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Effects of β blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke

Peter M Rothwell, Sally C Howard, Eamon Dolan, Eoin O'Brien, Joanna E Dobson, Bjorn Dahlöf, Neil R Poulter, Peter S Sever, on behalf of the ASCOT-BPLA and MRC Trial Investigators

Summary

Background **Analyses of some randomised trials show that calcium-channel blockers reduce the risk of stroke more than expected on the basis of mean blood pressure alone and that β blockers are less effective than expected. We aimed to investigate whether the effects of these drugs on variability in blood pressure might explain these disparities in effect on stroke risk.**

Methods **The Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm (ASCOT-BPLA) compared amlodipine-based regimens with atenolol-based regimens in 19 257 patients with hypertension and other vascular risk factors and the Medical Research Council (MRC) trial compared atenolol-based and diuretic-based regimens versus placebo in 4396 hypertensive patients aged 65–74 years. We expressed visit-to-visit variability of blood pressure during follow-up in the two trials as standard deviation (SD) and as transformations uncorrelated with mean blood pressure. For the ASCOT-BPLA we also studied within-visit variability and variability on 24-h ambulatory blood pressure monitoring (ABPM).**

Results **In ASCOT-BPLA, group systolic blood pressure (SBP) SD was lower in the amlodipine group than in the atenolol group at all follow-up visits ($p<0·0001$), mainly because of lower within-individual visit-to-visit variability. Within-visit and ABPM variability in SBP were also lower in the amlodipine group than in the atenolol group (all $p<0·0001$). Analysis of changes from baseline showed that variability decreased over time in the amlodipine group and increased in the atenolol group. The lower risk of stroke in the amlodipine group (hazard ratio=0·78, 95% CI 0·67–0·90) was partly attenuated by adjusting for mean SBP during follow-up (0·84, 0·72–0·98), but was abolished by also adjusting for within-individual SD of clinic SBP (0·99, 0·85–1·16). Findings were similar for coronary events. In the ABPM substudy, reduced variability in daytime SBP in the amlodipine group ($p<0·0001$) partly accounted for the reduced risk of vascular events, but reduced visit-to-visit variability in clinic SBP had a greater effect. In the MRC trial, group SD SBP and all measures of within-individual visit-to-visit variability in SBP were increased in the atenolol group compared with both the placebo group and the diuretic group during initial follow-up (all $p<0·0001$). Subsequent temporal trends in variability in blood pressure during follow-up in the atenolol group correlated with trends in stroke risk.**

Interpretation **The opposite effects of calcium-channel blockers and β blockers on variability of blood pressure account for the disparity in observed effects on risk of stroke and expected effects based on mean blood pressure. To prevent stroke most effectively, blood pressure-lowering drugs should reduce mean blood pressure without increasing variability; ideally they should reduce both.**

Funding **None.**

Introduction

Hypertension is the most prevalent treatable risk factor for stroke.[1,2] Randomised controlled trials have shown that blood-pressure lowering is effective in prevention of stroke, but recent meta-analyses have suggested that there are important drug-class effects, with calcium-channel blockers reducing stroke risk to a greater extent, and β blockers to a lesser extent, than expected by their observed effects on mean blood pressure.[3–10] Although it is widely believed that underlying usual blood pressure is of most importance in the aetiology of vascular disease,[11,12] and hence in the diagnosis and treatment of hypertension,[13–15] and this idea now underpins all major clinical guidelines,[16–19] it is possible that the differences between drug classes in their effects on stroke risk are caused by effects on some other parameter of blood pressure. Visit-to-visit variability in systolic blood pressure (SBP) is increased in cohorts at high risk of stroke,[20,21] reproducible over time,[22] and a powerful predictor of stroke independently of mean SBP.[23,24] Other evidence that instability and variability in SBP are important in causing end-organ damage is detailed in the accompanying review,[25] but more evidence of a causal link is needed.

The Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm (ASCOT-BPLA), a large randomised trial of a treatment regimen involving a β blocker (atenolol) compared with one involving a calcium-channel blocker (amlodipine), reported that an

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Stroke Prevention Research Unit, University Department of Clinical Neurology, John Radcliffe Hospital, Oxford, UK (Prof P M Rothwell FMedSci, S C Howard DPhil); **Stroke and Hypertension Unit, Connolly Hospital, Dublin 15, Ireland** (E Dolan MRCP); **Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Belfield, Dublin 4, Ireland** (Prof E O'Brien FRCP); **International Centre for Circulatory Health, Imperial College London, London, UK** (J E Dobson MSc, N R Poulter FMedSci, Prof P S Sever FRCP); **Department of Medicine, University of Goteborg, Goteborg, Sweden** (Prof B Dahlöf MD)

Correspondence to: Prof Peter M Rothwell, Stroke Prevention Research Unit, University Department of Clinical Neurology, Level 6, West Wing, John Radcliffe Hospital, Headington, Oxford OX3 9DU, UK **peter.rothwell@clneuro.ox.ac.uk**

amlodipine-based regimen was more effective than expected on the basis of changes in mean blood pressure in preventing stroke and coronary events than was an atenolol-based regimen.[3,4] This effect was also independent of changes in all other measured vascular risk factors during follow-up.[4] The Medical Research Council (MRC) trial investigated the effects of atenolol, a diuretic combination, or placebo in elderly patients with hypertension.[26] In both this trial and an associated trial in younger patients with hypertension,[27] treatment with a β blocker had no effect on stroke risk for the first 2–3 years of follow-up, although the early risk of stroke was reduced substantially in groups allocated to diuretics. Thereafter, the risk of stroke in the β-blocker groups was reduced. We suggest that this consistent time course in treatment effect in the MRC trials was caused by an initial increase in variability in blood pressure in the β-blocker groups, which was then reversed, probably by the addition of other classes of second-line drugs, the use of which was particularly high in the β-blocker groups in both MRC trials.

We aimed to investigate whether effects of β blockers and calcium-channel blockers on variability in blood pressure in the ASCOT-BPLA and the MRC trial could explain the unexpected effects of treatment on stroke risk.

	Atenolol-based regimen (n=9228)	Amlodipine-based regimen (n=9302)	Difference (95% CI)
Systolic blood pressure			
Mean	141·8 (13·0)	139·1 (11·1)	2·68 (2·58 to 2·78)
Maximum	164·2 (18·9)	157·4 (16·1)	6·80 (6·68 to 6·92)
Minimum	122·6 (13·5)	123·0 (11·8)	–0·40 (–0·50 to 0·30)
≥180 mm Hg*	1776 (19%)	851 (9%)	10·1% (9·1 to 11·1)
≥200 mm Hg*	438 (5%)	164 (2%)	3·0% (2·5 to 3·5)
Visit-to-visit variability			
SD	13·42 (5·77)	10·99 (4·79)	2·43 (2·36 to 2·50)
CV	9·41 (3·78)	7·87 (3·23)	1·54 (1·49 to 1·59)
VIM	13·13 (5·21)	11·14 (4·52)	1·99 (1·93 to 2·05)
ASV	13·79 (6·50)	11·28 (5·32)	2·51 (2·44 to 2·58)
RSD†	12·15 (5·13)	9·97 (4·32)	2·18 (2·12 to 2·24)
Within-visit variability			
SD	5·91 (0·02)	5·42 (0·02)	0·49 (0·44 to 0·54)
Range	5·16 (0·04)	4·85 (0·04)	0·31 (0·20 to 0·42)
White coat effect‡	11·21 (0·04)	10·28 (0·04)	0·93 (0·83 to 1·03)
Diastolic blood pressure			
Mean	82·1 (7·6)	80·2 (7·4)	1·98 (1·90 to 2·06)
Maximum	93·5 (9·6)	90·4 (9·0)	3·10 (3·00 to 3·20)
Minimum	71·8 (8·4)	70·8 (8·1)	1·00 (0·90 to 1·10)
≥100 mm Hg*	2257 (24%)	1326 (14%)	10·2% (9·1 to 11·3)
≥105 mm Hg*	1071 (12%)	568 (6%)	5·5% (4·7 to 6·3)
Visit-to-visit variability			
SD	6·98 (2·72)	6·26 (2·42)	0·72 (0·67 to 0·77)
CV	8·54 (3·30)	7·86 (3·04)	0·68 (0·63 to 0·73)
VIM	6·95 (2·66)	6·30 (2·41)	0·65 (0·60 to 0·70)
ASV	7·12 (3·14)	6·24 (2·70)	0·88 (0·83 to 0·93)
RSD†	6·20 (2·47)	5·47 (2·16)	0·73 (0·69 to 0·77)

Data are mean (SD) or number (%). Parameters were calculated using all measurements from 6 months onwards. p<0·0001 for comparison of each measure between the atenolol group and the amlodipine group. *number of patients with blood pressure measured at this level or higher on at least one clinic visit during follow-up. †9068 in the atenolol group and 9163 in the amlodipine group. ‡The first SBP measurement at each visit minus the mean of the second and third measurements, averaged across all visits for each patient. CV=coefficient of variation. VIM=variation independent of mean. ASV=average successive variability. RSD=residual SD.

Table 1: **Variability of clinic blood pressure by randomised treatment allocation in ASCOT-BPLA**

Methods

Cohorts

The methods of the ASCOT-BPLA were reported previously.[3,4] Patients aged 40–79 years who had hypertension and at least three other vascular risk factors but no coronary heart disease were randomly assigned, by use of the PROBE (prospective randomised open, blinded endpoint) design, to one of two antihypertensive regimens instead of any existing treatment for hypertension: amlodipine adding perindopril as needed (amlodipine-based) versus atenolol adding bendroflumethiazide and potassium as needed (atenolol-based). Treatment was titrated to achieve a clinic blood pressure of less than 140/90 mm Hg, or less than 130/80 mm Hg in patients with diabetes. Patients with total cholesterol 6·5 mmol/L or higher could also be randomly assigned to atorvastatin 10 mg daily or to placebo.[28]

At every follow-up visit (baseline, 6 weeks, 3 months, 6 months, and every 6 months thereafter) clinic blood pressure was measured three times in the sitting position after 5 min rest by use of a validated, semiautomated oscillometric device (Omron HEM-705CP; OMRON Healthcare, Kyoto, Japan).[29] Participants at four centres had yearly 24-h ambulatory blood pressure monitoring (ABPM) (SpaceLabs 90207, SpaceLabs, Hertford, UK).[30–32] No editing criteria were applied to individual readings. Mean time-weighted daytime (0900–2100 h), night-time (0100–0600 h) and 24-h, SBP, diastolic blood pressure (DBP), and pulse pressures were calculated.[32]

The methods of the MRC trial were reported previously.[26] Patients with mean SBP of 160–209 mm Hg and mean DBP of less than 115 mm Hg during an 8-week run-in period were randomly assigned, single-blind, to 50 mg atenolol daily versus 25 mg hydrochlorothiazide plus 2·5 mg amiloride daily (diuretic group) versus daily placebo. At randomisation and at each follow up visit (every 3 months to 24 months and then annually) clinic blood pressure was measured three times in the sitting position using a random zero sphygmomanometer, and the mean of the second two readings was recorded. Treatment was titrated to achieve a clinic blood pressure of less than 150 mm Hg if mean run-in SBP was 160–179 mm Hg, or less than 160 mm Hg if mean run-in SBP was 180 mm Hg or greater. When blood pressure was inadequately controlled in the atenolol group, the dose was increased to 100 mg. If further control was necessary in the atenolol group, hydrochlorothiazide was added. When blood-pressure control was inadequate in the diuretic group, atenolol

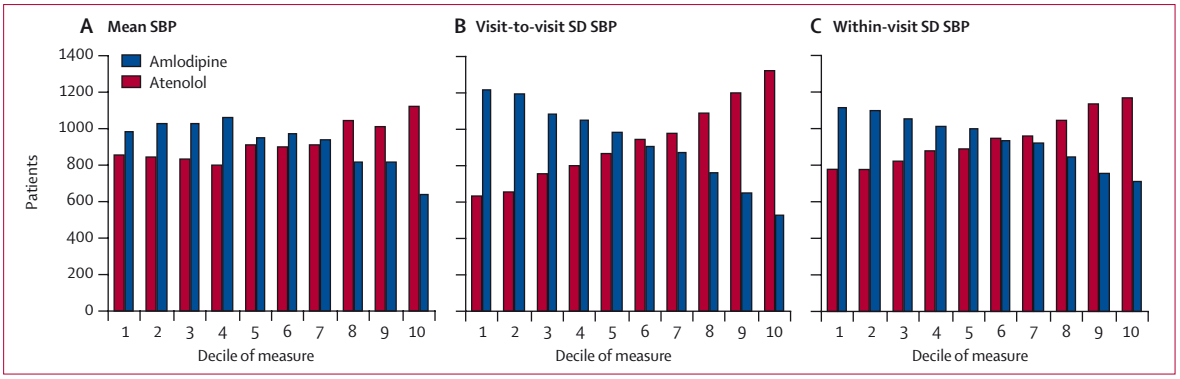

***Figure 1*: Distribution of patients in the two treatment groups in ASCOT-BPLA.**
Distribution according to deciles of mean SBP across all follow-up visits (A), within-individual variability (SD) in SBP across all follow-up visits (B), and within-visit variability (SD) SBP averaged across all follow-up visits (C).

was added. Thereafter, up to 20 mg of nifedipine daily could be added in both groups.

Statistical analysis

Within-individual visit-to-visit variability in SBP, DBP, and pulse pressure was expressed as the standard deviation (SD) and coefficient of variation (SD/mean) of readings taken over multiple follow-up visits (mean of the second and third readings at each visit was used in ASCOT-BPLA). If the coefficient of variation remained correlated with mean blood pressure, a transformation, defined as variation independent of mean (VIM), was derived as $SD/mean^x$, with x estimated from curve fitting. In ASCOT-BPLA, visit-to-visit heart-rate variability was also calculated with measurements (mean of second and third reading at each visit) from 6 months onwards. Because the SD and mean heart rate were correlated (r^2=0·34, p<0·0001), the coefficient of variation of mean heart rate was also calculated.

The trials aimed to achieve good early control of blood pressure; therefore, we took account of the initial reduction in blood pressure caused by treatment initiation and dose adjustment. First, some analyses of mean blood pressure and within-individual variability were only done on the basis of visits after the main initial fall in group blood pressure—from the 6-month visit in ASCOT-BPLA and from the 3-month visit in the MRC trial. Second, we used average successive variability (ASV, the average absolute difference between successive values), which is affected less by trends. Third, variability over and above any linear time trend in blood pressure was calculated with the residual SD: the square root of the total squared deviation of data points from a linear regression of blood pressure values against time, divided by (n–2), where n is the number of readings.

In the ASCOT-BPLA, analyses adjusted for known cardiovascular risk factors (eg, bodyweight and heart rate) showed that the reported treatment effects were independent of changes in these risk factors.[4] Thus, we did not adjust for these risk factors in the present analysis. We show in an accompanying paper that the effects of randomised treatment on within-individual vistit-to-visit variability in SBP in ASCOT-BPLA is independent of all the measured risk factors at baseline and during follow-up.[24]

Blood pressure parameters were compared by treatment group, both as means and as distributions across deciles. In ASCOT-BPLA, sensitivity analyses excluded patients with blood pressure readings taken after a vascular event and those with previous transient ischaemic attack (TIA) or stroke. Analyses were by intention to treat unless specified. On-treatment analyses were done in ASCOT-BPLA patients whose therapy type (atenolol-based or amlodipine-based) did not change after the 6-month visit and was uninterrupted for at least 42 days before each visit (protocol definition).

Within-visit variability in blood pressure was available in ASCOT-BPLA, which was expressed as the SD and range of the three readings taken at each visit, averaged across all visits from 6 months onwards. Within-visit coefficient of variation was used to assess how within-visit variability changed during follow-up. To differentiate between any effects of stopping previous drugs versus starting allocated treatment, a separate analysis was done in patients who had no blood pressure lowering drugs in the month prior to randomisation.

In the ASCOT-BPLA ABPM substudy, we also assessed mean blood pressure and variability in each treatment group. Analysis was stratified by daytime versus night-time and the morning surge (highest SBP from 0900 h to 1100 h minus the lowest from 0600 h to 0800 h) was also calculated. All analyses were done for the first ABPM during follow-up and for parameters averaged across all ABPMs during follow-up.

To establish to what extent differences in mean blood pressure and variability could account for the effect of randomised treatment on risk of stroke and coronary events in ASCOT-BPLA, hazard ratios (HRs) for treatment effect were derived from Cox models, and adjusted for

each measure of variability separately (in deciles and as continuous variables) and in conjunction with mean blood pressure.

In the MRC trial, the time-course of stroke risk in the atenolol group compared with the placebo and diuretic groups was assessed by testing for time-dependent variation in the treatment effect HRs. Differences between treatment groups in within-individual variability were assessed in the early phase of follow-up (nine visits before 21 months) versus the later phase (seven visits from 21 months onwards)—the 21-month cut-point was a compromise between a sufficient length of follow-up in the early phase and a sufficient number of visits in the later phase. Any time trends in group mean, SD, and coefficient of variation of blood pressure were also assessed: within-individual visit-to-visit variability in SBP usually explains about 50% of the group variance in SBP at each follow-up visit.[24] Within-individual variability changed over time in the atenolol group and therefore adjusted treatment effects could not be established.

	Systolic blood pressure		Diastolic blood pressure	
	HR (95% CI)	p	HR (95% CI)	p
Stroke				
Randomised treatment (Rx)	0·78 (0·67–0·90)	0·001	0·78 (0·67–0·90)	0·001
Blood pressure				
Rx + minimum	0·81 (0·70–0·94)	0·005	0·77 (0·66–0·90)	0·001
Rx + mean	0·84 (0·72–0·98)	0·025	0·77 (0·66–0·89)	0·001
Rx + maximum	0·88 (0·76–1·03)	0·10	0·78 (0·67–0·91)	0·001
Visit-to-visit blood pressure variability				
Rx + SD	0·94 (0·81–1·10)	0·47	0·85 (0·73–0·99)	0·038
Rx + CV	0·92 (0·79–1·07)	0·27	0·84 (0·72–0·97)	0·019
Rx + VIM	0·90 (0·77–1·04)	0·16	0·84 (0·72–0·98)	0·027
Rx + ASV	0·91 (0·78–1·07)	0·25	0·86 (0·74–1·00)	0·046
Rx + RSD	0·94 (0·80–1·10)	0·43	0·87 (0·74–1·02)	0·079
Rx + mean + SD	0·96 (0·82–1·12)	0·59	0·83 (0·71–0·97)	0·018
Rx + mean + CV	0·95 (0·82–1·11)	0·55	0·83 (0·71–0·97)	0·016
Rx + mean + VIM	0·96 (0·82–1·12)	0·58	0·83 (0·71–0·97)	0·015
Rx + mean + ASV	0·93 (0·80–1·09)	0·37	0·83 (0·72–0·97)	0·021
Rx + mean + RSD	0·95 (0·81–1·12)	0·54	0·84 (0·72–0·98)	0·030
Within-visit and visit-to-visit blood pressure variability				
Rx + within-visit SD	0·84 (0·72–0·98)	0·024	0·82 (0·71–0·95)	0·01
Rx + mean + VIM + WVSD	0·99 (0·85–1·16)	0·89	0·85 (0·73–0·99)	0·033
Coronary events				
Randomised treatment (Rx)	0·85 (0·77–0·94)	0·002	0·85 (0·77–0·94)	0·002
Blood pressure				
Rx + minimum	0·87 (0·79–0·97)	0·011	0·84 (0·76–0·93)	0·001
Rx + mean	0·88 (0·80–0·98)	0·019	0·82 (0·74–0·91)	<0·0001
Rx + maximum	0·92 (0·83–1·02)	0·11	0·84 (0·75–0·93)	0·001
Visit-to-visit blood pressure variability				
Rx + SD	1·00 (0·90–1·11)	0·96	0·92 (0·83–1·03)	0·14
Rx + CV	0·99 (0·89–1·10)	0·81	0·91 (0·82–1·01)	0·079
Rx + VIM	0·97 (0·87–1·08)	0·57	0·92 (0·83–1·02)	0·12
Rx + ASV	0·98 (0·88–1·09)	0·74	0·93 (0·84–1·03)	0·18
Rx + RSD	0·99 (0·89–1·11)	0·89	0·94 (0·84–1·04)	0·23
Rx + mean + SD	1·00 (0·90–1·11)	0·98	0·89 (0·80–0·98)	0·023
Rx + mean + CV	1·00 (0·90–1·11)	0·99	0·88 (0·80–0·98)	0·021
Rx + mean + VIM	1·00 (0·90–1·10)	0·99	0·89 (0·80–0·98)	0·024
Rx + mean + ASV	0·99 (0·89–1·10)	0·83	0·89 (0·81–0·99)	0·037
Rx + mean + RSD	1·00 (0·90–1·11)	0·97	0·90 (0·81–1·00)	0·056
Within-visit and visit-to-visit blood pressure variability				
Rx + within-visit SD	0·88 (0·79–0·97)	0·013	0·86 (0·78–0·96)	0·005
Rx + mean + VIM + WVSD	1·01 (0·91–1·12)	0·88	0·89 (0·80–0·99)	0·026

Parameters calculated using all blood pressure measurements from (and including) 6 months. Mean, SD, CV, ASV, and VIM are entered into the model as deciles. HR=hazard ratio. CV=coefficient of variation. VIM=variation independent of mean. ASV=average successive variability. RSD=residual SD. WVSD=within-visit SD

Table 2: **Effects of randomised treatment allocation in ASCOT-BPLA on risk of stroke and coronary events adjusted for parameters of blood pressure during follow-up**

Role of the funding source

ASCOT-BPLA and the MRC trial were investigator designed and led studies. None of the agencies that funded ASCOT-BPLA or the MRC trial had any input into the design, performance, analysis, or reporting of the analysis reported in this Article. The report was sent to the major sponsor of ASCOT-BPLA (Pfizer) for information before final acceptance for publication. The contractual agreement between Imperial College, London, UK and the sponsor allows the sponsor the opportunity to see and comment upon any paper, but not to exercise any right of veto. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

Results

Of 19 257 patients in ASCOT-BPLA, 18 530 (96·2%; 9228 in the atenolol group and 9302 in the amlodipine group) had at least two scheduled follow-up visits (median 10, IQR 9–11) from 6 months onwards. Baseline characteristics were balanced (webappendix p 1). From 6 months onwards, there were 350 strokes and 704 coronary events in the atenolol group, and 279 strokes and 611 coronary events in the amlodipine group. 11 019 patients met the criteria for the on-treatment analysis: 5195 in the atenolol group and 5824 in the amlodipine group. Results of analyses based on pulse pressure and SBP were similar (data not shown). Visit-to-visit SD SBP (r=0·37) and coefficient of variation SBP (r=0·17) were correlated with mean SBP and so VIM SBP (proportional to SD/mean$^{1·78}$) was calculated. VIM DBP was proportional to SD/mean$^{0·41}$.

Mean SBP from 6 months follow-up onwards was 2·68 mm Hg higher in the atenolol versus amlodipine group (p<0·0001; table 1), mainly because of a 6·80 mm Hg difference in maximum SBP (p<0·0001), with little difference in minimum SBP (table 1). Visit-to-visit variability in SBP was higher in the atenolol group than in the amlodipine group (table 1, figure 1), independently of any time trend in SBP (residual SD 12·15 [SD 5·13] *vs* 9·97 [4·32] mm Hg, p<0·0001). The odds of being in the top versus bottom decile of visit-to-

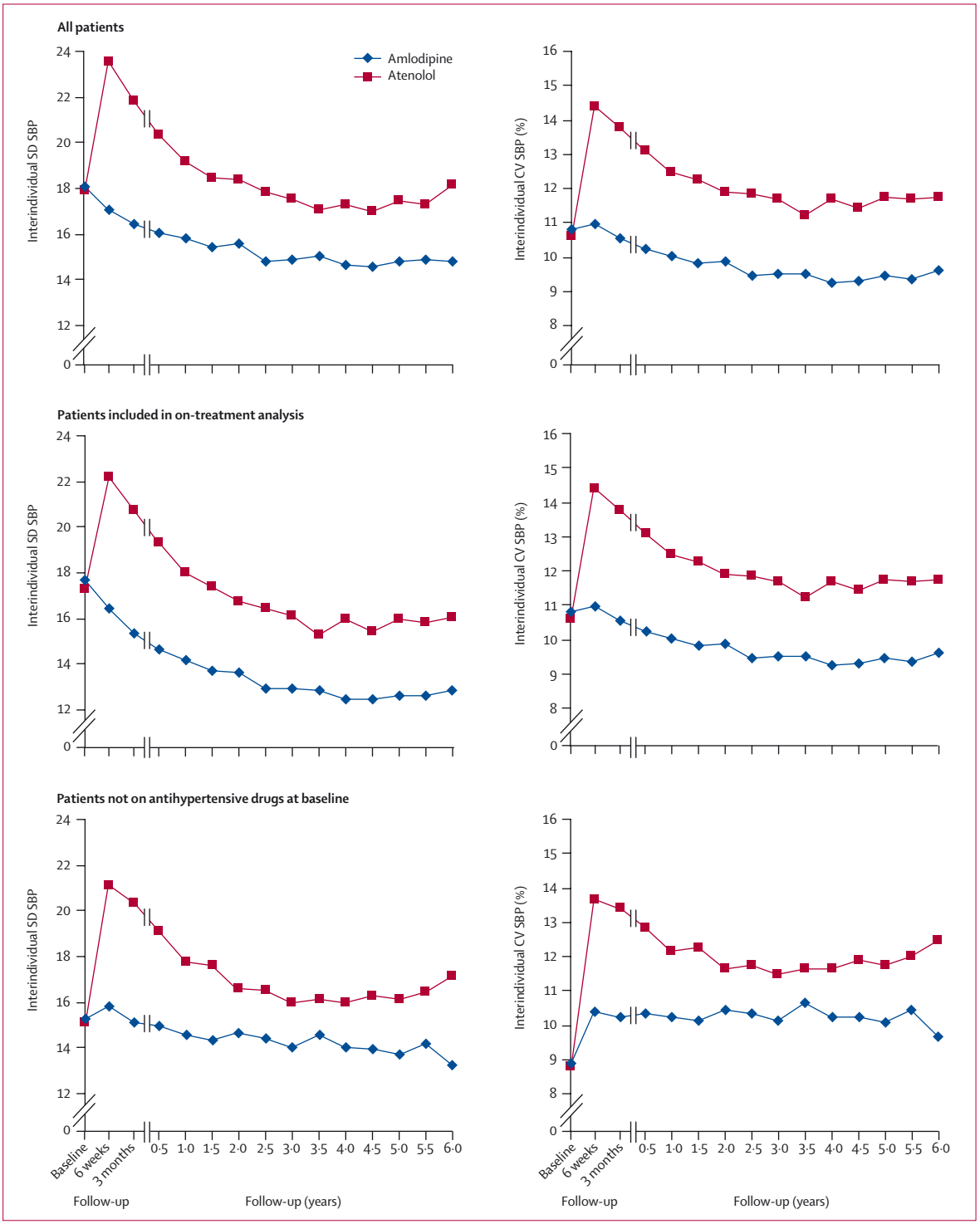

Figure 2: **Interindividual group distribution of measurements of SBP at baseline and at each follow-up visit in ASCOT-BPLA**
SBP=systolic blood pressure. CV=coefficient of variation.

visit SD for the atenolol versus amlodipine group was 4·76 (4·13–5·48, p<0·0001, figure 1), and over twice as many patients in the atenolol group (438 of 9228 [4·7%]) as in the amlodipine group (164 of 9302 [1·8%]) had an SBP of at least 200 mm Hg at some point after the 6-month follow-up (table 1). These results were not affected by exclusion of all visits after an outcome event or by exclusion of all patients with TIA or stroke before

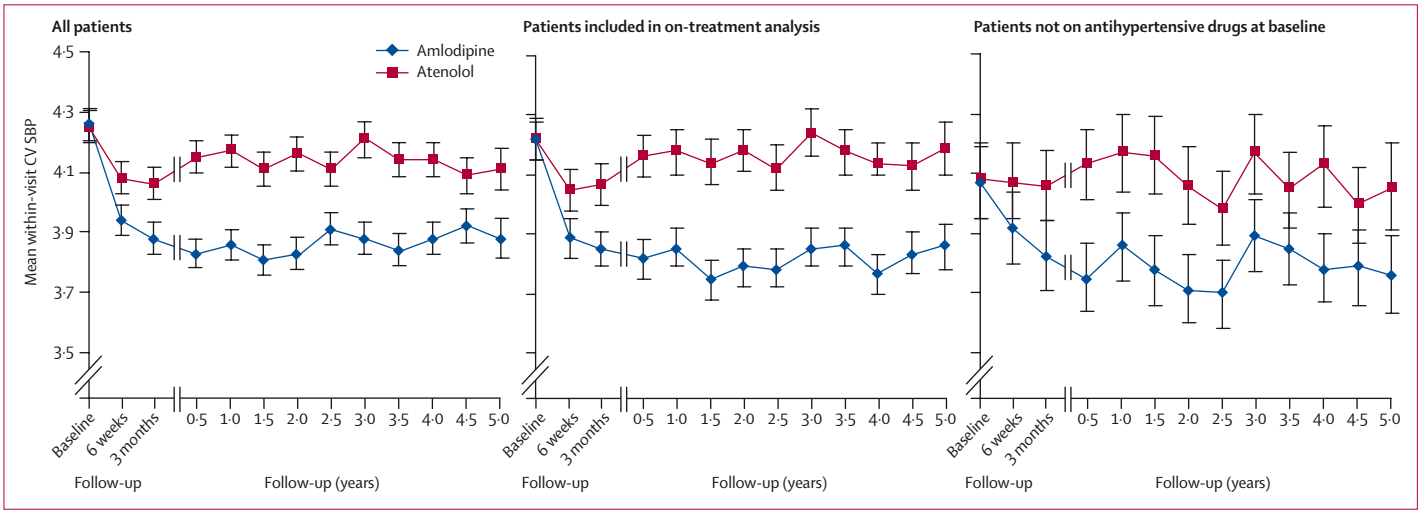

Figure 3: **Within-visit variability of systolic blood pressure in ASCOT-BPLA**
Mean CV SBP during follow-up in all patients, those in the on-treatment cohort, and those who were not on blood pressure lowering drugs before randomisation. Bars are 95% CI.

randomisation, and differences in variability were greater in the on-treatment group (webappendix p 2). Visit-to-visit SD and VIM SBP were also reduced in the group randomised to atorvastatin treatment versus placebo in the ASCOT substudy (difference in VIM 0·33 mm Hg, 95% CI 0·13–0·54; p=0·001), with a non-significantly larger effect in the amlodipine group compared with that in the atenolol group.

The treatment effect HR for risk of stroke in the amlodipine group compared with the atenolol group (0·78, 95% CI 0·67–0·90; p<0·0001; table 2) diminished less after adjustment for mean SBP during follow-up (0·84, 0·72–0·98, p=0·02) than after adjustment for visit-to-visit SD SBP (0·94, 0·81–1·10, p=0·47, table 2). The HR for stroke after 30 months changed from 0·83 (95% CI 0·68–1·02) to 0·97 (0·79–1·20) after adjusting for mean and SD SBP from 6 months to 30 months. The treatment HR for coronary events (0·85, 0·77–0·94, p=0·002) changed slightly after adjusting for mean SBP (0·88, 0·80–0·98; p=0·019; table 2) but was abolished by adjusting for SD SBP (1·00, 0·90–1·11, p=0·96). For both stroke and coronary events, adjustment for DBP variability had less effect on the HR compared with adjustment for SBP (table 2). Results were similar irrespective of whether blood pressure parameters were entered into the models as deciles or as continuous variables.

The group distributions of SBP at baseline and at follow-up are shown in webappendix p 6. Group SD SBP decreased after randomisation in the amlodipine group (figure 2), with a smaller change in coefficient of variation, whereas both SD and coefficient of variation increased in the atenolol group, and remained higher than in the amlodipine group for the duration of follow-up ($p<1\times10^{-20}$). The number of patients with SBP lower than 130 mm Hg was slightly greater in the atenolol group than in the amlodipine group, but the number of patients with very high SBP was substantially greater in the atenolol group than in the amlodipine group at each follow-up (webappendix p 3), particularly in the on-treatment cohort (eg, odds ratio for SBP ≥180 mm Hg at the 5-year follow-up 5·00, 95% CI 2·70–9·09; p<0·0001). Overall, 60% of the difference between the amlodipine group and the atenolol group in group SD at each follow-up was accounted for by the difference in within-individual visit-to-visit variability.

Mean heart rate was similar at baseline,[3,4] but decreased in the atenolol group and increased in the amlodipine group during follow-up (eg, 59·6 [10·7] in the atenolol group *vs* 77·2 [12·7] in the amlodipine group at 6 weeks and 61·3 [11·5] in the atenolol group *vs* 74·0 [12·6] in the amlodipine group at 18 months). There was no association between heart rate and SBP or DBP on follow-up in either treatment group, and no association with visit-to-visit variability in blood pressure (r=0·01 for SD SBP in both groups).

At each follow-up, within-visit variability in SBP was lower in the amlodipine group (figure 1). The mean within-visit SD was 5·91 (95% CI 5·87–5·94) and the mean range was 11·21 (11·14–11·29) in the atenolol group and 5·42 (5·38–5·45) and 10·28 (10·21–10·35) in the amlodipine group (both p<0·0001). In patients not on blood-pressure-lowering drugs before randomisation, within-visit coefficient of variation decreased in the amlodipine group but was unchanged in the atenolol group (figure 3). The treatment effect HRs for stroke and coronary events were only slightly attenuated by adjustment for within-visit variability (table 2).

In the ABPM substudy, 1905 patients had an average of 3·25 (range 1–10) ABPMs from 6 months. 157 patients had a stroke or coronary event. Baseline characteristics were similar between the treatment groups. Mean daytime SBP on ABPM was slightly higher in the amlodipine group than in the atenolol group during follow-up, whereas mean night-time SBP was lower

	Systolic blood pressure			Diastolic blood pressure		
	Atenolol group (n=947)	Amlodipine group (n=918)	p	Atenolol group (n=947)	Amlodipine group (n=918)	p
First ABPM after 6 months						
Daytime mean	134·9 (13·8)	135·9 (12·0)	0·11	78·4 (9·4)	80·1 (8·6)	<0·0001
Daytime SD	11·82 (3·80)	11·02 (3·43)	<0·0001	8·00 (2·52)	7·71 (2·48)	0·008
Daytime CV	8·76 (2·76)	8·14 (2·47)	<0·0001	10·34 (3·38)	9·69 (3·20)	<0·0001
Daytime ASV	10·81 (3·14)	10·56 (2·97)	0·087	7·39 (2·29)	7·40 (2·34)	0·99
Daytime maximum	158·5 (18·0)	158·3 (16·2)	0·76	94·1 (11·4)	95·8 (11·4)	0·001
Daytime minimum	114·0 (14·1)	116·3 (12·6)	<0·0001	63·9 (10·5)	66·3 (9·6)	<0·001
Night-time mean	125·1 (17·0)	123·5 (14·1)	0·028	69·2 (10·0)	70·2 (9·1)	0·015
Night-time SD	9·38 (3·75)	8·97 (3·60)	0·018	7·37 (2·90)	7·17 (2·69)	0·14
Night-time CV	7·56 (3·05)	7·30 (2·93)	0·060	10·85 (4·42)	10·34 (4·04)	0·009
Night-time ASV	9·77 (4·06)	9·37 (3·64)	0·032	7·71 (3·11)	7·51 (3·01)	0·17
Night-time maximum	140·6 (19·4)	138·7 (16·9)	0·027	81·3 (11·8)	82·1 (10·8)	0·15
Night-time minimum	110·3 (17·0)	109·5 (14·1)	0·29	57·7 (10·4)	59·0 (9·4)	0·004
Average of all ABPMs after 6 months						
Daytime mean	133·9 (11·6)	134·9 (10·4)	0·059	77·3 (8·3)	78·8 (8·0)	<0·0001
Daytime SD	11·74 (3·08)	11·14 (2·71)	<0·0001	7·94 (1·92)	7·75 (1·89)	0·03
Daytime CV	8·76 (2·22)	8·28 (1·97)	<0·0001	10·37 (2·61)	9·90 (2·45)	<0·0001
Daytime ASV	10·76 (2·50)	10·48 (2·21)	0·013	7·41 (1·74)	7·38 (1·80)	0·73
Daytime maximum	157·3 (14·7)	157·5 (13·2)	0·78	93·1 (9·5)	94·6 (9·5)	0·001
Daytime minimum	112·8 (11·5)	114·9 (10·6)	<0·0001	62·8 (8·7)	64·8 (8·1)	<0·001
Night-time mean	125·2 (14·7)	123·0 (12·7)	0·001	68·6 (8·7)	69·4 (8·3)	0·057
Night-time SD	9·32 (2·76)	9·02 (2·70)	0·016	7·34 (2·13)	7·28 (2·01)	0·51
Night-time CV	7·51 (2·22)	7·37 (2·16)	0·18	10·87 (3·35)	10·62 (3·09)	0·096
Night-time ASV	9·65 (2·95)	9·35 (2·72)	0·03	7·63 (2·41)	7·53 (2·30)	0·41
Night-time maximum	140·6 (16·3)	138·4 (14·5)	0·002	80·8 (9·8)	81·4 (9·3)	0·16
Night-time minimum	110·6 (14·4)	109·0 (12·3)	0·014	57·3 (8·9)	58·1 (8·3)	0·062

Data are mean (SD). ABPM=ambulatory blood pressure monitoring. CV=coefficient of variation. ASV=average successive variability.

Table 3: **Blood pressure parameters on ambulatory blood pressure monitoring by randomised treatment allocation in ASCOT-BPLA**

(table 3). Daytime minimum SBP was lower in the atenolol group but there was no difference in maximum blood pressure. The morning surge was similar in both groups (eg, mean first ABPM after 6 months 28·1 mm Hg [95% CI 26·9–29·3] in the amlodipine group *vs* 27·5 mm Hg [26·2–28·8] in the atenolol group), and was weakly correlated with visit-to-visit variability in clinic SBP (r^2=0·02 for SD SBP).

Intra-ABPM variability in SBP (SD of daytime SBP) correlated with mean daytime SBP (r=0·26, p<0·0001), but coefficient of variation of daytime SBP was only weakly associated (r=–0·08, p=0·01). Intra-ABPM SD and coefficient of variation of daytime SBP were lower during follow-up in the amlodipine group (figure 4), with a similar trend in coefficient of variation of night-time SBP (table 3), but a smaller difference in daytime ASV. Differences in visit-to-visit variability in clinic blood pressure in the ABPM substudy cohort were similar in size to those in the main study: (SD SBP 12·70 mm Hg in the atenolol group *vs* 10·38 mm Hg in the amlodipine group; VIM SBP 12·58 mm Hg in the atenolol group *vs* 10·65 mm Hg in the amlodipine group; both p<0·0001). Results were much the same for DBP (table 3).

Patients in one centre also had ABPM during the 6 months before randomisation (78 in the atenolol group and 80 in the amlodipine group). Average intra-ABPM coefficient of variation of daytime SBP increased after randomisation in the atenolol group (7·66 before randomisation *vs* 8·74 after randomisation, p<0·0001), but not in the amlodipine group (8·25 *vs* 8·45; p=0·49).

In the ABPM substudy the treatment effect HR for risk of any stroke or coronary event during follow-up in the amlodipine compared with the atenolol group (0·77, 95% CI 0·56–1·05) was little changed by adjustment for mean daytime SBP (0·76, 0·57–1·04), mean night-time time SBP (0·78, 0·57–1·07), or minimum SBP or DBP (webappendix p 4). Adjustment for coefficient of variation of daytime SBP on ABPM had a small effect (HR 0·83, 95% CI 0·61–1·14), but adjustment for visit-to-visit coefficient of variation of clinic SBP had the largest effect (0·98, 0·71–1·36). Results were similar when the outcome of all cardiovascular events and procedures was used (webappendix p 4), for which the unadjusted treatment effect was statistically significant.

In the MRC trial there were no treatment-group differences in group SD and coefficient of variation SBP

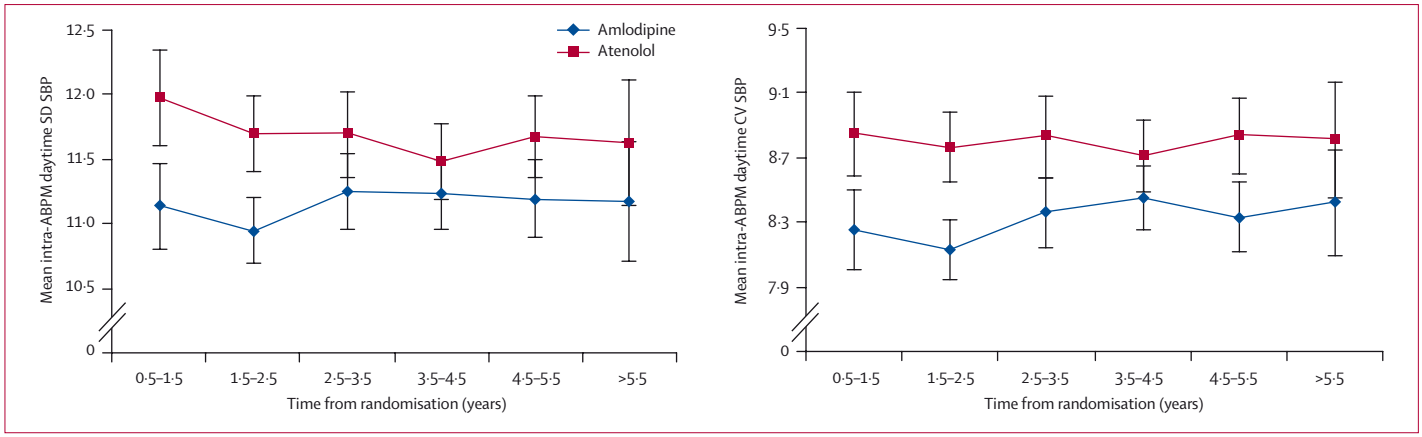

Figure 4: **Variability in daytime systolic blood pressure on ambulatory blood pressure monitoring by randomised treatment allocation in ASCOT-BPLA**
Daytime SD SBP (A) and CV SBP (B) from annual ABPM recordings during follow-up in ASCOT-BPLA. ABPM=ambulatory blood pressure monitoring. SBP=systolic blood pressure. CV=coefficient of variation. ASCOT-BPLA= Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm. Bars are 95% CI.

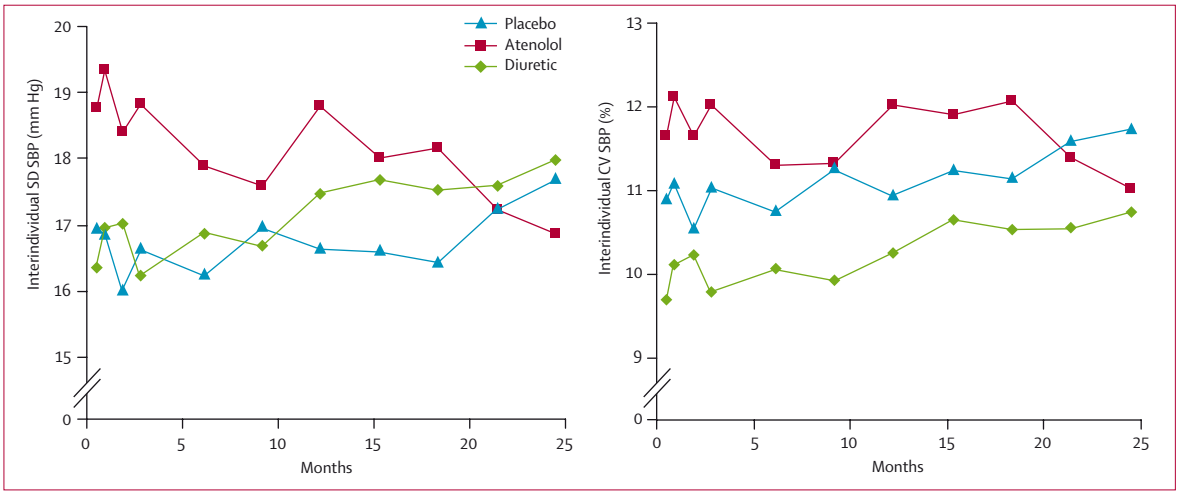

Figure 5: **Interindividual group SD and CV systolic blood pressure during the initial follow-up phase by randomised treatment allocation in the MRC trial.**
CV=coefficient of variation. SBP=systolic blood pressure.

at baseline, but there were significant differences during the initial follow-up phase (0–24 months, figure 5). Both the SD and the coefficient of variation were initially increased in the atenolol group ($p<0·0001$ for difference in group SD for all but one follow-up to 18 months for atenolol group *vs* diuretic group), but were no longer different to the other groups by the end of the period. There were no differences between the groups at follow-ups between months 18 and 24 (figure 5).

Visit-to-visit SD SBP was positively correlated ($r=0·12$) with mean SBP and coefficient of variation was negatively correlated ($r=-0·11$), and so VIM SBP (proportional to SD/mean$^{0·49}$) was calculated. All measures of SBP variability were higher in the atenolol group than in the diuretic group and placebo group in the early phase (before the 21 month follow-up), but these differences were no longer present in the later phase (from 21 months onwards, table 4). Mean SBP was higher in the atenolol group (156·61 mm Hg [SD 12·1]) than in the diuretic group (151·2 [12·1]) in the early phase, mainly because of a higher maximum SBP in the atenolol group (178·2 [16·1]) than in the diuretic group (168·8 [15·7]) as a consequence of increased variability, with little difference in minimum SBP (135·9 [13·5] in the atenolol group *vs* 134·2 [12·7] in the diuretic group). Mean and maximum SBP were more similar between the two groups in the later phase when variability no longer differed. Findings were similar for DBP (webappendix p 5).

The risk of stroke in the atenolol group compared with that in the placebo group followed the same time course as the changes in variability in SBP, with significant time dependence of treatment effect ($p=0·008$). The risk of stroke was higher with atenolol than with placebo in the first 2 years (HR 1·31, 95% CI 0·81–2·10), despite the substantially lower mean blood pressure in the atenolol group (table 4). By contrast, the risk of stroke was lower in the atenolol group than in the placebo group after 2 years follow-up (0·62, 0·40–0·94), during which time

the difference in mean blood pressure remained large, but variability no longer differed. In the comparison of atenolol with diuretic, the risk of stroke was again high in the first 2 years (1·83, CI 0·98–3·42) and low at follow-up after 2 years (0·93, 0·56–1·56).

Discussion

In the accompanying Article on the prognostic implications of blood pressure variability,[24] increased visit-to-visit variability in blood pressure was a strong predictor of the long-term risk of stroke after TIA, and patients with good control of mean blood pressure but a high residual variability in SBP had a five times higher risk of stroke than did those with low residual SBP variability in ASCOT-BPLA. In this paper, we have added to the evidence that the link between variability in blood pressure and risk of stroke is likely to be causal. First, atenolol-based treatment and amlodipine-based treatment had opposite effects on within-individual variability in blood pressure (within-visit, visit-to-visit, and ABPM), independently of their effects on mean blood pressure. Second, the reduced event rates in the amlodipine group in ASCOT-BPLA, which could not be fully accounted for by changes in mean blood pressure or in other risk factors,[4] can be explained by effects on visit-to-visit variability in SBP. Third, in the MRC trial, atenolol increased visit-to-visit variability in SBP compared with placebo, whereas the diuretic combination did not, and temporal trends in variability in the atenolol group (probably caused by add-on use of thiazides and nifedipine) were associated with stroke risk.

We cannot conclude that the effects of the specific drugs used in the ASCOT-BPLA and MRC trials on variability are necessarily class effects. However, the accompanying meta-analysis[36] of all published data on group SD in SBP in all trials of blood-pressure-lowering drugs shows consistent drug-class effects, with reduced group SD on calcium-channel blockers and increased group SD on β blockers. The mechanisms underlying these effects on variability in blood pressure are uncertain,[25] but changes in peripheral vascular resistance are perhaps the most likely explanation: atenolol reducing arterial compliance by vasoconstriction and amlodipine increasing it by vasodilatation. Structural remodelling of the vasculature might also be responsible,[25] but the early effects of treatment on variability in ASCOT-BPLA and the MRC trial, and the immediate reduction in blood pressure variability on home blood-pressure-monitoring after starting calcium-channel blockers[25] show that short-term mechanisms are mainly responsible. Reduction in heart rate is also a possible explanation for the effect of atenolol, but heart rate and blood-pressure variability were not correlated in ASCOT-BPLA or the MRC trial.

Amlodipine also reduced central blood pressure in ASCOT-BPLA,[33] but this did not explain the treatment effect, and has since been accounted for by differences in heart rate,[34] which were not correlated with variability in blood pressure and did not account for the effect of treatment on risk of vascular events in our analyses. Benefit from the amlodipine-based regimen in ASCOT-BPLA was also independent of baseline pulse rate.[35] The longer half-life of amlodipine could affect variability, but most clinics took place at similar times of day, patients usually took medication in the morning, and the extent of the morning-surge was much the same in both treatment groups. Moreover, the effect of calcium-channel blockers on variability in the accompanying systematic review of other trials was independent of drug half-life.[36] Differences in compliance with study drugs are also unlikely to be confounding given that the difference between treatment groups in visit-to-visit variability was most notable in the stringently-defined on-treatment cohort and that within-visit and ABPM variability were both also reduced in the amlodipine group. The smaller benefit from amlodipine for coronary events than for stroke might be because of their opposite effects on heart rate, although neither mean heart rate nor variability had prognostic value,[24] and neither accounted for the treatment effect in ASCOT-BPLA. Alternatively, mean SBP is a stronger risk factor for stroke than for coronary heart disease and so this might also be the case for variability.

Both within-visit variability in sitting SBP and daytime variability in SBP on ABPM were lower in the amlodipine

	Diuretic	p	Atenolol	p	Placebo
On the basis of nine visits from 2 weeks until 18 months*					
Mean	151·2 (12·1)	<0·001	156·6 (12·1)	<0·001	167·4 (12·0)
SD	11·64 (4·39)	0·004	14·38 (5·34)	<0·001	12·12 (4·48)
CV	7·69 (2·77)	<0·001	9·18 (3·33)	<0·001	7·26 (2·70)
VIM	11·98 (4·38)	0·60	14·55 (5·31)	<0·001	11·89 (4·38)
ASV	12·40 (5·09)	<0·001	14·71 (5·65)	<0·001	13·20 (5·30)
RSD	10·97 (4·36)	<0·001	13·11 (4·88)	<0·001	11·54 (4·28)
Maximum	168·8 (15·7)	<0·001	178·2 (16·1)	<0·001	185·4 (14·6)
Minimum	134·2 (12·7)	<0·001	135·9 (13·5)	<0·001	149·4 (13·7)
Peak	17·54 (8·12)	0·12	21·54 (9·56)	<0·001	18·01 (7·87)
Trough	17·03 (7·49)	0·001	20·75 (8·87)	<0·001	17·98 (7·79)
On the basis of seven visits from 21 months until end of follow-up‡					
Mean	150·3 (13·6)	<0·001	151·8 (13·0)	<0·001	166·3 (14·2)
SD	12·11 (5·82)	0·018	12·30 (6·24)	0·12	12·68 (6·21)
CV	8·07 (3·86)	0·013	8·13 (4·13)	0·005	7·69 (3·83)
VIM	12·34 (5·89)	0·55	12·50 (6·32)	0·95	12·48 (6·12)
ASV	13·88 (7·21)	0·021	14·02 (7·97)	0·074	14·59 (7·87)
RSD	11·28 (5·80)	0·017	11·42 (6·01)	0·070	11·87 (6·09)
Maximum	164·9 (16·5)	<0·001	166·8 (15·8)	<0·001	181·5 (16·4)
Minimum	135·9 (14·6)	<0·001	137·3 (14·7)	<0·001	151·1 (16·5)
Peak	14·67 (8·00)	0·12	14·99 (8·47)	0·55	15·19 (8·40)
Trough	14·39 (7·69)	0·02	14·53 (8·03)	0·061	15·15 (8·30)

Data are mean (SD). p values are for comparison of each treatment group with placebo. *1056 in the diuretic group, 1080 in the atenolol group, and 2178 in the placebo group. †922 in the diuretic group, 927 in the atenolol group, and 1899 in the placebo group. MRC=Medical Research Council. CV=coefficient of variation. VIM=variation independent of mean. ASV=average successive variability. RSD= residual SD.

Table 4: **Visit-to-visit systolic blood pressure variability by randomised treatment group in the MRC trial**

group than in the atenolol group in the ASCOT-BPLA but were weaker predictors of vascular events than visit-to-visit variability[24] and accounted less well for the reduced event rate in the amlodipine group, suggesting that the larger variations in blood pressure that are seen from visit-to-visit better reflect the factor or factors that are causally related to the risk of vascular events. Indeed, in the analysis of ASCOT-BPLA ABPM data, ASV SBP did not predict stroke,[24] and accounted less well for the clinical benefit of amlodipine versus atenolol than did SD or coefficient of variation SBP. ASV measures short-term changes between adjacent blood pressure readings, whereas SD or coefficient of variation are influenced by changes over hours, give more weight to extreme values, and are therefore more sensitive to instability in blood pressure related to specific stressors. Of note, maximum SBP reached was more predictive of stroke than mean SBP in ASCOT-BPLA, on the basis of either clinic or ABPM measures, and in the UK-TIA trial.[24] Atenolol was associated with lower minimum daytime SBP and DBP, possibly because of a higher frequency of postural falls, which in the case of DBP might reduce coronary perfusion. Further research is needed to establish whether variability in DBP might be more closely associated with risk of coronary events than stroke.

Our analyses of ASCOT-BPLA had some limitations. First, the treatment group comparison was not only between atenolol and amlodipine. The trial protocol required that high blood pressure at any follow-up should trigger either an increase in medication or an additional clinic visit,[3,4] and increased variability and high maximum blood pressure were therefore associated with use of additional drugs in both treatment groups.[24] The time course of within-visit and ABPM variability in SBP during follow-up suggests that addition of bendroflumethiazide and other add-on drugs in the atenolol group reduced the high initial variability of SBP. Second, interpretation of apparent correlates with treatment effects in randomised trials on the basis of data collected after randomisation is not straightforward and is potentially subject to bias. However, our approach is not new in this respect. Many previous investigators have attempted to relate changes in mean blood pressure on follow-up to randomised treatment in similar trials, which will be subject to the same potential biases. Moreover, all of our main analyses were done on an intention-to-treat basis, which reduces the risk of bias, and there were no differences between the treatment groups in loss to follow-up. There were also no differences in the number of missing follow-up visits (3·7% overall), and so any bias in estimation of visit-to-visit variability is unlikely.

Third, our findings are not proof of a causal link between variability in blood pressure and vascular risk. However, the fact that visit-to-visit variability accounts for the previously unexplained treatment effects in ASCOT-BPLA and other trials,[25,36] and can explain the greater reduction in stroke risk with calcium-channel blockers than expected on the basis of changes in mean blood pressure and the less than expected reduction with β blockers, supports a causal link. The accompanying review provides other supporting evidence.[25] A collaboration to study within-individual variability in blood pressure in all available trials will assess the generalisability of our findings in the ASCOT-BPLA and MRC trial (further information available from corresponding author). However, assuming that our findings are generalisable, absolute proof of a causal association would require a trial of an intervention that only affected variability in blood pressure, with no effects on mean blood pressure or other known and as yet unknown vascular risk factors. Such an intervention is unlikely to exist, although in stroke-prone spontaneously hypertensive rats, increased short-term variability in blood pressure causes ischaemic stroke and other end-organ damage,[37] and experimental sinoaortic denervation (which substantially increases variability in blood pressure without changing mean blood pressure) also causes end-organ damage,[38] even at normal mean blood pressure.[38,39]

Our analyses of the MRC trial also had limitations. Most importantly, we did not have data for individual patients on add-on treatment with other drugs, and so we cannot be certain that the parallel reductions in group SD SBP and within-individual variability after the initial follow-up period in the atenolol group were due to the initiation of other drug classes. However, use of other drugs was particularly high in the atenolol group compared with the diuretic group (52% *vs* 38% at 5 years),[26] and the add-on drugs specified in the protocol (particularly nifedipine) would have reduced variability. Irrespective of the explanation, the temporal association between the reductions in variability and in stroke risk in the atenolol group is consistent with the primary hypothesis,[25] and the initial increase in variability on atenolol versus placebo confirms the suggestion from ASCOT-BPLA that atenolol increases variability.

The effect of the diuretic combination versus placebo on variability in blood pressure in the MRC trial is less clear. Absolute within-individual variability in SBP (ie, SD and ASV) was lower in patients receiving the diuretic combination than in those on placebo, but there was no difference in variability relative to the lower mean SBP (ie, coefficient of variation). Analysis of group coefficient of variation SBP in other trials suggests that thiazide and thiazide-like diuretics might reduce variability,[35] but to a lesser extent than calcium-channel blockers.

Although more work is needed to fully understand the nature and consequences of variability in blood pressure, our findings have implications for the routine management of hypertension, choice of medication, design and reporting of trials, and drug development. We have shown that effects of specific agents on within-individual variability of blood pressure can explain differences in clinical efficacy, consistent with the findings in the accompanying systematic review of all published data on group distributions of blood pressure

during follow-up in trials of blood pressure-lowering drugs.[36] Data on blood pressure during follow-up should be reported in more detail in future trials, and stabilisation of blood pressure is a potentially important target for drug development and combination therapy. New drugs or combinations of drugs that reduce variability even more effectively than calcium-channel blockers could have a great effect on risk of stroke. Analysis of treatment effects in relation to variability in blood pressure assessed in a pre-randomisation run-in period might also be informative.

Contributors

PMR derived the hypothesis, planned and supervised the analyses, and wrote the paper. SCH and JED did the analyses. ED and EO'B were investigators in the ASCOT ABPM study, advised on analyses of the ABPM data, and commented on drafts of the manuscript. NRP and PSS advised on analyses of the main ASCOT-BPLA cohort, designed the ASCOT-BPLA, along with BD, and commented on successive drafts of the manuscript.

ASCOT-BPLA ABPM collaborators

Ireland Molecular and Cellular Therapeutics and RCSI Research Institute, Royal College of Surgeons in Ireland, Dublin (Alice V Stanton). *UK* National Heart and Lung Institute at St Mary's Hospital, Imperial College London (Simon Thom), St Bartholomew's Hospital, London (Mark Caulfield, David Collier), University of Glasgow, Glasgow (Gordon McInnes).

Conflicts of interest

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