Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension

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Summary

Background **The mechanisms by which hypertension causes vascular events are unclear. Guidelines for diagnosis and treatment focus only on underlying mean blood pressure. We aimed to reliably establish the prognostic significance of visit-to-visit variability in blood pressure, maximum blood pressure reached, untreated episodic hypertension, and residual variability in treated patients.**

Methods **We determined the risk of stroke in relation to visit-to-visit variability in blood pressure (expressed as standard deviation [SD] and parameters independent of mean blood pressure) and maximum blood pressure in patients with previous transient ischaemic attack (TIA; UK-TIA trial and three validation cohorts) and in patients with treated hypertension (Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm [ASCOT-BPLA]). In ASCOT-BPLA, 24-h ambulatory blood-pressure monitoring (ABPM) was also studied.**

Findings **In each TIA cohort, visit-to-visit variability in systolic blood pressure (SBP) was a strong predictor of subsequent stroke (eg, top-decile hazard ratio [HR] for SD SBP over seven visits in UK-TIA trial: 6·22, 95% CI 4·16–9·29, p<0·0001), independent of mean SBP, but dependent on precision of measurement (top-decile HR over ten visits: 12·08, 7·40–19·72, p<0·0001). Maximum SBP reached was also a strong predictor of stroke (HR for top-decile over seven visits: 15·01, 6·56–34·38, p<0·0001, after adjustment for mean SBP). In ASCOT-BPLA, residual visit-to-visit variability in SBP on treatment was also a strong predictor of stroke and coronary events (eg, top-decile HR for stroke: 3·25, 2·32–4·54, p<0·0001), independent of mean SBP in clinic or on ABPM. Variability on ABPM was a weaker predictor, but all measures of variability were most predictive in younger patients and at lower (<median) values of mean SBP in every cohort.**

Interpretation **Visit-to-visit variability in SBP and maximum SBP are strong predictors of stroke, independent of mean SBP. Increased residual variability in SBP in patients with treated hypertension is associated with a high risk of vascular events.**

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Introduction

Hypertension is the most prevalent treatable risk factor for stroke and other vascular events.[1,2] Underlying usual blood pressure (conceived as the true underlying average blood pressure over a period of time) is widely considered to be of primary importance in the cause of vascular disease,[3,4] and hence in diagnosis and treatment of hypertension,[5–7] and this notion underpins all major clinical guidelines.[8–11] Yet, the mechanisms by which raised blood pressure causes stroke and other vascular events are poorly understood. Mean blood pressure is clearly important, but other factors, such as variability or maximum blood pressure reached, might also play a part,[12] particularly at older ages when most vascular events occur.[13] However, visit-to-visit variability in blood pressure is usually dismissed as random, noteworthy only as an obstacle to the reliable estimation of usual blood pressure.[14–18] Consequently, although substantial visit-to-visit variability in clinic blood pressure is common,[19–24] episodic hypertension tends not to be treated.[12] In patients with occasional high blood pressure, guidelines recommend continued monitoring or 24-h ambulatory blood-pressure monitoring (ABPM),[8–11] with treatment decisions based on mean blood pressure. Yet, although situational variability in blood pressure has been studied,[25,26] the prognostic value of visit-to-visit variability and episodic hypertension in the same setting has not been reliably established.

We showed previously that visit-to-visit variability in blood pressure is increased in cohorts at high risk of stroke,[19,20] that it is consistent within individuals over time (ie, not random),[27] and that it seems to predict stroke independently of mean systolic blood pressure (SBP).[28] Prompted by these observations and by shortcomings in the usual blood-pressure hypothesis,[12] we aimed to reliably establish the prognostic significance of visit-to-visit variability in blood pressure, maximum blood pressure reached, episodic hypertension, and residual variability in blood pressure in patients already receiving antihypertensive drugs. We studied a large cohort of patients with previous transient ischaemic attack (TIA; UK-TIA aspirin trial),[29] with validation in three similar

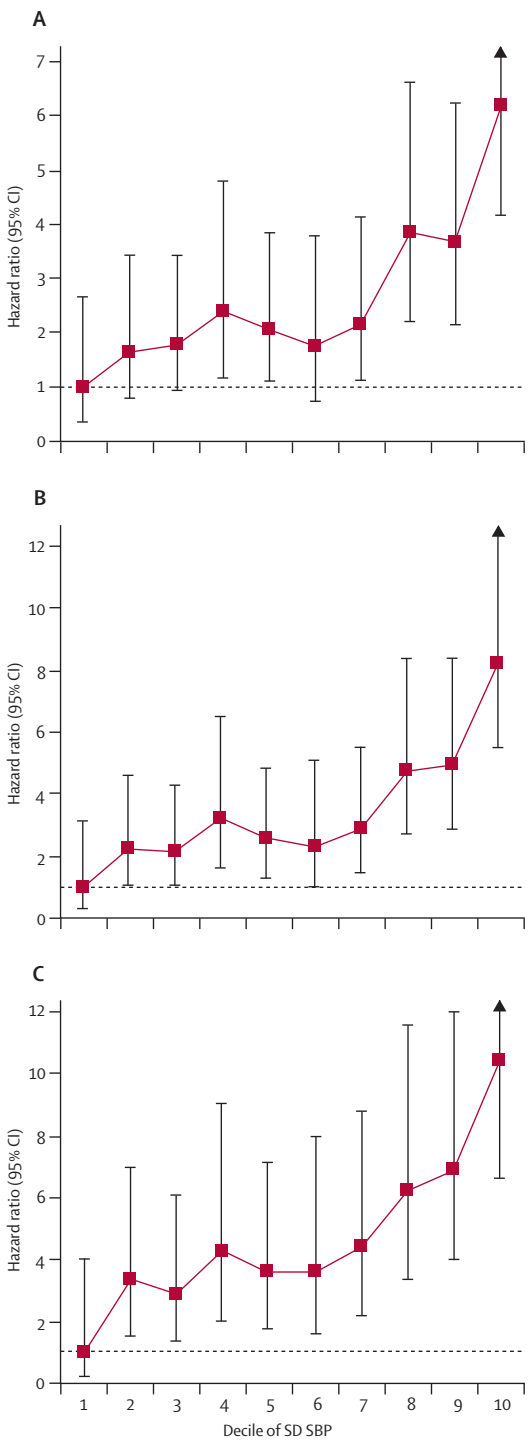

Figure 1: **Hazard ratios for risk of any subsequent stroke by deciles of SD SBP based on the first seven measurements (baseline to 2 years) in the UK-TIA trial, with the first decile as the reference category**
Analyses for all patients (A), excluding those with a past history of stroke (B), and excluding those with either a past history of stroke or infarction on baseline CT brain imaging (C). SBP=systolic blood pressure.

cohorts,[30–32] and a broad population of patients with hypertension in the Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm (ASCOT-BPLA).[32,33] In ASCOT-BPLA, we also measured the prognostic value of short-term variability during individual visits and on 24-h ABPM.

Methods

Cohorts

The UK-TIA aspirin trial was a double-blind randomised trial of aspirin (1200 mg *vs* 300 mg *vs* placebo) in 2435 patients with a recent TIA or ischaemic stroke, which was undertaken from 1979 to 1985.[29] Visit-to-visit variability in blood pressure was not affected by the randomised treatment.[27] To avoid confounding due to any effect of recent stroke on variability in blood pressure,[34,35] analysis was confined to 2006 patients presenting with TIA only. Sitting blood pressure was measured once at every 4-month follow-up visit with a mercury sphygmomanometer and with the patient rested. Details of all vascular events and deaths were recorded during follow-up, and reviewers were masked to treatment allocation and data for blood pressure.

The main results from the UK-TIA analysis were tested in three other TIA and stroke cohorts. The first cohort was from the European Stroke Prevention Study (ESPS-1),[30] in which 2500 patients were randomly assigned to dipyridamole 75 mg plus aspirin 325 mg versus placebo three times daily. Blood pressure (mean of left and right arm; sitting after rest; mercury sphygmomanometer) was measured at follow-up visits every 3 months for 2 years. Because dipyridamole is itself vasoactive, we studied only the placebo group. The second cohort was from the Dutch TIA trial,[31] in which 3150 patients were randomly assigned to aspirin 30 mg versus aspirin 283 mg. A subgroup of 1473 patients was randomly assigned to atenolol 50 mg versus placebo. Blood pressure (sitting after rest; mercury sphygmomanometer) was measured at follow-up visits every 4 months for a mean of 2·6 years. The third cohort was from the ASCOT-BPLA trial,[32,33] which included 2011 patients with previous TIA or stroke.

The generalisability of the findings in the TIA cohorts was tested in the main ASCOT-BPLA trial.[32,33] Patients with hypertension, aged 40–79 years, with three or more other vascular risk factors, but no coronary heart disease, were randomly assigned, by the PROBE design, to one of two antihypertensive regimens instead of any existing antihypertensive drugs: 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. At every 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 with a validated, semiautomated oscillometric device (Omron HEM-705CP, OMRON Healthcare, Kyoto, Japan).[36] Participants at four centres had yearly 24-h ABPM (SpaceLabs 90207, SpaceLabs, Hertford, UK) with blood-pressure readings every 30 min.[37–39] No editing criteria were applied to individual readings. Mean time-weighted daytime (0900–2100 h), night-time (0100–0600 h), and 24-h SBP and diastolic blood pressure (DBP) were calculated.[39]

Statistical analysis

Visit-to-visit variability of blood pressure was defined as the standard deviation (SD) or coefficient of variation (SD/mean). Since the coefficient of variation and mean blood pressure can still be correlated, we created a further transformation: variation independent of mean, proportional to SD/mean^x, with x derived from curve fitting. In the UK-TIA cohort, variables were calculated from visits 1 to 7 (0–24 months) and from 1 to 10 (0–36 months)—the latter providing more reliable estimates of blood-pressure values (webappendix p 1), but less subsequent follow-up to predict outcomes. In the other cohorts, variability was calculated over all follow-ups and separately over an initial period up to median follow-up.

We measured the contributions of within-individual visit-to-visit variability versus between-individual differences in mean blood pressure to the distribution of group blood pressure at every follow-up visit. Expected variance of SBP values at one follow-up was estimated as the sum of: between-individual variance in mean SBP, within-individual visit-to-visit variance in SBP, and between-individual variance in within-individual visit-to-visit SBP. The proportion of variance attributable to within-individual variability was estimated as the sum of the latter two components divided by the total variance (webappendix p 2).

In the UK-TIA cohort, mean and visit-to-visit variability in blood pressure during initial follow-up were related to risk of subsequent stroke. Patients who had events in the measurement period were excluded. To allow for non-linearity, variables were split into deciles and hazard ratios (HRs) calculated in relation to the first decile. Analyses were adjusted for mean blood pressure during the measurement period, and for age, sex, and baseline vascular risk factors. We also measured: (1) overall predictive power (area under receiver operating characteristic curve) of each blood-pressure parameter; (2) effect of increasing reliability of estimation of variability by analyses limited to patients with increasing numbers of blood-pressure readings before stroke; (3) predictive value of maximum and minimum blood pressure; and (4) risk in four exclusive categories based on maximum and minimum SBP: stable normotension (maximum ≤140 mm Hg), episodic moderate hypertension (minimum ≤140 mm Hg and maximum 140–179 mm Hg), episodic severe hypertension (minimum ≤140 mm Hg and maximum ≥180 mm Hg), and stable hypertension (minimum >140 mm Hg).

In ASCOT-BPLA, the mean of the second and third readings at every visit was used to calculate blood pressure and heart rate. Estimation of visit-to-visit variability took account of the initial reduction in blood pressure attributable to treatment initiation and dose adjustment: (1) mean blood pressure and variability were based only on readings from the 6-month follow-up onwards; (2) we calculated average successive variability (average absolute difference between successive values); and (3) for patients with three or more visits after 6 months we calculated variability over and above any linear time trend in blood pressure—residual SD, the square root of the total squared deviation of data points from a linear regression of blood pressure against time, divided by (n–2), where n is the number of readings.

Blood-pressure parameters, split into deciles with both treatment groups combined, were related to the risks of stroke and of the predefined ASCOT total coronary events outcome,[32,33] taking the first decile of the amlodipine group as the reference. Analyses included only events occurring after the 6-month follow-up visit. Several sensitivity analyses were done: (1) adjusted for mean blood pressure during the measurement period, age, and sex; (2) further adjusted for all baseline variables in the

See Online for webappendix

	HR for mean SBP		HR for variability in SBP	
	HR (95% CI)	p value	HR (95% CI)	p value
SD SBP				
Two readings	2·44 (1·53–3·89)	<0·0001	1·15 (0·73–1·81)	0·55
Four readings	2·44 (1·39–4·29)	0·002	1·51 (0·86–2·66)	0·16
Six readings	2·49 (1·24–4·97)	0·01	2·02 (0·97–4·22)	0·061
Eight readings	1·85 (0·84–4·10)	0·13	6·01 (1·72–20·96)	0·005
Ten readings	1·44 (0·58–3·57)	0·43	13·04 (1·66–102·6)	0·015
CV SBP				
Two readings	2·67 (1·74–4·11)	<0·0001	1·09 (0·73–1·62)	0·67
Four readings	2·82 (1·67–4·76)	<0·0001	1·50 (0·90–2·48)	0·12
Six readings	3·07 (1·62–5·83)	0·001	1·98 (1·05–3·77)	0·036
Eight readings	2·68 (1·29–5·56)	0·008	5·00 (1·75–14·30)	0·003
Ten readings	2·26 (0·98–5·17)	0·055	13·05 (1·74–97·66)	0·012
VIM SBP				
Two readings	2·86 (1·88–4·36)	<0·0001	1·25 (0·86–1·82)	0·25
Four readings	3·18 (1·90–5·33)	<0·0001	1·59 (1·00–2·54)	0·053
Six readings	3·70 (1·97–6·94)	<0·0001	2·31 (1·26–4·23)	0·007
Eight readings	3·70 (1·81–7·56)	<0·0001	6·04 (2·14–17·03)	0·001
Ten readings	3·31 (1·46–7·47)	0·004	15·35 (2·08–113·1)	0·007

Every row shows the estimates from a Cox model applied to data from patients who survived for at least n follow-up visits, where n ranges from 2 (3 months) to 10 (3 years). Quintiles were used rather than deciles to provide sufficient group sizes to extend the analysis to ten blood-pressure readings. SBP=systolic blood pressure. HR=hazard ratio. CV=coefficient of variation. VIM=variation independent of mean.

Table 1: **Hazard ratios (top *vs* bottom quintile) for risk of subsequent stroke (ie, after the measurement period) in the UK-TIA trial from a model combining mean SBP and visit-to-visit variability in SBP (SD or CV or VIM), repeated with increasingly precise estimates of both variables**

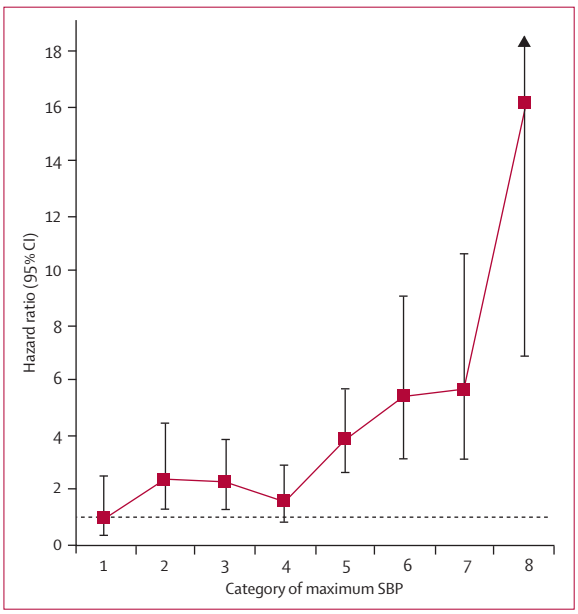

***Figure 2*: Hazard ratios for risk of any subsequent stroke by categories of maximum SBP of the first seven measurements of blood pressure during the first 2 years of follow-up in the UK-TIA trial, adjusted for mean SBP during the same period**

The first category is the reference category. Digit preference in the recording of high values limited maximum SBP to eight roughly equally sized categories based on visits 1–7 (≤140, 141–150, 151–160, 161–170, 171–180, 181–190, 191–219, and ≥220 mm Hg). SBP=systolic blood pressure.

previous ASCOT-BPLA analysis;[33] (3) stratified by mean SBP during follow-up (above *vs* below the median); (4) blood-pressure parameters calculated from only 6–30-month visits (n=5) and related to risk of events after 30 months; (5) on-treatment analysis (ie, patients who were consistently complaint with medication, as defined in previous reports);[32,33] (6) adjusted for randomisation to statin treatment; (7) excluding patients with past history of TIA or stroke; and (8) adjusted for visit-to-visit coefficient of variation of heart rate from all visits from 6 months onwards (SD and mean heart rate were correlated; r^2=0·34, p<0·0001). The number of antihypertensive drugs being taken at last follow-up was also related to visit-to-visit variability and maximum SBP. Within-visit variability in blood pressure was expressed as the SD and range of the three readings at each visit, averaged across all visits from 6 months onwards.

In the ABPM substudy, we correlated daytime and night-time variability in ABPM blood pressure with visit-to-visit variability. To measure any effect of differences in time of day of blood-pressure measurement on observed visit-to-visit variability, we used data from repeated ABPMs to compare variability between ABPM in SBP measured at the same time of day during office hours (0900–1700 h), with readings selected at random during office hours. We also correlated the morning surge (highest SBP from 0900–1100 h minus lowest from 0600–0800 h) with visit-to-visit variability in clinic blood pressure. We compared predictive value of ABPM variability versus visit-to-visit variability in blood pressure for stroke and coronary events with Cox models both for the first ABPM during follow-up and for parameters averaged across all ABPMs. In view of the smaller numbers of outcomes in the ABPM substudy, HRs were calculated for continuous variables with both randomised treatment groups combined.

Role of the funding source

There was no funding for this study. ASCOT was an investigator designed and led study. None of the sponsors of ASCOT-BPLA had any input into the design, performance, analysis, or reporting of the analyses reported in this Article. The report was sent to the major sponsor 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 on any report, but not to exercise any right of veto. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

In the UK-TIA cohort, 2006 patients (1438 men; mean age 60·3 years, SD 9·1; median time since TIA 23 days, IQR 8–46) had a median of 10 (range 1–20) follow-up visits before stroke or death. Results of analyses based on pulse pressure and SBP were similar (data not shown). Mean SBP was 150·3 mm Hg (SD 25·3) at baseline and fell to 146·4 mm Hg (23·3) at 1 year, but was stable thereafter (webappendix p 13). However, systolic blood pressure in individuals was highly variable from one visit to the next (r^2=0·25–0·35, webappendix p 14). Within-individual visit-to-visit variability accounted for 41·5% of the variance in group SBP at each follow-up (webappendix p 2).

Visit-to-visit coefficient of variation of SBP correlated with mean SBP (r=0·22), but variation independent of mean of SBP (SD/mean$^{1·67}$) did not (r=0·01). Coefficient of variation of DBP was not correlated with mean DBP (data not shown). Reproducibility of variability was moderate (eg, intraclass correlation coefficient [ICC] for SD SBP=0·34, 95% CI 0·26–0·41, for visits 1–7 *vs* 8–14). Visit-to-visit variability of SBP over visits 1–7 was unrelated to subsequent mean SBP or DBP. Simulations showed that mean blood pressure based on seven to ten readings provided a reasonable estimate of usual blood pressure (webappendix p 1), and reproducibility of mean blood pressure (visits 1–7 *vs* 8–14) was good (ICC=0·76, 95% CI 0·74–0·79).

Of 1324 (66%) patients who reached visit 7, 270 had a subsequent stroke (n=104) or coronary event (166). Mean SBP over visits 1–7 predicted stroke (HR 1·43, 95% CI 1·18–1·74 per 20 mm Hg, p<0·0001; top-decile HR 2·44, 1·56–3·82, after adjustment for age, sex, and baseline risk factors). However, visit-to-visit variability in SBP was a stronger predictor (top-decile HR for SD SBP: 6·22,

	UK-TIA Aspirin trial	ASCOT–BPLA trial*		ESPS-1†	Dutch TIA trial‡
		Atenolol group	Amlodipine group		
Number of cases	1324	1012	999	1247	3150
Frequency of follow-up (months)	4	6	6	3	4
Mean (SD) baseline SBP	150·2 (25·3)	163·7 (18·7)	164·4 (17·9)	156·3 (22·7)	157·9 (26·3)
Mean (SD) 1 year SBP	146·6 (23·4)	148·3 (19·7)	143·3 (17·4)	154·8 (22·3)	151·7 (22·5)
Mean (SD) within-individual visit-to-visit variability in SBP					
SD	14·2 (6·6)	14·4 (6·1)	11·4 (4·9)	14·6 (6·8)	14·9 (6·4)
CV	9·6 (3·9)	10·00 (4·0)	8·2 (3·3)	9·3 (4·1)	9·7 (3·9)
Range of SBP ≥50 mm Hg (%)	31·0%	32·2%	15·3%	28·3%	34·8%
Group variance in SBP attributable to intra-individual variation (%)	41·5%	56·9%	53·1%	42·9%	46·8%
HR (95% CI) for stroke (unadjusted)					
Mean SBP	3·63 (2·41–5·48)	1·81 (0·89–3·67)	0·94 (0·36–2·42)	1·89 (0·96–3·71)	2·34 (1·41–3·89)
SD SBP	6·22 (4·16–9·29)	4·37 (1·85–10·33)	4·46 (1·73–11·50)	1·90 (1·34–2·70)	4·35 (2·17–8·69)
CV SBP	4·61 (3·11–6·83)	3·81 (1·70–8·53)	3·41 (1·39–8·36)	2·31 (1·60–3·35)	3·85 (1·84–8·09)
VIM SBP	3·88 (2·13–5·38)	4·17 (1·75–9·92)	3·53 (1·37–9·09)	1·86 (1·28–2·69)	1·76 (0·73–4·23)
HR (95% CI) for stroke adjusted for mean SBP					
SD SBP	4·84 (3·03–7·74)	4·29 (1·78–10·36)	4·39 (1·68–11·50)	1·78 (1·21–2·62)	3·35 (1·63–6·87)
CV SBP	3·82 (2·54–5·73)	3·51 (1·56–7·93)	3·25 (1·32–8·00)	2·22 (1·52–3·22)	3·41 (1·62–7·19)
VIM SBP	3·27 (2·06–5·21)	3·96 (1·66–9·43)	3·57 (1·38–9·19)	1·86 (1·28–2·69)	1·83 (0·76–4·39)

SBP=systolic blood pressure. CV=coefficient of variation. HR=hazard ratio. VIM=variation independent of mean. *Subgroup of patients with previous stroke or transient ischaemic attack (TIA). †Placebo group only. ‡Results were similar after exclusion of the atenolol substudy (data not shown).

Table 2: **Blood-pressure parameters and their predictive values (HRs and 95% CI for risk of stroke in the top *vs* bottom decile of each measure) in the four independent cohorts of patients with TIA and minor stroke**

4·16–9·29, figure 1; HR 4·37, 2·73–6·99, after adjustment for mean SBP, age, sex, and other risk factors; HR 12·08, 7·40–19·72, when based on visits 1–10; p<0·0001). Visit-to-visit variation independent of mean of SBP also predicted stroke (visit 1–7 top-decile HR: 3·27, 2·06–5·21, p<0·0001), both in patients receiving (3·67, 2·34–5·75, n=808) and not receiving (2·27, 1·41–3·67, n=516) antihypertensive drugs at baseline; however, coefficient of variation of DBP was a weak predictor (1·37, 0·81–2·31).

Predictive power of visit-to-visit variability of SBP increased with precise estimation (table 1). Results were unaffected by exclusion of 43 patients with previous stroke (visit 1–7 top decile HR for SD SBP: 8·23, 5·51–12·30, p=0·001) and a further 90 patients with asymptomatic infarction on baseline CT (HR 10·44, 6·65–16·38, p=0·002; figure 1); adjustment for any temporal trend in blood pressure in individuals (residual SD, data not shown); and adjustment for mean arterial pressure or mean pulse pressure (data not shown). Predictive value of visit-to-visit variability was similar in men and women, but decreased with age (visit 1–7 top-quartile HR of SD SBP by tertile of age: 9·43, 1·96–45·5 at <56 years; 3·01, 0·97–9·36 at 56–64 years; and 1·71, 0·74–3·98 at ≥65 years).

Maximum SBP predicted stroke independently of mean SBP (figure 2; adjusted HR for top-decile over seven visits: 15·01, 6·56–34·38, p<0·0001, after adjustment for mean SBP), with the strength of the association increasing with the number of visits used (top-quintile adjusted HR: 3·03, 1·18–7·76, p=0·021, based on four visits and increasing to 11·74, 3·23–42·57, p<0·0001, based on ten visits). Maximum SBP was more predictive of stroke than was mean SBP (webappendix p 3) and maximum minus mean (peak) was more predictive than was mean minus minimum (trough) (webappendix p 4). Maximum SBP was most predictive at lower values of mean SBP (based on visits 1–7, excluding the maximum): HR for maximum SBP adjusted for mean SBP was 4·95 (1·28–22·4, p=0·007) at mean SBP less than 130 mm Hg; 3·19 (1·65–6·23, p=0·0001) at 130–159 mm Hg; and 1·13 (0·50–2·53, p=0·75) at 160 mm Hg or higher. Patients with episodic severe hypertension had a higher risk of stroke than did those with stable hypertension (36 [13·7%] *vs* seven [4·5%], p=0·003, webappendix p 5; age and sex adjusted HR 3·58, 1·58–8·10) despite a lower mean SBP (157·9 mm Hg [SD 8·7] *vs* 167·3 mm Hg [7·2], p=0·001).

Visit-to-visit variability in SBP was similar in the four TIA cohorts (table 2), as was its contribution to the variance in group SBP at follow-up visits (table 2, webappendix p 2). Visit-to-visit variability of SBP was consistently more predictive of stroke than was mean SBP (table 2), and tended to be most predictive in patients with lower baseline SBP (<median *vs* ≥median).

In the main ASCOT-BPLA study, 18 530 (96%) patients had two or more scheduled follow-up visits from 6 months onwards (median 10, IQR 9–11). Visit-to-visit variability in SBP was similar to that in the four TIA cohorts and accounted for more than 50% of the

variance in group SBP at each follow-up (webappendix p 2). Reproducibility (visits at 6–36 *vs* 42–72 months) of visit-to-visit (ICC 0·30, 95% CI 0·27–0·33) and within-visit (0·43, 0·40–0·45) SD SBP was independent of treatment group or seasonal trends in blood pressure. Visit-to-visit SD SBP correlated with mean SBP (r=0·37) as did coefficient of variation of SBP (r=0·17). Variation independent of mean of SBP was SD/mean$^{1·78}$.

Mean SBP was a weak predictor of stroke and coronary events, whereas visit-to-visit variability was a strong predictor of both (figure 3), independent of any time trend in SBP during follow-up (eg, residual SD top-decile HR for stroke in atenolol group: 3·96, 2·54–6·18). Visit-to-visit variability in SBP was greater in the atenolol group than in the amlodipine group,[40] but the risk relations were similar in both groups (figure 3), and in the on-treatment cohort, and remained similar after adjustment for age, sex, and mean SBP (webappendix p 6) and all other baseline risk factors (eg, adjusted HRs for variation independent of mean in amlodipine group: stroke 2·97, 1·32–6·71; coronary events 3·41, 1·98–5·88). Variability during the five visits at 6–30 months predicted risk of events after 30 months (webappendix p 7). Variability in DBP was less predictive (webappendix p 15). With the same categories of behaviour of SBP defined in webappendix p 5 (based on the visits at 6–30 months), episodic severe hypertension was associated with a higher subsequent risk of stroke than was stable hypertension (33/815 [4·0%] *vs* 75/2828 [2·7%], p=0·03), despite a lower mean SBP during the risk period (142·1 mm Hg [SD 14·8] *vs* 147·3 mm Hg [13·8], p<0·0001).

Visit-to-visit variability in SBP was more predictive of ischaemic than haemorrhagic stroke (webappendix p 8), remained predictive after exclusion of patients with previous TIA or stroke (top-decile HRs: average successive variability=4·04, 2·39–6·83; variation independent of mean=2·52, 1·58–4·03), was a stronger predictor of stroke in patients with less than median (142·8 mm Hg) mean SBP during follow-up (interaction p=0·006 for variation independent of mean, figure 4), and predicted risks of myocardial infarction, angina, and heart failure (all p<0·0001, webappendix p 16). Prediction of stroke or coronary events varied only in relation to age (interaction p=0·01), the strongest association being in the youngest (≤57 years) quartile (eg, top-decile HR for stroke: 5·06, 2·09–12·26, for visit-to-visit variation independent of mean of SBP).

Since a high follow-up blood pressure would often trigger patients to receive an add-on drug, use of three or more agents increased with variation independent of mean of SBP and with maximum SBP (webappendix p 9). However, risks of stroke and coronary events still increased in relation to maximum SBP (eg, top-decile HR: 2·51, 1·69–3·73, p=0·0008, for risk of stroke in the atenolol group). Minimum SBP did not predict stroke or coronary events (data not shown).

Heart rate was not correlated with SBP at baseline or on follow-up in either treatment group, or with visit-to-visit SD SBP (r=0·01 in both groups). Visit-to-visit coefficient of variation of heart rate was weakly correlated with visit-to-visit variation independent of mean of SBP (r^2=0·02 in both groups), but was of little prognostic value (webappendix p 17).

Within-visit SD SBP was a weak predictor of vascular events (webappendix p 18; top-decile HR for stroke adjusted for mean SBP: 1·52, 1·09–2·13). The association with stroke risk was stronger in patients with lower mean SBP and varied with age (interaction p=0·04), with the strongest relations in the youngest (≤57 years) quartile (eg, top-decile HR for stroke: 3·22, 1·16–8·89). However, the difference between the first SBP during a clinic visit and the mean of the second two (white-coat effect) was not predictive of stroke or coronary events (data not shown), and was not correlated with visit-to-visit variability (r=0·01 for visit-to-visit SD, coefficient of variation, and variation independent of mean). Overall within-visit SD SBP was weakly correlated with visit-to-visit variability (SD r=0·18, p<0·0001; variation independent of mean r=0·23, p<0·0001).

In the ASCOT-BPLA ABPM study, 1905 patients had a mean of 3·25 (range 1–10) ABPMs from 6 months onwards. In 843 patients with four or more ABPMs, the difference in mean daytime SBP between adjacent ABPMs after adjustment for any linear trend in that individual (mean 7·9 mm Hg [SD 4·8]) correlated with visit-to-visit variability in clinic SBP over the same period (both as residual SD: r=0·34 based on ≥four ABPMs; r=0·43 based on ≥five ABPMs; both p<0·0001). Inter-ABPM variability for single SBP readings at the same time of day was consistent during 0900–1700 h; SD SBP was 13·3 mm Hg at 1000 h versus 14·3 mm Hg for times taken at random. The morning surge in SBP was not correlated with visit-to-visit variability in clinic SBP (r^2=0·02) and did not predict stroke (HR per SD increase: 0·88, 0·65–1·10, p=0·44).

Intra-ABPM SD of daytime SBP correlated with mean daytime SBP (r=0·26, p<0·0001), but coefficient of variation of daytime SBP did not (data not shown). Intra-ABPM coefficient of variation SBP correlated with visit-to-visit coefficient of variation in clinic SBP (atenolol group r=0·38, amlodipine group r=0·29; both p<0·0001), but visit-to-visit variability in clinic SBP was more predictive of vascular events (webappendix p 10). However, both parameters predicted risk of vascular events independently of average daytime mean SBP across all ABPMs (HRs per SD increase: daytime mean SBP=1·09, 95% CI 0·94–1·27, p=0·26; daytime coefficient of variation SBP=1·17, 1·01–1·36, p=0·04; visit-to-visit coefficient of variation of clinic SBP=1·48, 1·28–1·71, p<0·0001). Visit-to-visit coefficient of variation of SBP during 6–30 months of follow-up also predicted events thereafter independently of mean and SD daytime SBP on ABPM (HR per SD

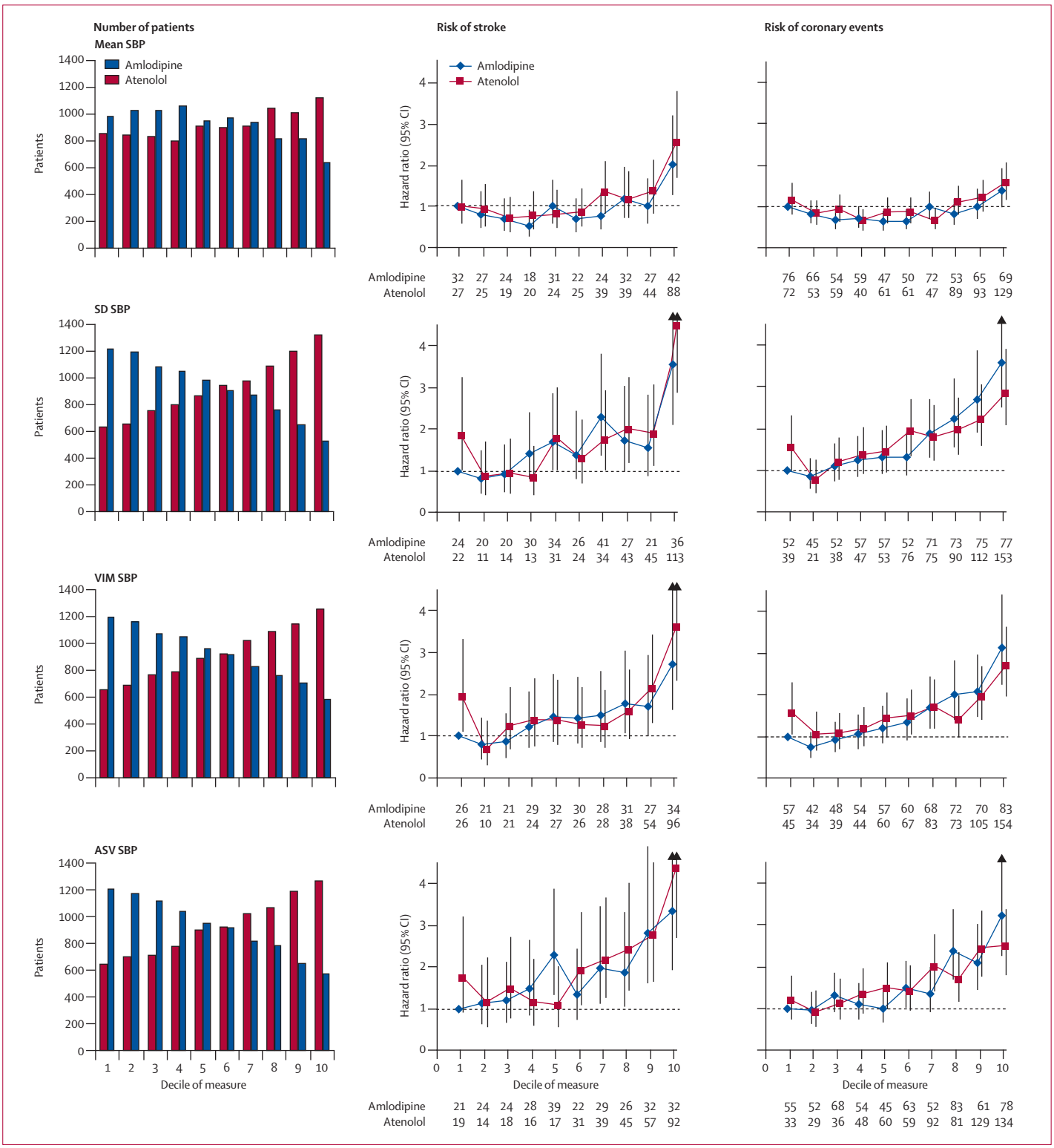

Figure 3: **Distribution of patients in the two treatment groups in ASCOT-BPLA according to deciles of mean, SD, VIM, and ASV of SBP (left) and the associations of each of these variables with risk of stroke (middle) and risk of coronary events (right)**

The middle and right columns show the hazard ratios (95% CI) for risks of stroke and acute coronary events, respectively, by deciles of the same parameters. The first decile in the amlodipine-based group is the reference category. Numbers of outcome events by decile and treatment group are given below each graph. SBP=systolic blood pressure. VIM=variation independent of mean. ASV=average successive variability.

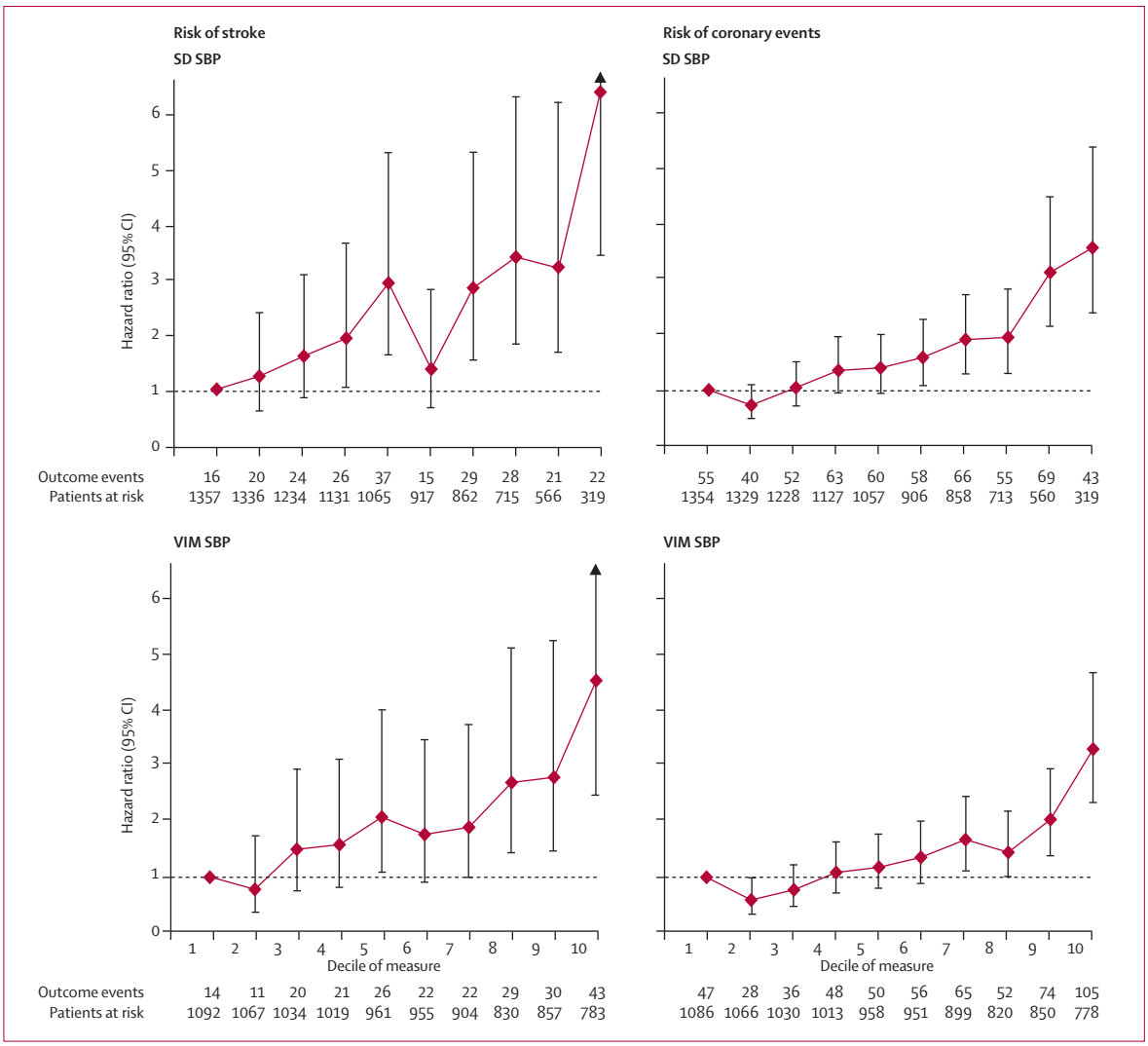

Figure 4: **Hazard ratios for risks of stroke and acute coronary events in ASCOT-BPLA patients with mean SBP during follow-up less than the median value for the trial population (<142·8 mm Hg) by deciles of SD and VIM SBP**

Treatment groups are combined, but allocation is adjusted for in the model. The first decile is the reference category. Deciles are based on the cut-points used for the full trial population. SBP=systolic blood pressure. VIM=variation independent of mean.

increase=1·29, 1·08–1·55, p=0·007). Daytime coefficient of variation of SBP on ABPM was most predictive in patients with lower (<median) mean daytime SBP (HR per SD increase: 1·42, 1·18–1·71).

Maximum daytime SBP on ABPM predicted risk of stroke and coronary events (HR per SD for both: 1·23, 1·08–1·41, p=0·005; webappendix p 10), particularly after adjustment for mean daytime SBP on ABPM (1·44, 1·12–1·84, p=0·002). Minimum daytime SBP on ABPM was less predictive than was maximum daytime SBP (webappendix p 10).

Variability in SBP is related to baseline characteristics in webappendix p 11 for ASCOT-BPLA and in webappendix p 12 for UK-TIA. Randomisation to atorvastatin in the lipid-lowering group of ASCOT resulted in a small reduction in variation independent of mean of SBP (difference=0·33, 95% CI 0·54–0·13, p=0·001), but all risk relations described above were independent of this effect (data not shown).

Discussion

We have shown that visit-to-visit variability in SBP is a powerful predictor of stroke and coronary events independent of mean SBP, that maximum SBP is more predictive than is mean SBP (on clinic readings or on ABPM), that residual variability in SBP on treatment has a poor prognosis, and that stable hypertension has a better prognosis than does episodic hypertension. Along with accompanying reports,[12,40,41] these findings challenge the usual blood-pressure hypothesis and have implications for diagnosis, treatment, and monitoring of patients with hypertension.

There has been uncertainty about the prognostic value of variability in blood pressure on ABPM.[12] There is some evidence that day-to-day variability in home blood pressure predicts fatal stroke,[42] but no previous studies of the prognostic value of maximum blood pressure, and only a few small studies of the prognosis of visit-to-visit variability in clinic blood pressure.[43–47] Hata and colleagues[44] showed that coefficient of variation of previous clinic SBP from case notes was slightly greater in 138 patients with stroke than in controls,[43] but not in patients with myocardial infarction.[44] Variability in office blood pressure in 144 patients on renal dialysis predicted mortality, but was based on only six vascular deaths.[45] Havlik and co-workers[46] reported a weak association between SBP variability (three clinic readings over 6 years) and white matter lesions on brain imaging 25 years later. However, a substudy of the Syst-Eur trial[47] recorded no relation between the SD of six blood-pressure readings (from three visits over 8 weeks) and vascular risk.[47] None of these studies was adequately powered or fully adjusted for mean blood pressure, or had enough readings to estimate usual blood pressure reliably (webappendix p 1). Our study of four large cohorts provides reliable evidence that visit-to-visit variability in SBP is a strong independent predictor of stroke and other vascular events.

We studied trial cohorts with previous TIA from the 1980s because the high risk of stroke and the scrutiny of stroke outcomes meant that we could define risk relations reliably, and because high blood pressure was often left untreated after TIA or stroke at that time,[48,49] allowing us to compare the prognoses of episodic and stable hypertension. Moreover, by contrast with many trials investigating lowering of blood pressure, patients with variable blood pressure were not excluded by screening before the trials, and patients with a full range of baseline blood-pressure values were recruited, so that the prognostic value of mean SBP would not be underestimated. We studied the UK-TIA trial in most detail because usual SBP was a strong predictor of stroke in that cohort,[50] such that blood-pressure readings must have been reliable, and because the frequency (every 4 months) and length (up to 6 years) of follow-up allowed reasonably reliable estimation of visit-to-visit variability and mean blood pressure with sufficient subsequent follow-up to measure predictive values.

Analysis of ASCOT-BPLA (based on 1·12 million blood-pressure readings) provided six important insights. First, residual visit-to-visit variability in blood pressure was as high as in the TIA cohorts, despite standardised measurement and aggressive blood-pressure lowering. Second, variability in clinic SBP was a strong predictor of stroke, heart failure, angina, and myocardial infarction. Third, the extent and prognostic value of visit-to-visit variability in SBP were independent of heart rate and variability in heart rate. Fourth, within-visit variability in SBP correlated with visit-to-visit variability, but was a weak predictor of vascular events. Fifth, visit-to-visit variability in SBP was unrelated to the white-coat effect. Finally, the lower event rate in the amlodipine group than in the atenolol group, which could not be explained by changes in mean blood pressure or other risk factors,[33] can be explained by reduced visit-to-visit variability in SBP.[40]

The ASCOT-BPLA ABPM study provided four further insights. First, visit-to-visit variability in clinic blood pressure was not due to variation in the time of measurement within office hours (0900–1700 h). Second, variability in mean daytime SBP on repeated ABPMs correlated with visit-to-visit variability in clinic SBP, indicating a contribution from fluctuations in underlying blood pressure. Third, variability in blood pressure on ABPM was a weaker predictor of vascular events than was visit-to-visit variability, and it accounted less well for the reduced event rate in the amlodipine group than the atenolol group,[40] suggesting that average variability from minute to minute (best exemplified as average successive variability on ABPM) does not capture elements of variability that are associated with risk of stroke. Finally, the predictive value of visit-to-visit variability in SBP was independent of mean value averaged across all clinic visits and averaged across several ABPMs.

Visit-to-visit variability in SBP was related to factors that correlate with arterial stiffness, including age, female sex, smoking, diabetes, and peripheral vascular disease, but only age and mean blood pressure affected the prognostic value of variability. Variability increased with age, but its effect on stroke risk was greatest at young ages, perhaps because of fewer competing causes of stroke or death or because of greater susceptibility to target organ damage.

Our study had several potential shortcomings. First, in the TIA cohorts, some variability in clinic blood pressure could have been due to non-adherence to guidelines for measurement or inadequate calibration of measuring devices. However, such errors would not account for a visit-to-visit range of SBP of 50 mm Hg or greater, which was noted in about a third of patients, including the atenolol group of ASCOT-BPLA, in which blood-pressure measurement was standardised. Second, blood pressure was measured only once at every visit in the UK-TIA and Dutch TIA trials, but the alerting response was of no prognostic value in ASCOT-BPLA. Third, in some analyses, we related variability in blood pressure to outcomes during the measurement period. However, visit-to-visit, within-visit, and ABPM variability during 6–30 months in ASCOT-BPLA all predicted vascular events thereafter, and measurement and outcome periods were separate in all analyses of the UK-TIA cohort. Fourth, we had no data for use of, or compliance with, antihypertensive drugs during follow-up in the older TIA cohorts. However, visit-to-visit variability was a strong predictor of stroke in the ASCOT-BPLA on-treatment cohort that was fully compliant. Fifth, mean SBP over visits 7–10 will not have fully accounted for usual blood

pressure (webappendix p 1), but it was highly reproducible in the UK-TIA cohort, much more so than was visit-to-visit SD SBP. Sixth, our findings cannot be generalised to healthy cohorts.

Our findings do not prove a causal link between variability in blood pressure (or maximum SBP) and stroke. However, the risk relations were strong and consistent in several cohorts, despite imprecision in estimation of variability. Pre-existing cerebral ischaemia could lead to both altered central autonomic control of blood pressure[34,35] and an increased risk of stroke, but the risk relation in the UK-TIA trial strengthened after exclusion of patients with previous stroke or cerebral infarction and it was present in patients without previous TIA or stroke in ASCOT-BPLA. Experimental data from animal models also lend support to a causal link;[12] there are plausible mechanisms,[12] and effects on visit-to-visit variability in SBP explain differences between classes of antihypertensive drugs in their effect on stroke risk.[12,40,41] However, more research is needed to fully understand the association between visit-to-visit variability in blood pressure and risk of vascular events, and large-scale pooled analyses of multiple cohorts will be required. The risk association for coronary events needs further study, particularly since antihypertensive drug class effects are less obvious for coronary events in most trials than for stroke.[41]

More work is also needed to identify measures that would combine the prognostic information associated with visit-to-visit variability in blood pressure with ease of use in routine clinical practice. For example, associations with postural instability in blood pressure and the pressor response to other stimuli should be determined. However, our findings do have immediate implications for the diagnosis and management of hypertension, choice of drug, design and reporting of trials, and drug development.[12] Briefly, patients with episodic hypertension should no longer be excluded from trials of antihypertensive drugs; increased residual variability in SBP in treated patients has a poor prognosis, despite greater use of add-on drugs; and stabilisation of blood pressure should be regarded as a potentially important target in the development of new agents and new combinations of drugs. Furthermore, in secondary prevention after TIA or stroke, for which rates of treatment with antihypertensive drugs are low in routine clinical practice[51] despite good evidence of benefit,[52] the high risk of stroke in patients with episodic hypertension draws attention to the false reassurance of a few normal blood-pressure readings.

Contributors

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

Conflicts of interest

JED has institutional research funds from Pfizer. PSS has received payment from Pfizer for lectures, travel, and accommodation and has received research grants from Pfizer and Servier. NRP has received research grants from Pfizer and Servier as well as payment for consultancy, travel, lectures, advisory boards, and preparation of reports. BD has received payment for consultancy or board membership from MSD, Novartis, Boehringer Ingelheim, Daiichi Sankyo, and Pfizer, and has received speaker fees from all these companies. He also has stock options in Mintage Scientific. PMR has no conflicts of interest in relation to the topic of this paper, but has received payment from Servier for lectures and steering committee membership in relation to the PERFORM trial. SCH, ED, and EO'B declare that they have no conflicts of interest.

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