in Supplementary material online, *Table S1*. The two groups of surviving patients followed up during the extended phase were similar for the pre-randomization characteristics. Within the first 2 years of post-trial (open-label phase), approximately two-thirds of patients previously assigned either atorvastatin or placebo were taking lipid-lowering treatment.

In the UK, median duration of follow-up in LLA was 3.02 years [interquartile range (IQR) 2.60–3.47] from randomization and a further 8.25 years since the original LLA study was terminated. Of the 4605 patients originally enrolled in the UK ASCOT-LLA, 173 were known to have died by the end of the trial in October

**Table 1** Event rate of causes of mortality by trial period

Cause of death	LLA		Post-LLA ^a				Total follow-up					
	Placebo		Atorvastatin		Placebo		Atorvastatin		Placebo		Atorvastatin	
	n (%)	Rate ^b	n (%)	Rate ^b	n (%)	Rate ^b	n (%)	Rate ^b	n (%)	Rate ^b	n (%)	Rate ^b
All-cause	90 (3.9)	1.28	83 (3.6)	1.18	430 (19.6)	2.66	377 (16.9)	2.27	520 (22.7)	2.24	460 (19.9)	1.94
CV	36 (1.6)	0.51	30 (1.3)	0.43	131 (6.0)	0.82	124 (5.6)	0.75	167 (7.3)	0.73	154 (6.6)	0.65
Non-CV	54 (2.4)	0.77	53 (2.3)	0.75	299 (13.6)	1.85	253 (11.3)	1.52	353 (15.4)	1.52	306 (13.2)	1.29
Cancer	37 (1.6)	0.53	39 (1.7)	0.55	175 (8.0)	1.08	162 (7.3)	0.98	212 (9.3)	0.92	201 (8.7)	0.85
Infect Infection/ Respiratory	6 (11.1)	0.09	3 (5.7)	0.04	50 (16.7)	0.31	34 (13.4)	0.20	56 (15.9)	0.24	37 (12.1)	0.16
Infection	3 (5.6)	0.04	1 (1.9)	0.01	34 (11.4)	0.21	22 (8.7)	0.13	37 (10.5)	0.16	23 (7.5)	0.10
Respiratory	3 (5.6)	0.04	2 (3.8)	0.03	16 (5.4)	0.10	12 (4.7)	0.07	19 (5.4)	0.08	14 (4.6)	0.06

CV, cardiovascular.

^aParticipants who died during the LLA period were excluded. Post-LLA is from end of the LLA period to 31 December 2010.^bPer 100 person-years.

Table 2 Unadjusted hazard ratios (95% confidence interval) of atorvastatin effect on mortality and causes of death during lipid-lowering arm trial, post-lipid-lowering arm and total follow-up period

Cause of death	LLA	P-value	Post-LLA ^a	P-value	Total follow-up	P-value
All-cause	0.92 (0.68, 1.24)	0.60	0.85 (0.74, 0.98)	0.02	0.86 (0.76, 0.98)	0.02
CV	0.83 (0.51, 1.35)	0.45	0.91 (0.71, 1.16)	0.46	0.89 (0.72, 1.11)	0.32
Non-CV	0.99 (0.67, 1.44)	0.94	0.82 (0.70, 0.97)	0.02	0.85 (0.73, 0.99)	0.03
Cancer	1.05 (0.67, 1.65)	0.82	0.90 (0.73, 1.11)	0.33	0.92 (0.76, 1.12)	0.43
Infection/respiratory	0.51 (0.13, 2.04)	0.34	0.66 (0.43, 1.02)	0.06	0.64 (0.42, 0.97)	0.04
Infection	0.34 (0.04, 3.26)	0.35	0.63 (0.37, 1.07)	0.09	0.60 (0.36, 1.02)	0.06
Respiratory	0.68 (0.11, 4.07)	0.67	0.73 (0.34, 1.54)	0.41	0.72 (0.36, 1.44)	0.35

CV, cardiovascular.

^aParticipants who died during the LLA period were excluded. Post-LLA is from end of the LLA period to 31 December 2010.

2002. During extended follow-up, an additional 377 (16.9%) deaths occurred among the 2234 in-trial survivors in the atorvastatin group and 430 (19.6%) among the 2198 in the placebo group (Figure 1 and Table 1). This cohort is made up of 45% of the entire ASCOT-LLA trial.

Proportionality-hazard assumption was not violated for all unadjusted models fitted over the full period of follow-up. Figure 2 shows cumulative incidence curves for all-cause, CV, non-CV, and cancer mortality in the atorvastatin and placebo groups over the entire follow-up. Beyond the end of the LLA period, incident curves for all-cause mortality began to diverge in favour of the atorvastatin group with no observable diminishing of benefit over time. However, for non-CV deaths, the curves began to diverge after 6 years since randomization. Though not statistically significant, the CV mortality showed a sustained benefit in favour of the atorvastatin group throughout the entire follow-up period. No such difference was seen in cancer mortality.

The cumulative incidence of death from infection or respiratory illness is shown in Figure 3. Similar benefits throughout the entire follow-up, from original assignment to atorvastatin, were also noted in deaths caused by infection and respiratory illness combined ($n = 201$ vs. 212) and death caused by infection alone ($n = 23$ vs. 37) [$P = 0.06$ (unadjusted model); $P = 0.045$ (adjusted model)].

There was no evidence that atorvastatin effects on all-cause mortality were different between randomized BP groups, both in- and post-trial. Table 2 shows the benefits of atorvastatin in the trial and during the extended follow-up phase. Additional significant reductions in all-cause mortality in the atorvastatin group compared with the placebo group were observed during the extended follow-up phase for death from all-causes ($P = 0.02$) and deaths from non-CV causes ($P = 0.03$). There was a significant RRR in death from all-causes (RRR 14%, $P = 0.02$), deaths from non-CV causes (15%, $P = 0.03$), and deaths from infection or respiratory illness (36%, $P = 0.04$), over the entire 11-year follow-up. For infection-related deaths, the reduction was of borderline significance (40% $P = 0.06$). These reductions remained significant in multivariable analyses, after adjustment for baseline risk factors and death from infection-cause became statistically significant (Supplementary material online, Table S2). There was no evidence of an effect of atorvastatin on cancer deaths either in-trial or on

prolonged follow-up. After adjusting for baseline confounding factors, there was little change in the hazard ratios (Supplementary material online, Table S2). There was no evidence of interaction between atorvastatin treatment and trial period ($P = 0.63$ and $P = 0.59$ for unadjusted and adjusted models, respectively). From our UK ASCOT data, the number to treat (NNT) to prevent 1 death from treatment with atorvastatin for 3.3 years was 286, but followed up for a total of 11 years was 35. There was no evidence of significant heterogeneity of treatment effect for any of the following subgroups: age ≤ 60 vs. > 60 , sex, diabetic status, ethnicity (white vs. non-white), and randomized atenolol/amlodipine (data not shown). We are unaware of any post-trial deaths attributable to rhabdomyolysis.

Discussion

The main findings from this extended follow-up of mortality in UK patients originally recruited into ASCOT-LLA are that a median 11 years from initial randomization into either atorvastatin 10 mg daily or placebo, and 8 years after closure of the trial, during which time most patients from both active and placebo treatment groups were taking statins,⁴ significant benefits on all-cause mortality were observed in those formerly assigned atorvastatin compared with placebo. Cardiovascular deaths were reduced but not significant, and the major contribution to the reduction in all-cause mortality was a reduction in non-CV deaths. Among the non-CV deaths, there was no difference in deaths from cancer but a significant reduction in deaths from infection and respiratory illness in favour of atorvastatin. Legacy effects observed in statin trials have previously been reported. In our earlier paper, describing a 2-year follow-up post-trial closure of LLA,⁴ risk reduction in most CV endpoints was virtually identical to those reported at the end of the trial, and at a time when lipid profiles were similar in the two groups formerly assigned either atorvastatin or placebo. In an attempt to provide some insight into what is driving these long-term benefits, we conducted a retrospective on-treatment analysis of those originally assigned atorvastatin and who continued to take a statin until the end of 5.5 years follow-up (i.e. end of BPLA) and compared mortality outcomes with those formerly assigned placebo and did not take a statin throughout the 5.5 years of the trial. Substantially greater

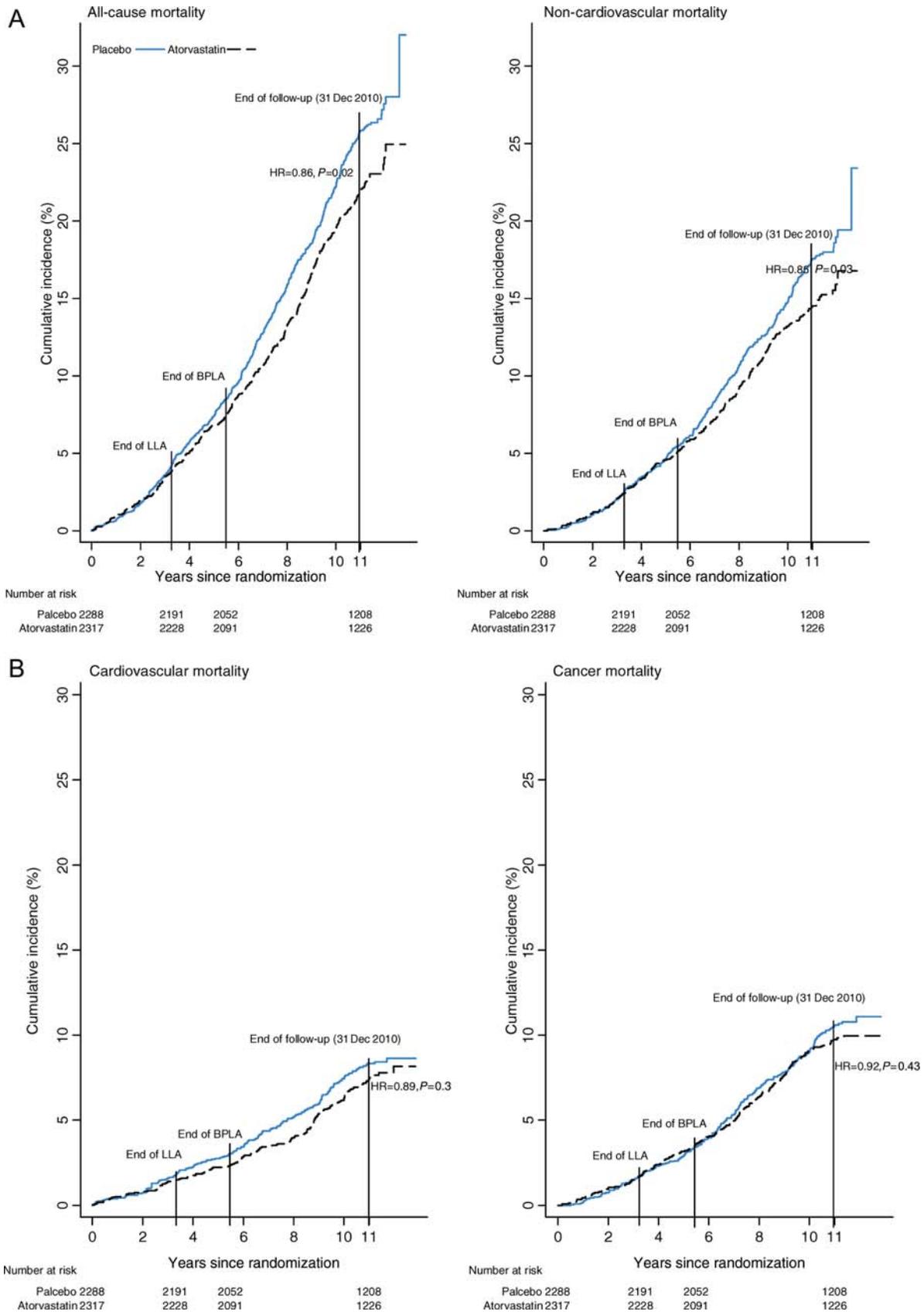


Figure 2 (A) Cumulative incidence of all-cause mortality and non-cardiovascular mortality. (B) Cumulative incidence of cardiovascular mortality and cancer mortality.

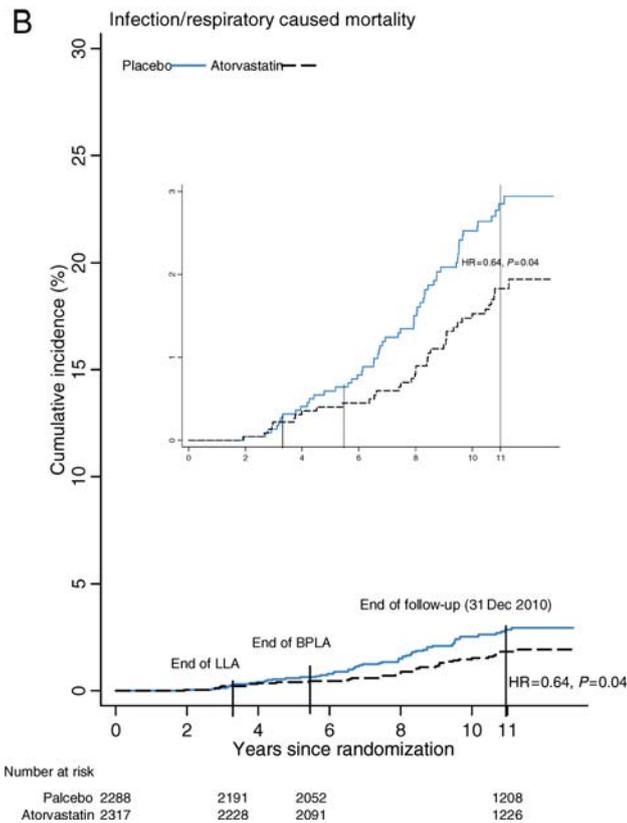
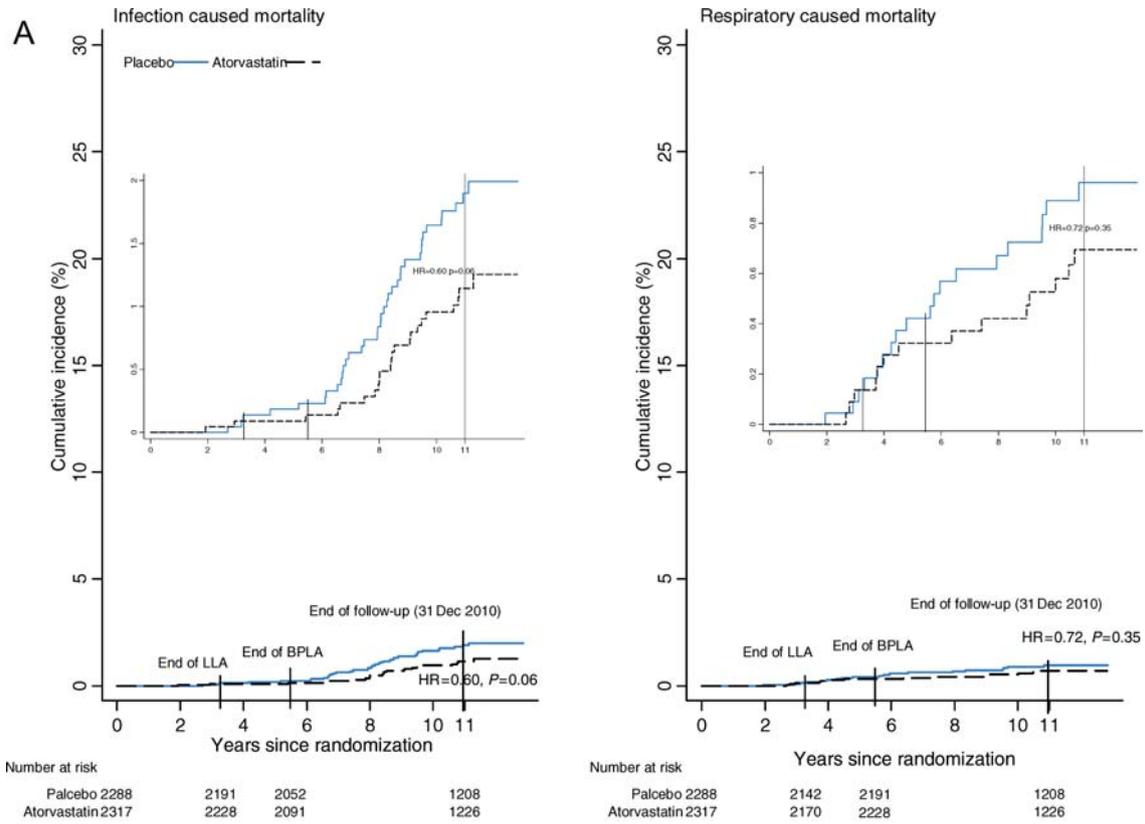


Figure 3 (A) Cumulative incidence of mortality due to infection and respiratory disease mortality. (B) Cumulative incidence of mortality due to combined infection and respiratory disease.

RRRs in all-cause, CV, and non-CV mortality were observed than that we reported previously,⁴ providing some indication that this cohort may have importantly contributed to the long-term benefits that we report in the 11-year follow-up.

Long-term follow-up of patients recruited into the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study⁶ demonstrated a continuing benefit on CV events in those formerly assigned pravastatin compared with placebo after a 6-year period of observation.

Similarly, a 10-year post-trial follow-up of survivors of the West of Scotland Coronary Prevention Study (WOSCOPS)⁷ has demonstrated that 10 years after termination of the trial, there was a continuing reduction in coronary events in those previously assigned pravastatin compared with the placebo. Contrasting results were, however, reported from the Scandinavian Simvastatin Survival Study (4S)⁸ where after a 5-year post-trial period of observation there were no differences in CV deaths in those originally assigned simvastatin or placebo.

The present report, however, suggests an important new finding that the legacy effect may be largely contributed to by benefits on non-CV deaths, and particularly those due to infection and respiratory illness, thereby raising the question as to possible underlying mechanisms.

There has been much debate and discussion as to the role of non-lipid-lowering benefits of statins particularly in the context of the very early benefits observed on the reduction in CHD events reported from the original LLA trial,⁹ and also the rapid time course of event reduction in patients at high risk of recurrent coronary ischaemia in the Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering Study (MIRACL)¹⁰ and the Pravastatin or Atorvastatin Evaluation and Infection Therapy trial (PROVE-IT).¹¹

The non-lipid lowering benefits of statins are linked to the inhibition of mevalonic acid synthesis which is a consequence of inhibitor of HMG-CoA reductase and the subsequent reduction in synthesis of isoprenoid intermediates.¹² By inhibition of isoprenoids, a number of critical intracellular signalling processes are prevented, including Ras, Rho, Rap, and Rab, which in turn effect inflammatory cell signalling.^{12,13} Indeed, we have recently demonstrated that in LLA, atorvastatin reduced C-reactive protein by 27% compared with placebo.¹⁴ It is these anti-inflammatory effects of statins together with known anti-thrombotic effects and beneficial effects on endothelial function which have been put forward as explanations for early vascular protection in the context of statin use.^{12,13}

Is it possible, therefore, to ascribe these pleiotropic action of statins to protection against non-CV deaths, particularly those associated with infection and respiratory illness?

Experimental studies show that statins modulate neutrophil function, reduce pro-inflammatory cytokine release, improve vascular function, are anti-thrombotic, and improve the outcome from pneumonia and sepsis.¹⁵ In addition, observational studies have shown that prior statin use reduces mortality from sepsis and community-acquired pneumonia.¹⁵ A review and meta-analysis of randomized trials and cohort studies has examined the relationship between statin use and risk of outcome from infections.¹⁶ In nine cohorts addressing the role of statins in treating infection,

the pooled effect estimate was 0.55 (CI 0.36–0.83) in favour of statin use, and in cohort studies investigating the prevention of infection in patients with vascular disease, the pooled effect estimate was 0.57 (CI 0.43–0.75) in favour of statin use.¹⁶

A recent editorial¹⁷ also highlights a number of observational studies of statin use and outcomes in patients with pneumonia, but urges caution in their interpretation, on account of the fact that observational, retrospective, and meta-analytical studies cannot eliminate the possibility of confounding bias, and highlights the need for formal prospective, randomized, controlled trials to be conducted.

However, even if we accept that these pleiotropic effects of statins could contribute to protection against deaths due to infection and other respiratory illness, we would still have to find an additional explanation for the legacy effect of the benefits of those formerly assigned atorvastatin use in the present trial, and the long-term outcome benefits on non-CV deaths. Some insight into longer term benefits of statins may be inferred from the results of recent studies on genome-wide RNA expression in human liver cells, which suggest that a number of transcriptional regulators may be influenced by atorvastatin-responsive regulation of metabolism and other metabolic processes.¹⁸

The limitations of our report include, first, the fact that we were restricted in our observations to deaths occurring in the UK. No post-trial data are available on mortality from patients recruiting into the trial from the Nordic countries and Ireland. We do, however, believe that outcome from the UK patients would be representative of the whole trial population. Secondly, follow-up data on mortality from two UK sites were unavailable. These two sites, however, contributed small numbers of patients to the trial, and the lack of information on their deaths is therefore extremely unlikely to have influenced the final outcome. Thirdly, we did not, *a priori*, plan to study non-CV deaths and although the numbers are large, and the reduction in favour of early statin use vs. placebo convincing, the subsequent sub-division into individual causes of death in this group, including respiratory illness and infection, is retrospective, and the differences observed could have occurred by chance. Fourthly, we relied on information as to the cause of the death from death certificates, and in individual cases, the cause of death may be uncertain or inaccurately defined. Nevertheless, randomization should, to a certain extent, allow for this lack of precision in individual cases.

In conclusion, we report a long-term follow-up of the benefits of early treatment of hypertensive patients with atorvastatin compared with placebo on all-cause mortality, best attributed to a reduction in non-CV deaths, and contributed to by a reduction in death from infection and respiratory illness. Pleiotropic effects of statin use are speculated to play a role in the protection afforded by statins, but our hypothesis that there remains a longer term legacy effect has, to date, no definitive explanation but, in any event, should not be considered a case for discontinuation of statin use.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: P.S.S. and N.R.P. have served as consultants or received travel expenses, or payment for speaking at meetings, or funding for research from one or more pharmaceutical companies that market blood-pressure-lowering or lipid-lowering drugs, including Pfizer for ASCOT.

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