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)

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Summary

Background **Results of the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) show significantly lower rates of coronary and stroke events in individuals allocated an amlodipine-based combination drug regimen than in those allocated an atenolol-based combination drug regimen (HR 0·86 and 0·77, respectively). Our aim was to assess to what extent these differences were due to significant differences in blood pressures and in other variables noted after randomisation.**

Methods **We used data from ASCOT-BPLA (n=19 257) and compared differences in accumulated mean blood pressure levels at sequential times in the trial with sequential differences in coronary and stroke events. Serial mean matching for differences in systolic blood pressure was used to adjust HRs for differences in these events. We used an updated Cox-regression model to assess the effects of differences in accumulated mean levels of various measures of blood pressure, serum HDL-cholesterol, triglycerides and potassium, fasting blood glucose, heart rate, and bodyweight on differences in event rates.**

Findings **We noted no temporal link between size of differences in blood pressure and different event rates. Serial mean matching for differences in systolic blood-pressure attenuated HRs for coronary and stroke events to a similar extent as did adjustments for systolic blood-pressure differences in Cox-regression analyses. HRs for coronary events and stroke adjusted for blood pressure rose from 0·86 (0·77–0·96) to 0·88 (0·79–0·98) and from 0·77 (0·66–0·89) to 0·83 (0·72–0·96), respectively. Multivariate adjustment gave HRs of 0·94 (0·81–1·08) for coronary events (HDL cholesterol being the largest contributor) and 0·87 (0·73–1·05) for stroke events.**

Interpretation **Multivariate adjustment accounted for about half of the differences in coronary events and for about 40% of the differences in stroke events between the treatment regimens tested in ASCOT-BPLA, but residual differences were no longer significant. These residual differences could indicate inadequate statistical adjustment, but it remains possible that differential effects of the two treatment regimens on other variables also contributed to the different rates noted, particularly for stroke.**

Introduction

In the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA),[1] an antihypertensive treatment regimen of amlodipine adding perindopril as required to reach blood-pressure targets (amlodipine-based regimen) was associated with beneficial effects on almost all cardiovascular outcomes compared with a regimen of atenolol adding bendroflumethiazide and potassium as required (atenolol-based regimen).

Results of metaregression analyses of more than 30 randomised trials of blood pressure-lowering therapy done by the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC)[2] indicate that for a given reduction in blood pressure the major drug classes seem to produce similar overall net effects on total cardiovascular events. That is, the absolute reduction in blood pressure was a more important determinant of the relative reduction in cardiovascular outcome than the choice of antihypertensive drug. Some possible exceptions to this rule have been cited—for example, calcium-channel blockers seem to be less effective for the prevention of heart failure but to be more effective for the prevention of stroke than other drug classes. The large and broad-ranging cardiovascular benefits of the amlodipine-based regimen over the atenolol-based regimen in ASCOT-BPLA do not, however, seem to concur with the overall findings of the BPLTTC.[2]

Possible explanations for the different cardiovascular event rates in those allocated the two blood pressure-lowering regimens were suggested when the preliminary results of ASCOT-BPLA were announced, and include: better blood pressure lowering achieved by the amlodipine-based regimen; benefits of the amlodipine-based regimen that were unrelated to lowering of blood pressure; some disadvantages of the atenolol-based regimen that were unrelated to blood

pressure lowering; or an interaction between antihypertensive and lipid-lowering regimens.

The amlodipine-based regimen did lower blood pressure more effectively than the atenolol-based regimen, with an accumulated mean in-trial systolic difference of 2·7 mm Hg. Based on the benefits observed in previous randomised trials[2,3] this difference in blood pressure should generate a difference of 4–8% in coronary events and 11–14% in strokes. Based on long-term observational data,[4] this systolic difference should translate into a difference in rates of coronary events of about 8% and in rates of stroke of about 11%. These proportions contrast with the actual differences in coronary and stroke events of 14% and 23%, respectively, reported in ASCOT-BPLA.[1]

Our aim was to assess the extent to which differences in blood pressure and in other cardiovascular risk factors are likely to account for the differences in the cardiovascular outcomes reported in ASCOT-BPLA.[1]

Methods

Participants

The detailed ASCOT protocol has been published,[1,5] and additional details are available on the ASCOT website. In summary, patients with hypertension, who were aged 40–79 years, and who had at least three other cardiovascular risk factors, but no previous history of coronary heart disease (CHD), were randomised, using the PROBE design,[6] to receive one of two antihypertensive regimens instead of whatever was being taken for hypertension at time of randomisation. These two treatment regimens involved either amlodipine adding perindopril as required to reach blood-pressure targets or atenolol adding bendroflumethiazide and potassium as required.[1] Of the patients enrolled, a proportion had a total cholesterol concentration of 6·5 mmol/L or less and were eligible to be randomised, double-blind, by way of a two-by-two factorial design, to receive atorvastatin 10 mg daily or matching placebo. Statin use was equally distributed between those allocated the two antihypertensive regimens. Like ASCOT-BPLA[1] the lipid-lowering arm of ASCOT (ASCOT-LLA)[7] was terminated early because of a significant benefit associated with allocation to atorvastatin.

Procedures

We assessed potential explanatory variables for two of the endpoints that differed between those randomised to the two blood pressure-lowering regimens in ASCOT-BPLA: the primary endpoint (fatal CHD plus non-fatal myocardial infarction) plus coronary revascularisation and fatal plus non-fatal stroke. We selected these endpoints because they arose at significantly different rates in the two treatment groups, and because they have potentially different underlying mechanisms and involved sufficient numbers of events to allow meaningful analyses.

We assessed systolic and diastolic blood pressure and calculated pulse pressure. We also assessed the mean of the systolic blood pressure and diastolic blood pressure, which has previously been reported to be the best predictor of blood-pressure related cardiovascular events.[4] In the updated Cox models, we used the last pressure reading, the accumulated mean from randomisation, and the 1-year recurrent average pressures before each coronary or stroke event occurred.

The size of the differences in blood pressure between the groups varied considerably during follow-up, so we compared these differences over time with the differences in the cardiovascular events over time, thereby allowing some assessment of any temporal association between differences in blood pressure and cardiovascular events. To further assess the extent to which differences in blood pressure might explain the different rates of cardiovascular events, we did analyses with a serial mean matching technique similar to that applied to the VALUE trial data.[8]

Statistical analysis

For certain timepoints—0·5, 1, 2, 3, and 4 years—we selected a subset of patients on the atenolol-based regimen by adding individuals sequentially while on a group basis maintaining similarity to all those on the amlodipine-based regimen with respect to systolic blood pressure. In addition, at the 0 year time point all those on the atenolol-based regimen could be included. The newly-selected subsets from the atenolol-based regimen included more than 7500 individuals at every time point and thereby constituted over 86% of those allocated to the atenolol-based regimen, and included 91% of the coronary events and 86% of the stroke events that arose in this group. The mean systolic blood pressures of the two treatment groups at every time point after randomisation differed by no more than 0·02 mm Hg. We then compared the cardiovascular event rates in the newly constructed subsets on the atenolol-based regimen to those on the amlodipine-based regimen in the time periods that followed each of the six time points selected, using multiple Cox regression to adjust for age and number of risk factors at baseline. A pooled HR (95% CI) was calculated over the periods for both endpoints.

The major analyses involved the use of an updated (time-dependent) Cox regression model to assess the effect of adjustment for baseline age and number of risk factors and for differences in the accumulated mean levels of each of those variables that differed significantly between treatment groups after randomisation, and which were significantly associated with either coronary or stroke events in this trial, on the differential coronary and stroke event rates. We established whether the association between each of the variables and either coronary or stroke events was significant with updated Cox regression techniques, whereby the association

	Amlodipine-based regimen		Atenolol-based regimen		Difference between regimens (amlodipine-based minus atenolol-based regimen)	
	Baseline	Change from baseline to final visit	Baseline	Change from baseline to final visit	Mean change from baseline to final visit	p for change from baseline to final visit
Systolic blood pressure (mm Hg)	164·07 (18·06), (n=9639)	−27·50 (21·11), (n=8281)	163·95 (17·96), (n=9618)	−25·72 (22·25), (n=8017)	−1·78	<0·0001
Diastolic blood pressure (mm Hg)	94·79 (10·37), (n=9639)	−17·65 (11·27), (n=8281)	94·52 (10·38), (n=9618)	−15·60 (11·59), (n=8017)	−2·05	<0·0001
Heart rate (bpm)	71·93 (12·69), (n=9639)	0·64 (13·00), (n=8268)	71·85 (12·59), (n=9618)	−10·48 (13·87), (n=8007)	11·12	<0·0001
Glucose (mmol/L)	6·24 (2·12), (n=8748)	0·15 (1·84), (n=6907)	6·24 (2·11), (n=8687)	0·35 (1·97), (n=6691)	−0·20	<0·0001
LDL cholesterol (mmol/L)	3·79 (0·97), (n=8578)	−1·12 (1·05), (n=6728)	3·78 (0·96), (n=8532)	−1·14 (1·06), (n=6473)	0·02	0·3766
HDL cholesterol (mmol/L)	1·30 (0·36), (n=9639)	0·13 (0·28), (n=7991)	1·30 (0·37), (n=9618)	0·02 (0·26), (n=7734)	0·11	<0·0001
Triglycerides (mmol/L)	1·84 (1·00), (n=8760)	−0·40 (0·91), (n=6916)	1·85 (1·00), (n=8712)	−0·17 (1·06), (n=6706)	−0·23	<0·0001
Creatinine (μmol/L)	98·66 (16·59), (n=6558)	1·16 (21·87), (n=5424)	98·68 (17·00), (n=6563)	6·22 (20·68), (n=5259)	−5·06	<0·0001
Potassium (mmol/L)	4·22 (0·47), (n=9258)	0·08 (0·55), (n=7687)	4·21 (0·46), (n=9227)	0·03 (0·63), (n=7433)	0·05	<0·0001
Bodyweight (kg)	84·59 (15·68), (n=9639)	0·62 (6·55), (n=8090)	84·59 (15·34), (n=9618)	1·41 (6·91), (n=7822)	−0·79	<0·0001

Data are mean (SD), (number of patients).

Table 1: **Differences within and between treatment groups in change from baseline to final-visit measurements by variable**

between continuously updated mean levels of variables in the whole trial population and subsequent coronary and stroke events was assessed. To allow a degree of comparability among the variables tested, we calculated the HRs associated with 1 SD of each variable. We then extended these analyses to assess the effect of differences in these individual variables on the differences in coronary and stroke event rates noted in the two treatment groups. We repeated these comparisons with multivariate analyses, including all the individual variables plus baseline age and number of risk factors in the model. Because raised serum creatinine might be the result of renal target organ damage as well as a putative risk factor for the cardiovascular events, we decided to exclude creatinine from the multivariate explanatory analyses. These analyses are, therefore, presented without creatinine in the model. Two-sided p values are presented throughout.

Role of the funding source

The sponsor 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 commitee. 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

19 257 patients were assessed in ASCOT-BPLA. There were significant differences between the two groups of patients in ASCOT-BPLA during follow-up for: blood pressure; heart rate; fasting blood glucose; serum HDL-cholesterol, triglycerides, creatinine, and potassium; and bodyweight (table 1). All of these variables were significantly associated with rates of coronary events or stroke during the trial (table 2).

We noted no temporal link between the size of the difference in blood pressure between those allocated the two antihypertensive regimens and differences in coronary or stroke events (figure 1). For coronary events, when the largest differences in blood pressure were apparent—during the first year—more events arose in those allocated the amlodipine-based regimen than in those allocated the atenolol-based regimen, though these differences were not significant.

	Primary endpoint and coronary revascularisations		Fatal and non-fatal stroke	
	HR (95% CI)	p	HR (95% CI)	p
Systolic blood pressure (SD=14·17 mm Hg)	1·16 (1·11–1·22)	<0·0001	1·38 (1·31–1·47)	<0·0001
Diastolic blood pressure (SD=7·97 mm Hg)	0·94 (0·89–0·99)	0·0262	0·99 (0·92–1·06)	0·7518
Mean blood pressure* (SD=9·49 mm Hg)	1·10 (1·04–1·15)	0·0004	1·28 (1·21–1·37)	<0·0001
Pulse pressure (SD=12·96 mm Hg)	1·23 (1·17–1·29)	<0·0001	1·45 (1·37–1·54)	<0·0001
Heart rate (SD=12·35 bpm)	0·94 (0·89–1·00)	0·0439	0·90 (0·84–0·97)	0·0043
Glucose (SD=2·02 mmol/L)	1·15 (1·09–1·20)	<0·0001	1·12 (1·05–1·19)	0·0006
HDL cholesterol (SD=0·35 mmol/L)	0·78 (0·73–0·83)	<0·0001	1·02 (0·95–1·09)	0·6270
Triglycerides (SD=0·93 mmol/L)	1·06 (1·00–1·11)	0·0370	0·99 (0·92–1·06)	0·7539
Creatinine (SD=18·18 μmol/L)	1·18 (1·13–1·22)	<0·0001	1·20 (1·14–1·26)	<0·0001
Potassium (SD=0·38 mmol/L)	1·10 (1·05–1·15)	<0·0001	0·99 (0·92–1·06)	0·6803
Bodyweight (SD=15·75 kg)	0·98 (0·92–1·03)	0·3920	0·81 (0·75–0·87)	<0·0001

*Mean blood pressure=(systolic+diastolic blood pressure)/2. HR for 1 SD of accumulated mean up to 2-year visit.

Table 2: **In-trial associations between accumulated mean concentrations of selected variables and coronary and stroke events (Cox regression analyses)**

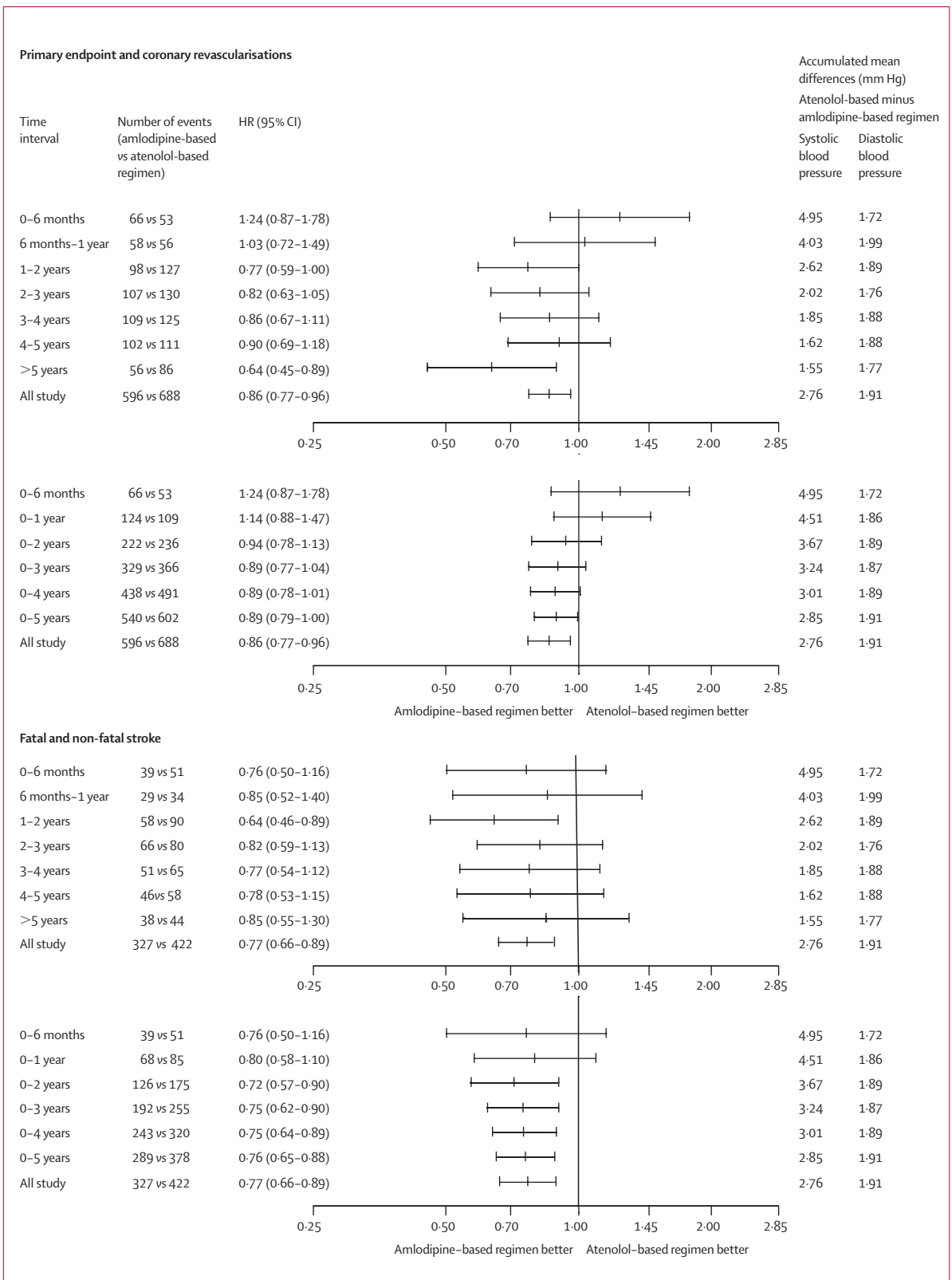

Figure 1: **HRs (95% CI) for coronary and stroke events associated with amlodipine-based versus atenolol-based regimens at various time points, and accumulated mean differences in systolic and diastolic blood pressures**

The effect of the accumulated mean blood pressures on HRs for coronary and stroke endpoints was more pronounced than were the 1-year recurrent mean or the last pressure measured (Cox regression analyses; data not shown). Consequently, we used this measure of blood pressure in all analyses described hereafter. The effect of pulse pressure on the cardiovascular HRs seemed greater than the other measures of blood pressure (table 2). However, in multivariate analyses done to assess the effect of differences in the four measures of blood pressure on the differences in cardiovascular endpoint rates in the two groups, different measures of blood pressure seemed to exert the largest effect on HRs. Hence, results of all further analyses are presented for each of these four measures of blood pressure.

With serial mean matching of systolic blood pressures during six periods throughout the trial follow-up, pooled HRs associated with the amlodipine-based regimen compared with the atenolol-based regimen rose from 0·86 to 0·87 for coronary events and from 0·77 to 0·83 for strokes (table 3).

In Cox-regression analyses, adjustment for accumulated mean systolic pressure resulted in small changes to the HRs for coronary events (from 0·86 to 0·88) and in larger changes to the HRs for stroke events (0·77 to 0·83; table 4). Both HRs remained significant after adjustment, and other measures of blood pressure produced similar effects. By contrast, adjustment for the accumulated mean values of heart rate, bodyweight, serum potassium, creatinine, and triglycerides, and blood glucose had little or no appreciable effect on the HRs of either of the endpoints. Serum HDL-cholesterol concentrations attenuated the HR for coronary events by about 30% (table 4).

In the full multivariate model (which excluded creatinine), the addition of all the covariates not related to blood pressure had a small further effect on the HRs for stroke events compared with the HRs adjusted for blood pressure (figure 2), although the difference in stroke event rates between treatment groups was no longer significant. For coronary events, the full adjustment (largely showing the effect of differences in HDL cholesterol) reduced the HR to between 0·93 and 0·94, and this result too was no longer significant (figure 2). Consequently, full adjustment of these HRs, including blood pressure and other risk factors, accounted for about half of the difference in coronary events and about 40% in stroke event differences noted between the two treatment groups in ASCOT-BPLA.

Discussion

In ASCOT-BPLA, allocation to an antihypertensive regimen based on amlodipine adding perindopril as required rather than atenolol adding bendroflumethiazide and potassium as required was associated not only with fewer cardiovascular events, but also with a

	Unadjusted HR (95% CI)[1]	Adjusted HR (95% CI)	p for adjusted HR
Primary endpoint and coronary revascularisations	0·86 (0·77–0·96)	0·87 (0·78–0·98)	0·0177
Fatal and non-fatal stroke	0·77 (0·66–0·89)	0·83 (0·71–0·96)	0·0147

Table 3: **Pooled HR (95% CI) for coronary and stroke events associated with amlodipine-based therapy compared with atenolol-based therapy adjusted after serial mean matching of systolic blood pressure**

	Primary endpoint and coronary revascularisations		Fatal and non-fatal stroke	
	HR	p	HR	p
Unadjusted[1]	0·86 (0·77–0·96)	0·0058	0·77 (0·66–0·89)	0·0003
Systolic blood pressure	0·88 (0·79–0·98)	0·0258	0·83 (0·72–0·96)	0·0144
Diastolic blood pressure	0·86 (0·77–0·96)	0·0065	0·80 (0·69–0·93)	0·0033
Mean blood pressure*	0·88 (0·78–0·98)	0·0205	0·84 (0·72–0·97)	0·0170
Pulse pressure	0·87 (0·78–0·98)	0·0170	0·80 (0·69–0·93)	0·0026
Heart rate	0·85 (0·75–0·98)	0·0201	0·74 (0·62–0·88)	0·0007
Glucose	0·85 (0·76–0·95)	0·0041	0·78 (0·67–0·90)	0·0007
HDL cholesterol	0·90 (0·81–1·00)	0·0610	0·76 (0·65–0·88)	0·0002
Triglycerides	0·85 (0·76–0·95)	0·0043	0·78 (0·67–0·90)	0·0008
Creatinine	0·86 (0·77–0·96)	0·0091	0·79 (0·68–0·91)	0·0014
Potassium	0·85 (0·76–0·95)	0·0045	0·76 (0·66–0·88)	0·0002
Bodyweight	0·86 (0·77–0·95)	0·0053	0·76 (0·66–0·88)	0·0002

*Mean blood pressure=(systolic+diastolic blood pressure)/2.

Table 4: **HRs associated with amlodipine-based therapy compared with atenolol-based therapy after adjustment for accumulated mean values of each of the selected variables**

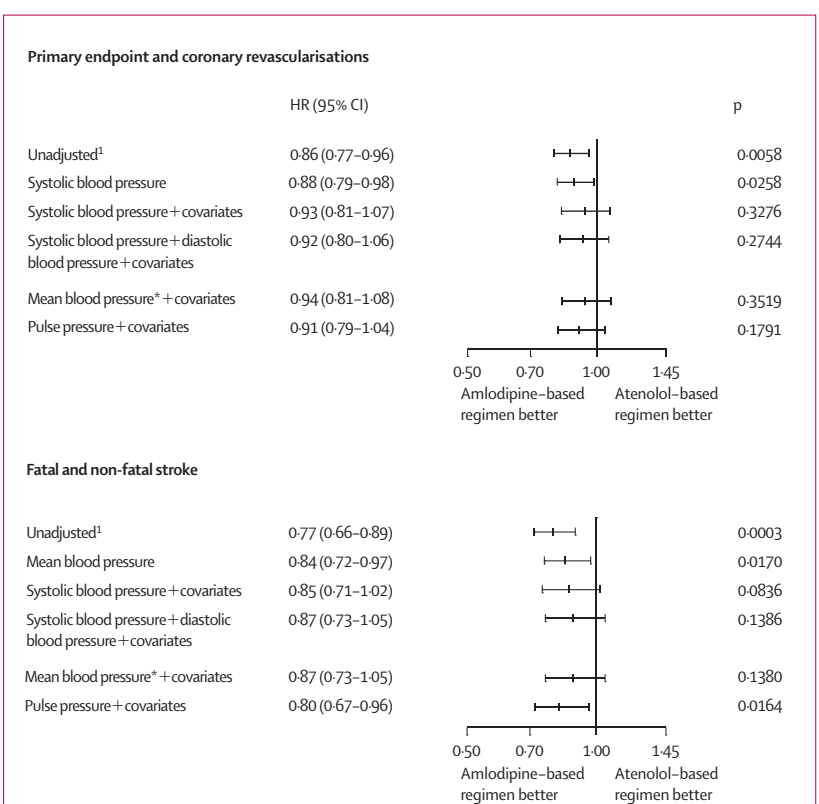

Figure 2: **Unadjusted and adjusted HRs for coronary and stroke events associated with amlodipine-based versus atenolol-based regimens**
Covariates at baseline: age and number of risk factors. Updated covariates: heart rate, glucose, HDL cholesterol, triglycerides, potassium, bodyweight. *Mean blood pressure=(systolic+diastolic blood pressure)/2.

faster pulse rate and, potentially, relatively beneficial effects on blood pressure, bodyweight, serum HDL cholesterol, triglycerides, creatinine and potassium, and fasting blood glucose. All of these variables are independent risk factors for various cardiovascular events.[4,9–14]

Our findings show that differences in serum HDL cholesterol had the biggest effect on differences in the rates of coronary events, but for stroke event rate differences only measures of blood pressure materially affected risk. Hence, in multivariate analyses, inclusion of all the biochemical variables, heart rate, and bodyweight added only slightly to the effect of adjusting for blood pressure alone with respect to risk of stroke, but for coronary events a greater additional effect was apparent. Overall, the previously reported significant differences in coronary or stroke event rates between the two groups in ASCOT-BPLA[1] were attenuated after full multivariate adjustment by about half for coronary events and by just under half for strokes, though after adjustment results were not significant. Adjustment procedures might not have been complete, resulting in residual confounding that would have caused an underestimation of the role of the explanatory variables considered. Alternatively, other variables that might have been differentially affected by the two antihypertensive regimens could explain the remaining differences, which in the case of stroke were considerable.

We were not sure a priori what measure of blood pressure would best predict cardiovascular events, but in ASCOT-BPLA it was pulse pressure. We were also unclear about the point or points at which in-trial differences in blood pressure should be considered. A priori, we thought that the accumulated mean blood pressure was most likely to indicate the blood pressure load throughout the trial (representing area under the curve) and as such was the preferred measure. This measure was confirmed as the best predictor of in-trial events (data not shown).

We noted no direct temporal association between differences in the coronary and stroke events in the two treatment groups and the size of the differences in blood pressure. The effects of antihypertensive treatment withdrawn at randomisation could have affected cardiovascular event rates during the first 6 months of the trial. However, patients with a history of CHD were excluded from the trial, and before randomisation β blockers were withdrawn gradually at the investigators' discretion. Moreover, after the first 6 months of the trial, differences in event rates and in blood pressure continued to be disassociated. Nevertheless, as previously reported,[15] early differential blood pressure control rates might have an important long-term effect on cardiovascular event rates that would not necessarily be apparent in the data as shown in figure 1. Unlike blood pressure, differences in the other variables considered were relatively constant after the first 6 months of the trial, and hence the need to use accumulated mean levels of these variables was less important than for blood pressure. In the HOPE trial,[16] the extent to which cardiovascular benefits attributed to the use of ramipril were dependent on the relatively small blood pressure reduction induced by this drug were assessed with results of observational studies, the results of meta-analyses of other trials, and in-trial data for blood pressure. The average of four in-trial blood pressure readings taken at baseline, 1 month, 2 years, and at study end were used in these HOPE analyses. However, by using the accumulated mean in these ASCOT-BPLA analyses we hoped that a more accurate indication of duration of exposure to the variable differences in blood pressure would be achieved.

In the VALUE trial,[8] an attempt was made to assess whether the better cardiovascular effects associated with amlodipine use than with valsartan was attributable to improved blood pressure lowering by use of the technique of serial median matching. This technique has various shortcomings,[17] not least the removal of the benefits of randomisation. However, we have tried to improve on the method used in the VALUE analyses by more closely matching those in the amlodipine-based group and those in the atenolol-based group by sequentially matching data for mean systolic blood pressure (the data were sufficiently normally distributed to allow the use of means rather than medians) at six sequential intervals after randomisation. The model also included adjustment for baseline age—which differed after the group selection process—and baseline number of risk factors—which was of large predictive importance (data not shown). The effect on HRs for coronary and stroke events with this technique was similar in magnitude to those seen after adjustment for differences in systolic blood pressure in the Cox regression analyses.

In summary, blood pressure was the biggest single contributor to stroke events, but differences in HDL cholesterol were more important for coronary events. Overall, after adjustment for the combined effect of differences in weight, heart rate, biochemical variables, and blood pressure, the HRs for differences in the effects of treatments on coronary and stroke events were no longer significant. This adjustment, however, only explained about 50% and 40% of the differences in coronary and stroke events, respectively. Some of the benefits of the amlodipine-based regimen might relate to differences in some variable linked to differences in blood pressure, but not measured or considered in these analyses—such as blood pressure variability or central blood pressure[18]—or to other as yet unidentified variables not related to blood pressure. Irrespective of the mechanism of action, the amlodipine-based regimen was more effective in reducing cardiovascular events than the atenolol-based regimen. Even if all of the cardiovascular benefits noted in ASCOT-BPLA

were attributed to more effective lowering of blood pressure, which seems unlikely, the results clearly suggest that for many patients benefits of the amlodipine-based regimen, in terms of lowering of blood pressure and prevention of cardiovascular events, are greater than the well established benefits of the standard combination therapy of β blockers plus a diuretic.

Contributors

N Poulter, H Wedel, B Dahlöf, and P Sever, 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 Beevers, M Caulfield, S E Kjeldsen, A Kristinsson, G T McInnes, J Mehlsen, M Nieminen, E O'Brien, and J Östergren, as members of the steering committee, approved the protocol and analysis plan, supervised the undertaking of the study, and had input to the report. S Pocock advised on the analysis plan and had input into the report.

Conflict of interest statement

N R Poulter, H Wedel, B Dahlöf, P Sever, D G Beevers, M Caulfield, S E Kjeldsen, A Kristinsson, G McInnes, J Mehlsen, M S Nieminen, E O'Brien, and J Östergren have served as consultants to and received travel expenses, payment for speaking at meetings, or funding for research from one or more pharmaceutical companies marketing 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. S Pocock has no conflict of interest.

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