

## Review Article

# Blood Pressure Variability: Prognostic Value and Therapeutic Implications

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Blood pressure variability (BPV) is considered nowadays a novel risk factor for cardiovascular disease. Early findings in sinoaortic denervated rats have clearly shown that enhanced fluctuation of blood pressure induced left ventricular hypertrophy, vascular stiffness, and renal lesion. A large number of clinical trials confirm that short-term and long-term blood pressure variability independently contributes to target organ damage, cardiovascular events, and mortality not only in hypertensive patients but also in subjects with diabetes mellitus and chronic kidney disease. Therefore, amelioration of BPV has been suggested as an additional target of the treatment of cardiovascular diseases. Preliminary evidence obtained from meta-analysis and controlled clinical trials has shown that antihypertensive classes differ in their ability to control excessive BP fluctuations with an impact in the prevention of cardiovascular events. Calcium channel blockers seem to be more effective than other blood pressure lowering drugs for the reduction of short-term and long-term BPV. 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.

## 1. Introduction

The role of high blood pressure levels on target organ damage and the protective effects of antihypertensive therapy have been extensively established in clinical practice [1]. Mortality from ischemic heart disease and stroke doubles every increment in 20 and 10 mmHg of systolic and diastolic blood pressure [1]. Nowadays, it is clear that besides usual blood pressure other parameters contribute to TOD in hypertensive patients [2]. Blood pressure is not a constant variable; rather, it shows marked spontaneous oscillations over short-term (minutes to days) and long-term (month) periods [3]. Early reports from animal models of cardiovascular variability have clearly demonstrated the relationship between excessive fluctuation in blood pressure values and the development of target organ damage [4]. 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 [5]. In recent years, a large number of preclinical and clinical studies have clearly identified the contribution of BPV to the cardiovascular complications associated with hypertension [6]. Moreover, preliminary data from retrospective analysis of clinical trials suggest that attenuation of BPV by antihypertensive agents contribute in the prevention of major cardiovascular events in hypertensive patients [7]. Considering the recent advances in the knowledge of the pathological role and clinical significance of BPV in cardiovascular diseases, the aim of the present spotlight paper is to summarize the preclinical and clinical evidence linking BPV with target organ damage in hypertension and the prognostic impact of the pharmacological attenuation of BPV in the treatment of cardiovascular diseases.

TABLE 1: Classification of blood pressure variability and its clinical implication.

Type of BPV	Time range	Measurement equipment or devices	Clinical implications
Ultrashort-term (very low frequency, low frequency and high frequency BPV)	Beat-to-beat variation	Direct continuous intra-arterial recordings coupled to spectral analysis	Estimation of neurohumoral systems involved in blood pressure regulation [8]
Short-term	Minutes-to-hours	Direct continuous intra-arterial recordings, ABPM	Increased variability in daytime, nighttime, and whole 24 h period associated with increased TOD [4]
Long-term	day-to-day, visit-to-visit	Office blood pressure, ABPM, home blood pressure monitoring	Large visit-to-visit BPV independently associated with increased incidence of stroke [9, 10]

ABPM: ambulatory blood pressure measurement; BPV: blood pressure variability.

## 2. Types of Blood Pressure Variability

Blood pressure oscillates over the 24-hour period due to the interplay among different neurohumoral systems [5]. BPV increases proportionally to mean blood pressure in the hypertensive stage and contributes independently to the presence and severity of TOD [5]. However, BPV is complex and includes both short-term (in the range of minutes to hours) and long-term (within days and months) variations, which can be estimated by different blood pressure devices and using diverse calculation and statistical methods (Table 1).

## 3. Ultra-short-Term Blood Pressure Variability

Blood pressure 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 [11]. 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 [11]. The frequency components of blood pressure variability (BPV) detected by power spectral analysis include oscillations at the very low frequency (0.02–0.20 Hz in rats and 0.02–0.07 Hz in humans), low-frequency (0.2–0.6 Hz in rats and 0.077–0.15 Hz in humans), and high-frequency domain (1–4 Hz in rats and 0.15–0.40 Hz in humans) (Table 2) [11]. In this context, while myogenic vascular function, renin angiotensin system, and endothelium-derived NO affect BPV at VLF [8, 11], LF variability is modulated by sympathetic modulation of vascular tone and endothelial-derived NO in rats [11]. In addition, normalized LF (LF/HF ratio) has been validated as a marker of sympathetic vascular activity in preclinical and clinical studies [9, 10]. Variability in the HF domain is mainly influenced by changes in cardiac output [12].

In addition, beat-to-beat BPV can also be estimated as total power spectral density, an index of global variability, by integrating the power spectra over the frequency range. Different mechanisms can contribute in the increase of beat-to-beat BPV, including enhanced central sympathetic drive, reduced arterial or cardiopulmonary baroreflex, humoral and

TABLE 2: Role of neurohumoral systems in beat-to-beat BPV in rats and humans.

Frequency domain	Rats	Humans
Very low frequency	Myogenic vascular function, renin angiotensin system, endothelial-derived NO	Myogenic vascular function
Low frequency	Endothelial-derived NO, sympathetic nervous system	Sympathetic nervous system, myogenic vascular function
High frequency	Cardiac output	Endothelial-derived NO

NO: nitric oxide.

rheological factors, behavioral and emotional mechanisms, and changes in ventilation [13].

Beat-to-beat BPV has been used for the study of the mechanism of action of antihypertensive drugs and the diagnosis and treatment of patients with cardiovascular diseases [8, 9, 11]. For instance, in our laboratory, we have shown that carvedilol induced a greater hypotensive response in spontaneously hypertensive rats in comparison with normotensive control animals [14]. 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 [14]. More recently, we have compared the effects of different beta blockers on vascular sympathetic activity by means of spectral analysis of blood pressure recording in sinoaortic denervated rats [15]. Carvedilol and nebivolol significantly reduced the LF/HF ratio compared with the effects of atenolol in this experimental model, suggesting the ability of the third generation beta blockers to reduce vascular sympathetic activity [15].

Detection of changes in beat-to-beat BPV could contribute to a rational selection of antihypertensive drugs. For instance, hypertensive patients with elevated LF BPV may have enhanced sympathetic modulation of vascular tone and a good response to sympatholytic drugs [11]. 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 haemorrhagic stroke, treatment with calcium channel blockers may be harmful in these patients considering further impairment of myogenic function [11].

#### 4. Short-Term Blood Pressure Variability

Short-term blood pressure variability is usually defined as the oscillation of blood pressure within 24 hours [13]. Fluctuation of blood pressure in a time range from minutes to hours mainly reflects the influence of central and autonomic modulation and the elastic properties of arteries [13]. In this way, the reduction of the ability of the arterial and cardiopulmonary reflexes to buffer changes in blood pressure due to behavioral or postural challenges and the alteration of arterial compliance can result in enhanced short-term BPV [13].

A myriad of indices have been used to assess short-term BPV in preclinical and clinical trials, including 24 hours, daytime and nighttime standard deviation (SD), and coefficient of variation (CV) of systolic and diastolic blood pressure [13]. As BPV largely depends from mean blood pressure values, average SD can be divided by the corresponding mean arterial pressure to normalize short-term BPV as CV [13]. Although estimation of short-term BPV theoretically requires continuous blood pressure recording, its assessment is also possible through the use of intermittent, noninvasive 24 h ambulatory blood pressure monitoring (ABPM) [13]. Nevertheless, due to the intermittent nature of blood pressure monitoring by ABPM, estimation of short-term BPV using this device is less accurate [13].

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 [16]. In order to improve the prognostic value of short-term BPV, the average real variability (ARV) of daytime and nighttime 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 [16]. Different studies have shown that ARV better predicts cardiovascular risk in hypertensive patients in comparison to the traditional SD of short-term BPV [16, 17].

#### 5. Long-Term Blood Pressure Variability

Blood pressure also shows long-term variability (day-to-day, visit-to-visit, or seasonal) that has been associated with increased risk of cardiovascular disease. Nowadays, factors contributing in long-term BPV are relatively unknown; it has been suggested that behavioral changes play a central role in day-to-day variation [13]. More recently, increased arterial stiffness has been found to contribute in long-term BPV as a pathological mechanism. The Multiethnic Study of Atherosclerosis (MESA) has recently demonstrated a reduction in aortic distensibility and arterial elasticity in patients

while it increased in hypertensive patients with higher visit-to-visit BPV [18].

In addition, large variation in visit-to-visit BPV could be a consequence of poor BP control in treated patients or inconsistent office BP readings [13]. Therefore, patient compliance with the prescribed therapeutic regimen and correct dosing and titration of blood pressure lowering medication can influence day-to-day and visit-to-visit BPV.

Measurement of day-to-day BPV can be performed using ABPM over consecutive days or by HBPM. Although utility of self-measurement of blood pressure for long-term BPV is limited by its fairly standardized conditions, it can be used to monitor BP changes over several days in patients with stable treatment regimen [13]. Visit-to-visit BPV can be assessed by OBPM or between-visit ABPM; however, estimation of long-term BPV using OBPM requires a consistent number of visits to achieve a meaningful value. In addition, measurement of BP at the office does not provide data regarding BP during usual activities and has limited value as indicator of BP control [13]. The use of 24 h ABPM overcomes limitations of OBPM considering that it provides extensive information on BP levels within a given 24 h period. Nevertheless ABPM cannot be routinely used to assess visit-to-visit BPV [13].

#### 6. Effect of Blood Pressure Variability on Target Organ Damage and Cardiovascular Events

As the degree of BPV is largely influenced by the mean BP level, the assessment of the effects of BPV on target organ damage and cardiovascular events has been complex. In this regard, a key issue is to establish if the cardiovascular risk in hypertensive patients is only determined by increase in mean BP or the enhanced BPV also contributes to the target organ damage [5]. In addition, several problems have been detected in the evaluation of the cardiovascular impact of short-term and long-term BPV, including limited reproducibility of BPV, the lack of normal reference values, and limitations of conventional devices for ABPM [5].

Considering the limitations of the evaluation of the clinical relevance of BPV, preclinical studies have clearly contributed in the actual knowledge of the role of BPV in cardiovascular disease. The sinoaortic denervated (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 [19]. 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 [19].

#### 7. Target Organ Damage in Sinoaortic Denervated Rats

Several studies have shown the influence of enhanced BPV on target organ damage in SAD rats (Table 3). Miao and Su demonstrated that chronic increase in BPV in this experimental model produces aortic hypertrophy early at 2

TABLE 3: Target organ damage in chronic sinoaortic denervated rats.

Tissue	Alterations
Heart	Late left ventricular hypertrophy
	Impairment of diastolic function in both left and right ventricle
	Increase cardiac expression of type I and III collagen
	Interstitial fibrosis and wall thickening
Vessels	Aortic hypertrophy
	Increase in wall thickness
	Collagen accumulation
	Smooth muscle cell growth Impaired arterial distensibility
Kidney	Increase in mesangial matrix
	Glomerular collapse
	Fibrohyalinosis
	Thickening of basement membrane of Bowman's capsule

weeks of the surgical intervention. In contrast, left ventricular hypertrophy was evident only after 10–16 weeks of SAD [20]. Moreover, the authors also found a positive correlation between BPV assessed by SD and both aortic and left ventricular hypertrophy [20].

Vascular hypertrophy induced by SAD is characterized by an increase in wall thickness, wall area, and wall thickness to internal diameter ratio with raise in the relative area of collagen and a decline in the relative area of elastin [21]. Therefore, aortic hypertrophy in SAD rats is partially due to collagen accumulation and smooth muscle cell growth [22].

Histological analysis of left ventricular tissues obtained from SAD shows the presence of several abnormalities, including cardiomyocyte necrosis, mononuclear cell infiltration, interstitial fibrosis and thickening of the wall, narrowing of the lumen, and an increase in perivascular collagen in coronary arterioles [21]. The earlier development of aortic hypertrophy could be explained by the fact that vascular hypertrophy induced by enhanced BPV may lead to an impaired arterial distensibility, increasing thereby left ventricular load and, in turn, favoring left ventricular hypertrophy [19].

More recently, Flues et al. have evidenced cardiac and pulmonary remodeling in 10-week SAD rats. In comparison with sham operated rats, SAD induces pulmonary hypertension, ventricular hypertrophy, and impairment of diastolic function in both left and right ventricle. In addition, increase of BPV induced by SAD increases cardiac expression of type I and III collagen, atrial natriuretic peptide, and  $\alpha$ -skeletal [22].

In addition to vascular and myocardial damage, renal lesions have been identified in 16-week SAD rats. Increase in mesangial matrix associated with focal proliferation, marked glomerular collapse and fibrohyalinosis, and thickening of basement membrane of Bowman's capsule were detected in rats after sinoaortic denervation [21].

Moreover, preclinical studies suggest that BPV is more important than blood pressure level in determination of end-organ damage in rats [23]. By comparing target organ damage in sham-operated and sinoaortic-denervated Wistar

Kyoto rats and spontaneously hypertensive rats, Miao et al. established a greater contribution of BPV than BP in left ventricular hypertrophy, glomerular damage, and aortic hypertrophy [23].

## 8. Clinical Impact of Short-Term BPV on Target Organ Damage and Cardiovascular Events

Expanding evidence has clearly demonstrated the influence of short-term and long-term BPV on target organ damage and cardiovascular events in hypertensive patients (Table 4). Degree of short-term BPV is independently associated with target organ damage and rate of cardiovascular events in both the general population and in subjects with hypertension [5]. Parati et al. first demonstrated the existence of an independent association between both 24 h mean BP and 24 h BPV with the prevalence and severity of target organ damage in 108 mild-to-severe essentially hypertensive patients [24]. Moreover, for any given 24 h mean BP value, the prevalence and severity of target organ damage were linearly related to the extent of short-term BPV [24]. In another study, the prognostic relevance of short-term BPV was assessed in 73 hypertensive patients using intra-arterial BP measurement. After a follow-up period of 7 years, baseline BPV was found to be a contributor for the development of cardiovascular complications, particularly left ventricular hypertrophy [25]. Daytime systolic BPV estimated by SD obtained from 24 h ABPM has been found to be associated with increased vascular damage and left ventricular hypertrophy in over 700 subjects with normotension or hypertension of different degrees of severity [26]. In addition, the European Lacidipine Study on Atherosclerosis (ELSA) has shown that carotid intima-media thickness was related with 24 h systolic BPV assessed by SD suggesting the relationship between short-term BPV and alterations of large artery structure in hypertension [27].

In the elegant PAMELA study, Sega et al. have studied the association between residual short-term BPV and left ventricular hypertrophy in untreated hypertensive patients [28]. The authors estimated different BPV parameters including overall BPV obtained from SD of the 24-hour ABPM, the cyclic components assessed by Fourier spectral analysis, and the residual BPV as the fraction of the overall BPV not accounted for by the 2 cyclic components [28]. A positive relationship was found between overall and residual BPV with left ventricular mass index. Conversely, the cyclic components of BPV do not influence ventricular hypertrophy, suggesting that only erratic fluctuations in BPV have a negative impact on target organ damage of hypertensive patients [28].

Daytime systolic BPV represents also a strong predictor of early carotid atherosclerosis progression in general population [29]. In a 3-year follow-up study, progression of intima-media wall thickness was significantly greater in the patients with increased systolic BPV even after adjustment for other risk factors [29]. Moreover, daytime systemic BPV was associated with a greater risk of cardiovascular events [29].

Clinical evidence of the prognostic value of short-term BPV in hypertension and general population has been grown

TABLE 4: Short-term blood pressure variability and target organ damage and cardiovascular events in patients.

Study	Study population	Blood pressure variability index	Outcome
Parati et al. [24]	Hospitalized subjects with essential hypertension	24 h BPV	Increase rate and severity of TOD
Palatini et al. [26]	Patients with mild to severe hypertension	Daytime systolic BPV	Higher degree of retinal abnormalities
Mancia et al. [27]	Hypertensive patients	24 h systolic BPV	Increase in carotid intima-media thickness
Sega et al. [28]	General population	Overall and residual short-term BPV	Left ventricular mass index
Sander et al. [29]	General population	Daytime systolic BPV	Progression of intima-media wall thickness
McMullan et al. [30]	Patient with chronic kidney disease	Systolic BPV	Increased overall and cardiovascular mortality
Kawai et al. [31]	Hypertensive patients	Daytime systolic BPV Nighttime systolic BPV	Increased renal vascular resistance Increased intima-media thickness and plaque score
Iwata et al. [32]	Hypertensive patients	Nighttime systolic BPV	Large arch plaque
Schillaci et al. [33]	Hypertensive patients	24 h BPV	Aortic stiffness Higher risk of restenosis after percutaneous coronary intervention
Cay et al. [34]	Normotensive patients	Systolic and diastolic 24 h BPV	
Schutte et al. [35]	Normotensive Africans	24 h systolic BPV	Left ventricular hypertrophy
Ozawa et al. [36]	Patients with type 2 diabetes	Nighttime systolic and diastolic BPV	Increased risk of incident cardiovascular disease
Sakakura et al. [37]	Elderly patients	Daytime systolic BPV	Cognitive dysfunction and reduction in quality of life

the last years. A prospective observational study of 908 participants with a follow-up period of 3–6.4 years showed a 2.82- and 4.9-fold increase of overall mortality and cardiovascular mortality in patients with chronic kidney disease and high systolic BPV [30].

Different studies have recently established the prognostic role of BPV for the development of arterial pathological changes. Fukui et al. also found a positive relationship between short-term BPV and arterial stiffness in subjects with type 2 diabetes [38]. The authors demonstrated that average morning home-measured systolic blood pressure and the SD of morning home-measured systolic blood pressure on one occasion were independently associated with pulse wave velocity in 332 patients with type 2 diabetes [38]. Another recent report proved the existence of differences between daytime and nighttime blood pressure variability regarding systemic atherosclerotic change and renal function. Using ABPM for assessment of BPV, meanwhile SD of daytime systolic BPV, was strongly correlated with renal vascular resistance; nighttime systolic BPV was significantly associated with intima-media thickness and plaque score [31].

Moreover, assessment of BPV, including 24 hour, awake and sleep, may be useful for assessment of arterial stiffness in hypertensive patients, considering the fact that ABPM is more accessible at the clinical setting than the pulse wave velocity [39]. Systolic BPV showed a positive correlation with different indexes of arterial stiffness, including ambulatory

arterial stiffness index, the pulse wave velocity, and the carotid intima-media thickness [39]. Iwata et al. also evidenced that nighttime systolic BPV is independently associated with large arch plaque suggesting that excessive fluctuations of BP could contribute to the formation and progression aortic arch atherosclerosis [32].

In another report, Schillaci et al. added insights in the knowledge of the impact of short-term BPV in large-artery stiffness in hypertensive patients [33]. The analysis of 2 large databases demonstrated that different parameters of BPV, especially weighed 24-hour SD, are independently associated with aortic stiffness both in 911 untreated, nondiabetic patients with uncomplicated hypertension and in 2089 mostly treated hypertensive patients [33].

Increased short-term BPV assessed by ABPM is associated with higher risk of restenosis after percutaneous coronary intervention in normotensive patients [34]. Higher values of systolic and diastolic BPV indices, including SD and CV, were found to be highly sensitive and specific for predicting binary restenosis 6 months after percutaneous coronary intervention [34].

In addition to vascular damage, short-term BPV has been associated with left ventricular hypertrophy in normotensive Africans in the SABPA Study [35]. The study included 409 African and Caucasian teachers aged 25–60 years showing a positive correlation between 24 hour systolic BPV and markers of left ventricular hypertrophy in African but not

TABLE 5: Long-term blood pressure variability and target organ damage and cardiovascular events in patients.

Study	Study population	Blood pressure variability index	Outcome
Kikuya et al. [50]	General population	Day-to-day systolic BPV	Increased hazard ratios for cardiovascular and stroke mortality
Muntner et al. [51]	General population	Visit-to-visit systolic BPV	Increased all-cause mortality
Johansson et al. [52]	General population	Day-to-day morning systolic BPV	Increased rate of cardiovascular events
Hsieh et al. [53]	Patients with type 2 diabetes	Visit-to-visit systolic and diastolic BPV	Increased all-cause mortality
Ushigome et al. [54]	Patients with type 2 diabetes	Day-to-day systolic and diastolic BPV	Development of macroalbuminuria
Kilpatrick et al. [55]	Patients with type 1 diabetes	Annual visit-to-visit BPV	Development or progression of nephropathy
Di Iorio et al. [56]	Subjects with chronic renal failure	Visit-to-visit systolic BPV	Elevated risk of death
Yokota et al. [57]	Patients with nondiabetic chronic kidney disease	Visit-to-visit systolic BPV	Deterioration of renal function
Di Iorio et al. [58]	Patients with end stage renal disease under hemodialysis	Dialysis-to-dialysis BPV	Increased cardiovascular mortality

Caucasian normotensive subjects. Considering this association, the authors stress out that the assessment of short-term BPV could potentially add to the early detection of normotensive Africans at increased risk for the development of cardiovascular complications [35].

Data from Ozawa et al. also suggest that increased short-term BPV estimated by ABPM represents a coronary risk factor in diabetic hypertensive patients [36]. By comparing hemodynamics of patients with or without coronary artery disease, the authors found greater nighttime systolic BPV in the absence of significant differences in mean BP values in diabetic patients with coronary artery disease with regard to subjects without coronary artery disease [36]. Another interesting report confirms the role of short-term BPV in the development of cardiovascular events in patients with type 2 diabetes. Using multivariable analyses, Eguchi et al. reported a modest association between sleep systolic and diastolic BPV and incident cardiovascular events in 300 patients with uncomplicated diabetes without known cardiovascular disease. Interestingly, neither nondipper and riser patterns nor the morning BP surge was associated with incident CVD events in this study [40].

Short-term BPV also contributes to cerebrovascular damage and decline in cognitive function in hypertensive patients. Specifically, exaggerated ambulatory SD of daytime systolic BP was associated with cognitive dysfunction in the elderly and lower quality of life [37]. In addition, Verdecchia et al. demonstrated that patients with higher systolic and diastolic BPV suffered from an increased rate of cardiovascular and cerebrovascular events in comparison with subjects with low BPV [41]. Evidence from the Syst-Eur trial also showed an increase by 80% in the risk of stroke for every 5 mmHg elevation in nighttime systolic BPV in hypertensive patients treated with placebo [42]. In addition, Liu et al. have shown that enhanced BPV impacts on the progression of cerebral microbleeds and white matter lesions in patients with a

history of ischemic stroke. In this regard, systolic BPV was an independent risk factor for deep and infratentorial cerebral microbleeds progression, whereas diastolic BPV was associated with cerebral microbleeds development in deep regions [43].

In addition to the degree of short-term BPV, the rate of BP variation also contributes in the likelihood of development of early carotid atherosclerosis [44]. Steeper fluctuations in BP produce greater stress on the arterial wall and may have an additive role in the detection of the severity of coronary artery lesions in normotensive individuals with suspected coronary artery disease [44]. Although ample evidence establishes the existence of a positive relationship between short-term BPV and the severity and rate of progression of end-organ damage, cardiovascular events and mortality [45, 46], a number of reports fail to demonstrate the prognostic relevance of BP fluctuations in hypertensive patients [47–49]. For instance, Pierdomenico et al. found that BPV assessed by noninvasive monitoring is not an independent predictor of outcome in uncomplicated mild hypertensive patients [49].

## 9. Impact of Long-Term BPV on Target Organ Damage and Cardiovascular Events

In the last years, a huge number of studies have demonstrated that long-term BPV (day-to-day and visit-to-visit variations) contributes in target organ damage and cardiovascular events in patients with hypertension and/or diabetes (Table 5). The Ohasama study establishes that day-to-day BPV by self-measurement at home brings insights for the assessment cardiovascular risk [50]. The evaluation of day-by-day variability in 2455 Ohasama residents showed an association between systolic and diastolic day-to-day BPV with greater risk of cardiovascular and stroke mortality but not for cardiac mortality [50]. The relationship between

increased visit-to-visit variability in blood pressure and all-cause mortality was examined by Muntner et al. using data from the Third National Health and Nutrition Examination Survey [51]. After adjusting for confounding factors, SD of visit-to-visit systolic variability greater than 4.80 mmHg was associated with a 57% increase in overall mortality in the general population [51]. In addition, the Finn-Home Study established the prognostic value of the day-to-day variability in home-measured blood pressure. Greater variability of morning home BP self-measurements performed on 7 consecutive days has been found to independently predict cardiovascular events in a representative sample of the Finnish adult population ( $n = 1866$ ) aged 45–74 years [52].

Day-to-day and visit-to-visit BPV also negatively impacts mortality, microvascular, and macrovascular complications in patients with type 2 diabetes. A longitudinal cohort study of 2161 patients with type 2 diabetes and a mean follow-up period of 5.5 years showed that visit-to-visit variability in systolic and diastolic BP significantly predicts all-cause mortality in patients with type 2 diabetes after adjusting for confounding factors [53]. In another report, Ushigome et al. assess the association between day-to-day variability in home blood pressure on 14 consecutive days and macroalbuminuria in 858 patients with type 2 diabetes [54]. The authors found that the increase in CV of morning systolic and diastolic BP and evening systolic BP is strongly related to the development of macroalbuminuria in diabetic patients [54]. More recently, a relationship between visit-to-visit variability in systolic BP and change in urinary albumin excretion or development of albuminuria has been found in patients with type 2 diabetes [59]. Long-term BPV also contributes to microvascular complications associated with type 1 diabetes. Retrospective analysis of the data from Diabetes Control and Complications Trial demonstrated that increased systolic and diastolic annual visit-to-visit BPV was related to the risk of the development or progression of nephropathy but not of retinopathy [55]. Therefore, long-term visit-to-visit BPV could be considered a novel risk factor for the development and progression of diabetic nephropathy in patients with diabetes [59].

Visit-to-visit BPV also contributes to target organ damage and cardiovascular events in patients with chronic kidney disease or under hemodialysis. A longitudinal retrospective, observational, and multicentre study has found an association between systolic BPV, defined as the ratio of the SD to the mean systolic BP of five values recorded during 4–5 months, and the risk of death but not of progression to dialysis in 374 elderly subjects with chronic renal failure [56]. In addition, Yokota et al. demonstrated that SD and CV of office systolic BP measured at 12 consecutive visits were significantly associated with deterioration of renal function in patients with nondiabetic chronic kidney disease [57]. In the same way, results from The Fosinopril in Dialysis Study showed that visit-to-visit BPV is extremely high in hemodialysis patients compared with other populations and a major determinant of cardiovascular events in this setting [60]. Di Iorio et al. have performed a historical cohort study in 1,088 prevalent hemodialysis patients with a follow-up period of 5 years in order to assess the risk of cardiovascular

death in relation to dialysis-to-dialysis BPV [58]. Although maximum BP and pulse pressure did not show any effect on cardiovascular death, long-term variability in BP was a predictor of cardiovascular mortality in patients with end-stage renal disease under hemodialysis [58].

It is important to stress out that short-term and long-term BPV are separately useful for cardiovascular outcomes prognosis. Specifically, Eguchi et al. demonstrated that both variability of BPV of clinic systolic BP and nighttime systolic BPV are independent predictors for cardiovascular events in hypertensive patients [61]. Besides the strong evidence of the prognostic role of long-term BPV, the European Lacidipine Study on Atherosclerosis failed to show an association between enhanced visit-to-visit BPV and cardiovascular outcomes in treated mildly to moderately hypertensive patients [62]. Mancia et al. demonstrated that carotid intima-media thickness and cardiovascular outcomes in patients with mild to moderate hypertension were related to the mean clinic or ambulatory systolic BP achieved by treatment but not to on-treatment visit-to-visit clinic or 24-hour BPV [62].

## 10. Drug Effects on Blood Pressure Variability

Considering that short-term and long-term BPV independently contributes to target organ damage and cardiovascular events in patients with hypertension or diabetes, attenuation of excessive fluctuation of systolic and diastolic BP may be an additional therapeutic target in cardiovascular prevention [63, 64]. The efficacy of different drugs on reducing short-term and long-term BPV has been assessed in several pre-clinical and clinical studies, demonstrating the existence of differences in the ability of specific drugs to control this novel risk factor.

## 11. Preclinical Evidence

Drug effects on short-term BPV have been assessed in different animal models of cardiovascular disease after acute and long-term administration. Several antihypertensive drugs have been able to attenuate excessive fluctuations of BP in SAD rats. Wang et al. compared the effects of acute oral administration of nine different antihypertensive drugs on BPV in conscious, freely moving SAD rats [65]. Calcium channel blockers (nifedipine, nitrendipine, and amlodipine) and sympatholytic agents (atenolol, prazosin, and clonidine) effectively control excessive fluctuations in BP after sinoaortic denervation [65]. Conversely, acute application of drugs acting at the renin-angiotensin system (captopril and telmisartan) and the diuretic hydrochlorothiazide did not show beneficial effects on BPV attenuation in rats with labile BP [65]. 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 [15] (Figure 1). On the other hand, cardioselective blockade of  $\beta_1$ -adrenoceptor with atenolol induces only minor beneficial effects on BP fluctuations in SAD animals (Figure 1) [15].

Acute effects of different antihypertensive agents on BPV have also been assessed in spontaneously hypertensive and

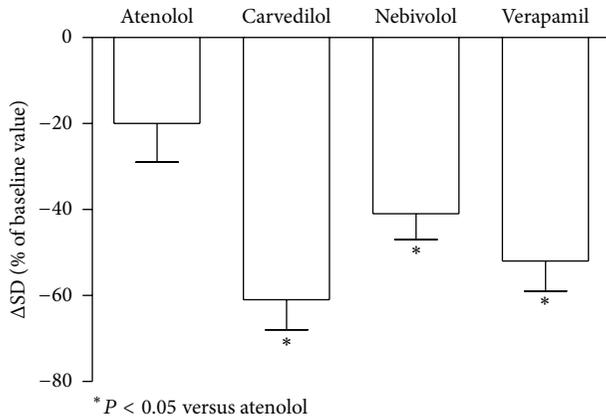


FIGURE 1: Effects of acute administration of atenolol, carvedilol, nebivolol, or verapamil on short-term BPV in SAD rats. Adapted from Bertera et al. [15].

normotensive control rats. Intra-gastric administration of ketanserin has been shown to attenuate BPV and mean BP values and to improve baroreflex sensitivity in spontaneously hypertensive rats [66]. In another report, Han et al. studied the effects of the combination of hydrochlorothiazide and nitrendipine on short-term systolic and diastolic BPV in spontaneously hypertensive rats [67]. Although only nitrendipine at a high dose was able to reduce systolic BPV, combination of hydrochlorothiazide + nitrendipine significantly attenuated BP fluctuations in spontaneously hypertensive rats [67]. In addition, synergism of atenolol and amlodipine coadministration on attenuation of short-term BPV has been evidenced in spontaneously hypertensive rats [68]. Meanwhile, acute oral administration of a single dose was not able to reduce BP fluctuations, atenolol + amlodipine attenuated both systolic and diastolic SD of BP recoding [68].

Acute intravenous administration of a single dose of third-generation beta blockers, carvedilol, and nebivolol, also effectively controls short-term BPV in freely moving spontaneously hypertensive rats and normotensive control animals [14, 69]. An interesting finding of this set of experiments is the fact that nebivolol markedly attenuates short-term BPV in spontaneously hypertensive rats and normotensive animals and this beneficial effect is evident at low dose levels associated with limited effects on mean BP values (Figure 2) [69].

Evidence from long-term studies has clearly demonstrated the ability of different cardiovascular drugs to chronically reduce BPV and target organ damage in different experimental models. In an elegant study, Kai et al. have found that the chronic administration of candesartan at a subpressor dose abolishes SAD-induced inflammatory changes and cardiac remodeling and subsequently prevents systolic dysfunction in spontaneously hypertensive rats with sinoaortic denervation [70, 71]. Moreover, treatment with fosinopril during 16 weeks effectively prevented increase in BPV and vascular remodeling of pulmonary arteries in SAD animals [72]. Works from Miao et al. 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 [73].

The contribution of beneficial drug effects on BPV on target organ damage has also been demonstrated in spontaneously hypertensive rats. By multiple regression analysis, Shang et al. have found that the reduction in BPV induced by the chronic administration of irbesartan and amlodipine contributes to ameliorate left ventricular hypertrophy and renal lesion in spontaneously hypertensive rats [74]. In another report, the effect of chronic administration of different antihypertensive drugs on target organ damage was studied in spontaneously hypertensive rats. 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 [75].

Compared with BP level, degree of BPV and baroreflex sensitivity values showed a much closer relationship with target organ damage in treated hypertensive rats [75]. 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 [75]. 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 [76]. Ketanserin significantly decreased BP and BPV 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 [76]. In another report, long-term administration of nitrendipine has been shown to prevent target organ damage in spontaneously hypertensive rats and the beneficial effect was closely related to the attenuation of long-term systolic BPV but not to BP level [77]. In addition to these findings, research from Xie et al. 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 [78, 79].

To sum up, ample preclinical evidence confirms the pathological role of increased BPV in the development of target organ damage and cardiovascular events in experimental models of cardiovascular disease and the protective role of antihypertensive therapy associated with the reduction of short-term and long-term BPV.

## 12. Clinical Evidence

In last years, growing evidence from controlled clinical trials suggests that positive effects of antihypertensive therapy on short-term and long-term BPV contribute to the prevention of cardiovascular events in hypertensive patients. Rothwell et al. 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

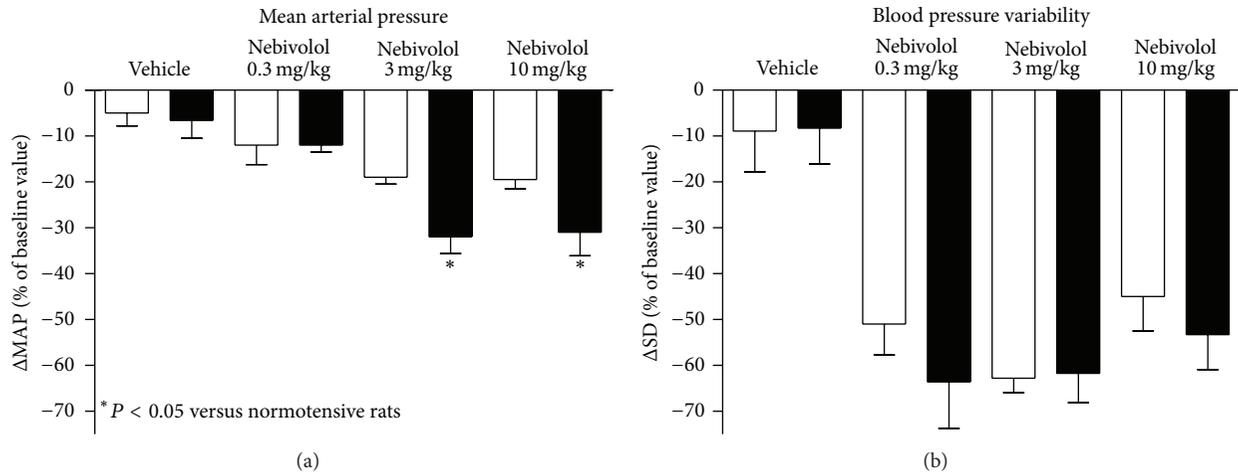


FIGURE 2: Effects of acute administration of vehicle or nebivolol on mean arterial pressure (MAP) and short-term BPV in normotensive (open bars) and spontaneously hypertensive rats (filled bars). Adapted from Bertera et al. [69].

whether drug effects on BPV explain the differences of antihypertensive treatment in stroke prevention [7, 80]. Different components of BPV variability, including variability on 24 h ambulatory blood pressure measurement (ABPM), within-visit and visit-to-visit variability, was studied during followup in the ASCOT-BPLA trial and was expressed as standard deviation (SD), coefficient of variation, and transformations uncorrelated with mean blood pressure [80]. 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, for example, 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 [80]. In the MRC trial analyzed by Rothwell et al., SD of all measures of within-individual visit-to-visit variability in systolic BP was increased in the atenolol group compared with both the placebo group and the diuretic group during initial followup. The authors also detected a correlation between stroke risk in patients treated with atenolol and subsequent temporal trends in BPV during followup [7, 80]. Rothwell et al. concluded that the opposite effect of calcium channel blockers and  $\beta$ -blockers on BPV explains the disparity in the risk of stroke of patients under antihypertensive treatment [7]. Therefore, to effectively prevent cerebrovascular events, blood pressure-lowering agents need to both reduce mean blood pressure and its short-term and long-term variability [80].

Webb et al. also reviewed the effect of different classes of blood pressure treatment on blood pressure variability in trials [81]. Specifically, the authors examined the effect of antihypertensive treatment on interindividual variance in

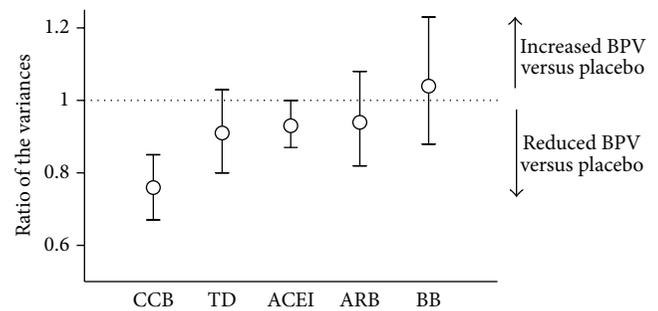


FIGURE 3: Meta-analysis of antihypertensive drug effects on long-term BPV. CCB: calcium channel blockers; TD: thiazide-like diuretics; ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers; BB: beta blockers. Adapted from Webb et al. [81].

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 calcium channel blockers. Conversely, drugs acting at the renin-angiotensin system, thiazide-type diuretics, and beta-blockers were the least effective and showed neutral effects in comparison with placebo (Figure 3) [81]. Meanwhile, the addition of calcium channel blockers to another antihypertensive drug significantly reduces visit-to-visit BPV; adding other agents to calcium channel blockers did not contribute to further attenuation of long-term systolic BPV. Treatment with higher doses of calcium channel blockers allows a greater reduction in visit-to-visit BPV, whereas randomization to a higher dose of  $\beta$ -blockers increased systolic BPV.

Although clinical evidence suggests that  $\beta$ -blockers increase BPV in hypertensive patients, this negative effect seems to be influenced by the reduction of heart rate and the type of  $\beta$ -blocker. Cahan et al. have demonstrated that intracating variability in BP measurement is influenced by

heart rate, and treatment with  $\beta$ -blockers is not associated with increase in BPV after correction by heart rate [82]. A recent systematic review has also found that variability in systolic blood pressure is increased more by nonselective  $\beta$ -blockers than by selective  $\beta_1$ -adrenergic antagonists [83].

Findings from the aforementioned studies are limited by the fact that they evaluate the clinical impact of drug effects on BPV by the retrospective analysis of clinical trials not specifically designed for this purpose. 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 [7]. To obtain relevant information, the design of these clinical trials must include the following points: a head-to-head comparison of specific antihypertensive drugs rather than therapeutic classes; the relationship between magnitude of BPV and the 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) [80].

In this line, in the last years several clinical trials were designed to assess the effect of medical interventions on short-term and long-term BPV in hypertensive patients. Zuern et al. [84] have studied the effects of renal sympathetic denervation on 24-hour BPV in eleven consecutive patients with therapy-refractory arterial hypertension. 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 [84].

Clinical trials have also shown beneficial effects of angiotensin II type 1 receptor blockers on BPV and target organ damage in patients on dialysis. Losartan treatment significantly reduced nighttime short-term BP variability in hypertensive patients on hemodialysis, in contrast to neutral effects of placebo. 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 [85]. In another report, Masuda et al. compared the effect of telmisartan or losartan on short-term BPV hypertensive patients with overt diabetic nephropathy [86]. After 12 weeks of treatment, 24 h, daytime, and nighttime short-term BPV was significantly decreased by telmisartan but not by losartan. In addition, telmisartan reduced effectively proteinuria in hypertensive patients with overt diabetic nephropathy, partly through inhibitory effects on ambulatory short-term BPV [86]. Relevance of BPV attenuation in the prevention of target organ damage by angiotensin II type 1 receptor blockers has also been documented in hypertensive patients on chronic peritoneal dialysis [87]. In the study, 45 hypertensive patients on chronic peritoneal dialysis therapy were randomly assigned to the candesartan ( $n = 15$ ), valsartan ( $n = 15$ ), or control

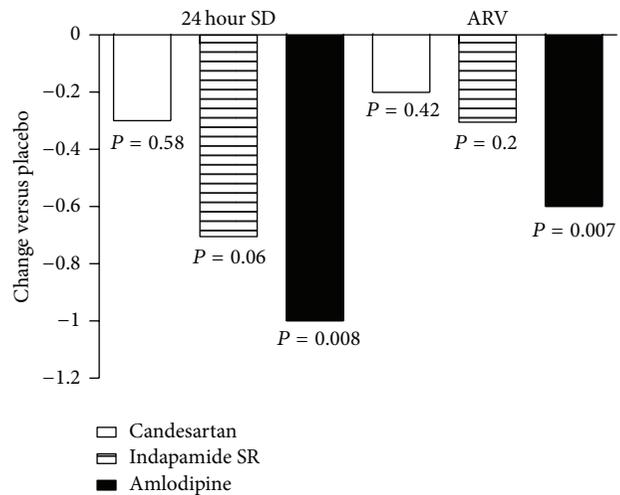


FIGURE 4: Effect of treatment with candesartan, indapamide SR, and amlodipine on short-term BPV in hypertensive patients. ARV: average real variability; SD: standard deviation. Adapted from Zhang et al. [88].

treatment ( $n = 15$ ) during a follow-up period of 6 months [87]. Although angiotensin II type 1 receptor blockers and control antihypertensive treatment similarly controlled 24-hour ABP values, only candesartan and valsartan decreased short-term BPV improving parameters of cardiovascular remodeling, including natriuretic peptides, echocardiography, and brachial-ankle pulse wave velocity [87].

Considering the importance of BPV control in the prevention of microvascular complications of diabetes mellitus, Ushigome et al. compared home BPV among patients treated with calcium channel blockers ( $n = 44$ ) or angiotensin II receptor blockers and/or angiotensin-converting enzyme inhibitors ( $n = 159$ ) [89]. Patients treated with calcium channel blockers benefited from a lower coefficient variation of morning systolic BP in comparison with the group receiving drugs acting at the renin angiotensin system [89].

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 [88, 90]. Amlodipine treatment showed greater effects on short-term BPV variables in comparison with candesartan and indapamide sustained release (Figure 4) [90]. Specifically, after adjustment for the corresponding mean BP reduction, only amlodipine consistently ameliorated short-term BPV indexes, including daytime, nighttime, and 24 h SD of systolic BP and ARV [90]. Meanwhile candesartan showed neutral effects on short-term BPV; indapamide only was able to reduce daytime SD [90].

Added to the evidence of trials evaluating antihypertensive monotherapy, different 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. have evaluated the efficacy

and safety of a fixed-dose combination of lercanidipine and enalapril in daily practice using office, self-measured, and ambulatory blood pressure measurement [91]. In this prospective, open-label, uncontrolled multicenter trial 622 hypertensive patients were treated with a fixed-dose combination of 20 mg enalapril maleate and 10 mg lercanidipine hydrochloride and followed during 3 months. 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 h and nighttime BPV.

In another report, bedtime administration combination therapy with amlodipine-olmesartan ameliorated BPV by controlling morning surge of BP and reduced urinary albumin excretion in 31 essential hypertensive patients [92]. By using 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. The ability of bedtime administration of amlodipine-olmesartan to reduce BPV was associated with a reduction in urinary albumin/creatinine ratio [92].

To sum up, preclinical and clinical evidence largely confirms the ability of antihypertensive therapy to reduce short-term and long-term BPV in addition to mean BP values. Although BPV is directly related to BP level, attenuation in BPV induced by BP lowering drugs seems to be partially independent from their antihypertensive activity and further contributes in target organ protection. Preliminary clinical evidence obtained from meta-analysis and retrospective analysis of clinical trials suggests that calcium channel blockers exhibit greater capacity to ameliorate elevated BPV in comparison with other BP lowering classes.

### 13. Perspectives

Growing evidence relates excessive short-term and long-term BPV with target organ damage and cardiovascular events in hypertensive patients. In addition, BPV also seems to contribute in the development of microvascular complications in type 1 and type 2 diabetes and with the progression of renal failure and mortality in patients at end-stage chronic kidney disease. Therefore, increased BPV is nowadays considered a new risk factor of cardiovascular disease and a possible new target for antihypertensive therapy [6, 64, 93–96].

More recent clinical trials 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, findings from these trials must be interpreted with caution considering the recognized limitations in their design and the fact that most data have been obtained from retrospective analysis and systematic review of clinical 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 [64]. Modifications in BPV associated with antihypertensive treatment are difficult to assess in the daily clinical practice due to the use of different drug regimens and the introduction of frequent changes

according to clinical needs [64]. Another important issue is the limitation of conventional discontinuous, low frequency, ABPM devices for the assessment of BPV that results in oversmoothing, aliasing, overmodeling, and failure to assess fast changes in BP [5]. For instance, conventional ABPM techniques measure BP by automated readings every 15 and 30 min and do not allow quantification of short-lasting variation of BP values [80]. Nevertheless, with the development of the Portapres device (Finapres Medical Systems, Arnheim, The Netherlands), the shortcomings of conventional ABPM have been overcome [5]. 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 [97]. Moreover, the use of Portapres for the estimation of BPV has been validated with intra-arterial blood pressure monitoring showing similar results [98–100].

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](http://clinicaltrials.gov) include assessment of BPV as a secondary efficacy end point for the evaluation of different interventions in hypertensive patients (Table 6).

In addition, international scientific associations need to urgently recognize the importance of BPV in the development of target organ damage in hypertensive subjects and elaborate task force documents to guide the investigators in methodological and statistical aspects of BPV assessment. For instance, although most studies used the SD as an index of BPV, as commented previously, this parameter only reflects the dispersion of values around the mean and does not account for the order of blood pressure measurements [80]. Conversely, ARV better characterized short-term BPV, considering that it estimates the average of the absolute differences of consecutive measurements and is therefore sensitive to BP assessment order and less influenced by the low sampling frequency of ABPM [80]. Until recently, treatment guidelines for the management of hypertension have largely ignored the role of BPV during the selection of antihypertensive therapy [1]. In the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, short-term and long-term BPVs have not been mentioned as a risk factor of target organ damage and cardiovascular events in hypertensive patients [1]. Nevertheless, 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 [101, 102]. 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 BO values [101]. 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 [101]. The 2011 NICE Guideline for the Clinical Management of Primary Hypertension in Adults

TABLE 6: Ongoing clinical trials that evaluate drug effects on BPV.

Trial denomination	Objective	Endpoint	ClinicalTrials.gov Identifier
Indapamide versus hydrochlorothiazide in elderly hypertensive patients with renal insufficiency	Evaluate the effects of indapamide SR 1.5 mg on renal function, endothelial function, blood pressure variability 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, blood pressure variability	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 blood pressure variability.	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 nighttime, early-morning, and daytime 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 noninferiority 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 h, daytime and nighttime BP 24-hour variability of BP	NCT01508325

Source: [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

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 [102]. As recognized by the guideline, calcium channel blockers 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 [102].

#### 14. Conclusions

Both short-term and long-term BPVs are independently associated with target organ damage and cardiovascular events in patients with hypertension, diabetes mellitus, and chronic kidney disease. Excessive fluctuations in BP increase

the likelihood of myocardial, vascular, and renal alterations and contribute to mortality and cardiovascular events. Visit-to-visit BPV has also been identified as a strong predictor of microvascular complications in type 1 and type 2 diabetic patients. Preliminary evidence demonstrates the ability of some antihypertensive drugs, either as monotherapy or in combination, to effectively reduce short-term and long-term BPV. Nevertheless, available data suggest a greater capability of calcium channel blockers in comparison to other therapeutic classes to attenuate long-term BPV. For instance, amlodipine exerts greater protection against cerebrovascular events in hypertensive patients than atenolol partially due to its ability to reduce short- and long-term BPV. Therefore, amelioration of BPV can be considered a potentially important target for drug development and combination therapy, and new

drugs or combinations of drugs that reduce variability even more effectively than calcium channel blockers could greatly reduce the occurrence of stroke [103]. Actually, it is important to consider reducing BPV by the use of long-acting calcium channel blockers, the best available evidence-based treatment option, which may help to prevent cardiovascular morbidity and mortality [104].

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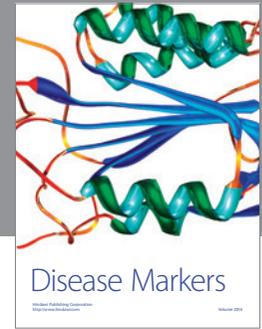
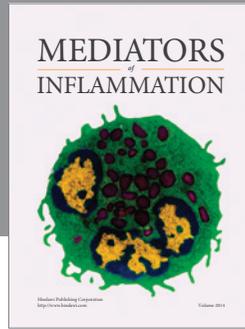
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