https://doi.org/10.31925/farmacia.2021.2.2 **REVIEW**

ANTIHYPERTENSIVE DRUGS AND BLOOD PRESSURE VARIABILITY

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Abstract

Blood pressure variability (BPV), including both short-term and long-term blood pressure fluctuations, has recently gained interest and has emerged as an independent cardiovascular risk predictor. Controlling blood pressure levels in hypertension is extremely important in order to reduce cardiovascular risk. However, lowering BPV could also become a therapeutic target, although the ideal method for assessing BPV is still under debate. The effects of antihypertensive drugs on BPV are variable, since BPV depends on many factors. Nevertheless, fixed combinations of drugs, such as calcium channel blocker plus angiotensin-converting enzyme inhibitor or angiotensin II receptor blockers, have been proven to reduce both the calculated average blood pressure and BPV in hypertensive patients, while optimizing adherence. Customized medication according to the circadian rhythm of blood pressure, evaluated by ambulatory blood pressure monitoring, is another method to control BPV. The aim of this paper is to review emerging data about BPV and the therapeutic impact of various antihypertensive drugs.

Rezumat

Variabilitatea tensiunii arteriale (VTA), care include fluctuaţii pe termen scurt şi lung ale tensiunii arteriale, a devenit recent un parametru de interes ca predictor independent al riscului cardiovascular. Controlul valorilor tensiunii arteriale în hipertensiune este extrem de important pentru scăderea riscului cardiovascular. Totodată, controlul VTA ar putea deveni o ţintă terapeutică în sine, deşi cea mai bună metodă de a evalua VTA este încă în dezbatere. Efectele medicaţiei antihipertensive asupra VTA variază, deoarece VTA este influenţată de numeroşi factori. Totuşi, combinaţiile fixe antihipertensive, precum blocanţii canalelor de calciu plus inhibitori ai enzimei de conversie a angiotensinei sau blocanţi ai receptorilor angiotensinei II, s-au dovedit a reduce atât media calculată a tensiunii arteriale, cât şi VTA la pacienţii hipertensivi, totodată optimizând aderenţa la tratament. Adaptarea medicaţiei la ritmul circadian al tensiunii arteriale, evaluat prin monitorizare ambulatorie automată a tensiunii, este o metodă utilă pentru controlul VTA. Scopul acestui articol este de a prezenta cele mai noi date despre VTA şi impactul terapeutic al diferitelor clase de medicamente antihipertensive.

Keywords: blood pressure variability, arterial hypertension, antihypertensive drugs, cardiovascular risk

Definition, classification and assessment of blood pressure variability

BP shows spontaneous fluctuations during the same day, from one day to the next, and from one month to the next. The majority of trials so far have analysed blood pressure (BP) values in normal subjects or hypertensive patients with respect to the circadian rhythm, especially in hypertensive patients. The prognostic significance of BP variability (BPV) has only recently started to become of interest, while attempting to establish a cut-off value [5, 14]

Historically, BPV has been perceived as a problem in accurately measuring BP, possibly overcome by a closer monitoring. BPV is the result of complex interactions between extrinsic factors (behavioural, environmental) and factors linked to regulatory neuro-hormonal mechanisms acting within the CV system [43]. Increased BPV may be explained by impaired autonomic function, and is common in circumstances with increased arterial stiffness, such as aging [16]. BP fluctuations may occur over very short periods of time, as well as over longer periods, therefore these types must be differentiated, the mechanisms generating them are distinct, and their prognostic relevance and therapeutic approach may be different (e.g. BP in old age versus pregnancy) [43, 49]. Four types of BPV have been defined: very short-term, short-term (over 24 h), mid-term (from day to day) and long-term (visit to visit) BPV. Very short-term BPV refers to beat-to-beat variability, requires continuous laboratory BP recording with spectral analysis, and has mostly been used experimentally [43]. The mechanisms and the evaluation methods of these types of BPV are summarized in Table I.

Table I

The main types of blood pressure variability [adapted from 43]

Type of BPV	Method of measurement	Interval	Indices	Possible mechanism
Short-term BPV (24h)	ABPM	Every 15-30 minutes over 24h	SD, CoV, day-to-night changes	↑central sympathetic drive, ↓cardiopulmonary/arterial reflex, emotional/hormonal factors, activity/sleep, possibly inadequate therapy dosing
Mid-term BPV (day-to-day)	ABPM, HBPM	Daily, over days, weeks or months	SD, CoV	↓ arterial compliance; inadequate therapy dosing; BP measurement errors
Long-term BPV (visit-to-visit)	ABPM, OBPM, HBPM	During office visits, spaced by weeks, months, years	SD, CoV	Inadequate therapy dosing/↓ adherence; BP measurement errors, seasonal changes

BPV = blood pressure variability, ABPM = ambulatory blood pressure monitoring, OBPM=office blood pressure measurement, HBPM = home blood pressure monitoring, SD = standard deviation, CoV = coefficient of variation (the standard deviation normalized for mean blood pressure)

Normally, night-time BP decreases by 10% - 20% of daytime BP, this is considered the normal dipper pattern, and the circadian rhythm of BP is partially governed partly by the intrinsic neurohumoral and CV systems, and partially by the sleep-wake behavioural pattern. The normal values of nocturnal arterial pressure are: mean systolic BP < 120 mmHg and/or diastolic BP < 70 mmHg during the night (during sleep) [55]. Hypertensive patients with end organ damage tend to exhibit diminished night-time BP fall. The night-time systolic BP dipping (%) is calculated by ambulatory blood pressure monitoring (ABPM) as:

(1 - average night-time systolic BP/average daytime systolic BP) × 100,

and the following four dipping patterns are defined: extreme dipper (> 20%), dipper (≤ 20%, > 10%), non-dipper (≤ 10%, > 0%), riser (reverse dipper, ≤ 0%) [23].

The indices used to define BPV estimations are under debate, and so is which BP to use (systolic or diastolic). The various methods to assess BPV favour certain indices. Continuous beat-to-beat BP recordings are best used by calculating the standard deviation (SD); repeated office BP measurement generates the SD, CoV (coefficient of variation = SD normalized for mean BP, CoV = SD/BP × 100), and 24 h ABPM data will be used to calculate SD, CoV. For home BP monitoring and visit-to-visit BPV, SD and CoV have been proven as the best estimators [43]. Day-to-night variability, translated by dipping status and night-to-day BPV (morning surge) are also important parameters. A generally accepted cut-off has yet to be set, but a CoV under 10% will discriminate between low and high BPV [31, 43]. The 10% cut-off may not be more discriminative than other cut-off points around this value, but, although arbitrary, it is easy to use and has proven quite practical so far [6].

Blood pressure variability and cardiovascular risk

ABPM has evolved into an important method for establishing the diagnosis of arterial hypertension (HTN) and its various types, but also monitoring the response to therapy, according to the new European recommendations [55]. Recent trials have documented ABPM as a better prediction tool for target organ damage than office BP, offering supplementary indices *versus* the office and home BP monitoring, such as 24-hour variability, stiffness index, morning BP surge [13, 23, 55]. Average BP over a period of time, in everyday life circumstances, offers better information about CV outcomes, when compared to isolated office BP measurements. Increased BPV may prove itself an additional independent CV predictor, and BPV has recently been documented as a potential risk factor [43, 47]. There is growing evidence that both short-term and long-term BPVs are independently linked to target organ damage and cardiovascular (CV) events in hypertensive and diabetic patients [20]. Regardless of type, BPV has prognostic significance in terms of subclinical organ damage, CV events and mortality, all-cause mortality, progression of microalbuminuria, proteinuria, progression to end-stage renal disease [15, 43].

Some data are not in favour of the fact that BPV is an independent predictor of CV risk. The study population from ONTARGET "Ongoing Treatment Alone and in Combination With Ramipril Global End Point Trials" and TRANSCEND "The Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease" trials included 28790 patients for which systolic visit-to-visit BPV was compared to the mean systolic BP. On-treatment mean systolic BP proved to be a better predictor of CV risk than visit-to-visit systolic CoV, while the combination of both parameters improved prediction [28].

Some intriguing research has recently been published regarding visit-to-visit BPV. An Australian study on 496 elderly hypertensive patients attempted to determine whether antihypertensive treatment changes BPV over time, and the impact on mortality. Average BPV declined on antihypertensive therapy over the 2 years of follow-up, while higher BPV, no matter the evolution, was associated with increased long-term mortality [9]. A study on 1122 untreated patients demonstrated that an increased long-term BPV is

predictive of arterial stiffness progression, after a follow-up of 10 years [48]. The prognostic value of systolic visit-to-visit BPV has been analysed by 2 major clinical trials: the observational extension of the ADVANCE trial (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) and the SPRINT trial (Systolic Blood Pressure Intervention Trial) [8, 40]. The *post-hoc* analysis of the SPRINT trial, with 7879 participants randomized to intensive (< 120 mmHg) or standard (< 140 mmHg) systolic BP targets, showed only marginal association of visit-to-visit office BPV with all-cause mortality, with no BPV difference between treatment groups. Lower office BPV was associated with thiazide diuretics or dihydropyridine CCB, while ACEI/ARB use was a determinant of higher BPV [8]. The ADVANCE-ON observational study suggested that the SD of systolic BP has more than independent prognostic value, as it improves the 8-year risk classification beyond traditional CV risk factors. This study included subjects with diabetes mellitus (DM) and HTN, making these findings highly relevant, as the value of long term BPV was additional to the already high-risk profile of the patients [40]. In a *post-hoc* analysis of the data from the ALLHAT trial (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) the association between visit-to-visit BPV and CV outcomes, was analysed in 25814 participants, supporting visit-to-visit BPV as an important prognostic indicator. What remained unclear was the clinical applicability of BPV, not readily available at clinic visits, or whether metrics such as SD should be integrated into the electronic medical record [35].

The impact of antihypertensive medication on blood pressure variability

Guidelines have repeatedly emphasized the extremely valuable reduction of BP levels, somewhat obscuring the beneficial effects of lowering BPV, which could become a therapeutic target. Fixed combinations of drugs such as CCB/ACEI or CCB/ARB, those reduce both average BP and BPV, an important step in the treatment of HTN, provide the possibility of lowering both BP and BPV, while increasing adherence [39].
Results in literature concerning the prognostic impact of BPV with or without treatment are conflicting. A recent ABPM study on 80 patients with inefficiently treated HTN concluded that low BPV could also be associated with high BP and greater BP load, while high BPV is not necessarily dangerous in the setting of low BP values, but both parameters are mandatory for a comprehensive evaluation of the antihypertensive therapy [27]. A large cohort of 9855 patients with type 2 DM from Swedish primary healthcare, without pre-existing CV disease, and without any change of antihypertensives during the observation period, was followed for 4 years. Systolic BPV was independently associated with all-cause mortality, but it may be of minimal clinical use beyond routine predictors, such as mean BP [4].
Recent studies shed light on drugs, such as CCB, that have been shown to reduce various types of BPV, while BB appears to increase BPV [36]. Although most BP-lowering drugs reduce short-term and long-term BPV, CCB as monotherapy or in fixed combinations are apparently the most effective in influencing BPV and this has been suggested by data from comparative trials [11, 17, 19]. Since no large clinical trials focused on BPV *per se*, the data about the impact of drugs on BPV and CV risk in hypertensive patients are from meta-analyses and *post-hoc* analyses. Two such meta-analyses have been published in 2010 and in 2014 [52, 53]. The Webb *et al*. analysis from 2010 used inter-individual BPV to evaluate the effect of anti-hypertensives, concluding that CCB (most data for amlodipine) and non-loop diuretics reduce inter-individual systolic BPV, while ACEI, angiotensin II receptor blockers - ARB and BB increase it [53]. The meta-analysis performed by Wang *et al*. in 2014 studied intra-individual BPV and proved amlodipine to be more effective in lowering visit-to-visit BPV [52]. Mechanisms explaining the CCB-induced reduction in BPV have not been clarified yet, but some ideas have emerged. Results from the X-CELLENT study regarding indapamide SR *versus* candesartan and amlodipine in the reduction of systolic blood pressure have shown that both indapamide and amlodipine reduce systolic BPV, but the reduction caused by amlodipine was also accompanied by a drop in the mean BP levels and heart rate variability, suggesting an improvement in the regulation of the autonomic nervous system [56]. Other mechanisms, such as vasodilation, and improvement in arterial stiffness, may also explain the impact of CCB on BPV [12, 24].
In the ALLHAT study, three parallel treatment groups (chlorthalidone, amlodipine and lisinopril) were analysed for long-term BPV, and the amlodipine and lisinopril treatment arms displayed a drop and increase in systolic BPV, respectively, compared with chlorthalidone, after 6 months post randomization [33]. In the COLM trial, the olmesartan/CCB combination was more efficient in reducing long-term systolic BPV compared with olmesartan/diuretic [44]. Therapy impact on visit-to-visit BPV was also assessed by three combinations (benidipine/diuretic, benidipine/ARB, benidipine/BB), and benidipine/diuretic was the most effective [50]. The telmisartan-amlodipine combination's effect on short-term BPV induced lower daytime BPV compared with various monotherapies [42]. A trial from 2018 showed that the triple therapy (olmesartan/dihydro-pyridine/thiazide diuretic) and the dual therapy (olmesartan/dihydropyridine CCB or olmesartan/ thiazide diuretic) combinations induced a greater decrease in short-term BPV compared with mono-

therapies [41]. The HOMED-BP study assessed day-to-day BPV of self-measured home BP on CCB, ARBs or ACEI, and the results were similar in the 3 treatment arms [1].

ABPM in hypertensive diabetics has shown that restoring the nocturnal BP decrease in non-dippers may be difficult with standard antihypertensive treatment [3]. Recent trials suggest that some antidiabetic drugs, the selective inhibitors of sodium glucose cotransporter 2 in the kidney (SGLT2), may help reduce both office and ambulatory BP, even on top of usual antihypertensives [38, 57]. In the SACRA study (NCT03050229, Japan), a randomized, placebo-controlled trial involving SGLT2 treatment in 132 patients with type 2 DM and uncontrolled nocturnal HTN, reductions in BP after adding empagliflozin to existing antihypertensive therapy (including ARB) were clinically significant, and should lower the CV risk [22]. Regarding the therapeutic BP target, a study investigated whether intensive antihypertensive therapy (BP ≤ 140/90 mmHg), compared to standard treatment (BP ≤ 150/90 mmHg), could bring a supplementary improvement in the CV outcomes of 724 Chinese hypertensive patients older than 70 years, randomly assigned to intensive or standard antihypertensives, and followed-up for 4 years. The systolic and diastolic visit-to-visit BPV were lower in the intensive group, where total and CV mortality decreased by 50.3% (*vs*. standard - 41.7%), and long-term systolic BPV positively correlated with CV events [54].

Adherence to therapy is essential, as non-adherence to antihypertensive treatment has been linked to an increased risk for CV events, and missed doses could also explain BP variations between visits. The idea has become increasingly popular, as adherence varies among hypertensive patients, showing pronounced time-related variations within the same patient, and influences patient outcome regardless of sex and age [29]. The lack of adherence is considered if the patient reports having taken < 80% of their assigned drugs at least on one visit, but quantifying adherence by patient self-reporting may be rather inaccurate, although it correlates with other measures of adherence. In an investigation on 2075 patients followed for 4 years, low, medium and high adherence to antihypertensives by medication possession ratio (pharmacy refill) *versus* the eight-item Morisky Medication Adherence Scale (MMAS-8) was assessed. MMAS-8 was not correlated to CV risk, while medication possession ratio was [26]. Adherence is a dynamic phenomenon; therefore, the objective assessment and variation over time are equally important [29].

The population-based Third National Health and Nutrition Examination Survey (NHANES III, 1988 - 1994) included 956 young patients (mean age 41.3 ± 15.5 years) followed for mortality through 2006. Systolic, but not diastolic, BPV was associated with increased all-cause mortality. Low medication adherence was identified as a possible explanation for the connection between antihypertensive medication use and higher visit-to-visit BPV, but an association between visit-to-visit BPV and a higher risk for all-cause mortality was also documented in those not taking any anti-hypertensives [34]. Data from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) suggests that antihypertensive medications with longer half-lives and less BP rebound after missed doses may reduce the impact of non-adherence on visit-to-visit BPV. In this analysis, SD independent of mean of BP was higher in the 2912 non-adherent participants than in the 16 878 adherent patients, both in systolic and in diastolic BP, even after multivariable adjustment. However, adjusting for non-adherence did not account for the correlation between visit-to-visit BPV and fatal or non-fatal coronary events, stroke, heart failure, or mortality, therefore BPV remains an independent predictor of CV outcomes [25]. Two previous studies had also found that SD is higher in non-adherent patients: a Medicare program including 1391 patients on antihypertensive medication, but restricted to BP levels from patient charts (no standard protocol), and the African American Study of Kidney Disease and Hypertension (AASK) Trial on 988 patients with chronic kidney disease [21, 32].

Chronotherapy means a tailored timing of doses to match the body's natural circadian rhythms and behavioural patterns, aiming to maximize the beneficial effects and/or minimize any adverse effects throughout the day and night, in light of the well-documented 24 h pattern of BP [7]. Given the morning surge with a peak in CV events, morning doses of antihypertensive drugs have been classically prescribed. An absence of nocturnal decrease in BP is also associated with a high CV risk, therefore a number of studies have focused on moving one or more doses to bed-time. More recent studies of chronotherapy have studied comorbidities such as obstructive sleep apnoea, chronic kidney disease, DM and night-time administration of antihypertensive therapy generally improves overall 24 h BP profiles, but there are inconsistencies between trials. It is hard to instantaneously evaluate the circadian phase, so probably no drugs are precisely administered [30]. More prospective randomized controlled trials are necessary, including experimental studies to clarify the mechanisms by which chronotherapy works [7]. Medication bioavailability and duration of action can be influenced by circadian and behavioural physiological patterns, but also by receptor availability and function, which in turn may be affected by the circadian system and by behaviour (exercise) [37]. Improvement in sleep quality by medication is only effective in restoring the dipping status in some non-dippers, suggesting that the dipping status is affected by more than differences in sleep [46].

A study of 24h ABPM dipping index on 144 patients taking ACEI, ARB, BB, diuretics, and CCB proved that taking drugs at bedtime vs morning increased dipping [10]. Ayala *et al*. analysed CV events, CV death, total death in 776 participants on diuretics, ARB, ACEI, CCB, BB, showing higher survival rates, lower CV risk with CCB, BB, or ARB at bedtime compared to morning, and non-significance for other drugs [2]. In a meta-analysis including 3582 chronic kidney disease hypertensive patients, evening dosing decreased the percentage of non-dipper patterns, nocturnal systolic and diastolic BP [51]. Another meta-analysis of 35075 patients with evening dosing compared with 312057 patients with usual dosing of ACEI and CCB, using office BP, concluded that evening dosing reduced the risk of coronary artery disease and stroke *versus* usual dosing [45]. Studies focusing on morning *versus* evening administration of BP-lowering drugs have started as early as 1987, and table II briefly displays the results obtained by the most recent and largest trials in which the evening administration of BP-lowering drugs reduced the mean nocturnal BP and the non-dipping pattern and was associated with reduced CV risk and reduced risk of new onset of DM.

Table II

The most recent and largest trials on time-dependent dosing of antihypertensive drugs [7, 11, 17 -19]

Trial; year; design	Participants (number; mean age in years)	Antihypertensive medication	Investigations, endpoints	Results
Hermida *et al*; 2010; MAPEC Study.	2156 (2 groups: 1084 and 1072); 55 ± 13.	Bedtime chronotherapy, all recommended classes (one group on awakening, the other at bedtime).	Total CV morbidity and mortality.	Bedtime administration of ≥ 1 antihypertensive was associated with a reduced mean nocturnal BP and lower CV risk.
Hermida *et al*; 2013; Cross-sectional.	2899 in 3 groups (1084, 1436, 379); 64 ± 12.	All drugs on waking (group 1), full daily dose of ≥ 1 drug at bedtime (group 2), or split twice daily (group 3).	48 h ABPM, and markers of CV risk: microalbuminuria, CKD, albumin/creatinine, eGFR, glucose, cholesterol.	Bedtime dose (group 2) compared to groups 1 or 3 reduced non-dipping and reverse dipping BP and reduced CV risk.
Crespo *et al*; 2013; Cross-sectional.	2659; 65 ± 13; patients with hypertension and CKD.	All drugs on waking (group 1), ≥ 1 drugs at bedtime (group 2).	48 h ABPM, office BP; laboratory tests (total and LDL-cholesterol, glucose, creatinine, uric acid).	Bedtime dose reduced non-dipping, improved laboratory data. If all drugs at bedtime, benefit was greater.
Hermida *et al*; 2016; Prospective, open-label, single-centre RCT.	2012 (group 1, n = 1029); 52 ± 13.	Replacing one antihypertensive with a new one on waking (group 1) vs. at bedtime (group 2). All drugs.	48 h ABPM annually (or quarterly if treatment was adjusted).	Bedtime drugs increased dipping. ACEI, BB, or ARB at bedtime decreased the risk of new-onset diabetes.

ABPM = ambulatory blood pressure monitoring, ACEI = angiotensin-converting enzyme inhibitors, ARB = angiotensin II receptor blockers, BB = beta-blockers, BP=blood pressure, CV = cardiovascular, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, LDL = low-density lipoprotein, RCT = randomized-controlled trial

Conclusions

Despite the improved therapeutic options available in the past decades, BP levels remain largely un-controlled. Current guidelines for the management of HTN underline the importance of lowering BP, which may be evaluated not only by office BP measurement, but also by home, and 24-hour BP values, which have become increasingly used. However, especially in uncontrolled HTN, an increased BPV could carry an additional risk of advancing organ damage and CV events. BPV is a complex phenomenon, depending on both neurohormonal, and extrinsic, behavioural factors, including adherence to treatment and applying chronotherapy. A better BP control is associated with a lower BPV. Differences between antihypertensive classes effect on BPV could be optimized by using the circadian BP profile and combination therapy, leading to a better control of both BP and BPV, and reducing global CV risk.

Conflict of interest

The authors declare no conflict of interest.

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