Online Supplement

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

Professor Peter S Sever

Corresponding author: Professor Peter Sever, International Centre for Circulatory Health, Imperial College London, 59 North Wharf Road, London W2 1LA, UK

Tel: +44 (0)207 594 1100, Fax: +44 (0)207 594 1145, Email: p.sever@imperial.ac.uk

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 Hypertension[4] and in Older Hypertensive Subjects,[5] the Australian Trial in Mild Hypertension[6] 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[13] 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.[14]

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.[15]

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

1. Dublin LI, Lotka AJ, and Spiegelman M. *Length of Life, a study of the life table*. 1949, 2nd ed. New York: Ronald Press. (178-180).

2. Veterans Administrative Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension: results in patients with diastolic blood pressures averaging 115 through 129 mmHg. *JAMA.* 1967;202:116-122.

3. Veterans Administrative Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension: results in patients with diastolic blood pressures averaging 90 through 114 mmHg. *JAMA.* 1970;213:1143-1152.

4. Medical Research Council Working Party. MRC trial of mild hypertension: principal results. *BMJ.* 1985;291:97-104.

5. Medical Research Council Working Party. MRC trial of treatment of hypertension in older adults: principal results. *BMJ.* 1992;304:405-412.

6. Australian Therapeutic Trial in Mild Hypertension. Report by the Management Committee. *Lancet.* 1980;1:1261-1267.

7. SHEP Co-operative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). *J Am Med Assoc.* 1991;265:3255-3264.

8. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. *Lancet.* 2000;355:1955-1964.

9. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet.* 2003;362:1527-1535.

10. Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-dependent and independent effects of agents that inhibit the renin-angiotensin system. *J Hypertens.* 2007;25:951-958.

11. Davis BR, Cutler JA, Gordon DJ, Furberg CD, Wright JT, Cushman WC, Grimm RH, LaRosa J, Whelton PK, Perry HM, Alderman MH, Ford CE, Oparil S, Francis C, Proschan M, Pressel S, Black HR, Hawkins CM. Rationale and design for the Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT). *Am J Hypertens.* 1996;9:342-360.

12. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J. Rationale, design, methods and baseline demography of participants of the Anglo-Scandinavian Cardiac Outcomes Trial. ASCOT investigators. *J Hypertens.* 2001;19:1139-1147.

13. MacMahon SW, Cutler JA, Furberg CD, and Payne GH. The effects of drug treatment for hypertension on morbidity and mortality from cardiovascular disease: a review of randomised controlled trials. *Prog Cardiovasc Dis.* 1986;29(3 Suppl 1):99-118.

14. Collins R and Peto R. Antihypertensive drug therapy: effects on stroke and coronary heart disease. In *Textbook of Hypertension* (ed J.D.Swales), pp. 1156-1164. Blackwell Scientific, Oxford.

15. Conlin PR and Williams GH. Use of calcium channel blockers in hypertension. *Adv Intern Med.* 1998;43:533-562.

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

1. Sever PS, Poulter NR, Dahlöf B, Wedel H, Collins R, Beevers G, Caulfield M, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial - lipid-lowering arm (ASCOT-LLA). *Diabetes Care.* 2005;28:1151-1157.

2. Lindholm LH and Samuelson O. What are the odds at ASCOT today? *Lancet.* 2003;361:1144-1145.

3. Lindgren P, Buxton M, Kahan T, Poulter NR, Dahlöf B, Sever PS, Wedel H, Jonsson B; on behalf of the ASCOT investigators. Cost-effectiveness of atorvastatin for the prevention of coronary and stroke events: an economic analysis of the Anglo-Scandinavian Cardiac Outcomes Trial-lipid-lowering arm (ASCOT-LLA). *Eur J Cardiovasc Prev Rehabil.* 2005;12:29-36.

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

1. Poulter NR, Wedel H, Dahlöf B, Sever PS, Beevers DG, Caulfield M, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J, Pocock S; for the ASCOT Investigators. Role of blood pressure and other variables in the differential cardiovascular event rates noted in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA). *Lancet.* 2005;366:907-913.

2. Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, McInnnes GT, Mitchell L, Plat F, Schork A, Smith B, Zanchetti A; for the VALUE trial Group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens

based on valsartan or amlodipine: the VALUE randomisation trial. *Lancet.* 2004;363:2022-2031.

3. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. *Lancet.* 2000;355:1955-1964.

4. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet.* 2003;362:1527-1535.

Appendix 5 – Supplementary on-line ASCOT Bibliography

Deshmukh HA, Colhoun HM, Johnson T, McKeigue PM, Betteridge DJ, Durrington PN, Fuller JH, Livingstone S, Charlton-Menys V, Neil A, Poulter N, Sever P, Shields DC, Stanton AV, Chatterjee A, Hyde C, Calle RA, Demicco DA, Trompet S, Postmus I, Ford I, Jukema JW, Caulfield M, Hitman GA; on behalf of the CARDS, ASCOT, and PROSPER investigators. Genome-wide association study of genetic determinants of LDL-c response to atorvastatin therapy: importance of Lp(a). *J Lipid Res*. 2012;53:1000-1011.

Saxena R, Elbers CC, Guo Y, Peter I, Gaunt TR, Mega JL, Lanktree MB, Tare A, Castillo BA, Li YR, Johnson T, Bruinenberg M, Gilbert-Diamond D, Rajagopalan R, Voight BF, Balasubramanyam A, Barnard J, Bauer F, Baumert J, Bhangale T, Böhm BO, Braund PS, Burton PR, Chandrupatla HR, Clarke R, Cooper-DeHoff RM, Crook ED, Davey-Smith G, Day IN, de Boer A, de Groot MC, Drenos F, Ferguson J, Fox CS, Furlong CE, Gibson Q, Gieger C, Gilhuijs-Pederson LA, Glessner JT, Goel A, Gong Y, Grant SF, Grobbee DE, Hastie C, Humphries SE, Kim CE, Kivimaki M, Kleber M, Meisinger C, Kumari M, Langaee TY, Lawlor DA, Li M, Lobmeyer MT, Maitland-van der Zee AH, Meijs MF, Molony CM, Morrow DA, Murugesan G, Musani SK, Nelson CP, Newhouse SJ, O'Connell JR, Padmanabhan S, Palmen J, Patel SR, Pepine CJ, Pettinger M, Price TS, Rafelt S, Ranchalis J, Rasheed A, Rosenthal E, Ruczinski I, Shah S, Shen H, Silbernagel G, Smith EN, Spijkerman AW, Stanton A, Steffes MW, Thorand B, Trip M, van der Harst P, van der A DL, van Iperen EP, van Setten J, van Vliet-Ostaptchouk JV, Verweij N, Wolffenbuttel BH, Young T, Zafarmand MH, Zmuda JM; Look AHEAD Research Group; DIAGRAM consortium, Boehnke M, Altshuler D, McCarthy M, Kao WH, Pankow JS, Cappola TP, Sever P, Poulter N, Caulfield M, Dominiczak A, Shields DC, Bhatt DL, Zhang L, Curtis SP, Danesh J, Casas JP, van der Schouw YT, Onland-Moret NC, Doevendans PA, Dorn GW 2nd, Farrall M, FitzGerald GA, Hamsten A, Hegele R, Hingorani AD, Hofker MH, Huggins GS, Illig T, Jarvik GP, Johnson JA, Klungel OH, Knowler WC, Koenig W, März W, Meigs JB, Melander O, Munroe PB, Mitchell BD, Bielinski SJ, Rader DJ, Reilly MP, Rich SS, Rotter JI, Saleheen D, Samani NJ, Schadt EE, Shuldiner AR, Silverstein R, Kottke-Marchant K, Talmud PJ, Watkins H, Asselbergs FW, de Bakker PI, McCaffery J, Wijmenga C, Sabatine MS, Wilson JG, Reiner A, Bowden DW, Hakonarson H, Siscovick DS, Keating BJ. Large-scale gene-centric meta-analysis across 39 studies identifies type 2 diabetes loci. *Am J Hum Genet*. 2012;90:410-425.

Cholesterol Treatment Trialists' (CTT) Collaboration, Emberson JR, Kearney PM, Blackwell L, Newman C, Reith C, Bhala N, Holland L, Peto R, Keech A, Collins R, Simes J, Baigent C. Lack of effect of lowering LDL cholesterol on cancer: meta-analysis of individual data from 175,000 people in 27 randomised trials of statin therapy. *PLoS One*. 2012;7(1):e29849.

Johnson T, Gaunt TR, Newhouse SJ, Padmanabhan S, Tomaszewski M, Kumari M, Morris RW, Tzoulaki I, O'Brien ET, Poulter NR, Sever P, Shields DC, Thom S, Wannamethee SG, Whincup PH, Brown MJ, Connell JM, Dobson RJ, Howard PJ, Mein CA, Onipinla A, Shaw-Hawkins S, Zhang Y, Davey Smith G, Day IN, Lawlor DA, Goodall AH; Cardiogenics Consortium, Fowkes FG, Abecasis GR, Elliott P, Gateva V; Global BPgen Consortium, Braund PS, Burton PR, Nelson CP, Tobin MD, van der Harst P, Glorioso N, Neuvrith H, Salvi E, Staessen JA, Stucchi A, Devos N, Jeunemaitre X, Plouin PF, Tichet J, Juhanson P, Org E, Putku M, Sõber S, Veldre G, Viigimaa M, Levinsson A, Rosengren A, Thelle DS, Hastie CE, Hedner T, Lee WK, Melander O, Wahlstrand B, Hardy R, Wong A, Cooper JA, Palmen J, Chen L, Stewart AF, Wells GA, Westra HJ, Wolfs MG, Clarke R, Franzosi MG, Goel A, Hamsten A, Lathrop M, Peden JF, Seedorf U, Watkins H, Ouwehand WH, Sambrook J, Stephens J, Casas JP, Drenos F, Holmes MV, Kivimaki M, Shah S, Shah T, Talmud PJ, Whittaker J, Wallace C, Delles C, Laan M, Kuh D, Humphries SE,

Nyberg F, Cusi D, Roberts R, Newton-Cheh C, Franke L, Stanton AV, Dominiczak AF, Farrall M, Hingorani AD, Samani NJ, Caulfield MJ, Munroe PB. Blood pressure loci identified with a gene-centric array. *Am J Hum Genet*. 2011;89:688-700.

Gupta AK, Nasothimiou EG, Chang CL, Sever PS, Dahlöf B, Poulter NR; ASCOT investigators. Baseline predictors of resistant hypertension in the Anglo-Scandinavian Cardiac Outcome Trial (ASCOT): a risk score to identify those at high-risk. *J Hypertens*. 2011;29:2004-2013.

Sever PS, Chang CL, Gupta AK, Whitehouse A, Poulter NR; ASCOT Investigators. The Anglo-Scandinavian Cardiac Outcomes Trial: 11-year mortality follow-up of the lipid-lowering arm in the U.K. *Eur Heart J*. 2011;32:2525-2532.

Sever PS, Poulter NR, Chang CL, Hingorani A, Thom SA, Hughes AD, Welsh P, Sattar N; on behalf of the ASCOT Investigators. Evaluation of C-reactive protein prior to and on-treatment as a predictor of benefit from atorvastatin: observations from the Anglo-Scandinavian Cardiac Outcomes Trial. *Eur Heart J*. 2012;33:486-494.

Chapman N, Chang CL, Caulfield M, Dahlöf B, Feder G, Sever PS, Poulter NR. Ethnic variations in lipid-lowering in response to a statin (EVIREST): a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT). *Ethn Dis*. 2011;21:150-157.

Uusimaa P, Peuhkurinen S, Ylitalo A, Vuolteenaho O, Risteli J, Peuhkurinen K; Anglo-Scandinavian Cardiac Outcomes Trial Investigators. Natriuretic peptides and collagen biomarkers in patients with medical treatment for hypertension. *Acta Cardiol*. 2011;66:21-27.

Collier DJ, Poulter NR, Dahlöf B, Sever PS, Wedel H, Buch J, Caulfield MJ; ASCOT Investigators.Impact of amlodipine-based therapy among older and younger patients in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA). *J Hypertens*. 2011;29:583-591.

Collier DJ, Poulter NR, Dahlöf B, Sever PS, Wedel H, Buch J, Caulfield MJ; ASCOT Investigators. Impact of atorvastatin among older and younger patients in the Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering Arm. *J Hypertens*. 2011;29:592-599.

Gupta AK, Poulter NR, Dobson J, Eldridge S, Cappuccio FP, Caulfield M, Collier D, Cruickshank JK, Sever PS, Feder G; ASCOT. Ethnic differences in blood pressure response to first and second-line antihypertensive therapies in patients randomized in the ASCOT Trial. *Am J Hypertens*. 2010;23:1023-1030.

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

Investigators. Wave reflection predicts cardiovascular events in hypertensive individuals independent of blood pressure and other cardiovascular risk factors: an ASCOT (Anglo-Scandinavian Cardiac Outcome Trial) substudy. *J Am Coll Cardiol*. 2010;56:24-30.

Horne R, Clatworthy J, Hankins M; ASCOT Investigators. High adherence and concordance within a clinical trial of antihypertensives. *Chronic Illn*. 2010;6:243-251.

Chapman N, Chen CY, Fujita T, Hobbs FD, Kim SJ, Staessen JA, Tanomsup S, Wang JG, Williams B. Time to re-appraise the role of alpha-1 adrenoceptor antagonists in the management of hypertension? *J Hypertens*. 2010;28:1796-1803. Review. Erratum in: *J Hypertens*. 2010;28:2351.

Lindgren P, Eriksson J, Buxton M, Kahan T, Poulter NR, Dahlöf B, Sever PS, Wedel H, Jönsson B; ASCOT trial investigators. The economic consequences of non-adherence to lipid-lowering therapy: results from the Anglo-Scandinavian-Cardiac Outcomes Trial. *Int J Clin Pract.* 2010;64:1228-1234.

Gupta AK, Dahlof B, Sever PS, Poulter NR; Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm Investigators. Metabolic syndrome, independent of its components, is a risk factor for stroke and death but not for coronary heart disease among hypertensive patients in the ASCOT-BPLA. *Diabetes Care*. 2010;33:1647-1651.

Tapp RJ, Sharp A, Stanton AV, O'Brien E, Chaturvedi N, Poulter NR, Sever PS, Thom SA, Hughes AD, Mayet J; ASCOT Investigators. Differential effects of antihypertensive treatment on left ventricular diastolic function: an ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) substudy. *J Am Coll Cardiol*. 2010;55:1875-1881.

Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, Poulter NR, Sever PS; ASCOT-BPLA and MRC Trial Investigators. Effects of beta blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. *Lancet Neurol.* 2010;9:469-480.

Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, Sever PS, Poulter NR. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet*. 2010;375:895-905.

Sharp AS, Tapp RJ, Thom SA, Francis DP, Hughes AD, Stanton AV, Zambanini A, O'Brien E, Chaturvedi N, Lyons S, Byrd S, Poulter NR, Sever PS, Mayet J; ASCOT Investigators. Tissue Doppler E/E' ratio is a powerful predictor of primary cardiac events in a hypertensive population: an ASCOT substudy. *Eur Heart J*. 2010;31:747-752.

Poulter NR, Dobson JE, Sever PS, Dahlöf B, Wedel H, Campbell NR; ASCOT Investigators. Baseline heart rate, antihypertensive treatment, and prevention of cardiovascular outcomes in ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial). *J Am Coll Cardiol*. 2009;54:1154-1161.

Manisty C, Mayet J, Tapp RJ, Sever PS, Poulter N, McG Thom SA, Hughes AD; ASCOT Investigators. Atorvastatin treatment is associated with less augmentation of the carotid pressure waveform in hypertension: a substudy of the Anglo-Scandinavian Cardiac Outcome Trial (ASCOT). *Hypertension*. 2009;54:1009-1013.

Williams B, Lacy PS; CAFE and the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) Investigators. Impact of heart rate on central aortic pressures and hemodynamics: analysis from the CAFE (Conduit Artery Function Evaluation) study: CAFE-Heart Rate. *J Am Coll Cardiol.* 2009;54:705-713.

Clunn GF, Sever PS, Hughes AD. Calcium channel regulation in vascular smooth muscle cells: synergistic effects of statins and calcium channel blockers. *Int J Cardiol*. 2010;139:2-6.

Dolan E, Stanton AV, Thom S, Caulfield M, Atkins N, McInnes G, Collier D, Dicker P, O'Brien E; ASCOT Investigators. Ambulatory blood pressure monitoring predicts cardiovascular events in treated hypertensive patients--an Anglo-Scandinavian cardiac outcomes trial substudy. *J Hypertens.* 2009;27:876-885.

Lindgren P, Buxton M, Kahan T, Poulter NR, Dahlöf B, Sever PS, Wedel H, Jönsson B; ASCOT investigators. The lifetime cost effectiveness of amlodipine-based therapy plus atorvastatin compared with atenolol plus atorvastatin, amlodipine-based therapy alone and atenolol-based therapy alone: results from ASCOT. *Pharmacoeconomics.* 2009;27:221-230

Sever PS, Poulter NR, Dahlof B, Wedel H; ASCOT Investigators. Antihypertensive therapy and the benefits of atorvastatin in the Anglo-Scandinavian Cardiac Outcomes Trial: lipid-lowering arm extension. *J Hypertens*. 2009;27:947-954.

Stettler C, Witt N, Tapp RJ, Thom S, Allemann S, Tillin T, Stanton A, O'Brien E, Poulter N, Gallimore JR, Hughes AD, Chaturvedi N. Serum amyloid A, C-reactive protein, and retinal microvascular changes in hypertensive diabetic and nondiabetic individuals: an Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) substudy. *Diabetes Care*. 2009;32:1098-1100.

Sever PS, Poulter NR, Mastorantonakis S, Chang CL, Dahlof B, Wedel H; ASCOT Investigators. Coronary heart disease benefits from blood pressure and lipid-lowering. *Int J Cardiol.* 2009;135:218-222.

Patel JV, Lim HS, Dubb K, Hughes EA, Lip GY. Circulating levels of adiponectin, leptin, and tumour necrosis factor alpha in hypertension. *Ann Med*. 2009;41:291-300.

Williams B, Lacy PS, Cruickshank JK, Collier D, Hughes AD, Stanton A, Thom S, Thurston H; CAFE and ASCOT Investigators. Impact of statin therapy on central aortic pressures and hemodynamics: principal results of the Conduit Artery Function Evaluation-Lipid-Lowering Arm

(CAFE-LLA) Study. *Circulation*. 2009;119:53-61.

Ostergren J, Poulter NR, Sever PS, Dahlöf B, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E; ASCOT investigators. The Anglo-Scandinavian Cardiac Outcomes Trial: blood pressure-lowering limb: effects in patients with type II diabetes. *J Hypertens*. 2008;26:2103-2111.

Sharp A, Tapp R, Francis DP, McG Thom SA, Hughes AD, Stanton AV, Zambanini A, Chaturvedi N, Byrd S, Poulter NR, Sever PS, Mayet J. Ethnicity and left ventricular diastolic function in hypertension an ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) substudy. *J Am Coll Cardiol*. 2008;52:1015-1021.

Chapman N, Chang CL, Dahlöf B, Sever PS, Wedel H, Poulter NR; ASCOT Investigators. Effect of doxazosin gastrointestinal therapeutic system as third-line antihypertensive therapy on blood pressure and lipids in the Anglo-Scandinavian Cardiac Outcomes Trial. *Circulation*. 2008;118:42-48.

Gupta AK, Dahlof B, Dobson J, Sever PS, Wedel H, Poulter NR; Anglo-Scandinavian Cardiac Outcomes Trial Investigators. Determinants of new-onset diabetes among 19,257 hypertensive patients randomized in the Anglo-Scandinavian Cardiac Outcomes Trial--Blood Pressure Lowering Arm and the relative influence of antihypertensive medication. *Diabetes Care.* 2008;31:982-988.

Sever PS, Poulter NR, Dahlof B, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes G, Mehlsen J, Nieminen MS, O'Brien ET, Ostergren J; ASCOT Investigators. The Anglo-Scandinavian Cardiac Outcomes Trial lipid lowering arm: extended observations 2 years after trial closure. *Eur Heart J.* 2008;29:499-508.

Lindgren P, Buxton M, Kahan T, Poulter NR, Dahlöf B, Sever PS, Wedel H, Jönsson B; ASCOT trial investigators. Economic evaluation of ASCOT-BPLA: antihypertensive treatment with an amlodipine-based regimen is cost effective compared with an atenolol-based regimen. *Heart.* 2008;94:e4.

Varughese GI, Patel JV, Tomson J, Blann AD, Hughes EA, Lip GY. Prognostic value of plasma soluble P-selectin and von Willebrand factor as indices of platelet activation and endothelial damage/dysfunction in high-risk patients with hypertension: a sub-study of the Anglo-Scandinavian Cardiac Outcomes Trial. *J Intern Med*. 2007;261:384-391.

Sever P, Dahlöf B, Poulter N, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen S, Kristinsson A, McInnes G, Mehlsen J, Nieminem M, O'Brien E, Ostergren J; ASCOT Steering Committee Members. Potential synergy between lipid-lowering and blood-pressure-lowering in the Anglo-Scandinavian Cardiac Outcomes Trial. *Eur Heart J*. 2006;27:2982-2988. Erratum in: *Eur Heart J*. 2007;28:142.

Julkunen J, Ahlström R. Hostility, anger, and sense of coherence as predictors of health-related quality of life. Results of an ASCOT substudy. *J Psychosom Res*. 2006;61:33-39.

Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, Hughes AD, Thurston H, O'Rourke M; CAFE Investigators; Anglo-Scandinavian Cardiac Outcomes Trial Investigators; CAFE Steering Committee and Writing Committee. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation*. 2006;113:1213-1225.

Sever PS. Lipid-lowering therapy and the patient with multiple risk factors: what have we learned from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)? *Am J Med.* 2005;118:Suppl 12A:3-9.

Nadar SK, Blann A, Beevers DG, Lip GY. Abnormal angiopoietins 1&2, angiopoietin receptor Tie-2 and vascular endothelial growth factor levels in hypertension: relationship to target organ damage [a sub-study of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)]. *J Intern Med.* 2005;258:336-343.

Poulter NR, Wedel H, Dahlöf B, Sever PS, Beevers DG, Caulfield M, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J, Pocock S; ASCOT Investigators. Role of blood pressure and other variables in the differential cardiovascular event rates noted in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA). *Lancet.* 2005;366:907-913.

Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J; ASCOT Investigators. 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. *Lancet.* 2005;366:895-906.

Sever PS, Poulter NR, Dahlöf B, Wedel H; Anglo-Scandinavian Cardiac Outcomes Trial Investigators. Different time course for prevention of coronary and stroke events by atorvastatin in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA). *Am J Cardiol.* 2005;96:39F-44F. Review.

Sever PS, Poulter NR, Dahlöf B, Wedel H, Collins R, Beevers G, Caulfield M, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial--lipid-lowering arm (ASCOT-LLA). *Diabetes Care*. 2005;28:1151-1157.

Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J; ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Drugs*. 2004;64:Suppl 2:43-60.

Lindgren P, Buxton M, Kahan T, Poulter NR, Dahlöf B, Sever PS, Wedel H, Jönsson B; ASCOT investigators. Cost-effectiveness of atorvastatin for the prevention of coronary and stroke events: an economic analysis of the Anglo-Scandinavian Cardiac Outcomes Trial--lipid-lowering arm (ASCOT-LLA). *Eur J Cardiovasc Prev Rehabil*. 2005;12:29-36.

Tayebjee MH, Nadar S, Blann AD, Gareth Beevers D, MacFadyen RJ, Lip GY. Matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 in hypertension and their relationship to cardiovascular risk and treatment: a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT). *Am J Hypertens*. 2004;17:764-769.

Nadar SK, Blann AD, Kamath S, Beevers DG, Lip GY. Platelet indexes in relation to target organ damage in high-risk hypertensive patients: a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT). *J Am Coll Cardiol.* 2004;44:415-422.

Spencer CG, Martin SC, Felmeden DC, Blann AD, Beevers GD, Lip GY. Relationship of homocysteine to markers of platelet and endothelial activation in "high risk" hypertensives: a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial. *Int J Cardiol*. 2004;94:293-300.

Spencer CG, Gurney D, Felmeden DC, Blann AD, Beevers DG, Lip GY. Platelet and haemorheological markers in 'high risk' hypertensives are improved by tighter blood pressure control and cardiovascular risk management: a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT). *J Intern Med*. 2004;255:59-67.

Felmeden DC, Spencer CG, Chung NA, Belgore FM, Blann AD, Beevers 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.

Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J; ASCOT investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian

Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet*. 2003;361:1149-1158.

Felmeden DC, Spencer CG, Blann AD, Beevers DG, Lip GY. Physical activity in relation to indices of endothelial function and angiogenesis factors in hypertension: a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT). *J Intern Med.* 2003;253:81-91.

Spencer CG, Gurney D, Blann AD, Beevers DG, Lip GY; ASCOT Steering Committee, Anglo-Scandinavian Cardiac Outcomes Trial. Von Willebrand factor, soluble P-selectin, and target organ damage in hypertension: a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT). *Hypertension.* 2002;40:61-66.

Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J. Rationale, design, methods and baseline demography of participants of the Anglo-Scandinavian Cardiac Outcomes Trial. ASCOT investigators. *J Hypertens*. 2001;19:1139-1147.

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

1. Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, Hughes AD, Thurston H, O'Rourke M, CAFÉ Investigators, ASCOT Investigators, CAFÉ Steering Committee and Writing Committee. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFÉ) Study. *Circulation.* 2006;113:1213-1225.

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

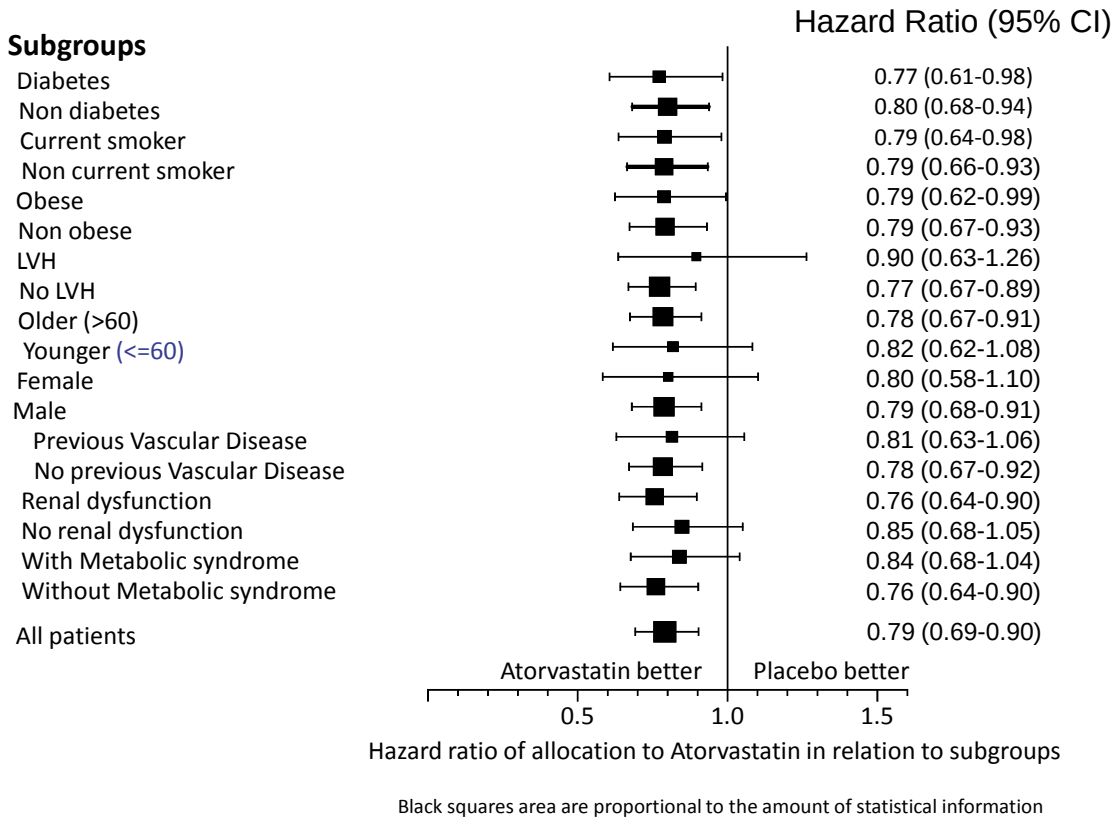

Figure S1 – ASCOT-LLA total cardiovascular events and procedures by subgroups (LVH = left ventricular hypertrophy)

Figure S2

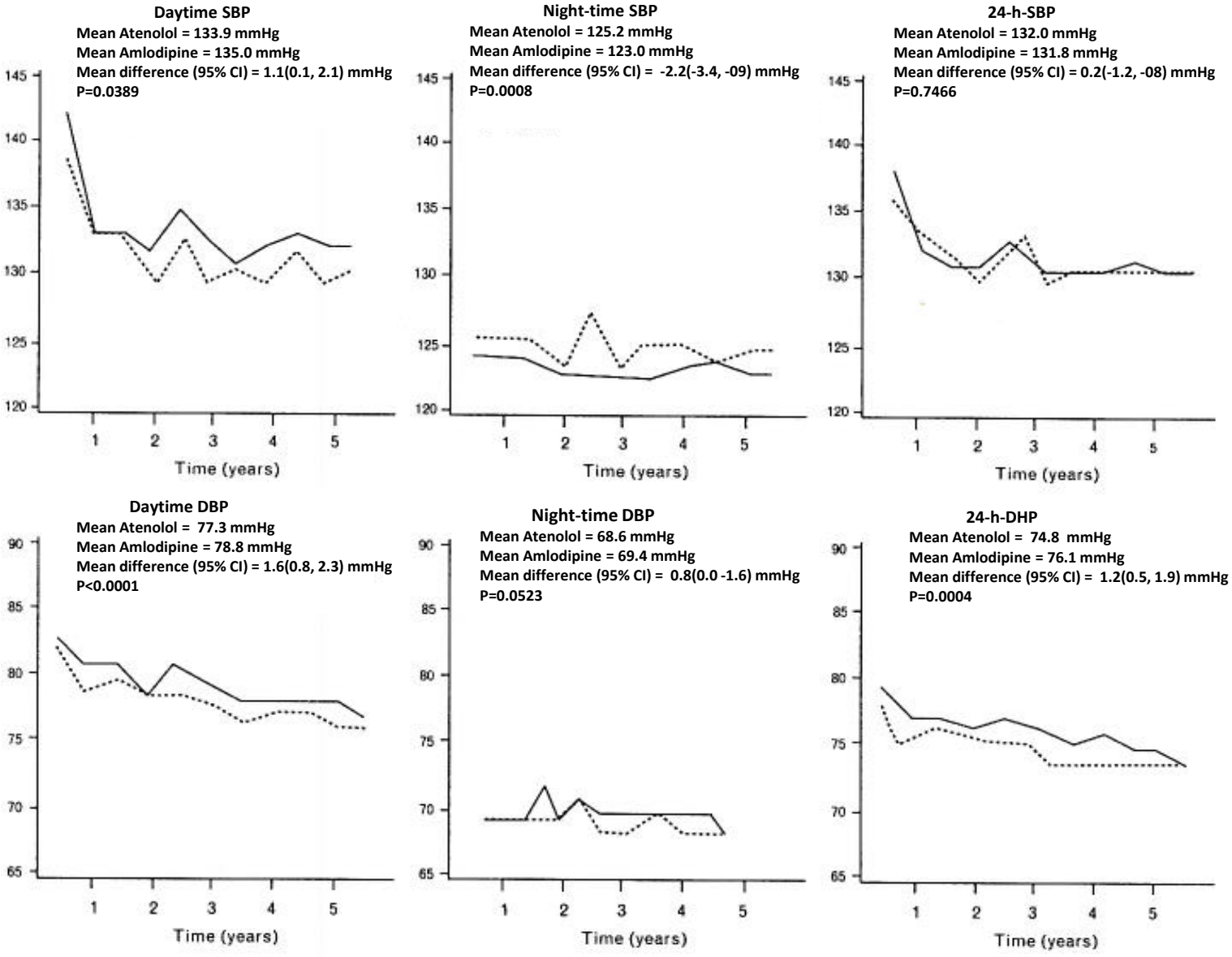

Figure S2 – 24-hour ambulatory blood pressure recordings on an average 1-year following randomisation in the two blood pressure treatment groups. Atenolol-thiazide (hashed line), amlodipine-perindopril (solid line). SBP=systolic blood pressure. DBP=diastolic blood pressure. Modified from Dolan et al,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

Figure S3

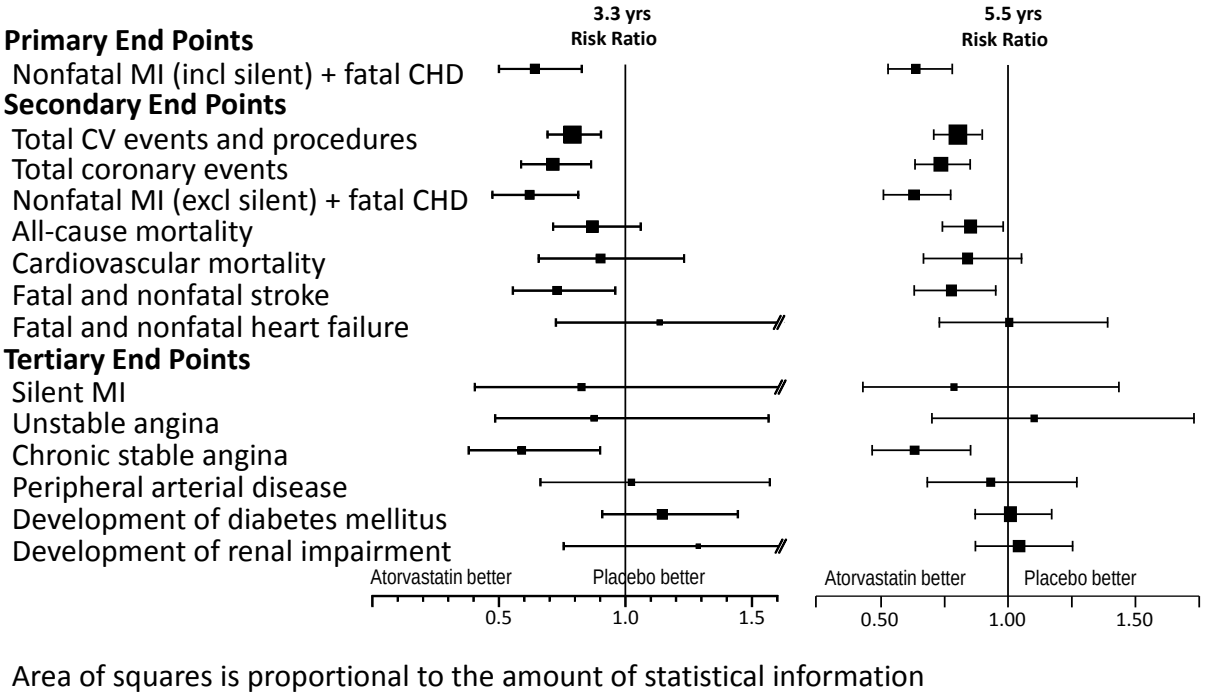

Figure S3 – ASCOT-LLA summary of cardiovascular endpoints at the end of the trial (3.3 years) and following 2.2 years extension (5.5 years). Modified from Sever et al, Eur Heart J 2008;29:498-508.

Figure S4

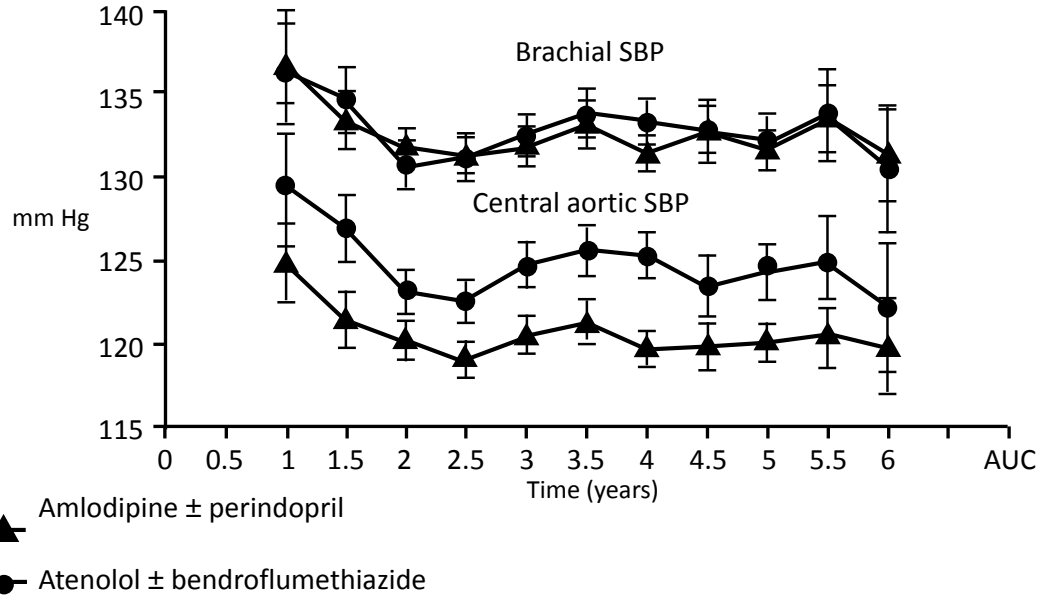

Figure S4 – CAFÉ study – lower central aortic blood pressure with newer versus older antihypertensive regimens despite similar brachial blood pressures. Modified from Williams et al, in Poulter NR, Sever P. Anglo-Scandinavian Cardiac Outcomes Trial: Latest perspectives on this landmark trial. Sherborne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

Figure S5

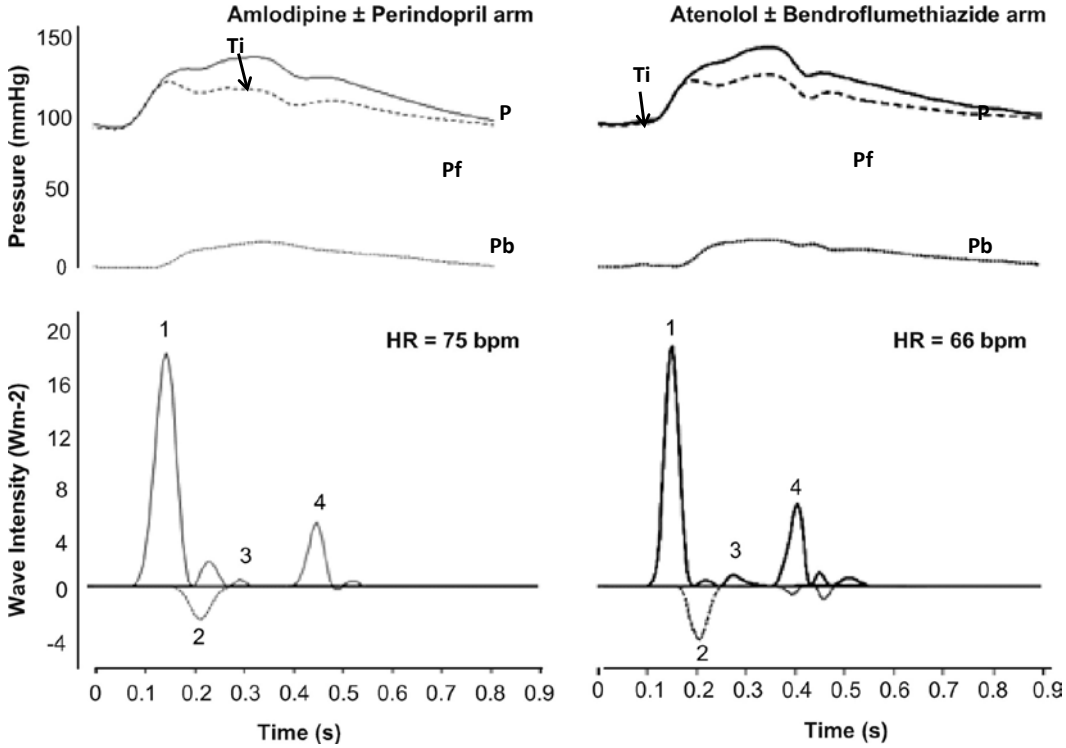

Figure S5 – Example traces comparing measured pressure waveforms P_{total}, Pf and Pb separated pressure waveforms and wave intensity between treatment regimens. The shoulder or inflection point in the pressure wave form (Ti) is indicated. The S wave (1), the C-1 wave (2), the C+1 wave (3), and the D 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

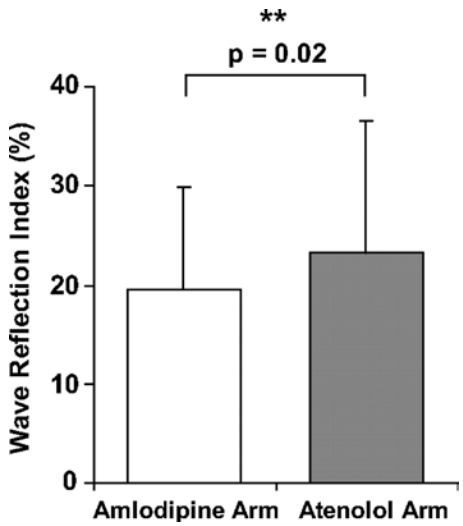

Figure S6 - The wave reflection index was significantly lower in patients randomised to amlodipine±perindopril-based therapy than atenolol±thiazide-based therapy (19.8% [10.9%] vs 23.3% [13.3%]. Modified from Manisty et al, in Poulter NR, Sever P. Anglo-Scandinavian Cardiac Outcomes Trial: Latest perspectives on this landmark trial. Sherborne Gibbs Ltd Publications, 2011.