Finding a Signal in the Noise

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The importance of BP as a risk factor for cardiovascular and renal disease is well established. In all BP trials, precise protocols are enforced when measuring BP to minimize extraneous factors that could obscure an individual’s true BP free from noise (1). However, despite these protocols, an individual’s BP varies from visit to visit, even within the context of a trial. Far from being unwelcome noise, there may well be a useful signal embedded in this visit to visit variability. The association of visit to visit variability in clinic BP (VVV) with cardiovascular disease was first appreciated in the Honolulu Heart Study (2); however, it was a seminal series of papers by Rothwell and coworkers (3–5) in 2010 and 2011 describing the relation of greater VVV with higher risk of stroke that spurred the recent interest in BP variability as a predictor of cardiovascular events.

Nephrologists, who value BP control as a key means of preventing and slowing progression of CKD in addition to reducing cardiovascular events in patients with CKD, have asked whether VVV holds similar predictive value for renal events. Using the SD of systolic BP measured over successive clinic visits, a common VVV metric, several groups have shown that greater VVV is associated with increased risk for cardiovascular events in patients with diabetic and nondiabetic CKD; the corresponding relation of VVV with renal events has largely been limited to diabetic individuals (6–9). In this issue of the Clinical Journal of the American Society of Nephrology, Whittle et al. (10) report the association of VVV with renal events in 21,245 participants from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Those individuals in the highest compared with lowest quintile of VVV (defined over five to seven visits) were more than twice as likely to develop a composite renal event, defined as either a 50% decline in eGFR or incident ESRD, after controlling for age, sex, baseline eGFR, mean systolic BP, adherence to BP medications, history of diabetes, and cardiovascular disease. The association was similar among both participants who were nondiabetic and participants who were diabetic (65% and 35% of the population, respectively), suggesting that the relation of greater VVV with renal end points does not depend on diabetic status. As with all observational studies, reverse causality may be responsible for the association described. In this study underlying kidney disease, present at baseline but undetected by baseline eGFR, may lead to increased VVV and also predict future eGFR decline. For example, albuminuria is associated with increased VVV and also predicts eGFR decline but was not available at baseline for inclusion in multivariate adjustment.

A unique characteristic of the study by Whittle et al. (10) is the extended duration of follow-up gained by incorporation of ESRD information from the US Renal Data Systems. The availability of this information allowed the investigators to determine if the association of VVV with renal events was sustained over the long term. This addresses a recurring limitation of previous studies of VVV; namely, because assessment of VVV in post hoc analyses of BP trials requires incorporation of multiple measurements over time (often over a period of 9–24 months), the subsequent period of follow-up is usually short. In addition, participants who develop a renal event during the time period of VVV ascertainment are typically excluded; this has the effect of both reducing the statistical power of the analysis and reducing the likelihood of finding an association, even if one exists.

The availability of long–term follow-up in the study by Whittle et al. (10) is also important, because a seldom-mentioned characteristic of VVV is instability over successive periods of measurement (i.e., the variability of BP over time is, in fact, variable over time). As an example, in the original paper by Rothwell et al. (5), the correlation coefficient of VVV ascertained during one time period with VVV ascertained during a later time period was only 0.34 (95% confidence interval, 0.26 to 0.41); in a more recent study of patients with diabetes, this “intra-class” correlation coefficient was 0.42 (95% confidence interval, 0.35 to 0.49) (8). This variability of VVV over time may explain, at least in part, the finding from the work by Whittle et al. (10) that, in the analysis of ESRD during 10 years of follow-up, the proportional hazards assumption was violated. As a result, Whittle et al. (10) analyzed the association of VVV with ESRD occurring through the first 3.7 years of follow-up separately from events after 3.7 years. Interestingly, VVV was associated with ESRD during the initial 3.7 years but not after 3.7 years; this result could be caused by temporal instability VVV.

One interesting finding described in the original paper by Rothwell et al. (4) and reproduced in other studies is that different BP medications are associated with different levels of VVV. As an example, in the Anglo-Skandinavisch Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) Trial, individuals assigned to β-blockers had higher VVV than those assigned to calcium channel blockers, despite achieving a similar mean BP.
Similarly, in the African American Study of Kidney Disease and Hypertension (AASK) Trial, individuals treated with calcium channel blockers had lower mean VVV relative to those assigned β-blockers or angiotensin–converting enzyme inhibitors. This pattern was the same in the ALLHAT; VVV was lowest with amlopidine therapy and higher with lisinopril and chlorthalidone. If VVV was causally associated with adverse events, it could be expected that calcium channel blockers would produce lower event rates compared with other drugs. Although this was true in the ASCOT-BPLA Trial (individuals receiving amlodipine had lower risk of stroke and cardiovascular disease than those receiving β-blockers, which was almost all accounted for by VVV), this was not true for renal events in the AASK Trial and the ALLHAT. In the AASK Trial, those assigned to calcium channel blockers had a higher rate of renal events relative to those treated with angiotensin–converting enzyme inhibitors, which led to the calcium channel blocker arm being terminated early (11). In a separate analysis of the ALLHAT, treatment assignment to chlorthalidone, amlopidine, or lisinopril did not produce disparate renal outcomes (12). However, it is possible that amlopidine has an adverse effect on renal progression that counteracts the benefit obtained from reduced VVV.

Previous studies examining the association of VVV with renal events have principally included patients with CKD at baseline. The paper by Whittle et al. (10) reveals a relation of greater VVV with renal events in a population with relatively normal renal function at baseline and therefore, at a much lower risk of renal events than previously studied populations. Their findings are consistent with those of a post hoc analysis evaluating the association of VVV with renal events in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) Trial of individuals with type 2 diabetes (mostly without CKD), supporting the argument that the association is present among individuals without existing kidney disease (9). The findings from the work by Whittle et al. (10) and the ADVANCE Trial beg several questions. Why does a variable BP signal a more rapid decline in renal function? Is VVV a surrogate marker that captures poor medication adherence, impaired BP regulation caused by endothelial function, variability in sympathetic tone, and increased salt sensitivity interacting with daily changes in diet, thereby behaving like a cumulative risk score for vascular and renal damage? Or is the variability in BP itself the mechanism for renal damage, with daily fluctuations in BP, outside the range of autoregulation, leading to either recurring episodes of medullary ischemia and tubular damage or increased intraglomerular pressure and hyperfiltration?

Part of the difficulty in unraveling what constitutes VVV is that it is a time-varying covariate (i.e., temporal variability of BP), which itself may be a function of other time-varying covariates (such as temporal variability in dietary sodium intake, variability in medication adherence, variability in daily stressors, and variable number of cigarettes smoked as well as variable numbers or types of antihypertensive medications to name just a few possibilities) (13–15). Because this level of information is seldom captured in cohorts, it is difficult to fully account for all of the factors that are potentially responsible for BP variability. What is needed now is an improved understanding of the mechanisms of VVV. To understand VVV will likely require several approaches, including repeated measurement of BP with simultaneous measurement of its potential determinants over several visits to permit modeling of BP over time and determination of potential mechanisms. Extension of current genetic epidemiology efforts, including application of genome–wide association studies to VVV, may prove fruitful in larger cohorts to help elucidate novel mechanisms underlying VVV (16).

At present, the study by Whittle et al. (10) along with the myriad of studies that preceded it have identified VVV as an important and independent predictor of renal and cardiovascular events and a factor deserving of more intense investigation.

Disclosures
None.

References


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