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Blood pressure parameters are associated with all-cause and cause-specific mortality in chronic kidney disease

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Abstract

Previous observational studies reported J or U-shaped associations between blood pressure parameters and mortality in patients with chronic kidney disease (CKD). Here we examined the associations of different blood pressure levels with various causes of death in a CKD population that included patients with eGFR 15–59 ml/min/1.73 m² with underlying hypertension receiving at least one antihypertensive agent. We obtained data on date and cause of death from State Department of Health mortality files and classified deaths into three categories: cardiovascular; malignancy-related; and non-cardiovascular/non-malignancy related. Cox models were fitted for overall mortality, and separate competing risk regression models for each major cause of death

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Research idea and study design: SDN, SA, JDS, JVN; Data acquisition: SA; Data analysis and interpretation: SDN, SEJ, SA, JDS, MB, WCW, JVN; Statistical analysis: SA, JDS; Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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category, to evaluate their associations with various systolic and diastolic blood pressures. During a median follow-up of 3.9 years, 13,332 of 45,412 patients died. Systolic blood pressures under 100, 100–109, 110–119, and over 150 (vs. 130–139 mm Hg) were associated with higher all-cause and cardiovascular mortality. Systolic blood pressures under 100 mm Hg and 100–109 were associated with higher non-cardiovascular/non-malignancy related mortality. Diastolic blood pressures under 50 and 50–59 (vs. 70–79 mm Hg) were associated with higher all-cause and non-cardiovascular/non-malignancy-related mortality while diastolic blood pressures over 90 mm Hg was associated with higher cardiovascular but lower non-cardiovascular/non-malignancy related mortality. Thus, in a non-dialysis dependent CKD population, systolic blood pressures under 110 and over 150 mm Hg were associated with cardiovascular and non-cardiovascular/non-malignancy related deaths. However, diastolic blood pressures under 60 mm Hg was associated in contrast, with all-cause mortality and non-cardiovascular/non-malignancy-related deaths.

Keywords

blood pressure; death; kidney disease; outcomes

Introduction

Hypertension is a global public health problem and high blood pressure was found to be the leading risk factor for the global disease burden in 2010(1). Recent systematic reviews suggested potential benefits of intensive blood pressure control in the general population(2, 3). It is well established that blood pressure rises with decline in glomerular filtration rate(4) and most patients with chronic kidney disease (CKD) have concomitant hypertension. The ideal blood pressure target for CKD population (with and without diabetes) has been a matter of debate. Several observational studies have examined the associations between blood pressure parameters (systolic blood pressure [SBP], diastolic blood pressure [DBP], and pulse pressure), renal outcomes, and all-cause mortality(5–13). Most observational studies have reported that higher SBP and DBP are associated with higher risk of death. Several reports have also noted that higher SBP and DBP are associated with rapid kidney disease progression(5, 8). In contrary, some studies have noted that both lower SBP and DBP were associated with higher mortality(7, 9). In contrast to these observational data, recent clinical trial evidence from the Systolic Blood Pressure Intervention Trial (SPRINT) trial in patients without diabetes demonstrated that patients randomized to a target BP of < 120/80 mm Hg experienced fewer cardiovascular events and had lower mortality(14). When examining for effect modification, or when stratifying by CKD (defined as eGFR <60 ml/min/1.73 m²), it was found that the main findings from SPRINT were similar among those with and without kidney disease.

While most of the observational studies examined associations of blood pressure with all-cause mortality, and some with cardiovascular mortality, comprehensive examinations of the specific causes of death across different ranges of blood pressure in a large CKD population have remained elusive. In the present study, we hypothesized that in a CKD population, the observed higher mortality rates with lower BP (among observational studies) may be attributed to underlying comorbidities and the patterns of cause-specific deaths would be

different across various BP strata. Therefore, we examined the associations of SBP and DBP with categories of cause-specific mortality (cardiovascular, malignancy related, non-cardiovascular/non-malignancy related deaths) among a large CKD population.

Results

Patient characteristics—Our study population comprised of 45,412 patients with CKD stage 3 or 4 (Supplemental Figure 1). The mean age was 72.6 ± 11.4 years, 45.7% were men, and 13.8% were blacks. Mean SBP was 131 ± 20 mm Hg and mean DBP was 72.6 ± 11.3 mm Hg. Mean BMI of the study cohort was 29.9 ± 6.6 kg/m². Prevalence of diabetes, malignancy and coronary artery disease were 29.3%, 24.9% and 26.2% respectively. Mean eGFR of the study population was 47.5 ml/min/1.73 m². Table 1 outlines other details of the study population based on SBP categories, and Table 2 shows the clinical characteristics by DBP categories.

Mortality

During a median follow up of 3.9 years, 13,332 (29.3%) patients died; cause of death was available for 13,154 (98.6%) of those. Thereof, 4,824 (36.6%) died of cardiovascular causes, 3,315 (25.2%) due to malignancy and 4,737 (36.0%) due to other causes. Supplemental Tables 1 and 2 show the causes of death overall and by SBP and DBP categories, respectively.

SBP and overall and cause-specific death—In multivariable models, and compared with patients who had SBP 130–139 mm Hg, SBP <100, 100–110 and 110–119 mm Hg were associated with higher overall mortality, and with higher sub-distribution hazards for cardiovascular mortality; SBP <100 and 100–109 mm Hg were also associated with increased mortality from non-cardiovascular/non-malignancy-related deaths (Table 3). SBP 160 and 150–159 mm Hg (vs. 130–139 mm Hg) were associated with higher risk for all-cause and cardiovascular deaths (Table 3). Figure 1 shows the associations between SBP (as a continuous measure) and all-cause death. Figure 3 shows the associations between SBP (as a continuous measure) and various causes of death.

DBP and overall and cause-specific death—In the models adjusting for potentially confounding variables, DBP < 50 mm Hg and 50–59 mm Hg (vs. 70–79 mm Hg) were associated with higher hazards of all-cause mortality, and higher sub-hazards of non-cardiovascular/non-malignancy related deaths (Table 4). Diastolic blood pressure 90 mm Hg (vs. 70–79 mm Hg) was associated with higher sub-hazards of cardiovascular mortality but lower risk of non-cardiovascular/non-malignancy related deaths. Figure 2 shows the associations between DBP (as a continuous measure) and all-cause death. Figure 3 shows the associations between DBP (as a continuous measure) and various causes of death.

Sensitivity analyses

Excluding patients with history of malignancy at baseline—In the analysis excluding patients with malignancy (n=34,084), results were qualitatively similar to the primary analysis (Supplemental Tables 3 and 4).

Adjusting for proteinuria—The test for two-way interaction between SBP groups, DBP groups and proteinuria on all-cause mortality was not significant. In the analysis restricting to those who had proteinuria data (n=21,015), inclusion of proteinuria in the multivariable model yielded results similar to the primary analyses (Supplemental Table 5 and 6).

Adjusting for both SBP and DBP group—When we evaluated the associations between SBP group and mortality while adjusting for DBP group, we found results that were mostly similar to our main analysis, except that the lower SBP categories were not associated with non-cardiovascular/non-malignancy related death (Supplemental Table 7). When we evaluated the associations between DBP group and mortality while adjusting for SBP group, we found results that were mostly similar to our primary analysis (Supplemental Table 8).

Interactions with SBP

The test for two-way interaction between SBP groups and history of diabetes, and number of anti-hypertensive medications on overall mortality was not significant. The interaction with age >65 years ($P<0.001$) was significant suggesting the increased mortality risk associated with very low blood pressure was strongest among patients >65 years (Supplemental Table 9). The interaction with history of congestive heart failure ($P<0.01$) was also significant suggesting stronger hazards associated with low blood pressure among those with heart failure compared to those without, and significantly stronger hazard of death associated with higher blood pressure only among those without CHF (data not shown). The interaction between CKD stage and SBP group was significant, and the stratified analysis suggested that the higher mortality hazard associated with lower SBP was stronger among CKD stage 3a, lower in stage 3b, and lowest among those with CKD stage 4 (Supplemental Table 10). In the stratified analysis, higher SBP categories was not significantly associated with increased mortality for any CKD stage.

Interactions with DBP

The two-way interactions between DBP categories, and diabetes, CKD stage, and number of anti-hypertensive medications on overall mortality were not significant. The interaction with age >65 ($P<0.001$) was significant suggesting the increased mortality risk associated with low diastolic blood pressure was stronger among younger than in older patients (Supplemental Table 11).

Discussion

In a large population of patients with non-dialysis dependent CKD followed in a single health system, both lower and higher levels of SBP and DBP were associated with increased all-cause mortality. SBP 150 mm Hg and DBP 90 mm Hg were associated with higher risk of cardiovascular deaths. Lower SBP categories (110–119 mm Hg, 100–109 mm Hg and <100 mm Hg) were associated with increased risks of cardiovascular and non-cardiovascular/non-malignancy-related deaths and lower DBP levels were associated with higher mortality from non-cardiovascular and non-malignancy causes. Also, it is important

to note that among those whose SBP were in the 120–149 mm Hg range and those within the DBP 70–89 mm Hg range, both, overall and cause-specific mortality risk did not differ.

Previously, a U-shaped association of SBP and DBP with all-cause mortality was also noted in a population of U.S. Veterans with CKD(9). This association appeared to be consistent across various categories of eGFR and in those with and without albuminuria(15). A secondary analysis of the Study of Heart and Renal Protection trial noted that the U-shaped associations of blood pressure with mortality was noted only among CKD patients with underlying cardiovascular disease but not in those with pre-existing cardiovascular disease(16). The present study adds important information, in that it provided further insights into the potential reasons for the increased risks for death (both cardiovascular and non-cardiovascular) in those with lower BP. In those with lower SBP, cardiovascular causes contribute to a disproportionate number of deaths (confirmed in the cohort that excluded those with malignancy at baseline). In particular, the prevalence of CHF was higher in those with lower SBP or DBP and CHF contributed a higher share of cardiovascular deaths (5.7% in those with SBP <100 mm Hg vs. 2.3% in those with SBP 130–139 mm Hg; 4.3% in those with DBP <50 mm Hg vs. 2.9% in those with DBP 60–69 mm Hg). Indeed, CHF state limits end-organ perfusion and, hence, may contribute to poorer outcomes in patients with CKD. Recent data from the Chronic Renal Insufficiency Cohort (CRIC) cohort also suggested that higher SBP and DBP measurements were associated with CHF in those with stage 4 CKD; however, no association between higher blood pressure and death was noted in the same cohort(6, 11). In the general population, high risk for CHF with high SBP has also been found(17). In observational studies such as ours, whether the low BP was secondary to underlying heart disease and other comorbid conditions or the consequence of physicians attempting to optimize their antihypertensive medication regimen could not be distinguished suggesting the complex nature. We observed that the mean number of antihypertensive agents used was 1.8 in those with SBP <110 mm Hg vs. 2.1 in those with SBP 150 mm Hg, thus suggesting that the low blood pressure might reflect the comorbidity burden. In contrast, the intensive treatment group in the SPRINT trial received an average 2.8 antihypertensive medications vs. 1.8 medications in the less intensive group.

Similar to the CKD population, U or J-shaped associations between SBP and DBP with all-cause mortality have been reported in other diseases or conditions. For instance, in a study that used registry clinical practice data from 45 countries that included patients with coronary artery disease and hypertension, SBP <120 mm Hg and DBP <70 mm Hg were associated with higher mortality(18). We found that deaths due to non-cardiovascular/non-malignancy causes were also higher with lower DBP and SBP levels. In particular, we noted higher rates of death due to diabetes (7.3% in those with DBP <50 mm Hg vs. 4.4% in those with DBP 70–79 mm Hg) and liver disease (3.0% in the DBP <50 mm Hg vs. 0.8% in those with DBP 70–79 mm Hg). In those with low SBP categories, the proportions of deaths due to chronic lung disease and influenza/pneumonia were higher. Liver disease (cirrhotic state) and chronic lung diseases/sepsis are often associated with hypotension and, hence, observed associations in those with lower SBP and DBP might be explained by the higher comorbidity burden. However, adjustment for these factors did not attenuate these associations. We also acknowledge that due to the nature of analysis (lack of adjudicated events and access to records when patients died), we cannot also state if these patients were

continued on their antihypertensive medications while they had low blood pressure thereby limiting causal interpretations.

While much of the discussion has focused on the mortality associations at the extremes of the BP distribution, highlighting the role of comorbid conditions, equally important insights can be gained from examining the middle range of SBP and DBP. In fact, the risks of both total and cause-specific deaths did not differ among categories of SBP and DBP that are commonly seen in the clinical setting, with no apparent differences in mortality for those with SBP in the 120–149 mm Hg and DBP in the 70–89 mm Hg ranges. Past guideline statements on the BP target to be used in patients with CKD have differed in their recommendations (e.g., SBP of 130 vs. 140 mm Hg);(19) our data and those from others do not suggest benefit of targeting relatively lower BP levels in patients with CKD and argue for dedicated clinical trials in those with CKD (including those with diabetes).

Given the observational nature of this analysis, however, it is difficult to draw conclusions about ideal blood pressure targets in CKD which requires well-designed clinical trials. However, apart from the recently published SPRINT trial showing cardiovascular benefits of lower blood pressure target (including those aged >75 years), studies examining the effects of difference blood pressure targets in CKD are limited(14, 20). In the SPRINT trial, only limited number of patients with eGFR <45 ml/min/1.73 m² were included and, further, patients with diabetes and those with >1g proteinuria (UACR >600 mg/g) were excluded limiting its generalizability(14). Mean age of the SPRINT study population differs from the general and this study CKD population and the observed mortality rate among CKD participants in SPRINT was much lower than our study population(9). In addition, BP was obtained in SPRINT using a standardized protocol while we utilized data collected in a clinical setting(21).

On the other hand, intensive blood pressure control did improve outcomes among patients with type 2 diabetes in the ACCORD trial and in those with stroke, a nadir SBP of 120–128 mm Hg was associated with lower risk of adverse events(18, 22). We did not find effect modification of the observed associations by diabetes. Recently, the American College of Physicians and the American Academy of Family Physicians issued clinical practice guidelines for managing hypertension in older adults (age >60 years). It recommends that clinicians initiate antihypertensive treatment in those with SBP ≥150 mm Hg and achieve a target of <150 mm Hg (strong recommendation based on high-quality evidence) except among those with a history of TIA or stroke wherein a target <140 mm Hg is recommended(23, 24). No specific recommendations for patients with CKD were included. In general, these guidelines were similar to the 2014 evidence based guidelines for the management of high blood pressure in adults(19, 25). In contrary, KDIGO guidelines recommend (irrespective of age) 140/90 mm Hg among those with urine albumin: creatinine ratio of <30 mg/g and 130/80 mm Hg for those with ACR ≥30 mg/g(26). We noted that the mortality risk with lower blood pressure was higher among those aged <65 year. Exact reasons for this finding are unclear but might point towards a particularly high-risk group for adverse outcomes in CKD and are in line with findings from another report(13). It is also important to note that Weiss and colleagues reported SBP <130 and >140 mm Hg being associated with higher risk of death in patients with CKD aged over 70 years(13). Kovesdy

and colleagues noted that the increased risk for adverse outcomes with higher BP was attenuated among older adults with incident CKD(27). Additional studies to address if BP targets should differ across age categories are warranted.

This study has several strengths, but also important limitations. Strengths include a large diverse clinical population of patients with stage 3 and 4 CKD and availability of information not only on all-cause mortality, but also on the reported causes of these deaths. However, as stated before, causality cannot be established due to the observational study design where the blood pressure reflects care that they received and other health-related behavior rather than being determined through randomization to a specific blood pressure treatment target. Further, blood pressure was measured in diverse clinical settings unlike clinical trials wherein standard protocols are followed. However, the study population reflects a broadly generalizable population and many patients may not have qualified for inclusion in, or may not have chosen to be part of, a clinical trial such as SPRINT. Even though the majority of the study population had primary care physicians and obtained the majority of their care within the Cleveland Clinic health care system, we cannot account for care that may have occurred outside of the Cleveland Clinic system. We also lacked data on detailed longitudinal medication use to measure adherence or treatment modifications to investigate any differences across medication subgroups or from medication changes over time. We also acknowledge that in observational studies, blood pressure achieved during the follow-up and the various interventions performed could confound the associations between baseline BP and outcomes.

In summary, while confirming the existence of U-shaped associations of SBP and DBP with all-cause mortality, our study suggests potential reasons for these excess risks in those in the tails of the BP distribution. Lower SBP and DBP levels were associated with higher cardiovascular deaths in patients with CKD. Further, diseases and conditions other than cardiovascular or cancer (e.g., diabetes and liver disease) seemed to provide plausible explanations for the higher mortality noted in those with lower BP. At the same time, all-cause and cause-specific mortality did not seem to differ across usual ranges of SBP (120–149 mm Hg) and DBP (70–89 mm Hg) in patients with CKD.

Methods

Patient population

We used the electronic health records (EHR)-based CKD registry previously established at the Cleveland Clinic to address the study objectives; its development and validation have been described in detail elsewhere(28). We included patients who had: a) at least one face-to-face outpatient encounter with a Cleveland Clinic health care provider and at least two estimated glomerular filtration rate (eGFR) measures <60 ml/min/1.73 m², more than 90 days apart, between January 1, 2005 and December 31, 2013 (the second eGFR was 15–59.9 ml/min/1.73 m² and patients were not on dialysis or had a functioning kidney transplant), b) blood pressure measurements recorded and had an active anti-hypertensive medication prescription on the date of second eGFR <60 ml/min/1.73 m²; and c) who were residents of the State of Ohio.

Patient Characteristics

Demographic details (age, sex, race, insurance details) were extracted from the EHR. Comorbid conditions such as diabetes mellitus, hypertension, coronary artery disease, malignancy, congestive heart failure, and hyperlipidemia were defined using prespecified and previously validated criteria(28). These conditions existed prior to the second eGFR <60 ml/min/1.73 m². We also extracted relevant laboratory data (serum albumin, hemoglobin, and bicarbonate, proteinuria details) from the EHR.

Kidney function

All serum creatinine measurements were performed in the same clinical laboratory using a Hitachi D 2400 Modular Chemistry Analyzer (Roche Diagnostics, Indianapolis, IN). We calculated eGFR using the CKD-EPI equation(29). CKD was classified into the following stages: stage 3 CKD (eGFR 30–59 ml/min/1.73 m²) and stage 4 CKD (eGFR 15–29 ml/min/1.73 m²). We further categorized stage 3 into CKD stage 3a (eGFR 45–59 ml/min/1.73 m²) and stage 3b (eGFR 30–44 ml/min/1.73 m²). Details relating to assessment of proteinuria for this study population have been described previously(30, 31).

Blood pressure

We used the blood pressure measurement obtained closest to the date to the second eGFR <60 ml/min/1.73 m² (baseline blood pressure) for the primary analysis. When multiple measurements were taken in the same day, we took the average of all measures obtained in the same day. Only outpatient blood pressure data were included in this analysis. Measurements obtained from the emergency room and urgent care settings were excluded. Blood pressure (in mm Hg) was categorized as follows: <100; 100–109 110–119; 120–129; 130–139; 140–149; 150–159, 160 for SBP and <50; 50–59; 60–69; 70–79; 80–89; 90 for DBP.

Ascertainment of death and its causes

We ascertained dates and reported causes of death from the EHR as well as through linkage of the CKD registry with Ohio Department of Health death records. The underlying cause of death was coded according to the *International Classification of Diseases*, Tenth Revision (ICD-10). We grouped the underlying causes of death according to the National Center for Health Statistics for each coding system, except as defined here(30, 31). We classified deaths into three categories: a) deaths from cardiovascular causes, b) deaths from malignancy, and c) deaths from other (non-cardiovascular and non-malignancy-related) causes. We defined cardiovascular deaths as deaths reportedly due to diseases of the heart, essential hypertension, cerebrovascular disease, atherosclerosis, or other diseases of the circulatory system (ICD-10 codes I00–I78). We also categorized the cardiovascular deaths into the following clinically meaningful subcategories: ischemic heart disease (I20–I25), heart failure (I50), cerebrovascular diseases (I60s) and all other cardiovascular disease (include all others from I00 to I-78 except I20–I25, I50 and I60). Patients with death noted in the EHR but not found in Ohio death files were included in the analysis of all-cause mortality and excluded from the cause-specific analysis.

Statistical analysis

We compared baseline characteristics among patients in defined categories of SBP and DBP using Chi-square and ANOVA tests for categorical and continuous variables, respectively. We summarized the leading causes of death for various SBP and DBP categories as percent of total deaths observed. We evaluated the relationship between the SBP categories and overall mortality using a Cox proportional hazards model and the relationship between SBP categories and cause specific death categories using competing risks regression models. Similar models were fitted using DBP categories. We inspected log-log plots for violations of the proportional hazards assumption. We adjusted the models for the following covariates: age, sex, race, diabetes, hyperlipidemia, BMI category, albumin, hemoglobin, serum bicarbonate, malignancy, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, insurance group, ACE/ARB use, beta blocker use, diuretics, calcium channel blockers, number of antihypertensive agents, smoking, and CKD stage. We also evaluated the association between continuous SBP and DBP and overall mortality, and each cause-specific mortality category using splines at the 10th, 50th and 90th percentile of blood pressure. For all-cause mortality, we plotted continuous SBP vs. hazard ratio, and also DBP vs. hazard ratio using data from the first imputation. For each cause-specific mortality, we plotted continuous blood pressure vs. the predicted probability of death at 4 years of follow up using data from the first imputation. The plot estimates were obtained for a hypothetical patient with mean values on all baseline covariates. We evaluated two-way interactions on all-cause mortality between blood pressure group and each of the following: age ≥ 65, diabetes, congestive heart failure, proteinuria, number of anti-hypertensive medications (>2 vs. 1 or 2), and CKD stage. Approximately 15% of patients were missing serum albumin, 18% were missing hemoglobin data, 3% were missing BMI, 7% were missing smoking status, and 3% did not have insurance. We used multiple imputations (SAS proc MI) with the Markov Chain Monte Carlo method and a single chain to impute 5 datasets with complete continuous and binary data in a first step, and then in a second step we imputed insurance group on each of the 5 datasets using discriminant function analysis(32). All models were performed on each of the 5 imputed datasets, and parameter estimates were combined using SAS MIanalyze.

We conducted three additional sensitivity analyses to confirm the primary findings while excluding patients with malignancy at the time of CKD diagnosis and while including only those who had proteinuria details. We also conducted additional analysis by including SBP and DBP in the multivariable models. All analyses were conducted using Linux SAS version 9.4 (SAS Institute, Cary, NC), and graphs were created using R 3.3.2 (The R Foundation for Statistical Computing, Vienna, Austria) and rms and cmprsk packages. This study and the CKD registry were both approved by the Cleveland Clinic Institutional Review Board.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012; 380:2224–2260. [PubMed: 23245609]
2. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016; 387:957–967. [PubMed: 26724178]
3. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. *Lancet*. 2016; 387:435–443. [PubMed: 26559744]
4. Olsen MH, Angell SY, Asma S, et al. A call to action and a lifecourse strategy to address the global burden of raised blood pressure on current and future generations: the Lancet Commission on hypertension. *Lancet*. 2016; 388:2665–2712. [PubMed: 27671667]
5. Anderson AH, Yang W, Townsend RR, et al. Time-updated systolic blood pressure and the progression of chronic kidney disease: a cohort study. *Ann Intern Med*. 2015; 162:258–265. [PubMed: 25686166]
6. Bansal N, McCulloch CE, Lin F, et al. Different components of blood pressure are associated with increased risk of atherosclerotic cardiovascular disease versus heart failure in advanced chronic kidney disease. *Kidney Int*. 2016; 90:1348–1356. [PubMed: 27717485]
7. Kovesdy CP, Lu JL, Molnar MZ, et al. Observational modeling of strict vs conventional blood pressure control in patients with chronic kidney disease. *JAMA Intern Med*. 2014; 174:1442–1449. [PubMed: 25089540]
8. Peralta CA, Norris KC, Li S, et al. Blood pressure components and end-stage renal disease in persons with chronic kidney disease: the Kidney Early Evaluation Program (KEEP). *Arch Intern Med*. 2012; 172:41–47. [PubMed: 22232147]
9. Kovesdy CP, Bleyer AJ, Molnar MZ, et al. Blood pressure and mortality in U.S. veterans with chronic kidney disease: a cohort study. *Ann Intern Med*. 2013; 159:233–242. [PubMed: 24026256]
10. Agarwal R. Blood pressure components and the risk for end-stage renal disease and death in chronic kidney disease. *Clin J Am Soc Nephrol*. 2009; 4:830–837. [PubMed: 19339424]
11. Bansal N, McCulloch CE, Rahman M, et al. Blood pressure and risk of all-cause mortality in advanced chronic kidney disease and hemodialysis: the chronic renal insufficiency cohort study. *Hypertension*. 2015; 65:93–100. [PubMed: 25287404]
12. Chiang HP, Lee JJ, Chiu YW, et al. Systolic blood pressure and outcomes in stage 3–4 chronic kidney disease patients: evidence from a Taiwanese cohort. *Am J Hypertens*. 2014; 27:1396–1407. [PubMed: 24727359]
13. Weiss JW, Peters D, Yang X, et al. Systolic BP and Mortality in Older Adults with CKD. *Clin J Am Soc Nephrol*. 2015; 10:1553–1559. [PubMed: 26276142]
14. Wright JT Jr, Williamson JD, et al. SPRINT Research Group. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med*. 2015; 373:2103–2116. [PubMed: 26551272]
15. Weiss JW, Johnson ES, Petrik A, et al. Systolic blood pressure and mortality among older community-dwelling adults with CKD. *Am J Kidney Dis*. 2010; 56:1062–1071. [PubMed: 20961677]
16. Herrington W, Staplin N, Judge PK, et al. Evidence for Reverse Causality in the Association Between Blood Pressure and Cardiovascular Risk in Patients With Chronic Kidney Disease. *Hypertension*. 2017; 69:314–322. [PubMed: 28028192]
17. Haider AW, Larson MG, Franklin SS, et al. Systolic blood pressure, diastolic blood pressure, and pulse pressure as predictors of risk for congestive heart failure in the Framingham Heart Study. *Ann Intern Med*. 2003; 138:10–16. [PubMed: 12513039]
18. Vidal-Petiot E, Ford I, Greenlaw N, et al. Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study. *Lancet*. 2016; 388:2142–2152. [PubMed: 27590221]

19. Reisin E, Harris RC, Rahman M. Commentary on the 2014 BP guidelines from the panel appointed to the Eighth Joint National Committee (JNC 8). *J Am Soc Nephrol*. 2014; 25:2419–2424. [PubMed: 25114277]
20. Williamson JD, Supiano MA, Applegate WB, et al. Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged ≥ 75 Years: A Randomized Clinical Trial. *JAMA*. 2016; 315:2673–2682. [PubMed: 27195814]
21. Agarwal R. Implications of Blood Pressure Measurement Technique for Implementation of Systolic Blood Pressure Intervention Trial (SPRINT). *J Am Heart Assoc*. 2017; 6doi: 10.1161/JAHA.116.004536
22. Cushman WC, Evans GW, et al. ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010; 362:1575–1585. [PubMed: 20228401]
23. Qaseem A, Barry MJ, Humphrey LL, et al. Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline Update From the American College of Physicians. *Ann Intern Med*. 2017
24. Weiss J, Freeman M, Low A, et al. Benefits and Harms of Intensive Blood Pressure Treatment in Adults Aged 60 Years or Older: A Systematic Review and Meta-analysis. *Ann Intern Med*. 2017
25. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014; 311:507–520. [PubMed: 24352797]
26. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. *Kidney Int Suppl*. 2012; 2:337–414.
27. Kovesdy CP, Alrifai A, Gosmanova EO, et al. Age and Outcomes Associated with BP in Patients with Incident CKD. *Clin J Am Soc Nephrol*. 2016; 11:821–831. [PubMed: 27103623]
28. Navaneethan SD, Jolly SE, Schold JD, et al. Development and validation of an electronic health record-based chronic kidney disease registry. *Clin J Am Soc Nephrol*. 2011; 6:40–49. [PubMed: 21051745]
29. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009; 150:604–612. [PubMed: 19414839]
30. Navaneethan SD, Schold JD, Arrigain S, et al. Cause-Specific Deaths in Non-Dialysis-Dependent CKD. *J Am Soc Nephrol*. 2015; 26:2512–2520. [PubMed: 26045089]
31. Navaneethan SD, Schold JD, Arrigain S, et al. Body mass index and causes of death in chronic kidney disease. *Kidney Int*. 2016; 89:675–682. [PubMed: 26880461]
32. Montez-Rath ME, Winkelmayer WC, Desai M. Addressing missing data in clinical studies of kidney diseases. *Clin J Am Soc Nephrol*. 2014; 9:1328–1335. [PubMed: 24509298]

Figure 1.
Associations (adjusted) between systolic blood pressure and all-cause death in CKD

Figure 2.

Associations (adjusted) between systolic and diastolic blood pressure, and various causes of death in CKD.

Figure 3.
Associations (adjusted) between diastolic blood pressure and all-cause death in CKD

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Patient characteristics based on baseline systolic blood pressure categories (in mm Hg)

Table 1

Factor	Overall (N=45,412)	<100 (N=1,623)	100-109 (N=3,319)	110-119 (N=6,642)	120-129 (N=10,075)	130-139 (N=9,349)	140-149 (N=6,753)	150-159 (N=3,628)	160 (N=4,023)	p-value
Age (years, Mean ± SD	72.6±11.4	69.9±12.5	71.1±12.1	71.8±11.9	72.5±11.1	73.0±11.0	73.4±11.0	73.5±11.1	73.4±11.5	<0.001 ^a
Male, %	45.7	57.9	51.5	48.9	45.9	44.2	43.8	42.7	40.8	<0.001 ^c
African American,%	13.8	13.4	12.0	12.6	11.5	13.1	14.2	17.8	19.4	<0.001 ^c
Smoking, %										<0.001 ^c
No	85.8	81.3	85.7	87.0	87.2	86.4	84.9	84.5	84.1	
Yes	7.3	10.5	8.3	7.2	6.7	6.6	7.5	7.4	7.8	
Missing	6.9	8.1	6.0	5.8	6.1	7.0	7.6	8.1	8.1	
BMI, Mean ± SD	29.9±6.6	28.3±6.3	29.0±6.5	29.6±6.6	29.9±6.4	30.3±6.7	30.2±6.7	30.1±6.6	30.1±6.8	<0.001 ^a
BMI group,%										<0.001 ^c
<18.5 kg/m ²	1.2	2.7	1.8	1.2	0.99	0.99	1.3	0.83	0.97	
18.5-24.9 kg/m ²	20.7	27.2	26.3	21.6	19.8	18.7	19.3	21.0	21.1	
25-29.9 kg/m ²	34.3	34.3	34.3	35.5	35.7	33.8	33.6	33.1	32.7	
30-34.9 kg/m ²	22.7	20.1	20.0	21.7	23.3	24.4	22.7	22.5	22.4	
35-39.9 kg/m ²	10.7	8.1	9.0	10.3	10.6	11.0	11.7	11.5	11.4	
>40 kg/m ²	7.5	4.6	6.1	7.2	7.0	8.2	8.2	8.2	8.3	
Missing	2.8	3.1	2.5	2.6	2.5	2.8	3.1	2.7	3.1	
Diabetes,%	29.3	28.7	27.3	28.4	29.5	29.7	29.4	29.1	30.1	0.028 ^c
Malignancy,%	24.9	27.7	25.5	25.6	24.3	23.9	25.5	26.8	25.3	0.008 ^c
Hypertension,%	94.2	79.7	86.1	90.4	93.9	96.8	97.7	98.2	98.2	<0.001 ^c
Hyperlipidemia,%	83.4	82.7	81.2	84.3	84.8	84.1	83.0	81.3	81.1	<0.001 ^c
Coronary artery disease,%	26.2	39.1	33.1	29.4	26.8	23.7	23.4	22.4	22.1	<0.001 ^c
Congestive heart failure,%	10.1	32.1	18.9	12.7	8.8	7.2	7.1	7.0	7.0	<0.001 ^c
Cerebrovascular disease,%	11.1	13.1	11.5	11.3	11.1	10.4	11.0	10.6	11.5	0.067 ^c
ACEI/ARB use,%	79.5	82.6	79.1	79.6	78.5	78.2	79.2	80.5	82.0	<0.001 ^c
Diuretic use,%	77.0	83.1	76.8	75.6	76.1	76.5	76.8	77.4	79.1	<0.001 ^c
Statin use,%	66.2	70.4	67.3	68.8	67.2	65.9	64.6	62.9	63.1	<0.001 ^c
Beta Blocker use,%	69.3	80.5	74.7	70.2	67.6	67.0	66.7	68.5	71.1	<0.001 ^c
Calcium Channel Blocker,%	46.3	32.5	36.1	40.5	43.4	47.5	51.7	54.8	57.9	<0.001 ^c

Factor	Overall (N=45,412)	<100 (N=1,623)	100–109 (N=3,319)	110–119 (N=6,642)	120–129 (N=10,075)	130–139 (N=9,349)	140–149 (N=6,753)	150–159 (N=3,628)	160 (N=4,023)	p-value
Number of anti-hypertensive medications	1.9±0.89	1.8±0.79	1.8±0.82	1.8±0.84	1.8±0.85	1.8±0.88	1.9±0.91	2.0±0.94	2.1±1.00	<0.001 ^a
eGFR, Mean ± SD	47.5±10.3	44.9±11.2	46.7±10.8	47.6±10.1	48.3±9.9	48.0±10.1	47.5±10.2	46.8±10.6	46.3±10.9	<0.001 ^a
CKD stages, %										<0.001 ^c
Stage 3a (45–59	66.6	56.1	63.5	67.1	69.9	68.5	67.2	64.1	62.7	<i>TBD</i>
Stage 3b (30–44	25.3	32.0	26.8	25.5	23.4	24.2	25.0	26.6	27.1	
Stage 4 (15–29	8.1	11.9	9.7	7.4	6.6	7.3	7.7	9.3	10.3	
Albumin g/dL, Mean ± SD	4.1±0.43	4.0±0.56	4.1±0.48	4.1±0.42	4.1±0.41	4.1±0.41	4.1±0.42	4.1±0.42	4.1±0.44	<0.001 ^a
Hemoglobin mg/dL, Mean ± SD	12.8±1.8	12.3±2.0	12.6±1.9	12.8±1.8	12.9±1.8	12.8±1.7	12.8±1.7	12.7±1.7	12.7±1.7	<0.001 ^a
Proteinuria, %	27.2	25.4	23.5	22.5	22.1	26.1	29.2	35.5	39.6	<0.001 ^c
Insurance category, %										<0.001 ^c
Medicaid	0.31	0.49	0.30	0.38	0.22	0.26	0.22	0.55	0.50	
Medicare	80.5	75.4	76.8	78.5	80.8	81.8	82.5	81.7	81.3	
Missing	3.3	5.2	3.4	3.1	2.9	3.2	2.9	3.3	3.7	
Other	15.9	19.0	19.5	18.1	16.1	14.7	14.4	14.5	14.5	
Systolic Blood Pressure, Mean ± SD	131.2±20.0	91.8±6.4	104.0±3.0	114.0±3.2	123.6±3.0	133.4±3.1	143.0±3.0	153.2±3.0	163.2±13.7	<0.001 ^a
Diastolic Blood Pressure, Mean ±SD	72.6±11.3	57.5±7.8	63.4±8.0	67.6±8.4	71.3±8.9	73.8±9.5	76.0±10.2	78.4±10.9	81.3±12.4	<0.001 ^a

p-values: a=ANOVA, c=Pearson's chi-square test.

Missing data BMI 1273, albumin 6962, hemoglobin 8313, proteinuria 24397

Patient characteristics based on baseline diastolic blood pressure categories (in mm Hg)

Factor	Overall (N=45,412)	<50 (N=479)	50–59 (N=3,715)	60–69 (N=12,597)	70–79 (N=14,992)	80–89 (N=10,389)	90 (N=3,240)	p-value
Age (years), Mean ± SD	72.6±11.4	75.4±11.2	75.8±10.4	74.7±10.5	72.7±10.9	70.7±11.5	66.1±13.8	<0.001 ^a
Male gender, %	45.7	48.6	49.2	45.9	44.6	44.6	48.9	<0.001 ^c
African American, %	13.8	8.8	11.9	11.9	13.0	14.8	25.0	<0.001 ^c
Smoking, %								<0.001 ^c
No	85.8	85.6	85.7	86.6	86.4	85.2	81.9	
Yes	7.3	6.1	7.2	6.6	7.0	7.8	10.4	
Missing	6.9	8.4	7.1	6.8	6.6	7.0	7.7	
BMI, Mean ± SD	29.9±6.6	28.8±7.2	28.7±6.4	29.3±6.5	30.0±6.5	30.6±6.7	31.1±7.1	<0.001 ^a
BMI group, %								<0.001 ^c
<18.5 kg/m ²	1.2	1.9	1.7	1.5	0.93	0.90	1.1	
18.5–24.9 kg/m ²	20.7	28.8	27.3	23.2	19.9	17.4	16.7	
25–29.9 kg/m ²	34.3	32.6	34.9	35.3	34.9	33.3	30.6	
30–34.9 kg/m ²	22.7	19.2	18.5	21.3	23.2	24.5	25.6	
35–39.9 kg/m ²	10.7	7.9	8.3	9.2	11.1	12.3	13.1	
>40 kg/m ²	7.5	6.1	5.8	6.6	7.4	8.6	10.7	
Missing	2.8	3.5	3.4	2.9	2.6	3.0	2.1	
Diabetes, %	29.3	34.7	33.5	32.3	29.0	25.8	24.6	<0.001 ^c
Malignancy, %	24.9	31.9	29.4	26.5	24.8	22.2	21.9	<0.001 ^c
Hypertension, %	94.2	84.3	88.0	92.1	94.8	97.2	98.2	<0.001 ^c
Hypertlipidemia, %	83.3	80.2	83.4	84.6	84.0	82.7	78.0	<0.001 ^c
Coronary artery disease, %	26.2	38.8	39.1	31.0	25.1	19.9	15.3	<0.001 ^c
Congestive heart failure, %	10.1	25.9	19.5	12.4	8.2	6.7	7.5	<0.001 ^c
Cerebrovascular disease, %	11.1	15.2	14.7	12.4	11.0	9.2	8.4	<0.001 ^c
ACEI/ARB use, %	79.5	84.6	82.6	80.3	78.6	77.9	81.1	<0.001 ^c
Diuretic use, %	77.0	87.3	82.1	78.0	75.8	75.6	76.3	<0.001 ^c
Statin use, %	66.2	69.5	71.8	70.5	66.1	62.1	56.7	<0.001 ^c
Beta Blocker use, %	69.3	79.5	76.9	71.4	67.9	66.0	67.7	<0.001 ^c

Factor	Overall (N=45,412)	<50 (N=479)	50-59 (N=3,715)	60-69 (N=12,597)	70-79 (N=14,992)	80-89 (N=10,389)	90 (N=3,240)	p-value
Calcium Channel Blocker, %	46.3	42.0	46.3	45.4	45.8	46.6	52.1	<0.001 ^c
Number of anti-hypertensive medications	1.9±0.89	2.0±0.97	2.0±0.90	1.9±0.87	1.8±0.87	1.8±0.88	1.9±0.96	<0.001 ^a
eGFR, Mean ± SD	47.5±10.3	42.8±11.9	45.3±11.0	46.9±10.5	48.1±10.0	48.4±9.9	47.1±11.0	<0.001 ^a
CKD stages, %								<0.001 ^c
Stage 3a (45-59)	66.6	49.7	57.6	63.8	69.3	70.4	66.5	
Stage 3b (30-44)	25.3	32.8	30.9	27.6	23.7	23.0	23.4	
Stage 4 (15-29)	8.1	17.5	11.5	8.7	7.0	6.6	10.1	
Albumin g/dL, Mean ± SD	4.1±0.43	3.9±0.58	4.0±0.46	4.1±0.44	4.1±0.41	4.2±0.40	4.1±0.49	<0.001 ^a
Hemoglobin mg/dL, Mean ± SD	12.8±1.8	11.5±2.0	12.0±1.8	12.5±1.7	12.9±1.7	13.2±1.7	13.2±1.9	<0.001 ^a
Serum Bicarbonate mmol/L, Mean ± SD	25.8±3.2	25.5±3.9	25.7±3.5	25.8±3.3	25.9±3.2	25.9±3.1	25.6±3.3	<0.001 ^a
Proteinuria, %	27.2	27.6	25.6	25.2	25.2	28.1	42.5	<0.001 ^c
Insurance category, %								<0.001 ^c
Medicaid	0.31	0.42	0.38	0.17	0.27	0.36	0.80	
Medicare	80.5	83.5	85.7	84.6	81.1	76.8	67.4	
Missing	3.3	3.5	3.0	2.8	3.1	3.3	5.7	
Other	15.9	12.5	10.9	12.4	15.5	19.5	26.1	
Systolic Blood Pressure, Mean ± SD	131.2±20.0	105.4±19.5	115.3±17.8	123.9±16.9	131.4±16.6	138.8±17.2	156.0±21.5	<0.001 ^a
Diastolic Blood Pressure, Mean ± SD	72.6±11.3	44.9±3.5	55.2±3.0	63.7±3.1	73.4±3.1	82.5±2.8	95.6±7.1	<0.001 ^a

p-values: a=ANOVA, c=Pearson's chi-square test.

Missing data BMI 1273, albumin 6962, hemoglobin 8313, proteinuria 24397

Table 3

Associations of systolic blood pressure with all-cause and cause-specific mortality

Systolic Blood Pressure (mm Hg)	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
<u>All-cause death</u>		
<100	2.19 (2.02, 2.38)	1.55 (1.42, 1.68)
100–109	1.50 (1.40, 1.61)	1.24 (1.15, 1.33)
110–119	1.17 (1.10, 1.24)	1.13 (1.07, 1.21)
120–129	1.00 (0.95, 1.06)	1.00 (0.95, 1.05)
130–139	Ref	Ref
140–149	1.05 (0.99, 1.11)	1.0 (0.95, 1.06)
150–159	1.17 (1.09, 1.26)	1.08 (1.01, 1.16)
160	1.20 (1.13, 1.29)	1.09 (1.01, 1.16)
	Unadjusted SHR (95% CI)	Adjusted** SHR (95% CI)
<u>Cardiovascular death[^]</u>		
<100	2.42 (2.12, 2.77)	1.68 (1.46, 1.94)
100–109	1.67 (1.49, 1.87)	1.33 (1.18, 1.50)
110–119	1.27 (1.15, 1.40)	1.19 (1.08, 1.32)
120–129	1.05 (0.96, 1.15)	1.0 (0.91, 1.10)
130–139	Ref	Ref
140–149	1.08 (0.98, 1.19)	1.06 (0.96, 1.18)
150–159	1.20 (1.06, 1.35)	1.14 (1.01, 1.29)
160	1.43 (1.28, 1.59)	1.30 (1.16, 1.46)
<u>Malignancy death[^]</u>		
<100	1.53 (1.29, 1.81)	1.22 (1.02, 1.47)
100–109	1.12 (0.97, 1.30)	1.0 (0.86, 1.16)
110–119	0.96 (0.85, 1.09)	0.90 (0.80, 1.02)
120–129	0.94 (0.84, 1.04)	0.94 (0.85, 1.05)
130–139	Ref	Ref
140–149	1.03 (0.91, 1.15)	0.97 (0.86, 1.09)
150–159	1.27 (1.12, 1.45)	1.14 (1.00, 1.31)
160	0.91 (0.79, 1.05)	0.88 (0.76, 1.01)
<u>Non-cardiovascular non- malignancy death[^]</u>		
<100	1.57 (1.36, 1.82)	1.22 (1.05, 1.43)
100–109	1.32 (1.17, 1.49)	1.16 (1.03, 1.31)
110–119	1.11 (1.004, 1.22)	1.09 (0.99, 1.20)
120–129	0.98 (0.89, 1.07)	0.98 (0.89, 1.07)
130–139	Ref	Ref
140–149	1.03 (0.93, 1.13)	1.0 (0.90, 1.10)
150–159	1.02 (0.90, 1.15)	0.95 (0.84, 1.07)
160	1.16 (1.04, 1.30)	1.04 (0.93, 1.16)

* adjusted for age, sex, race, diabetes, hyperlipidemia, body mass index, albumin, hemoglobin, serum bicarbonate, malignancy, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, insurance type, ACE/ARB, beta blocker use, diuretics, calcium channel blockers, number of anti-hypertensive medications, smoking, CKD stage

Hazard and sub-hazard ratios presented in adjusted models were pooled using MIanalyze from 5 multiply imputed datasets;

[^] N = 45,234 due to some missing cause of death

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Table 4

Associations of diastolic blood pressure with all-cause and cause-specific mortality

Diastolic Blood Pressure (mm Hg)	Unadjusted HR (95% CI)	Adjusted* HR (95%CI)
All-cause death		
<50	2.5 (2.2, 2.9)	1.29 (1.12, 1.48)
50–59	1.8 (1.7, 1.9)	1.18 (1.11, 1.25)
60–69	1.3 (1.2, 1.3)	1.03 (0.98, 1.07)
70–79	Ref	Ref
80–89	0.84 (0.80, 0.88)	0.96 (0.91, 1.01)
90	0.84 (0.78, 0.91)	0.99 (0.92, 1.07)
	Unadjusted SHR (95% CI)	Adjusted* SHR (95% CI)
Cardiovascular death [^]		
<50	2.15 (1.73, 2.69)	1.08 (0.85, 1.38)
50–59	1.69 (1.53, 1.87)	1.06 (0.95, 1.18)
60–69	1.31 (1.22, 1.40)	1.03 (0.95, 1.11)
70–79	Ref	Ref
80–89	0.88 (0.81, 0.95)	1.01 (0.93, 1.10)
90	0.98 (0.86, 1.11)	1.27 (1.12, 1.44)
Malignancy death [^]		
<50	1.52 (1.13, 2.04)	1.03 (0.75, 1.40)
50–59	1.42 (1.26, 1.60)	1.12 (0.99, 1.27)
60–69	1.17 (1.07, 1.27)	1.05 (0.96, 1.15)
70–79	Ref	Ref
80–89	0.87 (0.79, 0.96)	1.00 (0.91, 1.11)
90	0.80 (0.69, 0.94)	0.92 (0.78, 1.07)
Non-cardiovascular non- malignancy death [^]		
<50	2.26 (1.82, 2.80)	1.31 (1.04, 1.65)
50–59	1.67 (1.52, 1.85)	1.17 (1.05, 1.29)
60–69	1.22 (1.13, 1.31)	1.00 (0.93, 1.08)
70–79	Ref	Ref
80–89	0.83 (0.76, 0.90)	0.92 (0.84, 0.998)
90	0.74 (0.65, 0.85)	0.81 (0.71, 0.94)

* adjusted for age, sex, race, diabetes, hyperlipidemia, body mass index, albumin, hemoglobin, serum bicarbonate, malignancy, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, insurance type, ACE/ARB, beta blocker use, diuretics, calcium channel blockers, number of anti-hypertensive medications, smoking, CKD stage

Hazard and sub-hazard ratios presented in adjusted models were pooled using MIanalyze from 5 multiply imputed datasets;

[^] N = 45,234 due to some missing cause of death