Potential synergy between lipid-lowering and blood-pressure-lowering in the Anglo-Scandinavian Cardiac Outcomes Trial

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Aims A prespecified objective of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) was to assess whether any synergistic effects were apparent between the lipid-lowering and blood-pressure-lowering regimens in preventing cardiovascular events.

Methods and results A total of 19 257 hypertensive subjects were randomized to an amlodipine-based regimen or an atenolol-based regimen. Of these, 10 305 subjects with total cholesterol ≤6.5 mmol/L were further randomized to atorvastatin 10 mg daily or placebo. In this analysis, the effects of atorvastatin were compared with placebo on coronary heart disease (CHD), cardiovascular and stroke events in those assigned amlodipine-based and atenolol-based regimens. In the ASCOT lipid-lowering arm (LLA), overall, atorvastatin reduced the relative risk of the primary endpoint of non-fatal myocardial infarction and fatal CHD events by 36% (HR 0.64, CI 0.50-0.83, P = 0.0005), total cardiovascular events by 21% (HR 0.79, CI 0.69-0.90, P = 0.0005), and stroke by 27% (HR 0.73, CI 0.56–0.96, P = 0.024). However, atorvastatin reduced the relative risk of CHD events by 53% (HR 0.47, CI 0.32–0.69, P < 0.0001) among those allocated the amlodipine-based regimen, and by 16% (HR 0.84, CI 0.60–1.17, P: n.s.) among those allocated the atenolol-based regimen (P = 0.025 for heterogeneity). There were no significant differences between the effects of atorvastatin on total cardiovascular events or strokes among those assigned amlodipine (HR 0.73, CI 0.60–0.88, P < 0.005 and HR 0.70, CI 0.45–1.06, P: n.s., respectively) or atenolol (HR 0.85, CI 0.71–1.02, P: n.s and HR 0.76, CI 0.53–1.08, P: n.s, respectively). Differences in blood pressure and lipid parameters (placebo corrected) between the two antihypertensive treatment limbs could not account for the differences observed in CHD outcome.

Conclusion These findings of an apparent interaction between atorvastatin and an amlodipine-based regimen in the prevention of CHD events are of borderline significance, and hence generate an hypothesis that merits independent evaluation in other trials.

Introduction In the lipid-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-LLA) among well-controlled hypertensive subjects without prior evidence of coronary heart disease (CHD), atorvastatin significantly reduced the incidence of CHD events and strokes.1 Compared with placebo, allocation to atorvastatin produced a significant 36% relative reduction in the primary endpoint of non-fatal myocardial infarction plus fatal CHD during a median follow-up period of 3.3 years, and this was associated with an average reduction of total and LDL cholesterol of 1.1 and 1.0 mmol/L, respectively. These results are compatible with observations from other trials of lipid-lowering with statins,2 and extended the evidence base for the primary prevention of CHD to hypertensive subjects, with well-controlled blood pressure, at modest CHD risk (about 10% over 10 years).

ASCOT-LLA was incorporated, by way of a 2×2 factorial design, into a substantially larger study among 19 257 hypertensive subjects randomly assigned to one of two different blood-pressure-lowering strategies: Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA).3 In ASCOT-BPLA, the prevention of CHD and other vascular events with a newer regimen of antihypertensive drugs based on the calcium channel blocker amlodipine, adding the angiotensin-converting enzyme inhibitor perindopril as required to reach blood pressure targets (amlodipine-based), was compared with an older regimen based on the beta-blocker atenolol, adding the diuretic bendroflumethiazide with potassium as required (atenolol-based).
ASCOT-BPLA continued following the premature closure of ASCOT-LLA, but it too was stopped early after a median follow-up period of about 5.5 years. Those assigned the amlodipine-based regimen had significantly fewer cardiovascular events (including all coronary events, strokes, total cardiovascular events and procedures, and cardiovascular deaths) than those assigned the atenolol-based regimen. In the present report, we have investigated whether the benefits of lipid-lowering with atorvastatin on coronary and other vascular events in ASCOT-LLA were influenced differentially by assignment to one or other of the blood-pressure-lowering regimens.

Methods

The detailed ASCOT protocol has been published previously and further information is available at www.ascotsstudy.org. In summary, patients were recruited between February 1998 and May 2000, largely from family practices in the UK, Ireland, and the Nordic countries. Hypertensive patients, on or off antihypertensive treatment, with no prior history of myocardial infarction or clinical CHD but with three or more risk factors for cardiovascular disease were eligible for ASCOT-BPLA. These risk factors included a history of smoking, left ventricular hypertrophy or other specified ECG abnormalities, history of early CHD in a first-degree relative, age > 55 years, microalbuminuria or proteinuria, non-insulin dependent diabetes, peripheral vascular disease, previous stroke or transient ischaemic attack, male sex, or ratio of plasma total cholesterol to HDL-cholesterol of six or higher. Exclusion criteria included prior myocardial infarction, currently treated angina, cerebrovascular event within previous three months, fasting serum triglycerides greater than 4.5 mmol/L, heart failure, uncontrolled arrhythmias, or any clinically important haematological or biochemical abnormalities.

Following a 4-week run-in period, during which eligibility and consent were confirmed, patients were randomized to one of the two blood pressure strategies in ASCOT-BPLA, either amlodipine-based or atenolol-based, and those with a fasting total cholesterol of ≤ 6.5 mmol (250 mg/dL) who were currently untreated with a statin or fibrate were randomized, using a factorial design, to either 10 mg atorvastatin daily or matching placebo in ASCOT-LLA. Overall, 19,257 patients were assigned either amlodipine-based treatment or atenolol-based treatment and 10,305 of these subjects were assigned atorvastatin or placebo. Management of those randomized to ASCOT-BPLA is detailed elsewhere. In summary, at each follow-up visit, antihypertensive drug therapy was titrated and additional drugs added (perindopril to amlodipine and bendroflumethiazide-K to atenolol) to achieve target blood pressure.

<table>
<thead>
<tr>
<th>Drug therapy</th>
<th>Amlodipine + atorvastatin n = 2584</th>
<th>Amlodipine + placebo n = 2554</th>
<th>Atenol + atorvastatin n = 2584</th>
<th>Atenol + placebo n = 2583</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous stroke / TIA</td>
<td>237 (9.2%)</td>
<td>243 (9.5%)</td>
<td>248 (9.6%)</td>
<td>273 (10.6%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>674 (26.1%)</td>
<td>686 (26.9%)</td>
<td>694 (26.9%)</td>
<td>682 (26.4%)</td>
</tr>
<tr>
<td>LVH</td>
<td>615 (23.8%)</td>
<td>573 (22.4%)</td>
<td>579 (22.4%)</td>
<td>619 (24.0%)</td>
</tr>
<tr>
<td>ECG abnormalities other than LVH</td>
<td>589 (22.8%)</td>
<td>595 (23.3%)</td>
<td>617 (23.9%)</td>
<td>582 (22.5%)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>136 (5.3%)</td>
<td>121 (4.7%)</td>
<td>125 (4.8%)</td>
<td>132 (5.1%)</td>
</tr>
<tr>
<td>Other relevant cardiovascular disease</td>
<td>101 (3.9%)</td>
<td>99 (3.9%)</td>
<td>87 (3.4%)</td>
<td>108 (4.2%)</td>
</tr>
</tbody>
</table>

Values given are mean (SD) except for %.
levels of <140/90 mmHg for non-diabetic patients and <130/
80 mmHg for diabetic patients.

Following randomization, information was recorded about
adverse events and any new cardiovascular event or procedure
including the cause for any hospital admission. Central review of
endpoints by the Endpoint Committee was carried out blinded to
treatment allocation using criteria for classifying diagnoses that
have been reported at www.ascotstudy.org. The primary endpoint
of both ASCOT-LLA and ASCOT-BPLA was the composite of non-fatal
(including silent) myocardial infarction and fatal CHD. Secondary
endpoints included non-fatal or fatal stroke and a number of
additional composite cardiovascular endpoints. Prespecified tertiary
objectives included an evaluation of any synergy between the
blood-pressure-lowering and lipid-lowering regimens.

Statistical methods

The statistical analysis plan is available at www.ascotstudy.org.
Time to first events in the atorvastatin and placebo groups were
compared on an intention to treat basis until close-out of ASCOT-LLA
(median follow-up time 3.3 years) using the log-rank and Cox pro-
portional hazard models. In order to check the proportional
hazard assumption, we have assessed the proportionality by consid-
ering the interactions of the treatment indicators and time. The
P-values for time-interaction were for all endpoints larger that
0.30. Wald’s test for interaction between atorvastatin and the two
blood pressure treatment strategies were performed using the full
Cox model. All significance tests were two-tailed and conducted
at the 0.05 level.

Results

The overall demographics of the ASCOT-LLA population have
previously been published. The patients assigned to the two
blood pressure regimens were comparable in terms of patient
characteristics (Table 1). At the close of ASCOT-LLA,
complete information was available on 98.8% of the 10 305
randomized patients. Overall, compared with placebo, allo-
cation to atorvastatin was associated with average
reductions in total cholesterol and calculated LDL choles-
terol levels of 1.3 and 1.2 mmol/L, respectively, after 1
year of follow-up, and of 1.0 and 1.0 mmol/L, respectively,
by the end of the study. There were no apparent differ-
ences between the amlodipine-based and atenolol-based
regimens in the extent to which total and LDL cholesterol
were lowered by atorvastatin (Figure 1A and B). Among
those allocated the amlodipine-based regimen, there was
a tendency for HDL to increase slightly both on atorvastatin
and on placebo, whereas in the atenolol-based group there
was a small reduction in HDL cholesterol both with atorvas-
tatin and with placebo (Figure 1C). However, compared with
placebo, atorvastatin produced a similar, although small,
absolute increase in HDL-cholesterol among those allocated

![Figure 1](https://academic.oup.com/eurheartj/article-abstract/27/24/2982/2887444)

The effect of atorvastatin compared with placebo on total (A), LDL cholesterol (B), HDL cholesterol (C), and triglycerides (D) by blood pressure treatment group.

![Figure 1](https://academic.oup.com/eurheartj/article-abstract/27/24/2982/2887444)

The effect of atorvastatin compared with placebo on total (A), LDL cholesterol (B), HDL cholesterol (C), and triglycerides (D) by blood pressure treatment group.
either the amlodipine-based or atenolol-based regimens (Figure 1C, Table 2). Among those assigned amlodipine-based therapy, serum triglyceride levels fell throughout the trial, whereas among those assigned atenolol-based therapy, mean levels rose initially and only fell after the first year (Figure 1D). However, compared with placebo, atorvastatin produced similar reductions in serum triglycerides among those allocated either amlodipine- or atenolol-based therapy (Table 2).

By the end of ASCOT-LLA, in the amlodipine and atenolol groups combined, mean blood pressure levels were similar among those allocated atorvastatin and placebo (138.3/80.4 and 138.4/80.4 mmHg respectively). Blood pressures were controlled to target levels <140/90 mmHg in 58% of non-diabetic patients and <130/80 mmHg in 31% of diabetic patients. There were minimal differences in blood pressure between those allocated atorvastatin and placebo in each of the blood pressure treatment limbs considered separately (Figure 2). On average during ASCOT-LLA, blood pressures fell by 2.9/2.0 mmHg more on amlodipine-based than atenolol-based treatment, but these differences were very similar among those allocated either atorvastatin or placebo (Figure 2, Table 2).

Overall, in both blood pressure treatment groups combined, the primary endpoint of non-fatal myocardial infarction and fatal CHD was significantly lower in the atorvastatin group than in the placebo group (HR 0.64, 95% CI 0.50–0.83, \( P = 0.0005 \)). Compared with placebo, allocation to atorvastatin reduced the incidence of the primary endpoint significantly by 53% (HR 0.47, CI 0.32–0.69, \( P = 0.0001 \)) among those allocated the amlodipine-based regimen, whereas it reduced the incidence of this outcome by only 16% (HR 0.84, CI 0.60–1.17, \( P = 0.30 \)) among those allocated the atenolol-based regimen (Table 3, Figure 3). The difference between these risk reductions with atorvastatin was of borderline significance (heterogeneity \( P = 0.025 \)).

Compared with placebo, atorvastatin reduced the relative risk of total cardiovascular events and procedures by 27% (HR 0.73 CI 0.60–0.88, \( P = 0.001 \)) among those allocated amlodipine-based treatment and by 15% (HR 0.85 CI 0.71–1.02, \( P = 0.079 \)) among those allocated atenolol-based

![Figure 2](image-url)
treatment (Figure 4). The difference between these effects was not significant (heterogeneity $P = 0.25$), and is due entirely to the observed difference in the primary endpoint. The effects of atorvastatin on non-fatal or fatal strokes in those allocated amlodipine-based treatment ($HR = 0.69, CI 0.45–1.06, P = 0.09$) compared with those allocated atenolol-based treatment ($HR = 0.76, CI 0.53–1.08, P = 0.13$) were not significantly different from each other (heterogeneity $P = 0.73$) (Figure 5).

**Discussion**

In a previous report on ASCOT-BPLA, an attempt was made to evaluate to what extent the observed differences between the two blood-pressure-lowering strategies could be explained by differences in blood pressure and other risk factors that were differentially affected after randomization. Despite certain inevitable shortcomings, these analyses suggested that differences in factors other than blood pressure (particularly HDL-cholesterol) may have contributed to at least some of the observed differences in CHD and stroke event rates. However, it remained possible that additional mechanisms could have contributed to the event rate differences. In the present report, we have investigated in a prespecified analysis the placebo-controlled effects of atorvastatin allocation in ASCOT-LLA among patients in each of the two different blood-pressure-lowering groups to evaluate whether potential interactions between the antihypertensive and lipid-lowering regimens could contribute to the explanation of the differences seen in ASCOT-BPLA.

Compared with placebo, the relative risk reduction in the primary endpoint of non-fatal myocardial infarction or fatal CHD with atorvastatin allocation was greater among those allocated the amlodipine-based regimen than among those allocated atenolol-based treatment. Dihydropyridines suppress experimental atherosclerosis and some clinical studies have suggested that calcium channel blockers may have anti-atherosclerotic properties. Additionally, ACE-inhibitors may contribute to reductions in CHD events by non-blood-pressure-dependent mechanisms and synergy with statins has been suggested in one study.

The more likely basis for the proposed synergy being related to the statin interaction with the dihydropyridine calcium channel blocker, however, is supported by the observation that significant benefits ($P = 0.02$) of atorvastatin were seen in the amlodipine-based treatment limb within 3 months of assignment to treatment, and unpublished observations, by which time a minority of patients had progressed to add-on therapy with the ACE-inhibitor. Furthermore, some cellular and molecular studies provide supporting evidence for an interaction between calcium channel blockers and statins.

In interpreting the present evidence for synergy, it is important to consider whether it might merely represent

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**Table 3**  The effects of atorvastatin vs. placebo for amlodipine-based and atenolol-based treatment for fatal CHD and non-fatal myocardial infarction, total cardiovascular events and procedures, and fatal and non-fatal stroke

<table>
<thead>
<tr>
<th>Endpoint and blood pressure regimen</th>
<th>Atorvastatin</th>
<th>Placebo</th>
<th>Unadjusted HR</th>
<th>$P$-value</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-fatal myocardial infarction + fatal CHD</td>
<td>n (%)</td>
<td>Rate $^a$</td>
<td>n (%)</td>
<td>Rate $^a$</td>
<td>95% CI</td>
</tr>
<tr>
<td>Amlodipine-based</td>
<td>38 (1.5%)</td>
<td>4.6</td>
<td>80 (3.1%)</td>
<td>9.8</td>
<td>0.47 (0.32–0.69)</td>
</tr>
<tr>
<td>Atenolol-based</td>
<td>62 (2.4%)</td>
<td>7.5</td>
<td>74 (2.9%)</td>
<td>9.0</td>
<td>0.84 (0.60–1.17)</td>
</tr>
<tr>
<td>Total cardiovascular events and procedures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amlodipine-based</td>
<td>173 (6.7%)</td>
<td>21.3</td>
<td>233 (9.1%)</td>
<td>29.4</td>
<td>0.73 (0.60–0.88)</td>
</tr>
<tr>
<td>Atenolol-based</td>
<td>216 (8.4%)</td>
<td>27.0</td>
<td>253 (9.8%)</td>
<td>31.7</td>
<td>0.85 (0.71–1.02)</td>
</tr>
<tr>
<td>Fatal and non-fatal stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amlodipine-based</td>
<td>35 (1.4%)</td>
<td>4.2</td>
<td>50 (2.0%)</td>
<td>6.1</td>
<td>0.69 (0.45–1.06)</td>
</tr>
<tr>
<td>Atenolol-based</td>
<td>54 (2.1%)</td>
<td>6.5</td>
<td>71 (2.7%)</td>
<td>8.6</td>
<td>0.76 (0.53–1.08)</td>
</tr>
</tbody>
</table>

*a per 1000 patient years.*
the play of chance. The apparent interaction between the effects of atorvastatin on the primary coronary endpoint among those allocated the amlodipine or atenolol regimens was of borderline significance for a tertiary endpoint ($P = 0.025$). Moreover, there were no significant differences between the relative reductions in stroke or in all other cardiovascular events and procedures associated with atorvastatin use among those allocated the amlodipine or atenolol regimens. However, different biological processes are involved in the pathogenesis of coronary and stroke events. Compared with placebo, allocation to atorvastatin produced almost identical effects on total and LDL cholesterol among those allocated the amlodipine or atenolol regimens. Differences in the effects of atorvastatin on levels of HDL-cholesterol and serum triglycerides between these blood pressure regimens cannot readily explain any differences in effects on coronary endpoints, since the small effects of atorvastatin favoured, if anything, those allocated atenolol-based treatment (Table 2). Similarly, no material interaction was observed between the effects on blood pressure of the lipid-lowering and blood-pressure-lowering treatments.

In the Pravastatin Pooling Project, which combined data from three trials of cholesterol lowering with pravastatin, the relative reduction in CHD events was significantly less in those with hypertension at study entry than in those without it (14 vs. 33%; heterogeneity $\chi^2/1 = 0.41$, R. Collins personal communication) and, if anything, were somewhat greater among those who were receiving beta-blockers than among those who were not (40 vs. 24%; heterogeneity $\chi^2/1 = 5.8$). Similarly, in the recently reported Cholesterol Treatment Trialists (CTT) meta-analysis of 14 large randomized trials of statin therapy, there was no evidence that the relative reductions in coronary or other vascular events differed significantly among people who presented with or without treated hypertension.

The future role of beta-blockers in the primary prevention of cardiovascular disease has been called into question by the results of ASCOT-BPLA, as well as by some other trials and recent reviews, although the evidence remains strong for the beneficial effects of beta-blockers in secondary prevention and heart failure. The apparently smaller effect on coronary events of atorvastatin in combination with an atenolol-based regimen in ASCOT-LLA does raise the question of whether the benefits of statins might
also be attenuated by beta-blocker use—or even diuretics—in secondary prevention. But, this possibility is not supported by the results for simvastatin in HPS and for a range of other statins in CTT, and it remains a possibility that the smaller effect observed with atorvastatin in the presence of atenolol in ASCOT-LLA was due at least in part to the play of chance.

In summary, we report on a potential interaction between blood-pressure-lowering treatments and statin use in ASCOT-LLA. Although we accept these observations could represent the play of chance and need to be confirmed in future studies, we believe there are plausible explanations based upon molecular studies for such an interaction which could lead to increased stability of atherosclerotic plaques and perhaps account for why the apparent interaction reported here was on CHD events rather than other cardiovascular endpoints where the underlying pathophysiological processes are more diverse.

Acknowledgements

P. Sever, B. Dahlöf, N.R. Poulter, H. Wedel, constituting the Executive Committee and members of the Steering Committee designed the study, wrote the protocol, supervised the undertaking of the study, coordinated data collection, wrote the analysis plan, supervised the analyses, interpreted the results, and wrote the report. D.G. Beever,S. cauliflower, R. Collins, S.E. Kjeldsen, A. Kristinsson, G.T. McInnes, J. Mehlisen, M. Nieminen, E. O’Brien, and J. Östergren, as members of the Steering Committee, approved the protocol and analysis plan, supervised the undertaking of the study, and had input to the report.

Conflict of interest: P. Sever, B. Dahlöf, N.R. Poulter, H. Wedel, D.G. Beever, S. cauliflower, R. Collins, S.E. Kjeldsen, A. Kristinsson, G. McInnes, J. Mehlisen, M.S. Nieminen, E. O’Brien, and J. Östergren have served as consultants or received travel expenses, or payment for speaking at meetings, or funding for research from one or more pharmaceutical companies that market blood-pressure-lowering or lipid-lowering drugs, including Pfizer for ASCOT.

References


10. Sever PS, Poulter NR. Blood pressure reduction is not the only determinant of outcome. Circulation 2006;113:2754–2774.


