EXPERT REVIEWS

Importance of blood pressure variability in the assessment of cardiovascular risk and benefits of antihypertensive therapy

Expert Rev. Clin. Pharmacol. 3(5), xxx–xxx (2010)

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Evaluation of: Rothwell PM, Howard SC, Dolan E *et al.* Effects of β blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. *Lancet Neurol.* 9(5), 469–480 (2010).

Although there is no doubt regarding the relationship between short-term blood pressure variability (BPV) and cardiovascular events in the hypertensive population, to date the association between long-term blood pressure variability and target organ damage is unknown. Rothwell *et al.* recently published a *post hoc* analysis of two large randomized trials, Anglo Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm (ASCOT-BLPA) and the Medical Research Council (MRC), aimed at demonstrating whether drug effects on short-term and long-term blood pressure variability explain the differences of antihypertensive treatment in stroke prevention. Analysis found that short-term and long-term blood pressure variability was lower in hypertensive patients treated with amlodipine with regards to atenolol. The amlodipine group showed a lower risk of stroke and coronary events with respect to subjects assigned to atenolol. Interestingly, the lower stroke risk detected in hypertensive patients treated with amlodipine was abolished after adjusting by within-individual BPV. Taking into account these findings, the authors concluded that the opposite effect of calcium channel blockers and β-blockers on BPV explains the disparity in the risk of stroke of patients under antihypertensive treatment. Therefore, to effectively prevent cerebrovascular events, blood pressure lowering agents need both to reduce mean blood pressure and its short-term and long-term variability.

KEYWORDS: amlodipine • atenolol • blood pressure variability • hypertension • stroke • target organ damage

Diagnosis, risk classification and management of hypertension have been traditionally guided by the assessment of usual blood pressure with office blood pressure measurement, ambulatory blood pressure monitoring and home blood pressure determination [1]. The role of high blood pressure levels on target organ damage (TOD) and the protective effects of antihypertensive therapy have been extensively established in clinical practice [2]. Mortality from ischemic heart disease and stroke doubles every increase of 20 and 10 mmHg of systolic and diastolic blood pressure, respectively [2].

However, nowadays it is clear that besides usual blood pressure other parameters contribute to TOD in hypertensive patients [3]. Vast preclinical and clinical evidence has demonstrated that blood pressure variability (BPV) is an independent risk factor for the incidence of cardiovascular events associated with hypertension [4,5]. It is well know that blood pressure oscillations exist over a 24-h period due to the interplay among different neurohumoral systems [4]. Variation in blood pressure is increased in the hypertensive stage and contributes independently to the presence and severity of TOD [4]. However, BPV is complex and includes both short-term (in the range of minutes to hours) and long-term (within days and months) variability, which can be estimated by different blood pressure devices and using diverse calculation and statistical methods (TABLE 1) [4,6–8].

To date, most studies have been focused on the evaluation of the relationship between short-term BPV and risk of TOD and cardiovascular events in hypertensive subjects. Preclinical

 10.1586/ECP.10.44 ISSN 1751-2433

Table 1. Types of blood pressure variability and their clinical implications.

Type of BPV	Time range	Measurement equipment or devices	Clinical implications
Short-term (very low frequency, low frequency and high frequency BPV)	Minutes, beat to beat variation	Direct continuous intra-arterial recordings coupled to spectral analysis	Estimation of neurohumoral systems involved in blood pressure regulation [5]
Short-term	Minutes to hours	Direct continuous intra-arterial recordings, ABPM	Increased variability in day-time, night-time and whole 24-h period associated with increased TOD [4]
Long-term	Days to months, visit-to-visit	Office blood pressure, ABPM	Large visit-to-visit BPV independently associated with increased incidence of stroke [6,7]

ABPM: Ambulatory blood pressure measurement; BPV: Blood pressure variability; TOD: Target organ damage.

evidence obtained from sinoaortic denervated (SAD) rats, an experimental model with significant BPV but normotensive average blood pressure values, clearly demonstrated the involvement of BPV in cardiovascular lesions. Myocardial damage, vascular remodeling and renal injury was detected in SAD rats but not in sham-operated animals, suggesting that BPV is sufficient to produce TOD [5]. In the clinical setting, the role of BPV in the development of cardiovascular events in hypertensive patients has been elucidated in several clinical trials. Parati *et al.* first reported that the prevalence and severity of TOD in 108 mild-to-severe essentially hypertensive patients were linearly related to the extent of 24 h BPV [9]. In addition, hypertensive subjects with high 24 h and daytime BPV showed a faster progression of vascular lesions assessed by intima-media thickness (IMT) of the common carotid artery [10]. Finally, the Ohasama study has demonstrated that increased variability in systolic arterial pressure is an independent predictor of cardiovascular mortality in Japanese hypertensive patients [11].

Although there is no doubt regarding relationship between short-term BPV and cardiovascular events in the hypertensive population, to date the relationship between long-term BPV and TOD is unknown.

Summary of methods & results

Rothwell *et al.* recently published a *post hoc* analysis of two large randomized trials, Anglo Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm (ASCOT-BLPA) and the Medical Research Council (MRC), aimed at demonstrating whether drug effects on BPV explain the differences of antihypertensive treatment in stroke prevention [6]. The ASCOT-BPLA was a large randomized trial comparing blood pressure-lowering treatment with amlodipine or atenolol regimens in 19,257 hypertensive patients with at least three other vascular risk factors. Subjects were randomly assigned to blood pressure lowering treatment with amlodipine or atenolol and dosing was titrated to achieve a clinic systolic and diastolic blood pressure of less than 140/90 mm Hg, or less than 130/80 mm Hg in patients with diabetes. Clinic blood pressure was measured at every follow-up visit (baseline, 6 weeks, 3 months, 6 months and every 6 months thereafter). In the MRC trial, 4,396 hypertensive patients were randomly assigned to 50 mg atenolol daily versus 25 mg hydrochlorothiazide plus 2.5 mg amiloride daily (diuretic group) versus daily placebo. At randomization and at each follow-up visit (every 3 months to 24 months and then yearly) clinic blood pressure was measured. Treatment was titrated to achieve a clinic systolic arterial pressure of less than 150 mm Hg if mean run-in SBP was 160–179 mm Hg, or less than 160 mm Hg if run-in SBP was 180 mm Hg or greater.

Different components of BPV variability, including variability on 24 h ambulatory blood pressure measurement (ABPM), within-visit and visit-to-visit variability, were studied during follow up in the ASCOT-BPLA trial and expressed as standard deviation (SD), coefficient of variation and as transformations uncorrelated with mean blood pressure.

Several results obtained by Rothwell *et al.* confirm the involvement of BPV on the incidence of cerebrovascular events in treated hypertensive subjects [6]. Briefly, in ASCOT-BPLA, systolic blood pressure SD was lower in the amlodipine group than in the atenolol group at all follow-up visits ($p < 0.0001$) due to lower within visit-to-visit variability. In addition, short-term BPV, for example, within-visit and ABPM variability in SBP, was also lower in the amlodipine group than in the atenolol group (all $p < 0.0001$). When compared with baseline values, whilst BPV was reduced in the amlodipine group, atenolol treatment has been associated with opposite effects. Amlodipine group showed a lower risk of stroke and coronary events with respect to subjects assigned to atenolol. Interestingly, the lower stroke risk detected in hypertensive patients treated with amlodipine was abolished after adjusting by within-individual BPV.

In the MRC trial, SD of all measures of within-individual visit-to-visit variability in SBP were increased in the atenolol group compared with both the placebo group and the diuretic group during initial follow-up (all $p < 0.0001$). The authors also detected a correlation between stroke risk in patients treated with atenolol and subsequent temporal trends in BPV during follow up.

Taking into account these findings, Rothwell *et al.* concluded that the opposite effect of calcium channel blockers and β-blockers on BPV explains the disparity in the risk of stroke of patients under antihypertensive treatment [6]. Therefore, to effectively prevent cerebrovascular events, blood pressure lowering agents need both to reduce mean blood pressure and its short-term and long-term variability.

Discussion

The recently published report by Rothwell *et al.* provides several important insights for the development of new strategies for the improvement of the benefits of antihypertensive treatment [6]. Although the relationship between short-term BPV and development of TOD has been previously demonstrated by preclinical and clinical studies, the authors have shown, for first time, that visit-to-visit variability on systolic blood pressure is also an independent determinant of risk of stroke [6]. Moreover, findings from the ABPM substudy of the ASCOT-BLPA trial suggest that visit-to-visit variability in clinic systolic blood pressure has a greater effect on stroke risk than daytime systolic BPV [6]. Therefore, in the future, clinical trials must not only include the evaluation of drug effects on mean blood pressure but also their actions on short-term and long-term BPV. In addition, to fully characterize changes in short-term BPV induced by antihypertensive treatment, it is necessary to use devices that allow continuous monitoring of systolic and diastolic arterial pressure along 24 h. For instance, conventional ABPM techniques are limited by the fact that these devices assess arterial pressure by automated readings every 15 and 30 min and do not allow quantification of short-lasting variation in blood pressure [4].

Nowadays, with the development of the Portapres device (Finapres Medical Systems, Arnheim, The Netherlands), the shortcomings of conventional ABPM have been overcome [4]. This technique is able to monitor blood pressure noninvasively on a beat-by-beat basis at the finger level in ambulant subjects and under daily activities [12]. Moreover, the use of Portapres for the estimation of BPV has been validated with intra-arterial blood pressure monitoring showing similar results [13]. Therefore, the increased knowledge of the role of short-term and long-term BPV on TOD associated to hypertension and the availability of sophisticated devices for continuous arterial pressure recording give us the opportunity to design large randomized clinical trials aimed to fully evaluate the ability of different antihypertensive agents to prevent cardiovascular and cerebrovascular events by reducing mean arterial pressure and its variability. In addition, international scientific associations need to urgently recognize the importance of BPV in the development of TOD in hypertensive subjects and elaborate task force documents to guide the investigators in methodological and statistical aspects of BPV assessment. In this way, although most studies used the SD as an index of BPV, this parameter has been criticized because it only reflects the dispersion of values around the mean and does not account for the order of blood pressure measurements [14]. Conversely, the average real variability (ARV) that estimates the average of the absolute differences of consecutive measurements is sensitive to blood pressure assessment order and less influenced by the low sampling frequency of ABPM [14]. Pierdomenico *et al.* have recently compared the prognostic value of SD and ARV as indices of BPV in hypertensive patients, showing that high ARV of daytime systolic blood pressure, but not high SD, results in an independent predictor of cardiovascular risk in hypertensive subjects [14].

The report by Rothwell *et al.* has also demonstrated that the benefits of antihypertensive agents not only depend on the ability to reduce mean arterial pressure but also on the attenuation of short-term and long-term BPV [6]. Specifically, blood pressure-lowering agents that reduce daytime and visit-to-visit variation in clinic blood pressure demonstrated a greater stroke protection in comparison with antihypertensive drugs with neutral or negative effects on BPV [14]. As previously mentioned, the authors concluded that calcium channel blockers exert greater protection as β-blockers against cerebrovascular events due to their ability to reduce BPV [14]. However, it is possible to extrapolate the results obtained for a specific β-blocker, atenolol, to other agents within the therapeutic class? β-blockers have several beneficial effects in patients with cardiovascular disease, including blood pressure reduction, antianginal actions, antiarrhythmic and cardioprotective effects. In addition, β-blockers are highly heterogeneous in their pharmacological properties; they differ in cardioselectivity, presence of vasodilatadory action and inverse agonism at β-adrenoceptors [15]. Moreover, β-blockers show different effects on short-term BPV. In a recent report we found that carvedilol intravenous administration in normotensive and L-NAME hypertensive rats greatly reduced very low and low frequency BPV [16]. Conversely, metoprolol only showed minimal ability to attenuate BPV in these frequency domains [AUTHOR Unpublished Data]. The trough:peak ratio represents a mathematical index for the evaluation of the duration of antihypertensive effect and was traditionally used for the quantification of drug actions on BPV [3]. Trough:peak ratio is assessed by dividing blood pressure reduction recorded just before next dose by the blood pressure diminishment at the time of peak effect and gives insight in the homogeneity of antihypertensive action [3]. For instance, a trough:peak ratio of 1 indicates that the drug provides a good blood pressure control throughout the dosing interval and will probably reduced short-term BPV [3]. As shown in **Table 2** [15,17–19], atenolol shows a trough:peak ratio less than 0.5 and, therefore, has little effect on or increases BPV [17]. Conversely, third-generation β-blockers, such as carvedilol and nebivolol, exhibit a trough:peak ratio of nearly 1.0 and provide a constant blood pressure-lowering effect for 24 h [19]. In conclusion, effects on BPV clearly differ between β-blockers and results obtained for atenolol must not be

Table 2. Pharmacological properties of main β-blockers.

β-blocker	Cardioselectivity	Vasodilatadory action	Inverse agonism	Trough:peak ratio
Atenolol	+	-	+	0.10
Metoprolol	+	-	+++	0.71
Bisoprolol	+++	-	++	0.58
Carvedilol	-	+	+	0.85
Nebivolol	+	+	++	0.91

Data from [15,17–19].

translated to other β-blockers, especially carvedilol and nebivolol. Moreover, the trough:peak ratios of carvedilol and nebivolol are comparable to value obtained for amlodipine (trough:peak ratio: 0.77) [20], the calcium channel blocker used in ASCOT-BPLA. It will be highly interesting to compare the ability of amlodipine or carvedilol or nebivolol to reduce short-term and long-term BPV and to prevent the risk of stroke.

In conclusion, our point of view of antihypertensive therapy is changing due to the advent of new analysis of large clinical trials. To effectively prevent cardiovascular events, hypertensive patients must be treated with antihypertensive agents able to reduce not only mean arterial pressure but also its short-term and long-term variability. Although antihypertensive agents of different therapeutic classes exert similar blood pressure lowering actions, they differ in the ability to attenuate BPV associated with hypertension. For instance, amlodipine, but not atenolol, reduced visit-to visit BPV showing an additional benefit in stroke prevention. Although some authors extrapolate the results obtained for atenolol to other β-blockers, the fact that third generation agents, such as carvedilol and nebivolol, exhibit a greater trough:peak ratio and attenuate very low and low frequency BPV suggests that β-blockers must not be considered equivalent.

Five-year view

As perspective for the next 5 years, the highly relevant findings of the work by Rothwell *et al.* will give rise to the design and execution of well designed clinical trials aimed to compare effects of specific antihypertensive drugs on both short-term and long-term BPV and their relationship with the ability to prevent cardiovascular events associated with hypertension. In our opinion, to obtain relevant information, the design of these clinical trials must include the following points: a head-to-head comparison specific antihypertensive drugs rather than therapeutic classes; the relationship between magnitude of BPV and rate of cardiovascular events as the primary end point; the use of blood pressure monitoring devices that allow continuous beat-to-beat arterial pressure; and the application of sensitive statistical indices of BPV (ARV rather than SD). In actual guidelines for the management of hypertension [2], BPV has not been considered as an important parameter during the selection of antihypertensive therapy. To the extent that future evidence will confirm short-term and long-term BPV as an independent risk factor of TOD in hypertensive patients, scientific associations will acknowledge the relevance of pharmacological attenuation of BPV in their guidelines and task force documents, and cardiologists will consider the effects of antihypertensive drugs on BPV as an important issue in the selection of optimal blood pressure-lowering treatment modalities.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

Key issues

- Vast preclinical and clinical evidences have demonstrated that short-term blood pressure variability is an independent risk factor for the incidence of cardiovascular events associated to hypertension.
- Results obtained from a *post hoc* analysis of Anglo Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm trial suggest that visit-to-visit variability in clinic systolic blood pressure has a greater effect on stroke risk than daytime systolic blood pressure variability.
- Amlodipine exerts greater protection against cerebrovascular events than atenolol due to its ability to reduce short-term and long-term blood pressure variability.
- To effectively prevent cerebrovascular events, blood pressure-lowering agents need to reduce mean blood pressure and its short-term and long-term variability.
- Effects of atenolol on blood pressure variability are drug specific and can not be extrapolated to other β-blockers, especially the third-generation agents carvedilol and nebivolol.

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