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REVIEW ARTICLE

Blood Pressure Variability and Therapeutic Implications in Hypertension and Cardiovascular Diseases

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Abstract
Blood pressure (BP) is characterized by continuous dynamic and spontaneous oscillations occurring over lifetime and defining the so-called blood pressure variability (BPV). BPV has been associated with target organ damage, cardiovascular (CV) risk and death, suggesting the use of BPV as a new target in hypertension management in addition to mean BP values lowering. The purpose of the review is to focus on the therapeutic implications of BPV and summarize the effects of different drug classes on various types of BPV. Despite most first-line antihypertensive medications contribute to reduce both short and long term BPV, calcium channel blockers (CCBs) as monotherapy or fixed-combination therapy appear to be the most effective on BPV control. Further randomized interventional trials are needed to investigate which drug combinations are most appropriate according to patient CV risk stratification, in order to improve their CV outcomes.

1 Introduction

Blood pressure variability (BPV) is defined by continuous dynamic and spontaneous fluctuations occurring over lifetime. BPV can be seen in very short-term (seconds or minutes, beat-to beat BPV), short-term (within a day, 24-h BPV), mid-term (between days, day-to-day BPV) and long-term (between clinic visits over months and years, visit-to-visit BPV). These oscillations are physiological and reflect the interplay of different mechanisms in response to internal and external stimuli, such as the cardiovascular (CV) control systems (beat-to-beat BPV), circadian rhythm (24-h BPV) and seasonal variations (visit-to-visit BPV). The detailed characteristics of the different type of BPV are summarized in Table 1 [1]. However, much is still unknown regarding the underlying factors [2]. Over the years, a growing number of clinical and observational studies have demonstrated an independent relationship between both short and long term BPV and the risk of CV events and death, regardless of mean blood pressure (BP) levels. Recent data from the Valsartan Antihypertensive Long-term Use Evaluation trial (VALUE), of approximately 14,000 hypertensive middle aged and older subjects, reported a 10% increase in risk of death and a 15% increase in risk of CV events for 5 mmHg increase in standard deviation (SD) of visit-to-visit and within-visit systolic BPV, respectively [3]. Palatini and co-workers, focusing on 1206 stage 1 young hypertensives (mean age 33 ± 8 years), found that a 24-h higher systolic BP variability was associated with a greater number of fatal and non-fatal CV events during a median follow up of 15.4 years [4]. Indeed, changes in BPV have been associated with target organ damage such as arterial stiffness [5, 6], left ventricular hypertrophy [7], decline in renal function [8], subclinical brain small vessel disease [9] and the risk of developing foot ulcers in diabetes [10]. Therefore, although the current guidelines do not include the use of BPV as a target in hypertension management, controlling BPV should be considered as a new goal in addition to mean BP values lowering.

The current narrative review of the literature focuses on the therapeutic implications of BPV, summarizing the effects of different drug classes on various types of BPV and the role of lifestyle modifications, in order to improve the management of CV risk associated with hypertension.

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Table 1 Characteristics, indices of assessment and determinants of the different types of BPV

Type of BPV	Methods for assessment	Main types of index	Determinants
Very short-term BPV (seconds or minutes, beat-to beat)	Continuous BP recordings	SD CoV ARV Spectral analysis	Neurohormonal factors (baroreceptor reflex, sympathetic drive) Emotion and stress
Short-term BPV (within a day, 24-h)	ABPM HBPM	SD CoV 24-h weighted SD ARV 24-h VIM Spectral analysis	Circadian rhythm Nocturnal dipping of BP; night/day ratio Obstructive sleep apnea Neurohormonal factors (glucocorticoids, RAAS system) Emotional and behavioural factors
Mid-term BPV (between days, day-to-day)	ABPM over 48 h HBPM	SD CoV ARV VIM	Choice of antihypertensive treatment Adherence to therapy Vascular factors (endothelial damage, arterial compliance)
Long-term BPV (between seasons, visit-to visit)	ABPM HBPM OBPM	SD CoV ARV VIM	Choice of antihypertensive treatment Adherence to therapy Vascular factors (endothelial damage, arterial compliance) Seasonal changes

BPV blood pressure variability, *SD* standard deviation of BV values, *CoV* coefficient of variation, assessed by dividing SD by the corresponding mean BP and multiplied by 100, *ARV* average real variability, the average of the absolute differences between consecutive BP measurement, *VIM* variability independent of the mean, *ABPM* ambulatory blood pressure monitoring, *HBPM* home blood pressure monitoring, *OBPM* office blood pressure monitoring, *RAAS* renin–angiotensin–aldosterone system

2 Short Term Blood Pressure Variability and Therapeutic Implications

2.1 Circadian Blood Pressure Variability

Given the influence of circadian rhythm on short-term BPV, some clinical studies have been mainly focused on the ability of drugs of restoring the normal 24-h pattern of BP, reducing morning surge and re-establishing the nocturnal dipping pattern (see Table 2). Therefore, drugs administration-time differences have been studied in order to normalize circadian BP profile and reduce short-term BPV. In the MAPEC study (Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares, i.e., Ambulatory Blood Pressure Monitoring for Prediction of Cardiovascular Events), Hermida and colleagues, focusing on bedtime chronotherapy, hypothesised that the administration of ≥ 1 antihypertensive drug at bedtime could be associated with a better BP control and a greater reduction in CV risk compared with conventional therapy. They found that subjects taking medications at bedtime exhibited a lower mean nocturnal BP and a lower CV risk after a median follow up of 5.6 years compared with those who ingest all drugs in the morning [11]. Other trials have demonstrated the beneficial effects of angiotensin receptor blockers (ARBs) bedtime intake on nocturnal BP dipping and within-day BPV [12, 13]. Blocking the overnight increase in RAAS activity by nocturnal ingestion of ARBs and ACE (angiotensin-converting enzyme) inhibitors, regardless of their half-life, has been seen to be superior to any other treatment mechanism in reducing not only CV risk but also diabetes [14]. The sleep-time administration of calcium channel blockers (CCBs) as monotherapy or fixed-combination therapy has been also associated with decreased BPV and morning surge of BP, together with a better tolerance [15, 16]. Relatively few studies have investigated the role of beta blockers (BBs) in bedtime chronotherapy. Acelajado and colleagues reported a better control of circadian BPV after nocturnal ingestion of nebivolol, although their cohort was very small (N = 42) [17]. Despite these evidences, it should be specified that the bedtime chronotherapy may not be recommended as a general approach for all hypertensives, but it may be beneficial for subjects without nocturnal BP fall, in order to improve their BP control and to reduce circadian BPV. A personalised approach to individual BP pattern may represent the optimal strategy to manage CV risk in hypertensive patients.

2.2 Non-circadian Blood Pressure Variability

Evidences collected in the last years have suggested that most first-line antihypertensive medications contribute to reduce short term BPV. However, some differences between drug classes in the degree of beneficial effects have been reported (see Table 2).

Many trials compared the effects of CCBs, ARBs and diuretics on short term BPV. In the X-CELLENT Study (the Natrilix SR Versus Candesartan and Amlodipine in

Table 2 Clinical trials evaluating the drug effects on BPV

Name of the study	Type of BPV	Treatment regimen	Main findings
MAPEC Study Hermida et al. (2010)	Short term BPV	Bedtime chronotherapy	The administration of ≥ 1 antihypertensive drug at bedtime was associated with a lower mean nocturnal BP and a lower cardiovascular risk after a median follow up of 5.6 years compared with all drugs ingestion in the morning
Hermida et al. (2007)	Short term BPV	Bedtime administration of telmisartan	Bedtime administration of telmisartan was associated with a greater sleep-time relative BP decline without loss in 24-h efficacy
Hermida et al. (2009)	Short term BPV	Bedtime administration of olmesartan	Bedtime intake of olmesartan was significantly more efficient than morning dosing in reducing the nocturnal BP mean and improving the awake/asleep BP ratio
Hoshino et al. (2010)	Short term BPV	Bedtime administration of amlodipine-olmesartan combination	Bedtime administration of amlodipine–olmesartan combination reduced morning BP surge without an excessive nocturnal BP decline
Acelajado et al. (2012)	Short term BPV	Bedtime administration of nebivolol	Nocturnal ingestion of nebivolol decreased pre-waking systolic BP from baseline
X-CELLENT Study Zhang et al. (2011)	Short term BPV	4 parallel treatment groups (placebo, candesartan, indapamide sustained release and amlodipine)	Indapamide sustained release and amlodipine were the only agents associated with a significantly reduction in BPV after 3-month treatment
Parati et al. (2014)	Short term BPV	Telmisartan-amlodipine combination	Telmisartan–amlodipine combination exhibited a lower daytime BPV compared with various monotherapies
Omboni et al. (2018)	Short term BPV	ACE inhibitors, dihydropyridine CCBs, thiazide diuretics in monotherapy or combination	The triple (olmesartan/dihydropyridine/thiazide diuretic) and the dual (olmesartan/dihydropyridine CCB or olmesartan/thiazide diuretic) combinations were associated with a greater decrease in BPV compared with monotherapies
ASCOT-BPLA trial Rotwell et al. (2010)	Short term BPV Long term BPV	Amlodipine versus atenolol based regimen	Visit-to-visit, ABPM and within-visit systolic BPV were lower in the amlodipine treatment group
Nishioka et al. (2015)	Short term BPV	ARBs, BBs, CCBs and ACE inhibitors	BBs were associated with higher BPV rather than CCBs and ARBs in patients affected by cerebrovascular disease
Levi-Marpillat et al. (2014)	Short term BPV	ARBs, BBs, CCBs, diuretics and ACE inhibitors	CCBs and diuretics showed a greater decrease in BPV
Liu-Deryke et al. (2013)	Short term BPV	Nicardipine versus labetalol	In acutely hypertensive stroke patients the nicardipine treatment group exhibited a lower BPV than the labetalol treatment group
HOMED-BP Study Asayama et al. (2016)	Mid-term BPV	CCBs, ARBs, or ACE inhibitors	Day-to-day variability of self-measured home BP did not differ among the three treatment arms
Matsui et al. (2012)	Mid-term BPV	Olmesartan/hydrochlorothiazide versus olmesartan/azelnidipine combination	Olmesartan/azelnidipine combination regimen based was associated with a lower day-to-day BPV than the olmesartan/hydrochlorothiazide based regimen
MRC Trial Rotwell et al. (2010)	Long term BPV	Atenolol versus diuretic based regimens	Thiazide like diuretics were more effective than BBs on long-term BPV
ALLHAT Study Muntner et al. (2015)	Long term BPV	3 parallel treatment groups (chlorthalidone, amlodipine and lisinopril)	The amlodipine and lisinopril treatment arms were associated with a lower and higher systolic BPV, respectively, compared with chlorthalidone treatment group after 6 months following randomization
COLM Trial Rakugi et al. (2015)	Long term BPV	Olmesartan/CCBs versus olmesartan/diuretic combination	Olmesartan/CCB combination was more efficient in reducing systolic BPV compared with olmesartan/diuretic combination in very elderly hypertensives

Table 2 (continued)

Name of the study	Type of BPV	Treatment regimen	Main findings
COPE Trial Umemoto et al. (2015)	Long term BPV	3 parallel treatment groups (benidipine/diuretic,benidipine/ARBs and benidipine/BBs)	The benidipine/diuretic combination was more effective on long-term BPV than benidipine/ARBs and benidipine/BBs combinations
ELSA Trial Mancia et al. (2012)	Long term BPV	Atenolol versus lacidipine	Visit-to-visit BPV did not differ between atenolol and lacidipine
Shiga et al. (2015)	Long term BPV	Single-pill fixed-dose combination of ARB/CCB versus ARB/diuretic	Seasonal BPV was similar between ARB/CCB and ARB/diuretic combinations

BP blood pressure, *BPV* blood pressure variability, *ARB* angiotensin receptor blockers, *ACE* angiotensin-converting enzyme, *CCB* calcium channel blocker, *BB* beta blocker

the Reduction of Systolic Blood Pressure in Hypertensive Patients) 577 middle-aged hypertensive subjects were recruited and treated according to 4 parallel treatment groups (placebo, candesartan, indapamide sustained release and amlodipine). The authors found that after 3 months of treatment, despite similar BP lowering effects, only amlodipine and indapamide sustained release were associated with the greater reduction in daytime, night-time and 24-h and daytime and 24 h systolic BPV, respectively. Interestingly, they also showed that the BPV lowering effect of amlodipine was associated with reduction of both BP and heart rate variability (HRV), whereas reduced HRV at night was the main alteration associated with indapamide [18]. In a large analysis of approximately 4000 adults the telmisartan/amlodipine combination exhibited the lower daytime BPV [19], whereas another previous meta-analysis of approximately 5000 patients reported a greater BPV reduction in the telmisartan/amlodipine treatment arm compared with telmisartan/hydrochlorothiazide group [20]. Omboni and colleagues demonstrated that the triple combination olmesartan/dihydropyridine CCB/thiazide diuretic and the dual combinations (Olmesartan/dihydropyridine CCB or dihydropyridine CCB/thiazide diuretic) were associated with the larger decrease in BVP compared with placebo and monotherapies. The association was maintained, albeit weak, even after adjustment for treatment effect on mean BP, suggesting that an independent effect of these drugs on BPV may be present [21].

Of the relatively few studies investigating the effect of BBs on short term BPV, most demonstrated their inferiority on BPV reduction compared with the other antihypertensive drug classes. In the ASCOT-BPLA trial (Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm) daytime systolic BPV was lower in the amlodipine-based regimen than atenolol based regimen in a population of approximately 20,000 hypertensive subjects at high CV risk [22]. Nishioka and colleagues investigated a population of 309 patients with a history of cerebrovascular disease and found a higher BPV associated with BBs rather than CCBs or ARBs [23]. These findings have been also confirmed by other authors in subjects with essential hypertension [24] and stroke [25].

In summary, data from comparative clinical trials suggest that, although most first-line antihypertensive medications contribute to reduce short term BPV, treatment regimen containing CCBs are more favourable on BPV reduction than the other drug classes. This suggestion should be taken in account for the management of hypertensive patients, especially those at high CV risk or with CV diseases.

The effects of lifestyle modifications on short term BPV reduction have not been fully investigated. The largest study assessing the relationship between lifestyle and 24-h BPV has been published in 2017 by Maseli and colleagues [26].

In their large cohort of approximately 2000 healthy subjects aged 25–41 years, they found an inverse correlation between healthy lifestyle and daytime, nighttime and weighted 24-h BPV. Interestingly this relationship, albeit attenuated, was maintained after adjustment for mean BP values. Endothelial dysfunction, baroreceptor reflex alterations and arterial stiffness, which are associated with unhealthy habits like smoking, could partly explain this correlation. However, it should be noted that the cohort was young, healthy and thus likely more sensitive to lifestyle modifications. Therefore, further researches are needed, in order to elucidate the effects of healthy lifestyle on short term BPV in hypertensive adults.

3 Mid-term Blood Pressure Variability and Therapeutic Implications

Day-to-day BPV finds its location halfway between short term BPV and long term BPV. Indeed, it may be influenced by mechanisms acting both over a short time, such as subject's activities, sleep wakefulness cycle and physiological factors, and over a long time, like climate variations and patient adherence. Despite its demonstrated association with target organ damage [27] and CV death [28], relatively few studies have investigated the impact of antihypertensive therapy on mid-term BPV (see Table 2). In the HOMED-BP Study (The multicenter Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure) 2484 middle-aged hypertensive participants were randomized to first-line treatment with CCB, ARB, or ACE inhibitor. After a median of 7.3 years following randomization, the authors found that only self-measured evening BPV predicted CV outcomes and day-to-day variability of self-measured home BP did not differ among the three treatment arms [29]. In The Japan Combined Treatment With Olmesartan and a Calcium-Channel Blocker Versus Olmesartan and Diuretics Randomized Efficacy Study, 207 hypertensive subjects were randomly allocated to treatment with hydrochlorothiazide or azelnidipine after 12 weeks of olmesartan monotherapy [30]. Despite similar systolic BP lowering between the two groups, a higher decrease in day-to-day BPV was associated with CCB/ARB combination treatment compared with diuretic/ARB group during the follow up period. Interestingly, an independent relationship between changes in BPV and aortic pulse wave velocity, a marker of arterial stiffness, was found. This suggests that CCB's effect on BPV may be mediated not only from peripheral muscular arteries relaxation but also by an improvement of large arteries stiffness.

4 Long Term Blood Pressure Variability and Therapeutic Implications

Poor drug adherence has been hypothesised to be one of the most common factors affecting visit-to-visit BPV [31]; indeed, recent data reported that many patients (nearly 50%) do not take all their medications [32]. Although the statistically significant association between non-adherence and increased visit-to-visit BPV does not fully explain the relationship between BPV and CV risk [33], improving drug-adherence should be the first target for BPV reduction.

Growing evidences from post-hoc analyses of controlled clinical trials suggest that the effects of antihypertensive drugs on long-term BPV may contribute to reduce CV risk associated with hypertension (see Table 2). Webb and colleagues performed a metanalysis of 398 trials reviewing the effects of antihypertensive treatments on interindividual BPV, a surrogate of systolic visit-to-visit BPV, and risk of stroke. The metanalysis showed that CCBs and non-loop-diuretics decreased interindividual BPV, whereas ARBs, ACE inhibitors and BBs increased it. Particularly, compared with placebo, CCBs were the most effective in reducing interindividual BPV. This may partly explain the drug-class disparities on risk of stroke [34]. ASCOT-BPLA, MRC (Medical Research Council) and ALLHAT studies are the largest multicentre randomized controlled trials taken into account for retrospective analyses regarding the effects of different treatment arms on long term BPV. Data from ASCOT-BPLA study, of approximately 19,000 hypertensive subjects, showed an increased visit-to-visit BPV associated with atenolol compared with CCB based treatments, whereas in the MRC trial thiazide like diuretics were more effective than BBs on long-term BPV [22]. In the ALLHAT study 24,000 participants were randomized to chlortalidone, amlodipine or lisinopril. After 6–28 months following randomization, subjects in the amlodipine arm showed a 0.36 lower SD of systolic BP, whereas those treated with lisinopril exhibited a 0.77 higher SD of systolic BP compared with chlorthalidone treatment group [35]. The superiority of CCBs on reducing BPV compared with ARB, BB or diuretic based regimens has been confirmed from other authors. In a sub-analysis of COLM trial (The Combination of OLMesartan), Rakugi and colleagues found that visit-to-visit systolic BPV was smaller in the olmesartan/CCBs treatment group compared with olmesartan/diuretic group, especially in very elderly Japanese hypertensives with isolated systolic hypertension [36]. In the COPE trial (The Combination Therapy of Hypertension to Prevent Cardiovascular Events), the benidipine/diuretic combination was more effective on long-term BPV than benidipine/ARBs and benidipine/BBs combinations [37]. However, conflicting data have been reported from other authors. In the ELSA trial (European

Lacidipine Study on Atherosclerosis) no differences on visit-to-visit BPV were found between BBs and CCBs in mild-to-moderate hypertensive subjects [38]. Similar effects on seasonal BPV between the single-pill fixed-dose combination of ARB/CCB and ARB/diuretic were also reported by Shiga and colleagues [39].

In summary, either as monotherapy or in combination, CCBs have been associated with the most effective long term BPV lowering. The mechanisms responsible for the beneficial effects of CCBs on BPV have not been completely clarified. Through their arterial vasodilatory effects, they might increase arterial compliance and improve baroreceptor function and autonomic nervous system regulation.

Among non-pharmacological interventions weight loss and salt reduction have not been associated with long term BPV lowering. 1820 subjects with high-normal diastolic BP were randomized to weight loss, salt reduction, their combination or usual care. The authors found no significant differences in visit-to-visit BPV between treatment groups after 36 months of follow up. However, some limitations should be cited: the cohort was relatively young and normotensive and systolic high-normal BP was not taken in account [40]. Thus, an independent effect of lifestyle modifications on long term BPV control cannot be excluded, suggesting the need of further researches.

5 Conclusions

Data available from literature demonstrate that reduce BPV may contribute to CV risk prevention, suggesting the use of BPV as a new target in hypertension management. Although most first-line antihypertensive drug classes contribute to attenuate BPV, long-acting CCBs appear to be the most effective treatment on BPV control. However, further randomized interventional trials are needed to investigate which drug combinations are most appropriate according to patient CV risk stratification. Given their role on short term BPV control, lifestyle modifications should also be taken in account as an effective strategy to ameliorate CV risk management in hypertensive patients.

The current guidelines do not include the use of BPV as a target in hypertension treatment, considering it as an optional index, probably because of its uncommon routine clinical use. This may be due to the absence of established threshold levels to discriminate pathological from physiological BPV, together with the lack of a standardized method of BPV assessment during daily clinical activity. These limitations lead to the need of further trials in order to make the BPV available and easy to use as a routine approach in daily clinical practice.

Compliance with Ethical Standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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