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Association of Blood Pressure Variability and Diuretics with Cardiovascular Events in Patients with CKD Stages 1-5

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Abstract

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Disclosures

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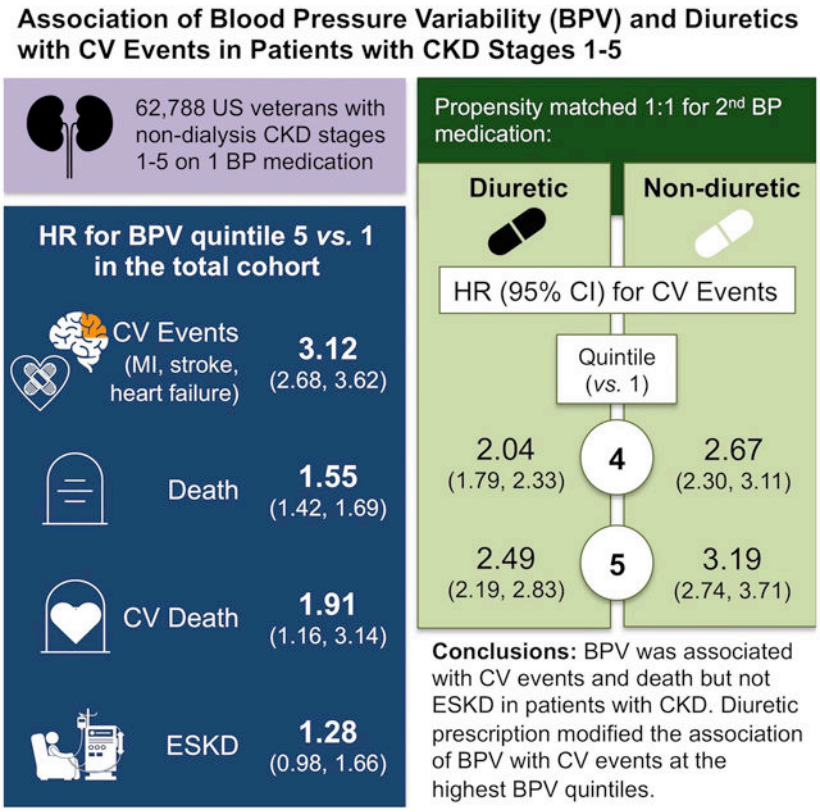
Visit-to-visit blood pressure variability (BPV) is associated with cardiovascular events in the general population. Data are scarce in chronic kidney disease (CKD). We hypothesized that BPV would be associated with cardiovascular outcomes, death, and end-stage kidney disease (ESKD) and that diuretics would modify these associations in patients with CKD.

We studied U.S. Veterans with non-dialysis CKD stages 1-5 and hypertension on non-diuretic antihypertensive monotherapy. At the time of second antihypertensive agent prescription, we propensity-matched for exposure to a loop or thiazide diuretic *vs.* any other antihypertensive. BPV was defined as the coefficient of variation of systolic blood pressure over 6 months after second agent prescription. Cox proportional hazards regression measured associations of BPV with a primary cardiovascular event composite (fatal or non-fatal myocardial infarction or ischemic stroke; heart failure hospitalization). Secondary outcomes included all-cause death, each primary outcome component, ESKD, and cardiovascular death.

There were 31,394 participants in each group. BPV was associated with composite cardiovascular events, hazard ratio (95% confidence interval) at second, third, fourth, and fifth *vs.* first quintile: 1.79 (1.53-2.11), 2.32 (1.99-2.71), 2.60 (2.24-3.02), and 3.12 (2.68-3.62). Diuretics attenuated associations between the fourth and fifth BPV quintiles with composite events ($P_{interaction}$=0.03 and 0.04, respectively). BPV was associated with all secondary outcomes except ESKD, with no diuretic interactions.

BPV was associated with cardiovascular events and death but not ESKD in patients with CKD, with attenuated associations with CV events in the diuretic-treated group at high BPV quintiles. Future studies should investigate whether other antihypertensive classes modify these risks.

Graphical Abstract



Keywords

chronic kidney disease; blood pressure variability; diuretics; cardiovascular events; death

INTRODUCTION

Individuals with chronic kidney disease (CKD) are at disproportionately high cardiovascular (CV) risk, and traditional CV risk factors such as diabetes and hypertension, although more common in individuals with CKD, do not predict risk as well in these patients as in the general population.[1, 2] This highlights the need to identify novel factors to improve CV risk stratification in patients with CKD. Outpatient visit-to-visit blood pressure variability (BPV) has been shown to be independently associated with poor CV outcomes in the general population.[3, 4] However, data in patients with CKD are scarce and restricted to advanced stage CKD, when interventions may not be as effective late in the course of disease.[5-7]

Furthermore, no studies investigated whether antihypertensive medication class may affect BPV and its association with outcomes. Secondary analyses from clinical trials suggest that treatment with diuretics, as compared to other antihypertensives, may be associated with decreased BPV in the general population,[8-10] and one observational study in patients with advanced CKD noted lower BPV in those treated with diuretics compared to other drug classes.[7] The potential ameliorating effect of diuretics on BPV could be particularly

pronounced in patients with CKD given that volume overload is common and contributes to hypertension in this population.

Given that extracellular volume plays a significant role in hypertension in patients with CKD and may affect BPV, we hypothesized that loop and thiazide diuretics would mitigate BPV and its association with long-term CV outcomes and end-stage kidney disease (ESKD) compared to non-diuretic antihypertensive agents among patients with prevalent non-dialysis CKD stages 1-5. Our specific aims were to 1) determine if thiazide or loop diuretic prescription was associated with decreased BPV compared to non-diuretic antihypertensive medications; 2) determine whether BPV was associated with CV outcomes, death, and ESKD in patients with prevalent CKD stages 1-5; and 3) determine whether diuretic prescription modified the association of BPV with CV events, death, and ESKD.

MATERIALS AND METHODS

Data Sources

Applications to access the dataset from qualified researchers trained in human subject confidentiality protocols may be submitted through the Veterans Affairs (VA) Data Access Request Tracker. Real-world national data were obtained from January 1, 2010 to December 31, 2016 from inpatient and outpatient demographic, comorbidity, laboratory, and pharmacy datasets from the VA Corporate Data Warehouse and accessed via the VA Informatics and Computing Infrastructure. Dates of diagnosis of incident ESKD during follow up were obtained from United States Renal Data System (USRDS) data.

Study Design and Participants

We conducted an observational cohort study using real-world clinical data from a national sample of United States veterans with prevalent non-dialysis CKD stages 1-5.[11] The study was approved by the Institutional Review Board at the VA North Texas Health Care System (protocol number 17-107) and a waiver of informed consent was granted.

We identified adult individuals ≥18 years of age from January 1, 2010 through December 31, 2016 with prevalent CKD using laboratory values from routine care. CKD was defined as 2 outpatient instances ≥3 months apart of either an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 or the presence of proteinuria or albuminuria, defined as a spot urine albumin-to-creatinine ratio ≥30 mg/g, a spot urine protein-to-creatinine ratio >0.15 g/g, 24-hour urine albumin ≥30 mg/day, 24-hour urine protein >150 mg/day, or a dipstick urinalysis positive for protein ≥30 mg/dL.[12, 13] CKD stages 1-5 were defined by Kidney Disease Outcomes Quality Initiative criteria.[12] Individuals with prevalent ESKD at the index date were identified by date of incident ESKD diagnosis data from the USRDS and were excluded. Inclusion in the study required prescription of a non-diuretic medication as initial monotherapy for hypertension, with the prescription of a second antihypertensive agent during the observation period (Figure 1A). Those who were prescribed diuretic antihypertensive monotherapy, 2 initial medications simultaneously for the treatment of hypertension, or were already prescribed ≥2 antihypertensive agents when inclusion criteria were met were excluded. Individuals with any exposure to loop or thiazide diuretics within 3

months prior to the index date were also excluded to ensure washout of any previously prescribed diuretic medications and inclusion of truly new users of diuretics.[14] The index date was defined as the time of prescription of the second antihypertensive medication (Figure 1A).

Exposure Variable

The exposure variable was defined by the prescription of a second antihypertensive medication after initial monotherapy with a non-diuretic antihypertensive agent. Participants exposed to a loop or thiazide diuretic as the second agent were compared to those whose second medication was a non-diuretic, including angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), mineralocorticoid receptor antagonists, calcium channel blockers, beta blockers, alpha blockers, hydralazine, clonidine, aliskiren, minoxidil, or amiloride (a complete list of anti-hypertensive agents in each category can be found at http://hyper.ahajournals.org).

Clinical Variables

Comorbid medical conditions were defined using International Classifications of Disease, Clinical Modification, revisions 9 and 10 (ICD-9, ICD-10) codes (please see http://hyper.ahajournals.org). Baseline characteristics, including demographics, comorbidities, and laboratory values, were captured within 1 year prior to the index date. Quantitative measures of albuminuria and proteinuria were divided into deciles to account for the degree of albuminuria or proteinuria at baseline, with an additional category added to represent missing values (please see http://hyper.ahajournals.org). Body mass index (BMI) was calculated from baseline weight and height prior to the index date. Baseline systolic and diastolic blood pressure values were defined as the most recent outpatient blood pressure measurement recorded on or prior to the index date.

Blood Pressure Variability

For the primary analysis, BPV was defined as the coefficient of variation of outpatient systolic blood pressure values for 6 months after the index date. Blood pressures obtained in emergency department or urgent care settings were excluded. When multiple blood pressures were measured on a single date, only the first measurement from that date was used in the BPV calculation. The coefficient of variation was calculated by dividing the standard deviation by the mean of the systolic blood pressure values. In sensitivity analyses, BPV was additionally calculated by other common definitions, including the average real variability and the standard deviation of the systolic blood pressure, to account for different blood pressure patterns that can be uncovered by these alternative measures.[15]

Outcome Variables

Participants were followed for up to 5 years for outcome events. The primary composite outcome was CV events, defined as fatal or non-fatal myocardial infarction, fatal or non-fatal ischemic stroke, or hospitalization for heart failure. Secondary outcomes included all-cause death (identified by the National Death Index, VA death data, and the Centers for Medicare and Medicaid Services), each component of the primary composite outcome,

ESKD, and CV death, defined as death within 31 days of a myocardial infarction, ischemic stroke, or hospitalization for heart failure. Definitions of outcome events by ICD codes can be found at http://hyper.ahajournals.org.

Statistical Analysis

Logistic regression models were used to create the propensity score for diuretic exposure, which modeled the probability of exposure use given 38 study covariates at baseline, including demographic characteristics, comorbidities, medications, laboratory values, and clinical data (complete list of variables included in the propensity model can be found at http://hyper.ahajournals.org). Participants who received diuretics as their second antihypertensive medication were propensity-matched 1:1 without replacement with individuals who received non-diuretic antihypertensive medications. Nearest-neighbor matching was performed with a caliper of 0.0001. Baseline characteristics between matched groups were compared using standardized differences.[16] BPV before and after the index date and the change in BPV were compared between groups using standardized differences. In the absence of data to support clinically useful cutoffs, BPV was divided into quintiles in the entire cohort for analysis, consistent with prior similar studies.[7, 10, 17] Associations of BPV with outcomes were calculated using Cox proportional hazards regression, including diuretic treatment x BPV interaction terms. Outcomes models were adjusted for the number of blood pressure measurements included in BPV calculations and the number of visits in 1 year prior to the index date to capture factors important to the calculation of BPV and the overall medical complexity of the participants.[18] Other covariates included age, sex, race, eGFR, systolic blood pressure, BMI, proteinuria, albuminuria, smoking, diabetes mellitus, congestive heart failure, vascular disease, malignancy, and any exposure in 1 year prior to the index date to ACEi, ARB, spironolactone, beta blockers, calcium channel blockers, clonidine, hydralazine, or statins. Participants were censored at the date of last follow up or death. Pre-specified sub-group analyses were performed by CKD stage, race, sex, diabetes mellitus, congestive heart failure, and prior exposure to ACEi or ARB. Statistical analysis was conducted using STATA 15 (StataCorp, College Station, TX).

Sensitivity Analyses

Several sensitivity analyses were conducted to test the robustness of the findings. First, we examined BPV as a continuous variable rather than by quintile. Then we selected for individuals who had been exposed to no more than 1 or 2 antihypertensive agents in 1 year prior to the index date, which identified a sample of participants whose antihypertensive agents had remained unmodified or minimally modified in 1 year prior to prescription of the second agent. Next, we selected only those who had 4-15 blood pressure measurements included in the calculation of BPV to exclude those who had too few measurements to calculate a true variability and to exclude the very ill who presented to the outpatient clinic setting as often as several times per month. Finally, we conducted survival analysis censoring individuals at the time of prescription of a third antihypertensive agent and treating death as a competing risk.

RESULTS

Baseline Characteristics

There were 1,536,758 participants who met criteria for prevalent non-dialysis CKD stages 1-5. A total of 332,401 met criteria for inclusion in the cohort. Of those, we identified 68,739 individuals on non-diuretic monotherapy for hypertension whose second antihypertensive medication was a diuretic and 263,662 whose second agent was a non-diuretic (Figure 1B). The 1:1 propensity matched cohort included 62,788 participants, with 31,394 participants in each group. Baseline characteristics were similar in the matched cohort (Table 1). Baseline characteristics of the unmatched cohort are available at http://hyper.ahajournals.org.

Blood Pressure Variability

After the index date, median (IQR) systolic BPV was 10.4 (7.4, 13.7) in the non-diuretic group and 10.5 (7.4, 13.8) in the diuretic group (please see http://hyper.ahajournals.org). Higher BPV was seen with more advanced CKD stages, in those prescribed hydralazine or clonidine, and in those with more frequent medical visits or specialists in the 12 months prior to the index date (please see http://hyper.ahajournals.org).

Outcomes

Increasing quintiles of BPV were associated with composite CV events, all-cause death, CV death, myocardial infarction, heart failure hospitalization, and stroke, but not ESKD (Figure 2). Similar associations with the primary outcome were seen when BPV was measured as the average real variability or standard deviation of the systolic blood pressure, and when evaluating quintiles of BPV prior to the index date (please see http://hyper.ahajournals.org). Those with the greatest decrease in BPV had a lower risk of composite CV events than those whose BPV increased from the 6 months before to the 6 months after the index date (please see http://hyper.ahajournals.org). There was a significant interaction of treatment group on the association of the fourth and fifth quintiles of BPV with the primary outcome, interaction P=0.03 and 0.04, respectively, indicating that diuretic treatment attenuated the association of BPV with composite CV events (Table 2).

Over 163,591 person-years of follow up, there were 3,391 (10.8%) composite CV events in the non-diuretic group and 3,935 (12.5%) in the diuretic group (P<0.0001), with the corresponding event rates being 42.29/1,000 person-years and 47.18/1,000 person years. More participants in the diuretic group than non-diuretic group reached all-cause death (9,123 [29.1%] *vs.* 7,444 [23.7%], P<0.0001), CV death (295 [0.9%] *vs.* 237 [0.8%], P=0.01), heart failure hospitalization (3,408 [10.9%] *vs.* 2,765 [8.8%], P<0.0001), and ESKD (1,163 [3.7%] *vs.* 866 [2.8%], P<0.0001). There was no difference in the number experiencing myocardial infarction (655 [2.1%] *vs.* 710 [2.3%], P=0.13) or stroke (398 [1.3%] *vs.* 438 [1.4%], P=0.16) between groups. Treatment group did not modify the relationship between quintiles of BPV with any of the secondary outcomes (Table 2). Sensitivity analyses showed similar relationships between quintile of BPV with CV events as the primary analysis (Table 3).

Subgroup Analysis

The relationship between quintiles of BPV and CV events did not differ based on subgroups by CKD stage, race, sex, or exposure to renin-angiotensin-aldosterone system (RAAS) blockade with an ACEi or ARB (Figure 3). The second, third, and fourth quintiles of BPV were more strongly associated with CV events in individuals without diabetes mellitus (interaction P=0.03, 0.04, and 0.002, respectively), and the fifth quintile was more strongly associated in those without heart failure (interaction P=0.02). Significant interactions of diuretic treatment were seen at the fourth and fifth quintiles of BPV for men and patients with diabetes and the fifth quintile in those with heart failure or not on RAAS blockade (Figure 3). BPV taken continuously was associated with CV events in all subgroups, with no treatment group x BPV interactions (please see http://hyper.ahajournals.org).

DISCUSSION

We demonstrated that among veterans with prevalent non-dialysis CKD stages 1-5, BPV was strongly and independently associated with CV events, all-cause death, CV death, myocardial infarction, heart failure hospitalization, and ischemic stroke, but not progression of CKD to ESKD. We further showed that the association of BPV with CV events was diminished in those with diabetes compared to those without diabetes, but there was no difference in this association based on CKD stage. Finally, thiazide or loop diuretic-based antihypertensive regimens were not associated with decreased BPV compared to non-diuretic regimens but did modify the association of BPV with CV events at the highest BPV quintiles.

Prior studies in the general population mostly showed associations between visit-to-visit BPV and CV outcomes.[19] In the general population and in individuals without CKD, BPV was associated with all-cause death, CV death, incident coronary heart disease, stroke, major adverse CV events, and incident atrial fibrillation.[3, 4, 19-23] In a secondary analysis of clinical trials of patients with diabetes, higher BPV was associated with death and a composite of death, CV events, and kidney events.[24] However, among 7,879 participants in the Systolic Blood Pressure Intervention Trial (SPRINT), BPV, defined as the coefficient of variation of systolic blood pressure, was associated with all-cause death but not with CV outcomes.[10]

Similarly, the few studies in patients with CKD showed direct associations between BPV and adverse CV outcomes and death. A secondary analysis of SPRINT revealed that among participants without diabetes and with non-dialysis CKD stages 3-5, diastolic BPV was associated with the composite of acute coronary syndrome, acute heart failure, and CV death.[5] Another study of 402 patients with CKD stages 1-5 (35% with diabetes) reported that systolic BPV was associated with the composite of death or CV event.[6] A secondary analysis of the African American Study of Kidney Diseases (which included only individuals without diabetes) with GFR 20-65 mL/min/1.73 m^2, revealed that systolic BPV was strongly associated with all-cause and CV death.[25] One real-world study of 114,900 patients with CKD stages 3-4, higher quintiles of systolic BPV were separately associated with outcomes of all-cause death, heart failure, and hemorrhagic stroke, but not with acute coronary syndrome, or ischemic stroke.[7] Recently, a study of 470 participants with CKD

stages 3-5 showed that systolic BPV was associated with the composite of non-fatal stroke, non-fatal MI, and all-cause death.[26] In contrast to these studies, one combined analysis of patients with diabetes and proteinuria enrolled in the Irbesartan Diabetic Nephropathy Trial (IDNT) and Reduction of End Points in Non-Insulin-Dependent Diabetes with Angiotensin II Antagonist Losartan (RENAAL) clinical trials showed that higher tertiles of systolic BPV were associated with death but not with CV death or CV events.[27] In sum, most but not all studies of patients with CKD showed associations between BPV and CV events or all-cause death. However, these studies predominantly included patients with advanced stages of CKD.

Our results are consistent with these prior studies but, importantly, extend these findings to include a large cohort of patients with earlier stages of CKD from a national health care system. In our study, higher quintiles of BPV were strongly associated with CV outcomes. The consistent association of BPV with CV death, myocardial infarction, heart failure, and ischemic stroke but not with ESKD suggests that BPV is likely associated specifically with poor CV health. Furthermore, quintile of BPV was associated with composite CV events across all evaluated subgroups, including by CKD stage, race, sex, diabetes mellitus status, heart failure, or exposure to an ACEi or an ARB, supporting that the relationship of BPV with outcomes was true of all-comers, rather than driven by particular subgroups. Our study adds to the literature inclusion of non-dialysis CKD stages 1-5 in a population of patients that has more chronic illness and higher BPV than populations previously studied. We further add a sufficiently sized cohort to robustly study even rare outcomes, as well as various subgroups with adequate power to adjust for important confounders.

The few prior studies of associations of BPV with kidney outcomes in patients with CKD are mixed. The study of participants enrolled in IDNT and RENAAL showed associations of higher tertile of BPV with incident ESKD, doubling of creatinine, and the composite of both,[27] and a prospective cohort study (N=470) showed that high systolic BPV was independently associated with eGFR decline >3 mL/min/1.73 m^2 per year.[26] However, in the large retrospective real-world observational study of patients with CKD stages 3-4, there was no association observed between BPV and incident ESKD,[7] similar to the results of our analysis. Further studies will be required to elucidate the relationships between BPV and progression of kidney disease to clinically meaningful outcomes such as ESKD in patients with non-dialysis CKD.

In addition to this, we evaluated the interaction of diuretics to test whether these commonly prescribed and widely available medications may modify BPV and its association with CV events. Despite the association of BPV with clinically important events as detailed above, few studies have investigated potential interventions to mitigate BPV and possibly improve outcomes. Although the mechanisms of BPV are poorly understood, it is possible that extracellular volume, which is considered to have a key pathophysiologic role in hypertension in patients with CKD, may contribute to BPV. Natriuretic peptides, clinically used to measure fluid overload in patients with heart failure, are associated with BPV, independent of other important clinical factors such as left ventricular hypertrophy and diastolic dysfunction.[28] This may explain prior secondary analyses of clinical trials showing that diuretic therapy may lower BPV compared to other classes of antihypertensive agents.

[7-10] In our analysis, although we observed no difference in BPV between those whose second antihypertensive agent was a diuretic *vs.* a non-diuretic, there were significant interactions of diuretic treatment on the association of the fourth and fifth quintiles of BPV with the primary composite CV outcome. This could be because extracellular volume may play a weightier role in the elevated CV risk among those with more severe BPV. Alternatively, BPV may have other complex underlying mechanisms, such that decreasing extracellular volume with diuretics may not fully account for other contributing causes of BPV. These may include vascular stiffness, sympathetic nervous system activation, medication nonadherence, stress and anxiety, physical activity, and endothelial dysfunction.[29, 30] This could also explain why we observed a diminished association of BPV with CV events in those with diabetes mellitus, who have high baseline CV risk likely due to mechanisms unrelated to BPV and extracellular volume. In addition, because calcium channel blockers have also been associated with decreased BPV compared to other antihypertensive medication classes, their inclusion in the non-diuretic group may have biased our results toward the null.[7, 9, 10, 31, 32]

Our study has several strengths. We identified participants with prevalent CKD using laboratory values, which allowed us to use more sensitive guideline-based definitions rather than diagnosis codes. The large sample drew from a national health care system with near universal health care coverage and had high numbers of outcome events, including CV death, allowing adequate power to evaluate these outcomes when adjusting for relevant covariates. This study also has important limitations. CV outcomes were drawn only from VA data, which may miss outcome events occurring outside the VA system and decrease the power of the study. However, given the large sample size, our study was still adequately powered to test our hypothesis. In an observational study with such a large sample size, the high precision of point estimates, multiple comparisons, and residual confounding could impact interpretation of these results, such that marginally statistically significant findings may not represent clinically meaningful relationships. However, we showed a strong and consistent dose-response relationships across quintiles of BPV with each outcome except ESKD, and the point estimates of associations with composite CV events were strong, supporting the robustness of these findings. Furthermore, the relationship between BPV and CV events was consistent across all evaluated subgroups, indicating that the association of BPV with adverse CV outcomes is not driven by specific sub-populations of particular risk. The lack of observed association between BPV and ESKD further supports a meaningful relationship between BPV and CV events, as it is less likely that individuals with higher BPV were simply more ill overall. We did not evaluate BPV over a longer period of time such as 12 months, but the timeframe of 6 months we used is consistent with other real-world studies.[7] A limitation of the subgroup analysis was the lower number of outcome events in women, although other subgroups had sufficient outcome events to conduct rigorous analysis. We do not know of any data to indicate that the observed associations would be different in women as compared with men. Finally, because the association of BPV with CV events was seen for each individual CV outcome and across each studied subgroup, it is possible that BPV is a marker of poor CV health rather than an intervenable risk factor.

In conclusion, we demonstrated that BPV was strongly associated with composite CV events, all-cause death, CV death, myocardial infarction, hospitalization for heart failure, and ischemic stroke in patients with prevalent non-dialysis CKD stages 1-5. There was no association between BPV and ESKD. The association of BPV with CV events was seen across all subgroups, but was attenuated in individuals with diabetes. Diuretic prescription modified the association of BPV with CV events at the highest BPV quintiles. BPV may be a promising potentially intervenable target to reduce CV events in patients with CKD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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PERSPECTIVES

These results suggest that although outpatient visit-to-visit BPV is strongly associated with CV events among patients with CKD, treatment with diuretics may only decrease the association of BPV with outcomes in those with the highest BPV. It is possible that BPV has a complex underlying pathophysiology mediated by factors other than extracellular volume, or that high BPV is a marker of overall poor CV health. Nonetheless, BPV remains a promising target to improve outcomes in patients with CKD, so further studies should investigate whether other classes of antihypertensive agents impact BPV and its associations with outcomes.

NOVELTY AND SIGNIFICANCE

What Is New?

- Little is known about the associations of BPV with adverse outcomes patients with CKD, particularly in the earliest stages.
- Although prior studies showed that diuretics may decrease BPV, none have investigated this as a potential strategy for reducing BPV and its association with adverse CV and kidney outcomes in patients with CKD.

What Is Relevant?

- BPV may be a promising potentially intervenable target to reduce CV events in patients with CKD.
- Diuretics may be effective to reduce the associations of high BPV with CV events.

Summary

BPV was associated with CV events and death but not ESKD in patients with non-dialysis CKD stages 1-5. Among individuals with high BPV, a decreased association of BPV with CV events was seen in those prescribed diuretics *vs.* non-diuretics.

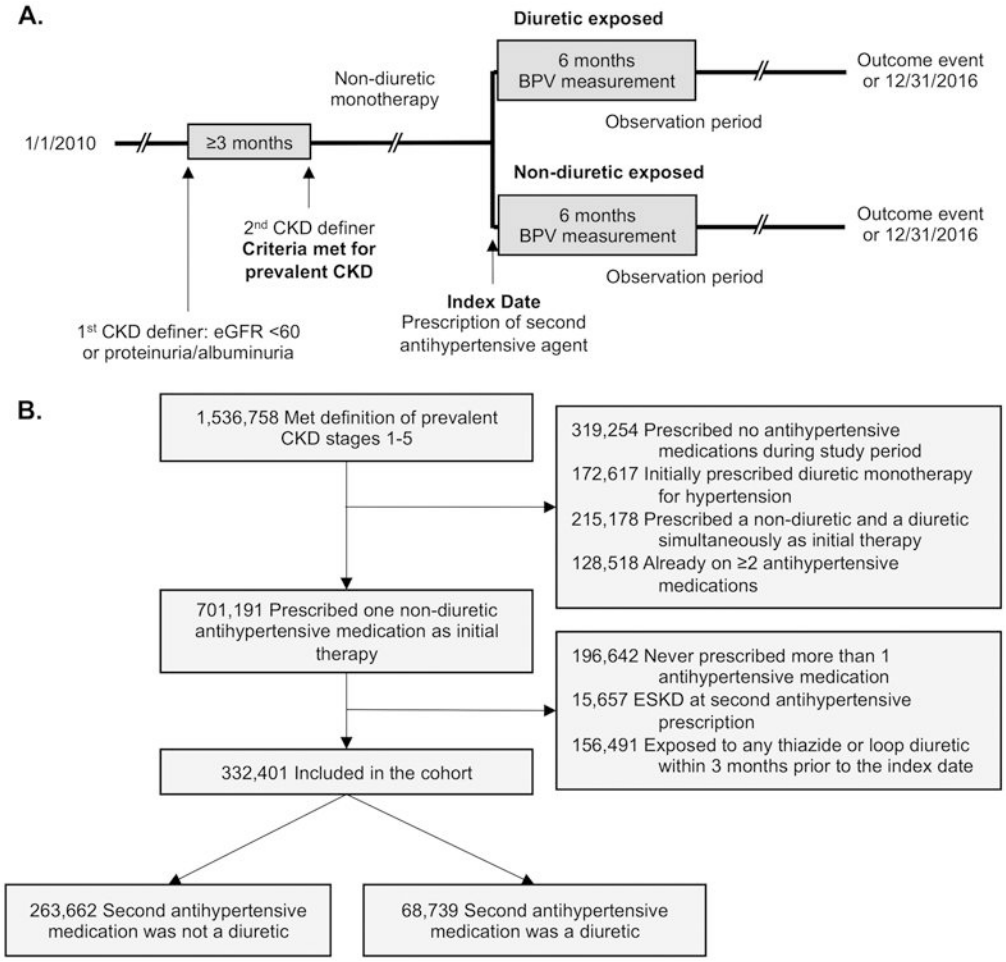

Figure 1.
Study design (A) and diagram of inclusion in the cohort (B)

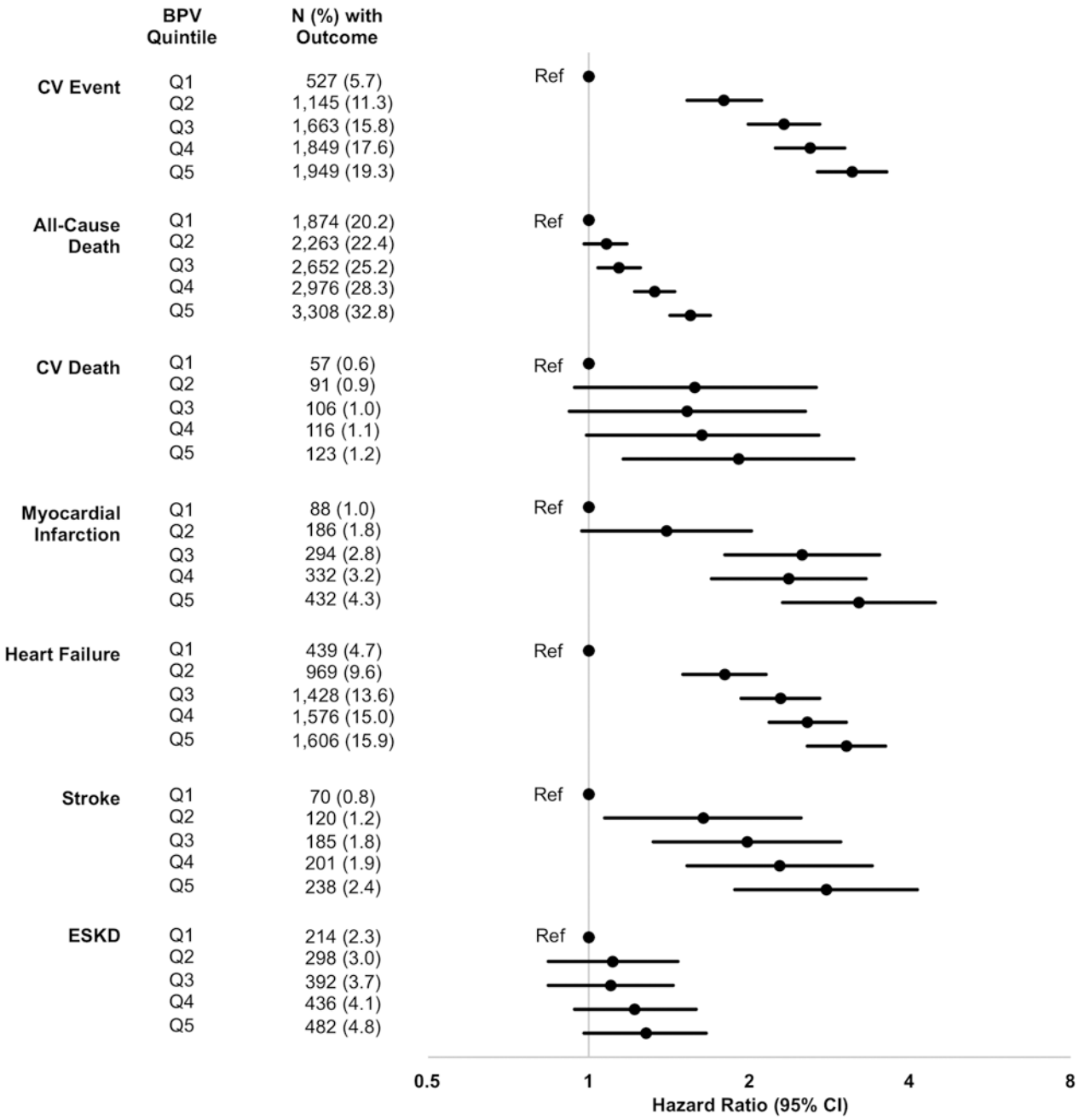

Figure 2. Outcome events by quintile of BPV in the entire matched cohort

Models were adjusted for the total number of blood pressure measurements in the BPV calculation, the total number of clinic stops in 1 year prior to the index date, age, sex, race, eGFR, systolic blood pressure, BMI, albuminuria, proteinuria, smoking, diabetes mellitus, congestive heart failure, vascular disease, and malignancy, treatment in 1 year prior to the index date with an ACEi or ARB, spironolactone, a beta blocker, a calcium channel blocker, clonidine or hydralazine, or a statin

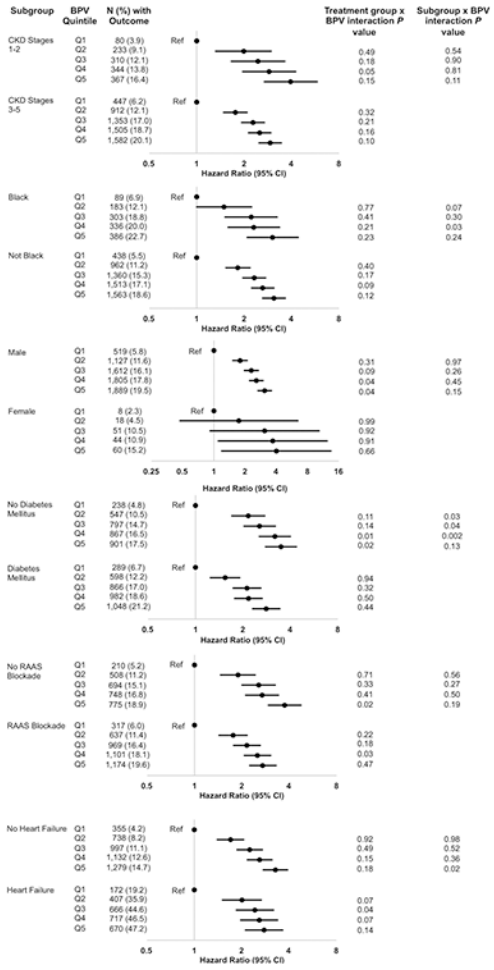

Figure 3. Association of quintile of BPV with composite CV events by subgroups

Models were adjusted for the total number of blood pressure measurements in the BPV calculation, the total number of clinic stops in 1 year prior to the index date, age, sex, race, eGFR, systolic blood pressure, BMI, albuminuria, proteinuria, smoking, diabetes mellitus, congestive heart failure, vascular disease, and malignancy, treatment in 1 year prior to the index date with an ACEi or ARB, spironolactone, a beta blocker, a calcium channel blocker, clonidine or hydralazine, or a statin

Table 1.

Baseline characteristics of the 1:1 propensity matched cohort

Variable	Non-Diuretic Exposed N=31,394	Diuretic Exposed N=31,394	Standardized Difference
Age, years, mean (SD)	72.2 (10.9)	72.2 (11.1)	0.008
Female Sex, N (%)	1,197 (3.8)	1,185 (3.8)	0.002
Race, N (%)			0.01
White	23,798 (75.8)	24,027 (76.5)	
Black	4,527 (14.4)	4,361 (13.9)	
Native Hawaiian or Pacific Islander	331 (1.1)	310 (1.0)	
American Indian or Alaska Native	173 (0.6)	203 (0.7)	
Asian	158 (0.5)	162 (0.5)	
Unknown or Multi-race	2,407 (7.7)	2,331 (7.4)	
Comorbidities *, N (%)			
COPD	6,746 (21.5)	6,750 (21.5)	0.0003
Diabetes mellitus	14,896 (47.5)	14,851 (47.3)	0.003
HIV	201 (0.6)	205 (0.7)	0.002
Peripheral vascular disease	3,666 (11.7)	3,750 (11.9)	0.008
Liver disease	780 (2.5)	782 (2.5)	0.0004
Malignancy	5,447 (17.4)	5,436 (17.3)	0.0009
Vascular disease	6,589 (21.0)	6,607 (21.1)	0.001
Hemiplegia or paraplegia	111 (0.4)	107 (0.3)	0.002
Myocardial infarction	1,063 (3.4)	1,086 (3.5)	0.004
Congestive heart failure	3,833 (12.2)	3,900 (12.4)	0.006
Dementia	490 (1.6)	488 (1.6)	0.0005
Rheumatic disease	596 (1.9)	602 (1.9)	0.001
Peptic ulcer disease	433 (1.4)	430 (1.4)	0.0008
Smoking, N (%)	611 (2.0)	585 (1.9)	0.006
Medications †, N (%)			
Nitrates	3,267 (10.4)	3,213 (10.2)	0.006
Statins	13,401 (42.7)	13,841 (44.1)	0.03
Aspirin	5,663 (18.0)	5,672 (18.1)	0.0008
ACE inhibitors	13,329 (42.5)	14,093 (44.9)	0.05
ARBs	4,469 (14.2)	4,372 (13.9)	0.009
Beta blockers	15,922 (50.7)	16,237 (51.7)	0.02
Calcium channel blockers	10,499 (33.4)	10,169 (32.4)	0.02
Spironolactone	1,612 (5.1)	1,383 (4.4)	0.03
Hydralazine	1,129 (3.6)	810 (2.6)	0.06
Clonidine	844 (2.7)	610 (1.9)	0.05

Variable	Non-Diuretic Exposed N=31,394	Diuretic Exposed N=31,394	Standardized Difference
Minoxidil	74 (0.2)	59 (0.2)	0.01
Amiloride	30 (0.1)	16 (0.1)	0.02
Laboratory and clinical variables			
Estimated glomerular filtration rate, mL/min/1.73 m^2, median (IQR)	51.9 (42.7, 59.3)	51.2 (41.5, 58.5)	0.07
Albuminuria, mg/g, median (IQR)	29.0 (8.8, 103.4)	31.5 (9.7, 122.4)	0.03
Proteinuria, g/g, median (IQR)	0.2 (0.1, 0.7)	0.3 (0.1, 0.8)	0.005
Serum potassium, mmol/L, mean (SD)	4.4 (0.5)	4.4 (0.5)	0.03
Serum albumin, g/dL, mean (SD)	3.9 (0.4)	3.9 (0.5)	0.006
Systolic blood pressure, mmHg, mean (SD)	138.1 (22.1)	137.5 (22.3)	0.03
Diastolic blood pressure, mmHg, mean (SD)	75.9 (13.2)	75.5 (13.8)	0.02
Body mass index, kg/m^2, mean (SD)	29.9 (6.2)	29.8 (6.1)	0.02
Number of visits in 1 year prior to the index date, mean (SD)	12.8 (11.2)	12.7 (11.6)	0.003
Number of specialists in 1 year prior to the index date, mean (SD)	2.2 (2.1)	2.2 (2.2)	0.008

Abbreviations: ACE inhibitors, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus

*Defined by International Classification of Diseases codes

†Defined as exposure in pharmacy records within 1 year prior to the index date

Table 2.

Association of quintile of systolic BPV with time to outcome event by diuretic exposure

Model	Non-Diuretic Exposed HR (95% CI) N=31,394	Diuretic Exposed HR (95% CI) N=31,394	Treatment group x BPV interaction *P* value
CV Event			
Q1	Ref	Ref	
Q2	1.83 (1.56, 2.15)	1.59 (1.39, 1.83)	0.31
Q3	2.37 (2.03, 2.76)	1.92 (1.69, 2.19)	0.10
Q4	2.67 (2.30, 3.11)	2.04 (1.79, 2.33)	0.03
Q5	3.19 (2.74, 3.71)	2.49 (2.19, 2.83)	0.04
All-Cause Death			
Q1	Ref	Ref	
Q2	1.07 (0.98, 1.18)	1.07 (0.99, 1.16)	0.86
Q3	1.13 (1.03, 1.24)	1.09 (1.00, 1.18)	0.35
Q4	1.31 (1.20, 1.43)	1.18 (1.09, 1.28)	0.03
Q5	1.53 (1.40, 1.67)	1.49 (1.37, 1.61)	0.37
CV Death			
Q1	Ref	Ref	
Q2	1.54 (0.91, 2.61)	1.28 (0.83, 1.98)	0.49
Q3	1.49 (0.89, 2.51)	1.26 (0.82, 1.94)	0.49
Q4	1.57 (0.94, 2.61)	1.36 (0.89, 2.09)	0.51
Q5	1.86 (1.12, 3.08)	1.55 (1.02, 2.36)	0.46
Myocardial Infarction			
Q1	Ref	Ref	
Q2	1.37 (0.95, 1.99)	1.86 (1.30, 2.65)	0.30
Q3	2.48 (1.77, 3.46)	1.83 (1.29, 2.59)	0.18
Q4	2.34 (1.67, 3.27)	2.31 (1.64, 3.24)	0.87
Q5	3.19 (2.29, 4.43)	3.52 (2.53, 4.90)	0.71
Heart Failure			
Q1	Ref	Ref	
Q2	1.83 (1.53, 2.18)	1.61 (1.39, 1.87)	0.40
Q3	2.32 (1.96, 2.76)	1.95 (1.70, 2.25)	0.22
Q4	2.64 (2.23, 3.13)	2.05 (1.78, 2.36)	0.06
Q5	3.11 (2.63, 3.69)	2.40 (2.08, 2.76)	0.05
Stroke			
Q1	Ref	Ref	
Q2	1.65 (1.08, 2.53)	1.11 (0.73, 1.70)	0.21
Q3	1.98 (1.31, 2.97)	1.77 (1.21, 2.60)	0.73
Q4	2.28 (1.53, 3.40)	1.68 (1.14, 2.48)	0.28

Model	Non-Diuretic Exposed HR (95% CI) N=31,394	Diuretic Exposed HR (95% CI) N=31,394	Treatment group x BPV interaction *P* value
Q5	2.74 (1.84, 4.08)	2.26 (1.55, 3.29)	0.46
ESKD			
Q1	Ref	Ref	
Q2	1.18 (0.88, 1.57)	1.04 (0.82, 1.32)	0.83
Q3	1.15 (0.87, 1.51)	1.06 (0.84, 1.33)	0.99
Q4	1.34 (1.02, 1.77)	1.18 (0.94, 1.48)	0.98
Q5	1.33 (1.01, 1.75)	1.30 (1.04, 1.62)	0.68

Abbreviations: BPV, blood pressure variability; CV, cardiovascular; ESKD, end-stage kidney disease; Q1, first quintile; Q2, second quintile; Q3, third quintile; Q4, fourth quintile; Q5, fifth quintile

Adjusted for the total number of blood pressure measurements in the BPV calculation, the total number of clinic stops in 1 year prior to the index date, age, sex, race, eGFR, systolic blood pressure, BMI, albuminuria, proteinuria, smoking, diabetes mellitus, congestive heart failure, vascular disease, and malignancy, treatment in 1 year prior to the index date with an ACEi or ARB, spironolactone, a beta blocker, a calcium channel blocker, clonidine or hydralazine, or a statin

Table 3.

Sensitivity analyses of association of systolic BPV with CV events

Quintile	Outcome Events N (%)	Main Effects HR (95% CI)	Non-Diuretic Exposed HR (95% CI)	Diuretic Exposed HR (95% CI)	Treatment group x BPV interaction *P* value
Takes BPV as a continuous variable *					
	7,326 (11.7)	1.05 (1.05, 1.06)	1.05 (1.04, 1.06)	1.05 (1.04, 1.06)	0.32
Excludes individuals exposed to more than 1 anti-hypertensive agent in 1 year prior to the index date					
Q1	213 (4.1)	Ref	Ref	Ref	
Q2	525 (9.0)	2.14 (1.63, 2.79)	2.16 (1.65, 2.83)	1.72 (1.41, 2.10)	0.21
Q3	710 (12.3)	2.89 (2.23, 3.74)	2.88 (2.22, 3.73)	2.23 (1.83, 2.70)	0.12
Q4	776 (13.7)	3.26 (2.53, 4.21)	3.26 (2.53, 4.21)	2.29 (1.88, 2.78)	0.03
Q5	834 (15.7)	4.34 (3.38, 5.58)	4.33 (3.37, 5.58)	2.88 (2.37, 3.49)	0.009
Excludes individuals exposed to more than 2 anti-hypertensive agents in 1 year prior to the index date					
Q1	468 (5.4)	Ref	Ref	Ref	
Q2	1,035 (11.0)	1.89 (1.59, 2.24)	1.92 (1.62, 2.28)	1.61 (1.40, 1.86)	0.20
Q3	1,473 (15.1)	2.40 (2.04, 2.83)	2.45 (2.08, 2.88)	1.92 (1.68, 2.21)	0.08
Q4	1,606 (16.6)	2.64 (2.25, 3.10)	2.73 (2.32, 3.21)	1.98 (1.73, 2.28)	0.02
Q5	1,715 (18.6)	3.25 (2.77, 3.81)	3.34 (2.84, 3.92)	2.50 (2.18, 2.87)	0.03
Excludes individuals who had <4 or >15 blood pressure measurements in 6 months after the index date					
Q1	325 (8.7)	Ref	Ref	Ref	
Q2	829 (12.1)	1.35 (1.11, 1.65)	1.36 (1.11, 1.66)	1.00 (0.84, 1.19)	0.02
Q3	1,109 (15.6)	1.52 (1.25, 1.85)	1.53 (1.26, 1.86)	1.25 (1.06, 1.47)	0.12
Q4	1,167 (16.5)	1.75 (1.45, 2.12)	1.76 (1.45, 2.14)	1.20 (1.02, 1.42)	0.004
Q5	1,270 (20.2)	2.07 (1.71, 2.52)	2.08 (1.71, 2.53)	1.72 (1.46, 2.02)	0.14
Censors participants at the time of prescription of the third antihypertensive agent					
Q1	248 (2.7)	Ref	Ref	Ref	
Q2	533 (5.3)	1.96 (1.50, 2.56)	2.07 (1.59, 2.71)	1.65 (1.38, 1.99)	0.38
Q3	787 (7.5)	2.73 (2.12, 3.52)	2.85 (2.21, 3.68)	1.97 (1.65, 2.35)	0.07
Q4	878 (8.3)	3.22 (2.51, 4.14)	3.42 (2.66, 4.39)	2.22 (1.86, 2.65)	0.04
Q5	944 (9.4)	4.19 (3.27, 5.37)	4.35 (3.39, 5.57)	2.60 (2.18, 3.10)	0.004
Treats non-CV death as a competing risk					
Q1	527 (5.7)	Ref	Ref	Ref	
Q2	1,145 (11.3)	1.79 (1.52, 2.11)	1.83 (1.56, 2.15)	1.61 (1.40, 1.84)	0.36
Q3	1,663 (15.8)	2.31 (1.99, 2.69)	2.36 (2.02, 2.76)	1.94 (1.70, 2.21)	0.13
Q4	1,849 (17.6)	2.52 (2.16, 2.94)	2.59 (2.22, 3.02)	2.05 (1.79, 2.34)	0.07
Q5	1,949 (19.3)	2.95 (2.54, 3.43)	3.01 (2.58, 3.51)	2.40 (2.11, 2.74)	0.07

Abbreviations: CV, cardiovascular; Q1, first quintile; Q2, second quintile; Q3, third quintile; Q4, fourth quintile; Q5, fifth quintile

Adjusted for the total number of blood pressure measurements in the BPV calculation, the total number of clinic stops in 1 year prior to the index date, age, sex, race, eGFR, systolic blood pressure, BMI, albuminuria, proteinuria, smoking, diabetes mellitus, congestive heart failure, vascular

disease, and malignancy, treatment in 1 year prior to the index date with an ACEi or ARB, spironolactone, a beta blocker, a calcium channel blocker, clonidine or hydralazine, or a statin

* Hazard ratios are per 1% increase in coefficient of variation of systolic blood pressure