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Systolic Blood Pressure and Mortality Among Older, Community-Dwelling Adults With CKD

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Abstract

Background—Chronic kidney disease (CKD) is an increasingly common condition, especially among older adults. CKD manifests differently in older versus younger patients, with a risk of death that far outweighs the risk of CKD progressing to the point that dialysis is required. Current CKD guidelines recommend a blood pressure target of <130/80 mmHg for all CKD patients, but it is unknown how lower versus higher baseline blood pressures may affect older adults with CKD.

Study Design—Retrospective cohort study

Setting and Participants—Older patients (age 75+ years) with CKD (eGFR <60 ml/min/1.73 m^2) in a community-based health maintenance organization.

Predictor—Baseline systolic blood pressure (SBP) <130, 130-160 (reference group), and >160 mm Hg.

Outcomes—Subjects followed for 5 years to examine rates of mortality (primary outcome) and cardiovascular disease hospitalizations (secondary outcome).

Results—At baseline, 3099 subjects (38.5%) had SBP <130 mm Hg, 3772 (46.9%) had SBP 131-160 mm Hg, and 1171 (14.6%) had SBP >160 mm Hg. A total of 3734 (46.4%) died and 2881 (35.8%) were hospitalized. Adjusted hazard ratios (HR) and 95% confidence intervals (CI) for mortality in SBP <130 and >160 mm Hg group were 1.22 (1.11-1.34) and 0.99 (0.89-1.10), respectively. Adjusted HR (CI) for cardiovascular hospitalization in these groups were 1.10 (1.09-1.45) and 1.26 (1.09-1.45), respectively.

Limitations—While causality should not be implied from this retrospective analysis, the results from this study can generate hypotheses for future randomized controlled trials to investigate the relationship between blood pressure and outcomes in older CKD patients.

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Conclusions—Our study suggests that lower baseline SBP (≤130 mmHg) may predict poorer outcomes in terms of both mortality and cardiovascular hospitalizations among older adults with CKD. Conversely, higher baseline SBP (>160 mmHg) may predict increased risk of cardiovascular hospitalizations but does not predict mortality. Clinical trials are required to test this hypothesis.

Keywords

aging; elderly; chronic kidney disease; blood pressure

Chronic kidney disease (CKD) is a significant medical problem affecting 16% of the US population. CKD is especially common among older adults; 37% of individuals over age 65 and 50% over age 85 are estimated to have CKD.[1,2] Older adults manifest CKD differently, with high rates of mortality and hospitalization that outweigh their rate of progressing to require dialysis or transplant.[2-4] Current CKD guidelines are age-neutral and are thus limited in their ability to account for possible age-related differences among CKD patients.[5]

Blood pressure control is known to slow CKD progression and is a cornerstone of CKD management.5 Current CKD guidelines recommend a blood pressure target of <130/80 mmHg for all patients.5 The trials upon which these recommendations are based, however, did not uniformly lower blood pressure to <130/80 mmHg and included predominantly patients 70 years old and younger.[6-8] Recent research in elderly patients without CKD has demonstrated that hypertension control reduces stroke and mortality even among the oldest old; these studies lowered systolic blood pressure to 140-150 mmHg on average (well above those levels recommended for CKD patients).[9-11] The potential benefits or harms of lowering blood pressure to <130mmHg systolic in older CKD patients remain unclear.

We performed a retrospective cohort analysis on community-dwelling older adults with CKD to examine the relationship between systolic blood pressure (SBP) and important outcomes in this population. The specific SBP thresholds examined are modeled upon current CKD guidelines and SBP targets identified as relevant for older adults without CKD, in order to examine how current hypertension management standards may affect older CKD patients. We hypothesized that older CKD patients might experience increased harm, in the form of increased mortality and hospitalizations, in association with lower baseline SBP values.

Methods

Sources of Data

We conducted a retrospective cohort study of older adults with stage 3-5 CKD, analyzed by SBP, to examine long term outcomes for this population including mortality. Patients in this cohort were identified from within the Kaiser Permanente Northwest health maintenance organization, which provides care for 450,000 individuals in the Portland, Oregon and Vancouver, Washington area. The demographic characteristics of these individuals mirror those of the surrounding community.[12] Kaiser Permanente Northwest has had an electronic medical record in place as the sole medical record system since 1997. This study was reviewed and approved by the Kaiser Permanente Northwest and Oregon Health and Science University institutional review boards.

Cohort definition

Patients age 75 or older with stages 3-5 CKD who were enrolled in Kaiser Permanente Northwest from January 1, 1999 to Dec 31, 2003 were eligible for inclusion. CKD was defined as two estimated glomerular filtration rate (eGFR) values <60 ml/min/1.73m^2

measured at least three, and fewer than 24, months apart (without intervening eGFR values of >60 ml/min/1.73m^2). The index date was the date of the second eGFR of <60 ml/min/1.73m^2. Patients were required to have one year of enrollment and one year of prescription benefits in the health plan prior to the index date. Patients were also required to have at least one outpatient blood pressure measurement in the year prior to index date; the SBP value closest and prior to the index date served as the baseline systolic blood pressure for that patient. Patients with a prior history of renal replacement therapy were excluded. (See Figure 1)

SBP cohorts were assigned based on the baseline SBP value. Blood pressure in the outpatient setting at Kaiser Permanente Northwest is measured per routine clinic protocol. The SBP cohorts were: 1) SBP ≤ 130 mmHg, 2) SBP 131-160 mmHg, or 3) SBP >160 mmHg. Additional outpatient SBP readings during the 5 year follow-up period were not required for inclusion, but if available, follow-up SBP values were averaged by year for each patient.

Patient data were reviewed for up to three years prior to the index date to evaluate baseline characteristics. The majority of these characteristics were identified via ambulatory ICD-9 diagnostic codes. The sources of comorbid illness history and other co-variables are listed in Table 1. Height, weight, and blood pressure were obtained from the outpatient. Age, gender, time at-risk, and death information were obtained from the enrollment database.[13]

Outcome variables

Patients were followed for 5 years after their index date for death and hospitalizations. Death was the primary outcome; confirmation of death was obtained from the enrollment database. An internal review found this database to be more than 90% accurate when compared to statewide death records. Two secondary outcomes included cardiovascular and fracture-related hospitalizations. The reason for hospitalization was identified via the primary discharge ICD-9 code. We also examined three subgroups within this cohort: patients who specifically carried a diagnosis of hypertension, patients without a prior diagnosis of heart failure, and patients with incident CKD. A patient was defined as having incident CKD if their eGFR closest and prior to their two qualifying eGFRs was >60 ml/min/1.73m^2. All patients who did not meet this definition for incident CKD were presumed to have prevalent disease.

Statistical analysis

We utilized Cox proportional hazards regression to examine outcomes by SBP cohort; the SBP 131-160 mmHg group served as the reference group. Patients were censored for loss of benefits and for initiation of renal replacement therapy for the mortality outcome, and for loss of benefits, initiation of renal replacement therapy, and death in non-mortality outcomes. We used a completed cases analysis, including only variables with less than 15% missing values in our adjusted models. The one exception was proteinuria, with an average of 36% missing data, which was included based on likelihood of high clinical impact.

Results

At total of 8,042 patients met inclusion criteria; baseline characteristics are described in Table 2. Of note, 71.5% of patients in the SBP ≤130 mmHg cohort were receiving at least 1 antihypertensive medication, compared to 76.8% of the SBP >160 mmHg cohort. The average number of days between the baseline SBP and index date was similar across cohorts (SBP ≤130 mmHg, 76.2 days; SBP 131-160 mmHg, 81.3 days; SBP >160 mmHg 70.4). We examined subsequent outpatient SBP values (when available) to determine the percent of

patients whose SBP remained consistent with their cohort assignment (90% after year 1 for SBP cohorts 131-160 and >160 mmHg versus 83% after year 1 for SBP cohort <130 mmHg).

The global likelihood ratio test of blood pressure found that blood pressure predicted mortality ($p < 0.001$). The unadjusted mortality rate during the five year follow-up was 55.3% in the SBP ≤ 130 mmHg group, and 44.2% and 44.3% for the SBP 131-160 and SBP >160 mmHg cohorts respectively. The SBP ≤ 130 mmHg had an increased unadjusted hazard for mortality (HR, 1.43; 95% CI, 1.33-1.52), whereas the unadjusted hazard for mortality in the SBP >160 mmHg cohort was inconclusive (HR, 0.98; 95% CI, 0.88-1.08). (Table 3) The global likelihood ratio test confirmed the prognostic value of blood pressure for cardiovascular hospitalization ($p = 0.003$), but not for fracture-related hospitalization ($P = 0.7$). We continued to include and discuss fracture-related hospitalization in our analyses because, while a clear relationship between fracture-related hospitalization and SBP cannot be defined by this study, the information derived may be of use to future investigators and trials which may further examine this outcome. The unadjusted hazards for cardiovascular hospitalization were 1.20 (95% CI 1.11-1.31) and 1.18 (95% CI 1.06-1.31) for the SBP ≤ 130 and >160 mmHg cohorts respectively. For the same cohorts, the hazards for fracture-related hospitalizations were 1.11 (95% CI, 0.95-1.31) and 1.03 (95% CI 0.83, 1.28).

The adjusted hazard for mortality for the SBP ≤ 130 mmHg cohort was 1.22 (95% CI, 1.11-1.34), while the adjusted hazard for mortality in the SBP >160 mmHg cohort remained inconclusive (HR 1.06, 95% CI 0.93, 1.22). The Kaplan-Meier survival graph for this analysis (Figure 2) shows clear and consistent separation for the absolute risk of mortality between the lowest SBP cohort and the two higher SBP cohorts. The adjusted hazard for cardiovascular hospitalizations for the SBP >160 mmHg cohort was 1.26 (95% CI 1.09, 1.45), whereas the hazard ratio was 1.10 (95% CI 0.99, 1.23) for the SBP ≤ 130 mmHg. The hazard for fracture-related hospitalization was 1.06 (95% CI 0.86, 1.32) for the SBP ≤ 130 mmHg cohort and 0.96 (95% CI 0.71, 1.30) for the SBP >160 mmHg cohort. (Table 3)

For each subgroup analysis, we examined the p values for interaction between that subgroup characteristic, SBP, and mortality. The only significant interaction found was between systolic blood pressure and patients with a prior diagnosis of hypertension ($P = 0.03$) for the outcome of mortality. We also examined the p values for interaction between the subgroup characteristic, SBP, and cardiovascular hospitalizations; none of those p values reached significance.

In the subgroup analysis including only patients with a prior diagnosis of hypertension, the adjusted hazard for mortality for the SBP ≤130 mmHg cohort and SBP >160 mmHg cohort did not differ meaningfully from those identified within the entire study population (HR 1.32, 95% CI 1.19, 1.47 and HR 1.11, 95% CI 0.96, 1.29 respectively). (Table 4) Based upon the significant interaction between SBP and this subgroup ($P = 0.03$), we also examined the converse population – patients without a prior diagnosis of hypertension. In the adjusted model of this population, there was no increased risk of mortality in either SBP cohort (HR 0.99, 95% CI 0.82; 1.19 and HR 0.92, 95% CI 0.63; 1.34 for SBP cohorts ≤130 and >160 mmHg respectively). The p-value for interaction for the subgroup of patients with a prior diagnosis of hypertension was non-significant for cardiovascular hospitalizations, so we cannot reliably examine the relationship between SBP and this outcome for this subgroup. This analysis suggests that the risk for cardiovascular hospitalization may be increased for both the SBP ≤ 130 and >160 mmHg cohorts within this subgroup (HRs of 1.13 [95% CI 1.00-1.28] and 1.29 [95%CI, 1.11-1.50], respectively), but additional studies would be needed to truly clarify this relationship.

The non-significant p-values for interaction for the incident subgroup and subgroup of patients without heart failure make it impossible to establish the relationships between these subgroups and mortality or cardiovascular hospitalizations within this study. We did examine these outcomes as these results might identify future research questions or areas of interest for future researchers. We found that patients with incident CKD may experience an increased hazard for mortality of 1.37 (95% CI 1.20, 1.56) for the SBP ≤ 130 mmHg cohort, but the hazard for mortality was inconclusive among the SBP >160 mmHg cohort (HR 0.99, 95% CI 0.80, 1.23). Risk of cardiovascular hospitalization among incident CKD patients was similar, with increased risk for the SBP ≤130 mmHg cohort (HR 1.18, 95% CI 1.02, 1.37) and inconclusive risk for the SBP >160 mmHg cohort (HR 1.19, 95% CI 0.96; 1.47). When the adjusted models were repeated with the exclusion of patients with a prior diagnosis of heart failure, results mirrored those of the original cohort analysis. The SBP ≤130 mmHg cohort continued to experience increased risk of mortality (HR 1.15, 95% CI 1.01; 1.31) but indeterminate risk of cardiovascular hospitalizations (HR 1.07, 95% CI 0.93; 1.24). The SBP >160 mmHg cohort experienced increased risk of cardiovascular hospitalization (HR 1.27, 95% CI 1.07; 1.50) but their mortality risk was inconclusive (HR 1.04, 95% CI 0.88; 1.23).

We also examined the average systolic and diastolic blood pressures and pulse pressures by year and SBP cohort. Systolic blood pressure largely reflects the SBP cohort assignment for SBP group <130 and 131-160 mmHg (SBP 129-130 and 136-140 mmHg respectively), but is lower than the expected 160 mmHg (range 141-151 mmHg) for the SBP >160 mmHg cohort. Pulse pressure increases across increasing SBP cohorts.

Discussion

Our study suggests a relationship between lower systolic blood pressure and mortality among the older adults with CKD. Individuals in our population in the SBP ≤130 mmHg cohort appeared to have a higher risk of death compared to their counterparts with SBP 131-160mmHg (HR 1.22, 95% CI 1.11, 1.34). The association between SBP and mortality was attenuated in the adjusted model (unadjusted HR 1.43 versus adjusted HR of 1.22).

We are unable to draw conclusions about the risk of mortality among individuals in the SBP >160 mmHg cohort (Hazard ratio 1.06, 95% CI 0.93, 1.22), but our analysis suggests an increased hazard for cardiovascular hospitalization for this higher SBP cohort (HR 1.26), compared to their counterparts with SBP 131-160mmHg. The adjusted hazard for cardiovascular hospitalization in the SBP >160 mmHg was actually higher than the unadjusted ratio (1.26 compared to 1.18 respectively). This difference may reflect the impact of potentially protective medication use (specifically renin angiotensin aldosterone system blockade) which was more common in the SBP >160 mmHg cohort and which was controlled for in the adjusted analysis. We did not find a significant relationship between systolic blood pressure and fracture-related hospitalizations for any SBP cohort.

The reason for the apparent increase in mortality risk in older CKD patients with SBP ≤130 mmHg within our cohort is likely multi-factorial. The clinical characteristics of older CKD patients may predict decreased potential benefit from lower blood pressures in terms of mortality and rate of decline in kidney function.[8,14,15] The impact of hypertension management on outcomes for CKD patients may hinge upon the presence and degree of proteinuria.[16] This may have particular relevance for older CKD patients, because kidney disease is less likely to be proteinuric in older compared to younger adults.[17]

We reviewed follow-up outpatient blood pressure values to assess the potential impact of pulse pressure on our findings, as higher pulse pressure has been associated with adverse

outcomes. Vaccarino and colleagues found a 32% increase in risk of heart failure with each 10 mmHg rise in pulse pressure.[18] Data from the Framingham Heart Study also identified an increased risk of heart disease among individuals with a widened pulse pressure, which has been associated with an increased risk of cardiovascular events.[19] Within our study, however, it is unlikely that pulse pressure is playing a significant role in the increased hazard for mortality in the SBP ≤ 130 mmHg cohort as pulse pressure is lowest within that cohort.

Of note, the retrospective nature of our study may also cause concern for residual confounding as a potential contributor to our results; this is of greatest concern in the lowest SBP cohort, in that a low baseline blood pressure can be a marker of a more severe illness profile. This concern is reinforced by the differentially high rates of heart disease and heart failure in the lowest SBP cohort. (Table 2) We have attempted to limit the risk of residual confounding by controlling for multiple comorbid illnesses in our adjusted Cox model, and also by examining the subgroup analysis of only patients without a prior diagnosis of heart failure (which was reassuring as the point estimates for mortality do not change in this subgroup analysis).

The results of our study highlight concerns surrounding hypertension management for older CKD patients. Importantly, data on safety and efficacy of very low blood pressure targets are lacking even among older adults without CKD. One prospective analysis identified a non-linear J-shaped relationship between blood pressure and outcomes for the elderly.20 In the SHEP (Systolic Hypertension in the Elderly Program) study, systolic blood pressure control was found to reduce the risk of fatal and non-fatal stroke in older adults; the systolic blood pressure achieved in the active treatment arm of this trial, however, was 143 mmHg. 10 Similarly, HYVET (Hypertension in the Very Elderly Trial) found higher rates of mortality and cardiovascular events among untreated hypertensive older veterans.11 The average SBP in the treated arm of this trial was 140-150 mmHg. Both SHEP and HYVET demonstrate risk reduction with antihypertensive therapy, but neither study lowered blood pressure to the level currently recommended by CKD guidelines (<130/80 mmHg).5 Additionally, these trials excluded patients with abnormal kidney function. It remains unknown how applicable trials examining hypertension control in older adults without CKD are to an age-matched CKD population, but our study suggests that more aggressive antihypertensive management may not be without risk for older CKD patients.

Our analysis of patients with a prior diagnosis of hypertension demonstrated increased mortality risk for the SBP ≤ 130 mmHg cohort, which was greater than the risk of mortality for the same cohort in the entire population (HR 1.32 versus 1.22 respectively). Importantly, the converse was also true, and patients without a prior diagnosis of hypertension did not incur increased hazard for mortality or cardiovascular hospitalization based on baseline SBP. The reason for this difference is unknown, but could suggest that blood pressure changes (high or low) among patients without a history of hypertension may reflect acute changes in status as opposed to chronic illness and therefore play a lesser role in prognosticating longer term mortality and hospitalization outcomes. Within the incident subgroup, the lowest SBP cohort continued to have an increased risk of mortality (HR 1.37) compared to incident CKD patients with SBP 131-160 mmHg, indicating that duration of CKD may not be harmful in relation to important outcomes. The analysis of patients without a prior diagnosis of heart failure continued to show increased mortality risk for the lowest SBP cohort (HR 1.15).

The use of a single outpatient SBP value to define the baseline SBP presents a potential source of error. We chose to use a single SBP value as SBP baseline in order to maintain as broad a cohort as possible. Limiting our cohort to patients with two or more SBP values

would potentially have excluded the sickest patients (who may have met CKD criteria but died prior to contributing their first SBP value). The use of a single SBP value may have resulted in some regression dilution bias, but in this scenario regression dilution bias would make it less likely to detect a significant difference between groups. As we were able to detect a difference between SBP cohorts, we suspect that correcting for regression dilution bias may have strengthened the harmful effect of a low systolic blood pressure at baseline.

We also could have potentially increased our cohort size by not including proteinuria in our adjusted analysis (given the high missing percent for this characteristic). We felt that the ability to examine the impact of the presence of proteinuria outweighed the harm of excluding those patients without a proteinuria measurement. In the future, prospective studies on this population could curb this limitation by improving the completeness of proteinuria data collection.

In examining our results, we considered how an alternate index date, such as using the first SBP value after the second qualifying eGFR <60 ml/min/1.73m2, might have impacted our results. A sensitivity analysis of three additional subgroups (only incident CKD patients with an SBP value within 90 days of the index date, only prevalent CKD patients, and only patients with at least one SBP value after their second low eGFR) yielded very similar hazard ratios to our original cohort analysis, with no change in directionality of point estimates.

Our decision to not pursue time varying analysis may be viewed as a limitation. We feel modeling BP level as a time-varying exposure could provide interesting information, but would essentially address a different research question. A time varying analysis, looking at blood pressures closest in time to outcomes, would examine the acute role of blood pressure and the outcome; our primary interest, however, was to examine the prognostic significance of blood pressure for these outcomes over time.

Our study specifically examined SBP values in alignment with current CKD guidelines goals (SBP <130 mmHg) and SBP values found to be associated with benefit (SBP 140-150 mmHg) and harm (SBP >160 mmHg) among older adults without CKD. We focused our analyses on these SBP cohorts in order to speak specifically to the relationship between significant outcomes and current hypertension management goals. Ongoing clinical trials, including SPRINT (the Systolic Blood Pressure Intervention Trial) will examine a target SBP of <140 versus <120 mmHg among CKD patients and will include older adults within the study population; results from this trial and other future research will augment our understanding of the relationship between different levels of blood pressure control on mortality, cardiovascular outcomes, and CKD progression among older CKD patients.

The retrospective nature of our data limits the conclusions that can be derived from our results, in that this study cannot establish causation between SBP and outcomes such as mortality and hospitalizations. This study does describe an interesting relationship between SBP and these outcomes to generate future hypotheses for research. The increased risk of mortality described for older adults with CKD who have baseline SBP ≤ 130 mmHg in our study population remains unexplained by conventional knowledge and raises new questions regarding the appropriateness of current CKD hypertension guidelines among the elderly with CKD. Future trials among older CKD patients are needed to help tailor CKD guidelines and care for this unique patient group.

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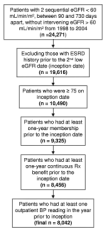

Figure 1.
Study design and derivation of the cohort.

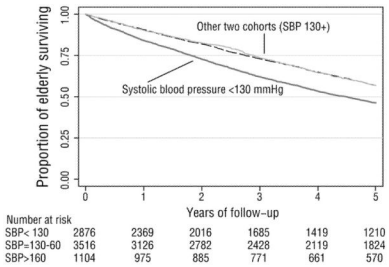

Figure 2.

Kaplan-Meier curve for mortality in original cohort (death versus time). The thick dark line represents the lowest blood pressure cohort (SBP<130 mmHg); the other two blood pressure cohorts (SBP 131-160 and SBP >160 mmHg) are superimposed on the upper line.

Table 1

Sources of baseline characteristics

Characteristic	Data source
Demographic characteristics	
Age	Membership file
Sex	Membership file
Clinical characteristics	
Hypertension	ICD9 codes 401, 402, 403, 404, 405; or treatment with antihypertensive medication
Current Smoking	Separate field in electronic medical record (smoking list); problem list (ICD9 code 305.1); reason for visit (smoking related visit)
Diabetes	Diabetes Registry
Coronary Artery Disease	ICD9 codes 410, 411, 412, 413, 414 and not including 414.10, 414.11, 414.19
Congestive Heart Failure	ICD9 codes 428.0, 428.9, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 429.4A, 429.9B, 429.9A, 428.1
Peripheral Vascular Disease	ICD9 codes 250.7x, 440.xx, 443.81, 443.9
Acute Kidney Injury	ICD9 codes 584.xx (Acute Renal Failure code)
Hypertension	ICD9 codes 401.xx – 405.xx, 440.1; blood pressure values recorded as separate fields in the electronic medical record (using latest values in up to last three years prior to index date)
Fracture	ICD9 codes 806-829 and 733.10-733.19 for pathologic fractures
Anemia[a]	Laboratory data within the electronic medical record
Use of ACEi, ARB	Pharmacy data within the electronic medical record
Use of statin	Pharmacy data within the electronic medical record
Use of diuretic	Pharmacy data within the electronic medical record
Death	Enrollment database
Renal replacement therapy	Transplant and dialysis registry
eGFR[b]	Electronic medical record
proteinuria[c]	Laboratory data within the electronic medical record

ACEi: angiotensin converting enzyme inhibitor

ARB: angiotensin receptor blocker

eGFR: estimated glomerular filtration rate

ICD9: International Classification of Diseases, Ninth Revision

[a] defined as hemoglobin < 12 g/dL

[b] calculated using serum creatinine and the 4 variable Modification of Diet in Renal Disease (MDRD) Study equation

[c] Urine protein-creatinine ratio > 300, urine dipstick 1+ or greater, or microalbuminuria

Table 2

Baseline characteristic by blood pressure groups

Variable	SBP group		
	≤130 mmHg (n = 3099)	131-160 mm Hg (n = 3772)	>160 mmHg (n = 1171)
Age			
75-85	74.1	77.2	75.7
>85	25.9	22.8	24.3
Female	40.5	33.0	27.8
*Tobacco use			
current	26.4	26.9	25.3
ever	59.9	56.3	52.8
CKD Stage[a]			
3	90.5	91.6	90.4
4	8.9	7.7	9.3
5	0.6	0.7	<1
Hypertension diagnosis	67.5	78.5	88.6
Acute kidney injury	2.8	1.8	<5
Diabetes	22.1	22.3	24.0
Coronary Artery Disease	44.3	33.7	29.5
Congestive Heart Failure	41.0	25.3	21.2
Peripheral Vascular Disease	15.3	11.6	13.2
±Use of antihypertensive medications			
ACEi/ARB	34.5	32.0	40.5
spironolactone	4.1	2.6	1.9
CCBs	10.6	11.6	13.8
alpha blockers, clonidine, and vasodilators	4.3	6.2	10.6
beta blockers	36.1	33.6	39.8
¥ Receiving no antihypertensive medications	28.5	30.8	23.2
¥ Receiving ≥3 antihypertensive medications	13.5	12.6	17.4
Use of statin medications	25.1	22.2	22.0
Anemia (Hb <12 g/dL)	69.7 [6.6]	70.8 [8.9]	69.8 [10.3]
‡Proteinuria	6.6 [33.6]	7.3 [36.1]	10.5 [39.1]
†Cancer	7.2	6.8	5.7
BMI <30 kg/m2	61.2 [18.8]	58.2 [15.8]	59.0 16.0]
Albumin level <2	<1 [74.0]	<1 [76.1]	<1 [77.5]

N for total cohort is 8042. All values shown are percentages; however, "<5" signifies fewer than 5 patients per cohort with that trait (in such cases, percentages were not calculated). Numbers in brackets, where shown, denote percent missing.

SBP systolic blood pressure; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; Hb, hemoglobin; BMI, body mass index; eGFR, estimated glomerular filtration rate

[*] Tobacco use current: use within 3 years of index date

[†] Cancer includes any diagnosis code for cancer in the three years prior to inception date into the cohort

[‡] Proteinuria as listed below is a composite of urine protein/creatinine ratio >300, urine dipstick 1+ or greater, or microalbuminuria.

[±] Antihypertensive medication use by cohort was determined by examining prescriptions for patients in the 90 days prior to index date.

[¥] Medication categories included in the determination of zero or 3 more antihypertensive medications by cohort included central and dihydropyridine CCBs, alpha blockers, clonidine, vasodilators, ACEi, ARBs, spironolactone, loop diuretics, Thiazide-type diuretics, and beta blockers.

[a] Stage 3 CKD corresponds to eGFR 31-60 ml/min/1.73m2; Stage 4, eGFR 15-30 ml/min/1.73m2; Stage 5, eGFR <15 ml/min/1.73m2.

Table 3

Cox proportion hazard model results

	Mortality	***Cardiovascular* hospitalizations**	***Fracture-related* hospitalizations**
Unadjusted model (n = 7496)			
SBP ≤130 mmHg	1.43 (1.33, 1.53)	1.20 (1.11, 1.31)	1.13 (0.96, 1.34)
SBP = 131-160 mmHg	1.00	1.00	1.00
SBP >160 mmHg	0.98 (0.88, 1.08)	1.18 (1.06, 1.31)	0.99 (0.79, 1.24)
Adjusted model (n = 4561)			
SBP ≤130 mmHg	1.22 (1.11; 1.34)	1.10 (0.99; 1.23)	1.06 (0.86; 1.32)
SBP = 131-160 mmHg	1.00	1.00	1.00
SBP >160 mmHg	1.06 (0.93; 1.22)	1.26 (1.09; 1.45)	0.96 (0.71; 1.30)

c The adjusted model controls for age, gender, CKD stage (3, 4, or 5), coronary artery disease, diabetes, heart failure, peripheral vascular disease, anemia, prior diagnosis of hypertension, angiotensin converting enzyme inhibitor or angiotensin receptor blocker use, diuretic use, spironolactone use, and dipstick positive proteinuria. Patients with diagnosis of cancer in the three years prior to the index date were excluded.

Table 4

Cox Proportional Hazards model on CKD subgroups of patients with and without prior diagnosis of hypertension

	Mortality	***Cardiovascular hospitalization***
CKD patients with prior diagnosis of HTN *(n = 3432)*		
SBP ≤130 mmHg	1.32 (1.19; 1.47)	1.13 (1.00; 1.28)
SBP = 131-160 mmHg	1.00	1.00
SBP >160 mmHg	1.11 (0.96; 1.29)	1.29 (1.11; 1.50)
CKD patients without prior diagnosis of HTN (n = 1129)		
SBP ≤130 mmHg	0.99 (0.82; 1.99)	0.99 (0.79; 1.24)
SBP = 131-160 mmHg	1.00	1.00
SBP >160 mmHg	0.92 (0.63; 1.34)	1.03 (0.67; 1.62)

HR (95% CI) reported. These models are all adjusted and control for gfr, age, gender, cad, diabetes, anemia, ace/arb, diuretic, spironolactone, proteinuria, and peripheral vascular disease. Patients with prior diagnosis of cancer were excluded from all models.