Brief Reviews

The Anglo-Scandinavian Cardiac Outcomes Trial
Implications and Further Outcomes

Peter S. Sever

Online Data Supplement

At a meeting of the European Blood Pressure Group held in Madonna di Campiglio, Italy, in the spring of 1988, concern was expressed that there were no plans to evaluate the long-term efficacy of newer classes of blood pressure–lowering drugs, including the calcium channel blockers and the angiotensin-converting enzyme inhibitors, in morbidity and mortality outcome trials. These drugs were being increasingly used in clinical practice worldwide, and there was a view that industry perceived there was no need for long-term studies. Much had been made of the potential benefits of these newer drugs in short-term studies on surrogate endpoints compared with older therapies, but there was little pressure for investment in outcome trials in hypertension.

At a further meeting of the European Blood Pressure group the following year, in 1989, a steering group outlined a proposal for a factorial-designed study to investigate not only whether newer treatments were better than old but also whether cholesterol lowering in a hypertensive population would confer benefits on coronary heart disease (CHD) events. At approximately the same time in the United States, proposals along similar lines were being discussed by the National Heart, Lung, and Blood Institute. However, further progress was delayed until September 1995, when it was proposed that if a group of United Kingdom trialists was to collaborate with the Gothenburg Trial Centre in Sweden, Pfizer would fund a major European outcome study.

Preliminary discussions between United Kingdom and Swedish colleagues reviewed ongoing trials, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, and focused on the design of a 2-way comparison trial comparing older treatment strategies with a newer treatment strategy based a calcium channel blocker and an angiotensin-converting enzyme inhibitor. The concept of a “combination treatment” trial germinated, particularly because it was recognized that most patients required >1 drug to control blood pressure and that no other trial was designed to compare specific treatment regimens. In addition, there was further discussion on a factorial design, involving a comparison of a lipid-lowering agent with placebo in a subgroup of patients with normal or modestly raised cholesterol levels for whom, at the time, there was no indication for lipid lowering. Further details on the background to Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) are given in Appendix 1 (available in the online-only Data Supplement).

An independent steering committee was set up in 1996. The trial protocol was agreed and finalized, named the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), and recruitment commenced in February 1998.

Summary of Trial Design

The ASCOT protocol has been published, and further information is available at www.ascotstudy.org. In summary, patients were recruited between February 1998 and May 2000, largely from family practices in United Kingdom, Ireland, and the Nordic countries. Hypertensive patients, on or off antihypertensive treatment, with no previous history of myocardial infarction or clinical CHD but with ≥3 risk factors for cardiovascular disease were eligible for the ASCOT-Blood Pressure–Lowering Arm (BPLA). These risk factors included male sex, age >55 years, a history of smoking, left ventricular hypertrophy or other specified ECG abnormalities, history of early CHD in a first-degree relative, microalbuminuria or proteinuria, noninsulin-dependent diabetes mellitus, peripheral vascular disease, previous stroke or transient ischemic attack, or ratio of plasma total cholesterol:high-density lipoprotein cholesterol of ≥6. Exclusion criteria included previous myocardial infarction, currently treated angina, cerebrovascular event within the previous 3 months, fasting serum triglycerides >4.5 mmol/L, heart failure, uncontrolled arrhythmias, or any clinically important hematologic or biochemical abnormalities.

In ASCOT-BPLA, patients were randomized to 1 of the 2 blood pressure–lowering strategies, either amlodipine with or without perindopril (amlodipine based) or atenolol with or...
without bendroflumethiazide (atenolol based). In the ASCOT-Lipid-Lowering Arm (LLA), those with a fasting total cholesterol of ≤6.5 mmol/L (250 mg/dL) who were currently untreated with a statin or fibrate were randomized, using a factorial design, to either 10 mg of atorvastatin daily or matching placebo. Overall, 19,342 patients were assigned either amlodipine-based treatment or atenolol-based treatment, and 10,305 of these subjects were assigned atorvastatin or placebo. In the BPLA, at each follow-up visit, antihypertensive drug therapy was titrated and additional drugs added (perindopril to amlodipine and bendroflumethiazide to atenolol) to achieve target blood pressure levels of <140/90 mm Hg for nondiabetic patients and <130/80 mm Hg for diabetic patients (Figure 1).

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

**ASCOT-LLA Main Results**

On September 2, 2002, ~3 years into the trial, the Data Safety Monitoring Board recommended that the lipid-lowering arm of the trial be stopped on the grounds that atorvastatin had resulted in a highly significant reduction in the primary end point of CHD events compared with placebo and a significant reduction in the incidence of stroke.2

The primary end point of nonfatal myocardial infarction, including silent myocardial infarction and fatal CHD, was significantly lower by 36% (hazard ratio [HR], 0.64 [95% CI, 0.50–0.83]; \( P = 0.0005 \)) in the atorvastatin group than in the placebo group (Figure 2). To assess the impact of baseline cholesterol on the effect of atorvastatin on the primary end point, data were stratified on the basis of the median total cholesterol value among patients who experienced a primary end point (5.6 versus 5.6 mmol/L). The HRs were 0.65 (\( P = 0.015 \)) and 0.63 (\( P = 0.012 \)), respectively, in these 2 groups. Similarly, in a further post hoc analysis, HRs for patients with baseline total cholesterol concentrations ≤5.00, 5.01–5.49, and ≥5.50 mmol/L were 0.72, 0.63, and 0.57, respectively. The impact of baseline cholesterol was also examined in patients with diabetes. The HR was 0.81 (95% CI, 0.63–1.05) for patients with baseline total cholesterol of 5.00–6.49 mmol/L compared with 0.65 (95% CI, 0.49–0.86) for patients with total cholesterol levels ≥6.50 mmol/L. Therefore, additional patients with high baseline cholesterol would likely have achieved a greater reduction in risk by being randomized to atorvastatin early in the trial.

**Figure 1.** Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) Study design.

**Figure 2.** Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)-Lipid-Lowering Arm (LLA) summary of all end points. Modified from Sever et al2 with permission of the publisher. Copyright © 2003, Elsevier.

<table>
<thead>
<tr>
<th>Primary End Points</th>
<th>Risk Ratio</th>
<th>Hazard Ratio</th>
</tr>
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<tbody>
<tr>
<td>Nonfatal MI (incl silent) + fatal CHD</td>
<td>0.64 (0.50-0.83)</td>
<td>0.64 (0.50-0.83)</td>
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<tr>
<td>Secondary End Points</td>
<td></td>
<td></td>
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<tr>
<td>Total CV events and procedures</td>
<td>0.79 (0.69-0.90)</td>
<td>0.79 (0.69-0.90)</td>
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<tr>
<td>Total coronary events</td>
<td>0.71 (0.59-0.86)</td>
<td>0.71 (0.59-0.86)</td>
</tr>
<tr>
<td>Nonfatal MI (excl silent) + fatal CHD</td>
<td>0.62 (0.47-0.81)</td>
<td>0.62 (0.47-0.81)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.87 (0.71-1.06)</td>
<td>0.87 (0.71-1.06)</td>
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<td>Cardiovascular mortality</td>
<td>0.90 (0.66-1.23)</td>
<td>0.90 (0.66-1.23)</td>
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<tr>
<td>Fatal and nonfatal stroke</td>
<td>0.73 (0.56-0.96)</td>
<td>0.73 (0.56-0.96)</td>
</tr>
<tr>
<td>Fatal and nonfatal heart failure</td>
<td>1.13 (0.73-1.78)</td>
<td>1.13 (0.73-1.78)</td>
</tr>
<tr>
<td>Tertiary End Points</td>
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<tr>
<td>Silent MI</td>
<td>0.82 (0.40-1.66)</td>
<td>0.82 (0.40-1.66)</td>
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<tr>
<td>Unstable angina</td>
<td>0.87 (0.49-1.57)</td>
<td>0.87 (0.49-1.57)</td>
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<td>Chronic stable angina</td>
<td>0.59 (0.38-0.90)</td>
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<tr>
<td>Peripheral arterial disease</td>
<td>1.02 (0.66-1.57)</td>
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<tr>
<td>Development of diabetes mellitus</td>
<td>1.15 (0.91-1.44)</td>
<td>1.15 (0.91-1.44)</td>
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<tr>
<td>Development of renal impairment</td>
<td>1.29 (0.76-2.19)</td>
<td>1.29 (0.76-2.19)</td>
</tr>
</tbody>
</table>

Area of squares is proportional to the amount of statistical information.
5.00 to 5.99, and ≥6.0 mmol/L were 0.63 (P = 0.098), 0.62 (P = 0.011), and 0.69 (P = 0.084), respectively.

There were also significant reductions in 4 of the 7 secondary end points, some of which incorporated the primary end point, total cardiovascular events including revascularization procedures (21%); total coronary events (29%); the primary end point excluding silent myocardial infarction (38%); and fatal and nonfatal stroke (27%; Figure 2). All-cause mortality was nonsignificantly reduced by 13%, with nonsignificantly fewer cardiovascular deaths and no excess of deaths from cancer (81 assigned statin versus 87 assigned placebo) or from other noncardiovascular causes (111 versus 130).

The proportional effect of atorvastatin on the primary end point did not differ significantly in any prespecified subgroup from that noted overall, although the benefit was not significant in 6 subgroups, including patients with diabetes mellitus, and no benefit was apparent among women. However, we noted no significant interaction between sex and the impact of statin on the primary end point, and total cardiovascular and total coronary events was reduced by 20% (P = 0.17) and 14% (P = 0.56), respectively, among women. The number of serious adverse events and rates of liver enzyme abnormalities did not differ between patients assigned atorvastatin or placebo.

Please see Appendix 2 for additional results.

**ASCOT-LLA Implication of Findings**

The results of ASCOT-LLA were influential in changing national and international guidelines. Both the British Hypertension Society IV guidelines of 2004 and the European Society of Hypertension-European Society of Cardiology guidelines produced in 2003 included the following statement:

*In view of the results of the ASCOT trial and other currently available trial data, it seems reasonable, in the interests of simplicity, to treat with a statin, all those patients at least up to the age of 80 years with a total cholesterol ≥3.5 mmol/L who have an estimated 10 year CVD risk of 20% or more. In reality, this would mean considering statin therapy in most hypertensive patients (especially men) more than the age of 50 years. As resources allow, a rationale for lowering this threshold could be made on the basis of trial evidence.*

In addition, the “Recommendations of the Joint British Societies” published in 2005 also endorsed this same threshold of ≥20% 10-year cardiovascular risk for the initiation of lipid-lowering therapy. Two areas of controversy followed publication of the results of the study. The first related to subgroup analysis of atorvastatin on the primary end point (Figure S1, available in the online-only Data Supplement) and the second to cost effectiveness of atorvastatin in this population. These issues are dealt with in Appendix 3.

**ASCOT-BPLA Results**

Between February 1998 and May 2000, 19257 patients were randomized to 1 of the 2 antihypertensive regimens (Figure 1). Patients were mainly white (95%) and male (87%), with a mean age of 63 years. The average number of additional cardiovascular risk factors was 3.7. Baseline blood pressures were almost identical at ~164 mm Hg systolic and 95 mm Hg diastolic, although >80% of patients were currently on antihypertensive medication. The study was stopped prematurely after 5.5 patient-years of follow-up on the recommendation of the Data Safety Monitoring Board because of highly significant benefits of the amloidipine-based regimen on all-cause mortality and stroke outcomes.

At the final BPLA visits, complete information was obtained on 99.5% of the 19257 patients originally randomized. Of the remainder, vital status was obtained on all but 122 patients (61 withdrew consent and 61 were lost to follow-up).

Mean blood pressure reductions were substantial in both arms. Compared with those allocated to the atenolol-based treatment, blood pressures were lower throughout the trial among those allocated to amloidipine-based treatment. These differences were largest (5.9/2.4 mm Hg) at 3 months, but the average difference throughout the trial was 2.7/1.9 mm Hg. At the final visit, mean BP had fallen to 137.7/79.2 mm Hg and 136.1/77.4 mm Hg in the atenolol-based and amloidipine-based limbs, respectively, representing mean falls of 25.7/15.6 mm Hg and 27.5/17.7 mm Hg.

As intended by design, the majority of patients, 71%, were taking ≥2 antihypertensive agents, and 51% and 52% in the atenolol and amloidipine-based limbs, respectively, were taking one or the other of step 1 or step 2 agents of the regimen to which they were allocated.

The primary end point of nonfatal myocardial infarction, including silent myocardial infarction and fatal CHD, was nonsignificantly lower by 10% (HR, 0.90 [95% CI, 0.79–1.02]; P = 0.105) in the amloidipine-based group than in the atenolol-based group (Figure 3). There were significant reductions in 6 of the 7 secondary end points of the trial among those allocated to the amloidipine-based regimen compared with the atenolol-based regimen, including all-cause mortality, which was reduced by 11%, nonfatal myocardial infarction (excluding silent myocardial infarction), and fatal CHD (13%); total coronary events (13%); total cardiovascular events and procedures (16%); cardiovascular mortality (24%); and fatal and nonfatal stroke (23%). The results for 4 of the 7 tertiary end points were significantly in favor of those allocated to the amloidipine-based regimen with a significant 30% reduction (P ≤ 0.00001) in new-onset diabetes mellitus. Only 1 end point (silent MI) was not affected favorably among those allocated the amloidipine-based regimen.

To facilitate comparisons with other major cardiovascular trials and because of the increasingly used diagnosis and treatment of acute coronary syndromes, 2 post hoc analyses were carried out; combined end points (cardiovascular death plus nonfatal myocardial infarction and stroke) and coronary revascularization plus the primary end point were evaluated. Both of these post hoc end points were significantly reduced among those allocated the amloidipine-based regimen. The proportional effect of allocation to the amloidipine-based regimen on the primary end point and on total cardiovascular events and procedures did not differ significantly in any prespecified subgroup, with benefits being significant in all of the subgroups for the latter composite end point.

Slightly less than 25% of patients stopped therapy because of adverse events, with no significant difference between groups. There was, however, a significant difference in favor
of the amlodipine-based regimen in the proportion stopping trial therapy because of serious adverse events ($P<0.024$).

**ASCOT-BPLA Implication of Findings**

The results of ASCOT-BPLA clearly demonstrated that, in hypertensive patients at increased risk of developing cardiovascular disease because of associated risk factors, the regimen based on amlodipine and perindopril was superior to one based on atenolol and bendroflumethiazide in reducing major cardiovascular events and all-cause mortality and also in inducing less new-onset diabetes mellitus.

Although statistically significant reductions in the primary end point were not achieved, there was a strong trend in this direction, and given that the trial was powered to detect differences in this end point based on reaching 1150 primary events, the likelihood of achieving such a result was thereby reduced. However, combining all of the coronary events resulted in a significant benefit of amlodipine-based treatment, and on most other end points the “newer” treatment strategy was clearly associated with a better cardiovascular outcome and also in inducing less new-onset diabetes mellitus.

![Figure 3. Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)-Blood Pressure-Lowering Arm (BPLA) summary of all end points. Modified from Dahlöf et al with permission of the publisher. Copyright © 2005, Elsevier.](http://hyper.ahajournals.org/)

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Synergy Between Atorvastatin- and Amlodipine-Based Treatment

In those allocated atorvastatin, the primary end point of nonfatal myocardial infarction plus fatal CHD was significantly reduced by 53% (HR, 0.47; 95% CI, 0.33–0.69; $P<0.0001$) among those allocated to atorvastatin compared with those allocated to placebo.8 This compares with a risk reduction of 36% reported previously for the benefits of atorvastatin in the combined BPLA treatment groups. In the atenolol-based group, this end point was reduced among those allocated atorvastatin compared with those allocated placebo by 16% (HR, 0.84 [95% CI, 0.60–1.17]; $P=0.30$). A test for interac-
tion between lipid-lowering and blood pressure-lowering regimen was significant for this end point (P=0.02; Figure 4). These effects were not compatible with any differential placebo-controlled effect of atorvastatin on either blood pressure or lipid subfractions in the 2 blood pressure treatment limbs of the trial. Among those allocated amiodipine-based therapy, total cardiovascular events and procedures were reduced by 27% (HR, 0.73 [95% CI, 0.60–0.88]; P=0.001) in association with allocation to atorvastatin compared with placebo. Among those allocated atenolol-based therapy, this end point was reduced by 15% (HR, 0.85 [95% CI, 0.71–1.02]; P=0.079) when allocation to atorvastatin was compared with placebo. No significant interaction was apparent for this end point. The effects of atorvastatin compared with placebo on fatal and nonfatal stroke events were not significantly different in those assigned amiodipine-based treatment compared with placebo. Among those allocated atenolol-based treatment, there was a significant risk reduction in the primary end point associated with the use of atorvastatin from 90 days of observation through to the end of the trial, but among those allocated to the atenolol-based regimen, benefits of atorvastatin were not statistically significant at any time point.9

There have been reports of synergy between amiodipine and atorvastatin based on a number of experimental studies. Electrochemical bonding between the oppositely charged molecules in the lipid bilayer of cell membranes leads to pronged tissue half-lives.10 We have reported on the basis of cellular and molecular studies that pleiotropic actions of atorvastatin prevent the phenotypic transformation of vascular smooth muscle cells that occurs in the development of atherosclerotic plaques and that contributes to apoptosis and destruction of the intercellular matrix, leading to plaque rupture. Our hypothesis is that the early benefits of atorvastatin, observed particularly in those assigned amiodipine, are accounted for by restoration of more differentiated smooth muscle cells and stabilization of vulnerable plaques.11 We reported that this apparent interaction between atorvastatin and the 2 antihypertensive regimens used in ASCOT in the prevention of acute CHD events could have important implications for optimal treatment strategies for hypertensive patients, and on the basis of these findings we attempted to explore the overall benefits in ASCOT from combined blood pressure and lipid lowering.

**Combined Blood Pressure and Lipid Lowering**

The cardiovascular outcome in hypertensive subjects treated with prespecified blood pressure-lowering and lipid-lowering strategies had not previously been explored. We obtained estimates of baseline Framingham risk for CHD events from the demographics of the subjects at trial entry. These were 22.8 per 1000 patient-years. After 3.3 years when LLA was stopped, in those assigned amiodipine-based treatment and atorvastatin, the actual CHD event rate had fallen to 4.8 per 1000 patient-years, a reduction of 79%. This risk reduction was larger than expected and compares with ≈50% risk reduction predicted from the pooled analyses of the outcome trials of blood pressure lowering and lipid lowering for the differences in the usual blood pressure of ≈15 mm Hg systolic and of low-density lipoprotein cholesterol of ≈1 mmol/L observed in the trial.12

**ASCOT Substudies**

One of the major advantages of an investigator-lead trial is the opportunity presented to the trial investigators to design and execute important substudies, to be carried out under the umbrella of the main trial. It cannot be overestimated the value of these studies, many of which could not be undertaken, de novo, because of the substantial costs incurred in recruitment of suitable patients. Before the commencement of recruitment into ASCOT, >20 substudies were proposed and ratified by the Substudies Committee.13 Several additional substudies and preplanned subanalyses were incorporated subsequent to the onset of the trial. By March 2012, of 60 full journal publications from ASCOT, 39 were reports of substudies and a further 11 from subanalyses of the ASCOT database. A full list of the substudies is available on the ASCOT web site and listed in the supplementary online ASCOT bibliography (Appendix 5). For the purpose of this review, the author has selected 4 key hemodynamic substud-
ies with which he has been associated, which have been highly cited, and which have important clinical implications.

Ambulatory Blood Pressure Monitoring Substudy of ASCOT

In this important substudy, 1905 patients from 4 ASCOT centers underwent repeated ambulatory blood pressure monitoring (ABPM) over a median follow-up period of 5.5 years. An average of 3.5 recordings was obtained from each participant. As expected from the whole ASCOT population, in this substudy clinic blood pressures were lower in the amlodipine/perindopril-treated patients compared with those treated with atenolol/thiazide (1.5/1.2 mm Hg).

On ABPM, daytime blood pressures during follow-up were higher in patients treated with amlodipine/perindopril (1.6 mm Hg). On the other hand, nighttime systolic but not diastolic blood pressure was lower in patients treated with amlodipine/perindopril therapy (2.2/3.8 mm Hg; Figure S4). It is important to note that, when comparing these blood pressure differences with those reported in the original ASCOT-BPLA article, the ABPM recordings and related clinic blood pressures were obtained from visits 1 year into the trial and on ≥2 occasions thereafter. Therefore, the early differences in blood pressure, for the first few months after randomization, in favor of amlodipine/perindopril, would not have been apparent in this ABPM substudy.

ABPM values were significantly associated with the rates of cardiovascular events, and nocturnal pressures provided complementary and incremental use over clinic blood pressures in the prediction of cardiovascular risk in these treated hypertensive patients.

Blood Pressure Variability as A predictor of Cardiovascular Outcome in ASCOT and the Differential Effect of Amlodipine/Perindopril and Atenolol/Thiazide Regimens

The hypothesis by Rothwell et al.15,16 based on observations in patients with recurrent transient ischemic attacks or strokes, that blood pressure variability rather than blood pressure alone is an important predictor of future events, was explored in the ASCOT population. Several measures of blood pressure variability were obtained throughout the trial. Visit-to-visit variability was expressed as the SD or coefficient of variation of between visit measures. In addition, a transformation of blood pressure variability independent of in-trial blood pressure was also determined. Three measures of blood pressure were obtained at each visit throughout the trial, which allowed an estimate of within-visit variability. Finally, blood pressure variability was determined from the subgroup of patients who underwent 24-hour ABPM.

In the first set of analyses, data were analyzed from 6 months after randomization to the end of the trial. The rationale for this was that, during the first few months of the trial, blood pressures were rapidly falling in both treatment arms as a result of dosage adjustment and the introduction of second- and third-line drugs. By 6 months in-trial, blood pressures had largely stabilized. Mean blood pressures within trial and measures of visit-to-visit variability throughout the trial were expressed as deciles.

In keeping with earlier analyses on the initial ASCOT database, in-trial mean blood pressure was a poor predictor of stroke outcome. Excess stroke risk was only seen in the highest decile of in-trial mean systolic blood pressure, and in-trial mean blood pressure did not predict coronary risk (Figure 5). On the other hand, all of the measures of visit-to-visit systolic blood pressure variability (SD, coefficient of variation, and variation independent of mean) were powerful predictors of both stroke and coronary outcome in both treatment groups (Figure 6). Comparing the top with the bottom decile of systolic blood pressure visit-to-visit variability, there was an ≈4-fold excess risk of stroke outcomes and a 2- to 3-fold increase in the risk of coronary events. Visit-to-visit blood pressure variability (by all measures) was consistently lower in the amlodipine/perindopril group than in the atenolol/thiazide group.16

Both stroke risk and coronary risk were also predicted by measures of within-visit variability in blood pressure, although the relationship was much weaker than observed with

![Figure 5. Visit-to-visit mean systolic blood pressure expressed in deciles, hazard ratios (95% CI), and number of stroke and coronary events in each decile. Modified from Rothwell et al16 with permission of the publisher. Copyright © 2010, Elsevier.](attachment:image.png)
between-visit variability. Likewise, intra-ABPM blood pressure variability and daytime systolic blood pressure also predicted both stroke and coronary events but less so than visit-to-visit variability. No measures of variability in heart rate were found to predict any cardiovascular outcomes.

We reported in the main trial results that risk reductions in stroke (23%) and coronary events (13%) were associated with assignment to amlodipine/perindopril treatment compared with atenolol/thiazide treatment. In a multiple regression model, incorporation of usual systolic blood pressure throughout the trial has been reported previously to have a minimal effect on the HRs for stroke in favor of amlodipine/perindopril treatment and to have no effect on coronary outcome. However, incorporation of measures of visit-to-visit variability and within-visit variability of blood pressure throughout the trial into the model totally eliminated the differences observed in both stroke and coronary outcome in favor of amlodipine/perindopril treatment.16

These data strongly suggest that blood pressure variability rather than blood pressure, per se, was an important determinant of cardiovascular outcomes in this large hypertensive population. In addition there were important differences between the 2 treatment arms in ASCOT that were explained almost exclusively by differences in blood pressure variability.

Figure 6. Visit-to-visit systolic blood pressure variability expressed in deciles, hazard ratios (90% CI), and number of strokes and coronary events in each decile. Modified from Rothwell et al16 with permission of the publisher. Copyright © 2010, Elsevier.
Conduit Artery Functional Evaluation Substudy
See Appendix 5.17

Studies on Wave Reflection, Differential Effects of Amlodipine/Perindopril Regimen Versus Atenolol/Thiazide Regimen on Central Blood Pressure, and Predictions of Cardiovascular Events
See Appendix 6.18,19

ASCOT Biomarker Program
An important initiative was undertaken before the commencement of ASCOT to support a repository of blood samples from all of the participants to be used for the subsequent identification of potential biomarkers for the future development of cardiovascular endpoints. A similar DNA resource was established from >9000 ASCOT patients.

Of 10 potential biomarkers, most have now been analyzed and presentations or publications on C-reactive protein, N-terminal pro-brain natriuretic peptide, and plasma renin activity completed20 (unpublished work). A full list of biomarkers is shown in Table S1. Genome-wide association scans have been performed on 4000 samples from the DNA repository, and extensive collaborations are in progress in the search for genetic loci associated with hypertension,21 loci predicting responses to statins, and a number of cardiovascular outcomes.

ASCOT Long-Term Follow-Up
One of the remarkable and largely unexplained findings from a number of cholesterol-lowering trials has been the demonstration of a legacy effect, that is the persistence of benefit from intervention many years after the completion of a trial and when treatments between those formerly allocated to one or other arms of the trial have been essentially similar.22 Such long-term observations have been reported from the Long-Term Intervention With Pravastatin in Ischemic Heart Disease Study23 and the West of Scotland Coronary Prevention Study.24 In 2006 we reported a 2.2-year follow-up of ASCOT-LLA patients after the premature closure of the trial in 2003.25 During the extended follow-up, approximately two thirds of subjects formerly assigned to either atorvastatin or placebo were on treatment with a statin, and lipid profiles by the end of the observation period were identical. However, relative risk reductions in all of the cardiovascular end points associated with atorvastatin remained essentially unchanged compared with those reported at 3.3 years of the trial (Figure S3).

In ASCOT, in the United Kingdom, all patients alive at the end of the trial were flagged with the Office for National Statistics for records of subsequent death. In those originally randomized to LLA, there were 960 deaths in the 11 years after initial randomization, and ~8 years after closure of LLA, all-cause mortality remained significantly lower in those originally assigned atorvastatin (HR, 0.86 [95% CI, 0.76–0.98]; P=0.02). Cardiovascular deaths were fewer but not significantly (HR, 0.89 [95% CI, 0.72–1.11]; P=0.32), and noncardiovascular deaths were significantly lower (HR, 0.85 [95% CI, 0.73–0.99]; P=0.03) in those formerly assigned atorvastatin attributed to a reduction in deaths because of infection and respiratory illness (Figure 7).22

We concluded that legacy effects of those originally assigned to atorvastatin may contribute to long-term benefits on all-cause mortality, but we were unable to provide an explanation for long-term benefits on noncardiovascular deaths. We are currently in the process of following up mortality data from those randomized into the BPLA, and morbidity follow-up of all United Kingdom subjects alive in 2012 is about to commence.

What Are the Implications for the Future Management of Hypertension?
Contemporary guidelines have clearly differed in their approach to the recommendations on selection of initial drug therapy for patients with hypertension with a North American view, largely based on the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, that diuretics remain first-line treatment for most patients unless there are specific contraindications or indications for other drugs.26 It is possible that the Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure will change these recommendations based on a radical review of the evidence base. British guidelines, for many years, favored the ABCD rule,27,28 and the most recent NICE guidelines29 have proposed a development of this algorithm, influenced by a comprehensive evaluation of the intervention trials, including ASCOT. The new ACD algorithm is based on the fact that age and race would appear to influence drug efficacy, that there is overwhelming evidence for the benefits of A drugs over β-blockers in uncomplicated hypertension (particularly with respect to stroke prevention and less new-onset diabetes mellitus),29,30 and that there is an accumulating evidence for the benefits of C over D drugs.29,31

The results of the ASCOT blood pressure arm confirm beyond doubt the greater efficacy in blood pressure lowering of calcium channel blockers over β-blockers in a largely elderly population, an issue that hitherto has been ignored by many guidelines. Although other trials, such as the International Verapamil-Trandolapril Study32 and the Nordic Diltiazem Study,33 compared calcium-channel blockers with β-blockers, in contrast with ASCOT, the International Verapamil-Trandolapril Study compared a nondihydropiridine calcium channel blocker (verapamil)–based treatment with atenolol-based treatment and recruited a high-risk group with established CHD in whom benefits of β-blockers might be expected. In the Nordic Diltiazem Study, another nondihydropiridine, diltiazem, was compared with either a diuretic or a β-blocker or both agents combined, thereby masking any potential advantage of the calcium channel blocker over one of the comparator agents.

There will be continuing debate over the ASCOT results and the attribution of the benefits of the amlodipine-based limb to the various possibilities discussed above. There remains no doubt that atenolol-based treatment increases the likelihood of new-onset diabetes mellitus. Inevitably, in the longer term, this must be associated with an increased
risk of cardiovascular events, and long-term observations on the ASCOT cohort are now in progress. The possibility of a positive interaction between amlodipine-based treatment and atorvastatin, if borne out by further studies, could have a major impact on the future management of the hypertensive patient, given the common concurrence of hypertension and dyslipidemia and the recent emphasis on multiple risk factor intervention to prevent cardiovascular disease.

The focus of attention will be to adopt antihypertensive treatment algorithms to achieve the levels of blood pressure control dictated by the guidelines and the realization from ASCOT and from other data that stroke and CHD events may be substantially reduced with the combined
management of hypertensive patients with both blood pressure and lipid lowering.

Reflections of a Chief Investigator

With the exception of the United States, where it remains possible to undertake large-scale trials funded by government agencies (although it must be emphasized that even the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial received substantial financial support from industry), it is rarely possible for independent investigators to raise the financial resources required to mount large-scale morbidity/mortality trials from government agencies, research councils, or major charities. Investigators, as in the case of ASCOT, had to turn to industry for support. In contrast, however, with most industry-sponsored trials, ASCOT was different. Concepts for the study arose from independent discussions between academic groups across the continent of Europe long before any funding was agreed. When eventually offers of support were forthcoming from Pfizer in New York, the design of the study and the drafting of the definitive protocol were drawn up by an international group of scientists and clinicians who were independent of the funding source. The steering committee had 2 observers from Pfizer who were nonvoting members. Details of patient recruitment are reported elsewhere, but data acquisition was obtained electronically and stored initially at the Scandinavian Coordinating Centre. All of the subsequent data analyses both in Gothenberg and at Imperial College London were totally independent of Pfizer, and all of the articles were produced by the independent executive committee on behalf of the ASCOT investigators. In retrospect we regard ASCOT as a prime example of an ideal partnership between academe and industry.

Little has been said about the ASCOT patients, recruited largely from general or primary care practices and whose commitment to the study was a major factor in its success. It has been consistently demonstrated that patients do well in trials, and their outcomes are better than if they remained under "usual" care, even if assigned placebo (the Hawthorne effect). This was certainly the case in ASCOT. Trial patients were nurtured by trial physicians and nurses, and in many of the trial centers in the United Kingdom, they believed they belonged to a privileged club! Such was their commitment to the study that when ASCOT closed down there was much concern that the long-term relationship between the patients and their trial teams was coming to an end. An eloquent account of the ASCOT experience by a trial patient has been published.

Future Trials in Hypertension

Some would say the future looks bleak! All of the major classes of antihypertensive drugs are now available in generic formulation, so there is little chance for industry support for new studies. The demise of the newest class of drugs, the direct renin inhibitors, and the withdrawal of support for studies involving aliskiren is unfortunate. Me-too drugs and combination therapies increasingly replace initiatives to find new targets for drug action, and the pipeline gives little cause for enthusiasm. Worryingly, major pharmaceutical companies are withdrawing investment in the search for new antihypertensive drugs. This is a particular disappointment in view of the fact that raised blood pressure remains the single most important risk factor for global disability and death and that all classes of drugs currently available in monotherapy are relatively ineffective at lowering blood pressure.

There is perhaps some light at the end of the tunnel. In the United Kingdom, the establishment of a National Institute for Health Research and the funding of a national framework set up to encourage both academically lead and industry-sponsored trials, to be conducted under the umbrella of the National Health Service and facilitated by series of disease-specific and comprehensive research networks, has made substantial progress in the conduct of trials in many disciplines. In hypertension, the Prevention And Treatment of Hypertension With Algorithm based therapy (PATHWAY) program, supported both by National Institute for Health Research and by the British Heart Foundation, addresses some key questions: what are the optimal drugs to treat resistant hypertension, are there advantages in initiating therapy with 2 drugs rather than sequential monotherapy, and how do different types of diuretics compare in efficacy and on metabolic end points. These are not rocket science but critically important questions that need to be answered if we are to optimize care for hypertensive subjects.

Perhaps the last and as-yet unresolved questions are as follows: what is the optimal systolic goal for therapy in hypertension and, based on observations in ASCOT, from >1.2 million blood pressure recordings showing that long-term blood pressure variability is a far more important predictor of cardiovascular outcomes than average achieved blood pressure, what are the clinical implications of these findings and how should they impact on clinical practice.

Conclusions

No trial is perfect, and there will be those who will seek to criticize aspects of its design and conduct. As always, one could have done better with the wisdom of hindsight. However, we believed that we asked the right question: is new better than old? In attempting to address this question, the various options for drug comparisons were considered at length. In some respects the design of Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, which very closely resembled the design of an earlier European trial, tipped the decision of the ASCOT executive toward the notion of evaluating an older combination with a newer combination of antihypertensive drugs. The fact that, in the selection of our older combination, we chose a β-blocker to which diuretic was added, rather than the reverse, has been questioned many times, and there is no right answer. We defended our choice on the basis that, in the mid-1990s, in Northern Europe, β-blockers were being used as first-line therapy as often as, if not more often than, diuretics. The diuretic was commonly the add-on drug, and this was our justification for the β-blocker/thiazide selection. With regard to the selection of the newer agents, again the order could have been reversed, and who knows whether that would have influenced outcome.
At the end of the day, we seek better treatment strategies to prevent cardiovascular disease. Randomized, controlled trials are the gold standard, and in the case of ASCOT, we believe that our objectives were met and, as we have seen, the results have changed clinical practice, which is, of course, what it is all about.

**Acknowledgments**

I acknowledge the valuable contributions of members of the ASCOT Steering Committee, the ASCOT Investigators, and the patients who participated in the trial.

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**Disclosures**

P.S.S. has received research grant support and consultancies from Pfizer and Laboratoire Servier.

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The Anglo-Scandinavian Cardiac Outcomes Trial: Implications and Further Outcomes
Peter S. Sever

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THE ANGLO-SCANDINAVIAN CARDIAC OUTCOMES TRIAL (ASCOT): IMPLICATIONS AND FURTHER OUTCOMES

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Short title: ASCOT REVISTED
Appendix 1

ASCOT – Background to the trial and early history

Early trials in hypertensive subjects addressed a number of simple questions such as, would benefits of treatment exceed harm from lowering blood pressure; should subjects with mild-moderate hypertension be treated and, should we treat the elderly hypertensive and those with isolated systolic hypertension? Such were the questions posed 40-50 years ago despite the overwhelming evidence from observational studies dating back almost a century that higher levels of blood pressure reduced life expectancy.¹

Uncertainty over the benefits of treatment, and widely held opinions that lowering blood pressure in hypertensive subjects would do more harm than good, provided the catalyst for the early placebo-controlled trials in hypertension including the Veterans Administration Trials,² ³ The Medical Research Council Trials in Mild Hypertension⁴ and in Older Hypertensive Subjects,⁵ the Australian Trial in Mild Hypertension⁶ and the Systolic Hypertension in the Elderly Programme.⁷ All these trials were sponsored and largely funded by government bodies and research councils with contributions from charitable organisations.

Over the past two decades, with the advent of newer classes of antihypertensive drugs, and the possibility that some drugs might confer advantages in cardiovascular protection compared with others, a raft of industry sponsored trials have been carried out, most of which, in head to head comparisons, failed to demonstrate any convincing overall benefit of one drug over another. However, the problem with most of these studies was that single drugs were not being compared and that dual, triple and often quadruple therapy regimens were compared, often with similar add-on therapies in the two arms of the trial. This important issue of differential cardiovascular outcomes conferred by different drugs has been addressed by the Blood Pressure Lowering Treatment Trialists’ Collaboration, by means of a series of prospectively planned meta-analyses of trials of treatment comparisons.⁸ ⁹ ¹⁰ Although largely supportive of the view that most drugs confer similar cardiovascular protection, as with the individual trials, complex and often poorly defined multiple drug regimens were being compared rather than individual drugs.

Towards the end of the twentieth century a number of outstanding questions were being proposed including:-
- What was the preferred first line drug to initiate treatment in hypertension?
- Would a comparison of a “newer” treatment combination (for example a calcium channel blocker and angiotensin converting enzyme inhibitor) confer better protection against cardiovascular outcomes than the “older” and widely used combination of a beta-blocker and a diuretic?
- Would the use of cholesterol-lowering agents in hypertensive patients, with normal or moderately raised cholesterol levels, confer greater protection against coronary events?
- What is the optimal target systolic blood pressure for treatment?

The first 3 of these important questions was addressed by the independent investigator-lead steering committees of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)¹¹ and the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT).¹² Regrettably, the fourth question has yet to be addressed!
By the end of the 1980s, the results of a number of placebo-controlled trials of the treatment of hypertension had been consolidated and meta-analyses indicated that lowering blood pressure with older drugs, including diuretics, beta blockers, methyldopa, hydralazine, reserpine and other drugs, reduced stroke incidence over a relatively short period of around 3-5 years, by an extent similar to that predicted from long-term observational studies. The situation for coronary heart disease, however, was much less clear. In individual trials, such as the Medical Research Council Trial in Mild Hypertension\(^4\) despite a patient population of around 18,000, there was no reduction in coronary heart disease (CHD) events when comparing active treatment with placebo. Analysts of these trials, however, pointed out that this study, and indeed other individual studies, were not powered to detect differences in coronary disease outcomes in the populations under investigation. When data from several trials were pooled, in the first meta-analysis\(^1\) there was a reduction in CHD events of around 8%, compared with 20-25% which would have been expected by extrapolation from observational studies, for the achieved difference in blood pressure. In subsequent analyses, when data from the Hypertension Detection and Follow-Up Program (HDFP) were included the average figure for CHD prevention increased to around 16%, but this still represented a shortfall compared with that which would have been predicted.\(^1\)

Many hypotheses were generated to account for this apparent shortfall. Some believed that this was simply a chance finding and that the upper confidence intervals surrounding the risk reduction for coronary heart disease events in the trials actually encompassed the figure of 20-25% predicted. Others believed that potential adverse effects of many of the antihypertensive drugs used in the early trials may have mitigated against the benefits of blood pressure lowering. Concern was expressed about the adverse metabolic side effects of thiazide diuretics used in moderately high dosage in these early studies, including hypokalaemia, hyperglycaemia and elevation of blood lipid fractions. For the beta-blockers, there was little doubt that they adversely affected the lipid profile, by raising serum triglycerides and lowering HDL cholesterol, and disturbed glucose homeostasis.

At a further meeting of the European Blood Pressure group the following year in 1989, a steering group outlined a proposal for a factorial designed study to investigate not only whether newer treatments were better than old, but also whether cholesterol-lowering in a hypertensive population would confer benefits on CHD events. At about the same time in the United States proposals along similar lines were being discussed by the National Heart, Lung and Blood Institute (NHLBI).

In 1991 the British Hypertension Society (BHS) established a working party to revisit the European Trial initiative and in October 1992, a formal announcement appeared in the Lancet and British Medical Journal drawing attention to the importance of the trial in the hope that interest could be reawakened with potential funding agencies.

In the US, however, in August 1993, it was announced that a Federal grant would fund a seven year study of 40,000 hypertensive patients (the ALLHAT Study) - a decision almost certainly influenced by the calcium channel blocker controversy.\(^1\)

In the UK, in January 1993, the US based pharmaceutical company, Pfizer, made an offer to support the BHS trial, conditional upon further funding being made available from other pharmaceutical companies, which at the time was not forthcoming. However, two years later, in September 1995, it was proposed that if the UK trialists were to collaborate with the Gothenburg Trial Centre in Sweden, Pfizer would fund a major European outcome study.
References


Appendix 2 – ASCOT-LLA : additional information

On Sept 2, 2002, approximately 3 years into the trial, the Data Safety Monitoring Board (DSMB) recommended that the lipid-lowering arm of the trial be stopped on the grounds that atorvastatin had resulted in a highly significant reduction in the primary endpoint of CHD events compared with placebo and a significant reduction in the incidence of stroke.

This recommendation was ratified by the steering committee, whereupon all patients in the lipid-lowering arm were recalled by their trial physicians between October and December, 2002, for a final end-of-study visit. All patients in the lipid-lowering arm were offered atorvastatin 10 mg daily to be continued to the end of the antihypertensive arm of the trial, which was anticipated to be in 2005.

Of the 19,257 randomised to one of the two antihypertensive regimens 10,305 were further randomly assigned atorvastatin 10 mg daily or placebo. Participants were mainly white (95%) and male (81%), with a mean age of 63 years. The average number of the additional cardiovascular risk factors required for inclusion in the trial was 3·7. The study was stopped prematurely after 33,041 patient-years of follow-up (median 3·3 years). At the close of follow-up for the lipid-lowering arm, complete information was obtained on 10,186 (98·8%) of the 10,305 patients originally randomised. Of the remainder, vital status was obtained on all but 17 patients. Compared with placebo at 1 year of follow-up, in the atorvastatin group, total cholesterol and calculated LDL-cholesterol were around 1·3 mmol/L and 1·2 mmol/L lower, respectively (24% and 35% relative reduction, respectively). By the end of the study, these differences were 1·0 mmol/L and 1·0 mmol/L (19% and 29%), respectively.

Compared with placebo, atorvastatin reduced triglycerides by about 0·3 mmol/L at 1 year—a relative decrease of 17%, which fell to 14% at study completion. After 3 years of follow-up, 87% of patients originally assigned atorvastatin were still taking a statin, and 9% of those in the placebo group had been prescribed open-label statins.

Blood-pressure control throughout the trial was similar in the patients assigned atorvastatin and placebo, with mean values of 138·3/80·4 mm Hg and 138·4/80·4 mm Hg, respectively, at the end of follow-up.
Appendix 3 – ASCOT-LLA : post trial issues

Two areas of controversy followed publication of the results of ASCOT-LLA. The first related to subgroup analysis of the effects of atorvastatin on the primary endpoint and the second to cost effectiveness of atorvastatin in this population.

As authors of the manuscript, in retrospect, we realized that at the design stage of trial we included too many prespecified subgroups - no trial of any size should incorporate 18 subgroups! However, we believed that it was important to restate the generalisibility of the data to all types of patients. The issue related to the limited power, to evaluate small individual subgroups, particularly when considering the primary outcome, despite the fact that there was no statistical heterogeneity across subgroups and hence the best estimate of benefit for any subgroup was the point estimate for the overall trial population.

To add further support for our conclusions, we analysed the impact of atorvastatin on total cardiovascular events and procedures among all the subgroups. The rationale for so-doing was that this endpoint included the largest number of events likely to be affected by statin use and hence would have most power to investigate the generalisibility of any/all cardiovascular benefits of atorvastatin in this hypertensive population. Figure S1 shows the results of these analyses and highlights the alignment of the results with this larger endpoint.

Whilst the results for women remain non-significant, due to the small number of events which occurred, the hazard ratio is essentially identical for men and women. Among the diabetic sub-population, the risk reductions were similar to those of the non-diabetic population and reached statistical significance.1

Another concern regarding the interpretation of the LLA was cost consideration. This was first articulated in the Lancet editorial that accompanied the publication of results, when it was suggested that the numbers needed to treat (NNT) to realise benefits was high.2

It is true that the NNT to save one primary endpoint was about 300, but to prevent a major cardiovascular event or procedure this figure fell to about 150. Furthermore, once this figure was adjusted for the fact that the absolute risk among the ASCOT hypertensives was much less than among normally-treated hypertensives, by virtue of their far superior blood pressure control (mean level 138/80), it was clear that the figure of 150 dramatically overestimated the true NNT in ‘real world’ hypertensives, whose mean systolic blood pressure is on average about 20mmHg higher than in the ASCOT population. Moreover, once the NNT is adjusted further for the drop- in and drop- out levels seen in ASCOT, the true NNT to prevent a major CV event or procedure is probably in the region of 75.

One of the pre-specified tertiary objectives of the trial was to investigate the cost-effectiveness of lipid-lowering treatment. In health economic analyses,3 using in-trial data and based on unit costs for Scandinavia and the UK, results showed that incremental cost-effectiveness rates for atorvastatin treatment were about 12,500 and 11,500 Euros per event avoided in Sweden and the UK respectively.

Based on these analyses, and put in the context of other health interventions, health economists concluded that treating hypertensives at modest risk of cardiovascular disease but without prior or current coronary heart disease with a statin was a cost-effective activity. Given that in most countries, atorvastatin is now available in generic formulation, markedly lower costs for atorvastatin make this intervention far more cost effective than reported in our original analyses.
References


Appendix 4 – ASCOT-BPLA : further analyses

Correcting for blood pressure differences in randomised trials is problematic and there is no perfect way of achieving this. We undertook further analyses in an attempt to explain the magnitude of the beneficial effect of the amlodipine-based arm that could have been explained by the differences in blood pressure.\(^1\)

First, we undertook a time dependent analysis of several endpoints using differing censoring points throughout the trial, and extended an analysis of the type carried out on the VALUE results.\(^2\) It was clear that, for a number of endpoints, particularly early in the trial when blood pressure differences were greatest - there was no difference in endpoints between the amlodipine- based and the atenolol- based arm. Interestingly, when blood pressure differences were minimal towards the end of the trial, for a number of endpoints the greatest hazard ratios, i.e. risk reductions, were seen in the amlodipine-based arm.

Second, we compared the risk reductions for several endpoints in ASCOT in association with the observed average blood pressure differences of about 3/2mmHg with reference to prospective observational studies and to the most recent pooled analysis of clinical trials reported by the Blood Pressure Lowering Treatment Trialists Collaboration.\(^3,4\) These analyses suggested that these differences in blood pressure might explain, approximately, a 4-8% reduction in coronary outcome and an 8-14% reduction in strokes.

It is important to note that assignment to the atenolol -based limb was associated with notable metabolic differences compared with the amlodipine-based arm. Although there were no differences in total and LDL-cholesterol between the two limbs (which would not have been expected), HDL-cholesterol was lower, triglycerides were higher and fasting glucose was higher in the beta-blocker based limb. All these metabolic parameters have previously been reported in association with beta-blockers, and it remains a possibility that these adverse metabolic changes could contribute to differences between the two arms of the trial, given that all have been implicated as risk factors.

A further analysis was undertaken using the Cox proportional hazards model in an attempt to provide additional information on the role that systolic and diastolic blood pressure, HDL-cholesterol, triglycerides and creatinine could have played in explaining the risk reductions observed in ASCOT-BPLA.\(^1\) In these post hoc analyses, interpretation of which needs to be cautious, it was suggested that systolic but not diastolic blood pressure contributed to the risk reduction in the primary endpoint (but the number of events here is relatively small). For stroke and all cardiovascular events, blood pressure could contribute to approximately one half of the benefits of amlodipine based treatment. Contribution of differences in HDL-cholesterol and triglycerides was small, probably only evident for HDL-cholesterol and then only for coronary events.

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Appendix 5 – Supplementary on-line ASCOT Bibliography


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Appendix 6 – The Conduit Artery Functional Evaluation (CAFE) sub-study

One of the many sub-studies associated with the ASCOT trial was the Conduit Artery Functional Evaluation (CAFE) study which has attracted wide interest. One interpretation of the superior protection against major cardiovascular events by the amlodipine/perindopril regimen was that the differences were simply due to the superior blood pressure reduction achieved. The ASCOT investigators did not fully believe this and suggested that other mechanisms may have been at work. The results of the CAFE trial have contributed to this debate by demonstrating much larger differences in central blood pressure between the two blood pressure-lowering regimens than in peripheral blood pressure.

This study included 2,199 patients from five of the ASCOT centres in the UK and Ireland. Central aortic pressures were derived using radial artery applanation tonometry and pulse wave analyses at various stages of follow-up in the trial. The usual systolic blood pressures measured routinely at the brachial artery in the trial were similar in the two treatment arms but the central aortic systolic pressures were significantly lower in those allocated the amlodipine/perindopril therapy (Figure S4).

The authors proposed that these lower central pressures may help to explain the superior clinical outcomes associated with the amlodipine/perindopril regimen.
Appendix 7 – Studies on wave reflection, differential effects of amlodipine/perindopril regimen versus atenolol/thiazide regimen on central blood pressure and predictions of cardiovascular events

Several factors contribute to the shape of the arterial pressure waveform. Essentially, this is determined by an interaction between the ventricular output and the arterial system. The final arterial pressure wave is made up of forward and backward pressure components, the latter comprising reflection of waves from distal sites of impedance mismatching in the vasculature and this accounts for the augmentation in pressure (Figure S5).

In an important ASCOT substudy, 259 subjects were investigated approximately 1 year after randomization. Measurements of brachial and carotid artery blood pressure were undertaken, together with carotid ultrasound and echocardiography. Wave intensity analysis was used to calculate wave reflection index (WRI), the ratio of peak backward to peak forward pressures (Pb/Pf), and carotid augmentation index (cAIx). Wave reflection was assessed principally using the wave reflection index (WRI). The WRI was calculated from the sum of the cumulative wave intensity of the reflected compression waves from the head and body (Figure S5) and expressed as a percentage of the cumulative intensity of the initial systolic (S) wave generated by left ventricular ejection.

Other measures of wave reflection included the ratio of peak backward to peak forward pressure (Pb/Pf) after wave separation and subtraction of diastolic pressure. In addition carotid artery augmentation index (cAIx) was determined as the pressure difference between the first shoulder of the pressure waveform and the systolic peak expressed as a percentage of the pulse pressure. Left ventricular mass was calculated by conventional methods.

The different measures of wave reflection were closely correlated and the reflection wave was demonstrated to be significantly positively associated with increased LV mass index. Although in this study there were only 33 cardiovascular events, over a median follow-up period of approximately 6 years, wave reflection index was a significant predictor of subsequent cardiovascular events. This relationship was independent of other cardiovascular risk factors (in a multivariate Cox regression model, hazard ratio was 2.1, CI 1.08 – 4.37, p = 0.03).

Further analyses in the same patient population demonstrated that there were treatment differences in their effects on wave reflection index, and that these values were significantly lower in patients randomised to amlodipine/perindopril therapy compared with atenolol/thiazide therapy (19.8% versus 23.3%, p = 0.02) (Figure S6). Consistent with the previously reported differences in central blood pressure between amlodipine/perindopril treatment and atenolol/thiazide treatment, in the current study, carotid systolic pressure was also lower on the amlodipine/perindopril regimen (127 mmHg) versus the atenolol/thiazide regimen (133 mmHg). In addition, carotid systolic pressure was a significant independent predictor of left ventricular mass index.

Reference

Table S1

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Figures

Figure S1

Subgroups

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Figure S1 – ASCOT-LLA total cardiovascular events and procedures by subgroups (LVH = left ventricular hypertrophy)
Daytime SBP
Mean Atenolol = 133.9 mmHg
Mean Amlodipine = 135.0 mmHg
Mean difference (95% CI) = 1.1(0.1, 2.1) mmHg
P=0.0389

Night-time SBP
Mean Atenolol = 125.2 mmHg
Mean Amlodipine = 123.0 mmHg
Mean difference (95% CI) = -2.2(-3.4, -0.9) mmHg
P=0.0008

24-h-SBP
Mean Atenolol = 132.0 mmHg
Mean Amlodipine = 131.8 mmHg
Mean difference (95% CI) = 0.2(-1.2, 0.8) mmHg
P=0.7466

Daytime DBP
Mean Atenolol = 77.3 mmHg
Mean Amlodipine = 78.8 mmHg
Mean difference (95% CI) = 1.6(0.8, 2.3) mmHg
P<0.0001

Night-time DBP
Mean Atenolol = 68.6 mmHg
Mean Amlodipine = 69.4 mmHg
Mean difference (95% CI) = 0.8(-0.1, 1.6) mmHg
P=0.0523

24-h-DHP
Mean Atenolol = 74.8 mmHg
Mean Amlodipine = 76.1 mmHg
Mean difference (95% CI) = 1.2(0.5, 1.9) mmHg
P=0.0004

Figure S2 – 24-hour ambulatory blood pressure recordings on an average 1-year following randomisation in the two blood pressure treatment groups. Atenolol-thiazide (hashed line), amlodipine-perindopril (solid line). SBP=systolic blood pressure. DBP=diastolic blood pressure. Modified from Dolan et al, in Poulter NR, Sever P. Anglo-Scandinavian Cardiac Outcomes Trial: Latest perspectives on this landmark trial. Sherborne Gibbs Ltd Publications, 2011.
**Figure S3**

**Primary End Points**
- Nonfatal MI (incl silent) + fatal CHD

**Secondary End Points**
- Total CV events and procedures
- Total coronary events
- Nonfatal MI (excl silent) + fatal CHD
- All-cause mortality
- Cardiovascular mortality
- Fatal and nonfatal stroke
- Fatal and nonfatal heart failure

**Tertiary End Points**
- Silent MI
- Unstable angina
- Chronic stable angina
- Peripheral arterial disease
- Development of diabetes mellitus
- Development of renal impairment

Area of squares is proportional to the amount of statistical information

**Figure S3** – ASCOT-LLA summary of cardiovascular endpoints at the end of the trial (3.3 years) and following 2.2 years extension (5.5 years). Modified from Sever et al, Eur Heart J 2008;29:498-508.

**Figure S4**

**Figure S4** – CAFÉ study – lower central aortic blood pressure with newer versus older antihypertensive regimens despite similar brachial blood pressures. Modified from Williams et al, in Poulter NR, Sever P. Anglo-Scandinavian Cardiac Outcomes Trial: Latest perspectives on this landmark trial. Sherborne Gibbs Ltd Publications, 2011.
**Figure S5**

Example traces comparing measured pressure waveforms $P_{\text{total}}$, $P_f$, and $P_b$ separated pressure waveforms and wave intensity between treatment regimens. The shoulder or inflection point in the pressure wave form (Ti) is indicated. The S wave (1), the C-1 wave (2), the C+1 wave (3), and the D wave (4) are shown on the wave-intensity profiles. Modified from Manisty et al, in Poulter NR, Sever P. Anglo-Scandinavian Cardiac Outcomes Trial: Latest perspectives on this landmark trial. Sherborne Gibbs Ltd Publications, 2011.

**Figure S6**

The wave reflection index was significantly lower in patients randomised to amlodipine+perindopril-based therapy than atenolol+thiazide-based therapy (19.8% [10.9%] vs 23.3% [13.3%]). Modified from Manisty et al, in Poulter NR, Sever P. Anglo-Scandinavian Cardiac Outcomes Trial: Latest perspectives on this landmark trial. Sherborne Gibbs Ltd Publications, 2011.