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Drugs Affecting Blood Pressure Variability: An Update

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Abstract: Blood pressure variability (BPV) is considered nowadays a novel risk factor for cardiovascular disease. Clinical evidences support that short-term and long-term BPV independently contribute to target organ damage, cardiovascular events and mortality in patients with hypertension or diabetes. Attenuation of excessive fluctuations of systolic and diastolic BPV has been suggested as an additional therapeutic target in cardiovascular prevention. A growing number of preclinical and clinical studies have focused in the assessment of drug effects or other interventions on the different types of BPV and their contribution in the prevention of cardiovascular events. Prospective clinical trials have shown that antihypertensive classes differ in their ability to control excessive BP fluctuations with an impact in clinical outcomes. Current evidences suggest that calcium channel blockers are more effective than other blood pressure lowering drugs for the reduction of short-term, mid-term and long-term BPV. In order to increase actual knowledge regarding the therapeutic significance of BPV in cardiovascular disease, there is a need for additional clinical studies specifically designed for the study of the relevance of short-term and long-term BPV control by antihypertensive drugs.

Keywords: Blood pressure variability, hypertension, diabetes, calcium channel blockers, visit-to-visit variability.

INTRODUCTION

Nowadays it is clear that besides usual blood pressure (BP) other parameters contribute to target organ damage (TOD) in hypertensive patients [1]. BP is not a constant variable; rather, it shows marked spontaneous oscillations over short-term (minutes to days) and long-term (month to seasons) periods [2]. Early reports from animal models of cardiovascular variability have clearly demonstrated the relationship between excessive fluctuation in BP values and the development of TOD [3]. The initial hypothesis was further corroborated by clinical studies in hypertensive subjects showing that the assessment and quantification of blood pressure variability (BPV) is of physiopathological and prognostic importance [4].

BPV is complex and includes both short-term (in the range of minutes to hours) and long-term (within days and months) fluctuations, which can be estimated by different blood pressure devices and using diverse calculation and statistical methods (Table **1**) [5]. BP shows rapid beat-to-beat oscillation due to the interplay of different cardiovascular control systems, including the baroreceptor reflex, the renin–angiotensin system (RAS), the vascular myogenic response and the release of nitric oxide (NO) from the endothelium [6]. In addition, BP fluctuates during 24 hours due to random and circadian variation. In this way, by considering the change in BP between awake and sleep conditions, different patterns of circadian BPV may be identified, including dipping, non-dipping, inverted dipping and extreme dipping [5]. In the general non-hypertensive population, BP reduces during sleep by 10–20% of day-time values resulting in attenuation of myocardial workload [7]. Conversely, non-dipper hypertensive subjects are characterized by the absence or reduction of night-time BP values and a higher risk of cardiac adverse events [7]. Several clinical studies have shown that non-dipper subjects show greater risk of TOD, cardiovascular events and mortality when compared with the dipper population. Circadian BPV is also characterized by an abrupt increase in BP during morning [5]. Clinical evidences have documented a relationship between an increase in morning BP and higher incidence of cardiovascular events and mortality [5].

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Together with circadian fluctuations, BP also exhibits short-term random variation in a time range from minutes to hours during day-time and night-time as a consequence of the influence of central and autonomic modulation and the elastic properties of arteries [4]. It has been established that the reduction of the ability of the arterial and cardiopulmonary reflexes to buffer changes in BP and the arterial stiffness can result in enhanced short-term BPV and greater TOD, cardiovascular events and mortality [5]. Different clinical trials have established that the degree of short-term BPV is independently associated with TOD and rate of cardiovascular events in both the general population and in subjects with hypertension [8].

In addition, BP also shows mid-term (day-to-day) and long-term (visit-to-visit or seasonal) oscillations due to several factors, including arterial compliance, medication adherence and errors in BP measurement [5]. Increased arterial stiffness has been found to contribute in long-term BPV as a pathological mechanism. The Multi-ethnic Study of Atherosclerosis (MESA) has recently demonstrated that functional alterations in aortic distensibility and arterial elasticity are associated with elevated visit-to-visit BPV [9]. The contribution of mid-term and long-term BPV to the development of cardiovascular disease has been evidenced in several clinical trials. The Ohasama Study documents that day-to-day systolic and diastolic BPV are associated with greater risk of cardiovascular and stroke mortality [10]. In addition, increased visit-to-visit BPV has been associated with TOD, cardiovascular events (stroke, myocardial infarction, heart failure and renal failure) and mortality in different populations, including patients with hypertension or diabetes [11-15].

In summary, clinical evidences support that short-term and long-term BPV independently contribute to TOD, cardiovascular events and mortality in patients with hypertension or diabetes. Therefore, attenuation of excessive fluctuation of systolic and diastolic BP has been suggested as an additional therapeutic target in cardiovascular prevention [16, 17]. In the last years, a growing number of preclinical and clinical studies have focused in the assessment of drug effects or other interventions on the different types of BPV demonstrating the existence of differences in the ability of specific drugs to control this novel risk factor. The aim of the present review is to summarize the preclinical and clinical evidences of drug effects on the different types of BPV and their con-

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Table 1. Classification of blood pressure variability and its clinical implication.

Type of BPV	Time range	Measurement equipment or devices	Determinants	Clinical implications
Ultra Short-term (very low frequency, low frequency and high frequency BPV)	beat-to-beat variation	Direct continuous intra-arterial recordings coupled to spectral analysis	Central sympathetic drive Myogenic vascular function Arterial/Cardiopulmonary reflexes Neurohumoral factors ventilation	Estimation of neurohumoral systems involved in blood pressure regulation
Short-term	Minutes to hours	Direct continuous intra-arterial recordings, ABPM	Central sympathetic drive Myogenic vascular function Arterial/Cardiopulmonary reflexes Neurohumoral factors Activity/Sleep Arterial stiffness	Increased variability in day-time, night-time and whole 24-h period associated with increased TOD, cardiovascular events (stroke, myocardial infarction), cardiovascular mortality and renal dysfunction
Mid-term	Day-to-day	Home BP monitoring	Arterial stiffness Dosing and titration of antihypertensive drugs	Increased day-to-day BPV associated with TOD, microalbuminuria, cardiovascular events, cardiovascular mortality and all-cause mortality
Long-term	visit-to-visit, interseason	Office blood pressure, ABPM, home blood pressure monitoring	Arterial compliance Seasonal changes Adherence to antihypertensive therapy BP measurement errors	Large visit-to-visit BPV independently associated with increased incidence of stroke

ABPM: Ambulatory blood pressure measurement; BPV: blood pressure variability; TOD: target organ damage

tribution to the prevention of cardiovascular events. We reviewed main articles cited in PubMed or Google Scholar between 1995 and January 2014 focused on the evaluation of drug effects on BPV in experimental models and human subjects.

DRUG EFFECTS ON BEAT-TO-BEAT BPV

Assessment of beat-to-beat BPV has been mainly used in preclinical studies for the evaluation of the mechanism of action of antihypertensive drugs and the diagnosis and treatment of patients with cardiovascular diseases [6, 18, 19]. The response times at which different neurohormonal systems operate differ considerably and, therefore, the analysis of beat-to-beat BPV by means of spectral analysis allows the estimation of the relative contribution of neurohumoral systems in blood pressure regulation [6]. The frequency components of BPV detected by power spectral analysis include oscillations at the very low frequency (0.02–0.20Hz in rats and 0.02–0.07Hz in humans), low-frequency (0.2–0.6Hz in rats and 0.077–0.15Hz in humans), and high-frequency domain (1–4Hz in rats and 0.15–0.40Hz in humans) [6]. In this context, while myogenic vascular function, RAS, and endothelium-derived NO affect BPV at VLF [6, 18], LF variability is modulated by sympathetic activity of vascular tone and endothelial-derived NO in rats [6]. In addition, normalized LF (LF/HF ratio) has been validated as a marker of sympathetic vascular activity in preclinical and clinical studies [19, 20]. Variability in the HF domain is mainly influenced by changes in cardiac output [21].

i. Preclinical Studies

In our laboratory, we have demonstrated that carvedilol induces a greater hypotensive response in spontaneously hypertensive rats in comparison with normotensive control animals by means of spectral analysis of continuous intra-arterial BP recording [22]. The enhanced pharmacological response to carvedilol was partially mediated by a greater vascular sympatholytic activity of the drug in the hypertensive group evidenced by a significant reduction of LF/HF ratio [22]. More recently, using the same methodological approach, we have compared the effects of different beta blockers (BBs) on vascular sympathetic activity in sinoaortic denervated (SAD) rats [23]. Carvedilol and nebivolol significantly reduced the LF/HF ratio compared with atenolol in this experimental model, suggesting the ability of third generation BBs to reduce vascular sympathetic activity [23]. Consistent with these findings, Just *et al*. [24] have found that atenolol administration in chronically catheterized mice does not significantly change different domains of beat-to-beat BPV assessed by spectral analysis of continuously intra-arterial BP recording, despite its strong effects on heart rate [24].

In an unpublished study, we have assessed the effect of chronic treatment with different BBs on beat-to-beat BPV of N-nitro-l-arginine methyl ester (L-NAME) hypertensive rats. Drug effects on different domains of beat-to-beat BPV were evaluated by spectral analysis of BP recording in catheterized animals. L-NAME hypertensive rats showed greater LF/HF ratio when compared with normotensive control animals suggesting an enhancement of vascular sympathetic activity in this experimental model of hypertension. Meanwhile atenolol 30 mg/kg did not modify beat-to-beat BPV, chronic oral treatment of L-NAME hypertensive rats with nebivolol 15 mg/kg or carvedilol 30 mg/kg normalized LF/HF ratio due to their vascularsympatholitic action (Fig. **1**). In addition to these results, a recent study has revealed the ability of carvedilol to restore beat-to-beat BPV in rats with myocardial infarction. Autoregressive analysis of continuous intra-arterial BP recording in the awake animal has established that chronic treatment with carvedilol 2 mg/kg in drinking water is able to reverse changes in LF BPV induced by myocardial infarction [25].

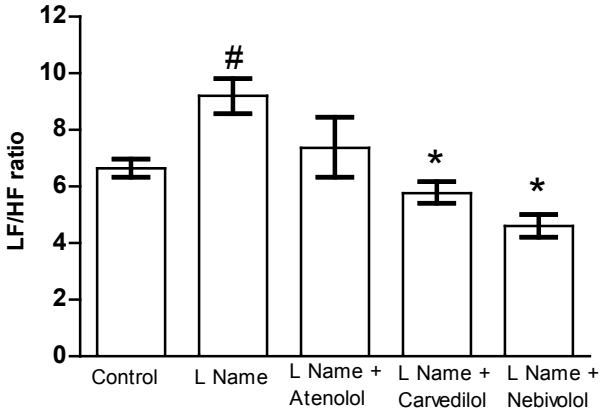

Fig. (1). Effect of chronic treatment with atenolol, carvedilol or nebivolol on LF/HF ratio in L-NAME hypertensive rats. #p<0.05 vs. control rats. *p<0.05 vs. L-NAME rats.

The effects of calcium channel blockers (CCBs) on beat-to-beat BPV have been established in normotensive Wistar-Kyoto rats. Nifedipine infusion induced a marked attenuation in VLF and LF BPV due to inhibition of myogenic vascular function and blockade of α-adrenoceptors [6]. In the same line, in catheterized awake SAD rats, we have found that the non-dyhydropiridine CCB verapamil also reduces beat-to-beat BPV at the VLF, LF and HF domain [23]. However, intravenous administration of verapamil did not modify LF/HF ratio suggesting the absence of a drug effect on vascular sympathetic activity [23].

Drugs acting at the RAS also modulate beat-to-beat BPV at different time domains. Analysis of spectral powers of the systolic and diastolic BP assessed in conscious two-kidney, one-clip hypertensive rats has established that the acute administration of losartan induces a reduction in VLF power density and an increase in LF and HF BPV suggesting the involvement of the renin angiotensin system on blood pressure regulation at a low-frequency domain [26].

Nobre *et al*. [27] have compared the effects of chronic oral treatment with different antihypertensive drugs on beat-to-beat BPV estimated by autoregressive spectral analysis of systolic blood pressure in catheterized awake two-kidney, one-clip hypertensive rats. The authors have reported an increase in LF BPV in two-kidney, one-clip hypertensive rats treated with water when compared with sham operated rats [27]. Treatment of hypertensive rats with ramipril, atenolol, amlodipine or hydrochlorothiazide normalizes the increase in LF variability of systolic blood pressure [27]. In contrast losartan did not exert a beneficial effect on this parameter of BPV suggesting the inability of the angiotensin receptor blocker to prevent activation of vascular sympathetic activity induced by the hypertensive state [27].

ii. Clinical Evidences

Assessment of beat-to-beat BPV could contribute to the rational selection of antihypertensive drugs. In humans, BP spectral powers between 0.07-0.15 Hz represent a marker of vascular sympathetic activity [28]. Laboratory stimuli associated with sympathetic overactivity, including head-up tilting and mental stress, have been shown to increase the power of LF BPV [28]. In contrast, BP spectral power at the LF domain decreases in human subjects with conditions that abolish sympathetic cardiovascular influences, such as sleep and α-adrenergic blockade [28]. Parati *et al*. [29] have analyzed spectral analysis of beat-to-beat BPV obtained from continuous intra-arterial BP recoding in normotensive and mild essential hypertensive subjects. The authors found a significant reduction of BPV in the LF domain during night-time in both normotensive and hypertensive patients suggesting a decline of sympathetic activity with sleep [29]. Therefore, the assessment of frequency domains of beat-to-beat BPV can be considered an attractive approach for a rational selection of cardiovascular therapy. For instance, hypertensive patients with elevated LF BPV may have enhanced sympathetic modulation of vascular tone and a good response to sympatholytic drugs [6]. Hypertensive patients with impaired cerebrovascular myogenic function, such as patients on chronic dialysis, can be identified by an abnormal reduction in VLF BPV. Considering the fact that impaired cerebrovascular myogenic function increases the risk of hemorrhagic stroke, treatment with calcium channel blockers may be harmful in these patients considering further impairment of myogenic function [6].

Beat-to-beat BPV can be assessed in the clinical practice with the Portapres device that allows continuous noninvasive, beat-to-beat finger BP monitoring [30]. By using the Portapres device, Frattola *et al*. [31] have monitored 24-hour ambulatory BP of 10 mild diabetic hypertensive patients treated with lacidipine or placebo. The computer analysis of beat-to-beat BPV has established that lacidipine induces a reduction in 24-hour BPV associated with an increase in baroreflex sensitivity [31]. The authors have concluded that the clinical use of Portapres device may offer relevant information about the effects of antihypertensive drugs on hemodynamic and autonomic parameters in patients during real-life practice [31].

DRUG EFFECTS ON SHORT-TERM BPV

Antihypertensive drugs can change short-term BPV by altering circadian variations of BP or its random oscillation during daytime, night-time or 24-hour. Drug effects on circadian BP profile have been previously reviewed showing the relevance of administration-time differences in effects of hypertension medications on ambulatory BP regulation [32]. Clinical studies on drug effects on circadian BPV have been mainly focused on establishing the ability of pharmacological treatment to recover the normal dipping pattern of BP and to abolish or diminish the morning surge of BP. The beneficial effects of antihypertensive drugs on circadian BP largely depend from the time of drug intake [32]. Several clinical trials have demonstrated that angiotensin receptor blockers (ARBs) improve awake/asleep BP ratio toward a greater dipper pattern restoring the normal circadian fluctuations of BP in non-dipper hypertensive patients [32]. For instance, Hermida *et al*. [33] have compared the effects of olmesartan morning and bedtime oral administration on 24 hour BP pattern in grade 1 and 2 hypertensive patients by ambulatory monitoring for 48 consecutive hours before and after treatment. Although mean reduction of 24-hour BP was independent of time administration of olmesartan, bedtime intake of the ARB induced a significant decrease in sleep-time BP reducing the prevalence of non-dipping hypertensive patients by 48% [33]. The benefits of night-time administration of olmesartan were confirmed in type 2 diabetic patients with newly diagnosed hypertension by means of 24-hour BP monitoring [34]. Bedtime dosing of olmesartan increases nocturnal BP reduction when compared with morning drug administration increasing the number of dipper diabetic hypertensive patients without affecting 24-hour control of BP [34]. The ability of olmesartan in restoring night-time blood pressure fall has been linked with the enhancement of day-time sodium excretion [35]. Other ARBs, including valsartan, telmisartan and irbesartan, have demonstrated their beneficial effects on circadian BPV after bedtime dosing suggesting that restoration of dipping pattern is a class effect related to blockade of angiotensin receptor [32, 36].

Bedtime intake of other antihypertensive agents induces similar beneficial effects as reported with ARBs. Hermida & Ayala [37] have found that night-time administration of ramipril significantly increase the awake: asleep BP ratio toward a more dipping pattern when compared with morning intake. Moreover, the proportion of patients with controlled ambulatory BP increased from 43% to 65% with bedtime treatment [37]. In another clinical trial, Meng *et al*.

[38] have found that administration of antihypertensive drugs at different times increases the diurnal/nocturnal blood pressure ratio, and normalized the circadian blood pressure pattern of hypertensive patients. For instance, fosinopril bedtime dosing combined with amlodipine at morning reduces the non-dipping pattern from 53.85% to 30.77% when compared with concomitantly intake of fosinopril and amlodipine in the morning [38].

In the same way, CCBs are more effective after bedtime than morning dosing, and for dihydropyridines night-time intake significantly reduces risk of peripheral edema [32]. A multicenter, open-label randomized study has shown that bedtime administration of a fixed-combination of amlodipine and diuretic improves BP control [39]. In comparison with morning intake of the combination, bedtime intake of amlodipine/diuretics induced a greater reduction of nocturnal BP, 24-hour mean BP and morning surge of BP, increasing the number of patients converted from non-dipper to dipper pattern [39]. The administration-time dependent antihypertensive efficacy of the slow-release, once-a-day nifedipine gastrointestinal-therapeutic-system (GITS) formulation has been established in a clinical trials enrolling 180 untreated hypertensive patients [40]. After 8 weeks of treatment, BP reduction was significantly greater after bedtime dosing of nifedipine GITS when compared with morning intake allowing a greater control of ambulatory BP [40]. Meanwhile morning dosing of nifedipine GITS did not modify the prevalence of non-dipping patients, the percentage of non-dippers was reduced from 51% to 35% in the patients assigned to bedtime administration. Nifedipine GITS was only able to reduce morning surge of BP after its bedtime dosing [40].

In another report, bedtime administration of combination therapy with amlodipine-olmesartan ameliorated BPV by controlling morning surge of BP and reduced urinary albumin excretion in 31 essential hypertensive patients [41]. By using 24-hour ambulatory blood pressure monitoring (ABPM), the authors have found that the bedtime administration of the combination of amlodipine and olmesartan significantly reduces BP morning surge with no excessive nocturnal BP fall [41]. The ability of bedtime administration of amlodipine-olmesartan to reduce BPV was associated with a reduction in urinary albumin/creatinine ratio [41].

Regarding BBs, a small study has shown that evening intake of carvedilol induces a greater 24-hour BP lowering effect and prevents morning surge of BP when compared with morning administration [42]. Acelajado *et al*. [43] have compared the effects of morning and evening administration of nebivolol on 24-hour BP profile in 42 patients with mild to moderate hypertension. After 3 weeks of follow-up, bedtime intake of nebivolol induced a similar decrease in nocturnal BP when compared with morning dosing but better controlled the morning surge of BP suggesting that evening administration of nebivolol may confer some advantage in preventing adverse circadian BPV [43].

Taking together, clinical studies have consistently demonstrated that bedtime administration of antihypertensive drugs restores normal circadian BPV with a possible beneficial effect on the prevention of cardiovascular events. The benefits of bedtime intake of antihypertensive drugs have been clearly demonstrated by the MAPEC prospective trial, which was specifically designed to test the fact that bedtime chronotherapy with ≥1 antihypertensive medications exerts better BP control and CVD risk reduction than the intake of all medications in the morning [44]. The authors found that subjects taking medication at bedtime showed lower mean sleep-time BP, higher sleep-time relative BP decline and reduced prevalence of non-dipping when compared with morning administration of all antihypertensive drugs [44]. Moreover, the incidence of total cardiovascular events was 61% lower in patients with bedtime administration of ≥1 medications than the intake of all drugs in the morning [44].

Nevertheless, the benefit of evening dosing of antihypertensive drugs depends on the circadian pattern of BPV of individual patients and must not to be recommended as a general strategy for all hypertensive subjects. Whereas reduction of nocturnal BP by bedtime drug administration is attractive for patients with non-dipping pattern, it can also be harmful for those patients who already have too large circadian amplitude of BP, condition defined as Circadian Hyper-Amplitude-Tension (CHAT). The presence of CHAT pattern of circadian BPV has been associated with an increase in adverse cardiovascular events, including cerebral ischemic events and nephropathy, even in the absence of an elevated mean value of BP [45, 46]. Bedtime administration of antihypertensive drugs can induce excessive circadian BP fluctuation in predisposed patients increasing the risk of cardiovascular events. In this way, Shinagawa *et al*. [47] have compared the effects of morning administration of bedipine or nifedipine twice daily on circadian BPV and cardiovascular events in 18 essential hypertensive patients. Although bedipine and nifedipine induced a similar decrease of day-time and night-time BP, nifedipine enhanced the amplitude of day-night difference in systolic BP increasing the risk of CHAT [47]. In another report, the effects of different antihypertensive drugs on circadian BPV have been compared in normotensive patients with CHAT [48]. The authors have found that the long-acting BB carteolol exhibits a greater efficacy in the reduction of amplitude of day-night BP when compared with atenolol [48]. Neither captopril retard nor nilvadipine and amlodipine were able to reduce abnormal circadian BPV in normotensive patients with CHAT [48].

In conclusion, the chronotherapeutic approach of antihypertensive treatment will lead to further preventive effects of morbid events due to normalization of abnormal circadian BPV. However, this approach needs from the chronodiagnosis of the circadian pattern of BP fluctuation –dipping, non-dipping or CHAT- in individual hypertensive patients in order to select the most adequate antihypertensive drugs and the best time of dosing [47].

i. Drug Effects on Non-Circadian BPV: Preclinical Evidences

Effects of antihypertensive drugs and other therapeutic interventions on short-term BPV have been investigated in a large number of preclinical studies. Experiments using animal models of cardiovascular disease have clearly shown the ability of different BP lowering agents to reduce excessive fluctuations of BP [8]. The SAD rat represents an excellent experimental model to investigate the consequences of BPV on target organs, considering the fact that SAD increases fluctuation in BP without affecting mean values [49]. Specifically, the ablation of carotid and aortic baroreceptor afferents in SAD rats induces a chronic increase in short-term BPV with normal average blood pressure level [49]. Wang *et al*. [50] have compared the effects of acute oral administration of nine different antihypertensive drugs on BPV in catheterized conscious, freely moving SAD rats. Short-term BPV was assessed by the SD of beat-to-beat systolic and diastolic BP. CCBs (nifedipine, nitrendipine, and amlodipine) and sympatholytic agents (atenolol, prazosin, and clonidine) effectively controlled excessive fluctuations in BP after SAD [50]. Conversely, acute application of drugs acting at the RAS (captopril and telmisartan) and the diuretic hydrochlorothiazide did not show beneficial effects on BPV attenuation in rats with labile BP [50]. More recently, we have found that intravenous administration of a single dose of nebivolol, carvedilol, or verapamil greatly reduces short-term BPV assessed by SD of continuous intra-arterial BP recording in SAD rats [23]. Conversely, cardioselective blockade of β-adrenoceptor with atenolol induces only minor beneficial effects on BP fluctuations in SAD animals [23].

Acute effects of different antihypertensive agents on BPV have also been assessed in spontaneously hypertensive and normotensive control rats. Shen *et al*. [51] have studied the effects of intragastric administration of ketanserin on barorreflex sensitivity, BP and

short-term BPV assessed by the SD of systolic and diastolic BP in catheterized spontaneously hypertensive rats. Ketanserin has been shown to attenuate BPV and mean BP values and to improve baroreflex sensitivity in this experimental model of hypertension [51]. In another report, Han *et al*. [52] studied the effects of the combination of hydrochlorothiazide and nitrendipine on short-term systolic and diastolic BPV in spontaneously hypertensive rats. Although only nitrendipine at a high dose was able to reduce SD of systolic BPV, combination of hydrochlorothiazide + nitrendipine significantly attenuated BP fluctuations in conscious freely moving spontaneously hypertensive rats [52]. In addition, synergism of atenolol and amlodipine coadministration on attenuation of short-term BPV has been evidenced in spontaneously hypertensive rats [53]. Effects of drug combination on BPV were quantified by the estimation of SD of systolic and diastolic 24-hour BP recording. Meanwhile, acute oral administration of a single dose was not able to reduce BP fluctuations, the association of atenolol and amlodipine attenuated both systolic and diastolic SD of BP recoding [53].

Acute intravenous administration of a single dose of third-generation BBs, carvedilol, and nebivolol, also effectively controls short-term BPV in freely moving spontaneously hypertensive rats and normotensive control animals [22, 54]. An interesting finding of this set of experiments is the fact that nebivolol markedly attenuated short-term SD of mean BP in catheterized freely moving spontaneously hypertensive rats and normotensive animals and this beneficial effect was evident at low dose levels associated with limited effects on mean BP values [54]. In addition, both carvedilol and nebivolol have shown to greatly reduce short-term BPV quantified by SD of mean BP in other experimental models of hypertension, including L-NAME hypertensive rats and fructose-fed rats, confirming the ability of third generation BBs to reduce short-term BPV [55-57]. These results reinforce the contribution of the vasodilatory action of carvedilol and nebivolol on the reduction of excessive fluctuations of BP in animal models of cardiovascular disease [55-57].

Evidences from long-term studies have clearly demonstrated the ability of different cardiovascular drugs to chronically reduce short-term BPV and TOD in different experimental models. In an elegant study, Kai *et al*. [58, 59] have found that the chronic administration of candesartan at a subdepressor dose abolishes SAD-induced inflammatory changes and cardiac remodeling and subsequently prevents systolic dysfunction in spontaneously hypertensive rats with SAD. Moreover, treatment with fosinopril during 16 weeks effectively prevented increase in short-term BPV quantified by SD of BP and vascular remodeling of pulmonary arteries in SAD animals [60]. Works from Miao *et al*. [61] have also demonstrated the ability of chronic oral treatment with candesartan to inhibit target organ damage induced by SAD, including cardiomyocyte hypertrophy, myocardial fibrosis, wall thickening of intramyocardial arterioles and aortae, and destruction of vascular internal elastin membrane.

The contribution of beneficial drug effects on BPV on TOD has also been demonstrated in spontaneously hypertensive rats. By multiple regression analysis, Shang *et al*. [62] have found that the reduction in SD of systolic and diastolic BP induced by the chronic administration of irbesartan and amlodipine contributes to ameliorate left ventricular hypertrophy and renal lesion in spontaneously hypertensive rats. In another report, the effect of chronic administration of different antihypertensive drugs on TOD was studied in spontaneously hypertensive rats. Mean BP and short-term BPV were assessed from 24-hour BP recording using the SD of systolic BP as an index of short-term BPV. Long-term treatment with atenolol, nifedipine, irbesartan, or hydrochlorothiazide all markedly reduced blood pressure variability, enhanced baroreflex sensitivity, and produced significant organ protection in this experimental model [63]. Compared with BP level, degree of BPV and baroreflex sensitivity values showed a much closer relationship with TOD in treated hypertensive rats [63]. Multiple regression analysis confirmed a strong association between BPV reduction induced by antihypertensive treatment and amelioration of left ventricular hypertrophy, aortic hypertrophy, and renal lesion [63].

The relevance of BPV to target organ damage development in spontaneously hypertensive rats has been elucidated by comparing the effects of chronic treatment with hydralazine and ketanserin [64]. Ketanserin significantly decreased BP and short-term BPV quantified as SD over mean BP preventing target organ damage in spontaneously hypertensive rats. Conversely, no organ protection was evidenced with hydralazine treatment, which was able to decrease BP but did not affect BPV [64]. In another report, long-term administration of nitrendipine has been shown to prevent TOD in spontaneously hypertensive rats and the beneficial effect was closely related to the attenuation of long-term systolic BPV but not to BP level [65]. In addition to these findings, research from Xie *et al*. [66, 67] also demonstrates the existence of a synergism of different antihypertensive drug combinations, including nitrendipine/atenolol and hydrochlorothiazide/nifedipine, in the decrease of BPV and organ protection in spontaneously hypertensive rats. In the same line, Shang *et al*. [68] have revealed a synergic effect of chronic administration of a low dose combination of amlodipine and irbesartan on short-term BPV and organ protection in spontaneously hypertensive rats using the SD of systolic and diastolic BP as quantitative parameter of BPV. Multiple regression analysis has shown that the decrease in left ventricular hypertrophy and amelioration in renal lesion induced by amlodipine/irbesartan are associated with the decrease in systolic BPV estimated by SD of systolic and diastolic BP [68].

Chronic treatment with vasodilatory BBs also has shown to reduce short-term BPV in L-NAME hypertensive rats. In an unpublished study, we have recently found that oral administration of nebivolol and carvedilol at a dose of 30 or 15 mg/kg during 8 weeks significantly reduced SD of BP in conscious L-NAME rats with small effects on mean BP (Fig. **2**). Conversely, chronic treatment with atenolol 30 mg/kg did not modify short-term BPV in this experimental model of hypertension suggesting the relevance of vasodilation on the attenuation of short-term BPV by third generation BBs (Fig. **2**).

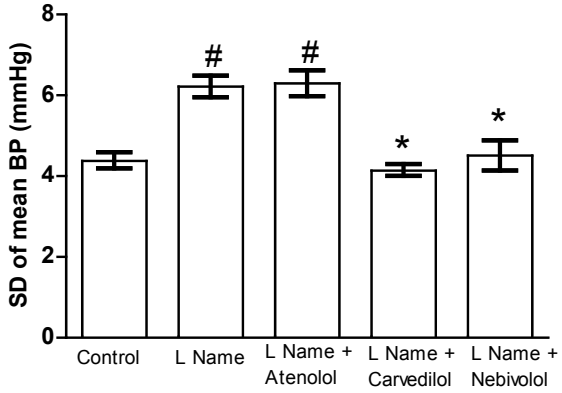

Fig. (2). Effect of chronic treatment with atenolol, carvedilol or nebivolol on short-term BPV in L-NAME hypertensive rats. #p<0.05 vs. control rats. *p<0.05 vs. L-NAME rats. SD: standard deviation.

ii. Drug Effects on Non-Circadian BPV: Clinical Evidences

At the clinical setting, drug effects on short-term BPV were assessed by means of a myriad of indices, including 24-hour, daytime and night-time standard deviation (SD), and coefficient of variation (CV) of systolic and diastolic BP [4]. As BPV largely depends from mean BP values, average SD can be divided by the corresponding mean arterial pressure to normalize short-term BPV

as CV [4]. Although estimation of short-term BPV theoretically requires continuous BP recording, its assessment is also possible through the use of intermittent, noninvasive 24-hour ABPM [4]. Nevertheless, due to the intermittent nature of BP monitoring by ABPM, estimation of short-term BPV using this device is less accurate [4]. SD has been questioned as an appropriate index of short-term BPV, considering that SD only reflects the dispersion of values around the mean, does not account for the order in which BP measurements are obtained, and is sensitive to the low sampling frequency of ABPM [69]. In order to improve the prognostic value of short-term BPV, the average real variability (ARV) of day-time and night-time BP has been introduced as a new index of BPV. ARV is the average of the absolute differences of consecutive measurements; therefore, this statistical parameter is sensitive to the individual BP measurement order and less sensitive to low sampling frequency of ABPM [69]. Different studies have shown that ARV better predicts cardiovascular risk in hypertensive patients in comparison to the traditional SD of short-term BPV [69, 70].

Clinical trials have evidenced that almost all first-line antihypertensive drugs are able to reduce short-term BPV, although differences in the degree of the beneficial effects have been detected in head-to-head clinical studies. Clinical trials have established that different ARBs, angiotensin converting enzyme inhibitors (ACEIs), CCBs and BBs reduce short-term BPV, including day-time, night-time and 24-hour indexes of BPV. In addition, some evidences suggest that attenuation of short-term BPV induced by antihypertensive agents contributes to cardioprotection in patients with different cardiovascular diseases.

In this context, the beneficial effects of ARBs on BPV and TOD have been demonstrated in patients on dialysis. The effects of losartan on short-term BPV have been evaluated in hypertensive patients on hemodialysis by means of the estimation of CV of day-time and night-time BP obtained from ABPM [71]. Losartan treatment significantly reduced night-time short-term BP variability in hypertensive patients on hemodialysis, in contrast to neutral effects of placebo [71]. Furthermore, multiple regression analysis evidenced a significant correlation between changes in left ventricular mass index and attenuation in sleep short-term BPV with losartan treatment, suggesting its contribution in the beneficial action of losartan on the suppression of pathological cardiovascular remodeling [71]. In another report, Masuda *et al*. [72] have compared the effect of telmisartan or losartan on short-term BPV quantified by CV of BP obtained from ABPM in hypertensive patients with overt diabetic nephropathy. After 12 weeks of treatment, 24-hour, day-time, and night-time short-term BPV was significantly decreased by telmisartan but not by losartan [72]. In addition, telmisartan reduced effectively proteinuria in hypertensive patients with overt diabetic nephropathy, partly through inhibitory effects on ambulatory short-term BPV [72]. Relevance of BPV attenuation in the prevention of TOD by angiotensin II type 1 receptor blockers has also been documented in hypertensive patients on chronic peritoneal dialysis [73]. In the study, 45 hypertensive patients on chronic peritoneal dialysis therapy were randomly assigned to candesartan (n = 15), valsartan (n = 15), or control treatment (n = 15) during a follow-up period of 6 months [73]. Drug effects on short-term BPV were established by the estimation of SD of 24-hour ABPM. Although ARBs and control antihypertensive treatment similarly controlled 24-hour BP values, only candesartan and valsartan decreased short-term BPV improving parameters of cardiovascular remodeling, including natriuretic peptides, echocardiography, and brachial-ankle pulse wave velocity [73].

Head-to-head comparative trials have established that antihypertensive drugs differ in their ability to control short-term BPV. The effects of carvedilol 25 mg bid or lercanidipine 10 mg qd on short-term BPV assessed by SD and CV of day-time, night-time and 24-hour BP have been compared in 24 mild-to-moderate essential hypertensive patients [74]. Although both treatments induced a similar decrease in systolic and diastolic BP, carvedilol elicited a reduction in 24-hours and day-time systolic and diastolic BP variability while lercanidipine showed neutral effects [74]. The authors concluded that carvedilol may be more effective than lercanidipine in the attenuation of short-term BPV suggesting the contribution of sympathetic activity on excessive fluctuations of BP [74].

In another clinical trial with crossover design, Zakopoulos *et al*. [75] have compared the effects of amiloride hydrochlorothiazide, atenolol, nifedipine and perindopril on the ambulatory circadian BP pattern in 20 essential hypertension patients. Results showed that antihypertensive drugs significantly differ in their effects on 24-hour BP profile; only atenolol was able to induce a significant reduction on short-term BPV estimated by SD of 24-hour BP [75]. A prospective clinical trial has compared the effects of valsartan or nebivolol on 24-hour BPV in 80 hypertensive patients. All patients underwent 24-hour ABPM for the assessment of drug effects on systolic and diastolic BP variation using the SD of day-time and night-time BP as an index of short-term BPV [76]. After 12 months treatment, both valsartan and nebivolol induced a significant reduction in day-time and night-time variability of systolic and diastolic BP; however, valsartan significantly reduced systolic BP variability during the night-time period when compared to nebivolol [76]. The authors concluded that the antihypertensive treatment with long-acting agents like ARBs or third generation ultraselective BBs could offer a better cardiovascular protection by reducing the BPV [76].

Drug effects on short-term BPV have also been assessed in acute stroke patients. A prospective study has compared the BP lowering effect of labetalol or nicardipine in 54 patients with confirmed hemorrhagic or ischemic stroke [77]. Drug effects on BP and short-term BPV were assessed from BP readings obtained by brachial cuff. The authors found that patients treated with nicardipine benefit from better maintenance of BP and lower short-term BPV quantified by the SD of BP readings when compared with labetalol suggesting a superior therapeutic response to calcium channel blockers in acute stroke patients [77].

In addition to these findings, the Natrilix SR versus Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients (X-CELLENT) Study compared the impact of antihypertensive treatment with candesartan, indapamide sustained release, or amlodipine on SD of 24-hour ABPM in 577 patients [78, 79]. Drug effects on short-term BPV were established by means of two indexes: the within-subject SD weighted for the time interval between consecutive validated readings and the read-to-read ARV [79]. Amlodipine treatment showed greater effects on short-term BPV variables in comparison with candesartan and indapamide sustained release [72]. Specifically, after adjustment for the corresponding mean BP reduction, only amlodipine consistently ameliorated short-term BPV indexes, including day-time, night-time, and 24 h SD of systolic BP and ARV (Fig. **3**) [79]. Meanwhile candesartan showed neutral effects on short-term BPV, indapamide only was able to reduce day-time SD [79].

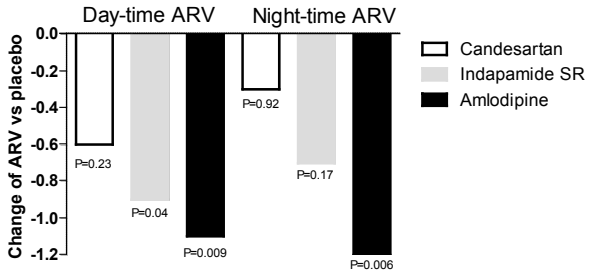

Fig. (3). Effect of treatment with candesartan, indapamide SR and amlodipine on short-term BPV in hypertensive patients. ARV: average real variability. Adapted from [72].

In contrast to first-line antihypertensive drugs, alfa-blockers have shown neutral effects on short-term BPV. Ruddy *et al*. [80] have evaluated the effect of add-on treatment with doxazosin 1 mg at bedtime on BP and its short-term variability in fourteen hypertensive patients on antihypertensive treatment. Although doxazosin treatment significantly reduced systolic and diastolic BP, it did not modify SD of day-time and night-time BP [80].

Added to the evidence of trials evaluating antihypertensive monotherapy, clinical studies have also demonstrated the ability of the combination of different BP lowering agents to reduce BPV in hypertensive subjects. For instance, Scholze *et al*. [81] have evaluated the efficacy and safety of a fixed-dose combination of lercanidipine and enalapril in daily practice using office, self-measured, and ABPM measurements. In this prospective, open-label, uncontrolled multicenter trial 622 hypertensive patients were treated with a fixed-dose combination of 20mg enalapril maleate and 10mg lercanidipine hydrochloride and followed during 3 months [81]. Short-term BPV was evaluated before and after treatment by the estimation of ARV from BP readings obtained from ABPM. At the end of the trial, enalapril/lercanidipine association was able to improve vascular surrogate end points, such as pulse pressure, BPV, and microalbuminuria. Comparing with baseline value, the fixed-dose combination significantly attenuated 24-hour and night-time BPV [81].

The effects of other non-pharmacological interventions have also been studied in clinical trials. Zuern *et al*. [82] have evaluated the effects of renal sympathetic denervation on 24-hour BPV in eleven consecutive patients with therapy-refractory arterial hypertension by estimation of SD of day-time and night-time BP readings. Six months after intervention, renal sympathetic denervation significantly reduced SD of 24-hour systolic BP. Moreover, effects of denervation on BPV were more pronounced than on average levels of BP in patients with refractory hypertension [82]. More recently, Pagonas *et al*. [83] have studied the effect of an 8-12-week treadmill exercise program on BP level and variability in 72 hypertensive subjects. Comparing with sedentary control subjects, aerobic exercise significantly decreased systolic and diastolic day-time BP but did not favorably modify CV of day-time and night-time BP [83].

In conclusion, first-line antihypertensive agents, including CCBs [78-80, 85-87], BBs [74-77], ARBs [71-73, 84], ACEIs [81] and diuretics [79], are able to control short-term BPV in addition to their BP lowering effects. Comparative clinical trials suggest that CCBs are more effective than ARBs or diuretics in the control of this novel cardiovascular risk factor.

DRUG EFFECTS ON MID-TERM BPV

Very few studies have examined the effects of antihypertensive treatment on mid-term day-to-day BPV and their impact on cardiovascular risk outcome. Considering the fact that exaggerated day-to-day BPV is associated with cardiovascular event, the Japan Combined Treatment With Olmesartan and a Calcium-Channel Blocker Versus Olmesartan and Diuretics Randomized Efficacy (J-CORE) Study has focused on the comparison of the effects of the combination of ARB/CCB or ARB/diuretics on day-to-day BPV in 207 hypertensive subjects treated with olmesartan monotherapy for 12 weeks [88]. Subjects were randomly assigned to the association of olmesartan with hydrochlorothiazide or azelnidipine for 24 weeks measuring drug effects on mid-term BPV by the within-individual SD of the 5-day home BP [88]. In addition, arterial stiffness was assessed by aortic pulse wave velocity at baseline and 24 weeks later. Although BP reduction was similar between both combinations, azelnidipine/olmesartan induced a greater reduction of systolic and diastolic day-to-day BPV when compared with hydrochlorothiazide/olmesartan (Fig. **4**) [88]. In the azelnidipine/olmesartan group, the change in aortic pulse wave velocity was independently associated with the change in SD of home day-to-day systolic BP, suggesting that the reduction of arterial stiffness induced by ARB/CCB contributes in the beneficial effect of the combination on mid-term BPV [88]. In addition, Ishikura *et al*. [89] have conducted a nationwide investigation to examine factors associated with day-to-day home BPV among 1933 hypertensive Japanese patients medicated with antihypertensive drugs [89]. By means of multivariate regression analysis, the Japan Home versus Office Blood Pressure Measurement Evaluation (J-HOME)-Morning Study has found that day-to-day home BPV is positively associated with ARBs treatment and negatively associated with taking CCBs, especially amlodipine [89]. Although limited evidences are available, CCBs seem to be particularly effective for the attenuation of mid-term day-to-day BPV due to its beneficial effect on arterial compliance.

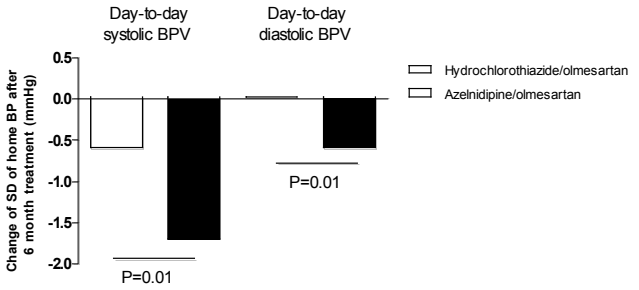

Fig. (4). Effect of hydrochlorothiazide/olmesartan or azelnidipine/olmesartan on day-to-day BPV in hypertensive patients. SD: standard deviation; BPV: blood pressure variability; BP: blood pressure. Adapted from [81].

In another trial, Ushigome *et al*. [90] have compared home BPV among patients treated with CCBs (n = 44) or ARBs/ACEIs (n = 159). Day-to-day BPV was assessed by the estimation of the CV of morning and evening home BP readings during 14 consecutive days [90]. Patients treated with CCBs benefited from a lower CV of morning systolic BP in comparison with the group receiving drugs acting at the RAS [90].

DRUG EFFECTS ON LONG-TERM BPV

In last year's, growing evidence from retrospective analysis of controlled clinical trials suggests that positive effects of antihypertensive therapy on long-term BPV contribute to the prevention of cardiovascular events in hypertensive patients. Rothwell *et al*. [91, 92] have recently published a post hoc analysis of two large randomized trials, the 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. Different components of BPV variability, including variability on 24-hour ABPM, within visit and visit-to-visit variability, were studied during follow-up in the ASCOT-BPLA trial and were expressed as SD, CV, and transformations uncorrelated with mean BP [92]. In the ASCOT-BPLA, SD of systolic BP was lower in the amlodipine group than in the atenolol group at all follow-up visits due to lower within visit-to-visit variability. In addition, short-term BPV, including within-visit and ABPM variability in SBP, was also lower in the amlodipine group than in the atenolol group. When compared with baseline values, while BPV was reduced in the amlodipine group, atenolol treatment has been associated with opposite effects. Interestingly, the amlodipine group showed a lower risk of stroke and coronary events with respect to subjects assigned to atenolol, and this beneficial effect was abolished after adjusting for within-individual BPV [92]. In the MRC trial analyzed by Rothwell *et al*. [91], SD of all measures of within-individual visit-to-visit variability in systolic BP

were increased in the atenolol group compared with both the placebo group and the diuretic group during initial follow-up. The authors also detected a correlation between stroke risk in patients treated with atenolol and subsequent temporal trends in BPV during follow-up [91, 92]. Rothwell *et al*. [91] concluded that the opposite effect of CCBs and BBs on BPV explains the disparity in the risk of stroke of patients under antihypertensive treatment. Therefore, to effectively prevent cerebrovascular events, BP lowering agents need to both reduce mean blood pressure and its short-term and long-term variability [91].

Webb *et al*. [93] also reviewed the effect of different classes of blood pressure treatment on BPV in trials. Specifically, the authors examined the effect of antihypertensive treatment on interindividual variance in BP—a surrogate marker for within-individual variability— expressed as the ratio of the variances (VR). The meta-analysis revealed that BPV was only effectively reduced by CCBs. Conversely, drugs acting at the RAS, thiazide-type diuretics, and BBs were the least effective and showed neutral effects in comparison with placebo (Fig. **5**) [93]. Meanwhile the addition of CCBs to another antihypertensive drug significantly reduced visit-to-visit BPV; adding other agents to calcium channel blockers did not contribute to further attenuation of long-term systolic BPV [93]. Treatment with higher doses of CCBs allowed a greater reduction in visit-to-visit BPV, whereas randomization to a higher dose of BBs increased systolic BPV [94].

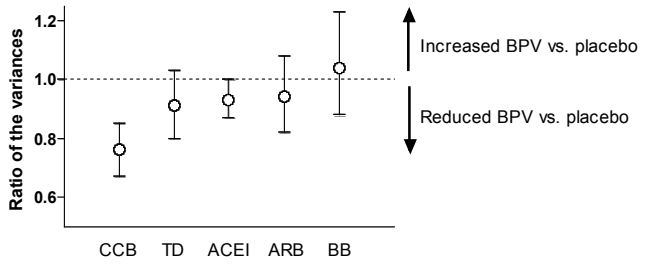

Fig. (5). Meta-analysis of antihypertensive drug effects on long-term BPV. BPV: blood pressure variability; CCB: calcium channel blockers; TD: thiazide like diuretics; ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers; BB: beta blockers. Adapted from [8, 85].

In another report, Webb *et al*. [95] have evaluated the effects of BB subclass on variability in BP and stroke risk in a systematic review of randomized controlled trials by comparing different types of BB with placebo or other agents. The analysis demonstrated that nonselective BBs, mainly propranolol, increase more interindividual variance in BP (VR: 1.23; 95% confidence interval: 1.13-1.59; p=0.002) than cardioselective BBs (VR: 1.09; 95% confidence interval: 1.00-1.19; p=0.053) when compared with other antihypertensive drugs [95]. The direct comparison revealed that variability in systolic BP was significantly lower with β_1-selective blockers with regards to nonselective agents (VR: 0.81; 95% confidence interval: 0.68-0.97; p=0.03). In comparison with other BP lowering agents, the increase in stroke risk with nonselective BBs is more marked than with cardioselective agents [95]. Moreover, the authors have found that BBs with vasodilatory properties due to α-antagonism, β_2-agonism or nitric oxide (carvedilol, celiprolol and nebivolol) do not increase interindividual variance in BP compared to other antihypertensive drugs (VR: 0.96; 95% confidence interval: 0.74-1.25) [95]. Therefore, the meta-analysis of Webb *et al*. [95] clearly suggests significantly differences in the deleterious effect of BBs on long-term BPV in favor to third-generation BBs with vasodilatory properties. In fact, the non-selective agents seem to increase interindividual variance in BP due to their blocking effect on β_2 vasodilatory receptors [96].

Although clinical evidence suggests that BBs increase BPV in hypertensive patients, this negative effect seems to be influenced by the reduction of heart rate and the type of BBs. Cahan *et al*. [97] have demonstrated that ambulatory BPV estimated by means of different indexes, including SD, CV and variability independent of the mean, is influenced by heart rate, and treatment with BBs is not associated with increase in BPV after correction by heart rate.

More recently, Wang *et al*. [98] have compared the effect of amlodipine and other antihypertensive drugs on visit-to-visit BPV by means of the retrospective analysis of five randomized controlled trials, including ASCOT-BPLA, ALLHAT (Antihypertensive & Lipid Lowering Treatment to Prevent Heart Attack Trial), CAMELOT (Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis), NY92011 and R-0510. In the trials BPV was assessed by means of the estimation of SD and CV of systolic BP across visits from 12 weeks [98]. The analysis of the individual clinical studies has shown that amlodipine significantly decreases visit-to-visit SD and CV of office BP readings compared with atenolol, lisinopril and enalapril. Conversely, visit-to-visit BPV of patients treated with amlodipine was similar to chlorthalidone and losartan [98]. The meta-analysis of the five clinical trials revealed that amlodipine reduces SD and CV of visit-to-visit office BP vs. all active comparators, suggesting that the CCB is particularly effective in the attenuation of long-term BPV [98].

The quality of the evidence of drug effects on visit-to-visit BPV is relative low considering that it has been obtained from post-hoc analyses of trial data and based on comparisons between nonrandomized groups, which may include a large number of potential confounders undermining the study conclusions [5]. Therefore, there is an urgent need to evaluate drug effects on long-term BPV in randomized prospective clinical trials. Recently, the European Lacidipine Study on Atherosclerosis (ELSA) compared the visit-to-visit intraindividual variations of both clinic and 24-hour mean BP in 1.600 hypertensive patients treated for 4 years with either atenolol or lacidipine [99]. The study has found that visit-to-visit BP variability does not differ substantially between BB and CCB. In fact, only visit-to-visit SD of clinic systolic BP was significantly higher in patients treated with atenolol than in lacidipine group [98]. Neither visit-to-visit SD of clinic diastolic BP nor visit-to-visit SD of ambulatory 24-hour BP showed differences between atenolol and lacidipine [99]. The authors have also demonstrated that interindividual BPV during treatment shows marked quantitative differences with intraindividual visit-to-visit BPV questioning the use of interindividual variance in BP as a surrogate marker for within-individual variability [99].

Another recent prospective clinical trial has evaluated the impact of non-pharmacological interventions, including weight loss and salt restriction, on visit-to-visit BPV [99]. The study enrolled 1.820 subjects with high-normal diastolic BP who were randomized to weight loss, sodium reduction, combination (weight loss and sodium reduction), or usual care groups. Visit-to-visit BPV was established by the SD of BP readings across six follow-up visits [100]. The level of visit-to-visit systolic and diastolic BPV was similar across treatment groups suggesting that weight loss and sodium reduction may not be effective interventions for lowering long-term BPV in individuals with high-normal diastolic BP [100].

PERSPECTIVES

Growing evidence relates excessive short-term, mid-term and long-term BPV with target organ damage and cardiovascular events in hypertensive patients. Recent clinical trials and meta-analysis suggest that amelioration of short-term and long-term BPV by antihypertensive drugs plays an important role in the cardiovascular benefits of drug therapy. However, these evidences must be interpreted with caution considering the recognized limitations in the design of clinical trials and the fact that most data have been obtained from retrospective analysis and systematic review of clinical

Table 2. Ongoing clinical trials that evaluate drug effects on BPV.

Trial denomination	Objective	Endpoint	ClinicalTrials.gov Identifier
The COMPAriSon of Systolic Blood Pressure Variability and Central Blood Pressure of Calcium Channel Blocker (Amlodipine) in Comparison With Angiotensin Receptor Blocker (Losartan) in Patients With Essential Hypertension	To test the hypothesis that an ARB is not inferior to a CCB in the reduction of SD of systolic BP in essential hypertensive patients.	Primary endpoint: SD of visit-to-visit systolic BPV Secondary endpoints: Central systolic BP, augmentation index of central BP, SD of within-visit systolic BPV, CV of visit-to-visit systolic BPV, variation independent of the mean of visit-to-visit systolic BPV, 24-hour ABPM	NCT01964079
Indapamide Versus Hydrochlorothiazide in Elderly Hypertensive Patients With Renal Insufficiency	Evaluate the effects of indapamide SR 1.5 mg on renal function, endothelial function, BPV by comparison with hydrochlorothiazide 25 mg, in patients with Mild to Moderate Renal Insufficiency and Hypertension.	Primary Outcome Measures: renal function Secondary Outcome Measures: endothelial function, BPV	NCT01172431
Compare the Effects of Lercanidipine Hydrochloride Tablet (Zanidip®) and Felodipine Sustained-Release Tablet for Hypertension	Compare felodipine sustained-release tablets, to Lercanidipine hydrochloride tablets (Zanidip®) for the treatment of patients with mild-to-moderate primary hypertension and to investigate the influence on patients' heart rate and BPV.	Primary Outcome Measures: Change from baseline in mean seated diastolic BP in clinical after 6 weeks of treatment Change from baseline in mean seated systolic BP after 6 weeks of treatment	NCT01520285
ARB and CCB Longest Combination Treatment on Ambulatory and Home BP in Hypertension With Atrial Fibrillation - Multicenter Study on Time of Dosing (ACROBAT)	Evaluate of 24-hour antihypertensive effect of long-acting ARB-CCB tablet administrated to hypertensive patients with atrial fibrillation, and comparison of 24-hour antihypertensive effect of long-acting ARB-CCB tablet between morning administration and bedtime administration.	Primary Outcome Measures: Change in 24-hour average BP from baseline to Week 12. Secondary Outcome Measures: Change in BP at night time, early-morning, and day-time from baseline to Week 12. Change in BPV from baseline to Week 12.	NCT01748253
Renal Sympathetic Modification in Patients With Metabolic Syndrome	Assess the incident of composite cardiovascular events after renal sympathetic modification using THERMOCOOL® catheter in patients with metabolic syndrome, and evaluate safety and efficacy of the intervention.	Primary Outcome Measures: composite cardiovascular events (myocardial infarction, heart failure, sudden death, cardiogenic death) Secondary Outcome Measures: effect on glucose and lipid metabolism, and BPV	
Comparison of Bisoprolol With Metoprolol Succinate Sustained-release on Heart Rate and Blood Pressure in Hypertensive Patients (CREATIVE)	Demonstrate the superiority and/or non-inferiority of bisoprolol on metoprolol succinate sustained-release (SR)	Primary Outcome Measures: Change of mean diastolic ABPM in the last 4 hours after 12-week treatment from baseline. Secondary Outcome Measures: Change of mean ambulatory 24-hour, day-time and nighttime BP 24-hour BPV	NCT01508325

Source: www.clinicaltrials.gov

Abbreviations: BP: blood pressure; BPV: blood pressure variability; ARB: angiotensin receptor blocker; CCB: calcium channel blocker; ABPM: ambulatory blood pressure monitoring; SD: standard deviation; CV: coefficient of variation.

studies. Therefore, some authors considered that the available evidence seems not to be solid enough to consider BPV as an additional goal for antihypertensive treatment, along with the reduction in average BP [17]. In order to increase actual knowledge regarding the prognostic value and therapeutic significance of BPV in cardiovascular disease, there is a need for additional clinical studies specifically designed for the study of the relevance of short-term and long-term BPV control by antihypertensive drugs. In this way, several clinical trials actually registered at clinicaltrials.gov include assessment of BPV as a secondary efficacy end point for the evaluation of different interventions in hypertensive patients (Table **2**).

Until recently, treatment guidelines for the management of hypertension have largely ignored the role of BPV during the selection of antihypertensive therapy [101]. The last guidelines from the European Society of Hypertension (ESH) and the National Institute for Health Care and Excellence (NICE) acknowledge the importance of BPV in hypertension [102, 103]. The Task Force for the Management of Arterial Hypertension of the ESH and of the European Society of Cardiology (ESC) has recognized that the worsening of organ damage and the incidence of events are related to BPV assessed by the SD around mean BP values [102]. In addition, the consensus recommends the use of long-acting drugs with more homogeneous BP lowering response over the 24 hours in order to

minimize BPV [102]. The 2011 NICE Guideline for the Clinical Management of Primary Hypertension in Adults establishes the existence of new data showing differential effects of antihypertensive treatments on BPV, suggesting that excessive fluctuations in BP per se represent an independent predictor of clinical outcomes [103]. As recognized by the guideline, CCBs appear to be the most effective treatment option to suppress BPV, recommending this therapeutic class as the best available evidence-based treatment options to ameliorate BPV in people with hypertension [103].

CONCLUSIONS

Preclinical and clinical evidences demonstrate the ability of first-line antihypertensive drugs, either as monotherapy or in combination, to effectively reduce short-term BPV. Although the mechanisms involved in the beneficial effects of CCBs, ACEs, BBs and diuretic on day-time, night-time and 24-hour BPV are relative unknown, the attenuation of short-term BPV induced by pharmacological treatment may be related to their BP lowering effect, to the amelioration of autonomic nervous system regulation and to the reduction of arterial stiffness. Large head-to-head clinical trials suggest that treatment with CCBs is generally most effective in the control of short-term BPV when compared with other antihypertensive groups. In addition, CCBs also reduce mid-term day-to-day BPV as a consequence of reduction of arterial stiffness. Post-hoc analysis demonstrates that amlodipine exerts greater protection against cerebrovascular events in hypertensive patients than atenolol partially due to its ability to reduce long-term BPV. These findings support the notion that attenuation of BPV can be considered a potentially important target of the treatment of hypertension [104]. Nowadays, it is important to consider reducing BPV by the use of long-acting CCBs, the best available evidence-based treatment option, which may help to prevent cardiovascular morbidity and mortality [105]. On the other hand, the chronodiagnosis of the circadian pattern of BP fluctuation –dipping, non-dipping or CHAT- in individual hypertensive patients and the selection of the most adequate antihypertensive drugs and the best time of dosing will lead to further preventive effects of morbid events due to normalization of abnormal circadian BPV.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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