BP variability can be observed over multiple time-frames (1). Beat to beat variability in BP can be due to physiologic and environmental changes, such as body position, stress, and the simple act of breathing. Variability in BP throughout the day, often referred to as short-term BP variability, is a consequence of similar factors, including physical activity, sleep, and variation in hormones and sympathetic tone. Longer-term BP variability, typically measured from visit to visit over the course of years, is due to aging, medication adherence, and BP measurement errors. BP variability adds to the complexity in diagnosing and managing hypertension—guidelines recommend multiple elevated readings before making a diagnosis of hypertension as well as before initiation and titration of antihypertensive medications.

In addition to complicating the management of hypertension, elevated BP variability is associated with adverse outcomes. Among 7112 participants without hypertension, elevated short-term BP variability, assessed by ambulatory BP monitoring, was associated with higher risk for all-cause and cardiovascular mortality (2). Interestingly, such as with average ambulatory BP, the relationship was stronger for nighttime BP variability than daytime BP variability. Long-term BP variability is also associated with adverse outcomes. In the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), elevated visit-to-visit BP variability was associated with higher risk for cardiovascular disease and all-cause mortality (3). These studies were conducted in the general population with normal kidney function.

The paper by Mallamaci et al. (4) in this issue of the Clinical Journal of the American Society of Nephrology evaluated the association between BP variability, cardiovascular events, and all-cause mortality in a cohort of patients with CKD. They recruited 402 patients from nephrology clinics in Italy between 2001 and 2009. Short-term BP variability was assessed by ambulatory BP monitoring, and long-term BP variability was assessed in patients with at least four outpatient office BP measurements (n=366; 91%). Over a median follow-up of 3.2 years, visit-to-visit BP variability was associated with higher risk for a composite outcome of death and cardiovascular events (hazard ratio, 1.24; 95% confidence interval, 1.01 to 1.51). However, there was no significant association between short-term (24-hour) BP variability and adverse outcomes. Strengths of the study are the prospective collection of data that allows for assessment of multiple demographic and clinical comorbidities at baseline, formal adjudication of outcomes, and the availability of both short-term and long-term measures of BP variability from one cohort. One concern is the overlap of the variable-length exposure and outcome periods, because they used all BP data “preceding the occurrence of nonfatal cardiovascular events, ESKD, or censoring” to define visit-to-visit BP variability (4). A time-varying analysis would be more appropriate.

The findings by Mallamaci et al. (4) are consistent with the few prior studies conducted in patients with CKD. In another cohort of 374 patients with CKD from Italy, elevated visit-to-visit BP variability was associated with higher risk for all-cause mortality but was not associated with higher risk for ESKD (5). In a large retrospective cohort from Kaiser Permanente Northern California, visit-to-visit BP variability was assessed over a 6-month baseline (6). Among 114,900 patients with CKD, elevated BP variability was associated with all-cause mortality, hemorrhagic stroke, ESKD, and heart failure (6). Only one prior study in CKD evaluated the association between short-term BP variability and adverse outcomes. Borrelli et al. (7) (in a cohort that seems to overlap with the study by Mallamaci et al. [4]) reported no association between short-term BP variability and a composite of ESKD or a 50% decline in eGFR. The study by Mallamaci et al. (4) confirms prior findings that elevated visit-to-visit BP variability is associated with adverse clinical outcomes in patients with CKD. However, the minimal data available to date do not show higher risk for adverse outcomes with elevated short-term BP variability in patients with CKD.

The effect of elevated BP variability in patients with CKD may be especially important given the higher risk for adverse cardiovascular outcomes in this population. Additionally, elevated BP variability may be more prevalent in patients with CKD. In the ALLHAT, eGFR was lowest among participants in the highest quintile of visit-to-visit BP variability (3). Similarly, in the Systolic Blood Pressure Intervention Trial (SPRINT), 22% of participants in the bottom
quintile of BP variability had CKD at baseline, whereas 35% of patients in the highest quintile of BP variability had CKD at baseline (8). Short-term BP variability is also associated with CKD. Investigators from Spain measured ambulatory BP in 16,546 patients. The weighted SD of systolic BP ranged from 11.9 in those without CKD and with stage 1 CKD to 13.5 in those with stages 4 and 5 CKD (9). Factors associated with elevated BP variability in patients with CKD included men, older age, obesity, diabetes, and clinic systolic BP (9). It is unknown whether the association between CKD and elevated BP variability is due to these shared risk factors or whether a causal mechanism exists (and if so, in which direction the causality arrow points).

In addition to CKD, elevated BP variability has been associated with nonadherence to antihypertensive medications. In the ALLHAT, only 10% of participants in the lowest quintile of visit-to-visit BP variability had low medication adherence compared with 18% in the highest quintile (3). A similar pattern was observed in the SPRINT (8). In the African American Study of Kidney Disease and Hypertension trial, participants with lower self-reported adherence had higher visit-to-visit BP variability compared with those with perfect adherence (10). These three landmark trials show a consistent association between nonadherence and elevated BP variability. Identifying and addressing nonadherence in patients with hypertension, a cornerstone to treating resistant hypertension, may also be an effective strategy to reduce BP variability.

Potential treatments specifically targeting elevated BP variability rather than the underlying hypertension present in so many with CKD are untested. Nonadherence is a contributor to resistant hypertension and as noted above, may be a contributor to elevated BP variability. Although a treatment or a multidisciplinary strategy that reduces BP variability could be developed, the potential for reduction in subsequent adverse outcomes is unknown and would require a randomized trial. The once promising ability to reduce elevated serum homocysteine levels did not prove, for example, to lessen the risk of cardiovascular outcomes aside from stroke.

Calcium channel blockers and thiazide diuretics may be another therapeutic option that could be studied as a strategy to reduce BP variability. In a cohort of patients with CKD, patients in the lowest quartile of visit-to-visit BP variability were more likely to be taking a calcium channel blocker than those in the higher quartiles (5). In the ALLHAT, participants randomized to chlorthalidone and amlodipine had lower visit-to-visit BP variability 6–28 months after randomization, whereas BP variability was elevated in those receiving lisinopril (3). Although not assigned by randomization, similar patterns were observed in the SPRINT, with lower BP variability seen in participants receiving thiazide-type diuretics and calcium channel blockers and higher BP variability seen among those on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (8). Given the relative ease of identifying patients with elevated visit-to-visit BP variability in the electronic health record era, a pragmatic randomized trial could test the hypothesis that elevated BP variability is modifiable and that lowering BP variability reduces adverse outcomes.

New guidelines recommend obtaining readings outside the clinic in the diagnosis and management of hypertension. Adherent clinicians are then left to deal with an array of variables, including office BP, daytime BP, nighttime BP, 24-hour BP, dipping status, and morning surge. Short-term and long-term BP variabilities can be added to this list. Abnormalities in all of these measures are associated with adverse outcomes. Additionally, most of these measures are modifiable by therapeutic strategies, such as chronotherapy for nondipping and elevated nighttime BP. However, reducing clinic BP is the only strategy proven to reduce adverse clinical outcomes. As for BP variability, additional studies are needed to determine whether elevated BP variability is modifiable and if so, whether interventions to lower BP variability reduce adverse outcomes. Until then, it is impossible to say whether elevated BP variability is like hyperhomocysteinemia, the lowering of which did not improve clinical outcomes.

Disclosures

None.

References


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