Evaluation of C-reactive protein prior to and on-treatment as a predictor of benefit from atorvastatin. A cohort analysis from the Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering Arm

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Abstract

Objectives

To determine whether baseline and on- statin C-reactive protein (CRP) are independent predictors of cardiovascular (CV) outcome beyond LDL-cholesterol (LDL-c).

Background

Use of CRP as a predictor of statin treatment remains controversial

Methods

We investigated the relationship of baseline and on-treatment CRP with subsequent CV events in Cox models using a subset of white subjects with no previous history of CV disease from the UK Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT).

Results

During 5.5 years of follow-up, a total of 488 subjects experienced a CV event. CV risk increased with loge baseline CRP [HR per one standard deviation 1.21 (95% CI: 1.09,1.33) in an adjusted model. In ASCOT-LLA, the relative statin effect in preventing CV events did not differ according to tertiles of baseline CRP (p=0.69). After 6 months atorvastatin, median LDL-c and CRP were reduced by 38.7% and 25.8% respectively. Those who achieved LDL-c below the median, had a reduced CV risk (HR 0.58 [CI 0.34, 0.97]) compared with those who did not. In contrast those who achieved a CRP level below the median did not have a reduced risk of CV (HR 0.95[CI 0.59, 1.55]). Amongst those who achieved an LDL-c below the median, there was no difference in CV risk whether they also achieved a CRP level below (HR 0.55[CI 0.30,1.02]) or above the median (HR 0.56 [CI 0.30,1.03]).
Conclusion

In these primary prevention patients, although baseline CRP independently predicted CV risk, achieved CRP on statin therapy did not predict CV events either alone or in combination with LDL-c.
Abbreviations

ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial

ASCOT-BPLA = Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm

ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm

BMI = body mass index

CRP = C-reactive protein

CVD = cardiovascular disease

CHD = coronary heart disease

CI = confidence interval

FHCHD = family history of coronary heart disease

HDL = high density lipoprotein

HR = heart rate

LDL = low density lipoprotein
Introduction

That inflammation plays an important role in the pathophysiology of atherosclerosis is undisputed (1,2,3). Moreover, various molecular and cellular components of the inflammatory response are activated and may contribute to plaque rupture and the presentation of acute coronary syndromes (4). Therefore the study of biomarkers of inflammation, notably C-reactive protein (CRP) and serum amyloid A, has been a focus of interest for many authors (5,6). Indeed CRP has been proposed, and in some places used, as a clinical tool for cardiovascular disease (CVD) risk prediction scores (7,8,9), yet there remains disagreement regarding its clinical utility, beyond that achieved with conventional biomarkers (10). There has also been notable debate over whether statin-associated CRP reduction is an independent predictor of CVD after consideration of concomitant LDL-cholesterol (LDL-c) reduction (11,12).

We have previously reported, using a nested case-control design, from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) in hypertensive patients selected on the basis of traditional risk factors, that CRP did not usefully improve the prediction of CV events and, critically, that reduction in CRP associated with statin therapy was not a predictor of CV outcome alone or in combination with LDL-c (12). One criticism of our findings was based on the relatively small number of patients in whom on-treatment levels of CRP were available (11), partly a consequence of the matched case-control methodology. Therefore, in order to address these concerns by increasing statistical power and to limit potential bias, we have now extended our observations to include a full cohort analysis of all eligible white patients in the UK and Ireland recruited into the Lipid-Lowering Arm of the ASCOT trial (ASCOT-LLA) from whom baseline and on-treatment values of CRP were obtained. Our hypothesis, was that on-treatment CRP would not meaningfully predict subsequent CVD events, whereas LDL-c was strongly and significantly predictive.
Methods

A cohort study based on subjects recruited into ASCOT-LLA cohort was used to determine the association between baseline CRP and subsequent CV outcomes. In separate analyses we assessed whether CRP levels following six months treatment with atorvastatin 10mg were independent predictors of CV outcomes. For the purpose of the present study, those with any history of prior CV disease were excluded.

Patients and recruitment

The detailed ASCOT protocol has been published previously (13) and further information is available at http://www.ascotstudy.org. Hypertensive patients, with three or more other risk factors for CVD but no history of prior myocardial infarction (MI) or currently treated angina were eligible.

In the Blood Pressure- Lowering Arm of the ASCOT trial (ASCOT-BPLA), 9098 patients were randomised in the UK and Ireland to either amlodipine adding perindopril as required (amlodipine-based) or atenolol adding bendroflumethiazide as required (atenolol-based).

In addition to randomisation into ASCOT-BPLA, those with a fasting total cholesterol of $\leq 6.5$ mmol/L (250mg/dl) were further randomised, using a factorial design, to either 10mg atorvastatin daily or matching placebo (ASCOT-LLA).

ASCOT-LLA was stopped prematurely after a median follow up of 3.3 years owing to highly significant benefits in favour of atorvastatin over placebo on the primary coronary endpoint. All patients in ASCOT-LLA were offered open label atorvastatin and continued in the ASCOT-BPLA until its termination after a median 5.5 years follow up.
Baseline characteristics of participants and primary outcomes of each arm of the trial have previously been reported (13,14,15). In the current analyses only white patients with no history of CVD were included from both ASCOT-LLA and BPLA combined.

**CV outcomes**

The major CV outcome evaluated in analyses was a composite of fatal coronary heart disease (CHD), symptomatic non-fatal MI, coronary revascularisation, fatal and non-fatal stroke, occurring in the UK and Ireland among participants in the ASCOT – LLA study, between February 1998 and October 2005. During the median follow-up period of 5·5 years, 488 CV outcomes were reported. In addition, associations with CHD events (fatal coronary heart disease (CHD), symptomatic non-fatal MI, coronary revascularisation) and stroke events were also investigated where numbers permitted.

**Laboratory methods**

Fasting lipids were routinely measured annually during the trial (www.ascotstudy.org). CRP samples were collected at baseline and after six months, and subsequently all stored serum samples were measured by a high sensitivity method, on an Abbott Architect, by technicians blinded to the CV outcome status of the participants’ samples. The lower limit of sensitivity was 0·1mg/L and coefficient of variation <4%.

**Statistical Analysis**

Continuous data are presented as mean and standard deviation (SD) or median and interquartile range (IQR), and categorical variables, as proportions. Baseline characteristics were compared by
event or no-event groups using t-tests, chi-square tests for proportions, and non-parametric Mann-Whitney tests for skewed data. Age- and sex- adjusted Spearman correlation was used to assess the correlation between baseline CRP and baseline clinical characteristics. For a given sample size of 3987 subjects with 456 CV events, the study had at least 90% power to detect a hazard ratio of 1.20 per SD increased in loge CRP. Analyses were performed on an intention-to-treat basis, and person-time was calculated until the first confirmed CV endpoint or to the end of the trial if no endpoint occurred. Kaplan-Meier curves were used to estimate cumulative incidence over time by baseline CRP tertile groups, and the log-rank test was used to compare survival curves. The association between CRP and the risk of each of CHD or stroke event was reported as a hazard ratio (HR) obtained from a Cox proportional hazard regression model, first by treating loge transformed baseline CRP as a continuous variable giving the risk of having an event per 1 SD change with 95% confidence intervals (CI) and secondly, by categorizing CRP into tertiles with the lowest as a reference. Two models were used to examine the association between baseline CRP and risk of CVD: Model 1: adjusted for age and sex; Model 2: adjusted for age, sex, current smoking status, diabetes mellitus, left ventricular hypertrophy, baseline systolic blood pressure (SBP), total- and HDL- cholesterol (HDL-c), randomized statin drug assignment, randomized blood pressure drug assignment, body mass index (BMI), fasting glucose, family history of CHD (FHCHD), creatinine, and educational attainment. However, two different models were used in the on-treatment CRP analyses: Model 1: adjusted for age, sex, loge baseline CRP, Model 2: adjusted for age, sex, current smoking status, diabetes mellitus, left ventricular hypertrophy, baseline SBP, total- and HDL- c, randomized atorvastatin/placebo, randomized blood pressure drug assignment, BMI, fasting glucose, FHCHD, creatinine, educational attainment, loge baseline CRP and LDL-c. The assumption of proportionality was tested with Schoenfield’s residuals. To test for effect modification by CRP tertiles, we included interaction terms between CRP or LDL-c tertile indicators and randomized assignment in the models. Because of the small
number of subjects (n=47: 26 on placebo and 21 on atorvastatin) with stroke outcomes in ASCOT-LLA, with complete data on both CRP, LDL-c, and covariates, we only reported the on-treatment effect on CVD and on CHD.

To investigate the predictive effect of baseline CRP and LDL-c on CVD and CHD, analyses used UK ASCOT-LLA and BPLA combined datasets, whereas for the on-treatment analyses we restricted analyses to those who participated in ASCOT-LLA. On treatment CRP/LDL-c levels were treated as time dependent covariates in these analyses.

Two sensitivity analyses were performed to assess the consistency of our results. Analysis on the association between baseline CRP and each endpoint was repeated on those who were not assigned atorvastatin. The second used imputed data for missing data values in order to repeat on-treatment CRP analyses.

Ten imputed datasets were created using Rubin’s rules (16) to combine effect estimates and estimate standard errors to allow for the uncertainty caused by missing data. Multiple imputation allows inclusion of subjects with incomplete data in analyses and makes full use of all the available data, increasing power and precision. Multiple imputation was undertaken using ICE (Imputation by Chained Equation) in Stata.

We further performed a post-hoc analysis to investigate the association between on-treatment non-HDL-c and CV and CHD events.

Analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC) and Stata version 11 (StataCorp, College Station, TX), using two-sided tests with a significance level of <0.05.
**Results**

*Baseline characteristics*

In total 488 subjects with an event and 3797 with no event during follow-up in ASCOT-LLA and ASCOT-BPLA were included in the analyses of predictive values of baseline CRP (Figure 1). The mean age was 64.3±8.1 years and 85.6% were male. A comparison of the baseline characteristics between those who developed an event and those who did not, demonstrated that those who did had a generally worse clinical profile (Table 1).

Baseline CRP was positively correlated with total cholesterol, LDL-c, triglycerides and BMI but negatively with HDL-c in both groups (Table S1).

*Baseline CRP and risk of subsequent cardiovascular events*

The risk of developing a CV event and CHD alone increased with baseline CRP (Table 2). Baseline CRP was not, however, significantly associated with risk of stroke alone, although there were trends towards a positive association. The hazard ratio for CV events was 1.21 (1.09, 1.33; p=0.003) per 1 SD increased in log$_e$-transformed CRP, after adjusting for classical risk factors and randomisation. Similar results were noted in the analyses by tertiles of CRP (Table 2, Figure 2). Similar results were observed in a sensitivity analysis of subjects who were not assigned atorvastatin (Table S2).

*Statin efficacy effect by baseline CRP*

There was no evidence of an interaction between baseline LDL-c or CRP and treatment effect (statin/placebo or atenolol/amlodipine-based treatment) on CV events or CHD or stroke;
specifically the statin effect in preventing CVD did not differ significantly according to the tertiles of baseline CRP (p>0.60; Table S3).

**Achieved CRP and LDL-c at 6 month and risk of cardiovascular event**

After 6 months of atorvastatin the median LDL-c was reduced by 38.7% [3.46 mmol/L (IQR (2.96, 3.95) to 2.12 (1.74, 2.56)], while in the placebo group the median fell by 1.7% [from 3.46 mmol/L (2.99, 3.96) to 3.40 (2.86, 3.92); comparing change, p<0.0001]. The concomitant changes for CRP were 25.8% reduction on atorvastatin [from 2.21 mg/L (1.12, 4.63) to 1.64 mg/L (0.82, 3.43) compared with 0.4% in the placebo group [from 2.25 mg/L (1.09, 4.4) to 2.24 mg/L (1.13, 4.48); p=0.02]. The Spearman correlation between the percentage change in CRP and the percentage change in LDL-c was modest (r=0.12, p<0.0001).

Changes in LDL-c or CRP from baseline to 6 months were normally distributed. Irrespective of treatment group assignment in the ASCOT-LLA cohort, a 1 mmol/L decrease in LDL-c between baseline and 6-months in-trial treatment was associated with a 17% (HR 0.83 (0.69, 0.99); p=0.04) and a 17% (HR 0.83 (0.67, 1.02); p=0.07) risk reduction in CV and CHD events respectively, after adjustment for baseline levels, age and sex. These estimated effects were essentially unchanged after multiple adjustments for other risk factors, but were no longer significant (HR 0.86 [0.66, 1.12], 0.87 [0.63, 1.19] respectively)). In contrast, the effect of a 10 mg/L decrease in CRP showed no evidence of an association with CV or CHD events (HR 1.03 (0.90, 1.18), p=0.69 for CV; 1.05 (0.92, 1.20), p=0.48 for CHD). Those who did not achieve CRP below the median value at 6-months in either the placebo (median: 2.24mg/L) or atorvastatin (median: 1.64mg/L) groups, did not have a significantly altered risk of CV or CHD events compared with those who did (Table 3).
Similar analyses were repeated using a separate imputed dataset. In this dataset, the multivariable analyses (Model 4) showed that the HRs for CV were similar to those reported in the complete case analysis of Table 3 (Table S4).

After adjusting for risk factors (including baseline CRP and LDL-c) subjects allocated to atorvastatin had a non-significant 19-22% reduced risk of CV events regardless of whether they achieved a CRP less than the median of 1.64 mg/L (Figure 3, Table 4). In contrast, those who achieved LDL-c below the median had a significant 46% reduction in risk of CV events (HR 0.54 (0.34, 0.85); p=0.008) in the multivariable-adjusted analysis. Within the atorvastatin group, those who achieved LDL-c below median had a 42% reduced risk compared with those who did not (HR 0.58 (0.34, 0.97), p=0.04) (Model 2 in Table 4). Similar results were also noted in the CHD analyses (Figure 3, Table 4). Post-hoc analyses of on-treatment non-HDL, showed similar significant results (data not shown).

On-treatment CRP and LDL-c analyses were repeated using a dataset including imputed data for missing data. A significant treatment effect for CHD (39% risk reduction) was observed in those who achieved CRP below median. However, in contrast to findings for achieved LDL-c there was, once again, no significant within atorvastatin group difference for achieved CRP below, versus above, the median [HR 0.75 (0.43,1.32) p=0.32]. Overall the effect estimates of on-treatment CRP and LDL-c on CV and CHD events were similar to those reported in the complete case analyses (Table 5).

Compared with placebo, the lowest risk of CV events was noted in subjects allocated to atorvastatin who achieved LDL-c below the median level (<2.1mmol/L) irrespective of on-treatment CRP levels. (Figure 4, Table 6.) A significantly lower risk of CHD was noted in subjects taking atorvastatin who achieved low LDL-c but had a high level of on-treatment CRP (Figure 5,
Table 6). However this result was based on 6 subjects with an event. Sensitivity analyses using imputed data showed similar results (Figure 6).

We conducted additional analyses using alternative cut-offs such as CRP above and below 2mg/L and either LDL-c above and below 2.59mmol/L (100mg/dl) or non-HDL-c above and below 3.37mmol/L (130mg/dl). In neither of these analyses was there an additional benefit to be gained by lowering CRP to below 2mg/L (data not shown).

Discussion

We report in this trial of hypertensive patients at modest risk of future CV events, that baseline CRP independently predicted subsequent CV events but neither baseline levels of CRP nor the achieved levels of CRP on-treatment with atorvastatin, 10mg, predicted the efficacy of the statin in preventing future CV events. The results of this cohort analysis are similar but more robust than those we reported from an earlier nested case-control study derived from the same population (12).

Several studies have shown that baseline CRP is an independent risk predictor for CV events and this has been confirmed in a recent meta-analysis (6) such that predictive benefits are, at best, modest (9). Whilst, there remains uncertainty about the relative benefit of CRP to risk prediction, the strength of the association, particularly when potential confounders are incorporated into the models, is weak (6). We also confirm in this study that there was no interaction between baseline values of CRP and the relative effect of the statin on CV events. These findings are consistent with those reported from the Heart Protection Study (17), PROSPER (18) and JUPITER (19).
Arguably the most controversial and debateable issue concerns the extent to which on-treatment levels of CRP predict the benefits of CV outcome associated with statin therapy. This has been proposed based on analyses from observations of on-treatment levels of CRP from a number of trials, many of which recruited high risk individuals (20,21,22) and, particularly, JUPITER which recruited low risk individuals with high CRP (19).

It has been suggested that data from our earlier nested case-control study in ASCOT-LLA showed that those who achieved lower levels of on-treatment CRP had a 25% greater relative risk reduction in CV events, and that our results were actually compatible with other studies (11). There are flaws in this argument. First, when controlling for confounding variables including CRP and LDL-c at baseline, the absolute difference in risk was 12% (not 25%) (12). Further, those who did not achieve median CRP reduction had an increased risk of 14% in the ASCOT case-control study, with figures of 5% and 12% increased risk in the analyses using complete-case data and imputed data respectively in the present study. These estimates appear appreciably different to the 47%, 33%, and 26% increased risk reported in JUPITER (19), A to Z (21), and PROVE-IT (20) for similar comparisons. Regardless of treatment group assignment in ASCOT, a 1 mmol/L decrease in LDL-c was shown to be associated with a significant 17% reduced risk of CV and CHD events. A reduction in CRP, however, did not have any association with CV outcome in the ASCOT-LLA population, once reduction of LDL-c was taken into account. Unless the argument is being made that statins are in fact primarily anti-inflammatory drugs (rather than cholesterol reducing drugs) selective or even additional reporting of the risk reduction association with CRP lowering appears of minimal benefit in delineating the impact of statins on CV risk. Figure 4 clearly shows that once achieved LDL-c is considered, further stratification by achieved CRP has little bearing on the relative risk of CV events. Because about half the patients recruited into ASCOT-LLA could be categorized as having the metabolic syndrome, thus sharing some characteristics with the JUPITER
population, we conducted a post hoc subgroup analysis on these patients. Compared with those in the placebo group, among those with metabolic syndrome, those who were assigned to atorvastatin and had a higher on-treatment LDL-c, and tended to have higher risk of CVD regardless of their on-treatment CRP levels. However, those with lower on-treatment LDL-c and lower on-treatment CRP had a non-significant 35% reduced risk of CVD but there was no evidence of interaction between metabolic syndrome and on-treatment CRP & LDL-c levels on CVD. Such analyses should be interpreted with caution, however, owing to limited number of events in individual subgroups.

A further commentary on our earlier findings from the case-control study was made on grounds of inadequate power (11). The current study reports on 456 CV events in total, and for the on-treatment CRP analysis 97 events (with imputed data). This compares with 103 CV events in JUPITER for the on-treatment analysis (19). Moreover, the JUPITER primary CV endpoint definition included hospitalisation for angina, which in the ASCOT CV definition was not considered as a hard endpoint and therefore not included. We therefore believe that the power of both studies is comparable. We have, however, subsequently conducted a further analysis incorporating 11 cases of development of unstable angina as a CV endpoint. This made no difference to our original conclusion that those achieving lower levels of LDL-c had lower risk of CV events regardless of achieved level of CRP.

Our results showing that on-treatment CRP has virtually no predictive value are in accord with the TNT study (23), and CARDS (unpublished data) but contrast with other trials performed on patients with acute coronary syndrome (20,21), and patients with angiographically documented coronary disease (20). Investigators have previously claimed that lower levels of CRP following statin therapy predict greater subsequent relative risk reductions in CV events...
Unfortunately none of these studies except REVERSAL (22) reported the relationship of change in CRP (from baseline to follow-up) with events.

Strengths and limitations of the present study require consideration. The relative merits of primary endpoints and power of studies reporting on treatment CRP and CV events are discussed above. The present study reports objectively imputed data, although these results are entirely consistent with results from non-imputed data. In terms of relative generalisability, PROVE-IT (20) and A to Z (21) recruited high risk patients with previous acute coronary events. REVERSAL recruited patients with at least 20% stenosis on coronary angiography and with mean baseline LDL of 3.9 mmol/L and geometric mean CRP of 2.9 mg/L (22). JUPITER recruited relatively healthy patients with low LDL-c (<3.4 mmol/L) but high CRP (≥2 mg/L) (19), whereas the ASCOT cohort in these analyses included patients without any previous history of CV and with median LDL-c of 3.6mmol/L and median CRP of 2.4 mg/L at baseline. It is possible that CRP may have different predictive ability in different patient types. However, we believe that, to date, ASCOT data most usefully reflects patients commonly seen in primary care.

In conclusion, our results challenge the need to measure CRP to guide statin dose changes. These clinical decisions appear usefully informed by change in LDL-c while on statin treatment, in line with the pharmacological role of statins in cholesterol reduction.

**Contributors**

P Sever and N Poulter were co-Chief Investigator and Secretary respectively of the ASCOT Executive Committee and members of the ASCOT Steering Committee. P Sever, N Poulter, C Chang, P Welsh and N Sattar constituted the writing committee for the current manuscript, designed the present study, wrote the protocol and the analysis plan and supervised the analyses,
interpreted the results and wrote the report. S Thom and A Hughes reviewed the protocol and analysis plan and commented upon the manuscript.

**Funding**

The sponsors of the study (Pfizer) had no role in the study design, data collection, data analyses, data interpretation or writing of the report. The database was held by the ASCOT Executive Committee who had final responsibility for the decision to submit for publication.

**Acknowledgments**

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**Conflict of Interest Statement**

P Sever, N Poulter have served as consultants to, received travel expenses from and payment for speaking at meetings for and received research funding from Pfizer to cover administrative staffing and analytical costs of the biomarker analyses. N Sattar has received consulting and lecture fees from Merck & Co, Pfizer, and AstraZeneca, and has received research grant support from Pfizer. A Hughes and S Thom have received research grant support from Pfizer. P Welsh and C Chang declare no conflict of interest.
Table and Figure Legend

Table 1 – Baseline characteristics of white study population with baseline CRP measurement by event status.

Table 2 – Hazard ratios (95% CI) of cardiovascular event (coronary heart disease (CHD) or stroke) in relation to loge baseline CRP (per SD increase in Log-transformed CRP and in CRP tertiles) among all white subjects with no previous cardiovascular disease (CVD).

Table 3 – Association between CRP value above median at 6-months and cardiovascular disease (CVD) and coronary heart disease (CHD) in relation to CRP of less than median value by atorvastatin and placebo.

Table 4 – Hazard ratios for cardiovascular disease (CVD) and coronary heart disease (CHD) associated with achieved level of CRP or LDL-c at 6-months relative to placebo.

Table 5 – Hazard ratios for cardiovascular disease (CVD) and coronary heart disease (CHD) associated with achieved level of CRP at 6-month relative to placebo using imputed data.

Table 6 – Hazard ratios for cardiovascular disease (CVD) and coronary heart disease (CHD) according to achieved levels of CRP and LDL-cholesterol after 6-months on atorvastatin.

Figure 1 – ASCOT C-reactive protein cohort trial profile.

Figure 2 – Cumulative probability of CVD events according to concentration of CRP at baseline.

Figure 3 – Multiple adjusted hazard ratios for CVD and CHD events according to achieved level of CRP or LDL-cholesterol at 6-months.

Figure 4 – Hazard ratios for CV events according to achieved LDL-cholesterol and CRP after 6-months of atorvastatin.
**Figure 5** – Multiple adjusted hazard ratios for CHD events according to achieved LDL-cholesterol and CRP after 6-months of atorvastatin.

**Figure 6** – Multiple adjusted hazard ratios for CVD and CHD events according to achieved level of LDL-cholesterol and CRP at 6-months using imputed data.

**Supplementary Tables**

**Table S1** – Age and sex adjusted Spearman correlation coefficients of baseline hsCRP with baseline clinical characteristics.

**Table S2** – Hazard ratios (95% CI) of cardiovascular event (coronary heart disease (CHD) or stroke) in relation to baseline CRP (per SD increase in Log-transformed CRP and in CRP tertiles) among white subjects who were not on statin and with no previous cardiovascular disease (CVD).

**Table S3** – The risk of cardiovascular disease (CVD), coronary heart disease (CHD) and stroke in each tertile of baseline CRP in the atorvastatin-assigned group compared to the placebo group.

**Table S4** – Association between CRP value above median at 6-months and cardiovascular disease (CVD) and coronary heart disease (CHD) or less than median value by atorvastatin and placebo using imputed data.
References


Figure 1: ASCOT C-reactive protein cohort trial profile

ASCOT – UK & Ireland (n=9098 subjects)

White European (n=8217)

6549 subjects met entry criteria as potential participants

490 with events & 6059 with non-event

2 cases & 2262 non-event with no baseline CRP

488 cases & 3797 non-event (BPLA CRP trial population)

32 cases & 266 non-event with missing baseline covariates

239 cases & 3192 non-event participating in ASCOT-LLA

456 cases & 3531 non-event (baseline CRP predictive analysis population)

198 cases & 2786 non-event with both CRP at baseline & at 6 month

28 cases & 184 non-event with missing baseline covariates or 17 events that occurred before 6-month blood sampling

170 cases & 2602 non-event (On-treatment CRP analysis population)
Figure 2. Baseline CRP and cumulative probability of CVD events

Outcomes according to (A) CVD: a composite of fatal coronary heart disease, symptomatic non-fatal MI, coronary revascularisation, fatal and non-fatal stroke; (B) CHD: fatal coronary heart disease, symptomatic non-fatal MI, coronary revascularisation and (C) fatal and non-fatal stroke. Dashed blue lines indicate highest tertile; solid black lines indicate middle tertile; dashed red lines indicate lowest tertile.
Figure 3. Hazard ratios for CVD and CHD events

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<th></th>
<th>CVD</th>
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<th>Rate*</th>
<th>HR (95% CI)</th>
<th>P-value</th>
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<td>42</td>
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<td>Placebo</td>
<td>Atorvastatin CRP &lt;1.64</td>
<td>33</td>
<td>0.93</td>
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<td>Placebo</td>
<td>Atorvastatin LDL-c &gt;2.1</td>
<td>44</td>
<td>1.24</td>
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<table>
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<td>0.44</td>
<td>0.50 (0.29-0.88)</td>
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* per 100 person-years

Units used: LDL-c: mmol/L, CRP: mg/L

Squares and lines are hazard ratios and 95% confidence intervals (CIs) for CVD and CHD according to atorvastatin users whose achieved LDL-c and CRP below or above the median value at 6-month (relative to placebo group). Adjusted for age, sex, current smoking, diabetes, randomised BP treatment, left ventricular hypertrophy, baseline SBP, BMI, HDL-c, glucose, Family history of CHD, creatinine, educational attainment, baseline CRP and LDL-c.

CVD: a composite of fatal coronary heart disease, symptomatic non-fatal MI, coronary revascularisation, fatal and non-fatal stroke;
CHD: fatal coronary heart disease, symptomatic non-fatal MI, coronary revascularisation; LDL-c: low density lipoprotein; CRP: C-reactive protein; BP: blood pressure; HDL-c: high density lipoprotein; SBP: systolic blood pressure; BMI: body mass index.
Figure 4. Hazard ratios for CV events

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<tr>
<th>Events</th>
<th>Rate*</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>89</td>
<td>1.35</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL≥2.1 &amp; CRP≥1.64</td>
<td>27</td>
<td>1.45</td>
<td>0.99(0.63-1.54)</td>
</tr>
<tr>
<td>LDL≥2.1 &amp; CRP&lt;1.64</td>
<td>17</td>
<td>1.07</td>
<td>0.90(0.53-1.53)</td>
</tr>
<tr>
<td>LDL&lt;2.1 &amp; CRP≥1.64</td>
<td>12</td>
<td>0.72</td>
<td>0.55(0.30-1.03)</td>
</tr>
<tr>
<td>LDL&lt;2.1 &amp; CRP&lt;1.64</td>
<td>12</td>
<td>0.68</td>
<td>0.55(0.30-1.02)</td>
</tr>
</tbody>
</table>

Atorvastatin better (log scale) Atorvastatin worse

* per 100 person-years
Units used: LDL:mmol/L, CRP:mg/L

Squares and lines are hazard ratios and 95% confidence intervals (CIs) for CVD according to atorvastatin users whose achieved LDL-c and CRP below or above the median value at 6-month (relative to placebo group). Adjusted for age, sex, current smoking, diabetes, randomised BP treatment, left ventricular hypertrophy, baseline SBP, HDL-c, BMI, glucose, Family history of CHD, creatinine, educational attainment, baseline CRP and LDL-c

Abbreviations as in Figure 2
Figure 5. Hazard ratios for CHD events

<table>
<thead>
<tr>
<th>Events</th>
<th>Rate*</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>64</td>
<td>0.98</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL≥2.1 &amp; CRP≥1.64</td>
<td>25</td>
<td>1.35</td>
<td>1.18(0.73-1.90)</td>
</tr>
<tr>
<td>LDL≥2.1 &amp; CRP&lt;1.64</td>
<td>8</td>
<td>0.51</td>
<td>0.57(0.27-1.20)</td>
</tr>
<tr>
<td>LDL&lt;2.1 &amp; CRP≥1.64</td>
<td>6</td>
<td>0.36</td>
<td>0.39(0.17-0.91)</td>
</tr>
<tr>
<td>LDL&lt;2.1 &amp; CRP&lt;1.64</td>
<td>10</td>
<td>0.55</td>
<td>0.66(0.33-1.30)</td>
</tr>
</tbody>
</table>

0.5 1 1.5 2.5
Atorvastatin better (log scale) Atorvastatin worse

* per 100 person-years
Units used: LDL mmol/L, CRP mg/L

Squares and lines are hazard ratios and 95% confidence intervals (CIs) for CHD according to atorvastatin users whose achieved LDL-c and CRP below or above the median value at 6-month (relative to placebo group). Adjusted for age, sex, current smoking, diabetes, randomised BP treatment, left ventricular hypertrophy, baseline SBP, HDL-c, BMI, glucose, Family history of CHD, creatinine, educational attainment, baseline CRP and LDL-c.

Abbreviations as in Figure 2
FIGURE 6. Hazard Ratios for CVD and CHD events (using imputed data)
Table 1: Baseline characteristics of white study population with baseline CRP measurement by event status

<table>
<thead>
<tr>
<th></th>
<th>Without (n=3797)</th>
<th>With (n=488)</th>
<th>p_value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>3258 (85.8%)</td>
<td>412 (84.4%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>64.21 (8.09)</td>
<td>65.35 (7.83)</td>
<td>0.003</td>
</tr>
<tr>
<td>Current Smokers</td>
<td>946 (24.9%)</td>
<td>128 (26.2%)</td>
<td>0.53</td>
</tr>
<tr>
<td>Alcohol: Never</td>
<td>831 (21.9%)</td>
<td>125 (25.6%)</td>
<td></td>
</tr>
<tr>
<td>Alcohol: ≤14/21 units/week</td>
<td>2248 (59.2%)</td>
<td>271 (55.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;14/21 units/week</td>
<td>718 (18.9%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Completed Education Age: ≤12</td>
<td>1151 (30.3%)</td>
<td>185 (37.9%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤15</td>
<td>1898 (50.0%)</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td>≤18</td>
<td>425 (11.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;19</td>
<td>323 (8.5%)</td>
<td>0.001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>162.34 (17.31)</td>
<td>164.65 (17.84)</td>
<td>0.01</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>92.84 (9.80)</td>
<td>92.98 (10.36)</td>
<td>0.76</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>70.26 (12.23)</td>
<td>69.68 (12.89)</td>
<td>0.33</td>
</tr>
<tr>
<td>BMI (Kg/m2)</td>
<td>29.16 (4.84)</td>
<td>28.69 (4.06)</td>
<td>0.04</td>
</tr>
<tr>
<td>Total Chol (mmol/L)</td>
<td>5.67 (0.93)</td>
<td>5.98 (1.06)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>3.60 (0.84)</td>
<td>3.90 (0.96)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.29 (0.34)</td>
<td>1.26 (0.34)</td>
<td>0.07</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)*</td>
<td>1.5 (1.10, 2.10)</td>
<td>1.7 (1.20, 2.30)</td>
<td>0.003</td>
</tr>
<tr>
<td>Glucose (mmol/L)*</td>
<td>5.6 (5.10, 6.50)</td>
<td>5.6 (5.10, 6.80)</td>
<td>0.12</td>
</tr>
<tr>
<td>Creatinine (mmol/L)</td>
<td>99.09 (16.35)</td>
<td>102.43 (19.18)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CRP (mg/L)*</td>
<td>2.4 (1.21, 4.69)</td>
<td>3.0 (1.54, 5.53)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1002 (26.4%)</td>
<td>151 (30.9%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>1626 (42.8%)</td>
<td>221 (45.3%)</td>
<td>0.30</td>
</tr>
<tr>
<td>FH CHD</td>
<td>687 (18.1%)</td>
<td>84 (17.2%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>1923 (50.6%)</td>
<td>230 (47.1%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Atorvastatin§</td>
<td>1637 (51.3%)</td>
<td>103 (43.1%)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Values are mean (SD) or n (%)

* median (inter-quartile ) p-values based on Wilcoxon tests

§ 3431 subjects participated in lipid-lowering arm
Table 2: Hazard ratios (95% CI) of cardiovascular event (CHD or Stroke) in relation to baseline CRP (per SD increase in Log-transformed CRP and in CRP tertiles) among all white subjects with no previous CVD

<table>
<thead>
<tr>
<th>Event/no-event</th>
<th>Model¹</th>
<th>P</th>
<th>Model²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest Tertile</td>
<td>106/1174</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td></td>
</tr>
<tr>
<td>Mid Tertile</td>
<td>160/1185</td>
<td>1.41 (1.11, 1.79)</td>
<td>1.45 (1.13, 1.87)</td>
<td>0.004</td>
</tr>
<tr>
<td>Highest Tertile</td>
<td>190/1172</td>
<td>1.75 (1.39, 2.20)</td>
<td>&lt;0.0001</td>
<td>1.51 (1.17, 1.94)</td>
</tr>
<tr>
<td>Trend</td>
<td>P&lt;0.0001</td>
<td></td>
<td>P=0.002</td>
<td></td>
</tr>
<tr>
<td>Log CRP per SD</td>
<td>456/3531</td>
<td>1.25 (1.15, 1.37)</td>
<td>&lt;0.0001</td>
<td>1.21 (1.09, 1.33)</td>
</tr>
<tr>
<td>CHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest Tertile</td>
<td>75/1174</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td></td>
</tr>
<tr>
<td>Mid Tertile</td>
<td>114/1185</td>
<td>1.44 (1.09, 1.91)</td>
<td>1.46 (1.08, 1.96)</td>
<td>0.01</td>
</tr>
<tr>
<td>Highest Tertile</td>
<td>145/1172</td>
<td>1.87 (1.43, 2.45)</td>
<td>&lt;0.0001</td>
<td>1.61 (1.20, 2.17)</td>
</tr>
<tr>
<td>Trend</td>
<td>P&lt;0.0001</td>
<td></td>
<td>P=0.002</td>
<td></td>
</tr>
<tr>
<td>Log CRP per SD</td>
<td>334/3531</td>
<td>1.32 (1.19, 1.46)</td>
<td>&lt;0.0001</td>
<td>1.27 (1.13, 1.43)</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest Tertile</td>
<td>31/1174</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td></td>
</tr>
<tr>
<td>Mid Tertile</td>
<td>46/1185</td>
<td>1.34 (0.86, 2.11)</td>
<td>1.55 (0.97, 2.47)</td>
<td>0.07</td>
</tr>
<tr>
<td>Highest Tertile</td>
<td>45/1172</td>
<td>1.52 (0.98, 2.37)</td>
<td>0.06</td>
<td>1.40 (0.86, 2.28)</td>
</tr>
<tr>
<td>Trend</td>
<td>P=0.06</td>
<td></td>
<td>P=0.20</td>
<td></td>
</tr>
<tr>
<td>Log CRP per SD</td>
<td>122/3531</td>
<td>1.12 (0.94, 1.33)</td>
<td>0.22</td>
<td>1.10 (0.91, 1.34)</td>
</tr>
</tbody>
</table>

Tertile: lowest: ≤1.42, mid: 1.43-3.46, highest: >3.46 mg/L

Model 1: Adjusted for age and sex
Model 2: Adjusted for age, sex, current smoking status, diabetes, baseline SBP, HDL, total cholesterol, randomised atenolol/amlodipine, randomised atorvastatin/placebo/not in LLA, left ventricular hypertrophy, BMI, glucose, family history CHD, creatinine and educational attainment
Table 3: Association between CRP value above median at 6-month and CVD and CHD in relation to CRP of less than median value by atorvastatin and placebo

<table>
<thead>
<tr>
<th>Model 1</th>
<th>CVD</th>
<th>CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events/No event</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>CRP&lt;median</td>
<td>33/647</td>
</tr>
<tr>
<td></td>
<td>CRP≥median</td>
<td>42/679</td>
</tr>
<tr>
<td>Placebo</td>
<td>CRP&lt;median</td>
<td>41/629</td>
</tr>
<tr>
<td></td>
<td>CRP≥median</td>
<td>54/647</td>
</tr>
<tr>
<td>Model 2</td>
<td>CVD</td>
<td>CHD</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>CRP&lt;median</td>
<td>33/647</td>
</tr>
<tr>
<td></td>
<td>CRP≥median</td>
<td>42/679</td>
</tr>
<tr>
<td>Placebo</td>
<td>CRP&lt;median</td>
<td>41/629</td>
</tr>
<tr>
<td></td>
<td>CRP≥median</td>
<td>54/647</td>
</tr>
</tbody>
</table>

Median value for atorvastatin group: 1.64 mg/L; Placebo group: 2.24 mg/L

Model 1: Adjusted for age, sex and log baseline CRP
Model 2: Adjusted for age, sex, current smoking, diabetes, randomised BP treatment, left ventricular hypertrophy, baseline SBP, total cholesterol, HDL, BMI, glucose, Family history of CHD, creatinine, educational attainment, and log, baseline CRP
Table 4: Hazard ratios for CVD and CHD associated with achieved level of CRP or LDL-c at 6-month relative to placebo

<table>
<thead>
<tr>
<th></th>
<th>CVD</th>
<th></th>
<th>CHD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events/No event</td>
<td>CRP</td>
<td>LDL</td>
<td>Events/No event</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>94/1251</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td></td>
<td>Atorvastatin:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ median</td>
<td>42/666</td>
<td>0.83 (0.57, 1.19)</td>
<td>0.30</td>
<td>0.93 (0.65, 1.33)</td>
</tr>
<tr>
<td>&lt; median</td>
<td>33/639</td>
<td>0.75 (0.50, 1.12)</td>
<td>0.16</td>
<td>0.52 (0.33, 0.83)</td>
</tr>
<tr>
<td>&lt; median vs ≥ median</td>
<td>0.91 (0.57, 1.46)</td>
<td>0.70</td>
<td>0.56 (0.34, 0.94)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>94/1251</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td>Atorvastatin:</td>
<td>42/666</td>
<td>0.81 (0.56, 1.18)</td>
<td>0.28</td>
<td>0.93 (0.65, 1.35)</td>
</tr>
<tr>
<td>&lt; median</td>
<td>33/639</td>
<td>0.78 (0.52, 1.17)</td>
<td>0.22</td>
<td>0.54 (0.34, 0.85)</td>
</tr>
<tr>
<td>&lt; median vs ≥ median</td>
<td>0.95 (0.59, 1.55)</td>
<td>0.85</td>
<td>0.58 (0.34, 0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>94/1251</td>
<td>1.00 (Ref)</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin:</td>
<td>48/846</td>
<td>0.70 (0.47, 1.05)</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>≥24.34% vs &lt;24.34%</td>
<td>43/651</td>
<td>0.88 (0.61, 1.28)</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.26 (0.79, 2.02)</td>
<td>0.34</td>
<td>1.44 (0.82, 2.52)</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>91/1234</td>
<td>1.00 (Ref)</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin:</td>
<td>57/833</td>
<td>0.81 (0.54, 1.20)</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>≥39.34% vs &lt;39.34%</td>
<td>34/664</td>
<td>0.68 (0.46, 1.02)</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.84 (0.52, 1.37)</td>
<td>0.49</td>
<td>0.85 (0.48, 1.50)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Among atorvastatin users, the median value for CRP at 6 month visit = 1.64 mg/L; LDL at 6 month visit = 2.12 mmol/L
Δ = reduction

Model 1: Adjusted for age, sex and log baseline CRP
Model 2: Adjusted for age, sex, current smoking, diabetes, randomised BP treatment, left ventricular hypertrophy, baseline SBP, total cholesterol, HDL, BMI, glucose, Family history of CHD, creatinine, educational attainment, and log, baseline CRP

Event/no event in LDL analyses: CVD: 91/1234, 44/639, 24/664, CHD: 66/1234, 33/639, 16/664
Table 5: Hazard ratios for CVD and CHD associated with achieved level of CRP at 6-month relative to placebo using imputed data

<table>
<thead>
<tr>
<th></th>
<th>CVD</th>
<th></th>
<th></th>
<th>CHD</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events/No event</td>
<td>CRP P</td>
<td>LDL P</td>
<td>Events/No event</td>
<td>CRP P</td>
<td>LDL P</td>
</tr>
<tr>
<td>Placebo</td>
<td>125/1556</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td>89/1556</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥median</td>
<td>58/812</td>
<td>0.87(0.63,1.20)</td>
<td>0.40</td>
<td>0.98(0.71,1.34)</td>
<td>0.88</td>
<td>47/814</td>
</tr>
<tr>
<td>&lt; median</td>
<td>39/826</td>
<td>0.64(0.44,0.92)</td>
<td>0.02</td>
<td>0.55(0.37,0.80)</td>
<td>0.002</td>
<td>22/824</td>
</tr>
<tr>
<td>&lt; median vs ≥ median</td>
<td>0.73(0.47,1.14)</td>
<td>0.16</td>
<td>0.56(0.36,0.88)</td>
<td>0.01</td>
<td></td>
<td>0.60(0.35,1.02)</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>125/1556</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td>89/1556</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td>Atorvastatin:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥median</td>
<td>58/812</td>
<td>0.80(0.57,1.11)</td>
<td>0.18</td>
<td>0.97(0.70,1.35)</td>
<td>0.86</td>
<td>44/817</td>
</tr>
<tr>
<td>&lt; median</td>
<td>39/826</td>
<td>0.70(0.48,1.02)</td>
<td>0.07</td>
<td>0.56(0.38,0.82)</td>
<td>0.003</td>
<td>25/821</td>
</tr>
<tr>
<td>&lt; median vs ≥ median</td>
<td>0.88(0.55,1.41)</td>
<td>0.59</td>
<td>0.57(0.36,0.91)</td>
<td>0.02</td>
<td></td>
<td>0.75(0.43,1.32)</td>
</tr>
<tr>
<td>Placebo</td>
<td>125/1556</td>
<td>1.00 (Ref)</td>
<td></td>
<td>89/1556</td>
<td>1.00 (Ref)</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ% CRP&lt; 25.29%¥</td>
<td>43/832</td>
<td>0.72(0.50,1.03)</td>
<td>0.07</td>
<td></td>
<td>30/827</td>
<td>0.64(0.41,0.99)</td>
</tr>
<tr>
<td>Δ% CRP≥ 25.29%</td>
<td>54/806</td>
<td>0.78(0.56,1.09)</td>
<td>0.15</td>
<td></td>
<td>39/811</td>
<td>0.80(0.54,1.18)</td>
</tr>
<tr>
<td>≥25.29% vs &lt;25.29%</td>
<td>1.08(0.70, 1.69)</td>
<td>0.72</td>
<td></td>
<td></td>
<td>1.26(0.74,2.14)</td>
<td>0.40</td>
</tr>
<tr>
<td>Placebo</td>
<td>125/1556</td>
<td>1.00 (Ref)</td>
<td>89/1556</td>
<td>1.00 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ% LDL&lt;41.53%¥</td>
<td>52/821</td>
<td>0.90(0.64,1.25)</td>
<td>0.52</td>
<td>43/828</td>
<td>0.91(0.62,1.34)</td>
<td>0.64</td>
</tr>
<tr>
<td>Δ% LDL≥ 41.53%</td>
<td>45/817</td>
<td>0.62(0.43,0.90)</td>
<td>0.01</td>
<td>26/810</td>
<td>0.56(0.36,0.86)</td>
<td>0.009</td>
</tr>
<tr>
<td>≥41.53% vs &lt;41.53%</td>
<td>0.69(0.44,1.09)</td>
<td>0.11</td>
<td></td>
<td></td>
<td>0.61(0.36,1.02)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Among atorvastatin users, the median value for CRP at 6 month visit =1.69 mg/L (CVD) & 1.70mg/L (CHD); LDL at 6 month visit = 2.13 mmol/L (CVD) & 2.12mmol/L (CHD)

Δ = reduction

¥ median value in atorvastatin group- CRP: 25.29% for CVD and 25.10% for CHD; LDL: 41.53% for CVD & 41.49% for CHD

Event/no event in LDL analyses: CVD: 125/1556, 59/797, 38/841, CHD: 89/1556, 47/814, 22/824

Model 1: Adjusted for age, sex and log baseline CRP

Model 2: Adjusted for age, sex, current smoking, diabetes, randomised BP treatment, left ventricular hypertrophy, baseline SBP, total cholesterol, HDL, BMI, glucose, Family history of CHD, creatinine, educational attainment, and loge, baseline CRP
Table 6: Hazard ratios for CVD and CHD according to achieved levels of CRP and LDL-cholesterol after 6-month atorvastatin

<table>
<thead>
<tr>
<th></th>
<th>Events/No-event</th>
<th>CVD</th>
<th></th>
<th>Events/No-event</th>
<th>CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>89/1175</td>
<td></td>
<td></td>
<td>64/1175</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>1.00 (Ref)</td>
<td>0.96</td>
<td>1.00 (Ref)</td>
<td>0.51</td>
</tr>
<tr>
<td>CRP≥1.64 &amp; LDL≥2.12</td>
<td>27/329</td>
<td>0.99(0.63,1.54)</td>
<td>0.69</td>
<td>1.18(0.73,1.90)</td>
<td>0.14</td>
</tr>
<tr>
<td>CRP&lt;1.64 &amp; LDL≥2.12</td>
<td>17/281</td>
<td>0.90(0.53,1.53)</td>
<td>0.57(0.27,1.20)</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>CRP≥1.64 &amp; LDL&lt;2.12</td>
<td>12/302</td>
<td>0.56(0.30,1.03)</td>
<td>0.39(0.17,0.91)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>CRP&lt;1.64 &amp; LDL&lt;2.12</td>
<td>12/331</td>
<td>0.55(0.30,1.02)</td>
<td>0.66(0.33,1.30)</td>
<td>0.23</td>
<td></td>
</tr>
</tbody>
</table>

Units used - CRP:mg/L
LDL: mmol/L

Adjusted for age, sex, current smoking, diabetes, randomised BP treatment, left ventricular hypertrophy, baseline SBP, HDL, BMI, glucose, Family history of CHD, creatinine, educational attainment, log, baseline CRP and LDL-c
Online Table 1: Age and sex adjusted Spearman correlation coefficients of baseline hsCRP with baseline clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Non-event</th>
<th>P-value</th>
<th>Events</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.0305</td>
<td>0.06</td>
<td>-0.0528</td>
<td>0.25</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.0300</td>
<td>0.078</td>
<td>0.0142</td>
<td>0.78</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.0161</td>
<td>0.34</td>
<td>0.0970</td>
<td>0.041</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>0.0627</td>
<td>0.0002</td>
<td>0.1465</td>
<td>0.002</td>
</tr>
<tr>
<td>LDL-c</td>
<td>0.0779</td>
<td>&lt;0.0001</td>
<td>0.1622</td>
<td>0.0006</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.1520</td>
<td>&lt;0.0001</td>
<td>0.1545</td>
<td>0.001</td>
</tr>
<tr>
<td>HDL</td>
<td>-0.1519</td>
<td>&lt;0.0001</td>
<td>-0.1330</td>
<td>0.005</td>
</tr>
<tr>
<td>BMI</td>
<td>0.2516</td>
<td>&lt;0.0001</td>
<td>0.1686</td>
<td>0.0004</td>
</tr>
<tr>
<td>SBP</td>
<td>0.0247</td>
<td>0.15</td>
<td>0.0048</td>
<td>0.92</td>
</tr>
<tr>
<td>DBP</td>
<td>-0.0105</td>
<td>0.54</td>
<td>0.0061</td>
<td>0.9</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>0.0764</td>
<td>&lt;0.0001</td>
<td>0.0300</td>
<td>0.53</td>
</tr>
</tbody>
</table>
Online Table 2: Hazard ratios (95%CI) of cardiovascular event (CHD or Stroke) in relation to baseline CRP (per SD increase in Log-transformed CRP and in CRP tertiles) among white subjects who were not on statin and with no previous CVD

<table>
<thead>
<tr>
<th>Events/Non-event</th>
<th>Model 1</th>
<th>P</th>
<th>Model 2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CVD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest Tertile</td>
<td>87/684</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td></td>
</tr>
<tr>
<td>Mid Tertile</td>
<td>134/731</td>
<td>1.42 (1.08, 1.86)</td>
<td>0.01</td>
<td>1.44 (1.09, 1.92)</td>
</tr>
<tr>
<td>Highest Tertile</td>
<td>164/745</td>
<td>1.68 (1.29, 2.19)</td>
<td>&lt;0.0001</td>
<td>1.56 (1.17, 2.07)</td>
</tr>
<tr>
<td>Trend</td>
<td>P=0.0001</td>
<td></td>
<td>P=0.003</td>
<td></td>
</tr>
<tr>
<td>Log CRP per SD</td>
<td>385/2160</td>
<td>1.25 (1.13, 1.39)</td>
<td>&lt;0.0001</td>
<td>1.21 (1.08, 1.36)</td>
</tr>
<tr>
<td><strong>CHD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest Tertile</td>
<td>65/684</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td></td>
</tr>
<tr>
<td>Mid Tertile</td>
<td>100/731</td>
<td>1.45 (1.06, 1.98)</td>
<td>0.02</td>
<td>1.45 (1.04, 2.02)</td>
</tr>
<tr>
<td>Highest Tertile</td>
<td>121/745</td>
<td>1.75 (1.29, 2.36)</td>
<td>&lt;0.0001</td>
<td>1.64 (1.18, 2.29)</td>
</tr>
<tr>
<td>Trend</td>
<td>P=0.0003</td>
<td></td>
<td>P=0.004</td>
<td></td>
</tr>
<tr>
<td>Log CRP per SD</td>
<td>286/2160</td>
<td>1.29 (1.15, 1.46)</td>
<td>&lt;0.0001</td>
<td>1.26 (1.10, 1.44)</td>
</tr>
<tr>
<td><strong>CVA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest Tertile</td>
<td>22/684</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td></td>
</tr>
<tr>
<td>Mid Tertile</td>
<td>34/731</td>
<td>1.39 (0.81, 2.38)</td>
<td>0.23</td>
<td>1.50 (0.87, 2.59)</td>
</tr>
<tr>
<td>Highest Tertile</td>
<td>43/745</td>
<td>1.63 (0.97, 2.74)</td>
<td>0.06</td>
<td>1.47 (0.84, 2.56)</td>
</tr>
<tr>
<td>Trend</td>
<td>P=0.07</td>
<td></td>
<td>P=0.20</td>
<td></td>
</tr>
<tr>
<td>Log CRP per SD</td>
<td>99/2160</td>
<td>1.18 (0.96, 1.45)</td>
<td>0.12</td>
<td>1.14 (0.91, 1.42)</td>
</tr>
</tbody>
</table>

Model 1: Adjusted for age and sex
Model 2: Adjusted for age, sex, current smoking status, diabetes, baseline SBP, HDL, total cholesterol, randomised atenolol/amiodrine, left ventricular hypertrophy, BMI, glucose, family history CHD, creatinine and educational attainment
Tertile: lowest: ≤1.42, mid: 1.43-3.46, highest: >3.46 mg/L
### Online Table 3. The risk of CVD and CHD in each tertile of baseline CRP in the atorvastatin-assigned group compared to the placebo group

<table>
<thead>
<tr>
<th></th>
<th>ORs (95% CI) by tertile of baseline CRP</th>
<th>Interaction*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low (0.38, 1.11)</td>
<td>0.88 (0.56, 1.40)</td>
</tr>
<tr>
<td>CVD</td>
<td>0.65 (0.38, 1.11)</td>
<td>0.88 (0.56, 1.40)</td>
</tr>
<tr>
<td>CHD</td>
<td>0.59 (0.30, 1.14)</td>
<td>0.81 (0.46, 1.43)</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, current smoking status, diabetes, baseline SBP, HDL, total cholesterol, randomised atenolol/amlodipine, left ventricular hypertrophy, BMI, glucose, family history CHD, creatinine and educational attainment

* Interaction between statin treatment across tertile of baseline CRP
Online Table 4: Association between CRP value above median at 6-month and CVD and CHD in relation to CRP of less than median value by atorvastatin and placebo using imputed data

<table>
<thead>
<tr>
<th></th>
<th>CVD</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events/no-event</td>
<td>HR (95% CI)</td>
<td>P</td>
<td>Event/no-event</td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td><strong>Model 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP&lt;median</td>
<td>39/826</td>
<td>1.00 (Ref)</td>
<td>0.16</td>
<td>25/821</td>
<td>1.00 (Ref)</td>
<td>0.16</td>
</tr>
<tr>
<td>CRP≥median</td>
<td>58/812</td>
<td>1.37(0.88,2.13)</td>
<td>0.07</td>
<td>44/817</td>
<td>1.65(0.97,2.80)</td>
<td>0.07</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP&lt;median</td>
<td>56/788</td>
<td>1.00 (Ref)</td>
<td>0.15</td>
<td>39/785</td>
<td>1.00 (Ref)</td>
<td>0.15</td>
</tr>
<tr>
<td>CRP≥median</td>
<td>63/768</td>
<td>1.33(0.91,1.95)</td>
<td>0.20</td>
<td>50/771</td>
<td>1.35(0.86,2.13)</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Model 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP&lt;median</td>
<td>39/826</td>
<td>1.00 (Ref)</td>
<td>0.60</td>
<td>25/821</td>
<td>1.00 (Ref)</td>
<td>0.60</td>
</tr>
<tr>
<td>CRP≥median</td>
<td>58/812</td>
<td>1.15(0.68,1.93)</td>
<td>0.44</td>
<td>44/817</td>
<td>1.27(0.69,2.32)</td>
<td>0.44</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP&lt;median</td>
<td>56/788</td>
<td>1.00 (Ref)</td>
<td>0.35</td>
<td>39/785</td>
<td>1.00 (Ref)</td>
<td>0.35</td>
</tr>
<tr>
<td>CRP≥median</td>
<td>63/768</td>
<td>1.24(0.78,1.97)</td>
<td>0.53</td>
<td>50/771</td>
<td>1.19(0.69,2.04)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Relative to value at 6 month < median value within each category

Median value for atorvastatin group: 1.69 mg/L (CVD); 1.70 mg/L (CHD)
Median value for placebo group: 2.36 mmol/L (CVD); 2.35 mmol/L (CHD)

Model 1: Adjusted for age & sex
Model 2: Adjusted for age, sex, current smoking, diabetes, randomised BP treatment, left ventricular hypertrophy, baseline SBP, total cholesterol, HDL, BMI, glucose, Family history of CHD, creatinine and educational attainment, and log baseline CRP