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Eamon Dolan and Eoin O'Brien

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Blood Pressure Variability Clarity for Clinical Practice

Eamon Dolan, Eoin O'Brien

A series of articles¹⁻⁴ published recently in *The Lancet* and *Lancet Neurology* raise an interesting issue that has implications for both the clinical management of hypertension and future research in hypertension, particularly in the development and use of different classes of blood pressure (BP)-lowering drugs. These studies, which were led by Peter Rothwell at the John Radcliffe Hospital in Oxford, United Kingdom, suggest that, whereas there is undoubted and well-proven benefit in the current practice of reducing mean BP to prevent cardiovascular events, there may be additional benefit in also reducing BP variability (BPV), especially to prevent stroke. The studies suggest, moreover, that different classes of drugs are superior to others in reducing BPV (calcium channel blockers being best and the β -blocker atenolol being worst). However, these articles, by virtue of their sheer volume (\approx 50 pages of printed text and many pages of supplementary web appendix data), could overwhelm all but the most stoic readers, and misinterpretation of the data could lead to confusion and have an adverse effect on clinical practice. It is important, therefore, to assess the scientific reality and determine how attention to BPV might benefit patients with hypertension.

A Summary of the Studies

In the first analysis, systolic BPV between visits and maximum BP reached in 4 cohorts of patients with previous transient ischemic attacks were strong predictors for subsequent stroke.¹ In treated hypertensive patients in the Anglo-Scandinavian Cardiac Outcome Trial-Blood Pressure Lowering Arm systolic BPV between visits was also a strong predictor of stroke and coronary events independent of mean clinic or ambulatory BP measurement (ABPM). BPV on ABPM was a weaker predictor overall but was related to visit-to-visit variability. Traditional measures of variability, such as SD and coefficient of variation (CV), were used in these analyses, but one of the problems encountered in the prognostic modeling of BPV and mean BP together is that the 2 variables are correlated, and it can be problematic to adjust usual measures of variability in a multivariate model. Therefore, a new measure of variability uncorrelated with mean BP was derived; named variation independent of mean (VIM), this measure is a transformation of SD uncor-

related with mean BP and is a statistical tool, rather than a clinical measure. VIM is calculated by fitting a curve through a plot of SD systolic BP (SBP; y axis) against mean SBP (x axis) with the parameter x estimated from the curve [VIM=(SD/mean^x)]. In the first analysis, VIM was consistent with other measures of BPV, suggesting that variability affects outcome independent of mean BP.

In the second analysis, visit-to-visit variability was evaluated in 2 large trials, the Anglo-Scandinavian Cardiac Outcome Trial-Blood Pressure Lowering Arm and the Medical Research Council Trial to determine whether the class of drug used might reduce BPV and by so doing reduce the occurrence of stroke.² In the Anglo-Scandinavian Cardiac Outcome Trial-Blood Pressure Lowering Arm, patients treated with amlodipine and perindopril had lower BPV both on clinic BP and ABPM than patients on atenolol and a thiazide diuretic.³ Importantly, the marked changes in BPV between the 2 treatment groups were seen very early in this study, and in contrast to previous analyses of these data⁵ the addition of BPV indices explained a large proportion of the treatment benefit in patients treated with the amlodipine-perindopril combination. In the Medical Research Council Trial, systolic BPV was increased in the patients treated with atenolol compared with patients in the diuretic and placebo groups. From these analyses, it would appear that the opposite effects of calcium-channel blockers and β -blockers on BPV account for the disparity in observed effects on the risk of stroke. These results would suggest, therefore, that the most effective approach to preventing stroke is to use BP-lowering drugs that reduce both mean BP and BPV and to avoid drugs that increase BPV even if they reduce mean BP.

In the third analysis (a meta-analysis of 389 trials), systolic BPV was reduced by calcium channel blockers and thiazide diuretics and increased by β -blockers, angiotensin-converting enzyme inhibitors, and angiotensin-receptor blockers.⁴ However, this result was derived from observed differences in SD in the treatment groups of these studies, and the effect of different drug classes on BPV should be interpreted with caution, at least until BPV has been evaluated in larger cohorts of hypertensive patients on treatment with different drug regimens, such as in the Blood Pressure Lowering Treatment Trialists' Collaboration.⁶

Collectively these 3 studies provide evidence to suggest that BPV, whether measured on clinic visits or on ABPM, is predictive for stroke and other cardiovascular events and that calcium channel blockers, and to a lesser extent thiazide diuretics, are superior to other drugs in reducing BPV and preventing stroke and other vascular events and that the older β -blocker atenolol, which increases BPV, should probably only be used as a first-line drug if there are other compelling clinical indications, such as ischemic heart disease. It should

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From the Hypertension Unit (E.D.), Connolly Hospital, Dublin, Ireland; Department of Molecular Pharmacology (E.O.), Conway Institute, University College Dublin, Belfield, Dublin, Ireland.

Correspondence to Eoin O'Brien, Department of Molecular Pharmacology, Conway Institute, University College Dublin, Belfield, Dublin, Ireland. E-mail cobrien@iol.ie

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Measures of Variability

- SD=square root [sum of (individual reading-sample mean)²/number of readings].
- CV=SD/mean.
- VIM=SD/mean^x; which is essentially similar to CV except that the mean BP denominator is raised to a certain power, x, that removes any correlation with mean BP. The derivation of x is explained in the text.
- ASV=average absolute difference between successive values.

SD indicates standard deviation; CV, coefficient of variation; VIM, variation independent of the mean; BP, blood pressure; ASV, average successive variability.

be stressed that there is no evidence one way or the other that the newer generation of β -blockers affects BPV.

These studies do not call into question the lowering of mean BP as recommended in all of the guidelines, but they do draw attention to BPV, which was identified as being associated with an adverse outcome by Parati and his colleagues over 20 years ago, and his group has continued to highlight the importance of BPV in hypertension.^{7,8} The findings are also in agreement with the Ohasama Study showing that medium-term BPV was an independent predictor of stroke after adjustment for mean BP,⁹ and a recent study in which subjects with greater BPV and higher mean BP had a greater risk of cerebrovascular disease than those with lower mean BP and nonfluctuating BP.¹⁰ However, in a large population cohort (8938 subjects), although short-term reading-to-reading BPV with ABPM was an independent risk factor, the level of the 24-hour ABPM was the primary BP-related risk factor in need of correction in clinical practice.¹¹

What Are the Implications for Clinical Practice and Research?

The body of research led by Rothwell is clearly important and should focus the minds of clinical scientists, the pharmaceutical industry, those interested in BP measurement, and doctors who care for patients with hypertension on the need to study the mechanisms of BPV, to devise methods for its accurate detection, and to determine how best to reduce it. As can be seen in Figures 1 and 2, the reduction in ABPM variability in the Anglo-Scandinavian Cardiac Outcomes Trial ABPM Study almost mirrors visit-to-visit variability, and it may be possible by concentrating on the many measures of variability already available within a single ABPM to identify an index of variability that would be equivalent to visit-to-visit variability. Work has already been done using ABPM to gauge the smoothness of BP control and the influence of the duration of action of BP-lowering medication.¹² Trials are now needed to determine whether drugs and combinations of drugs that reduce both mean BP and BPV will have a beneficial effect on outcome. It is likely that the duration of action and time of administration of drugs will be important considerations in reducing BPV.

So much for the future; what are the implications for today's doctors treating patients with hypertension? Detecting BPV appears straightforward in retrospective studies, but this is not readily done in practice. Improved methods of collecting and storing data electronically so as to detect trends in BP in the office and home and the increased use of ABPM are

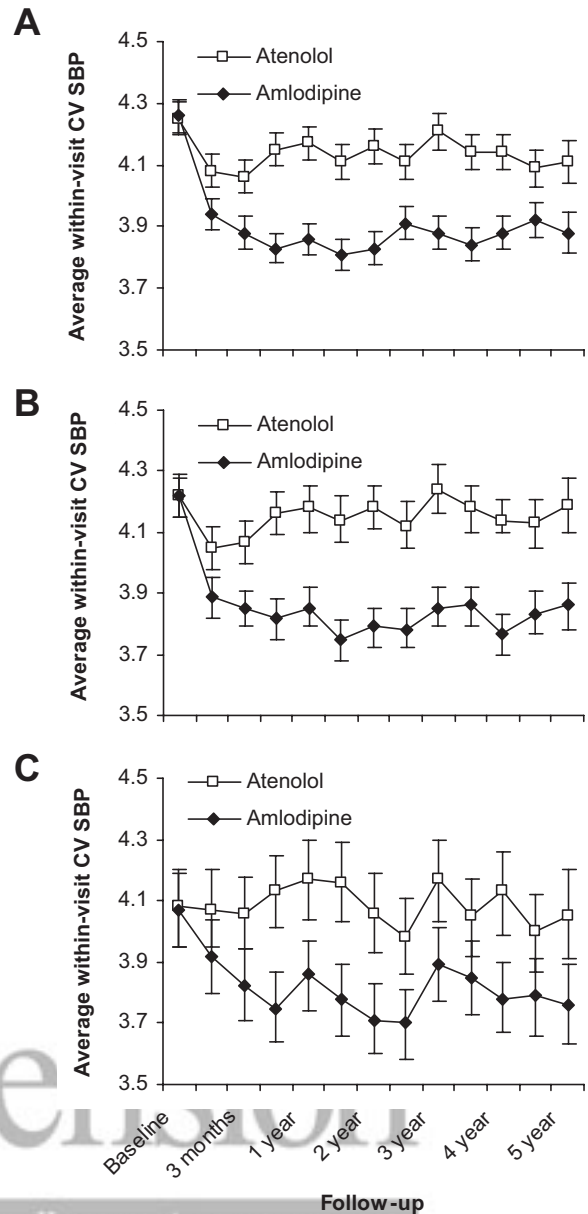


Figure 1. Within-visit variability of SBP in Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm.² Bars are 95% CI. Within-visit variability (CV) of SBP in Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm. A, All patients. B, Patients on treatment. C, Patients not on antihypertensive drugs at baseline.

methods that should be more widely available, but clearly research into such methodologies will take time. However, there are more positive solutions at hand on the therapeutic front.

The recent introduction of what we have termed the “flexipill” to distinguish it from its more primitive predecessor the “polypill” is a welcome therapeutic innovation.¹³ Polypills have been available for many years in different guises. The first polypill was introduced in 1967 for the Veterans’ Administration Study; SER-AP-ES was a combination of reserpine, Apresoline, and a thiazide diuretic.¹⁴ This was followed by combination pills composed of thiazide diuretics with potassium or with potassium-sparing diuretics and then by combination pills of β -blockers with thiazide diuretics and, more recently, by angio-

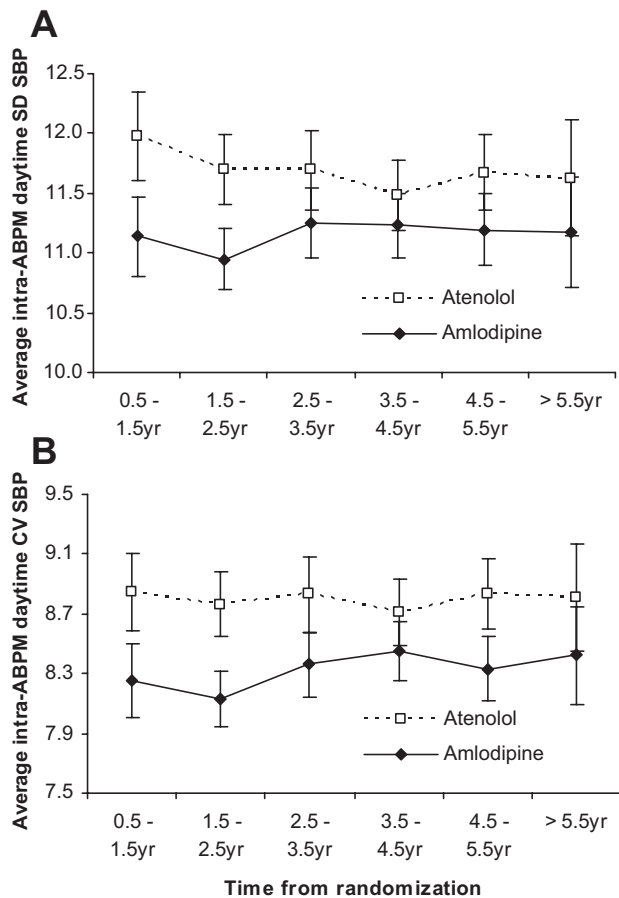


Figure 2. Variability in daytime SBP on ABPM by randomized treatment allocation in ASCOT-BPLA.² Daytime SD SBP (A) and CV SBP (B) from annual ABPM recordings during follow-up in Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm. Bars are 95% CI.

tensin-converting enzyme inhibitors and angiotensin-receptor blockers combined with thiazide diuretics. However, these early polypills had the major disadvantage of being fixed-dose combinations, making up-titration and tailoring of treatment to the individual patient impossible. The pharmaceutical industry has now recognized the need for flexible-dose combinations within 1 tablet allowing a prescribing physician to increase the dosage of the component parts in a single tablet according to BP response. In this regard, we now have flexipill combinations of

Clinical Messages From BPV Analyses

- Lowering mean BP remains the therapeutic goal of BP management.
- Prognostic information in the medium-term fluctuations of BP is not captured using mean BP alone.
- ABPM may indicate BPV and should be used more widely in clinical practice.
- Most patients need more than one drug for BP control, and consideration should be given to using combination drugs that lower both mean BP and BPV.
- Greater use of electronic recordings of BP allows for the calculation of BPV.
- Further prospective work is needed to elucidate whether altering BPV will improve outcome.

ABPM indicates ambulatory blood pressure measurement; BP, blood pressure; BPV, blood pressure variability.

angiotensin-receptor blockers and angiotensin-converting enzyme inhibitors with calcium channel blockers, angiotensin-receptor blockers and angiotensin-converting enzyme inhibitors with thiazide diuretics, and β -blockers and renin inhibitors with thiazide diuretics. Quite apart from the advantages of being able to prescribe low doses of 2 drugs in 1 tablet, thereby minimizing the adverse effects that might occur with higher doses of the individual components and the beneficial effects that this should have on compliance, the flexipill provides a means of not only lowering mean BP but of also reducing BPV by using medication with a contrasting mode of actions. So the concluding message for doctors managing patients with hypertension is that we acknowledge the exhortations of the guidelines that to achieve BP control requires more than one BP-lowering drug in most patients but that we may now consider availing of advantages offered in the flexipills, among which is the opportunity to lower both mean BP and BPV.

Disclosures

None.

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