



Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension

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Although hypertension is the most prevalent treatable vascular risk factor, how it causes end-organ damage and vascular events is poorly understood. Yet, a widespread belief exists that underlying usual blood pressure can alone account for all blood-pressure-related risk of vascular events and for the benefits of antihypertensive drugs, and this notion has come to underpin all major clinical guidelines on diagnosis and treatment of hypertension. Other potentially informative measures, such as variability in clinic blood pressure or maximum blood pressure reached, have been neglected, and effects of antihypertensive drugs on such measures are largely unknown. Clinical guidelines recommend that episodic hypertension is not treated, and the potential risks of residual variability in blood pressure in treated hypertensive patients have been ignored. This Review discusses shortcomings of the usual blood-pressure hypothesis, provides background to accompanying reports on the importance of blood-pressure variability in prediction of risk of vascular events and in accounting for benefits of antihypertensive drugs, and draws attention to clinical implications and directions for future research.

Introduction

Hypertension is the most prevalent treatable cause of vascular events,¹ accounting for about 50% of risk.² In developed countries, it affects half of adults,³ and is the leading indication for prescribed drugs.⁴ Yet, we understand little about how hypertension leads to vascular events. Nevertheless, one hypothesis has come to dominate research and practice—that all of us have an

underlying usual blood pressure (panel 1)^{5–17} that is the main determinant of blood pressure-related vascular risk and of benefit from antihypertensive drugs (the usual blood-pressure hypothesis). For example, the American Heart Association guidelines⁹ on measurement of blood pressure state that “it is generally agreed that conventional clinic readings, when made correctly, are a surrogate marker for a patient’s true blood pressure, which is

Panel 1: Definitions

Usual blood pressure

The theoretical true underlying level of blood pressure, which cannot be measured with total precision, but which is widely considered to be the most important component of blood pressure, determining its adverse effects and accounting for the benefits of antihypertensive drugs. Risk relations between measurements of blood pressure and risk of vascular events can be corrected for inaccuracy in estimation of usual blood pressure by adjustment for regression-dilution bias.^{5,6}

Mean blood pressure

The average of several readings of either systolic or diastolic blood pressure (as opposed to mean arterial pressure). Readings can be derived from several clinic visits, home measurement, or ambulatory monitoring, although all these techniques will result in different values. Modelling studies show that at least seven to ten measurements of blood pressure on different clinic visits (and ideally many more) are needed for mean blood pressure to be an accurate estimate of usual blood pressure.⁷

Blood-pressure variability

The variation in blood pressure with time, either the overall variability during a period of time (SD or coefficient of variation), with or without adjustment for time trends in underlying mean blood pressure (residual SD), or the average absolute difference between adjacent readings (successive variation).^{7,8} Variability has mainly been studied during periods of hours on ambulatory monitoring, but can also be measured over minutes during a clinic visit, or over days, weeks, and months with home measurements or repeated clinic visits (webappendix pp 5–9). These approaches yield different estimates of variability, which are only partly correlated,⁷ and which might have different primary determinants. Extent of variability is usually positively associated with mean blood pressure, but independent transformations can be generated.⁷ Measurements of variability in blood pressure are generally less precise than are estimates of usual blood pressure, and risk relations could in theory be adjusted for error in estimation of usual variability.

Blood-pressure instability

Describes transient fluctuations in blood pressure, usually in response to a specific stimulus, such as change in posture, emotional stress, or pain. Instability contributes to overall variability and will often have similar clinical associations, such as arterial stiffness and baroreceptor dysfunction. However, instability differs from variability in that it refers specifically to sudden changes in blood pressure, the consequences of which might differ from more gradual fluctuations.

conceived as the average over long periods of time, and which is thought to be the most important component of blood pressure in determining its adverse effects.” All major guidelines recommend that treatment should be on the basis of estimates of this true blood pressure, with or without consideration of other risk factors.^{9,10-13} By contrast, visit-to-visit variability in blood pressure is dismissed as random, merely an obstacle to reliable estimation of usual blood pressure.^{5,6,14-17}

Proponents of the usual blood-pressure hypothesis make three main points. First, average blood pressure differs between individuals, can be tracked from childhood to middle age,¹⁸ and predicts risk of vascular events. Second, reliable estimation of mean blood pressure or of usual blood pressure strengthens this risk association. Third, the benefits of antihypertensive drugs are correlated reasonably well with reduction in mean blood pressure during follow-up.¹⁹⁻²¹ This Review questions the interpretation of this evidence and provides background to accompanying reports that patients with only episodic hypertension have a high risk of vascular events,^{7,8} that residual visit-to-visit variability in blood pressure on treatment has poor prognosis despite good control of mean blood pressure,^{7,8} and that benefits of some antihypertensive drugs are due partly to reduced variability in blood pressure.^{8,22} As the outcome that is most strongly related to blood pressure, stroke is used to illustrate some of the arguments.

Application of the hypothesis in practice

Blood pressure often varies greatly from visit to visit,²³⁻²⁶ and so several readings are needed to estimate a usual value.^{9,10-13} The joint European guidelines state that, in the absence of substantially raised blood pressure, repeat readings “should be obtained over several months to define the patient’s usual blood pressure as accurately as possible”.¹² Hypertension should not be diagnosed on the basis of episodic rises in blood pressure, unless home monitoring or 24-h ambulatory blood-pressure monitoring (ABPM) show that mean blood pressure is raised.^{9,10-13} However, the prognosis of episodic hypertension or of increased visit-to-visit variability in blood pressure has not been reliably established (webappendix pp 5–9).

Episodic hypertension is very common. In a cohort of patients with previous transient ischaemic attack (TIA),⁷ for example, only 12% of patients had stable hypertension (systolic blood pressure [SBP] consistently >140 mm Hg), whereas 69% had episodic hypertension (some readings ≤140 mm Hg and some >140 mm Hg). Correlation between SBP at one visit and the next is therefore poor in such cohorts ($r^2 < 0.25$; figure 1). Similar variability is also seen before a stroke, but episodic hypertension is usually left untreated, because SBP is not raised on the requisite number of repeat visits^{9,10-13} and low readings are probably interpreted as indicating the likely underlying blood

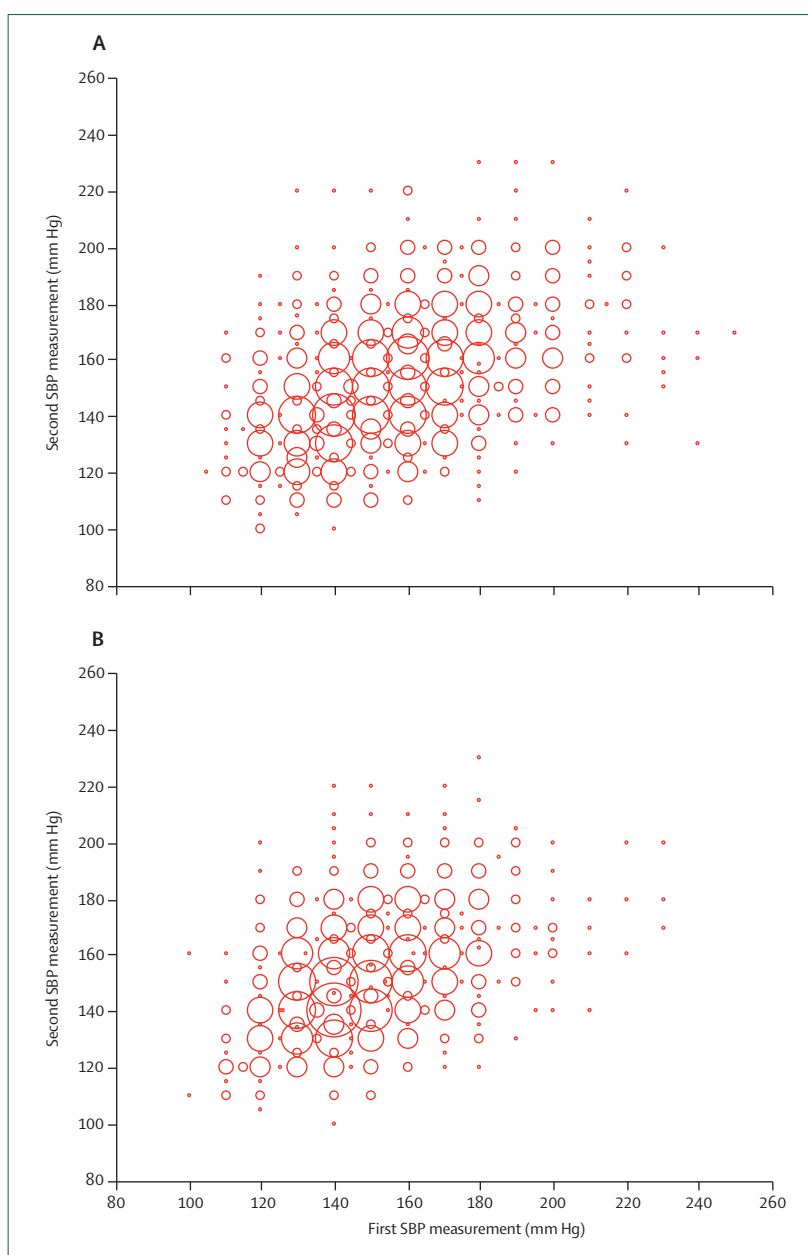


Figure 1: Systolic blood pressure at one clinic visit versus the next visit in two cohorts of patients with previous transient ischaemic attack and minor stroke²³

(A) Dutch transient ischaemic attack trial (n=2269). (B) European carotid surgery trial (n=2646). Dot size is proportional to number of cases at every point. Analysis of the Dutch trial excluded the subset of patients randomly allocated to atenolol. SBP=systolic blood pressure.

pressure. In the Oxford Vascular Study²⁷ between 2002, and 2005, of 150 consecutive patients not on antihypertensive drugs before a stroke, 87% had at least one SBP of 160 mm Hg or higher during the previous 10 years, but 69% of these also had SBP of 130 mm Hg or lower on at least two other visits.

See Online for webappendix

Guidelines recommend that patients with variable clinic blood pressure be assessed by 24-h ABPM or self-measurement at home, or both.^{9,10-13,28} Mean blood

pressure on ABPM is lower than clinic blood pressure,^{28,29} its use therefore reduces prescription of antihypertensive drugs,³⁰ it predicts vascular risk reasonably well,^{31–33} and one 24-h recording is assumed to provide a reasonable estimate of usual blood pressure.³⁴ However, mean blood pressure varies substantially on repeated ABPM,^{35,36} the extent of which is associated with visit-to-visit variability in clinic SBP.⁷ Thus, a raised office blood pressure and a normal mean blood pressure on a subsequent ABPM might suggest episodic hypertension rather than merely a misleading office reading (webappendix p 2). Self-monitoring at home could identify variable blood pressure, but is recommended only as an estimate of usual blood pressure,^{37,38} the European Society of Hypertension suggests duplicate morning and evening readings for 7 days, with the average of all readings from days 2–7 taken as the usual blood pressure.

Thus, guidelines regard visit-to-visit variability in blood pressure as noise that has to be purged from the diagnostic process. Some investigators argue that variability cannot be established with clinic readings.³⁴ Poor appreciation of the importance of blood-pressure variability might also partly account for why half of patients prescribed antihypertensive drugs stop within a year,^{39,40} presumably finding that their blood pressure is often normal even without the tablets.

Epidemiological evidence

Mean blood pressure is a very powerful risk factor for vascular events, but much other epidemiological evidence

suggests that instability and variability in blood pressure are also important. First, the predictive value of estimated usual blood pressure falls with age (figure 2), even though adjustment for regression-dilution bias increases with age,^{6,14–16,24,25,41} whereas incidence of stroke increases 100-fold from age 40–80 years,²⁷ and the relative benefit of antihypertensive drugs is maintained in elderly people.^{42–44} Second, most studies of estimated usual blood pressure versus vascular risk were done in young healthy cohorts (webappendix p 10), from which people with previous vascular events were excluded.⁶ Yet, most treatment of hypertension is in patients with vascular risk factors or previous events, in whom there is again a disparity between the weak predictive value of mean SBP^{7,8} and the benefits of blood-pressure reduction.^{45–47}

Third, the striking midmorning surge in stroke risk transposes almost exactly onto diurnal variation in blood pressure. An increased morning surge in blood pressure is predictive of stroke,⁴⁸ but is poorly associated with mean blood pressure,^{36,48} suggesting that the surge itself triggers vascular events. Fourth, other causes of transient increases in blood pressure (webappendix p 1) are also triggers of vascular events;^{49,50} orthostatic hypertension and sympathetic overactivity are associated with increased vascular risk,^{51,52} as are personality traits, such as hostility, which also associate with increased blood-pressure reactivity.^{53,54} Indeed, the association between increased variability in blood pressure and risk of stroke is strongest in young age groups in whom impaired control of blood pressure is least likely to be secondary to degenerative processes.⁷ Fifth, the opposite form of blood-pressure instability, orthostatic hypotension, is also a powerful risk factor for vascular events in both middle and old age,^{55,56} and is also subject to antihypertensive drug-class effects.⁵⁷

Sixth, in most cohorts, no threshold of baseline SBP has been reported below which vascular risk ceases to fall,^{5,6} and antihypertensive drugs reduce risk when baseline SBP is normal.^{45,46} Normal blood pressure in these studies could still be higher than optimum, but results from the accompanying report⁷ show that patients with consistently normal SBP (stable normotension) have very few vascular events, whereas those with normal mean SBP but high variability are at increased risk. Reductions in variability, rather than reductions in mean blood pressure, might therefore account for benefits of antihypertensive drugs at normal SBP.^{45,46}

Seventh, although scarce research has been done into the prognostic value of visit-to-visit variability in blood pressure (webappendix pp 5–9), situational variability has been studied. White-coat hypertension, in which blood pressure is high in the clinic, but normal at home or on ABPM,⁵⁸ was thought to be benign, but long-term follow-up suggests an association with target-organ damage that is independent of mean blood pressure.^{59,60} Although visit-to-visit variability in office blood pressure is not due to the so-called white-coat effect (it occurs in

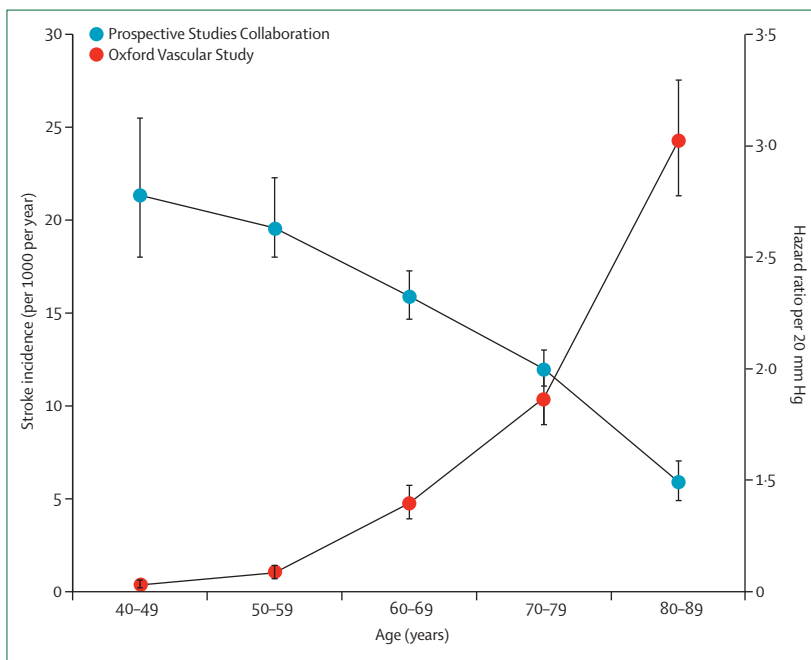


Figure 2: A comparison of age-specific incidence of stroke in the Oxford Vascular Study²⁷ and age-specific association between estimated usual systolic blood pressure and risk of stroke from the Prospective Studies Collaboration⁶

Error bars show 95% CIs.

one setting and was uncorrelated with the white-coat effect in ASCOT-BPLA⁷), both increase with age and are greatest in women.⁵⁸ Masked hypertension—normal office blood pressure, but raised blood pressure at home or on ABPM—is associated with increased risk of vascular events,^{60,61} which has been assumed to be due to the fact that mean blood pressure is higher than was recorded in the clinic. In fact, increased vascular risk is likely to be due, at least in part, to variability in blood pressure, masked hypertension being only one manifestation of variability.

Eighth, although hypertension is a risk factor for vascular dementia,^{62,63} trials of blood-pressure-lowering drugs have not shown a consistent reduction in risk of dementia.^{64–66} However, incidence of dementia was reduced substantially by the calcium-channel blocker, nitrendipine, in the Syst-Eur trial.⁶⁷ Calcium-channel blockers are the most effective drug class for reduction of blood-pressure variability.^{8,22} Ninth, specific group differences in risk of stroke are not accounted for by mean blood pressure, but could be due to variability. Women have fewer coronary events than do men, but have a similar risk of stroke,⁶⁸ and black people are more prone to stroke than are white people.⁶⁹ Variability in blood pressure is increased in women⁷ and in black people.⁷⁰ The high vascular risk in chronic renal failure is also associated with increased visit-to-visit variability in SBP.⁷¹

Finally, blood pressure is often very high in the hours after a stroke—so-called poststroke hypertension. That this finding is a consequence of the stroke (rather than the cause) has been universally assumed. However, an analysis of 18 035 pre-morbid blood-pressure readings from primary care in 1047 patients with TIA or stroke in the Oxford Vascular Study⁷² showed that although the acute postevent SBP was higher than the most recent pre-event reading in 65% of patients, 74% had had at least one higher blood-pressure reading in recent years. The acute postevent SBP was also highest after TIA and tended to decrease with stroke severity,⁷² suggesting that poststroke hypertension is not a unique physiological response to cerebral infarction, but rather that it shows an underlying instability in blood pressure and might even be the remnant of a preceding peak in blood pressure in some patients.

Statistical basis

Prediction of risk of vascular events on the basis of one blood-pressure reading is usually improved by use of the average of several readings from ABPM^{31–33} or home monitoring,^{37,38} but the strongest risk relations result from indirect statistical adjustment for the error in estimation of usual blood pressure, on the basis of the extent to which grouped baseline blood-pressure readings regress to the mean when repeated after follow-up.^{5,6,73} This correction for regression-dilution bias is widely accepted, but has mainly been studied in middle-aged healthy cohorts (webappendix p 10) and its interpretation

	UK trial	Dutch trial	Pooled*
Patients with low visit-to-visit variability†			
Unadjusted baseline SBP	1.58 (1.25–2.00)	1.35 (0.99–1.85)	1.50 (1.24–1.80)
Estimated usual SBP‡	1.93 (1.38–2.70)	1.60 (0.98–2.61)	1.82 (1.38–2.40)
Actual mean SBP§	1.72 (1.25–2.35)	1.68 (1.18–2.39)	1.70 (1.35–2.15)
Patients with high visit-to-visit variability‡			
Unadjusted baseline SBP	1.30 (1.11–1.52)	1.15 (0.95–1.40)	1.24 (1.09–1.40)
Estimated usual SBP‡	2.83 (1.51–5.30)	4.06 (0.57–28.8)	2.93 (1.61–5.32)¶
Actual mean SBP§	1.27 (1.00–1.61)	1.08 (0.76–1.54)	1.21 (1.00–1.47)¶

Data are hazard ratio (95% CI). Stroke risk calculation included all strokes after the measurement period (ie, after seventh follow-up visit); however, results were very similar when analysis also included events during and after the measurement period. SBP=systolic blood pressure. TIA=transient ischaemic attack. *Based on fixed-effect meta-analysis of the two trials. †Low variability includes patients with median variability or lower, and high those greater than the median; within-individual visit-to-visit variability is expressed as a transformation of the SD of measurements made at seven consecutive visits, which is uncorrelated with mean SBP. ‡Calculated by adjustment of baseline SBP for regression-dilution bias, with regression-dilution ratios of 0.42 (all patients), 0.70 (low variability), and 0.25 (high variability) in the UK trial and 0.38, 0.64, and 0.10, respectively, in the Dutch trial; ratios were calculated from the baseline measurement and the visit 7 (2-year) measurement. §Based on measurements of SBP made at the first seven consecutive follow-up visits. ¶p value for comparison of difference between hazard ratios was 0.006.

Table 1: Associations between SBP and stroke risk (hazard ratios per 20 mm Hg increase in SBP) in patients with low versus high visit-to-visit variability in SBP in UK and Dutch TIA trials*

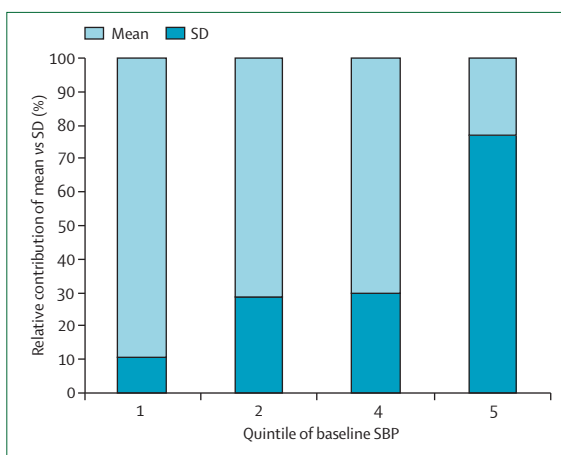


Figure 3: Relative strength of association of mean versus SD SBP* with baseline SBP in the UK TIA trial†

Contributions are determined from the Wald statistics from multinomial logistic regression (outcome is probability of being in a particular quintile, relative to quintile 3). SBP=systolic blood pressure. TIA=transient ischaemic attack. *On the basis of measurements at seven consecutive follow-up clinic visits.

might be more difficult in cohorts with variable blood pressure. The more variable blood pressure is in a population, the greater the degree of adjustment, with corrected risk relations up to five times steeper than the recorded relation in patients with previous TIA or stroke, for example.⁷³ From a physiological point of view, this finding makes little sense—the more variable blood pressure is, the less credible it becomes to argue that underlying usual blood pressure is likely to be pathologically relevant, yet the more the observed risk relation is amplified by the adjustment.

Moreover, in any cohort, adjustment is driven by patients with variable blood pressure, and the interpretation assumes that the predictive value of usual

	Treatment group			p value for difference in SD SBP	
	Amlodipine	Chlorthalidone	Lisinopril	Amlodipine vs lisinopril	Chlorthalidone vs lisinopril
Baseline	146.2 (15.7)	146.2 (15.7)	146.4 (15.7)	0.5	0.5
1-year follow up	138.5 (14.9)	136.9 (15.8)	140.0 (18.5)	9×10 ⁻⁷⁹	7×10 ⁻⁵⁵
2-year follow up	137.1 (15.0)	135.9 (15.9)	138.4 (17.9)	3×10 ⁻⁴⁸	1×10 ⁻²⁸
3-year follow up	135.6 (15.2)	134.8 (15.4)	136.7 (17.3)	9×10 ⁻²⁵	2×10 ⁻²⁵
4-year follow up	134.8 (15.0)	133.9 (15.7)	135.5 (17.2)	1×10 ⁻²⁴	2×10 ⁻¹⁴
5-year follow up	134.7 (14.9)	133.9 (15.2)	135.9 (17.9)	1×10 ⁻²⁴	8×10 ⁻²⁵

Data are mean (SD). p values for differences between treatment groups in inter-individual variation in systolic blood pressure (SBP; ie, SD SBP) are shown for every follow-up visit.

Table 2: Mean (SD) SBP at baseline and during follow-up in the ALLHAT trial,⁷⁴ stratified by randomised treatment group

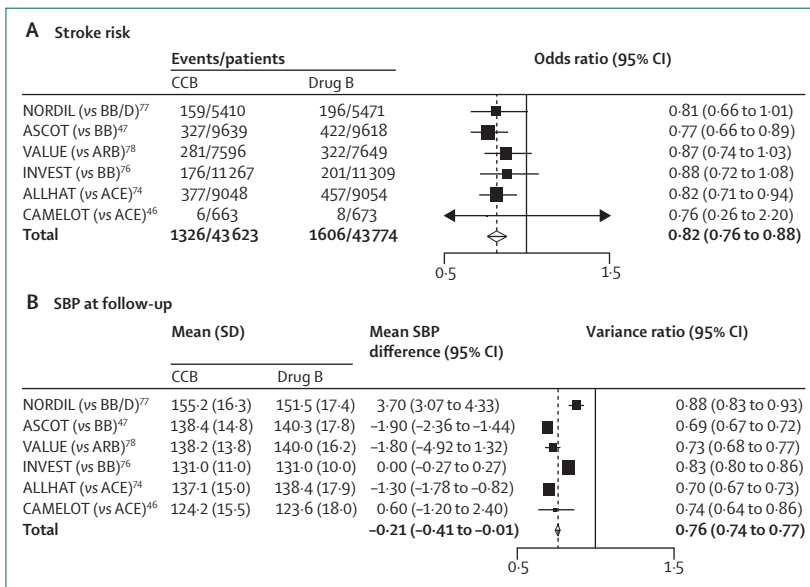


Figure 4: All large randomised trials of calcium-channel blocking drugs versus β blockers or ACE inhibitors in which the mean and SD SBP during follow-up were reported by treatment group (A) Stroke risk. (B) SBP at follow-up. The effect of the calcium-channel blocker versus other drug is shown for stroke risk during the trial and mean and SD SBP at the visit closest to the midpoint of follow-up (usually 2 years). The variance ratio is an estimate of the difference in variation in SBP between the groups (SD²/SD²). Pooled estimates of each of the measures were obtained by random effects meta-analysis. ACE=angiotensin-converting enzyme. BB=β blockers. CCB=calcium-channel blocker. D=diuretic. SBP=systolic blood pressure.

blood pressure is independent of variability. Table 1 compares the estimated relation between usual blood pressure and stroke risk with relations based on actual measured mean SBPs across seven clinic visits in two cohorts of patients with previous TIA or stroke. The estimated relation compares well with the observed relation in patients with stable blood pressure, but substantially overestimates the relation in those with variable blood pressure (HR 2.93 [1.61–5.32] vs 1.21 [1.00–1.47], p=0.006), even though actual mean blood pressure is measured equally well in both groups (intraclass correlation coefficients of mean blood pressure on visits 1–7 vs 8–14 were 0.77 and 0.82, respectively). Thus, in these cohorts at least, adjustment for regression-

dilution bias is driven by variability of blood pressure in patients in whom actual mean SBP is least predictive.

Standard interpretation of the adjustment for regression-dilution bias also assumes that all of the prognostic value of baseline blood-pressure readings is attributable to usual blood pressure—with variability being random. However, since variability is of prognostic value itself, and its relative contribution to a single blood-pressure reading is greatest at high blood pressure (figure 3), some of the increase in strength of the adjusted risk relation will be attributable to the prognostic value of variability rather than to precise estimation of usual blood pressure.

Trial evidence

The usual blood-pressure hypothesis also relies on the finding that in trials of antihypertensive drugs, effects on vascular risk are usually correlated with differences in mean blood pressure during follow-up.^{19–21} However, this result could partly be an artefact of the design of trials, which have often recruited only patients with blood pressure consistently within a specific range on repeated screening visits. After exclusion of patients with variable blood pressure, treatment effects will be accounted for mainly by effects on mean blood pressure. Some trials have not required stable hypertension before entry, but despite completion of nearly 2000 trials, the effect of treatment of episodic hypertension is unknown, and no investigators have ever reported the effects on within-individual visit-to-visit variability in blood pressure.²²

The accompanying reports^{8,22} provide the first trial evidence that benefits of antihypertensive drugs are determined by effects on variability in blood pressure as well as on mean blood pressure. Since about 50% of group SD of SBP at a single follow-up is due to within-individual visit-to-visit variability, as opposed to differences between individuals in underlying mean SBP,^{7,8} data for difference in group SD are also informative.²² For example, in ALLHAT,⁷⁴ investigators noted small differences in mean follow-up SBP between treatment groups, but there were also large differences in SD (table 2), which paralleled the group differences in stroke risk: lowest on amlodipine, intermediate on chlorthalidone, and highest on lisinopril. Group SD SBP in the chlorthalidone group was also lower than in the prematurely stopped doxazosin group⁷⁵ (variance ratio 0.78 [95% CI 0.75–0.81], p<0.00001). These arcane differences in SD have been ignored, but betray large differences in the number of patients with very high blood pressure at that particular follow-up visit, despite only small differences in group mean blood pressure. At the 1-year follow-up visit in ASCOT-BPLA,⁸ for example, modal SBP did not differ between the two treatment groups (webappendix p 3), but more patients on atenolol had SBPs of 180 mm Hg or higher (OR 2.44 [2.05–2.86] or 200 mm Hg or higher (3.45 [2.32–5.00]). This difference was not due to non-compliance (it was greatest in the on-treatment analysis)⁸ or to persistent hypertension in the

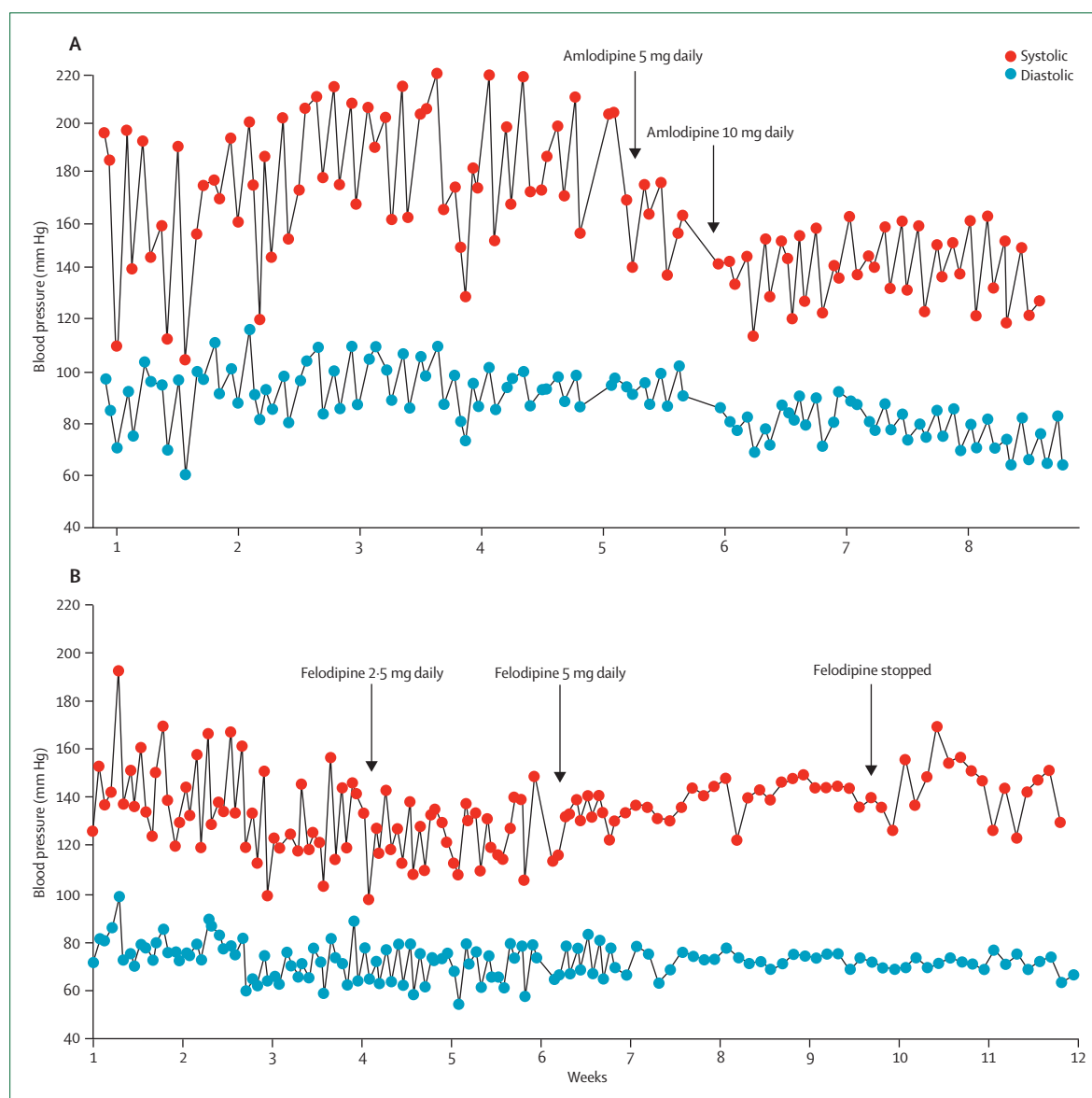


Figure 5: Effects of initiation and increase in dose of calcium-channel blockers on within-individual variability in blood pressure

Home blood-pressure measurements (average of three readings over 10 minutes) on three occasions per day in two patients during follow-up after transient ischaemic attack or minor stroke in the Oxford Vascular Study.²⁷

atenolol group; rather, it was caused by differences in visit-to-visit variability and peak SBP,⁸ which accounted fully for the treatment effect in ASCOT-BPLA after adjustment for mean blood pressure.

Figure 4 shows all major trials of calcium-channel blockers versus angiotensin-converting enzyme inhibitors or β blockers that reported treatment group SD SBP at follow-up.^{46,47,74,76-78} Group SD SBP and stroke risk were lower on calcium-channel blockers, despite no overall difference in mean SBP. The accompanying analysis of data from all trials of antihypertensive drugs²² shows consistent effects of drug class on group SD SBP (reduced most by calcium-channel blockers and increased

most by β blockers), which accounts for why β blockers are less effective, and calcium-channel blockers more effective, for prevention of stroke than can be accounted for by their effects on mean blood pressure.^{21,79,80} Calcium-channel blockers are no more effective than are other agents for prevention of myocardial infarction and are less effective for prevention of heart failure,²² but do seem to be of most overall benefit in patients with normal blood pressure⁴⁶ or mild hypertension.⁸¹

The accompanying re-analysis of the Medical Research Council trial of blood-pressure reduction in elderly hypertensive patients²² casts most doubt on the usual blood-pressure hypothesis. In this trial and its sister trial

Panel 2: Testable predictions stemming from the hypotheses set out in this Review

- Visit-to-visit variability in blood pressure will be associated with other measures of impaired control of blood pressure, such as postural instability or sympathetic overactivity, which will also be subject to drug-class effects
- Increased variability and instability in blood pressure will be a risk factor for vascular dementia, the incidence of which might therefore also be best reduced by drugs that reduce variability in blood pressure
- Differences in within-individual variability in systolic blood pressure (SBP) will also account for results of other randomised trials of antihypertensive drugs, such as ALLHAT,^{74,75} in which effects on stroke risk were not accounted for by mean blood pressure
- Patients with normal mean blood pressure but increased variability in blood pressure and episodic hypertension will benefit more from antihypertensive drugs than will patients with stable normotension
- Patients with episodic hypertension will benefit most from drugs such as calcium-channel blockers that reduce variability in blood pressure
- Patients already on treatment for hypertension who have variable SBP despite good compliance and good control of mean SBP will benefit from the addition of a drug that will reduce variability
- Drug-class effects on variability in blood pressure will differ in extent between individuals, such that response to treatment will be best established by individual monitoring (figure 5)
- That statins reduce variability in blood pressure will account for some of their benefit in stroke prevention, and could lead to synergism with calcium-channel blockers and other drugs that reduce variability
- Increased variability in blood pressure will be an additional confounding factor in the association between raised inflammatory markers, such as C-reactive protein, and risk of vascular events
- In at least some patients with poststroke hypertension, the acute increase in blood pressure will have occurred before the stroke and be the cause of the event rather than a consequence

in young hypertensive patients,^{82,83} β blockers had no effect on stroke risk for the first 2–3 years of follow-up, despite reducing mean SBP by more than 10 mm Hg compared with placebo, whereas risk of stroke was reduced substantially in patients allocated to diuretic drugs. Re-analysis showed that visit-to-visit variability in SBP was substantially higher in the atenolol group than in the placebo or diuretic groups during initial follow-up.²² Subsequent reductions in stroke risk in the atenolol group paralleled reductions in blood-pressure variability, very probably due to add-on use of diuretics and calcium-channel blockers. Thus, no reliable evidence exists that β blockers alone prevent stroke, despite substantially reducing mean SBP.

Mechanisms and causation

Although accelerated atherosclerosis is often cited as the mechanism by which hypertension affects vascular risk, strong risk factors for atherosclerosis, such as smoking and raised lipid concentrations, are weak risk factors for stroke. Increased atrial fibrillation and small-vessel disease might also play a part, but regression of these chronic pathological findings would not account for why

stroke risk falls within weeks of starting of calcium-channel blockers.^{46,47,76–78} Reduced variability in blood pressure is, however, maximum at first follow-up in such trials, and occurs so quickly in some patients (figure 5) that direct effects on neural control of blood pressure might be involved.⁸⁴ The opposite effect of β blockers is equally rapid and does not seem to be due merely to reduced heart rate.⁸

Increased variability in blood pressure could itself be due to subclinical cerebral ischaemia impairing central autonomic control,⁸⁵ resulting in reverse causation, but drugs that reduce variability should not then prevent stroke. Calcium-channel blockers decrease arterial stiffness,^{86,87} which reduces pulsatility of blood flow in cerebral vessels, and might reduce stroke risk.⁸⁸ However, other antihypertensive drug classes also reduce arterial stiffness,^{86,87} but do not reduce variability of blood pressure or stroke risk to the same extent as do calcium-channel blockers,²² and calcium-channel blockers reduce variability before arterial remodelling has time to occur. However, decreased visit-to-visit variability on atorvastatin in ASCOT-BPLA⁸ suggests that the reduction in arterial stiffness reported during statin treatment^{89,90} might accentuate the effect of calcium-channel blockers, accounting for the especially low stroke risk on the combination.^{90,91} Amlodipine reduced central blood pressure more than did atenolol in ASCOT-BPLA,⁹² but this finding did not account for the treatment effect,⁹² and was probably due to the different effects of the drugs on heart rate,⁹³ which is only weakly associated with variability in blood pressure.⁸

In stroke-prone spontaneously hypertensive rats, increased short-term variability in blood pressure causes ischaemic stroke and other end-organ damage,⁹⁴ and experimental sinoaortic denervation in the rat, which markedly increases variability in blood pressure without changing mean blood pressure, also causes left ventricular hypertrophy, and aortic vasoconstriction.⁹⁵ Importantly, in keeping with the accompanying evidence in man,^{7,8} increased variability in this model causes end-organ damage at normal mean blood pressure.^{95,96} Results in animals also show that variability in blood pressure is associated with raised inflammatory markers,^{95,96} which is also reported in man,⁹⁷ and confirm that statins reduce variability.⁹⁸

How then might variability and instability in blood pressure cause stroke? Sudden falls in blood pressure can cause cerebral ischaemia,⁹⁹ especially in patients with small-vessel disease, but autoregulation remains intact and so gradual reductions do not reduce perfusion,¹⁰⁰ unless there is stenosis of extracranial vessels.¹⁰¹ Indeed, the evolution of such a complex system for maintenance of constant cerebral perfusion, with resistance arterioles varying two-to-three fold in diameter (webappendix p 4),¹⁰² suggests that deviations in either direction might be harmful. Risk of ischaemia is likely to be greatest if both variability and instability are increased (which they will

often be, since both associate with arterial stiffness and baroreceptor dysfunction) such that changes in blood pressure are sudden and large. Interestingly, in parallel with differences in blood-pressure variability,^{7,8,22} orthostatic instability in blood pressure is also most common on β blockers and least common on calcium-channel blockers.⁵⁷

Anecdotally, acute increases in blood pressure can cause cerebral haemorrhage¹⁰³ and ischaemic stroke, as in pre-eclampsia, pheochromocytoma, and cocaine or amphetamine abuse. In patients with small-vessel disease, autoregulatory vasoconstriction due to a peak in blood pressure might reduce perfusion of subcortical or borderzone areas, which is already poor,¹⁰⁴ especially if blood pressure then falls. Peaks in blood pressure can cause spasm in large cerebral arteries,¹⁰⁵ but changes to small vessels due to repeated fluctuations is a more likely cause of ischaemia, possibly mediated by endothelial dysfunction. Different effects of calcium-channel blockers and β blockers on the structure of the analogous retinal microvasculature are very interesting in this respect.¹⁰⁶

Visit-to-visit variability in clinic blood pressure relates more closely to stroke risk and to effects of antihypertensive drugs on stroke risk than does variability on ABPM,^{7,8} perhaps because of a closer association with instability in blood pressure, or to changes in variability and instability with time. In view of the variation of underlying blood pressure with time (webappendix p 2),^{35,36} shifting of the cerebral autoregulation curve (webappendix p 4),^{107,108} and hence the thresholds needed to induce ischaemia, a complex interplay between mean blood pressure, instability, and variability is likely. Baroreceptors should reset over time and still buffer fluctuations in blood pressure,¹⁰⁹ but are impaired by age and arterial disease,¹¹⁰ and so falls in blood pressure might induce ischaemia when mean blood pressure is high, whereas peaks in blood pressure can lead to ischaemia when mean blood pressure is low—as noted in the accompanying reports.^{7,8} More research is needed into variability and risk of coronary events, for which troughs in diastolic blood pressure could be key.^{7,8}

Implications for guidelines, practice, and research

Incidence of stroke exceeds that of coronary events in developed countries,⁶⁸ and is rising steeply in developing countries. Yet, hypertension guidelines, based on the usual blood-pressure hypothesis, are poorly suited to prevention of stroke. First, diagnostic strategies should take into account the effect of increased visit-to-visit variability in blood pressure and episodic hypertension on vascular risk. More research is needed into how to quantify variability and instability in routine practice, and into variability in cohorts of younger adults, but the focus only on short-term variability on ABPM has been too narrow. Second, antihypertensive drugs should be chosen to reduce variability as well as usual level. Trials of calcium-channel blockers are needed in patients with

episodic hypertension, but effects in patients with normal baseline SBP⁴⁶ or mild hypertension are encouraging,⁸¹ and there is now good evidence that agents that reduce variability will be most effective for stroke prevention.^{24,25} It is also noteworthy that the polypill and polycap, as currently formulated, do not necessarily contain a calcium-channel blocker.

Third, data for blood-pressure variability during trial follow-up should be routinely reported. Stratification of results according to variability established during a run-in might also be informative. Fourth, irrespective of drug class, emphasis on consistency of blood-pressure control during treatment should be increased. In both treatment groups in ASCOT-BPLA,⁸ patients with well controlled mean blood pressure had a five-fold increased risk of vascular events if their visit-to-visit variability in SBP was high, even when fully compliant with trial drugs. Calls to abandon measurement of blood pressure after treatment¹⁷ may be premature. Fifth, new antihypertensive drugs should be developed to stabilise as well as to lower blood pressure. The reduction in variability achieved by calcium-channel blockers is fairly small on average, and so new agents, or combinations, that yield increased reductions could have a major effect on outcomes. Agents that reduce variability without reducing mean blood pressure should still prevent stroke, and could be used in patients who develop orthostatic symptoms on antihypertensive drugs. Finally, safety testing of all drugs should include assessment of effects on instability and variability in blood pressure.

Conclusion

Increased mean blood pressure is an important cause of arterial disease, but the usual blood-pressure hypothesis is inconsistent with much of the epidemiology of hypertension and stroke, and its clinical application is questionable in patients with variable blood pressure. Variability and instability in blood pressure also have important roles in the progression of organ damage and in triggering of vascular events. Further research is needed to refine understanding of the causes, consequences, and treatment of variability in blood pressure, and several testable predictions (panel 2) should facilitate this process. In the meantime, clinicians should be aware of the prognostic implications of visit-to-visit variability in blood pressure and of the related drug-class effects.

Conflicts of interest

I declare that I have no conflicts of interest.

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