

Treating Visit-to-Visit Blood Pressure Variability to Improve Prognosis Is Amlodipine the Drug of Choice?

Anastasios Kollias, George S. Stergiou, Konstantinos G. Kyriakoulis, Grzegorz Bilo, Gianfranco Parati

Blood pressure (BP) levels are linearly associated with cardiovascular risk, and hypertension is the most common modifiable risk factor for cardiovascular disease.¹ Moreover, antihypertensive treatment-induced BP lowering has been associated with reduction in all outcomes (stroke, heart failure, coronary events, cardiovascular, and all-cause mortality).² Apart from the established knowledge regarding the importance of hypertension and its effective treatment, during the last years, there has been an increasing interest in the possibility that BP variability (BPV) might carry an additional contribution to cardiovascular risk, on top of the impact of mean BP levels. BP fluctuates constantly and its variability not only may have diagnostic implications regarding the accurate assessment of hypertension but also seems to exert additional stress on the cardiovascular system over and above average BP levels.³ Different components of BPV have been identified, characterized by BP fluctuations between hours, days, or months/years, respectively, termed as short-, mid-, and long-term components.³ All these types of BPV have been shown to carry an independent prognostic value in terms of cardiovascular events and all-cause and cardiovascular mortality.⁴⁻¹⁰

Three interesting articles have been recently published in this journal regarding long-term visit-to-visit BPV (VTV). Tedla et al¹¹ showed that an increased VTV among 1122 untreated individuals was predictive of arterial stiffness progression after 10 years of follow-up. The 2 remaining papers reported data on the prognostic value of systolic VTV coming from 2 major trials: the observational extension of the ADVANCE trial (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation)¹² and the SPRINT (Systolic Blood Pressure Intervention Trial).¹³

However, it seems that at the present time, despite the accumulating evidence on the clinical relevance of VTV, the latter still remains a research tool failing to provide clinical application in practice.^{14,15}

Evidence on the Clinical Relevance of VTV

The first step for an index of BPV to be applied in clinical practice is the demonstration of its clinical relevance, in terms

of cardiovascular prognosis, as well as in terms of incremental value in risk stratification over and above average BP levels. Growing evidence suggests that BPV carries cardiovascular prognostic value independent of the average BP. A recent meta-analysis showed similar hazard ratios for all-cause mortality among all types of systolic BPV (VTV: 1.12 [95% confidence intervals, 1.05–1.20]; day-to-day home BPV: 1.15 [95% confidence intervals, 1.06–1.26]; 24-hour ambulatory BPV: 1.11 [95% confidence intervals, 1.04–1.18]).⁵ However, the strongest evidence has been provided for VTV.⁵ Recent meta-analyses of studies that used different methodologies (based on categorical or continuous analyses) showed that VTV—mainly assessed by standard deviation (SD) of BP values measured across repeated visits—is independently associated with total and cardiovascular mortality.⁴⁻⁶ In the last 2 years, several large studies (not included in the aforementioned meta-analyses) investigated the prognostic value of VTV in terms of mortality (Table).^{7,12,13,16,17} Interestingly, 4 of them included patients at high risk (Table).^{12,13,16,17} It is important to note that the ADVANCE-ON study (ADVANCE-Observational) showed that further to the independent prognostic value of the SD of systolic BP, its addition in the assessment of patients' cardiovascular risk significantly improved the 8-year risk classification beyond that provided by traditional risk factors, including average systolic BP.¹² This is highly relevant given that this study included subjects with diabetes mellitus and hypertension, which means that the incremental value of long-term BPV was evident despite the already high risk of these individuals.¹² Similar results were obtained also by considering other indices of VTV, such as the coefficient of variation, variation independent of mean, average successive variability, residual SD, and range of systolic BP values, which is reassuring for the consistency of the VTV clinical relevance.¹² On the contrary, the analysis of the SPRINT failed to show an independent prognostic value of systolic VTV regarding the primary end point, although a marginal association was found with all-cause mortality.¹³ It should be mentioned, however, that the latter trial presents different characteristics compared with the other trials, mainly regarding the office BP measurement methodology and the achieved BP levels which, along

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Table. Recent Large Studies on the Prognostic Value of Visit-to-Visit Blood Pressure Variability

Study	Study Characteristics	Index of Blood Pressure Variability	Results	
			All-Cause Mortality	CVD Events
Chang et al ¹³	Age >75 y or ≥50 y with ≥1 of the following: evidence of clinical/subclinical CVD, 10-year Framingham risk score for CVD events ≥15%, or CKD (n=7.879)	CV SBP	± (adjusted <i>P</i> =0.07)	–
Vidal-Petiot et al ¹⁶	CHD patients (n=13.794)	SD;ARV SBP/DBP	+; -/+; +	+; +/+; +
Bangalore et al ¹⁷	MI patients (n=8.658)	ASV SBP/DBP	+/+	+/+
Ohkuma et al ¹²	Type 2 diabetic patients (n=9.114)	SD SBP	+	+
Gosmanova et al ⁷	US Database-Veterans Affairs (n=2.865.157; 63% HTN)	SD SBP	+	+*

ARV indicates average real variability; ASV, average successive variability; CHD, coronary heart disease; CKD, chronic kidney disease; CV, coefficient of variation; CVD, cardiovascular disease; DBP, diastolic blood pressure; HTN, hypertension; MI, myocardial infarction; SBP, systolic blood pressure; and SD, standard deviation.

*Coronary events.

with the relatively short period of follow-up, could have accounted, at least in part, for its results.

The prognostic importance of VVV in treated hypertensive individuals, might be, at least in part, attributed to the fact that VVV reflects the long-term degree of BP control and stability.^{18,19} A post hoc analysis of the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) showed that VVV was higher among subjects reporting to take <80% of their antihypertensive medications at ≥1 study visits.²⁰ However, notwithstanding the significant association between medication nonadherence and VVV, nonadherence did not explain the association between VVV and cardiovascular and mortality outcomes.²⁰

Despite the accumulating and consistent evidence on the prognostic value of VVV, several unanswered questions still remain, including the optimal protocol to be used for office BP assessment, the methodology for the assessment of average BP levels and BPV, the thresholds to identify subjects at risk, and most importantly, the therapeutic implications of BPV management.

Meta-Analyses Regarding Therapeutic Implications: Is There a Specific Role for Calcium-Channel Blockers?

In the absence of large clinical intervention trials providing ad hoc evidence on the importance of using BPV as a treatment target and on potential drug class-specific effects in reducing BPV, evidence is derived from post hoc analyses of previous studies and, indirectly, from a historical meta-analysis.²¹ Webb et al²¹ performed a meta-analysis regarding the effect of antihypertensive drugs on interindividual BPV and risk of stroke. The authors based their analysis on interindividual BPV taking into account reports showing that ≈50% of group SD of systolic BP at any follow-up duration was the result of within-individual VVV rather than of differences between individuals in underlying average systolic BP levels.²¹ Their 2 main results were that (1) when performing between-drugs comparisons, interindividual systolic BPV was reduced by calcium-channel blockers (CCBs) and nonloop diuretic drugs, while it was increased by angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β-blockers, and (2) across all trials, the effects of treatment on both systolic BP average levels and systolic BPV accounted for the treatment effects

on stroke risk, with both parameters remaining significant in a combined model.²¹ It should be noted that most of the available evidence concerning the favorable effect of CCBs on VVV regarded amlodipine.²¹

Wang et al²² performed a meta-analysis using data on the treatment-induced changes in intraindividual BPV available from randomized clinical trials involving amlodipine and other comparators and showed amlodipine to be more effective in minimizing VVV.

Aiming to simulate the analysis by Webb et al—but by using intraindividual BPV—we used the data of Wang et al and plotted the between-group differences (amlodipine versus comparators) in coefficient of variation of systolic BP (least squares means obtained from visits performed from 12 weeks onwards for each study) against the odds ratios (amlodipine versus comparators) for each study primary end point, stroke, and all-cause mortality from the respective randomized clinical trials (ASCOT-BPLA [Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm], ALLHAT, and CAMELOT [The Comparison of Amlodipine Versus Enalapril to Limit Occurrences of Thrombosis]).^{23–25} In general, there was a trend toward greater reductions in odds ratios for each end point, with greater decreases in coefficient of variation of systolic BP achieved by amlodipine versus other comparators (Figure 1). Most importantly, although the data are derived from a smaller number of trials, the pattern of plot regarding the risk of stroke was similar to that published by Webb et al,²¹ which is reassuring for consistency of the results provided by both approaches.

Mechanisms Regarding VVV and the CCBs-Induced Reduction in VVV

VVV seems to be influenced by biological and behavioral factors (advanced age, female sex, history of cardiovascular disease, smoking, alarm reaction in the office visit, etc), by seasonal climatic changes, and by treatment-related parameters as previously reported.^{3,13,20} Arterial stiffness and endothelial and smooth muscle dysfunction have been proposed as mechanisms underlying the association between VVV and outcome.^{26,27} Furthermore, the underlying mechanisms accounting for the beneficial effect of CCBs—especially amlodipine—on VVV have not been clarified, but there are a few hypotheses. Zhang et al²⁸ investigated the effect of

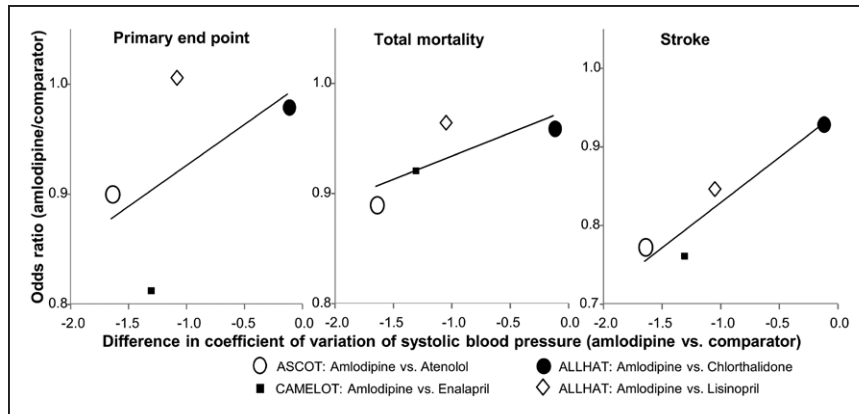


Figure 1. Plot of odds ratios (amlodipine/comparators) for several end points against the differences in coefficient of variation of systolic blood pressure between amlodipine and comparators. Size of symbols corresponds to the study sample size. ALLHAT indicates Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; and CAMELOT, The Comparison of Amlodipine Versus Enalapril to Limit Occurrences of Thrombosis.

candesartan, indapamide, and amlodipine on BPV using ambulatory BP data before and after 3 months of treatment. Both indapamide and amlodipine reduced systolic BPV, but the reduction induced by amlodipine was associated with reduction in both average BP levels and in heart rate variability, implying amelioration of the autonomic nervous system regulation.²⁸ Furthermore, other mechanisms related to the action of CCBs, including their profound vasodilatory effect, the potential improvements in arterial baroreflex sensitivity and arterial stiffness, as well as the attenuation of the myogenic response of vascular smooth muscle cells, may all contribute to the CCBs-induced reduction in VVV.^{29–31}

Hypothesis: Is There Any Contribution of BPV to the Findings of the ACCOMPLISH Trial?

The ACCOMPLISH trial (The Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension) was one of the landmark studies showing that an angiotensin-converting enzyme inhibitor-CCB (benazepril-amlodipine) combination is superior to an angiotensin-converting enzyme inhibitor-thiazide diuretic (benazepril-hydrochlorothiazide) combination in reducing cardiovascular events in patients with hypertension at high risk (high percentage of diabetics included).³² The risk reduction achieved with the benazepril-amlodipine combination could not be attributed to between-group differences in average BP levels (around 1 mmHg for systolic/diastolic BP).³²

We speculated that BPV may be more overtly reduced in the benazepril-amlodipine compared with the benazepril-hydrochlorothiazide arm. In one of the subanalyses of the ACCOMPLISH trial, according to body size, data on average

BP values, as well as on their SD, were given for both baseline and after 6 months of follow-up (titration completed at first 3 months).³³ We calculated the overall weighted (for sample size of body mass index subgroups) percent change ((follow-up minus baseline)/baseline) in coefficient of variation for systolic/diastolic BP corresponding to the changes in interindividual BPV for the 2 treatment arms. Although this approach does not exactly correspond to intraindividual VVV, as previously shown, it gives a rather rough estimate of this phenomenon.²¹ It appeared that interindividual BPV was increased in the benazepril-hydrochlorothiazide group as compared with the benazepril-amlodipine group, in which BPV values were decreased (Figure 2). A specific analysis of the raw study data would be desirable and could confirm whether a potential reduction of BPV induced by amlodipine did contribute, at least in part, to the outcome findings of this trial.

Regarding the available evidence on the comparison of CCBs versus diuretic-based combinations, it should be noted that in the COLM study (Combinations of OLMesartan), which included a smaller patient sample as compared with the ACCOMPLISH study, the olmesartan-CCB versus the olmesartan-diuretic combination was not found to be superior in terms of the primary end point, although the incidence of stroke tended to be lower in the elderly subjects of the former group.³⁴ Interestingly, in a subanalysis of this study, VVV of systolic BP was smaller in the olmesartan-CCB than in the olmesartan-diuretic group, especially in elderly patients, as well as in isolated systolic hypertensive patients.³⁵ Moreover, the incidence rate of the primary end point increased along with an increment in the SD of systolic BP in all of the age and treatment groups.³⁵ Furthermore, the study by Matsui et al²⁹ in

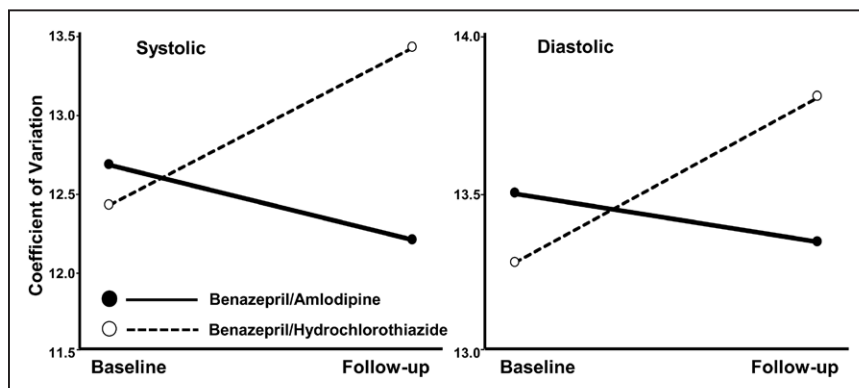


Figure 2. Change in coefficient of interindividual variation for systolic/diastolic blood pressure in the 2 treatment arms of the ACCOMPLISH trial (The Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension).

207 hypertensive subjects compared the olmesartan–azelnidipine combination versus the olmesartan–hydrochlorothiazide combination in terms of reduction of BPV and regression of arterial stiffness. Home BP monitoring was performed before each office visit (total of 7 visits during a 24-week period of follow-up). The authors concluded that for similar reduction in average home BP, the azelnidipine-based compared with the hydrochlorothiazide-based treatment reduced to a greater degree home BPV. Moreover, this change was associated with a reduction in arterial stiffness.²⁹

Perspectives

VVV seems to have an independent prognostic value over and above the impact of average BP. Accumulating evidence, mainly derived from post hoc analyses and meta-analyses of clinical trials, implies that CCBs—especially amlodipine—may have a more evident role in reducing VVV, which might lead to further risk reduction. Randomized outcome intervention trials are needed to explore whether a treatment-induced reduction in BPV using specific drug classes in specific patient categories is accompanied by an independent reduction in the cardiovascular events rate and mortality.

Disclosures

None.

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