Consensus Document

Blood pressure variability: methodological aspects, clinical relevance and practical indications for management - a European Society of Hypertension position paper*

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Blood pressure is not a static parameter, but rather undergoes continuous fluctuations over time, as a result of the interaction between environmental and behavioural factors on one side and intrinsic cardiovascular regulatory mechanisms on the other side. Increased blood pressure variability (BPV) may indicate an impaired cardiovascular regulation and may represent a cardiovascular risk factor itself, having been associated with increased all-cause and cardiovascular mortality, stroke, coronary artery disease, heart failure, end-stage renal disease, and dementia incidence. Nonetheless, BPV was considered only a research issue in previous hypertension management guidelines, because the available evidence on its clinical relevance presents several gaps and is based on heterogeneous studies with limited standardization of methods for BPV assessment. The aim of this position paper, with contributions from members of the European Society of Hypertension Working Group on Blood Pressure Monitoring and Cardiovascular Variability and from a number of international experts, is to summarize the available

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evidence in the field of BPV assessment methodology and clinical applications and to provide practical indications on how to measure and interpret BPV in research and clinical settings based on currently available data. Pending issues and clinical and methodological recommendations supported by available evidence are also reported. The information provided by this paper should contribute to a better standardization of future studies on BPV, but should also provide clinicians with some indications on how BPV can be managed based on currently available data.

Keywords: blood pressure variability, blood pressure variability assessment methodology, blood pressure variability management, cardiovascular prevention, cardiovascular risk factors, hypertension management

Abbreviations: ΔH, average of hourly blood pressure changes induced by treatment; ABPM, ambulatory blood pressure monitoring; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; ARV, average real variability; BB, beta blocker; BP, blood pressure; BPV, blood pressure variability; CCB, calcium channel blocker; CAD, coronary artery disease; CV, coefficient of variation; HBPM, home blood pressure monitoring; MBPS, morning blood presure surge; MH, masked hypertension; OBP, office blood pressure; PP, pulse pressure; PPV, pulse pressure variability; RDN, renal denervation; SD, standard deviation; SI, smoothness index; TOD, target organ damage; TOVI, treatment-on-variability index; VIM, variation independent on the mean; VVV, visit-to-visit variability; WCH, white-coat hypertension; wCV, weighted coefficient of variation; wSD, weighted standard deviation

INTRODUCTION

High blood pressure (BP) is an acknowledged important risk factor for cardiovascular disease. However, limited attention has so far been given in clinical practice to the fact that BP values change continuously over time as a result of the interaction between environmental and behavioural factors on one side and intrinsic regulatory mechanisms on the other side [1,2]. Increased BP variability (BPV) may in fact indicate an impaired cardiovascular regulation and has been shown to represent a risk factor itself for all-cause and cardiovascular mortality, stroke, coronary artery disease, heart failure, end-stage renal disease, and dementia, similarly to what was reported for the enhanced variability in cholesterol and glucose plasma levels or body weight [3]. Nonetheless, BPV was considered only a research issue in previous hypertension management guidelines because the current evidence on its clinical relevance presents several gaps and is based on heterogeneous studies with limited standardization of methods for BPV assessment.

Aim of this position paper is therefore to assess the available evidence on determinants of BPV, on the methodology for its assessment and on its clinical relevance, and to provide practical indications on how to measure and interpret BPV both in research and clinical settings. After a review of evidence updated until May 2022, a writing group prepared a draft of this paper that was circulated among a group of scientists expert in this field for review and approval.

BLOOD PRESSURE VARIABILITY COMPONENTS: DEFINITIONS AND PHYSIOLOGICAL MECHANISMS

BPV is a general term referring to BP variations over different time scales. More specific definitions are based on the duration of the observation window: very-short-term BPV (within beat and beat-to-beat), short-term BPV (within 24-h, from minute-to−minute to day/night variability, including BP nocturnal dipping and morning rise), mid-term BPV (over days), and long-term BPV (over weeks, months, seasons and years, including BPV among clinic visits) [2] (Fig. 1). BPV components of longer duration (several years) associated to ageing processes are not considered in this paper.

BPV components are mediated by a combination of cardiovascular regulatory mechanisms and by their complex interactions with environmental/behavioural factors, on the background of individual features, like genetic factors, emotional reactivity and ongoing treatments. These factors may interact in a complex manner and may have a different relative importance as a function of the type of BPV considered [2,4]. For instance, seasonal changes in weather conditions and outdoor temperature [5,6], result in lower BP levels in summer than winter [5,7,8]. However the common down-titration of antihypertensive drugs in summer may variably affect BP control during day and night, reducing the extent of 24-h BP coverage with a paradoxical increase in night-time BP levels in the warm season in some cases [5].

Head-to-head cross-sectional comparisons of BPV components suggest that office, home and ambulatory BP monitoring approaches reflect different pathophysiological phenomena and therefore are complementary in assessing BPV and its clinical relevance [9,10,11].

In physiological conditions BP variations maintain the 'homeostasis' guaranteeing adequate organ perfusion in response to changing metabolic demands and external stimuli. However, a sustained increase in BPV may also reflect cardiovascular alterations and impaired regulatory mechanisms, often associated with pathological conditions [12] with unfavourable haemodynamic, metabolic, or renal effects, increasing the risk of cardiovascular complications (Box 1).

Although studies on BPV are generally focused on systolic and/or diastolic variability, pulse pressure (PP) is commonly measured in mechanically ventilated patients because PP respiratory fluctuations reflect changes in left ventricular preload and stroke volume [13]. PP variability (PPV) correlates with the increase in cardiac output caused by fluid loading [14,15] and respiratory fluctuations of cardiovascular parameters are accepted measures of cardiac volume responsiveness in mechanically ventilated patients.

METHODOLOGY OF BLOOD PRESSURE VARIABILITY ASSESSMENT

Different BPV components can be measured by means of different BP monitoring methods, including: continuous beat-to-beat BP recordings, repeated conventional office BP (OBP) measures, discontinuous 24-h ambulatory BP

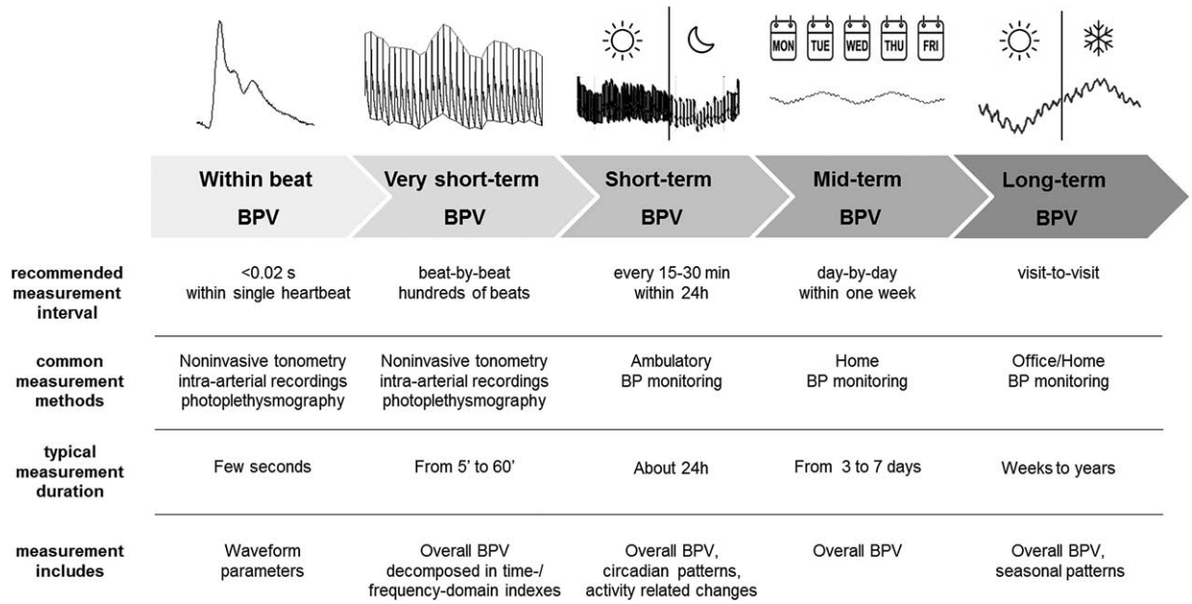

FIGURE 1 Classification of blood pressure variability (BPV) based on temporal frame of reference. Key features of measurement methodology are summarized for each BPV subtype. ''Overall'' variability indicates total variance, including all components of BPV over a given time window.

monitoring (ABPM), and home BP self-monitoring (HBPM) [16]. Each method should be implemented following the recommendations of international expert panels to ensure that valid BP measures are used for assessing the BPV components of interest [17–24]. Key general aspects directly related to different methods for BPV assessment are summarized below.

Continuous blood pressure monitoring

Beat-to-beat BP values can be obtained by intra-arterial recordings or non-invasive devices [25,26]. For intra-arterial recordings, Millar catheter tip transducers are the gold standard but their cost is elevated. Cheaper fluid-filled catheters require an adequate dynamic response and tubing free of air bubbles, which is not always the case in routine practice, frequently causing BP underdamping [27] and affecting the estimation of rapid BP changes. Ambulatory continuous BP recordings are feasible invasively or noninvasively (photoplethysmographic finger pressure devices) [28,29]. For non-invasive monitoring only validated systems should be used, although there is no universally accepted standard protocol for their validation in dynamic conditions. The newer cuffless and wearable devices based on arterial tonometry, pulse wave analysis or pulse transit time and other methods are not yet recommended due to immature or inadequately validated technologies [30].

Box 1. Factors determining BPV

INTRINSIC FACTORS

Neural mechanisms: central sympathetic drive, arterial and cardiopulmonary reflexes, chemoreflexes.
Humoral mechanisms: catecholamines, insulin, insulin resistance, renin, angiotensin II, bradykinin, cortisol, aldosterone and its metabolites, endothelin-1, nitric oxide, natriuretic peptides.
Vascular mechanisms: viscoelastic properties of large arteries, peripheral vasomotor modulation, endothelial dysfunction.
Cardiac function: changes in stroke volume and cardiac output caused by mechanical and hemodynamic factors, and arrhythmias.
Rheological mechanisms: changes in blood viscosity by anemia, hemodilution, erythrocytosis.
Metabolic activity: hypercapnia and hypoxia, acidosis and alkalosis.
Respiratory activity: spontaneous or device-induced changes in ventilatory mechanics.
Renal mechanisms: salt sensitivity, sodium excretion, renin secretion, tubuloglomerular feedback, hypo/hypervolemia
Genetic susceptibility: genes regulating the level of sympathetic cardiovascular modulation
Diseases affecting the autonomic function: neurodegenerative diseases (e.g.Parkinson's disease), sleep-related breathing disorders, carotid artery disease, arterial hypertension, chronic kidney disease, heart failure, diabetes mellitus, postural orthostatic tachycardia syndrome, orthostatic hypotension/ hypertension, post-COVID 19 syndrome.

EXTRINSIC FACTORS

Environmental factors: seasonal and altitude-related changes; barometric pressure changes (i.e. hypobaric hypoxia); changes in ambient temperature and humidity; sunshine, UV radiation, heat waves, wind chill, air pollution, noise.
Behavioural factors: job strain, physical activity, sleep/wakefulness cycles and jet lag, sleep quality and duration, postural changes, patterns of fluid and sodium intake, eating patterns, smoking/vaping, overeating, fasting, alcohol consumption, energy drinks, recreational drugs, screen time, e-gaming.
Emotional stimuli: psychological stress, depression, burnout.
Antihypertensive treatment factors: inconsistent BP control, poor patient's adherence; improper dosing/titration; dose omission or delays; differences in drugs class, pharmacokinetic and pharmacodynamic profiles.
Other treatments: drugs affecting BP.
Inappropriate BP monitoring: rare and irregular BP measurement; wrong brachial cuff size and placement; monitors sensitive to cardiac arrhythmias; not validated devices (finger/wrist monitors, cuffless devices).

Ambulatory arm-cuff based blood pressure monitoring

Validated oscillometric devices with appropriately sized upper-arm cuff should be preferred. According to current recommendations individuals under testing should follow their normal daily activities. However, activity patterns may influence BPV in a way difficult to determine in clinical studies and some degree of behaviour standardization should be considered in studies on BPV. At variance from its use for clinical purposes, a larger number of valid readings are needed when ABPM is applied in studies on BPV. The interval between measures should not exceed 15–20 min when assessing overall BPV [1] and at least 48 valid measurements over 24-h are suggested to achieve the full predictive value of BPV [31]. Based on this evidence, 15–20-min interval between measurements should be preferred for BPV assessments while 30-min interval is adequate only if the quality of the recording is good and focus is not on fast BP changes. Wearable watch-type oscillometric BP monitoring devices have been preliminarily validated [32] for their use either in short-, mid-, or long-term BPV but more studies are needed before recommending their use.

Home blood pressure self-monitoring

This low-cost, widely available approach may provide a consistent number of measurements in standardized conditions. Validated oscillometric devices are recommended, with appropriately sized arm cuffs [33,34], preferably equipped with data memory or transmission. There is heterogeneity among studies in terms of home BPV monitoring schedule. In the Finn-Home Study, day-to-day BPV predicted outcome using data from at least 3 days, with minor improvement by extending the monitoring to 7 days [35]. Thus, the general standards for HBPM methodology (including choice of device and cuff, measurement conditions and schedule) should reasonably apply also to home BPV assessment, with at least 3 (preferably 7) monitoring days, and duplicate measurements in the morning and evening [23,24].

Office blood pressure measurements

They are used to calculate visit-to-visit variability (VVV), which so far has usually been estimated *post hoc* in studies designed for other purposes, where OBP was measured following the conventional methodology for BP assessment in clinical studies. In case of *ad hoc* studies, current recommendations for OBP measurements should be followed, including use of validated oscillometric devices with appropriately sized arm cuffs and three seated measurements taken at each visit in standard conditions [9,33,34]. It is not clear how many visits/measurements should be used to optimally estimate VVV. In clinical trials with higher number of visits, VVV tended to increase [36] but also became more reproducible [37,38]. VVV was lower when averaging several BP measurements for each visit than considering individual measurements [39]. Also, a longer interval between visits favoured higher VVV [39]. Furthermore, VVV of unattended automated OBP, but not of attended auscultatory OBP, was related to short-term BPV by ABPM [40]. Overall, more evidence is needed to establish the minimum requirements for obtaining reliable VVV estimates and the role of unattended OBP.

The assessment of seasonal changes in BPV has distinct methodological features that can be achieved with either office, home or ambulatory measurements. Details can be found in a recent position paper [4].

BLOOD PRESSURE VARIABILITY INDICES AND PATTERNS

BPV indices can be classified by separately considering indices of overall variability and indices of specific BP patterns (Fig. 2). The most used indices are described below (see Table 1 for details).

Indices of overall blood pressure variability

Standard deviation

It represents the BP dispersion around the mean. It is less affected by isolated extreme values than the max-min range, if calculated from an adequate number of measurements. Disadvantages include its correlation with average BP levels and being affected by BP trends, the latter being particularly relevant in 24-h recordings due to day/night BP changes.

Coefficient of variation

Ratio between standard deviation (SD) and BP mean, it accounts for a dependence of SD on average BP levels. It may effectively remove the correlation of SD with average BP levels but it shares with SD the susceptibility to BP trends.

Weighted 24-h SD

It removes the contribution of night time BP fall to 24-h SD as a weighted average of daytime and night-time SD. A weighted coefficient of variation (wCV) may be calculated as well. Both weighted SD (wSD) and wCV may be affected by trends within day and night periods.

Residual variability

Twenty-four-hour BP power (total variance) evaluated by spectral analysis after removing the first and second harmonics to exclude circadian changes.

Average real variability

Overall variability of differences between successive readings over 24-h or over different days, thus largely unaffected by trends, average real variability (ARV) reflects within-subject variability [41] It is correlated with average BP levels and more affected than SD by poor data quality and missing values.

Variability independent of the mean

Refined transformation of SD that removes the correlation with average BP by nonlinear regression, its main limitation is that it requires previous derivation of equation coefficients for the given population to be applied in individuals and that different populations are difficult to be compared.

Time rate of blood pressure changes

It takes into account both magnitude and speed of BP changes. Its usefulness is limited in discontinuous

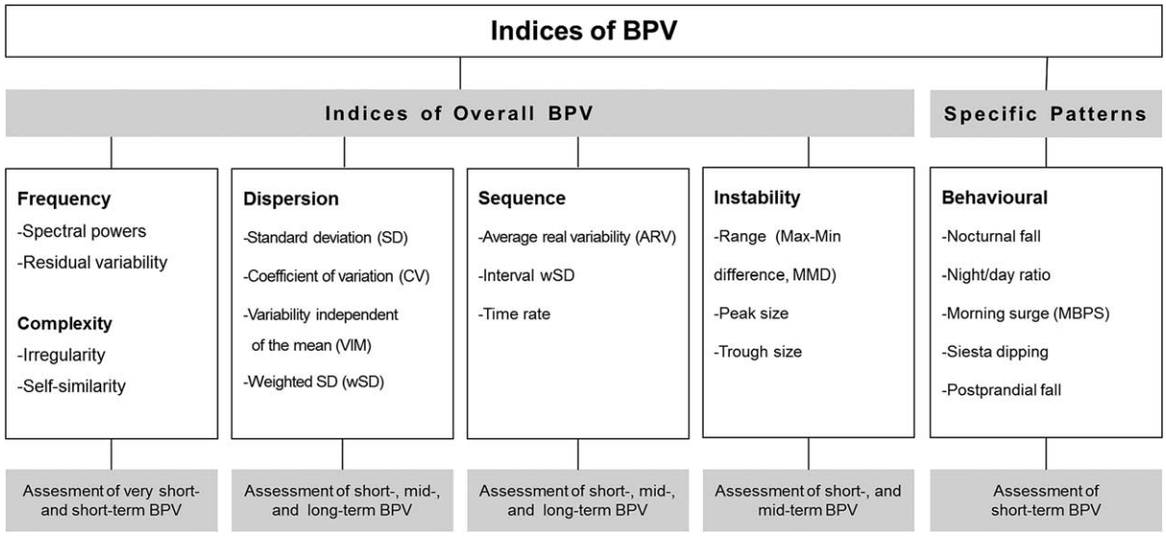

FIGURE 2 Main BPV indices. BPV, blood pressure variability.

recordings where the intervals between measurements are fixed (as in ABPM) and whenever multiple changes of BP trend direction take place between measurements (as in mid- and long-term BPV).

Frequency-domain indices

Recommended in the analysis of continuous beat-to-beat recordings, their usefulness is questionable in discontinuous ones for the need of evenly sampled series and the risk of undersampling/aliasing. Carefully standardized recordings are required, taking the respiratory frequency into consideration.

Complexity-domain indices

Recently introduced in BPV analysis of continuous beat-to-beat recordings, they quantify the BP irregularity through entropy measures or self-similarity through fractal exponents, possibly integrating traditional dispersion indices [42]

Range/maximum/minimum values

Being based on single values, these indices are heavily influenced by outliers and artefacts.

Blood pressure variability patterns

This class of indices quantify BPV patterns associated with the day/night cycle or other behavioural factors from 24-h ambulatory BP recordings. Systolic BP (SBP) is more used than diastolic BP (DBP) although both carry clinically relevant information [54].

Nocturnal blood pressure fall

It is the BP reduction during night expressed as percentage of daytime BP. Strictly related is the night/day BP ratio. Based on the nocturnal BP fall individuals are classified into four categories: normal dipping, with fall in night-time BP between 10% and 20%; non-dipping (or reduced dipping), with nocturnal fall between 0% and 10%; rising (or ''inverted'') dipping, with a nighttime BP increase, that is, a negative day/night BP difference; and extreme dipping, with nocturnal fall >20% [55,56]. Classifications using SBP or DBP may differ and there is no agreement on the BP measure to use. At present we suggest to use the less favourable dipping category, considering riser worse than nondipper, nondipper worse than dipper, and extreme dipper a favourable dipping pattern in most cases.

Morning blood pressure surge

It is commonly estimated from 24-h ABPM as difference between the lowest BP value at night and the highest BP value shortly after awakening. Since the correlation with nocturnal BP fall may represent a challenge in the interpretation of its relationship with outcomes, alternative definitions have been proposed.

Siesta blood pressure dipping and postprandial blood pressure fall

They respectively are the BP fall in populations where having an afternoon nap (siesta) is a common habit, and a measure of postprandial hypotension which may indicate an altered autonomic function or neuroendocrine effects of vasoactive peptides and excessive release of insulin. Since no standard definitions have been provided, their reproducibility is imperfect.

CLINICAL RELEVANCE OF BLOOD PRESSURE VARIABILITY

Blood pressure variability, hypertension diagnosis and follow-up

Given the dynamic behaviour of 24-h BP and the limitations of spot BP measures (see Figure S1, Supplemental Digital Content, http://links.lww.com/HJH/C121), office and out-of-office BP are only moderately correlated, with discrepancies in hypertension diagnosis. Simultaneous use of office and out-of-office BP monitoring led to identify new BP phenotypes such as sustained normotension (normal OBP and out-of-office BP), white-coat hypertension (WCH, elevated BP levels in-office but not out-of-office),

TABLE 1. Type of BPV indices and their definition

Type/time scale	Index [units]	Formula
Frequency domain/short-term and very short-term BPV	High frequency power [mmHg^2] [43]	$HF_P = \int_{HF_1}^{HF_2} P(f)df$ *where P(f) is the power spectrum of beat-by-beat BP values by Fast Fourier Transform or by AR modeling, HF_1=0.15 Hz and HF_2=0.40 Hz*
	Low frequency power [mmHg^2]	$LF_P = \int_{LF_1}^{HF_1} P(f)df$ *where LF_1=0.04 Hz*
	Very low frequency power [mmHg^2]	$VLF_P = \int_{VLF_1}^{LF_1} P(f)df$ *where VLF_1=0.003 Hz*
Frequency domain/short-term BPV	Residual variability [mmHg^2] [44]	$RV = \sum_{i=1}^{N}(BP_i - CC)^2$ *where BP_i are N ambulatory BP readings over 24-h, CC is the sum of the 1st and 2nd cycling components fitting the circadian BP pattern, with period of 24 and 12 h respectively, from Fourier analysis*
Complexity domain/short-term and very short-term BPV	Self-similarity scale exponents [45]	α_1 and α_2 *slopes of the regression line fitting in a log-log plot the variability of a detrended fluctuations function over small (<12 beats) and long (≥12 beats) blocks of BP segments respectively*
Complexity domain/short-term and very short-term BPV	Entropy [26]	SampEn *negative natural logarithm of the conditional probability that a BP sequence similar for m points remains similar at the next point*
Dispersion / short, mid, and long-term BPV	Standard deviation [mmHg]	$SD = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N}(BP_i - \overline{BP})^2}$ *with BP_i=N ambulatory home or office BP readings and $\overline{BP}$=their mean*
	Coefficient of variation [%]	$CV = 100 \times \frac{SD}{BP}$
Dispersion / short-term BPV	Weighted standard deviation [mmHg] [46]	$SD_W = \frac{SD_{wake} \times n_{wake} + SD_{sleep} \times n_{sleep}}{n_{wake} + n_{sleep}}$ *where SD_{wake} and SD_{sleep} are the standard deviations of the n_{wake} and n_{sleep} ambulatory BP readings taken over the wake and sleep periods*
Dispersion/long-term BPV	Variability independent of the mean [mmHg] [47]	$VIM = \frac{SD}{\overline{BP}^x} \times [\overline{BP}]^x$ *with SD and* $\overline{\text{BP}}$=standard deviation and mean of visit-to-visit BP measures in an individual, the power x calculated over a population fitting SD and $\overline{\text{BP}}$ with a log-log regression line and $[\overline{BP}]$=*the population average of individual* $\overline{BP}$
Sequence/ short, mid, and long-term BPV	Average real variability [mmHg] [48]	$ARV = \frac{1}{N-1}\sum_{i=1}^{N-1}\lvert BP_{i=1} - BP_i\rvert$ *where BP_i are N ambulatory, or home-, or office- BP readings*
Sequence/ short-term BPV	Time rate [mmHg/min] [49]	$TR = \frac{1}{N-1}\sum_{i=1}^{N-1}\frac{\lvert BP_{i+1} - BP_i\rvert}{t_{i+1} - t_i}$ *where BP_i are N ambulatory BP readings and t_i the time of their measurement*
Instability/short and mid-term BPV	Range [mmHg]	*Range = Max(BP_i)–Min(BP_i)* *where BP_i are N BP readings, Max and Min their highest and lowest value*
	Peak [mmHg]	$Peak = Max\langle BP_i\rangle - \overline{BP}$
	Through [mmHg]	$Through = \overline{BP} - Min\langle BP_i\rangle$
Patterns/short-term BPV	Nocturnal fall [%]	$NF = \frac{\overline{BP_{Day}} - \overline{BP_{Night}}}{\overline{BP_{Day}}}$ *with* $\overline{BP_{Day}}$ and $\overline{BP_{Night}}$ *means of ambulatory BP readings over day and night*
	Night/day ratio	$N/D = \frac{\overline{BP_{Night}}}{\overline{BP_{Day}}}$
	Morning surge [mmHg] [50,51]	$MorSur = BP_{Morning} - BP_{LowSleep}$ $BP_{Morning}$= *Average of BP readings during 2 h just after Wake-Up* $BP_{LowSleep}$= *average of 3 BP readings centered on the lowest nighttime reading*[a]
	Siesta dipping [%] [52]	$SieDip = \frac{\overline{BP_{DayW}} - \overline{BP_{DayS}}}{\overline{BP_{DayS}}}$ *where* $\overline{BP_{DayW}}$ and $\overline{BP_{DayS}}$ *are the mean values of 24-h ambulatory BP readings over the daytime wakeful period and the daytime sleep period*[a]
	Postprandial fall [mmHg] [53]	*difference between a single systolic BP reading just before lunch and a single systolic BP reading 30 min after the lunch*[a]

BPV, blood pressure variability.
[a]The literature proposes different formulas and a consensus has not yet been reached.

masked hypertension (MH, elevated out-of-office BP levels but not in-office) and sustained hypertension (elevated OBP and out-of-office BP). WCH and MH have an impact on cardiovascular prognosis, and care should be given to their identification, reproducibility, and management.

BPV appears more pronounced among individuals with MH and sustained hypertension than among normotensive individuals and those with WCH [57]. This suggests that elevated BPV may contribute to the increased cardiovascular risk in MH and sustained hypertension. BPV may interfere with hypertension diagnosis as individuals with elevated out-of-office BP values and increased BPV have larger probability to present with normal BP during spot office measurement. Therefore, labile OBP, even if within normal limits, should raise the suspicion of MH, especially in individuals with target organ damage (TOD) or at high cardiovascular risk, that needs to be confirmed with out-of-office BP measurements.

In prehypertensive patients, increasing values of short-term BPV predicted the subsequent development of hypertension. Indeed baseline 24-h ABPM and ARV and home SBP ARV were higher in individuals who developed hypertension [58].

Increased BPV from 24-h ABPM was found in some forms of secondary endocrine hypertension [59,60,61]. The clinical role of BPV indices in the clinical management of these rarer hypertensive phenotypes remains to be established.

Blood pressure variability, outcome prediction and risk stratification

An increased BPV may provide prognostic information independent from average BP levels for cardiovascular risk prediction but the clinical significance and prognostic implications of different BPV components may substantially differ. In spite of this, increased short-, mid-, or long-term BPV was found associated with development, progression, and severity of cardiac, brain, vascular and renal organ damage, and with increased risk of cardiac and cerebrovascular events and cardiovascular and all-cause mortality [2]. The incremental contribution of BPV to cardiovascular risk stratification is influenced by the methodology for BPV assessment and the study population, so that it remains to be established whether BPV provides the same additional predictive information in specific patients categories (high vs. low risk, treated vs. untreated, young hypertensive individuals, etc.) [62] As to the definition of BPV thresholds for risk stratification, some outcome studies proposed reference values and thresholds for BPV but the heterogeneity of BPV indices and populations considered have not allowed to definitely conclude in this regard [63]. (Table S1, Supplemental Digital Content, http://links.lww.com/HJH/C121 in the online supplement)

Preclinical target-organ damage

Very short-term and short-term blood pressure variability

Pioneering studies based on intra-arterial beat-to-beat BP recordings in hypertensive patients showed higher prevalence and severity of hypertension mediated organ damage in individuals with higher 24-h BPV [64] which predicted future development and progression of left ventricular hypertrophy [65]. The independent association of short-term BPV from ABPM recordings with preclinical organ damage is supported by a meta-analysis in which SD of 24-h SBP and daytime SBP, wSD and ARV of SBP were associated with greater left ventricular mass [66]. Other studies showed associations between short-term BPV and carotid atherosclerosis, arterial stiffness and renal dysfunction [67,68,69,70,71,72], with few exceptions [73,74]. Alterations of nocturnal BP fall, namely non-dipping or rising patterns, were found associated with preclinical organ damage, adverse outcomes [75,76], white-matter disease, silent cerebral infarcts, and brain atrophy [77]. These abnormal patterns were also associated with neuroimaging cerebral small vessel disease markers [78]. In hypertensive patients, increased short-term BPV assessed as CV was associated with cognitive impairment [79]. An association between nocturnal BP surge within seconds and left ventricular mass index has also been suggested [80].

Mid-term blood pressure variability

Increased day-to-day BPV by HBPM is associated with increased prevalence and severity of cardiac, vascular, and renal damage, but no index of preclinical organ damage showed an independent and consistent relationship with mid-term BPV [73,74,81–85].

Long-term blood pressure variability

Evidence on the predictive value of VVV for incidence or progression of renal dysfunction was found in diabetic patients [86–91]. In particular, VVV estimated by CV of SBP was associated with increased hazard of developing albuminuria in type 2 diabetes [86]. Conversely, in elderly individuals VVV was not associated with kidney disease progression [92]. VVV is also associated with left ventricular dysfunction [88,89], carotid atherosclerosis, arterial stiffness [89–91], cognitive deterioration, with cerebrovascular pathology and neurofibrillary tangles [93]. High BPV values (also in long-term) were associated with increased risk of dementia and cognitive impairment, with the BPV relative contribution exceeding that of mean BP in older adults [94–96].

Clinical outcomes

Very-short and short-term blood pressure variability

A number of studies associated short-term BPV with a higher risk of cardiovascular events. In the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study [44], the adjusted risk of cardiovascular death was inversely related to day/night DBP difference and had a positive relationship with residual DBP variability [44]. The International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO) study showed a predictive value of short-term BPV for total and cardiovascular mortality and all types of fatal combined with non-fatal endpoints, with ARV being a better predictor than SD [97]. In untreated hypertensive individuals, night-time SD of ambulatory BP was an independent predictor of cardiovascular events and death, and all-cause mortality [63]. In the Dublin Outcome Study daytime diastolic BPV was found to be associated with cardiovascular and all-cause mortality at different ages, while systolic BPV was stronger predictor of outcome than diastolic BPV and mean BP in the youngest age group [98], consistently with the Hypertension and Ambulatory Recording VEnetia STudy (HARVEST) Study results [99]. Meta-analyses [100] and systematic reviews [101] found increased short-term BPV from ABPM associated with a higher risk of cardiovascular events and death, and all-cause mortality [101]. Very-short term BPV was associated with the risk of recurrent stroke and cardiovascular events [102]. In haemodialysis patients [103], interdialytic short-term BPV from ABPM was associated with cardiovascular events and all-cause mortality, whereas both pre-dialysis BP and ambulatory average BP did not.

A nondipping or rising BP pattern was associated with an increased cardiovascular risk [54,104], although this association may be mainly driven by elevated night-time average BP levels rather than day/night BP changes [105]. A prospective study in mostly medicated hypertensive patients demonstrated that the riser pattern carries independent risk of heart failure even if 24-h BP is well controlled [106].

An increased morning BP surge was associated with higher 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 increased risk) and night-time BP fall (carrying reduced risk), which may affect the interpretation of the prognostic value of BP rise in the early morning [107,108,109,110].

In hypertensive patients excessive morning surge predicted stroke risk in dippers, not in nondippers [111]. Furthermore, either a very low or very high power of the morning surge (i.e. product of amplitude and rate of morning BP rise) was an independent risk factor for stroke particularly in women [112].

Very short-term PPV has been used in the decision-making process regarding volume expansion in patients with shock [113]. PPV may also help predicting hemodynamic changes in critical patients after mechanical ventilation or fluid restriction/depletion and in the operating room PPV monitoring may improve the outcome of patients undergoing high-risk surgery [113]. It has been suggested that an increase in short-term PPV predicts outcome in hypertension [114].

Mid-term blood pressure variability

The International Database of HOme blood pressure in relation to Cardiovascular Outcome (IDHOCO) database showed that BPV estimated from day-to-day morning home BP measurements is independently associated with all-cause and cardiovascular mortality [115], in line with the pioneering demonstration of the prognostic significance of day-to-day BPV in the Ohasama study [116]. Increasing mid-term BPV (day-to-day) was found associated with higher risk of cardiovascular events, cardiovascular and all-cause mortality even after accounting for different confounders [100,101]. The predictive value of home BPV was confirmed by the Didima study, aimed at exploring the prognostic value of home BP average and variability versus OBP measurements over a 19-year follow-up period, with indices of systolic HBPM variability showing a superior prognostic value than measures of OBP variability [117]. Morning day-to-day home BPV had higher prognostic value than either morning-evening or evening day-to-day home BPV [118,119]. Elevated day-to-day BPV was reported to be associated with the risk of stroke recurrence [120]. The Japan Morning Surge Home Blood Pressure (J-HOP) study demonstrated that the maximum and morning-evening difference in HBPM are independent predictors of stroke [121], particularly in patients with stiffened arteries [122].

Long-term blood pressure variability

Large randomized trials evaluated the prognostic relevance of VVV [100,123,47,124,125,126,127] and a number of meta-analyses have summarized the evidence that VVV independently predicts all-cause mortality, cardiovascular mortality and cardiovascular events including coronary artery disease (CAD) and stroke [100,101]. The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study showed increased risk of cardiovascular events in the highest quintile of VVV, with stronger associations among younger patients and patients with lower SBP, and higher risk of death among patients with established cardiovascular disease [128]. In CAD, long-term BPV was associated with mortality, especially in women [129] and in individuals with previous cardiovascular events [130]. However, in the *post hoc* analysis of the Systolic Blood Pressure Intervention Trial (SPRINT) study, discrepant conclusions were reached by different papers. While in one study [131] VVV was not found to be associated with the composite cardiovascular end point, according to different analyses [132] VVV independently predicted worse cardiovascular outcomes and hypoperfusion-related adverse events and systolic VVV combined with Framingham risk score predicted all-cause mortality [133]. It should be noted that the SPRINT study was largely based on automated unattended OBP measurements, which possibly influenced the BPV estimates [131]. In a post hoc analysis of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [134] VVV was associated with the primary cardiovascular disease outcome and major CAD, but not with stroke, these associations being more evident in low and high strata of baseline SBP/DBP. Interestingly, diastolic BPV was associated with CAD, especially in patients with history of prior CAD and low baseline BP, which could imply a reduced coronary perfusion during diastole in patients presenting increased diastolic BPV. Association of long-term BPV with renal and cardiovascular outcomes was reported in chronic kidney disease [135,136,137,138]. In participants aged $\geq$50 years, high long-term BPV (defined as the highest quartile of VIM) was associated with higher incidence of fracture [139].

Risk stratification

Some studies investigated whether short-term BPV improves cardiovascular risk stratification over and above average BP levels. In the ABP-International study, the relative integrated discrimination improvement for an increased value of the SD of night-time systolic BP ranged from 8.5 to 14.5% for cardiovascular and mortality outcomes in untreated hypertensives [63], while in the IDACO analysis, ARV added only 0.1% to prediction of the risk of a composite cardiovascular event in population cohorts including treated hypertensives [97]. However, there were significant differences in the methodology and populations characteristics between these studies, and large heterogeneity among studies characterizing the IDACO database.

Regarding mid-term BPV, the IDHOCO analysis revealed only a minor, nonsignificant incremental improvement in risk stratification for home BPV in terms of net reclassification and integrated discrimination improvements, but also this conclusion might be influenced by the heterogeneity of the studies considered [115].

Whether long-term BPV adds to risk stratification has been addressed in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE-ON) study which included patients with type 2 diabetes, showing that SD of clinic SBP improved the 8-year risk classification beyond traditional risk factors including average SBP [140]. In patients with cardiovascular disease, addition of CV of SBP resulted in a modest but significant improvement in the prediction model [141]. By contrast, VVV did not contribute to cardiovascular risk prediction in middle-aged patients with treated hypertension at low cardiovascular risk of the European Lacidipine Study on Atherosclerosis (ELSA) study [142].

Thresholds to define higher blood pressure variability

Due to lack in methodological standardization, at present, there are no universally accepted BPV cut-offs [18,143]. Few studies have adopted outcome-based approaches to

threshold definition [144,145], whilst the majority of the studies used thresholds either arbitrarily selected or based on BPV distribution in the available sample [118].

Short-term blood pressure variability

Studies focused on daytime SD distribution suggest that systolic BPV >15 mmHg is associated with progression of vascular organ damage and cardiovascular mortality [146,147]. Nocturnal systolic SD >12.2 mmHg and diastolic SD >7.9 mmHg were proposed to identify a higher risk of cardiovascular events and death (outcome-based threshold levels) [63]. Twenty-four-hour systolic wSD ≥12.8 mmHg was proposed as marker of increased risk for cardiovascular events [99].

Mid-term blood pressure variability

In the IDHOCO study, CV of HBPM >11% or >12.8% for SBP or DBP respectively was associated with increased cardiovascular morbidity and mortality (outcome-based threshold levels) [115].

Long-term blood pressure variability

Distribution-based threshold levels of VVV were identified in heterogeneous populations. In hypertensive patients systolic SD ≥17.9 mmHg was associated with an increased risk of cardiovascular events and stroke [128]. The cut-off of 15.6 mmHg identified patients at increased risk of all-cause mortality, CAD, stroke and end-stage renal disease [148] (details in Table S1, Supplemental Digital Content, http://links.lww.com/HJH/C121).

Therapeutic aspects

A major obstacle for the widespread clinical use of BPV is the uncertainty on how to manage patients with increased BPV. The lack of definite BPV thresholds and randomized controlled trials confirming the effect of BPV reduction by treatment on cardiovascular outcomes do not allow defining clear recommendations for clinicians. Evidence in animals [149] and humans [150] showed that antihypertensive treatment reduces BPV. However, this reduction is in part proportional to the reduction in average BP levels and data on reduction of BPV adjusted for the reduction in mean BP levels by treatment (as quantified by CV) are limited [151,152]. Centrally acting agents like clonidine or rilmenidine reduce short-term BPV but they are not first line choices for antihypertensive therapy [153,154].

However, evidence is available that antihypertensive drugs can modify the 24-h ABP profile patterns as a function of their pharmacokinetics/pharmacodynamics features (Fig. 3). When considering long-term BPV, titration of antihypertensive drugs on the basis of seasonal changes in office BP may differently affect daytime and night-time BP leading to changes in BPV [5].

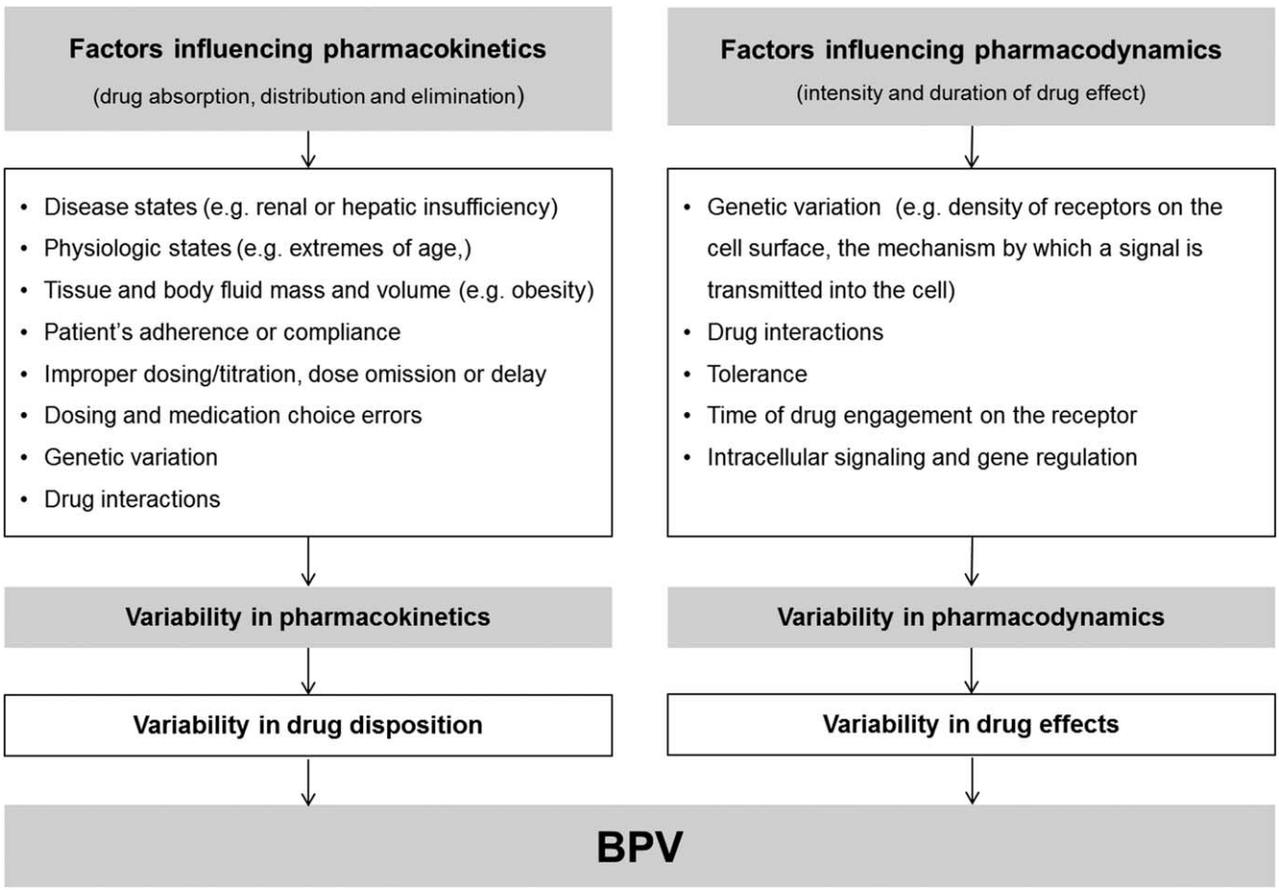

FIGURE 3 Impact of pharmacokinetic and pharmacodynamic features of antihypertensive drugs on BPV. BPV, blood pressure variability.

Dedicated indices assess the effects of antihypertensive treatment on both BP and BPV in clinical research and practice (details and references in Table S2, Supplemental Digital Content, http://links.lww.com/HJH/C121).

Smoothness index

Based on average BP values for each hour of the 24-h monitoring period before and during treatment, all hourly changes in BP induced by treatment are obtained. The average (ΔH) and SD (reflecting the dispersion of the antihypertensive effect over the 24 hourly values) of these hourly changes is computed. SD is divided by ΔH and SI is the inverse of this ratio indicating the degree of 'smoothness' of BP reduction by treatment. It can be applied to individual patients.

Trough: peak ratio

An index developed for assessment in clinical pharmacology studies of the time distribution of the efficacy of antihypertensive drugs based on the observed average BP lowering at the time of peak and through effect. It is obtained by dividing the BP reduction at the end of the between-dose interval (trough) by the BP reduction at the time of the maximal drug effect (peak) considering average values of groups of individuals.

Morning to evening home blood pressure ratio

It may provide similar information to the trough-peak ratio in assessing the duration of the BP lowering effect of antihypertensive drugs [155].

Treatment-on-variability index

This index was developed in order to explore the impact of a given treatment both on 24-h mean BP levels and on absolute estimates of 24-h BPV, accounting for the circadian BP fluctuations (which explain a major part of the variability in the SI), as well as for the dependence of 24-h SD on 24-h mean BP levels. TOVI is the ratio between the mean of 24-hourly BP reductions and 24-h wSD assessed under treatment.

Although these indices are commonly used in clinical research, their role in the clinical management of patients with elevated BPV remains to be evaluated.

Antihypertensive treatment and blood pressure variability

Some antihypertensive drugs and drug combinations could be more beneficial than others in patients with increased BPV [156] In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) study, calcium channel blockers (CCBs) reduced VVV, whereas β-blockers (BBs) had the opposite effect [124]. Similarly, in SPRINT amlodipine was associated with lower VVV [157] and the NatriliX SR versus CandEsartan and amLodipine in the reduction of systoLic blood prEssure in hyperteNsive patienTs (X-CELLENT) Study found that amlodipine and indapamide sustained release were associated with greater reduction in short-term BPV than candesartan or placebo [158]. In contrast, angiotensin-converting enzyme inhibitors (ACEIs), CCBs and angiotensin receptor blockers (ARBs) had similar effects on home BPV [159]. More recent studies evaluated the impact of antihypertensive drugs in monotherapy or in combination on 24-h BPV and on distribution of BP reduction over time [160]. In summary, different antihypertensive drug classes may have different effects on BPV, with some evidence that CCBs may induce the most effective long-term BPV lowering. This observation has been partly confirmed by *ad hoc* studies like the Reducing Blood Pressure Variability in Essential Hypertension With RAmipril vErsus Nifedipine GITS Trial (REVERENT) (ClinicalTrials.gov Identifier: NCT02499822) [161].

Double-blind, randomized ABPM studies showed a major reduction of BPV with the ARB olmesartan plus a CCB and/or a thiazide diuretic compared with placebo and monotherapies [151]. Greater BPV reduction is achieved with the use of combination therapy compared to monotherapies [160,162]. These results have to be interpreted taking into account the differences in the size of average BP reduction obtained by different treatments.

Apart from BBs, other cardiovascular interventions associated with BP reduction were unable to reduce BPV. For example, sodium-glucose co-transporter 2 inhibitors did not affect short-term BPV [163], despite producing a mild BP reduction [164], and guided dry-weight reduction that reduced BP in haemodialysis patients [165] did not reduced BPV [166]. Based on these results, it could be hypothesized that, in some conditions, not BP reduction *per se*, but rather the cardiovascular properties of specific drug classes are related to BPV modification.

Some studies focused on restoring the normal 24-h pattern of BP reporting beneficial effects of ARBs bedtime intake on nocturnal BP dipping and within-day BPV [167]. However, some methodological limitations warrant caution in the interpretation of these results. The sleep-time administration of CCBs as monotherapy or fixed-combination therapy has been associated with decreased BPV and MBPS [168].

BPV could be reduced also through corrections of lifestyle factors, like heavy alcohol use, or of clinical conditions, like obstructive sleep apnoea [169,170], or by implementing regular physical exercise or meditation [171,172,173]. Table S3, Supplemental Digital Content, http://links.lww.com/HJH/C121 provides a list of studies investigating the effects on BPV by different drugs.

Renal denervation and blood pressure variability

The relationship between increased sympathetic system activation and daytime BPV [174,175] suggests that the interventional treatment of hypertension with renal denervation (RDN), i.e. bilateral ablation of afferent renal sensory nerve fibres originating from the kidney, could beneficially impact on BPV. In this regard a recent meta-analysis showed that RDN in resistant hypertensive patients favourably affects short-term BPV, independently of the BP level reduction [176]. RDN also reduced the 24-h BP time rate [177]. Further investigation on whether RDN-induced reductions in BPV are translated in improved cardiovascular protection, is needed.

Treatment-induced blood pressure variability reduction and outcome

Few studies investigated the impact of antihypertensive therapy on mid-term BPV and outcome. The Hypertension

Objective treatment based on Measurement by Electrical Devices of Blood Pressure (HOMED-BP) Study randomized middle-aged hypertensive participants to first-line treatment with CCB, ARB, or ACE inhibitor: after a median of 7.3 years following randomization only self-measured evening BPV predicted the cardiovascular outcomes while on treatment day-to-day variability of self-measured home BP did not have any prognostic value [159].

Antihypertensive drugs with effects on long-term BPV may contribute to the reduction of cardiovascular risk associated with hypertension. A meta-analysis reviewing the effects of antihypertensive treatments on interindividual BPV, a surrogate of systolic VVV, and on risk of stroke, showed that CCBs and non-loop-diuretics decreased interindividual BPV, whereas ARBs, ACEIs and BBs increased it. Particularly, compared with placebo, CCBs were the most effective in reducing interindividual BPV. It was hypothesized that this could partly explain the drug-class related disparities in risk of stroke [178] but the conclusions of this paper are undermined by the choice of using interindividual BPV as a surrogate of intraindividual BPV, which is unacceptable from clinical and pathophysiological perspectives. In spite of this limitation, both Anglo-Scandinavian Cardiac Outcomes Trial: Blood Pressure-Lowering Arm (ASCOT-BPLA) and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) studies confirmed the superiority of CCBs on reducing BPV compared with ARB, BB or diuretic based regimens [124,179]. These different effects on BPV might have contributed to the between treatment differences in outcome. In fact, a trend toward greater reductions in odds ratios for several endpoints -mainly stroke- across randomized clinical trials with greater decreases in coefficient of intra-individual SBP variation achieved by amlodipine versus other comparators has been reported [152]. A possible mechanism explaining why CCBs are superior in reducing BPV, in addition to their action on arterial wall properties, is their duration of action: in fact, most of these studies used long acting CCBs, such as amlodipine or nifedipine-GITS.

FILLING THE GAPS: METHODOLOGICAL AND CLINICAL ISSUES WHICH SHOULD BE CONSIDERED IN CLINICAL STUDIES ON BLOOD PRESSURE VARIABILITY

BPV indices are mathematical constructs rather than directly measurable parameters prone to analytical errors, which may compromise the solidity of results when combined with inadequate BP measurement. Below we identify major issues which should be considered to avoid errors in the design and the interpretation of studies on BPV.

(1) *Relationship between BPV and average BP levels.* The risk of cardiovascular events is affected by both average BP and BPV, together with other known or unknown risk factors, among which there is a complicated interactive network of causal effects. Importantly, there is a well-known correlation between BPV and BP levels [1,180]. BP reduction by treatment is typically accompanied by BPV reduction, although the two reductions are correlated weakly [151]. This can be accounted for by calculating normalized estimates of BPV such as CV or VIM. As an alternative, statistical analyses of BPV should include the average BP as a covariate in multivariable models. So far none of these methods was shown to be clearly superior.

(2) *Systolic and diastolic BPV and their normalization by SBP and DBP mean levels.* Variability in both SBP and DBP should be considered. A potential pitfall lies in the choice of BP mean level for SBPV and DBPV normalization. Either SBPV and DBPV should be normalized for both SBP and DBP mean levels, respectively. This is a problem to consider especially when diastolic BPV emerges as a significant risk predictor. Since DBP mean level is poorly related to outcome, especially in older individuals, normalizing diastolic BPV only for DBP would disregard the prognostic impact of the more relevant SBP level, possibly overestimating the significance of diastolic BPV [97].

(3) *Daytime and night-time BPV.* Their physiological and clinical significance may be quite different depending on methodological aspects (daytime BPV heavily depends on activity; the number of measurements is lower during the night). Therefore, the results on their relationship with outcome may differ depending on population in study, statistical adjustments and other study methods [98,99]. Also the definition of wake and sleep time periods to be considered in the BPV calculation requires standardization ('daytime' vs. 'awake' BPV, inclusion of 'siesta-period' in 'daytime' or in 'night-time' etc.)

(4) *Interaction between BPV features by different estimates.* Typical examples include the relationship between 24-h SD and nocturnal BP fall [46] or the relationship between nocturnal BP fall and MBPS [109,110]. Appropriate choices of indices (e.g. wSD or ARV) and correct analytic approaches are needed to properly address these issues.

(5) *Dependence on the number of measurements.* When estimating short-term BPV over 24-h, between-measurement intervals no longer than 15 min should be allowed [181]. The number of BP measurements available is particularly relevant in the case of VVV studies with a limited number of office visits. It is not clear what the minimum number should be but, if there is a subgroup with few (3–4) visits used to compute VVV, a sensitivity analysis should be undertaken by excluding these individuals.

(6) *BP trends.* The effect of BP trends on overall BPV estimates is exemplified by day/night BP changes effect on 24-h SD (see above) but also by long-term BP changes, for instance induced by changes in antihypertensive treatment or by seasonal BP changes. Estimates such as ARV may help reducing this effect.

(7) *Effects of raw data handling.* Good quality recordings for a proper estimation of BPV is essential.

A recent study showed that ABPMs not matching the quality criteria set by the European Society of Hypertension [19] display higher BPV [182]. Removal of potentially erroneous BP readings at any stage (internal device algorithm, analysis software, manual review) may artificially affect variability estimates according to the procedure adopted, making the resulting estimates poorly comparable between studies. At the moment there is no standardized approach to this problem. Therefore, it is questionable whether generally applicable normalcy cut-off thresholds of BPV can be proposed when using different BP devices or BPV analysis software.

(8) *Lack of interchangeability of BPV indices*. Short-, mid- and long-term BPV may all be associated with outcomes to a similar extent but they are poorly correlated [9,183]. Therefore, they may not be considered as being interchangeable [184].

(9) *Reproducibility*. The presence of nondipper circadian pattern has limited reproducibility [185,186]. Regarding other BPV indices there are few studies on their reproducibility [38,187,188].

(10) *Added prognostic value*. Whether the added prognostic value of BPV makes it a clinically useful risk marker is controversial [63,97]. Indices such as net reclassification index or integrated discrimination improvement are currently used to explore the added prognostic relevance of BPV, although their actual clinical value is debated.

CONCLUSIONS SUPPORTED BY CURRENT EVIDENCE

The available evidence suggests that different types of BP fluctuations may unveil different patterns of cardiovascular modulation by control mechanisms. Thus BPV, rather than representing a "physiological noise" to be removed for accurately assessing BP levels, represents a valuable source of cardiovascular information. Consistent evidence from observational studies and their meta-analyses does also support the conclusion that an increased BPV should be regarded as a potential risk factor for cardiovascular complications.

This suggests to pay more attention on BPV also in current clinical management of hypertensive patients [2]. Although waiting for additional studies that should be aimed at addressing a number of methodological and clinical issues which still need to be clarified (see Box 2), some practical indications for current management of BPV in clinical practice and in research can nevertheless be provided. They are summarized in Box 3

Box 2 BPV: open issues for future research (based on experts' opinion)

Methodological	Clinical
BPV ASSESSMENT • What is the best BP measurement method for each BPV type ? • What is the optimal frequency of BP measurement for short-term, mid-term or long-term BPV assessment ? • Which BPV indices should be used for short-term, mid-term and long-term BPV? • BP Recording conditions to estimate BPV • Should individuals' behaviour be standardized while investigating short-term BPV over 24-h? • How to properly assess long-term, visit-to-visit BPV - what is the minimum number of visits and BP measures? - how to account for changes in treatment ? - how relevant is the relationship between time of BP measurement and drug intake? **ISSUES RELATED TO BPV DATA ANALYSIS** • How to best quantify differences in BPV while accounting for concomitant differences in average BP levels? • How to explore the independent contribution of BPV to outcome accounting for possible confounders (age, sex, BP average level) ? • How to assess the interaction between visit-to-visit long-term BPV and seasonal BP changes? • How to assess the interaction between morning BP surge and nocturnal BP dipping? • How do the different BPVs (short-term, mid-term, long-term) relate to each other?	**BPV MECHANISMS** • What is the relationship of BPV with physiological variables (e.g. Baroreflex sensitivity, muscle sympathetic nerve activity, SpO2, arterial stiffness)? • What are the main determinants of mid-term and long-term BPV? • What is the impact of age, sex, genetic and racial factors on BPV indices and predictive power ? • How do atrial fibrillation and cardiac arrhythmias influence BPV? • How does cardiac pacing impact BPV? • How is BPV in acute ischaemic stroke patients with high, normal and low BP? • What is the link between BPV and white coat and masked hypertension? • What is the interaction between visit-to-visit long-term BPV and seasonal BP changes? • Is BP response to laboratory stressors or to office BP measurement (white coat effect) a predictor of daily life BPV? **BPV PROGNOSTIC IMPACT** • Are short-term, mid-term and long-term BPV predictors of cardiovascular disease risk? • Are short-term, mid-term and long-term BPV predictors of non-cardiovascular outcomes (dementia, cancer, death)? • Which BPV type is the best predictor of outcome? • Are systolic and diastolic BPV comparable in risk prediction at different ages and gender? • What are the threshold levels to identify elevated BPV? • What is the clinical relevance of BPV changes in critical patients with hypotension/shock? **THERAPEUTIC ISSUES** • How to best assess the effects of treatment on BPV? Which indices should be used? • Is drug-induced BPV reduction accompanied by reduction in events rate? • How different drug classes affect BPV? • Is there evidence to consider BPV as a target for treatment? If so, which indices should be the targeted?

Box 3 Indications for BPV management in research and clinical settings, based on currently available data and on experts' opinion

- **Standardized methodology for BPV assessment** must be used in terms of BP measurement and indices to estimate BPV
- Currently there are no universally accepted **cut-off values to define elevated BPV**, but some indications are available
- Different types of BP fluctuations may unveil **different patterns of cardiovascular modulation** by control mechanisms
- High BPV was shown to reclassify patients to higher risk category, suggesting a **role for elevated BPV in cardiovascular risk stratification**
- **Elevated short-term BPV and nocturnal BP non-dipping are associated with higher cardiovascular risk**, although no evidence-based specific therapeutic interventions can be recommended yet to reduce BPV and restore nocturnal BP fall
- **Long-acting antihypertensive drugs and drug combinations including long-lasting compounds** may be preferred to avoid iatrogenic increase in BPV and to better smooth down the 24-h BP profile
- **Long-acting CCBs and diuretics** may be preferred to reduce elevated BPV, in absence of clinical indications to choose other specific drug classes
- **ABPM reports in clinical practice and in research** should include:
  -BPV estimates (e.g. 24-h weighted SD of SBP and DBP, or daytime SD and night-time SD of SBP and DBP)
  -An estimate of nocturnal SBP and DBP dipping (expressed as % reduction of daytime values or night/day SBP or DBP ratio)
  -Average 24-h, daytime and night-time HR values and their variability

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Conflicts of interest

There are no conflicts of interest.

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