Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial

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Summary

Background The apparent shortfall in prevention of coronary heart disease (CHD) noted in early hypertension trials has been attributed to disadvantages of the diuretics and β blockers used. For a given reduction in blood pressure, some suggested that newer agents would confer advantages over diuretics and β blockers. Our aim, therefore, was to compare the effect on non-fatal myocardial infarction and fatal CHD of combinations of atenolol with a thiazide versus amlodipine with perindopril.

Methods We did a multicentre, prospective, randomised controlled trial in 19 257 patients with hypertension who were aged 40–79 years and had at least three other cardiovascular risk factors. Patients were assigned either amlodipine 5–10 mg adding perindopril 4–8 mg as required (amlodipine-based regimen; n=9639) or atenolol 50–100 mg adding bendroflumethiazide 1·25–2·5 mg and potassium as required (atenolol-based regimen; n=9618). Our primary endpoint was non-fatal myocardial infarction (including silent myocardial infarction) and fatal CHD. Analysis was by intention to treat.

Findings The study was stopped prematurely after 5·5 years’ median follow-up and accumulated in total 106 153 patient-years of observation. Though not significant, compared with the atenolol-based regimen, fewer individuals on the amlodipine-based regimen had a primary endpoint (429 vs 474; unadjusted HR 0·90, 95% CI 0·79–1·02, p=0·1052), fatal and non-fatal stroke (327 vs 422; 0·77, 0·66–0·89, p=0·0003), total cardiovascular events and procedures (1362 vs 1602; 0·84, 0·78–0·90, p=0·0001), and all-cause mortality (738 vs 820; 0·89, 0·81–0·99, p=0·025). The incidence of developing diabetes was less on the amlodipine-based regimen (567 vs 799; 0·70, 0·63–0·78, p<0·0001).

Interpretation The amlodipine-based regimen prevented more major cardiovascular events and induced less diabetes than the atenolol-based regimen. On the basis of previous trial evidence, these effects might not be entirely explained by better control of blood pressure, but this issue is addressed in the accompanying article. Nevertheless, the results have implications with respect to optimum combinations of antihypertensive agents.

Introduction Hypertension is the most important preventable cause of premature death in developed countries,1 and the benefits of antihypertensive drugs for prevention of cardiovascular mortality and morbidity are well established.2 Although the findings of an early meta-analysis3 of the results of 17 hypertension trials—all of which used standard diuretic or β blocker therapy, or both—indicated that lowering of blood pressure was associated with a significant fall in coronary heart disease (CHD) events, the benefit noted was less than that expected from prospective observational data. Furthermore, no individual trial had shown a significant reduction in CHD events. The possibility was raised4 that newer antihypertensive agents, such as calcium-channel blockers and angiotensin-converting enzyme (ACE) inhibitors, might be more effective than therapy based on diuretics or β blockers. However, there were limited data on the relative effects of newer blood-pressure lowering agents compared with standard treatment options, especially in specific combination treatment regimens.5

The issue of which antihypertensive agent should be used in first-line treatment has been controversial for almost two decades. However, to reach the target blood pressures recommended in national and international guidelines,6,7 two or more antihypertensive agents need to be used in most patients.8 Furthermore, European9 and American10 guidelines include the recommendation to initiate therapy with a combination, although to date limited morbidity or mortality trial evidence for optimum combinations of
Calcium-channel blocker-based regimen | β-blocker-based regimen
--- | ---
Step 1 | Amlodipine 5 mg | Atenolol 50 mg
Step 2 | Amlodipine 10 mg | Atenolol 100 mg
Step 3 | Amlodipine 10 mg + perindopril 4 mg | Atenolol 100 mg + bendroflumethiazide 1.25 mg + potassium
Step 4 | Amlodipine 10 mg + perindopril 8 mg (2×4 mg) | Atenolol 100 mg + bendroflumethiazide 2.5 mg + potassium
Step 5 | Amlodipine 10 mg + perindopril 8 mg (2×4 mg) + doxazosin gastrointestinal transport system 4 mg | Atenolol 100 mg + bendroflumethiazide 2.5 mg + potassium + doxazosin gastrointestinal transport system 4 mg
Step 6 | Amlodipine 10 mg + perindopril 8 mg (2×4 mg) + doxazosin gastrointestinal transport system 8 mg | Atenolol 100 mg + bendroflumethiazide 2.5 mg + potassium + doxazosin gastrointestinal transport system 8 mg

Further treatment to achieve blood-pressure goal outlined at http://www.ascotstudy.org. All drugs given orally.

**Table 1: Treatment algorithm**

antihypertensive agents are available. This absence of trial evidence results in guidelines that offer different recommendations with respect to combinations of antihypertensive agents.

The most frequent combination of antihypertensive medications used worldwide when this trial was initiated was a β-blocker plus a diuretic, and the most commonly used drugs within these classes were atenolol and thiazides, respectively. Hence, we selected atenolol and bendroflumethiazide with potassium as the reference comparator drugs for ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm). The shortfall of beneficial effects on coronary events of treatment with β blockers or diuretics (often ascribed to their adverse metabolic effects) made comparison of atenolol and thiazide with a totally new combination without such metabolic side-effects a rational choice.

During the 1990s, some observational data raised questions about the safety of dihydropyridine calcium-channel blockers. These agents were in common use and were effective blood-pressure lowering agents, but no trials were available to establish their safety and efficacy until 1997, and then only in the context of isolated systolic hypertension. Similarly, despite the widespread use of ACE inhibitors in the 1990s, no placebo-controlled trials were done to establish their safety and efficacy. Consequently, along with their favourable metabolic profiles, we chose to compare the effect on non-fatal myocardial infarction and fatal CHD of a combination of a dihydropyridine calcium-channel blocker (amlodipine) and an ACE inhibitor (perindopril) with that of a β blocker and a thiazide diuretic.

**Methods**

**Participants**

The detailed ASCOT protocol, including study design, organisation, clinical measurements, endpoint definitions, power calculations, recruitment rates, and some preliminary baseline characteristics, has been published, and further detailed information is available on the ASCOT website.

Briefly, between February, 1998, and May, 2000, we recruited patients to an independent, investigator-initiated, investigator-led, multicentre, prospective, randomised controlled trial. Patients were eligible for ASCOT-BPLA if they were aged 40–79 years at randomisation, and had either untreated hypertension—systolic blood pressure of 160 mm Hg or more, diastolic blood pressure of 100 mm Hg or more, or both—or treated hypertension with systolic blood pressure of 140 mm Hg or more, diastolic blood pressure 90 mm Hg or more, or both. In addition, the study population had to have at least three of the following cardiovascular risk factors: left-ventricular hypertrophy (detected by electrocardiogram or echocardiogram); other specified abnormalities on electrocardiogram, type 2 diabetes; peripheral arterial disease; previous stroke or transient ischaemic attack; male sex; age 55 years or older; microalbuminuria or proteinuria; smoking; ratio of plasma total cholesterol to HDL-cholesterol of six or higher; or family history of premature CHD. Exclusion criteria included (among others): previous myocardial infarction; currently treated angina; a cerebrovascular event within the previous 3 months; fasting triglycerides higher than 4.5 mmol/L; heart failure; uncontrolled arrhythmias; or any clinically important haematological or biochemical abnormality on routine screening.

The study conformed to good clinical practice guidelines and was done in accord with the Declaration of Helsinki. The protocol and all subsequent amendments to the protocol were reviewed and ratified by central and regional ethics review boards in the UK, and by national ethics and
statutory bodies in Ireland and the Nordic (Sweden, Denmark, Iceland, Norway, and Finland) countries. Patients gave written informed consent to participate in the trial before randomisation.

Procedures
About 4 weeks before randomisation, we established that eligibility criteria for ASCOT-BPLA were satisfied and obtained relevant characteristics of patients.14,15 Blood pressure was measured three times, after 5 min rest in the sitting position. A semiautomated device was used,17 and the mean of the last two readings was used for analyses. We obtained non-fasting blood samples and sent them to one of two central laboratories—one for the UK and Ireland, and one for the Nordic countries—which analysed blood samples throughout the trial. We faxed recordings from 12-lead electrocardiography to the Scandinavian coordinating centre for central assessment at the electrophysiology core centre at Sahlgrenska University Hospital/Ostra, Sweden. After the 4-week run-in, we confirmed eligibility and obtained consent for randomisation. At the randomisation visit, we did a physical examination and recorded the blood pressure and heart rate of patients. We obtained fasting blood samples for measurement of total cholesterol, HDL-cholesterol, triglycerides, and glucose concentrations, and did another 12-lead electrocardiogram.14,16

We randomised patients to amiodipine adding perindopril as required to reach blood-pressure targets (amiodipine-based regimen) or atenolol adding bendroflumethiazide and potassium as required (atenolol-based regimen), according to a prespecified algorithm outlined in Table 1 and further described on the ASCOT website. The randomisation was a computer generated optimum allocation blinded for any person involved in the undertaking of the study. A PROBE (open treatment and blinded endpoint evaluation)15 design was used. Follow-up visits took place after 6 weeks, 3 months, 6 months, and subsequently 6 monthly. At the yearly visits, we obtained fasting blood samples for glucose and lipid concentrations, and urine samples for measurement of blood, sugar, and protein. At every follow-up visit, we titrated antihypertensive drug therapy to achieve target blood pressures (<140/90 mm Hg for patients without diabetes and <130/80 mm Hg for patients with diabetes), and recorded information about adverse events and any new cardiovascular event or procedure, including the cause for any hospital admission.

The primary objective of ASCOT-BPLA was to assess and compare the long-term effects of two regimens for the lowering of blood pressure on the combined endpoint of non-fatal myocardial infarction (including so-called silent myocardial infarction) and fatal CHD. The secondary endpoints were all-cause mortality, total stroke, primary endpoint minus silent myocardial infarction, all coronary events, total cardiovascular events and procedures, cardiovascular mortality, and non-fatal and fatal heart failure. Tertiary objectives were silent myocardial infarction, unstable angina, chronic stable angina, peripheral arterial disease, life-threatening arrhythmias, development of diabetes, development of renal articles.
improvement, and the effects on the primary endpoint and on total cardiovascular events and procedures among prespecified subgroups. We also did post-hoc analyses on two other combined endpoints: cardiovascular mortality plus non-fatal myocardial infarction and stroke; and the primary endpoint plus coronary revascularisation.

For the main analyses we used the log-rank procedure and Cox’s proportional hazards model to calculate CIs. We generated cumulative incidence curves by the Kaplan-Meier method for all major endpoints. Statistical analysis

We estimated that at least 18 000 patients needed to be followed up for an average of 5 years in ASCOT-BPLA. This number was based on an anticipated yearly primary endpoint rate in the control group of 14.2 per 1000 patient years, and in the study overall a total of 1150 patients with a primary endpoint. Assuming an HR of 0.84 for the primary endpoint, we calculated the study power to be 80% (β=0.20) at a two-sided significance level of 5% (α=0.05).

We compared the time to first event on an intention-to-treat basis. All analyses excluded endpoints deemed invalid by the endpoint committee, with statistical censoring enforced at the end of the study defined as midnight, local time, of the day of the last visit, or death before that date. The date used to indicate a silent myocardial infarction was taken as the mean time between the dates of two electrocardiograms, the first of which showed no myocardial infarction, and the second of which did.

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The DSMB decided a priori to use the symmetric Haybittle-Peto statistical boundary (critical value Z=3) as a guideline for deciding to recommend early termination of the trial. This boundary required no material adjustment to the final p values. In October, 2004, the DSMB recommended the trial be stopped on the grounds that compared with those allocated the amiodipine-based regimen those allocated the atenolol-based regimen had significantly higher mortality as well as worse outcomes on several other secondary endpoints. This recommendation was ratified by the steering committee, whereupon between December, 2004, and June, 2005, the trial doctors recalled all patients for a final end-of-study visit.

### Table 3: Percentage of time on antihypertensive medication by treatment group and study period

| Year | Randomised to amloidipine | Randomised to atenolol  
<table>
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<tr>
<td>---</td>
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</tr>
<tr>
<td>1</td>
<td>28.9</td>
<td>39.4</td>
</tr>
<tr>
<td>2</td>
<td>33.6</td>
<td>39.6</td>
</tr>
<tr>
<td>3</td>
<td>36.2</td>
<td>39.3</td>
</tr>
<tr>
<td>4</td>
<td>38.1</td>
<td>39.2</td>
</tr>
<tr>
<td>5</td>
<td>38.0</td>
<td>45.0</td>
</tr>
<tr>
<td>6</td>
<td>43.0</td>
<td>45.1</td>
</tr>
</tbody>
</table>

Data are mean (SD).

![Figure 3: Kaplan-Meier curves of cumulative incidence of non-fatal myocardial infarction, including silent myocardial infarction, and fatal CHD](http://www.scri.se/H32897/H11001/H1100129x0)

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Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report, though they did have three non-voting members on the steering committee. The executive committee had full access to all the data at the end of the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile and table 2 the baseline characteristics of the 19 257 patients randomised. In the Nordic countries, 686 family practices randomised patients, and in the UK and Ireland 32 regional centres to which patients were referred by their family doctors recruited patients. Two centres, including a total of 85 patients were excluded before the end of study because of irregularities with respect to blood-pressure measurements.18 Participants were well matched between groups; over 80% were on previous antihypertensive treatment, they were mainly white and male, and had a mean age of 63 years, a mean body-mass index (BMI) of almost 29 kg/m², a mean total cholesterol of 5·9 mmol/L, and a mean baseline sitting blood pressure of 164/95 mm Hg. In total the study accumulated 106 153 patient years (censored at death or last known
visit) after a median follow-up of 5·5 years. We collected complete endpoint information at the end of study for 18 965 people (99%; figure 1). Only 60 (0·3%) patients withdrew consent and 49 (0·3%) were lost to follow-up.

On average, in both treatment groups combined, blood pressure dropped from a mean of 164·0/94·7 (SD 18·0/10·4) mm Hg to a mean of 136·9/78·3 (16·7/9·8)—ie, an average reduction of 26·6/16·6 (21·7/11·5). At the trial close-out 10 070 (53%) patients had reached both the systolic and diastolic blood-pressure targets (32% [1646 of 5109] of patients with diabetes and 60% [8424 of 14 034] of those without). After 2 years the corresponding figures were 21% (965 of 4675) for the diabetic population and 49% (6452 of 13 065) for the non-diabetic group. Compared with those allocated the atenolol-based regimen, blood-pressure values were lower throughout the trial in those allocated the amlodipine-based regimen (figure 2). These differences were largest (5·9/2·4 mm Hg) at 3 months, and the average difference throughout the trial was 2·7/1·9 mm Hg. At the final visit, mean (SD) blood-pressure readings had fallen to 136·1 (15·4)/77·4 (9·5) mm Hg and 137·7 (17·9)/79·2 (10·0) mm Hg on the amlodipine-based and atenolol-based regimens, respectively, representing mean falls of 27·5 (21·1)/17·7 (11·3) mm Hg and 25·7 (22·3)/15·6 (11·6) mm Hg.

By the end of the trial, as intended by design, most patients (78%, 14 974 of 19 242) were taking at least two antihypertensive agents, and only 15% (1401 of 9634) and 9% (857 of 9608) were taking amlodipine and atenolol monotherapy, respectively. The percentage of the total years of follow-up in each treatment group, during every year of follow-up when amlodipine, atenolol, perindopril, and bendroflumethiazide, and amlodipine with or without perindopril, and atenolol with or without bendroflumethiazide were taken is shown in table 3. Overall, throughout the trial, a mean of 50% were taking the combination of amlodipine with perindopril as allocated with and without other antihypertensive drugs, and a mean of 55% were taking the combination of atenolol
with bendroflumethiazide as allocated with and without other antihypertensive drugs. On average, of total time, 83% (SD 33) were taking amlodipine as allocated, 79% (35) were taking atenolol, 59% (41) were taking perindopril, and 66% (38) were taking bendroflumethiazide (with or without other agents). Of those allocated the amlodipine-based regimen and the atenolol-based regimen, the average number of antihypertensive drugs used was 2-2 and 2-3, respectively, and 16% (1520 of 9634) and 26% (2503 of 9613) of patients had crossed over to a drug included in the group to which they were not allocated.

At the final visit, patients on the amlodipine-based regimen had significantly higher mean pulse rate (11·2 bpm [SD 12·2]; p<0·0001) and HDL-cholesterol (0.1 mmol/L [0.4]; p<0·0001), and significantly lower BMI (0.3 kg/m^2 [4·9]; p<0·0001), triglycerides (0.3 mmol/L [1·0]; p<0·0001), serum creatinine (5·3 μmol/L [26·2]; p<0·0001), and glucose (0·20 mmol/L [2·08]; p<0·0001) than did those on the atenolol-based regimen. There were no significant differences in either LDL-cholesterol or total-cholesterol concentrations.

The primary endpoint of non-fatal myocardial infarction (including silent myocardial infarction) plus fatal CHD was non-significantly lowered by 10% in those allocated the amlodipine-based regimen compared with those allocated the atenolol-based regimen (figures 3 and 4). There were, however, significant reductions in all of the secondary endpoints (except fatal and non-fatal heart failure) among those allocated the amlodipine-based regimen (figures 4 and 5). These endpoints were: non-fatal myocardial infarction (excluding silent myocardial infarction) and fatal CHD (reduced by 13%); total coronary events (13%); total cardiovascular events and procedures (16%); all-cause mortality (11%); cardiovascular mortality (24%); and fatal and non-fatal stroke (23%). The difference in all-cause mortality was due to the significant reduction in cardiovascular mortality, with no apparent difference in non-cardiovascular mortality (475 vs 478 deaths in the amlodipine-based and atenolol-based treatment groups, respectively).

Of the tertiary endpoints, there were significant reductions associated with the amlodipine-based regimen for unstable angina (32%), peripheral arterial disease (35%), development of diabetes (30%; figure 6), and development of renal impairment (15%). There was no significant heterogeneity among any of the pre-specified subgroups for total cardiovascular events and procedures (figure 7). Among those allocated the amlodipine-based regimen, compared with those allocated the atenolol-based regimen, the retrospectively defined combined endpoint of cardiovascular mortality, myocardial infarction, and stroke was significantly reduced by 16%, and that of the primary endpoint and coronary revascularisation was significantly reduced by 14% (figure 4).

Discussion
The findings of ASCOT-BPLA show that in hypertensive patients at moderate risk of developing cardiovascular events, an antihypertensive drug regimen starting with amlodipine adding perindopril as required is better than one starting with atenolol adding thiazide as required in terms of reducing the incidence of all types of cardiovascular events and all-cause mortality, and in terms of risk of subsequent new-onset diabetes. Compared with the atenolol-based regimen, the amlodipine-based regimen was not significantly more effective at reducing the risk of non-fatal myocardial infarction or fatal CHD. However, this study was powered for 1150 individuals to have such events, whereas only 903 had actually arisen at the last follow-up date because of early termination. The study was, therefore, underpowered for this endpoint. The extended secondary endpoint of total coronary events was, however, significantly reduced. Furthermore, since the design and inception of the ASCOT trial, a more aggressive approach to vascular intervention at an earlier stage in the clinical course of CHD has become routine clinical practice. We therefore feel an appropriate reflection of contemporary medical practice would be to consider the primary endpoint plus coronary revascularisations, for which a significant difference exists in favour of the amlodipine-based regimen.
The falls in mean blood pressure noted during the trial were larger than observed in most previous studies of therapy to lower blood pressure. At baseline, many patients were on antihypertensive treatment, and yet mean blood-pressure values were high. In both treatment groups, blood pressure fell substantially after initiation of study treatment—albeit more so among those allocated the amlodipine-based regimen—such that most patients reached current target blood-pressure levels. This finding lends support to the use of, and adherence to, standardised treatment algorithms for lowering blood pressure effectively unless contraindications exist or side-effects arise. The average number of drugs used to reach target blood-pressure levels in ASCOT was 2.2. About 40% of patients used antihypertensive drugs other than those pre-specified by us, and 8% were on four drugs or more. Throughout the trial the most frequent combinations of two antihypertensive drugs used (with or without other agents) were, as intended by design, amlodipine and perindopril and atenolol and bendroflumethiazide.

Until recently, the most common combination of antihypertensive agents used was a β-blocker plus diuretic, and these agents separately or together have been established in many major morbidity and mortality trials to be effective in terms of the prevention of cardiovascular events in hypertensive populations. Furthermore, results of more contemporary meta-regression analyses of more than 30 hypertension trials in the Blood Pressure Lowering Treatment Trialists' Collaboration suggest that the size of the absolute blood-pressure reduction is a more important determinant of the relative effects on total cardiovascular events than is antihypertensive drug choice. One possible exception to these conclusions was provided by the LIFE trial, in which a losartan-based regimen (mainly losartan plus thiazide) proved better than an atenolol-based regimen (mainly atenolol plus thiazide), particularly in terms of...

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**Figure 7:** Effect of treatments on total cardiovascular events and procedures in relation to prespecified subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Amlodipine-based regimen</th>
<th>Atenolol-based regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (%)</td>
<td>Rate per 1000</td>
</tr>
<tr>
<td>Diabetes</td>
<td>430 (17%)</td>
<td>33.3</td>
</tr>
<tr>
<td>No diabetes</td>
<td>932 (13%)</td>
<td>25.3</td>
</tr>
<tr>
<td>Current smoker</td>
<td>495 (16%)</td>
<td>30.5</td>
</tr>
<tr>
<td>Not current smoker</td>
<td>867 (13%)</td>
<td>25.9</td>
</tr>
<tr>
<td>Obese</td>
<td>423 (12%)</td>
<td>25.6</td>
</tr>
<tr>
<td>Not obese</td>
<td>931 (15%)</td>
<td>28.3</td>
</tr>
<tr>
<td>Age older than 60 years</td>
<td>1001 (17%)</td>
<td>32.7</td>
</tr>
<tr>
<td>Age 60 years or younger</td>
<td>361 (10%)</td>
<td>18.8</td>
</tr>
<tr>
<td>Female</td>
<td>271 (12%)</td>
<td>22.7</td>
</tr>
<tr>
<td>Male</td>
<td>1091 (15%)</td>
<td>28.9</td>
</tr>
<tr>
<td>Left-ventricular hypertrophy</td>
<td>314 (15%)</td>
<td>29.0</td>
</tr>
<tr>
<td>No left-ventricular hypertrophy</td>
<td>1048 (14%)</td>
<td>26.9</td>
</tr>
<tr>
<td>Previous vascular disease</td>
<td>360 (23%)</td>
<td>48.6</td>
</tr>
<tr>
<td>No previous vascular disease</td>
<td>1002 (12%)</td>
<td>23.6</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>825 (14%)</td>
<td>26.5</td>
</tr>
<tr>
<td>No renal dysfunction</td>
<td>537 (15%)</td>
<td>28.7</td>
</tr>
<tr>
<td>With metabolic syndrome</td>
<td>589 (15%)</td>
<td>28.3</td>
</tr>
<tr>
<td>Without metabolic syndrome</td>
<td>773 (14%)</td>
<td>26.7</td>
</tr>
<tr>
<td>All patients</td>
<td>1362 (14%)</td>
<td>27.4</td>
</tr>
</tbody>
</table>

The falls in mean blood pressure noted during the trial were larger than observed in most previous studies of therapy to lower blood pressure. At baseline, many patients were on antihypertensive treatment, and yet mean blood-pressure values were high. In both treatment groups, blood pressure fell substantially after initiation of study treatment—albeit more so among those allocated the amlodipine-based regimen—such that most patients reached current target blood-pressure levels. This finding lends support to the use of, and adherence to, standardised treatment algorithms for lowering blood pressure effectively unless contraindications exist or side-effects arise. The average number of drugs used to reach target blood-pressure levels in ASCOT was 2.2. About 40% of patients used antihypertensive drugs other than those pre-specified by us, and 8% were on four drugs or more. Throughout the trial the most frequent combinations of two antihypertensive drugs used (with or without other agents) were, as intended by design, amlodipine and perindopril and atenolol and bendroflumethiazide.

Until recently, the most common combination of antihypertensive agents used was a β-blocker plus diuretic, and these agents separately or together have been established in many major morbidity and mortality trials to be effective in terms of the prevention of cardiovascular events in hypertensive populations. Furthermore, results of more contemporary meta-regression analyses of more than 30 hypertension trials in the Blood Pressure Lowering Treatment Trialists' Collaboration suggest that the size of the absolute blood-pressure reduction is a more important determinant of the relative effects on total cardiovascular events than is antihypertensive drug choice. One possible exception to these conclusions was provided by the LIFE trial, in which a losartan-based regimen (mainly losartan plus thiazide) proved better than an atenolol-based regimen (mainly atenolol plus thiazide), particularly in terms of...
preventing stroke despite lowering systolic blood pressure by only 1 mm Hg relative to the atenolol-based regimen. Clearly, the effective blood-pressure lowering achieved in ASCOT-BPLA by the amlodipine-based regimen, particularly in the first year of follow-up, is likely to have contributed to the differential cardiovascular benefits. However, a 2-7 mm Hg systolic blood-pressure difference (the average difference between the two groups throughout ASCOT-BPLA) would be expected to generate a difference of only 4–8% in coronary events and 11–14% in strokes (based on the benefits observed in randomised trials), and about 8% and about 11%, respectively, based on long-term prospective observational data.

Consequently, the large and broad-ranging benefits of the amlodipine-based regimen that we noted seem incompatible with the conclusions of the Blood Pressure Lowering Treatment Trialists’ Collaboration, in that the benefits seem to be somewhat greater than might be anticipated from the observed difference in blood pressure.

Other possible explanatory factors for the difference in outcome in ASCOT include the higher BMI, serum triglyceride, creatinine concentrations, and fasting blood glucose values, and lower HDL-cholesterol concentrations, noted in those allocated the atenolol-based regimen. Assessment of the extent to which these variables and other potential mechanisms contribute to the differences in cardiovascular endpoints is described in an accompanying paper.

The significant reduction in all-cause mortality in those allocated the amlodipine-based regimen is unexpected, since such an effect has been noted in only one other hypertension trial. However, the findings of that trial might have been confounded by the inclusion of other interventions, such as smoking cessation, which in ASCOT-BPLA did not differ between groups. Furthermore, in ASCOT-BPLA, the significant effects on all-cause mortality were all attributable to the reduced cardiovascular mortality and less than half of deaths were cardiovascular in origin.

The significant excess of new-onset diabetes seen in those allocated the amlodipine-based regimen is unexpected, since such an effect has been noted in only one other hypertension trial. However, the findings of that trial might have been confounded by the inclusion of other interventions, such as smoking cessation, which in ASCOT-BPLA did not differ between groups. Furthermore, in ASCOT-BPLA, the significant effects on all-cause mortality were all attributable to the reduced cardiovascular mortality and less than half of deaths were cardiovascular in origin.

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Use of atenolol with a thiazide diuretic, some might argue, was not an appropriate comparator for a more contemporary antihypertensive regimen. However, β blockers and diuretics have been (and might still be) the most common antihypertensive drug combination used, and atenolol and thiazides are the most commonly used agents in their respective classes. Furthermore, several hypertension trials have repeatedly shown the benefits of each of these two drug classes, frequently used in combination, in the prevention of cardiovascular events.

In summary, ASCOT-BPLA has shown that blood pressure can be lowered effectively in most patients.

| Table 4: Adverse events with an incidence of more than 5% in one treatment group and a difference between treatment groups of more than 1% |
|-----------------------------------------------|-----------------------------------------------|----------------|
| Amlodipine-based regimen (n=9639) | Atenolol-based regimen (n=9618) | p     |
| Bradycardia 34 (0.4%) | 536 (6%) | <0.0001 |
| Cough 740 (8%) | 849 (9%) | 0.0040 |
| Diarrhoea 377 (4%) | 548 (6%) | <0.0001 |
| Dizziness 1383 (12%) | 1555 (16%) | <0.0001 |
| Dyspnoea 599 (6%) | 987 (10%) | <0.0001 |
| Eczema 493 (5%) | 383 (4%) | 0.0002 |
| Erectile dysfunction 556 (6%) | 707 (7%) | <0.0001 |
| Fatigue 782 (8%) | 1556 (16%) | <0.0001 |
| Joint swelling 1371 (14%) | 308 (3%) | <0.0001 |
| Lethargy 202 (2%) | 525 (5%) | <0.0001 |
| Oedema peripheral 2188 (23%) | 588 (6%) | <0.0001 |
| Peripheral coldness 81 (1%) | 579 (6%) | <0.0001 |
| Vertigo 642 (7%) | 745 (8%) | 0.0039 |

Data are number (%) unless otherwise indicated.
Furthermore, the preferential reduction in cardiovascular events associated with an antihypertensive regimen of a calcium-channel blocker (amlodipine) with addition of perindopril if necessary, particularly when used in combination with effective lipid lowering, results in the prevention of most major cardiovascular events associated with hypertension. We hope these results will be used to inform clinical practice in ways that should greatly reduce the burden of cardiovascular disease to which patients with hypertension are exposed.

**Contributors**

B Dahlöf, P Sever, N Poulter, and 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 Bevers, M Caulfield, R Collins, S E Kjeldsen, A Kristinsson, G McInnes, J Mehlsen, M Nissen, E O’Brien, and J Østergren, 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 statement**

B Dahlöf, P Sever, N R Poulter, H Wedel, D G Bevers, M Caulfield, R Collins, S E Kjeldsen, A Kristinsson, G McInnes, J Mehlsen, M S Nissen, E O’Brien, and J Østergren have served as consultants to and received travel expenses, payment for speaking at meetings, or funding for research from one or more pharmaceutical companies that market blood-pressure lowering or lipid-lowering drugs, or have received financial support from Pfizer to cover administrative and staffing costs of ASCOT, and travel, accommodation expenses, or both incurred by attending relevant meetings.

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