Population-based studies and large meta-analyses have shown that there is a continuous relationship between office blood pressure (BP) and cardiovascular risk starting from BP 115 mm Hg systolic and 75 mm Hg diastolic. It has also been consistently reported that the relationship between BP measured outside the medical environment (ie, via home and ambulatory monitoring) and the risk of hypertension-mediated organ damage (HMOD) and cardiovascular disease is closer than that measured in the medical setting. Although cardiac and extracardiac complications of hypertension increase markedly with exposure to increasing BP load, the prognostic value of BP values routinely assessed in clinical practice still remains unsatisfactory regardless of the methods used. It should be pointed out, however, that other unhealthy factors besides high BP such as ethnicity, age, gender, type 2 diabetes mellitus, obesity, sleep apnea syndrome, and renal disease contribute to the development of HMOD and cardiovascular events. Moreover, it deserves to be emphasized that BP is dynamic physiologic variable characterized by large short- and long-term variations (ie, beat-to-beat, over 24 hours, day-to-day, and visit-to-visit). From a physiological point of view, these BP changes substantially reflect an adaptive response to a variety of physical and mental stimuli aimed at preserving the cardiovascular homeostasis. On the other hand, an exaggerated increase in BP variability (BPV) may reflect impaired cardiovascular regulatory mechanisms and/or underlying pathological conditions resulting in cardiovascular system damage. 

The implications of BPV depend on the measurement method and sampling frequency. Most studies have evaluated the clinical value of BPV based on the standard deviation (SD) of 24-hour average ambulatory BP monitoring recordings, but this measure is an rough marker of BP variations as it does not deal with many characteristics of BPV. The average real variability (AVR) index proposed by Mena et al that focuses on short-time variations thus correcting some limitations of SD, which only reflects the dispersion of BP measurements around the mean, has been increasingly used for clinical research since 2005.

In the last decades, the clinical and prognostic significance of increasing BPV has been investigated by several cross-sectional and longitudinal studies conducted in hypertensive cohorts and population-based samples, in which high BPV has been related to a higher risk of HMOD, cardiovascular non-fatal events, and...
cardiovascular and all-cause death, independent of average BP values.\textsuperscript{6–9} However, it is worth noting that some studies have failed to show a robust relationship between BPV indices and cardiovascular outcomes. This, for instance, was the case of a post hoc analysis of the Systolic Blood Pressure Intervention Trial (SPRINT) in which office BPV (defined as the coefficient of variation of the systolic BP, using measurements taken during the 3-, 6-, 9-, and 12-month study visits) exhibited no significant association with the composite endpoint of fatal and non-fatal cardiovascular events nor with stroke or heart failure.\textsuperscript{20}

Some meta-analyses have also suggested that individuals with elevated variability in BP are at higher cardiovascular risk compared with their counterparts with the same mean BP level. A meta-analysis by Stevens et al of 41 papers, representing 19 observational cohort studies and 17 clinical trial cohorts, showed that long-term BPV measured at clinic visits is associated with risk of all-cause mortality (hazard ratio 1.15, 95% confidence interval 1.09–1.22) cardiovascular disease mortality (1.18, 1.09-1.28) and cardiovascular disease events (1.18, 1.07-1.30), over and above the effect of mean BP.\textsuperscript{11} Increased mid-term variability (home monitoring) and short-term variability (ambulatory monitoring) in systolic BP were also associated with all-cause mortality (1.15, 1.06-1.26 and 1.10, 1.04-1.16, respectively).

A systematic review addressed to assess the predictive power of various BPV indexes on HMOD and cardiovascular outcomes revealed that ARV was a better predictor of 24-hour BPV than other measures of dispersion, including SD, coefficient variation, and weighted 24-hour SD in most studies.\textsuperscript{12} Of note, 17 out of 19 reported significant associations between high ARR and the presence and progression of HMOD, as well as the incidence of hard endpoints, such as cardiovascular events (hazard ratio, 1.18; 95% confidence interval, 1.09-1.27).

The mechanism linking BPV to cardiovascular events is unclear.\textsuperscript{13} Short-term BPV is mainly affected by behavioral, emotional, and postural influences on cardiovascular hemodynamics and heart rate. The presence of HMOD and, particularly, increased arterial stiffness may contribute to both short-term BPV and long-term BPV. Moreover, poor control of BP and lack of adherence to antihypertensive treatment and healthy lifestyle recommendations may increase long-term BPV.

With regard to HMOD and specifically its relationship with the BPV, we are faced with a complex and not easy to solve topic. Cross-sectional studies are unable to offer a useful contribution to clarifying this controversial issue as they are unable to define a cause-effect relationship.

It is worth of mention that the first prospective study which focused on the association between HMOD and BPV dates back to the early 90s.\textsuperscript{14} That seminal paper by Mancia’s group, in whom BP was monitored intra-arterially by the Oxford technique at baseline and after a period of seven years in 73 essential hypertensive patients, provided a convincing evidence of an independent association of BPV (defined as among half-hour standard deviation of 24-hour mean BP) and target organ damage score (a composite of electrocardiographic and/or echocardiographic left ventricular hypertrophy, retinopathy, and renal dysfunction) assessed at the end of follow-up visit.

Since then, although growing evidence has accumulated on the adverse impact of high BPV on HMOD, other studies have not confirmed an independent relationship between the two phenotypes. These conflicting results might have been affected by different methods of 24-hour ABPM heterogeneity in the metrics and protocols used in different studies.

A recent single-center prospective study, including 300 hypertensive patients (mean age 63 years), investigated the value of five different parameters of BPV derived from ABPM (SD, weighted SD, coefficient of variation, successive variation, and ARV) in predicting renal damage (50% reduction in baseline estimated glomerular filtration rate) during a mean follow-up of 4.2 years.\textsuperscript{15} All BPV parameters were associated with incident hypertensive nephropathy in the univariate analysis only. These indexes, however, became insignificant in the multivariate analysis after adjusting for baseline characteristics, 24-h mean BP, and office BP. Therefore, the risk of renal dysfunction appeared to be independently associated with 24-h mean BP, but not with ambulatory BPV.

In this research area, the report by Triantafyllidi et al\textsuperscript{16} focuses on the association between changes in ambulatory BPV and HMOD regression in a selected group of 180 previously untreated essential hypertensive patients (mean age 51 ± 12 years, 64% men) without cardiac, cerebrovascular, and renal disease followed up after the initiation of antihypertensive treatment (based on renin-angiotensin-aldosterone antagonists, calcium antagonists, and hydrochlorothiazide) for a period of three years. Baseline and follow-up data collection included medical history, office BP, ABPM, standard blood examinations, echocardiography, carotid ultrasonography, carotid-femoral pulse wave velocity (PWV), and micro-albuminuria (MA). Systolic and diastolic BPV was determined as the SD of 24-hour average BP. In the whole sample, a large and significant reduction in both clinic and ambulatory systolic BP (−14, −15 mm Hg) and diastolic BP (−8, −12 mm Hg) was found at the end of the period of the study respect to the baseline values. This sustained reduction in office and out-of-office BP was accompanied by a parallel reduction in BPV (−2 mm Hg for both systolic and diastolic, P < 0.01). Regarding the markers of HMOD, significant, although modest, reductions in left ventricular mass index (−3 g/m\textsuperscript{2}), carotid intima-media thickness (−0.1 mm), and MA (−2 mg/24-h) were observed. Unfortunately, this was not the case for carotid-femoral PWV, coronary flow reserve, and left ventricular diastolic function whose modifications over time remained insignificant even in the group of patients (n = 119) who reached the therapeutic target at the end of the follow-up period (ie, 24-hour BP < 130/80 mm Hg). Furthermore, it should be remarked that the magnitude of BPV reduction was similar in the controlled and uncontrolled groups. In multiple regression analysis, changes in systolic and diastolic BPV were associated with LVM reduction, independently of confounders, including 24-h BP, both in the whole sample and in the controlled group but not in the group with persistent 24-hour BP values > 130/80 mm Hg.
The study by Triantafyllidi et al.\(^{16}\) supports the view that regression of subclinical cardiac damage requires an effective 24-hour BP control along with a reduction in BPV and suggests that the assessment of BPV and its modifications during the course of therapy may be an useful approach in predicting the beneficial effects of treatment on cardiac structure. However, some aspects and limitations of this study require caution in drawing firm conclusions. First, BPV was not independently related to other important markers of macro- and microvascular organ damage. Second, the reduction in LVMI after 3 years in patients with optimal blood pressure control was quite modest (approximately 6.5%). Third, the study was conducted in an uncomplicated hypertensive setting with a low or very low prevalence of HMOD (see mean values of LVMI, MA, PWV) not ideal for a trial aimed to target the reversal of organ damage.\(^{17}\)

So, further investigation is needed to determine whether reduction in BPV is actually associated with a regression in cardiac and extracardiac HMOD, to identify which classes of antihypertensive drugs are most effective in reducing BPV, and to elucidate whether those treatments provide additional clinical benefit, independent of the conventional BP targets.\(^{18}\)

**DISCLOSURE**

The authors report no conflicts of interest.

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**REFERENCES**

1. Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360:1903-1913.

2. Sega R, Facchetti R, Bombelli M, et al. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study. Circulation. 2005;111:1777-1783.

3. Parati G, Pomidossi G, Albini F, et al. Relationship of 24-hour blood pressure mean and variability to the severity of target organ damage in hypertension. J Hypertens. 1987;5:93-98.

4. Li J, Owusu IK, Geng Q, et al. Cardiometabolic risk factors and preclinical target organ damage among adults in Ghana: findings from a national study. J Am Heart Assoc. 2020;9(24):e017492.

5. Mena L, Pintos S, Queipo NV, et al. A reliable index for the prognostic significance of blood pressure variability. J Hypertens. 2005;23:505-511.

6. Manousopoulos K, Koroboki E, Barlas G, et al. Association of home and ambulatory blood pressure variability with left ventricular mass index in chronic kidney disease patients. Hypertens Res. 2021;44:55-62.

7. Vishram JKK, Dahlof B, Devereux RB, et al. Blood pressure variability predicts cardiovascular events independently of traditional cardiovascular risk factors and target organ damage: a LIFE substudy. J Hypertens. 2015;33:2422-2430.

8. Hsu P-F, Cheng H-M, Wu C-H, et al. High short-term blood pressure variability predicts long-term cardiovascular mortality in untreated hypertensives but not in normotensives. Am J Hypertens. 2016;29:806-813.

9. Saladini F, Fania C, Mos L, et al. Short-term but not long-term blood pressure variability is a predictor of adverse cardiovascular outcomes in young untreated hypertensives. Am J Hypertens. 2020;33:1030-1037.

10. Chang TI, Reboussin DM, Chertow GM, et al. Visit-to-visit office blood pressure variability and cardiovascular outcomes in the systolic blood pressure intervention trial (SPRINT). Hypertension. 2017;70:751-758.

11. Stevens SL, Wood S, Koshtiari C, et al. Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. BMJ. 2016;354:i4098.

12. Mena LJ, Felix VG, Melgarejo JD, et al. 24-hour blood pressure variability assessed by average real variability: a systematic review and meta-analysis. Am Heart Assoc. 2017;6:e006895.

13. Nardin C, Rattazzi M, Pauletto P. Blood pressure variability and therapeutic implications in hypertension and cardiovascular diseases. High Blood Press Cardiovasc Prev. 2019;26:353-359.

14. Frattola A, Parati G, Cuspidi C, et al. Prognostic value of 24-hour blood pressure variability. J Hypertens. 1993;11:1133-1137.

15. Hung M-H, Huang C-C, Chung C-M, et al. 24-h ambulatory blood pressure variability and hypertensive nephropathy in Han Chinese hypertensive patients. J Clin Hypertens. 2020;00:1-8. https://doi.org/10.1111/jch.14108

16. Triantafyllidi H, Benas D, Schoinas A, et al. Hypertension mediated organ damage regression associates with blood pressure variability improvement three years after successful treatment initiation in essential hypertension. J Clin Hypertens. 2021.

17. Bourdillon MT, Bourdillon VRS, MT, et al. A contemporary approach to hypertensive cardiomyopathy: reversing left ventricular hypertrophy. Curr Hypertens Rep. 2020;22(10): https://doi.org/10.1007/s11906-020-01092-8

18. Webb AJ, Lawson A, Wartolowska K, et al. Progression of beat-to-beat blood pressure variability despite best medical management. Hypertension. 2021;77:193-201.

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