Long-term mortality after the blood pressure and lipid-lowering treatment in hypertensive patients: 16-year follow-up of the Anglo-Scandinavian Cardiovascular Outcomes Trial (ASCOT) Legacy study

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Abstract

Background
In hypertensive patients, the long-term cardiovascular (CV) and all-cause mortality effects of alternative blood pressure (BP)- lowering regimens and of lipid- lowering treatment are not well documented, particularly in a clinical trial setting. The ASCOT Legacy Study reports mortality outcomes after 16 years follow-up of UK participants in the original trial.

Methods
8580 UK-based hypertensive ASCOT patients (mean age, 64.1 years) were followed post- trial for all-cause and CV mortality (median follow-up, 15·7 years). At baseline, all patients were randomized, using a 2x2 factorial design, to the BP-lowering arm (BPLA): either amlodipine- (4305) or atenolol- (4275)-based treatment. Of these, 4605 (54%) patients with total cholesterol ≤ 6·5 mmol/L and with no previous lipid-lowering treatment, were further randomised to either atorvastatin (2317) or placebo (2288)- into the lipid-lowering arm (LLA). The remaining 3875 patients formed the non-LLA group. A team of two physicians independently adjudicated all causes of death.

Results
3282 (38·3%) patients died; 1640 (38·4 %) and 1642 (38·1 %) of those allocated to atenolol- and amlodipine-based treatment respectively. 1768 deaths occurred in those assigned to LLA; 903 (39·5%) and 865 (37·3%) in those allocated to placebo and atorvastatin respectively. Of all deaths, a third (1210) were from CV-related causes. Amongst those in BPLA, there was no overall difference in all-cause mortality, but there were numerically fewer CV deaths (adjusted hazard ratio [HR] 0·90 [95% confidence interval, 0·81 to 1·01, p= 0·0776]) and significantly fewer stroke deaths (adjusted HR 0·71 [0·53 to 0·97], p=0·0305) in the amlodipine-based compared with the atenolol- based treatment groups. There was no interaction between treatment allocation in the BPLA and the LLA. However, in the non-LLA group, there were fewer CV deaths (adjusted HR 0·79 [0·67 to 0·93], p = 0·0046) amongst those assigned to amlodipine-based compared with atenolol-based treatment (test for interaction test between the two BP treatments and allocation to LLA or not, p=0·0220). Amongst those in LLA, there were significantly fewer CV deaths (HR 0·85 [0·72 to 0·99], p=0·0395] in those assigned to statin vs. placebo, and numerically fewer all-cause and coronary heart disease deaths (HR 0·92 [0·84 to 1·01], p=0·0913 and HR 0·78 [0·58 to 1·04], p=0·0884, respectively).

Interpretation
These findings demonstrate the long term beneficial effects on mortality from antihypertensive treatment with a calcium channel blocker-based treatment regimen and lipid-lowering with a statin: patients on amlodipine-based treatment had a fewer stroke deaths, and patients on atorvastatin had fewer CV deaths more than ten years after trial closure. Overall, the ASCOT Legacy study supports the view that interventions on blood pressure and cholesterol are associated with long term benefits on cardiovascular outcomes.

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Introduction

Guidelines for the management of patients with hypertension highlight the importance of blood pressure control, although the target blood pressures, particularly systolic pressure, remain controversial. Some guidelines advocate preferred drug treatment regimens[1,2] based on the results of cardiovascular (CV) disease outcome trials such as the Anglo-Scandinavian Cardiovascular Outcomes Trial (ASCOT)[3] and Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trials,[4,5] whereas others simply focus on blood pressure control irrespective of particular drug classes.[6-10] The trials on which the guidelines are based typically involved a duration of follow up around 5 years.

Previously, hypertension trials of active drug treatment compared with placebo, with substantial post randomization (in-trial) blood pressure differences between the two arms, have been linked to longer-term legacy benefits in favour of the active treatment arm.[11] In comparison, long-term post-trial follow-up data from trials comparing two active treatments is sparse.[12] It is uncertain, therefore, if more recent trials which compared active treatment regimens and demonstrated the benefits of a regimen based on a calcium channel blocker (CCB) and an angiotensin-converting enzyme (ACE) inhibitor, [3,4] would have a long-lasting beneficial effect. Several long-term post-trial follow-up of placebo-controlled trials of statins have been reported,[13,14,15] which have demonstrated persistent legacy benefits in those previously assigned statin, but none involving hypertensive patients who were also assigned an intervention with different antihypertensive strategies.

ASCOT was designed to compare two antihypertensive treatment strategies and, in a factorial design, to compare atorvastatin with placebo.[16]

In the present report we have evaluated the mortality data from the cohort of patients originally recruited into ASCOT from the UK (the ASCOT Legacy study), approximately16 years after entry into the trial and ten years after trial closure to establish whether assignment to either of the original blood pressure- lowering regimens, or to atorvastatin compared with placebo, conferred long-term legacy benefits on both all-cause and cause-specific mortality outcomes.

Methods

The detailed ASCOT protocol, including study design, conduct, and baseline characteristics has been published[16] and further detailed information is available on the ASCOT website (www.ascotstudy.org).

ASCOT Trial and patient profile

Briefly, ASCOT was designed to compare two antihypertensive treatment strategies, amlodipine to which perindopril was added as necessary (amlodipine-based) and atenolol, to which bendroflumethiazide was added as necessary (atenolol-based) (the blood pressure-lowering arm [BPLA]) and, in a 2x2 factorial design, for those with total cholesterol of < 6·5 mmol/L, and not currently taking a statin or a fibrate, to compare atorvastatin and placebo (the lipid-lowering arm [LLA]).

This population consisted of hypertensive men and women, aged 40 to 79 years at randomisation, with at least three additional risk factors for CV disease, but with no history of prior coronary heart disease (CHD) events, currently treated angina, or a recent cerebrovascular event within three months from randomization. The primary outcome was non-fatal myocardial infarction and fatal CHD. Patients were originally recruited between February 1998 and May 2000, mostly from family practices. In the Nordic countries, individual patients from 686 family practices were randomized, and in the United Kingdom (UK) and Ireland, most randomized patients were referred from family practices to regional study centres.

In all, 19257 patients were randomized to the BPLA, and of these, 10240 were randomized to the LLA. 9017 were in the non-LLA group, of whom, about a third were on previous lipid-lowering or aspirin therapy.

In late 2002, at the recommendation of the Data Safety Monitoring Board, the LLA was stopped prematurely,[17] after a median follow-up of 3·3 years, on account of substantial benefits of atorvastatin on the primary endpoint. These patients continued to be followed up until the end of the BPLA. During that period, these LLA-patients were offered

open-labelled statin, and approximately two thirds accepted, in addition to their assigned blood pressure--lowering treatment.

The BPLA was also prematurely stopped (at the recommendation of the Data Safety Monitoring Board), mainly on account of significantly higher mortality amongst those allocated to atenolol-based treatment compared with those on amlodipine-based treatment. Database lock was in June 2005, with the last follow-up of patients ranging from December 2004 to April, 2005.[3]

The study conformed to Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol and all subsequent amendments 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).

ASCOT Legacy cohort

All 8580 ASCOT trial patients from the UK, form the cohort of the ASCOT Legacy study. All these patients were followed until the end of the BPLA, during which period 717 died. Of the remainder, 7302 (from all but two trial sites in the UK, where consent from the patients for the follow-up was not obtained) were flagged for death with the Office for National Statistics and the General Register Office for Scotland for post trial follow-up. In this report, we have used all reported deaths on or before 31st December, 2015. However, there are no data on morbidity and treatment after the end of the BPLA.

A team of two physicians independently adjudicated the cause of death, using pre-specified criteria consistent with the definitions used during the in-trial period. In these analyses, we report on all-cause mortality, and deaths from CV and non-CV causes. All CV deaths were further adjudicated to report on deaths due to CHD or stroke. Similarly, non-CV deaths were sub-categorized to report on cancer-related deaths.

Statistical methods

All analyses were performed using the intention-to-treat principle, and thus in-trial follow-up is included for those 561 patients (from two sites) who were not flagged after the closure of the BPLA, and those who dropped-out of the BPLA early. For those still alive, censoring was defined as the end of follow-up (31st December 2015) or the end of BPLA for those survivors who did not consent. The end of the LLA period was defined as 1st October, 2002 and the end of the BPLA was the last follow-up before the database lock in June, 2005.

For both BPLA and LLA, and for each death outcome, separate Cox Proportional Hazards models were developed to estimate hazard ratios and 95% confidence intervals (CIs) comparing treatment groups. Both unadjusted and adjusted analyses were conducted. For analysis of each cause-specific death, all deaths from other causes were handled as censorings. We adjusted for the following pre-specified covariates at baseline: age, sex, ethnicity, age at leaving full-time education (reflecting socio-economic status [SES]), body-mass index (BMI), systolic blood pressure, total cholesterol, the presence of diabetes, smoking history, and the other treatment comparison (for example, for the treatment group comparisons in the BPLA, we adjusted for the allocation to statin or a placebo, with a dummy variable for those in the non-LLA group).

For each Cox model, the assumption of proportionality was tested using Schoenfield's residuals,[18] and we found no evidence of any deviation. We pre-specified tests for interaction between the two treatment comparisons: blood pressure lowering treatment regimens and allocation to statin or a placebo. Tests for interactions were also performed to determine whether the impact of the two blood pressure- lowering treatments differed between subgroups such as presence of diabetes, age, or allocation to the LLA or not.

Statistical tests were two-sided and a P-value of $<0{\cdot}05$ was considered statistically significant. All statistical analysis was performed using STATA 15 (STATA Corporation, College Station, TX, USA).

Role of the funding source

The original ASCOT-Trial was conceived, designed, and coordinated by an investigator-led independent Steering Committee with two non-voting members from the principal funding source (Pfizer). Data collection, analysis, and interpretation and preparation of all reports were done independently of the funding sources.

The ASCOT-legacy cohort was investigator initiated and led. Data collection, analysis, and interpretation and preparation of all reports were done independently. There was no inputs, or any kind of involvement, from any of the funding body (Foundation for Circulatory Health, and Pfizer). All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results:

ASCOT Legacy cohort

The ASCOT Legacy cohort consisted of 8580 hypertensive patients from the UK, with mean age at baseline 64.1 years. Baseline characteristics of these patients were similar to those randomized from the Nordic countries, except that those in the UK ASCOT Legacy cohort were more ethnically diverse (10% vs 1%, non-Caucasians), with more males (81·1% vs 72·9%) and fewer current smokers (23·8% vs 36·1%).

Table 1 shows the baseline characteristics of those in the ASCOT Legacy cohort, randomized to the BPLA (either amlodipine- (4305) or atenolol- (4275)-based treatments), and 4605 re- randomized to either atorvastatin (2317) or placebo (2288) in the LLA. **Supplementary table S1** describes the baseline characteristics of those in the ASCOT Legacy cohort, randomized to the LLA or not, 3975 of whom were in the non-LLA group. Compared with those allocated to the LLA, the non-LLA group had more women, more patients with > 4 CV risk factors at baseline, and higher mean baseline total-and LDL-cholesterol, more with a history of previous use of lipid- lowering therapy or previous vascular disease.

The trial profile in **Figure 1** describes numbers of patients and deaths by randomized treatment allocations of the ASCOT Legacy cohort. During a median follow-up of 15·7 years (interquartile range [IQR] 9·7 to 16·4 years), 3282 (38·3%) of all patients died: 1640 (38·4 %) and 1642 (38·1 %) in those allocated to atenolol- and amlodipine-based treatment respectively. 1768 (58%) of all deaths occurred in those assigned to LLA; 903 (39·5%) and 865 (37·3%) in those allocated to placebo and atorvastatin respectively. Of all deaths, a third (1210) were from CV-related causes.

ASCOT Legacy: the BPLA

Table 2a describes the number of events and incidence rates (per 100 person years) for both total and cause specific mortality by the two BP-lowering treatment regimens for the in-trial period, post-trial period and throughout all follow-up. During the in-trial period (median 5·5 years follow-up), those on atenolol-based treatment had more deaths compared with those on amlodipine-based treatment both for all-causes and CV- mortality, and for the CHD- and stroke- mortality components of the CV mortality. However, during the post-trial period (an extra 10·7 years of median follow-up) no additional treatment differences in mortality were noted, except for stroke mortality, where the differential in the event rates amongst those on 2 treatment regimens persisted.

Table 3a demonstrates that overall (during a median follow-up of 15·7 years), amongst those in the BPLA, there was no statistically significant treatment difference in all-cause mortality, but there were numerically fewer CV deaths (adjusted hazard ratio [HR] 0·90 [95% confidence interval, 0·81 to 1·01, p= 0·0776]) and significantly fewer stroke deaths (adjusted HR 0·71 [0·53 to 0·97], p=0.0305) in the amlodipine-based, compared with the atenolol-based, treatment groups (see **figures 2a to 2d** [and supplementary figures S1 a and b], for Kaplan-Meier plots). Compared with the risks (HRs) during the in-trial period, the risk of CV death attenuated subsequently (HR from 0·74 [0·58 to 0·95] to 0·90 [0·81 to 1·01]). However, for stroke mortality, within the trial effect size (HR 0·69) was similar to that at the end of the follow-up (HR, 0.71), becoming statistically significant (p=0·0305) with the accrual of more events.

There was no interaction between treatment allocation in the BPLA and the LLA (see supplementary table S2). Other subgroup analyses provided no evidence for treatment interactions with either age or diabetes status at baseline. However, there were differences in the effect of the two BP treatment regimens, based on whether a subject was allocated to the LLA or not (test for interaction, p=0·0220). Supplementary table S3 shows the number of events, and incidence rates, for cause-specific deaths in the two treatment groups, stratified by allocation to LLA or not (the non-LLA group). In the non-LLA group, compared with those on atenolol-based treatment, those allocated to amlodipine-based treatment had significantly fewer CV deaths (adjusted HR 0·79 [0·67 to 0·93], p =

0·0046) and CHD deaths (adjusted HR 0·76 [0·59 to 0·93], p=0·0439, and numerically fewer stroke deaths (adjusted HR 0·67 [0·43 to 1·04], p= 0·0751) (see supplementary **figures S2 a-d,** for corresponding KM plots in the LLA and non-LLA group).

ASCOT Legacy: the LLA

Table 2b describes the number of events and incidence rates for the cause specific mortality amongst those assigned to atorvastatin or a placebo in the LLA of the ASCOT Legacy cohort; during the in-trial period, post-trial period and throughout all follow-up. Compared with those assigned to placebo, those assigned to atorvastatin had numerically fewer all-cause -, CV - and CHD-deaths during both in trial and post-trial period. However, there was no evidence of a treatment difference in stroke deaths (see **figures 3 a-d**, for corresponding KM plots, and supplementary figures S3 a and b).

Table 3b presents estimates for these mortality differences between atorvastatin and placebo in the LLA of the Legacy cohort, both for in-trial period and overall follow-up. There were significantly fewer CV deaths (HR 0·85 [0·72 to 0·99], p=0·0395] in those assigned to atorvastatin vs. placebo, with non-significant differences in the same direction for all-cause and coronary heart disease mortality (0.92 [0.84 to 1.01], p=0.0913 and 0.78 [0·58 to 1·04], p=0·0884, respectively). Sub-group analyses by age or presence of diabetes at baseline showed no effect modification.

Discussion

These findings on hypertensive patients with no previous coronary event, demonstrate the long-term benefits from antihypertensive treatment with a CCB- based treatment regimen and lipid- lowering with a statin, in particular, assignment to amlodipine-(adding perindopril as required)- based treatment was associated with fewer stroke deaths throughout 16-years of follow-up (supplementary figure S4). We also confirm the long-term benefits of statin therapy in reducing the risk of CV deaths.[13,14,15,19,20] This study is the first to report that both blood pressure- and lipid-lowering treatments confer such long-term benefits. Furthermore, findings for the higher risk sub-group in the non-LLA group, confirm the long-term benefits of blood pressure lowering therapies in such patients. Also, there are differences in the benefits conferred with the use of different blood pressure lowering regimens, even if the in- trial blood pressure control gained is similar (see supplementary table S4 a and b)

The only other large trial to have studied CV outcomes of both antihypertensive therapy and lipid- lowering with statins, the Antihypertensive and Lipid Lowering to prevent Heart Attacks Trial (ALLHAT),[21,22] compared different monotherapies with similar add on antihypertensive treatments. Both ASCOT and ALLHAT trials evaluated the potential benefits of statins in hypertensive patients. In ASCOT, atorvastatin was compared with placebo, and in ALLHAT, pravastatin was compared with "usual care". Unfortunately in ALLHAT, many patients in the "usual care" arm received statins and only a small difference in cholesterol between the treatment groups was achieved, which resulted in the trial being underpowered to compare effects on major cardiovascular endpoints. [22, 23] The findings from the extended follow-up of those assigned to three limbs of the antihypertensive study: chlorthalidone, amlodipine and lisinopril were mixed.[24,25] The in-trial benefits apparent with the use of chlorthalidone vs. amlodipine and lisinopril, respectively, were no longer evident in the long-term follow-up.

In long-term follow-up of trials in hypertensive patients,[11] in which active treatment was compared with placebo, and where blood pressure differences in the trials were associated with substantial reductions in CV events, a legacy or carry over effect has been observed in the post-trial period, [26-29] with long-term reductions – on average 9%, in mortality in the group previously receiving active treatment[11]. However, in ASCOT, which compared different active (alternative) treatment strategies,[16] the long-term outcome benefits associated with the amlodipine-based regimen could not be attributed to earlier differences in blood pressures during the trial.[30] First, as previously reported with the main trial outcome[3] and a post-hoc analysis[30], there was only a small difference in blood pressure of 2·9/1·8 mmHg between the two treatment arms. Also, in the ASCOT UK Legacy population overall mean differences in blood pressure recorded during the trial were only around 1·2/1·6 mmHg (supplementary table S4a). This small magnitude of blood pressure difference cannot account for the sustained and significant differences in the stroke mortality apparent in this long-term follow-up.

Initially, we attributed the benefits of the amlodipine-based treatment to differences the in metabolic profile, including adverse effects of glycaemia associated with the atenolol-based therapy, and other differences including

small changes in lipids and electrolytes.[30] However, these changes alone were insufficient to explain the observed in-trial effects on mortality and CV events.[30] We have subsequently shown other important differences between the two treatment arms, with atenolol-based treatment lowering central aortic pressure substantially less than amlodipine-based treatment.[31] Also blood pressure variability was a major determinant of CV outcome in ASCOT,[32] and was reduced to a much greater extent with the amlodipine- based compared with the atenolol-based regimen.[33]

We believe these mechanisms, and potentially others as yet unknown, are likely explanations for findings in ASCOT-BPLA, and that they also contribute to the long term benefits we have observed in the ASCOT Legacy population. We are in the process of further investigating these, together with studies on potential genetic and other biomarker predictors of CV events, which may explain the differences we have observed during this 16 year follow-up.

For the blood pressure trial, the most striking treatment difference was in stroke death which, from our earlier reports, was closely associated with blood pressure variability[33]. Our observations also show that, whilst during the trial there was a significant reduction in CV mortality, this effect was attenuated in subsequent follow-up , except for stroke mortality, where the beneficial effect remained essentially the same even ten years after trial closure. These dilutional effects may reflect that after the trial, similar overall treatment strategies would have been used by both groups of patients. Nevertheless, by way of contrast, the persistence of the effect size on stroke deaths may reflect the close relationships that this outcome has with blood pressure treatment,[34]
We also observed a differential legacy between the two treatment groups, according to the baseline risk of the patients. Thus, when evaluating the event rates in the two blood pressure treatment arms, amongst those randomised in the LLA compared with the non-LLA (table 4), for those assigned amlodipine-based treatment, there was little difference in event rates for the stroke and CV mortality, and very small differences in the CHD mortality. This implies that this combination of medications confers a similar effect irrespective of baseline risk. However, for those assigned the atenolol-based treatment there was, compared with those in the LLA, an excess event rate amongst those not included in LLA.

Following early stopping of the LLA, the beneficial mortality effects of atorvastatin tracked, with little dilution of effect over the long-term. In the ASCOT-LLA Legacy cohort, the effect sizes of CV and all-cause mortality at the end of trial, and also 13 years later remained similar but, with an increasing number of events, the mortality benefits became more significant for CV deaths, with a trend towards long-term benefit for all cause and CHD mortality. Similar findings, particularly the relationship between the use of a statin and reduction in the cardiovascular mortality in long-term follow-ups have been reported in other trials,[13,14,1519,20] but the mechanism for these durable and legacy effects remains unclear.

These analyses have several limitations. After the trial closure, we have no data on anti-hypertensive and lipid-lowering medications, and indeed other treatments. Thus, we cannot reliably ascertain what differences, if any, in post-trial blood pressures and their treatment existed in the longer term. However, after the closure of the LLA, a similar number of patients assigned to atorvastatin or placebo received a statin during the 2·2 year extension during final years of the BPLA of the trial.[35] Another limitation is that we have no morbidity data following trial closure. We agree that the availability of such data would provide for a more comprehensive evaluation, and we are in the process of developing appropriate linkages to acquire them. However, we believe that the mortality data are robust. Generalizability of this population can be questioned. The patients in this cohort were of median age 64 years, hypertensive and with some common risk factors, which would make them fairly representative of those of similar age in the community. Indeed, in previous unpublished work, we have compared our population with the hypertensive patients from the community reported in the Health Survey of England and found them fairly similar. Lastly, these findings need replication in other studies. The biggest strength of this study is that it is the first to report on a large hypertensive cohort involving both blood pressure and lipid-lowering treatments and their impact on long-term mortality, with substantial power to evaluate mortality differences between treatments.

Conclusion

These legacy outcomes from the ASCOT trial demonstrate long term benefits from antihypertensive treatment with a CCB- based treatment regimen and lipid- lowering with a statin, 16 years after entry into the trial, and more than ten years following its closure. It is reported for the first time that the legacy benefit from the amlodipine-based regimen in reducing risk of stroke mortality appears independent of achieved blood pressure levels, and several

possible explanations have been provided. The long term benefits of statins on CV mortality reduction are confirmed. Overall, our findings support the belief that interventions on blood pressure and cholesterol are associated with long term benefits on CV outcomes.

Contributors
A Gupta and P Sever had the original idea for the Legacy study, designed the protocol, supervised the data collection and statistical analyses and wrote the initial drafts of the manuscript. J Mackay and A Whitehouse carried out independent and blinded classification of all deaths and commented on the manuscript. Statistical analyses were carried out by A Gupta, T Godec and T Collier. S Pocock provided statistical oversight and reviewed the manuscript. N Poulter contributed to protocol design and reviewed the manuscript.

Declaration of interests
AG received support for expenses incurred from the Foundation for Circulatory Health, and Servier. PS received research grants from Imperial College London, Pfizer and Servier and honoraria for advisory boards and speakers bureau from Pfizer and Servier. Neil Poulter has received financial support from several pharmaceutical companies which manufacture BP-lowering agents, for consultancy fees (Servier), research projects and staff (Servier, Pfizer) and for arranging and speaking at educational meetings (AstraZeneca, Lri Therapharma, Napi, Servier and Pfizer). N Poulter holds no stocks and shares in any such companies. All other authors declare no competing interests.

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Data sharing
Relevant and individual participant level data that underlie the results reported in this article (after de-identification) can be made available to the researchers, and after approval by the Scientific Committee of both the ASCOT trial, and the Legacy study, respectively. Proposals may be submitted to the ASCOT Scientific committee directly. Details can be accessed at www.ascotstudy.org.

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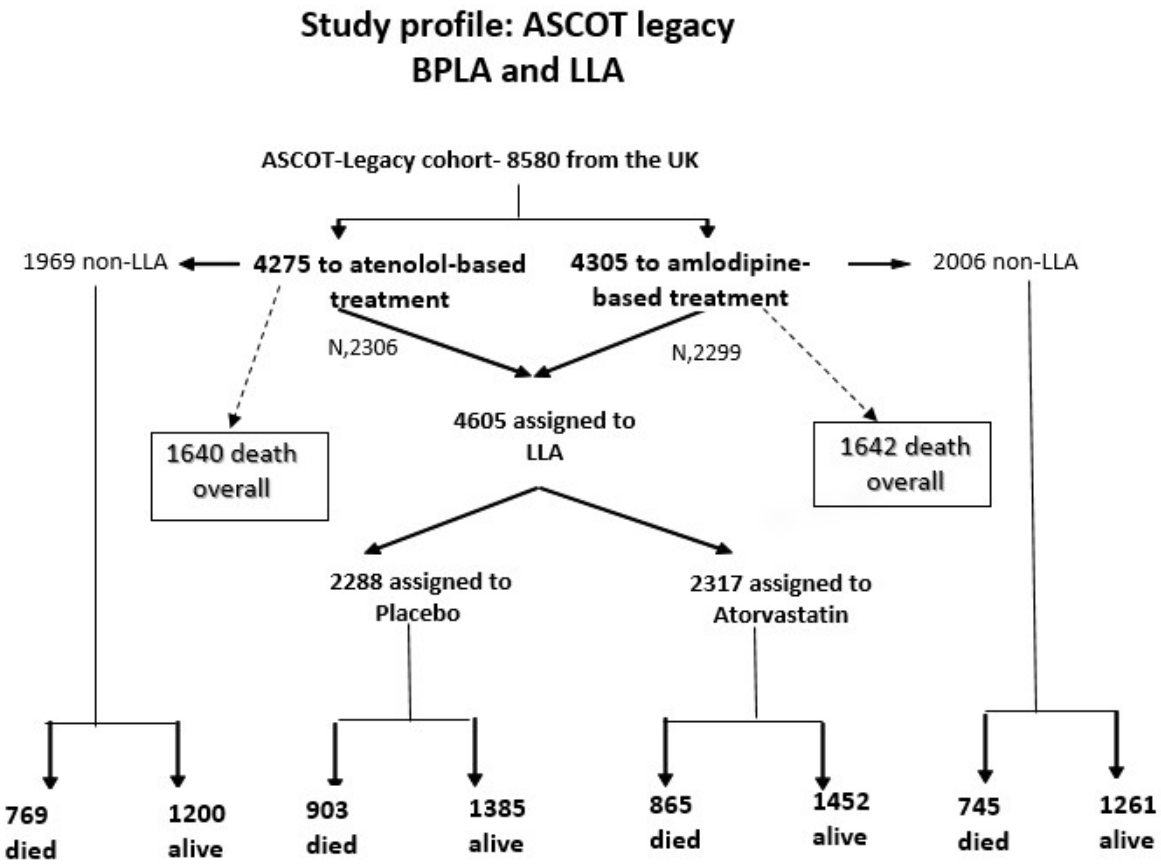
Figure Legend

Figure 1: The ASCOT-Legacy study profile: patient population stratified by the treatment allocation

Figure 2 (a-d): The risk of cause-specific deaths among those allocated to the amlodipine based treatment as compared to those on the atenolol-based treatment in the 16 year follow up of the ASCOT-Legacy cohort assigned to the BPLA

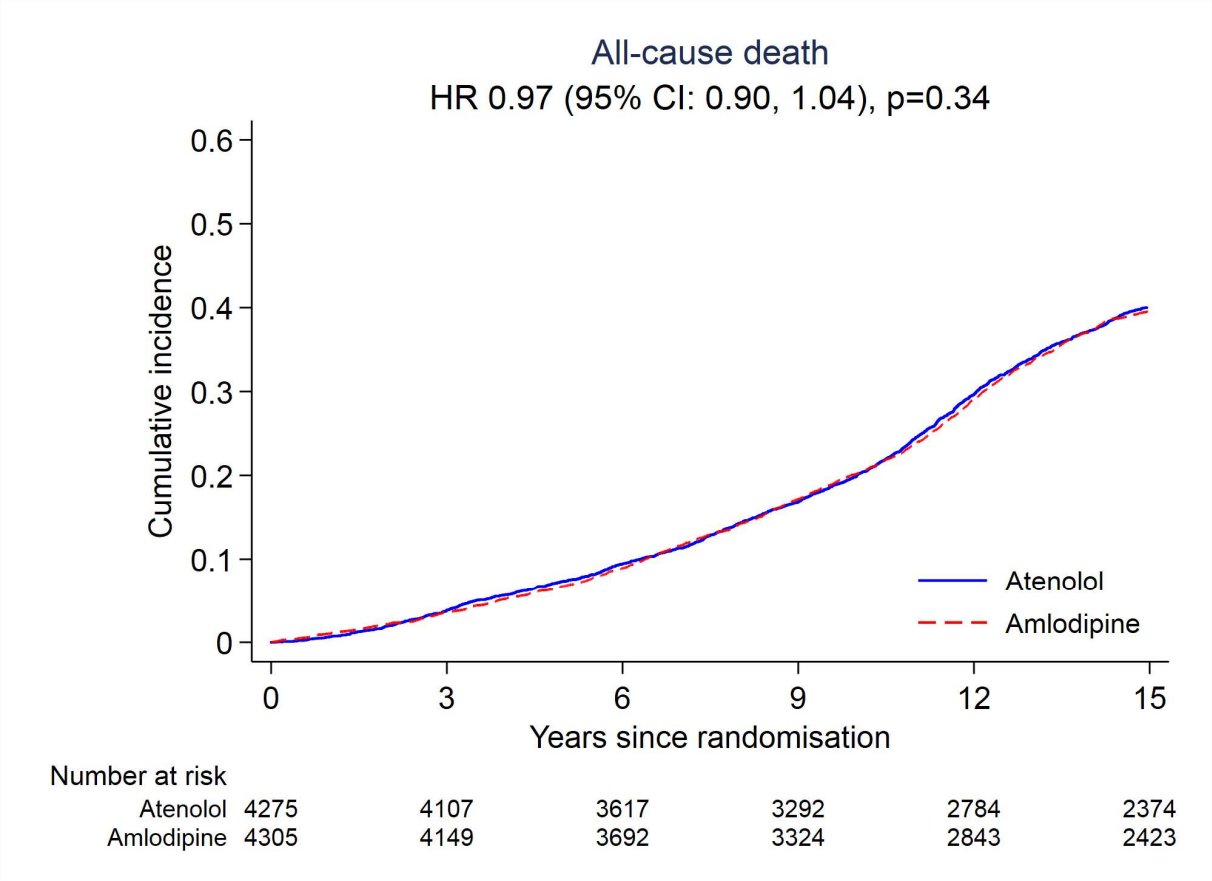
Figure 3 (a-d): The risk of cause-specific deaths among those allocated to the atorvastatin compared with placebo in the 16 year follow up of the ASCOT-Legacy cohort assigned to LLA

Figure 1: The ASCOT-Legacy study profile: patient population stratified by the treatment allocation



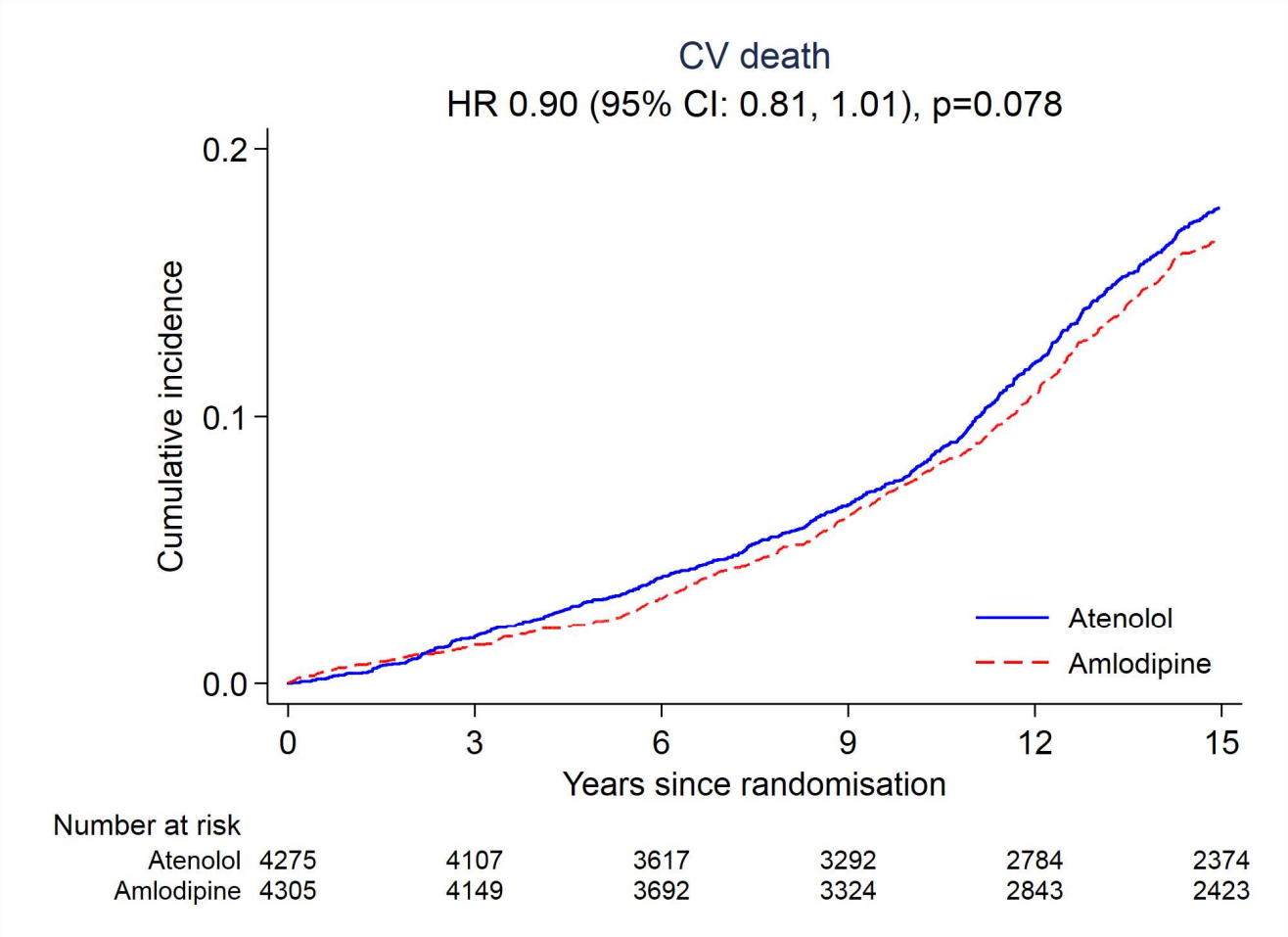
BPLA: blood pressure lowering arm ; LLA: lipid-lowering arm

Figure 2a: Kaplan Meirer plots for cumulative incidence of all-cause mortality amongst those allocated to the two BP-treatment groups



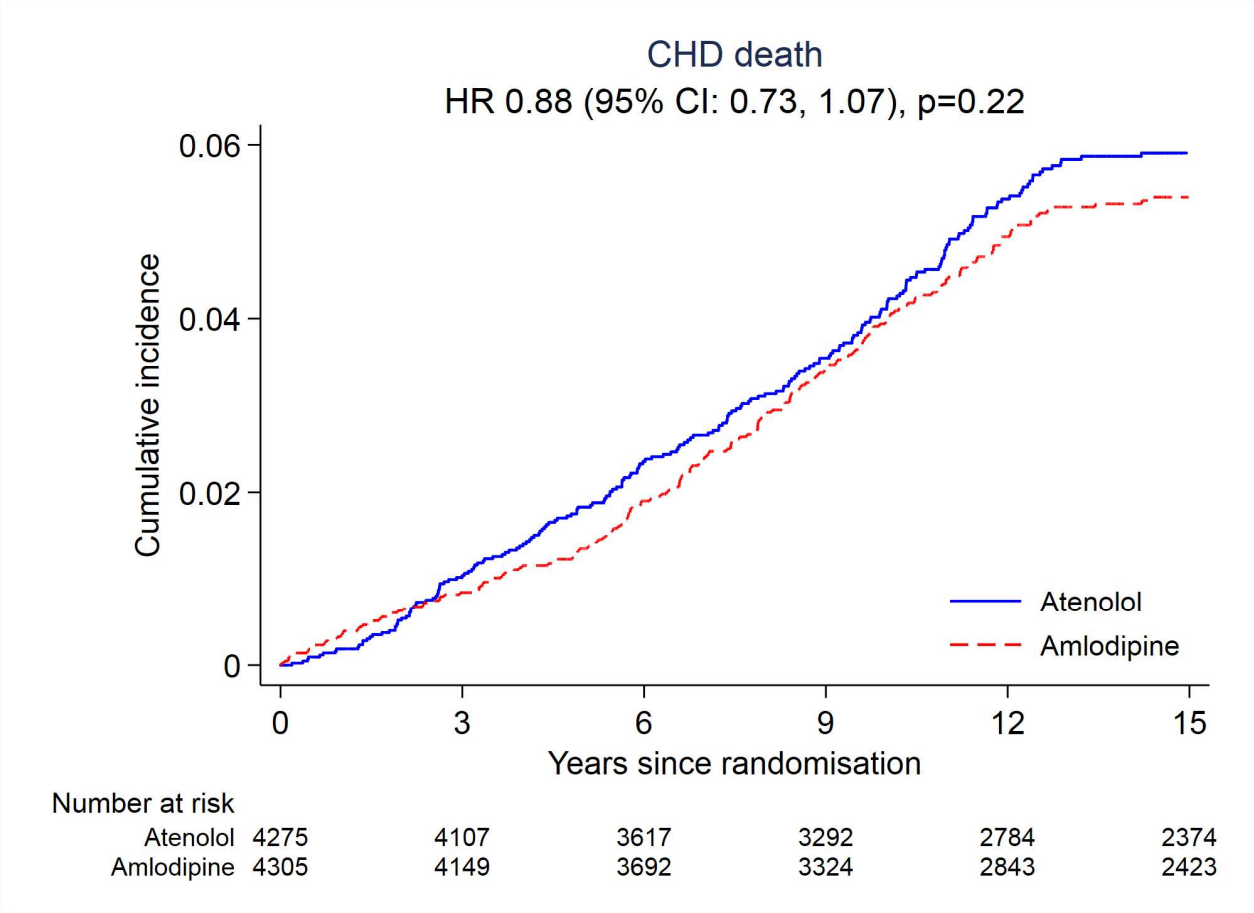
HR: hazard ratio

Figure 2b: KM plots for the cumulative incidence of the cardiovascular mortality amongst those allocated to the two BP-treatment groups



CV: cardiovascular mortality

Figure 2c: KM plots for the cumulative incidence of the coronary heart disease mortality amongst those allocated to the two BP-treatment groups



CHD: coronary heart disease -related mortality

Figure 2d: KM plots for the cumulative incidence of the stroke mortality amongst those allocated to the two BP-treatment groups

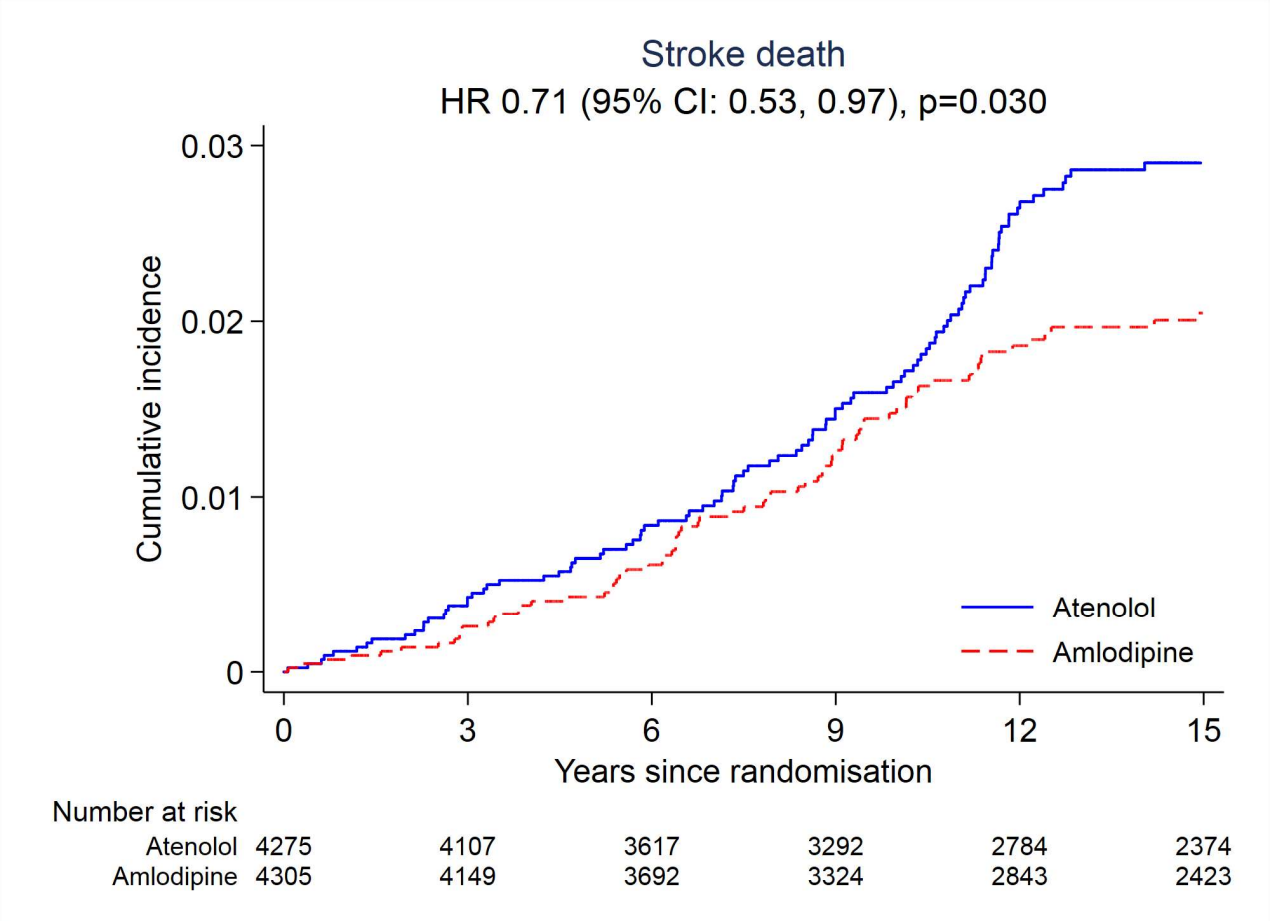


Figure 3a: KM plots for cumulative incidence of the all-cause mortality amongst those allocated to the atorvastatin or a placebo

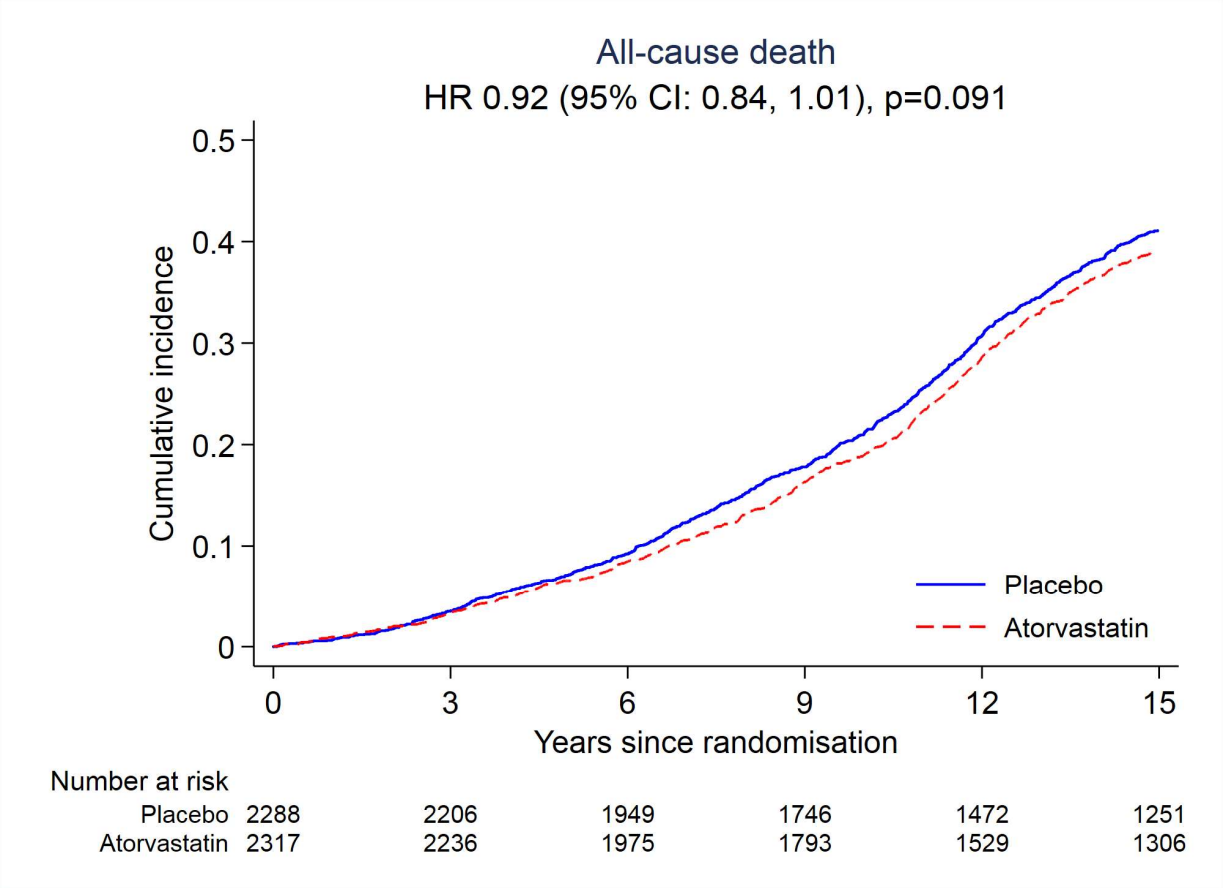


Figure 3b: KM plots for the cumulative incidence of the cardiovascular mortality amongst those allocated to the atorvastatin or a placebo

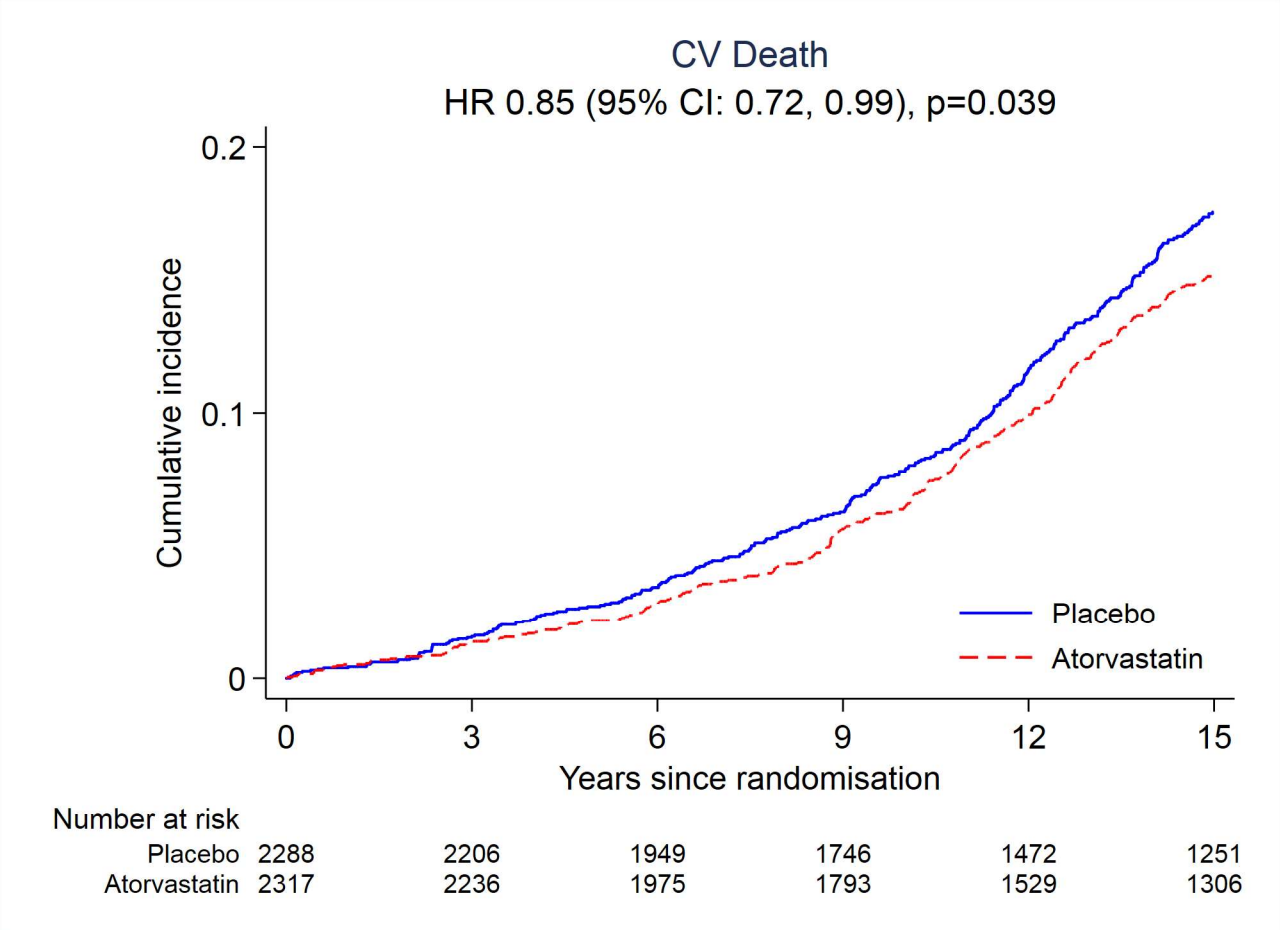


Figure 3c: KM plots for the cumulative incidence of the coronary heart disease mortality amongst those allocated to the atorvastatin or a placebo

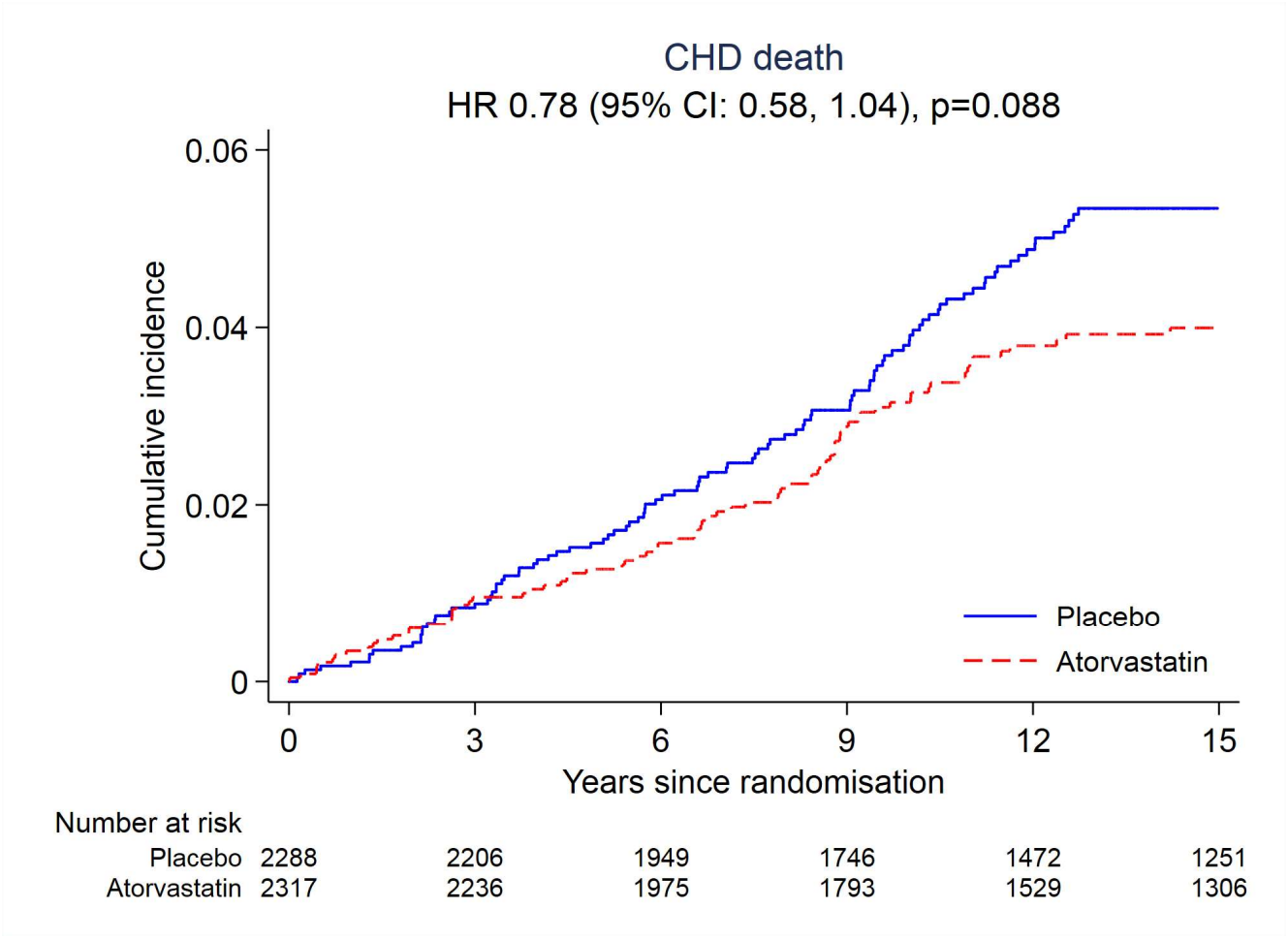


Figure 3d: KM plots for the cumulative incidence of the stroke mortality amongst those allocated to the atorvastatin or a placebo

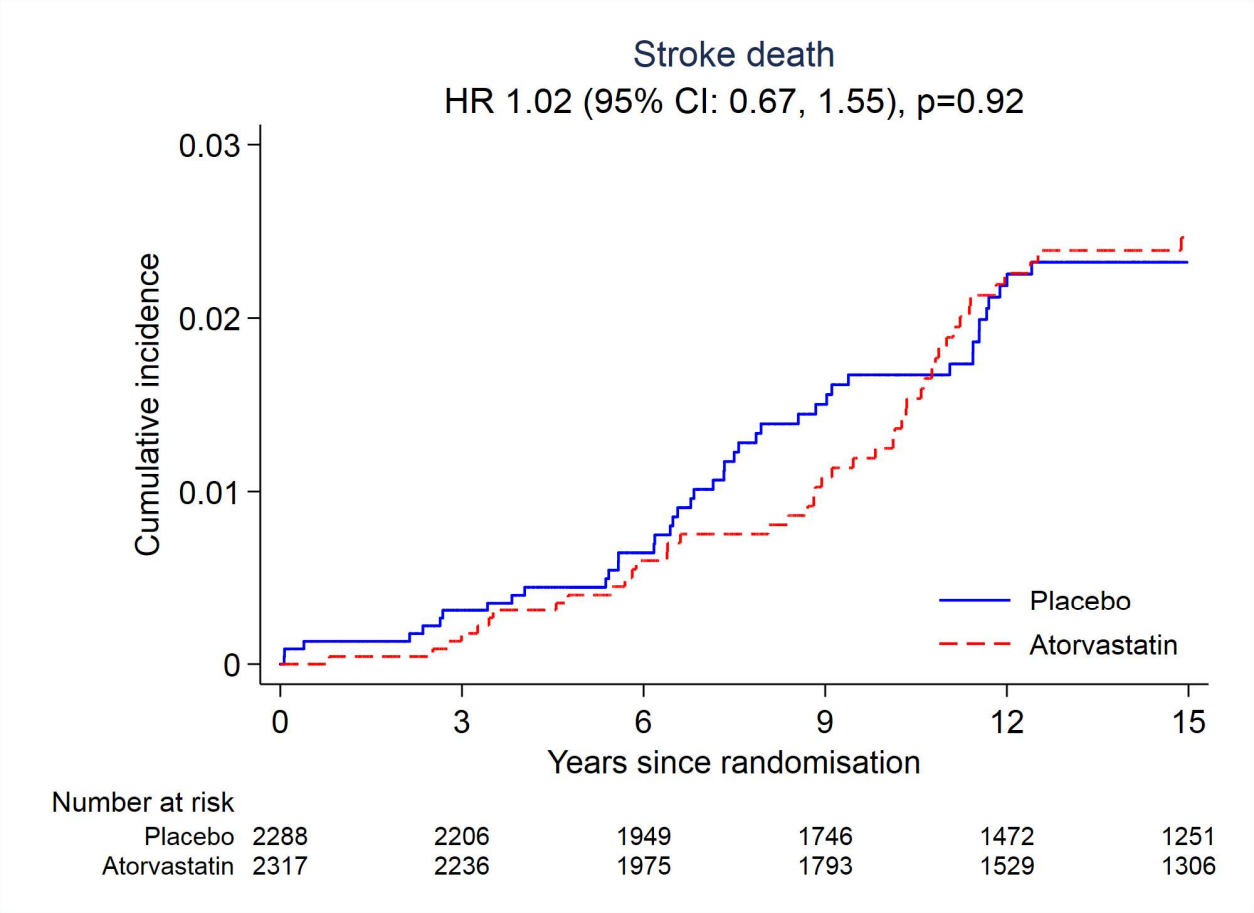


Table 1: Baseline characteristics of those in the ASCOT-Legacy cohort, randomized by blood pressure lowering arms and also by randomized atorvastatin or placebo in the LLA group

Baseline characteristics ASCOT-legacy		BPLA (n, 8580)		LLA (n, 4605)	
		Amlodipine (n, 4305)	Atenolol (n, 4275)	Atorvastatin (n, 2317)	Placebo (n, 2288)
		n (%), mean (SD) or median (IQR)		n (%), mean (SD) or median (IQR)	
Age (years)		64 (8)	64 (8)	64 (8)	64 (8)
Male gender	Male	3492 (81·1%)	3468 (81·1%)	2016 (87·0%)	2004 (87·6%)
Ethnicity	White/Europid	3861 (89·7%)	3840 (89·8%)	2045 (88·3%)	2019 (88·2%)
	South Asian	130 (3·0%)	109 (2·5%)	72 (3·1%)	80 (3·5%)
	Oriental	7 (0·2%)	3 (0·1%)	2 (0·1%)	2 (0·1%)
	Mixed/other	85 (2·0%)	86 (2·0%)	36 (1·6%)	33 (1·4%)
	African	222 (5·2%)	237 (5·5%)	162 (7·0%)	154 (6·7%)
Socio-economic status (age at leaving full time education)*	12-14	1282 (30·0%)	1272 (29·6%)	682 (29·8%)	658 (28·4%)
	15-16	2091 (48·9%)	2165 (50·3%)	1121 (49·0%)	1119 (48·3%)
	17-18	484 (11·3%)	465 (10·8%)	245 (10·7%)	287 (12·4%)
	18+	416 (9·7%)	400 (9·3%)	239 (10·5%)	252 (10·9%)
	Missing	2	3	1	1
Body mass index (kg/m2)		28·9 (4·7)	28·9 (4·6)	28·8 (4·9)	28·8 (4·6)
Smoking status	Current smoker	1035 (24·0%)	1006 (23·5%)	547 (23·6%)	541 (23·6%)
Alcohol status	Non-drinker	1088 (25·3%)	1089 (25·5%)	574 (24·8%)	571 (25·0%)
	1-13 units per week	1816 (42·2%)	1831 (42·8%)	1010 (43·6%)	983 (43·0%)
	14+ units per week	1401 (32·5%)	1355 (31·7%)	733 (31·6%)	734 (32·1%)
Systolic blood pressure (mmHg)		162 (18)	162 (17)	162 (17)	162 (18)
Diastolic blood pressure (mmHg)		92 (10)	92 (10)	92 (10)	93 (10)
Heart rate (bpm)		71 (13)	71 (12)	70 (12)	71 (13)
Total cholesterol (mmol/L)		5·9 (1·1)	5·9 (1·1)	5·5 (0·8)	5·5 (0·8)
HDL-cholesterol (mmol/L)		1·3 (0·4)	1·3 (0·4)	1·3 (0·3)	1·3 (0·3)
LDL-cholesterol (mmol/L)		3.8 (1.0)	3.8 (1.0)	3.5 (0.7)	3.5 (0.8)
Serum triglycerides (mmol/L)		1·6 (1·2 to 2·3)	1·6 (1·2 to 2·3)	1·4 (1·0 to 2·0)	1·4 (1·1 to 2·0)
Fasting plasma glucose (mmol/L)		5·6 (5·1 to 6·6)	5·6 (5·1 to 6·6)	5·6 (5·1 to 6·5)	5·6 (5·1 to 6·6)
Serum creatinine (umol/L)		99 (89 to 109)	98 (89 to 109)	99 (90 to 109)	99 (90 to 109)
Presence of diabetes mellitus		1139 (26·5%)	1145 (26·.8%)	621 (26·8%)	630 (27·5%)
Number of cardiovascular risk factors	3**	2055 (47·7%)	2044 (47·8%)	1201 (51·8%)	1141 (49·9%)
	4	1416 (32·9%)	1417 (33·1%)	716 (30·9%)	746 (32·6%)
	5 or more	834 (19·4%)	814 (19·0%)	400 (17·3%)	401 (17·5%)
History of stroke / TIA (> 3 months ago)		507 (11·8%)	492 (11·5%)	233 (10·1%)	239 (10·4%)
History of peripheral vascular disease		359 (8·3%)	383 (9·0%)	160 (6·9%)	150 (6·6%)
Presence of atrial fibrillation		60 (1·4%)	60 (1·4%)	36 (1·6%)	32 (1·4%)
Prior antihypertensive treatment		3961 (92·0%)	3924 (91·8%)	2118 (91·4%)	2106 (92·0%)
Prior lipid-lowering treatment		490 (11·4%)	478 (11·2%)	29 (1·.3%)	22 (1·0%)
Prior aspirin use		1083 (25·2%)	1040 (24·3%)	533 (23·0%)	519 (22·7%)

* 5 patient with missing SES status. ** including 37 who were with 2 risk factors only; BPLA: blood pressure lowering arm; LLA: lipid-lowering arm; HDL: high density lipoprotein; LDL: Low density lipoprotein; TIA: transient ischemic attack.

Table: 2a. Incidence rates for both total and cause specific mortality amongst those assigned to the two blood pressure lowering treatments in the ASCOT-Legacy cohort, during the in-trial period, post-trial period and throughout all follow-up

	In trial (BPLA) (mean follow-up, 5·5 year)				Post-BPLA (mean follow-up, 10·7 years)				Total follow-up (mea	
	Atenolol-based (N=4275)		Amlodipine-based (N=4305)		Atenolol-based (N=3613)		Amlodipine-based (N=3688)		Atenolol -based (N=4275)	
Cause of death	**n**	**Rate***	**n**	**Rate***	**n**	**Rate***	**n**	**Rate***	**n**	**Ra**
All-cause	370	1·62	347	1·50	1270	3·97	1295	3·98	1640	2·
CV	149	0·65	115	0·50	474	1·48	472	1·45	623	1·
CHD	86	0·38	66	0·29	127	0·40	132	0·41	213	0·
Stroke	30	0·13	21	0·09	69	0·22	51	0·16	99	0·
Non-CV	221	0·97	232	1.00	796	2·49	823	2·53	1017	1·
Cancer	135	0·59	146	0·63	440	1·37	451	1·39	575	1·

*Rate per 100 person years

Atenolol-based regimen: atenolol adding thiazide diuretic as required; Amlodipine-based regimen: amlodipine adding perindopril as required

Table: 2b. Incidence rates for the cause specific mortality amongst those assigned to either atorvastatin or a placebo in the lipid lowering arm of the ASCOT-Legacy cohort, during the in-trial period, post-trial period and throughout all follow-up

	In-trial (LLA) (mean follow-up, 3·1 year)				Post-LLA (mean follow-up, 13·2 year)				Total follow-up (mea	
	Placebo (N=2288)		Atorvastatin (N=2317)		Placebo (N=2198)		Atorvastatin (N=2234)		Placebo (N=2288)	
Cause of death	**n**	**Rate***	**n**	**Rate***	**n**	**Rate***	**n**	**Rate***	**n**	**Ra**
All-cause	90	1.28	83	1·18	813	3·67	782	3·42	903	3·
CV	36	0.51	30	0·43	289	1·30	255	1·11	325	1·
CHD	19	0.27	19	0·27	84	0·38	62	0·27	103	0·
Stroke	8	0.11	6	0.09	35	0·16	39	0·17	43	0·
Non-CV	54	0.77	53	0·75	524	2·36	527	2·30	578	1·
Cancer	37	0.53	38	0·54	297	1·34	292	1·28	334	1·

* Rate per 100 person years
LLA: Lipid lowering arm; CV : cardiovascular ; CHD: coronary heart disease

Table: 3a. Hazard ratios of both total and the cause-specific mortality amongst those assigned to amlodipine-based therapy as compared to the atenolol-based treatment in the ASCOT-Legacy cohort, during the in-trial, and the total follow-up period

	BPLA in-trial period (Hazard ratio[95%CI])				Total follow-up (Hazar	
Cause of death	**Unadjusted**	**P-value**	**Adjusted***	**P-value**	**Unadjusted**	**P-value**
All-cause	0·93 (0·80, 1·07)	p=0·3130	0·91 (0·78, 1·05)	p=0·2012	0·99 (0·92, 1·06)	p=0·6722
Cardiovascular	0·76 (0·60, 0·97)	p=0·0302	0·74 (0·58, 0·95)	p=0·0177	0·93 (0·83, 1·04)	p=0·1909
CHD	0·76 (0·55, 1·05)	p=0·0930	0·74 (0·53, 1·02)	p=0·0625	0·92 (0·76, 1·11)	p=0·3786
Stroke	0·69 (0·40, 1·21)	p=0·1969	0·69 (0·40, 1·21)	p=0·2013	0·72 (0·53, 0·97)	p=0·0316
Non-CV	1·04 (0·86, 1·25)	p=0·6965	1·02 (0·85, 1·23)	p=0·8292	1·02 (0·94, 1·11)	p=0·6403
Cancer	1·07 (0·85, 1·35)	p=0·5720	1·06 (0·84, 1·34)	p=0·6101	1·02 (0·91, 1·15)	p=0·7090

*Adjusted for baseline age, sex, ethnicity, systolic blood pressure, total cholesterol, body mass index, diabetes, smoking status, years of
status), randomization to the lipid lowering arm (placebo or atorvastatin) or not
CHD: coronary heart disease; non-CV: non-cardiovascular cause of death.

Table: 3b. The risk (hazard ratios) of the cause specific mortality amongst those assigned to the atorvastatin or a placebo in the lipid-lowering arm of the ASCOT-Legacy cohort, during the in trial, and total follow-up period

	LLA in-trial period (Hazard ratio[95%CI])				Total follow-up (Hazard ratio[95%CI])		
Cause of death	**Unadjusted**	**P-value**	**Adjusted***	**P-value**	**Unadjusted**	**P-value**	**Adjusted***
All-cause	0·92 (0·68, 1·24)	p=0·5970	0·93 (0·69, 1·25)	p=0·6379	0·93 (0·85, 1·02)	p=0·1211	0·92 (0·84, 1
Cardiovascular	0·83 (0·51, 1v35)	p=0·4483	0·85 (0·52, 1·38)	p=0·5128	0·85 (0·73, 1·00)	p=0·0459	0·85 (0·72, 0
CHD	0·99 (0·53, 1·87)	p=0·9805	1·02 (0·54, 1·92)	p=0·9594	0·77 (0·57, 1·03)	p=0·0735	0·.78 (0·58, 1
Stroke	0·75 (0·26, 2·17)	p=0·5995	0·80 (0·27, 2·32)	p=0·6774	1·02 (0·67, 1·55)	p=0·9353	1·02 (0·67, 1
Non-CV	0·99 (0·67, 1·44)	p=0·9393	0·98 (0·67, 1·43)	p=0·9227	0·97 (0·87, 1·09)	p=0·6420	0·96 (0·86, 1
Cancer	1·03 (0·65, 1·62)	p=0·9011	1·01 (0·64, 1·59)	p=0·9598	0·96 (0·82, 1·12)	p=0·5932	0·95 (0·82, 1

*Adjusted for age, sex, ethnicity, systolic blood pressure, total cholesterol, body mass index, diabetes at baseline, smoking status, years o
(socio-economic status), randomization to the blood pressure lowering treatment
CHD: coronary heart disease; non-CV: non-cardiovascular cause of death.