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 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 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.

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.

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 subpopulation, 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.

References


Appendix 5 – Supplementary on-line ASCOT Bibliography


Manisty C, Mayet J, Tapp RJ, Parker KH, Sever P, Poulter NR, Thom SA, Hughes AD; ASCOT


Felmeden DC, Spencer CG, Chung NA, Belgore FM, Blann AD, Béevers DG, Lip GY. Relation of thrombogenesis in systemic hypertension to angiogenesis and endothelial damage/dysfunction (a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial [ASCOT]). *Am J Cardiol*. 2003;92:400-405.


Lim PO, Donnan PT, MacDonald TM. Does the Dundee Step Test predict outcome in treated hypertension? A sub-study protocol for the ASCOT trial. Anglo-Scandinavian Cardiac Outcome Trial. *J Hum Hypertens.* 2000;14:75-78.
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,1 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

**ASCOT Biomarkers**

- C-reactive protein
- Apolipoprotein A
- Apolipoprotein B
- Cystatin-C
- N terminal-pro Brain Natriuretic Peptide
- MCP-1
- Osteoprotogerin
- Osteopontin
- Plasma renin activity
- Vitamin D
Figures

Figure S1

Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard Ratio (95% CI)</th>
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<tr>
<td>Diabetes</td>
<td>0.77 (0.61-0.98)</td>
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<tr>
<td>Non diabetes</td>
<td>0.80 (0.68-0.94)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.79 (0.64-0.98)</td>
</tr>
<tr>
<td>Non current smoker</td>
<td>0.79 (0.66-0.93)</td>
</tr>
<tr>
<td>Obese</td>
<td>0.79 (0.62-0.99)</td>
</tr>
<tr>
<td>Non obese</td>
<td>0.79 (0.67-0.93)</td>
</tr>
<tr>
<td>LVH</td>
<td>0.90 (0.63-1.26)</td>
</tr>
<tr>
<td>No LVH</td>
<td>0.77 (0.67-0.89)</td>
</tr>
<tr>
<td>Older (&gt;60)</td>
<td>0.78 (0.67-0.91)</td>
</tr>
<tr>
<td>Younger (&lt;=60)</td>
<td>0.82 (0.62-1.08)</td>
</tr>
<tr>
<td>Female</td>
<td>0.80 (0.58-1.10)</td>
</tr>
<tr>
<td>Male</td>
<td>0.79 (0.68-0.91)</td>
</tr>
<tr>
<td>Previous Vascular Disease</td>
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<tr>
<td>No previous Vascular Disease</td>
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<tr>
<td>Renal dysfunction</td>
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<tr>
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<tr>
<td>All patients</td>
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</table>

Figures S1 – ASCOT-LLA total cardiovascular events and procedures by subgroups (LVH = left ventricular hypertrophy)
Figure S2

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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(0.0, 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.
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 – 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 $P_{\text{total}}$, Pf, and Pb 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.