Association of BP Variability with Mortality among African Americans with CKD

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Summary

Background and objectives Increased systolic BP visit-to-visit variability (SBV) may be associated with higher overall mortality and cardiovascular events. However, few studies have examined these associations in patients with CKD, and the relation of SBV with CKD progression and ESRD has not been shown. This study analyzed the association of SBV with overall mortality, cardiovascular mortality, cardiovascular events, and renal events among individuals enrolled in the African American Study of Kidney Disease (AASK) trial.

Design, setting, participants, & measurements This was a prospective observational study of 908 participants during the trial phase of the AASK study, with at least 1 year of BP measurements available and followed for 3–6.4 years. SBV was calculated as the SD of the systolic pressure from five visits occurring 3–12 months after randomization. The association of SBV with risk of overall mortality, cardiovascular mortality, a composite of fatal and nonfatal cardiovascular events, and a composite of renal events was assessed using proportional hazards regression and adjusting for multiple potential confounders.

Results Greater SBV was associated with higher overall mortality. The adjusted hazard ratio (95% confidence interval) was 2.82 (1.14–6.95) comparing the highest with lowest tertile of SBV. A similar comparison revealed that greater SBV was also associated with cardiovascular mortality (adjusted hazard ratio, 4.91; 1.12–21.50). SBV was associated with both the cardiovascular renal composite endpoints in unadjusted but not adjusted analyses.

Conclusions In African Americans with CKD, SBV is strongly and independently associated with overall and cardiovascular mortality.

Introduction

Variation in BP that is captured at sequential office visits is called visit-to-visit variability. Formally considered “noise,” greater degrees of systolic BP visit-to-visit variability (SBV) may be associated with an increased incidence of stroke and overall mortality in several cohort studies (1–4). In a Northern European cohort, for example, individuals in the top decile of SBV had a 3.25-fold higher risk of subsequent stroke compared with those in the lowest decile (1). A similar relation was found between SBV and overall mortality in the Third National Health and Nutritional Examination Study (NHANES III) (2).

Few studies have examined the association of SBV with the incidence and progression of kidney disease. For example, greater SBV was associated with incident diabetic nephropathy in one study (5) and with renal arteriosclerosis in another (6). A small, retrospective study in elderly patients failed to show an association between SBV and the incidence of ESRD (hazard ratio [HR], 1.05 per 1% increase in SBV; 95% confidence interval [95% CI], 0.94–1.17) (3).

Given the high incidence of cardiovascular disease in individuals with CKD and the strong relation between BP and progression of CKD, the association of SBV with cardiovascular and renal events among individuals with established CKD is an important area of investigation. Thus, we analyzed the association of SBV with overall mortality, cardiovascular mortality, cardiovascular events, and renal events among individuals enrolled in the African American Study of Kidney Disease (AASK) trial.

Materials and Methods

Study Population

AASK was a multicenter randomized clinical trial of 1094 African Americans with hypertensive nephrosclerosis and a GFR of 20–65 ml/min per 1.73 m² enrolled from February 1995 to September 1998 and followed for 3–6.4 years. All participants were randomly assigned in a 3×2 factorial design to one of three antihypertensive medications (metoprolol, ramipril, or amlopidine) and one of two BP goals (mean arterial pressure ≤92 or 102–107 mmHg) (7). We performed a prospective cohort analysis of the 908 individuals from the original 1094 enrolled who had complete BP measurements during follow-up visits at months 4, 6, 8, 10, and 12 of the AASK trial (Figure 1).

Of 1094 individuals enrolled in the AASK trial, 186
participants had incomplete BP data available, having missed one or more of the scheduled protocol visits during the study period from 3 to 12 months and thus were excluded, leaving 908 participants in the current analysis. The maximum follow-up for these 908 participants was 75 months (median 52 months). During the period of follow-up from 12 months onward, 64 patients died and 133 had a cardiovascular event, including 22 cardiovascular deaths. Of the participants, 132 developed ESRD and 154 had a GFR decline 

\[ \text{or had a GFR decline from baseline} \]

All AASK participants provided informed consent. This study was approved by the institutional review board at Brigham and Women’s Hospital.

**Visit-to-Visit Variability**

In the AASK trial, BP was ascertained during the first year at months 0, 1, 2, 3, 4, 5, 6, and every other month thereafter. At each of these visits, measurements were taken using a random zero sphygmomanometer while participants were seated and after at least 5 minutes of rest. The BP that was recorded for each given visit was the mean calculated from last two of three consecutive readings (8).

The aim in AASK was to achieve the goal BP within the first 3 months of the trial by titrating antihypertensive medications during this initial period. Because of these frequent medication adjustments, and the variation likely to be induced by these adjustments, we calculated SBV using BP measurements only after this initial 3-month titration period. Thus, we calculated each participant’s SBV using BP measurements taken during protocol visits at months 4, 6, 8, 10, and 12. In our analyses, SBV was defined as the SD of the mean of systolic pressures at months 4, 6, 8, 10, and 12; the SD of systolic pressures has been used as the main measure of SBV in multiple other studies (1,2,9–13). If participants were missing BP measurements at month 4, then BP measurements from month 3 were used, whereas if participants were missing BP measurements from month 6, then BP measurements from month 5 were used so as to provide as many participants as possible with five complete BP measurements taken during the period from month 3 to month 12.

**Covariates**

Demographic, clinical, and laboratory data were collected on all participants in the AASK trial at baseline using standardized forms. Information about age, sex, weight, and height was collected and stored at a central data repository. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters.
squared. History of heart disease was self-reported. Study participants were asked to collect 24-hour urine samples using a standard protocol before the baseline visit and also at 6 months and 12 months. Urine total protein and creatinine were measured in the central laboratory of the data coordinating center. Blood samples were collected at the baseline visit and at 12 months. Serum chemistries were measured using an autoanalyser in the central data coordinating center laboratory.

Pill counts were assessed at each visit. Participants were considered compliant for that visit if the number of pills actually taken was between 80% and 110% of the number of pills prescribed for that interval. Each individual’s compliance with study medications during the first year was defined as the percentage of visits in which the patient was compliant during the first 12 months.

Endpoints

Because SBV was computed using BP measurements taken during the first 12 months of the study, only outcomes measured from 12 months onward were included in the analysis. This minimized the possibility that a cardiovascular or renal event may have influenced SBV.

The endpoints analyzed in this study were all-cause mortality, cardiovascular mortality, cardiovascular events, and renal events. Cardiovascular events were a composite consisting of cardiovascular death, cardiovascular revascularization, nonfatal myocardial infarction (MI), hospitalization for heart failure, or stroke as described in detail elsewhere (14). Renal events were a composite consisting of ESRD, a reduction in GFR by $50\%$ relative to mean of two baselines measurements, a decline in GFR of $\geq 25$ ml/min per 1.73 m$^2$ from baseline, or death (15).

Participants who reached ESRD ceased to be followed on a routine basis for certain nonfatal cardiovascular outcomes; therefore, all cardiovascular events included in composite endpoint occurred before ESRD, with participants censored at onset of ESRD in this analysis. GFR was measured by $^{131}$Iiothalamate clearance, which was ascertained at the central laboratory twice at baseline, months 3 and 6, and then every 6 months thereafter (16).

Statistical Analyses

SBV was analyzed as both a continuous variable (per 1 SD of SBV) and as a categorical variable (by tertile of SBV). The means and SDs of all continuous covariates were calculated for each tertile and a test of trend was performed with and without adjustment for covariates; for covariates that were measured at baseline (prerandomization) and at 12 months, we included values from the 12-month visit because this was the point in time after which events could accrue (i.e., 12 months was “baseline”). The proportional hazards assumption was checked by means of graphics and Schoenfeld residuals.

We included covariates that were established risk factors for cardiovascular disease and/or progression of CKD, or were noted to have associations with SBV, in our multivariable models. These included the following: age (continuous), sex, history of heart disease (yes/no), smoking status (current/prior/never), BMI (continuous), mean systolic BP during (from 3 to 12 months, continuous), log-transformed proteinuria at 12 months (continuous), serum albumin at 12 months (continuous), measured iohthalamate GFR at 12 months (continuous), study drug assignment (metoprolol/ramipril/amiodipine), and compliance with study medications over the first year.

We also performed a secondary analysis in order to reduce the possibility that an existing or imminent cardiovascular or renal event could influence SBV (i.e., reverse causation), thereby accounting for associations between SBV and these events. Specifically, we performed a lag-time analysis using only those events that occurred after month 18 or month 24.

Results

The mean SBV in the study population was 13.6 mmHg and, because of the large number of individuals in the study population and the minimal skew, the SBV distribution was assumed to be normal. Characteristics of the study population, including the distribution of covariates across tertiles of SBV, are shown in Table 1.

The mean age of the 908 participants in the study was 55 years; 62% were men. Individuals were assigned in a 2:2:1 distribution to metoprol, ramipril, and amiodipine, respectively, and in a 1:1 distribution to usual and low BP goals, consistent with the overall AASK trial population (15,16,17). Participants assigned to receive amiodipine had lower SBV than those assigned to either ramipril or metoprol. Both higher baseline systolic pressure and higher mean systolic pressure during months 3–12 were associated with greater SBV. Lower BMI, lower measured GFR, and poorer compliance with study medications were also associated with greater SBV. There were significantly more active smokers and individuals with a history of heart disease in the higher tertiles of SBV. Notably, there was no association between SBV and the assigned BP goal.

The incidences of all four clinical outcomes, including all-cause mortality, cardiovascular mortality, cardiovascular events, and renal events, were significantly higher across increasing tertile of SBV (Figure 2, log-rank $P$ values all $<0.05$). Using Cox proportional regression, the unadjusted HR of all-cause mortality was almost 3-fold higher (HR, 2.89; 95% CI, 1.50–5.56) among those in the highest tertile of SBV compared with those in the lowest tertile (Table 2).
1.58 (95% CI, 1.17–2.09) for cardiovascular events and from 2.49 (95% CI, 1.62–3.82) for renal events.

For the composite cardiovascular and renal endpoints, greater SBV was significantly associated with an increased risk in unadjusted models, consistent with the survival curves (Figure 2 and Table 2). However, after adjustment, these associations were no longer statistically significant; the adjusted HR in the highest compared with lowest tertile of SBV was 1.23 (95% CI, 0.65–2.34) for all cardiovascular events and 1.05 (95% CI, 0.67–1.62) for renal events.

Log proteinuria at 12 months was determined to be the major confounder of these associations. Using both bivariate and stepwise models testing the confounding effects of all covariates, the addition of log proteinuria to unadjusted models reduced the HRs for the highest compared with lowest tertile of SBV from 2.81 (95% CI, 1.77–4.54) to 1.43 (95% CI, 0.82–2.49) for cardiovascular events and from 1.58 (95% CI, 1.17–2.14) to 1.29 (95% CI, 0.88–1.89) for renal events.

Our results were robust in secondary analyses. When we imposed a lag-time (so that only events accruing after 18 months or 24 months were counted), SBV remained significantly associated with both all-cause and cardiovascular mortality.

### Discussion

We have shown that, in this large longitudinal study of African Americans with hypertensive nephrosclerosis, greater SBV measured early during the study was independently associated with increased overall mortality and also cardiovascular mortality. Although there was also an association with increased SBV with the composite cardiovascular and renal endpoints, these relations were confounded by log proteinuria. This is the largest study to date to examine the association of SBV with outcomes in African Americans with hypertensive nephrosclerosis, and is the only such study in blacks.

Potential mechanisms for the relation of SBV with cardiovascular disease have been examined in animals and humans. In rats, sinoaortic ablation increases BP variability without increasing mean BP; these rats develop increased left ventricular and aortic hypertrophy and glomerular and

### Table 1. Baseline characteristics and study assignment of patients by tertile of SBV

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Total</th>
<th>Tertile of SBV</th>
<th>P for Trenda</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>55 (11)</td>
<td>55 (11)</td>
<td>56 (10)</td>
</tr>
<tr>
<td>Baseline systolic BP (mmHg)</td>
<td>150 (24)</td>
<td>145 (21)</td>
<td>151 (25)</td>
</tr>
<tr>
<td>Baseline mGFR (ml/min per 1.73m²)</td>
<td>47 (14)</td>
<td>48 (14)</td>
<td>47 (13)</td>
</tr>
<tr>
<td>Baseline body mass index (kg/m²)</td>
<td>30.6 (6.6)</td>
<td>31.2 (6.6)</td>
<td>30.8 (6.5)</td>
</tr>
<tr>
<td>Baseline urine protein (g/d)</td>
<td>0.51 (0.91)</td>
<td>0.49 (0.85)</td>
<td>0.49 (0.89)</td>
</tr>
<tr>
<td>Baseline urine protein/creatinine</td>
<td>0.31 (0.51)</td>
<td>0.28 (0.47)</td>
<td>0.29 (0.49)</td>
</tr>
<tr>
<td>Baseline urine Na (g/d)</td>
<td>3.69 (1.98)</td>
<td>3.68 (2.01)</td>
<td>3.75 (1.89)</td>
</tr>
<tr>
<td>Mean systolic BP mo 3–12 (mmHg)</td>
<td>136 (14)</td>
<td>131 (12)</td>
<td>136 (13)</td>
</tr>
<tr>
<td>12-mo serum albumin (g/dl)</td>
<td>4.13 (0.34)</td>
<td>4.16 (0.37)</td>
<td>4.13 (0.32)</td>
</tr>
<tr>
<td>12-mo mGFR (ml/min per 1.73m²)</td>
<td>45 (17)</td>
<td>47 (18)</td>
<td>46 (17)</td>
</tr>
<tr>
<td>12-mo urine protein/creatinine</td>
<td>0.34 (0.68)</td>
<td>0.29 (0.35)</td>
<td>0.32 (0.64)</td>
</tr>
<tr>
<td>Compliance (%)</td>
<td>71 (29)</td>
<td>78 (26)</td>
<td>71 (30)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>562 (62)</td>
<td>178 (32)</td>
<td>198 (35)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>265 (29)</td>
<td>86 (28)</td>
<td>83 (31)</td>
</tr>
<tr>
<td>Previous smoker, n (%)</td>
<td>261 (29)</td>
<td>90 (34)</td>
<td>96 (37)</td>
</tr>
<tr>
<td>History of heart disease, n (%)</td>
<td>466 (51)</td>
<td>129 (43)</td>
<td>151 (50)</td>
</tr>
</tbody>
</table>

SBV is calculated as the SD of mean systolic BP measured during five follow-up visits at months 4, 6, 8, 10, and 12. Baseline covariates are measured during initial GFR measurement visit. Twelve-month covariates measured at the 12-month return visit for GFR measurement, BP measurement, and 24-hour urine collection. SBV, systolic BP visit-to-visit variability; mGFR, measured GFR.

aTrend testing performed using the Cochrane–Armitage trend test for categorical variables and univariate linear regression for continuous variables, with each individual assigned the mean value of SBV for its tertile of SBV.
renovascular sclerosis relative to control mice with sham sinoaortic ablation (18). In humans, SBV is associated with endothelial dysfunction (19) and arterial stiffness (20). Greater BP variability may produce vascular damage via an inability of certain vascular systems (e.g., cerebrovascular) to maintain autoregulation over wider ranges of BP; alternatively, variability in pressure may induce endothelial inflammation (19,21,22).

Table 2. Hazard ratio for selected outcomes by tertile of SBV

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of Events</th>
<th>Analysis</th>
<th>Hazard Ratio by SBV Tertilea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1b</td>
</tr>
<tr>
<td>Death</td>
<td>64</td>
<td>Unadjusted</td>
<td>1.38 (0.66–2.88)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adjusted</td>
<td>0.77 (0.28–2.16)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>22</td>
<td>Unadjusted</td>
<td>1.23 (0.33–4.59)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adjusted</td>
<td>1.09 (0.21–5.57)</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>133</td>
<td>Unadjusted</td>
<td>1.68 (1.03–2.76)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adjusted</td>
<td>1.28 (0.71–2.29)</td>
</tr>
<tr>
<td>Renal events</td>
<td>255</td>
<td>Unadjusted</td>
<td>1.08 (0.78–1.48)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adjusted</td>
<td>1.00 (0.66–1.51)</td>
</tr>
</tbody>
</table>

Adjustment includes age (continuous), sex, history of heart disease (yes/no), smoking status (current, prior, never), body mass index (continuous), mean systolic BP during (from 3 to 12 months, continuous), proteinuria at 12 months (continuous), serum albumin at 12 months (continuous), measured iothalamate GFR at 12 months (continuous), study drug assignment (metoprolol, ramipril, amlodipine), and compliance with study medications over the first study year (proportion of study visits). SBV, systolic BP visit-to-visit variability.

aHazard ratio of event relative to the lowest tertile of SBV. Hazard ratios for death, cardiovascular death, and renal events are calculated using Cox proportional hazards regression, whereas hazard ratios for cardiovascular events are calculated using Anderson–Gill regression.

bReference.
Several studies have shown that SBV is associated with overall mortality. In the largest of these, in which 2161 individuals with type 2 diabetes were followed for a mean of 67 months, every 1 SD higher SBV (a metric similar to what we have analyzed) was independently associated with a 5% higher risk of all-cause mortality (23). Similarly, among 956 individuals from NHANES III followed for a median of 14 years, the HR for death was 1.50 (95% CI, 1.03–2.18) in the highest compared with lowest tertile of SBV (2). The results of this study of blacks with established renal disease are consistent with these prior findings, suggesting that SBV is a strong predictor of mortality among individuals with CKD in addition to the general population.

The association of SBV with cardiovascular events has been extensively studied with varied conclusions. Greater SBV in the Honolulu Heart Program ($n=1433$), for example, was found to predict cardiac death or nonfatal MI (24). An association of SBV with cardiovascular death, MI, and stroke was also found in two other large studies: the Anglo-Saxon Cardiovascular Outcomes Trial (ASCOT) (25), and the Woman’s Health Initiative (WHI) (4). However, smaller studies have failed to show the association of SBV with these cardiovascular disease endpoints (10,13).

In the AASK trial, we found that SBV was strongly associated with cardiovascular mortality, but not with the composite endpoint including nonfatal MI, nonfatal stroke, revascularization, or hospitalization for heart failure. Notably, the analyses performed in the Honolulu Heart Program, ASCOT, and WHI did not control for baseline proteinuria, which was the principal confounding factor in our analysis.

The mechanisms that could explain a relation between SBV and renal disease are similar to those described above for cardiovascular disease, including endothelial dysfunction (19) and arterial stiffness (20), both known risk factors for renal outcomes (26–28). In addition, cross-sectional studies have shown that increased SBV is associated with increased renal resistive index, a marker of renal arteriosclerosis (6). Despite these potential mechanisms linking SBV with renal disease, SBV was not independently associated with renal events in our study, principally after controlling for proteinuria, which has been demonstrated in hypertensive individuals to be predictive of renal outcomes (15,29–32). In our analyses, the HRs for cardiovascular and renal events from highest compared with the lowest tertile of SBV decreased from 2.81 to 1.43 and 1.58 to 1.29, respectively, upon adjusting for log proteinuria. It is possible that both proteinuria and SBV share a common mechanism, such as endothelial dysfunction (19), which itself may be a risk factor for cardiovascular and renal events. It is also possible that proteinuria is on the causal pathway between SBV and cardiovascular or renal disease, but it is statistically difficult to distinguish between these alternatives. Similar to our findings, a small retrospective study in elderly patients with CKD and hypertension ($n=374$, median age 79 years) also showed no association between SBV and risk of renal outcome (3). The kidney’s unique role in modulating BP and its susceptibility to hypertension complicates the association of SBV and renal outcomes.

Our study has several strengths. First, the AASK trial consisted of black individuals. This is important as it pertains to BP variability and cardiovascular and renal disease because, relative to whites, blacks have a disproportionate burden of both hypertension as well as CKD that is presumed secondary to hypertension. In addition, blacks may have greater variation in BP than whites, both during a single 24-hour ambulatory BP monitoring period and over sequential 24-hour periods (33,34). Second, individuals in AASK had a high prevalence of hypertensive nephrosclerosis as the cause of renal disease; 38 of 39 individuals who underwent protocol renal biopsies had arteriosclerosis and arteriolosclerosis consistent with vascular changes associated with hypertension (35). Thus, this population with preexisting renovascular damage due to BP may be an ideal setting to determine the importance of SBV in progressive disease and vascular events, analogous to prior studies in patients with preexisting cerebrovascular damage due to BP to determine the relevance of SBV to stroke and other cardiovascular endpoints (1). Third, given the frequency with which participants were followed, we were able to assess BP variability over multiple study visits in a relatively short period of time; other studies have calculated SBV using fewer BP measurements. Fourth, we analyzed endpoints that were adjusted during the conduct of a randomized controlled trial and therefore were highly reliable. Fifth, we were able to control for potential confounders using detailed information, including measured as opposed to estimated GFR, 24-hour rather than spot measurements of proteinuria, and medication compliance.

Our study also has several limitations. First, although African Americans with CKD represent an important population for study, our findings cannot necessarily be extrapolated to nonblack patients with CKD or those whose renal disease is caused by other etiologies. Second, BP control in the AASK study was superior to that observed in many other trials and likely the general population (36). Although this also may somewhat detract from the generalizability of our findings, the attention paid to participants in AASK increases the internal validity of our findings by limiting the effect of external factors on SBV. Finally, although AASK was a randomized trial, the current analysis was observational, and there were important differences between baseline covariates across SBV tertiles, specifically in baseline systolic BP, baseline GFR, smoking, and history of heart disease. Although we carefully adjusted for these covariates in our multivariable analyses, we cannot exclude the possibility of residual confounding due to these factors or to other important covariates that were not ascertained in the AASK trial.

In conclusion, a greater SBV is highly predictive of subsequent overall and cardiovascular mortality, but not of nonfatal cardiovascular endpoints or CKD progression, in African Americans with CKD. Further studies are required to discover modifiers of SBV, and to test whether modification of SBV can reduce both overall and cardiovascular mortality.

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Disclosures

None.

References


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