Επίκαιρο Άρθρο

Blood pressure variability: clinical relevance and application

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ABSTRACT

Blood pressure (BP) is characterized by continuous and significant variations occurring over 24 hours [(short-term BP variability (V)], day-by-day (mid-term BPV) and from visit-to-visit (long term BPV). In physiological conditions BPV largely represents a response to environmental stimulations and challenges from daily life aimed at maintaining the so-called BP "homeostasis". However, sustained increases in BPV, may also reflect alterations in cardiovascular regulatory mechanisms with clinical significance and prognostic implications. Evidence in support of this concept has been provided by a series of studies showing that increasing values of BPV, are associated with a higher risk of subclinical organ damage, cardiovascular events and cardiovascular and all-cause mortality independently of elevated average BP values. This paper will review the available evidence on the complex features characterizing BPV, by addressing its current definition and classification, its mechanisms, the methodological aspects that should be considered for its assessment and its significance for cardiovascular prognosis. Still debated issues, such as whether BPV should be routinely assessed in clinical practice in addition to average BP levels, and whether antihypertensive treatment strategies should be targeted at reducing not only average BP levels but also the degree of BPV in order to optimize CV protection, will also be addressed.

Introduction

Blood pressure (BP) is characterized by continuous and significant changes occurring over 24 hours, day-by-day and from visit-to-visit. In physiological conditions this BP variability (BPV) largely represents a response to environmental stimulations and challenges from daily life aimed at maintaining the so-called BP "homeostasis" (i.e. adequate organ perfusion in response to the changing metabolic demands when facing physical or emotional stress and BP reduction during sleep). However, sustained increases in BPV, may also reflect alterations in cardiovascular regulatory mechanisms with clinical significance and prognostic implications. Evidence in support of this concept has been provided in recent years showing that increasing values of BPV, are associated with an increased risk of subclinical organ damage and cardiovascular events and cardiovascular and all-cause mortality independently of elevated average BP values[1]. More recently, studies have been conducted in order to explore whether pharmacological treatment may modulate BPV and its related complications, which could thus possibly become a target for antihypertensive treatment. Evidence is missing however, regarding the effects of treatment-induced reductions in BPV on cardiovascular outcomes. Finally, it should also be considered that increasing values of BPV may represent a source of noise that creates difficulties in assessing the individual's "true" BP level leading to missclassification of BP levels. This may prevent from identifying patients with white coat hypertension, classified as hypertensives based on emotionally elevated BP

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values measured in a clinic environment, while their daily life BP levels are within normal limits. An increase BPV may also prevent from identifying patients with sustained hypertension who may be erroneously classified as normotensive on the basis of normal office BP levels at rest, while their ambulatory BP levels, responding to daily challenges, are elevated (i.e a condition of elevated cardiovascular risk known as masked hypertension). This paper, will review the available evidence on BPV, by addressing its current definition and classification, its mechanisms, the methodological aspects related to its assessment and its significance for cardiovascular prognosis. Highly debated issues, such as whether BPV should be routinely assessed in clinical practice in addition to average BP levels, and whether antihypertensive treatment strategies should be targeted at reducing not only average BP levels but also the degree of BPV in order to optimize CV protection, will also be addressed.

Definitions, classification and mechanisms

Although BP variations represent a continuous phenomenon, definitions and classification of BPV have been proposed on the basis of the time window over which this phenomenon is assessed: from beat to beat or second to second (**very-short-term** BPV), within 24 hours (from minute to minute, hour to hour and from day to night; **short term** BPV), over different days (**mid-term** BPV), or over weeks, months, seasons and years, including BP variability among clinic visits (**long-term** BPV)[1] (Figure 1).

Overall, BP variations, are the result of a complex interaction between intrinsic cardiovascular regulatory mechanisms (i.e. neuro-humoral influences, renal control of extracellular volume), extrinsic environmental influences (eg, seasonal and altitude-related changes), and subjects' reactivity to emotional stimuli (psychological stress) and behavioural factors (i.e. degree of and frequency of daily life challenges, job strain, levels of physical activity, sleep/wakefulness cycles, quality and duration of sleep, postural changes, patterns of sodium intake, etc.). These factors may have a different relative importance as a function of the type of BPV under assessment[1] (Figure 1).

Very short-term and short-term BPV. BP fluctuations occurring beat-by-beat and within the 24 hours may represent a physiological response of neural (Central sympathetic drive; Arterial and cardio-pulmonary reflexes)[2-4], humoral (Catecholamines;

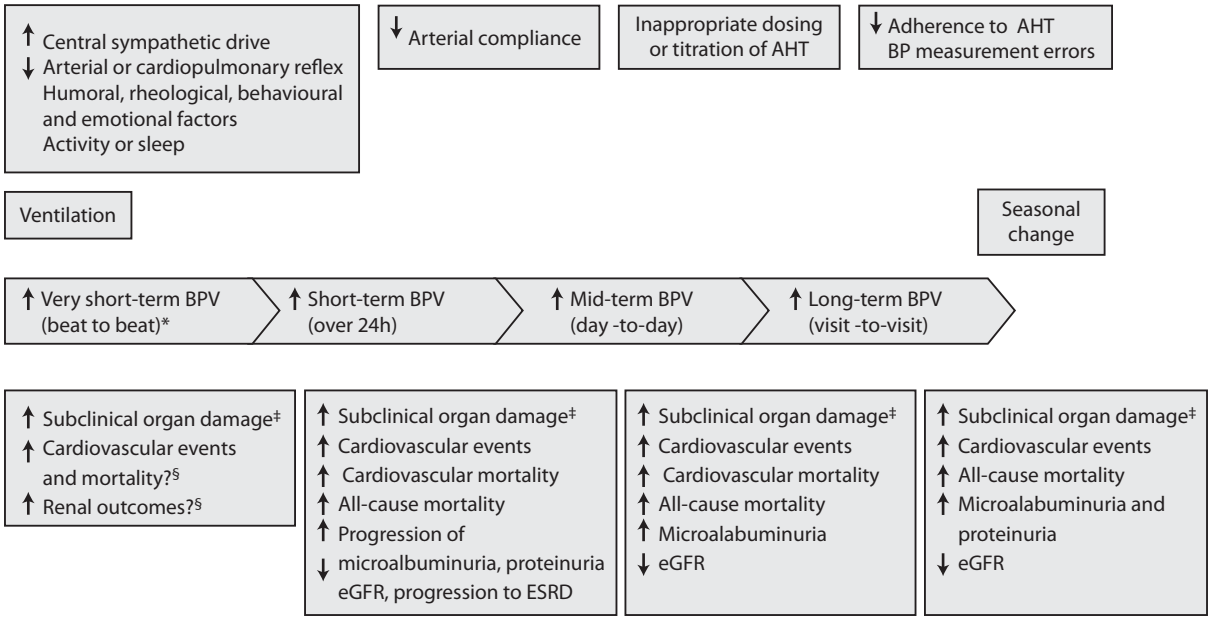

Figure 1. *Different types of blood pressure (BP) variability (BPV), their determinants, and prognostic relevance. Taken from (1) by permission. *Assessed in laboratory conditions; ‡cardiac, vascular, and renal subclinical organ damage; §BPV on a beat-to-beat basis has not been routinely measured in population studies. Abbreviations: AHT, antihypertensive treatment; BP, blood pressure; BPV, blood-pressure variability; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate.*

Insulin; insulin resistance; angiotensin II; Bradykinin; Endothelin-1; Nitric oxide; endothelial dysfunction), vascular (viscoelastic properties of large arteries), renal (salt sensitivity and sodium excretion)[5-8], and rheological mechanisms (Blood viscosity) to environmental stimulations and challenges from daily life (Figure 1). In physiological conditions, these fluctuations are aimed at maintaining the so-called BP "homeostasis" and to modulate organ perfusion in response to the changing metabolic demands when facing physical or emotional stress and BP reduction during sleep. However, when increases in short-term BPV are sustained, they may also reflect alterations in regulatory mechanisms in the context of pathological conditions associated with autonomic dysfunction, characterized by enhanced sympathetic drive and impaired baroreflex function (i.e. obstructive sleep apnea syndrome, carotid artery disease, arterial hypertension, chronic kidney disease, heart failure, diabetes mellitus, postural orthostatic tachycardia syndrome) or by more complex neurological disorders (i.e. Parkinson disease). In treated hypertensive patients, specific drugs and time of drug intake, may also have an effect on BPV.

Regarding slower BP variations occurring over the 24 hours (i.e. day-night BP changes), both cardiovascular regulatory mechanisms and behavioral factors such as subject's daytime levels of activity, quality and duration of sleep and overall changes in the sleep/wakefulness cycle have been shown to play an important role. In particular, night-time BP alterations (i.e. non-dipping or rising pattern of BP) have been reported to be associated with neural alterations (i.e. an increased sympathetic activity during night-time)[4,9], renal factors (i.e. salt sensitivity and reduced sodium excretion)[10,11], sleep related breathing disorders (i.e. OSAS), metabolic dysregulation (i.e. obesity and insulin resistance)[12], endothelial dysfunction[13], or specific drugs intake[14,15] (Figure 1).

Mid-term BPV. When considering mid-term BPV, behavioral factors such as job strain/home strain, levels of physical activity, changes of sleep/wakefulness cycles, quality and duration of sleep, postural changes, and patterns of sodium intake have been shown to play an important role in determining the degree of day-by-day BP fluctuations[16]. Also environmental factors such as changes in barometric pressure and altitude above sea level as well as seasonal changes in ambient temperature may also have a role. In treated hypertensive patients, treatment-related factors such as inconsistent BP control, poor patient's adherence to prescribed drugs, improper dosing/titration of antihypertensive drugs, dose omission or delay in drug intake may also influence levels of midterm BPV. Finally, incorrect home BP monitoring conditions may also lead to an increased variability of BP levels. In population studies, a number of factors have been found to be associated with increased values of day-by-day BPV in home measurements such as advanced age, female gender, increased arterial stiffness, elevated mean BP values, low body mass index, low heart rate, high heart rate variability, excessive alcohol intake, cigarette smoking, history of peripheral artery disease, cardiovascular disease, diabetes mellitus, diabetic nephropathy and sedentary lifestyle[17-22]. Studies focusing on treated hypertensive patients have found a higher day-by-day BPV among these individuals compared to untreated subjects[18,20], also reporting higher values of home BPV in case of treatment with beta-blockers, short duration of treatment[23], and increasing number of antihypertensive drugs[21].

Long-term BPV. Long-term BPV was originally described among treated hypertensive populations in the frame of large clinical trials in which BP values over several follow-up visits were available. In these conditions, visit to visit BPV might indeed reflect the stability of BP control (i.e. the number or percentage of visits with BP values controlled). Thus, factors known to influence achievement of BP control such as poor patient's adherence to prescribed drugs, improper dosing/titration of antihypertensive drugs, dose omission or delay in drug intake during the follow-up period, as well as improper BP measurement during assessment of BP control, may all induce important increases in visit to visit BPV[24] (Figure 1). However, this is unlikely to be the only factor involved, with biological and behavioral factors also playing a role. In the frame of large population studies, long term BPV has been found to be associated with advanced age, female gender, insomnia and long sleep duration, history of myocardial infarction or stroke, higher mean systolic BP

and pulse pressure[25,26]. Besides, observational studies have shown long-term BPV to be importantly influenced also by seasonal changes in weather conditions[27,28], and in particular by changes in outdoor temperature[28,29]. This has been supported by the finding that BP levels (either office, ambulatory or home BP) are consistently lower during the summer and higher during the winter[30]. However, not only the changes in outdoor temperature but also an improper downward titration of antihypertensive drugs on the basis of office BP reductions during the summer (with the consequent reduction of the extension of 24h BP coverage)[29] may lead to a paradoxical increase in night-time BP levels and to changes in BPV[29].

Assessment of BPV

The assessment of BPV over the different time windows described above (**very-short-term, short tem, mid-term and long-term** BPV) may be obtained through use of different indices[31]. Indices of BPV (see below) are estimated from the analysis of BP measurements obtained by means of different monitoring methods i.e., continuous beat-to-beat BP recordings, repeated conventional office BP (OBP) measures, 24-hour ambulatory BP monitoring (ABPM) and home BP monitoring (HBPM) through oscillometric BPM devices. Thus, adequate implementation of a proper BP monitoring method, according to current hypertension guidelines recommendations, is critical to guarantee an accurate estimation of BP values and hence of BPV indices, either for research purposes or in a clinical setting[32-36] (See figure 1 and table 1)[1].

Generally, BP variations can be divided into 1) Those without regular features (random or erratic changes) and 2) those characterized by well-defined patterns over time, typically related to biological rhythms or behavioral factors (eg, rhythmic fluctuations with periods of 3 seconds, 10 sec-

Table 1. Summary of principal indices of blood pressure variability. Adapted from Parati et al.[37] by permission

Overall BPV	
Type of Index	**Type of BPV assessed**
Frequency:	Short-term BPV
– Spectral Indices (HF, LF, VLF)*	Very short-term BPV (spectral analysis)
– Residual variability*	
Dispersion:	Short-term BPV
– Standard Deviation (SD)	Mid-term BPV
– Coefficient of variation (CV)	Long-term BPV
– Variability Independent of the Mean (VIM)	
– Weighted 24h SD (wSD)*	
Sequence:	Short-term BPV
– Average Real Variability (ARV)	Mid-term BPV
– Interval Weighted SD (wSD)	Long-term BPV
– Time rate of BP fluctuations*	
Instability:	
– Range (Maximum-minimum BP)	Short-term BPV
– Peak size (Maximum BP)	Mid-term BPV
– Trough size (Mean-minimum BP)	
Specific Patterns of BPV	
Nocturnal BP fall	Short-term BPV
Night/day ratio	
Morning Blood Pressure Surge (MBPS)	
Afternoon siesta dipping	
Postprandial Blood Pressure Fall	

*Assessment of Short term BPV only

onds or slower, nocturnal BP fall, siesta dip, morning BP surge, seasonal variations). The former are usually described using simple measures of dispersion (such as standard deviation [SD]) of average values over a given time window or estimates that also take into account the sequence of measurements over time (average real variability [ARV], the time rate of variations (See Table 1).

Among more sophisticated methods for BPV assessment, spectral analysis techniques are particularly relevant when describing faster BP changes in beat-by-beat recordings, but can also be used for discontinuous 24-hour BP monitoring. In fact, the so-called "residual" variability is obtained by removing the slower cyclic components of 24-hour BP variation using Fourier analysis.

The few studies directly comparing the prognostic value of different estimates of BPV did not provide clear indications as to which index should be preferred. At present, a reasonable choice could be to use the indices supported by the strongest outcome evidence, at least until better solutions are found. Based on a recent meta-analysis[38] the preferred indices might include SD for the clinic (visit-to-visit) and home BPV, and ARV, or SD (specifically, the "weighted" SD mentioned below) for 24-hour BPV. It is also important to consider that that these estimates of BPV are directly correlated with mean BP levels, and therefore it is important to adjust them for average BP values. For research purposes, this can be achieved with statistical methods, while in individual patients, a mathematical correction can be made by calculating the coefficient of variation (CV = SD*100/mean) or the variation independent of the mean (VIM). In regards to 24-hour BPV, one should consider that 24-hour SD is confounded by the contribution of nocturnal BP fall and generally should not be used for cardiovascular risk assessment[39]. Instead, indices unaffected by day-to-night changes should be preferred, such as ARV or weighted 24-hour SD (ie, the average of daytime and nighttime SD corrected for the respective duration of day and night). Daytime and nighttime SD, used separately, may also be applied, but it is unclear which should be preferred. Nocturnal BPV appeared superior to daytime BPV in 2 studies, but this finding should be further confirmed[40,41].

Clinical Relevance of BPV

The clinical relevance of BPV has been supported by the evidence accumulated over the last decades showing significant associations between different types of BPV with target-organ damage (TOD) and cardiovascular and mortality outcomes. A recent meta-analysis of observational cohorts and of clinical trials reported significant hazard ratios for cardiovascular events as well as for cardiovascular and all cause mortality in relation not only to an increased visit-to-visit clinic BPV, but also in relation to increased mid-term home BPV and short-term ambulatory BPV (See figure 2)[38].

Although evidence from some recent studies has indicated an incremental contribution of BPV to cardiovascular risk stratification, over and above the impact of average BP values, the relevance of such contribution has been shown to be influenced by the methodology employed for assessment of BPV and by the characteristics and baseline cardiovascular risk of the study populations. Future studies should establish whether there are specific categories (high versus low risk, treated or untreated, younger or older) of patients where BPV more clearly provides additional predictive information over and above the impact of average BP levels. Although some outcome studies addressing the prognostic value of BPV have suggested reference values and thresholds for BPV, the heterogeneity in the indices of BPV used and the different characteristics of study populations have not allowed to definitely conclude in this regard. In recent years, a series of studies or *post hoc* analyses of clinical trials in hypertension have also addressed the important issue of whether there are drugs able to specifically reduce BPV and whether such reduction is translated into an improved cardiovascular risk.

Short term BPV. A series of studies in the last decades, have provided evidence supporting the predictive value of short-term BPV either for TOD or for cardiovascular and non-cardiovascular events. Studies implementing intra-arterial beat-to-beat BP recordings in hypertensive subjects have shown a higher prevalence and severity of TOD in subjects with higher 24-hour BPV[42]. Of note, in the same studies, increasing values of BPV at baseline were significant predictors of development and pro-

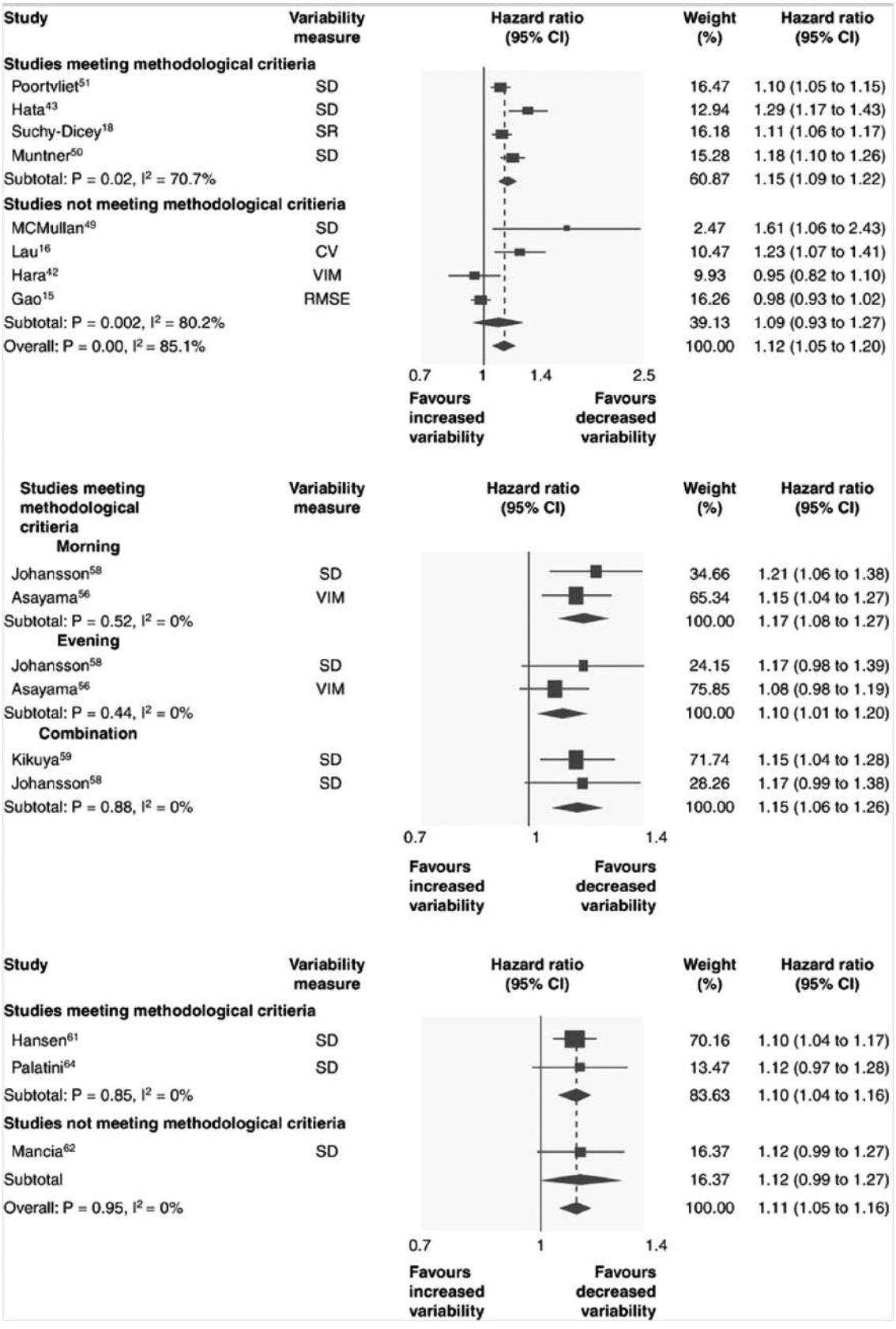

Figure 2. *Hazard ratios for all-cause mortality for increases in clinic systolic blood pressure variability (upper panel); in home systolic blood pressure variability (middle panel) or in ambulatory systolic BPV (lower panel). Modified from Stevens et al.*[38] *by permission.*

gression of TOD, in particular of left ventricular hypertrophy, during years of follow-up[43]. Measures of short-term BPV obtained from intermittent ABPM recordings, have also shown to be significantly associated with TOD as indicated by a recent meta-analysis in which SD of 24-hour systolic BP, SD of daytime systolic BP, wSD of 24-hour systolic BP and ARV of 24-hour systolic BP were all associated with higher values of left ventricular mass[44]. Other studies, with a few exceptions[45,46], have also shown significant associations between short-term BPV and carotid atherosclerosis, arterial stiffness and renal function[7,47,48,49].

Regarding CV outcomes, several studies and analyses of ABPM registries have confirmed the prognostic role of short-term BPV. An analysis of the International Database on Ambulatory blood pressure in relation to Cardiovascular Outcomes (IDACO) showed a significant predictive value for short-term BPV for most outcomes, ARV of 24-hour systolic/diastolic ambulatory BP being a better predictor than SD[50]. The analysis of the ABP-International database, composed of 7.112 untreated hypertensive subjects, showed SD of night-time systolic ambulatory BP to be an independent predictor of cardiovascular events, cardiovascular death, and all-cause mortality in contrast to daytime values[40]. In the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study, there was an independent relationship between the risk of death and SD of 24-hour, daytime, and night-time BP[51]. Moreover, the adjusted risk of cardiovascular death was inversely related to day-night diastolic BP difference and showed a significant positive relationship with residual diastolic BPV, as computed by spectral powers of 24h ABP recordings, after removing the contribution of day-night BP changes[51]. Accumulating evidence suggests that specific patterns of the diurnal BP variation may indeed have an important prognostic role[52-54]. A non-dipping or even a rising pattern of BP at night have been shown to be associated with increased cardiovascular risk, although recent evidence suggests that it is the night-time average BP level that mainly matters[53]. Likewise, an increased morning BP surge is associated with a high incidence of cardiovascular events and mortality, but this should be interpreted in the context of the significant relationship between the degree of morning BP surge (carrying high risk) and the degree of night-time BP fall (carrying low risk), which may affect calculation of the extent of BP rise in the early morning and the interpretation of its prognostic value[55,56].

Regarding the question on whether short-term BPV might improve cardiovascular risk stratification over and above average BP levels, the ABP-International study, showed a discrimination improvement for an increased value of the SD of night-time systolic BP from 8.5% to 14.5% for cardiovascular and mortality outcomes[40]. However, in the IDACO analysis, BPV (i.e. as assessed with ARV) added only 0.1% to prediction of the risk of a composite cardiovascular event[50], such a low predicting value being probably related to the heterogeneity in the ABPM methodology employed in the different Countries from which ABPM data were pooled.

Regarding possible threshold values for short-term BPV, an analysis of the ABP-International database showed that a SD of night-time systolic ambulatory BP ≥12.2 mm Hg was associated with greater risk of cardiovascular events (41%), cardiovascular death (55%), and all-cause mortality (59%)[40]. The corresponding values for the SD of diastolic BP ≥7.9 mm Hg were 48%, 132%, and 77%[40]. The IDACO analysis also presented the risk of total and cardiovascular mortality by fifths of distribution of ARV showing progressively increased risk among quantiles with higher event rate at systolic/diastolic ARV values of 16.2/12.4 mmHg respectively[50], in agreement with previous studies, including the Ohasama population study, suggesting a threshold for daytime SBPV of 15 mmHg.

Studies have also been conducted addressing whether short-term BPV may be reduced by specific classes of antihypertensive drugs. In the Natrilix SR Versus Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients (X-CELLENT) Study, the effect of different antihypertensive agents (candesartan, indapamide sustained release, and amlodipine) on ambulatory BPV was examined, amlodipine and indapamide being the only agents associated with a significantly decreased ambulatory BPV after a 3-month treatment[57]. In another study in hypertensive subjects, it was shown that those treated with CCBs or diuretics alone, or in addition to other drugs, had significantly lower SD of 24-hour systolic BP compared with those not treated with these classes[58].

Mid-term BPV. Although indices of mid-term BPV have been shown to be significantly associated with different types of TOD, there has not been a single index of BPV nor an index of TOD with consistent and independent relationships with mid-term BPV that might be found systematically in all the positive and negative studies available[45,46,59-65]. Regarding CV events, the most solid evidence supporting the prognostic value of mid-term BPV, is derived from the IDHOCO database[66] in which all indices of systolic/diastolic BPV (SD, CV, ARV, VIM) derived from day-to-day morning home BP measurements, showed to be independently associated with all-cause and cardiovascular mortality[66]. However, the IDHOCO analysis revealed only a minor-nonsignificant incremental improvement for home BPV in terms of net reclassification and integrated discrimination improvements[66]. A recent meta-analysis of observational cohorts and of clinical trials by Stevens et al. reported significant hazard ratios for cardiovascular events as well as for cardiovascular and all-cause mortality in relation to an increased mid-term BPV after accounting for confounders[38] (Figure 2) it appears that morning day-by-day home BPV has the strongest prognostic value as compared to morning-evening or evening home BPV[67,68]. Of note, this meta-analysis reported standardized hazard ratios to account for the heterogeneity in reporting of risk per different units across studies[38] (Figure 2). Recently, the independent predictive value of measures of home BPV was confirmed by a report of the Didima study, aimed at comparatively exploring the prognostic value of home BP average and variability versus office BP measurements over a 19-year follow-up. Although both office BP and HBP variability predicted total mortality and cardiovascular risk, indices of systolic home BP variability showed a superior prognostic value for incident total mortality and cardiovascular events than measures of variability obtained from office BP measures[69]. Regarding potential threshold values for mid-term BPV, the IDHOCO study provided some relevant evidence indicating that the risk of cardiovascular morbidity and mortality was steeply increased in the highest decile of systolic/diastolic home BPV (CV ≥11/12.8% respectively)[66]. However, hese data need to be validated by further studies.

Regarding the effects of antihypertensive treatment on BPV, a study by Matsui et al. evaluating the response of mid-term BPV to antihypertensive treatment, showed that, compared to olmesartan/hydrochlorothiazide combination, the combination of olmesartan/azelnidipine improved home BPV in addition to average home BP reduction, and that the reduction in home BPV was associated with the reduction in arterial stiffness in the group randomized to azelnidipine[63]. On the contrary, in a study conducted in 310 hypertensive subjects, the treatment-induced reduction in urine albumin excretion after a 6-month period of antihypertensive treatment with candesartan (+diuretics) was significantly associated with a reduction in average home BP but was not associated with a reduction in the SD of home SBP or in the maximum home SBP[70]. In the same line, a report of the HOMED-BP study did not find any significant impact of antihypertensive drug classes on BPV changes[71].

Long-term BPV. Rothwell et al. were the first to systematically emphasize the prognostic relevance of visit to visit BPV[26,72]. Thereafter, a series of reports have been published supporting the prognostic value of different indices of long-term BPV. Regarding TOD, the largest amount of evidence addressing the predictive value of long-term BPV comes mainly from studies in diabetic patients in whom the incidence or the progression of renal dysfunction in relation to long-term BPV has been evaluated[19,73-77]. In one of these studies, visit-to-visit BPV, assessed by CV of systolic BP, was associated with a significantly increased hazard of developing albuminuria in patients with type 2 diabetes[73]. Visit-to-visit BPV has been also shown to be associated with left ventricular dysfunction[75,76] as well as with carotid atherosclerosis and stiffness[19,76,77].

Regarding CV events, *post-hoc* analyses of large randomized trials and their meta-analyses have supported the prognostic value of long-term BPV[38,78,79]. In one of these reports visit-to-visit BPV independently predicted all-cause mortality, cardiovascular mortality and cardiovascular events including coronary heart disease and stroke events[38]. Of note, the available evidence regarding long-term BPV has been derived from studies conducted in general population, postmenopausal women, patients with hypertension, type 2 diabetes, chronic kidney disease, coronary heart disease and history of stroke[25,26,38,78-86].

The question on whether long-term BPV might add to risk stratification over and above average BP

levels and baseline cardiovascular risk, has been addressed by some recent studies. A report of the ADVANCE-ON study which included patients with type 2 diabetes, showed that, besides the independent prognostic value of the SD of systolic clinic BP, its addition in the model significantly improved the 8-year risk classification beyond the contribution by traditional risk factors including average systolic BP[81]. Also in another study including 2157 patients with cardiovascular disease, addition of CV of systolic BP resulted in a modest but significant improvement in the prediction model[87]. On the contrary, in the ELSA study, visit-to-visit BPV did not contribute to cardiovascular risk prediction[88]. It should be mentioned, however, that the latter study included middle-aged patients with treated, mild to moderate, systolic-diastolic hypertension at relatively low cardiovascular risk[88]. Very recently, an analysis of the VALUE (Valsartan Antihypertensive Long-term Use Evaluation) study[89] showed a significantly increased risk of cardiovascular events in the highest quintile of visit-to-visit BPV [hazard ratio (HR) 2.1, 95% confidence interval (95% CI) 1.7–2.4; $P < 0.0001$]. In the same study, a 5mmHg increase in SD of SBP was associated with a 10% increase in the risk of death (HR 1.10, 95% CI 1.04–1.17; $P = 0.002$). Associations were stronger among younger patients and patients with lower SBP, and similar between patients with different baseline risks, except for higher risk of death among patients with established cardiovascular disease[89].

Despite the large amount of evidence on the prognostic value of long-term BPV, there is no specific suggestion of thresholds for its clinical application, at present. The largest study addressing the clinical value of long-term BPV conducted among 2.865.157 US veterans, reported the risk of cardiovascular events among quantiles of SD of SBP with an incremental risk for SD quartiles 2 through 4 for all-cause mortality, coronary heart disease, stroke and end-stage renal disease[80]. The SD of SBP which corresponded to the highest quartile was 15.6 mmHg[80].

The question on whether long-term BPV might be modulated by antihypertensive treatment and whether this might be translated into improved CV prognosis has been addressed by post-hoc analyses of randomized clinical trials. Overall, these analyses have indicated a favorable effect of calcium-channel blockers (CCBs) versus other drugs, especially beta-blockers, in reducing visit-to-visit BPV and the risk of stroke[72,90,91].

Moreover, a recent study by Kollias et al showed a trend toward greater reductions in odds ratios for several endpoints –mainly stroke– across randomized clinical trials as a function of greater decreases in coefficient of variation of intra-individual systolic BP achieved by amlodipine versus other comparators[92].

Conclusions

Accumulating evidence in the las decades, has supported the concept that BPV may contribute to cardiovascular risk prediction over and above the impact of average BP levels. These findings suggest the possible usefulness of assessing BPV in clinical practice and of considering an elevated BPV as a possible target for treatment to further improve prognosis. However, currently available studies have not so far allowed to adequately answer a number of practical questions nor to clarify several important issues related to a clinical implementation of BPV assessment because of a number of limitations: significant heterogeneity in the methodology applied for estimating BPV indices, different design of most of the studies addressing the prognostic value of BPV (mainly post-hoc analyses of clinical trials), heterogeneity of the populations studied (general population, or patients with hypertension, diabetes, nephropathy), as well as the variable follow-up duration and the diversity of protocols used to estimate indices of BP. In addition, although many indices of BPV have been shown to be of prognostic value, no interventional longitudinal outcome study has yet been conducted specifically addressing what BPV levels should be regarded as normal, and which BPV level should be achieved as target for antihypertensive treatment. Similarly, no intervention study has yet explored the key question of whether a reduction in BPV by treatment translates into a better outcome. Regarding the type of BPV that should be considered in clinical practice (short-term, mid-term, or long-term), the poor correlation and agreement between indices of short-term (24 h) and long-term variability (visit-to-visit) indicate that they may reflect different pathophysiological and clinical phenomena and may thus not be interchangeable, but rather represent variables to be separately quantified.

Overall, whether BPV should be routinely as-

sessed in clinical practice in addition to average BP levels, and whether antihypertensive treatment strategies should be targeted at reducing not only average BP levels but also the degree of BPV in order to optimize CV protection, remain still debated issues and interesting topics for research, waiting to be clarified by further studies.

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