Systolic BP and Mortality in Older Adults with CKD

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Abstract

Background and objectives Optimal BP targets for older adults with CKD are unclear. This study sought to determine whether a nonlinear relationship between BP and mortality—as described for the broader CKD population and for older adults in the general population—is present for older adults with CKD.

Design, setting, participants, & measurements A cohort of 21,015 adults age 65–105 years with a moderate or severe reduction in eGFR (<60 ml/min per 1.73 m²) were identified within the Kaiser Permanente Northwest Health Maintenance Organization population. The relationship between baseline systolic BP (SBP; <120, 121–130, 131–140, 141–150, >150 mmHg; referent, 131–140 mmHg) and all-cause mortality across age groups (65–70, 71–80, and >80 years) was examined; patients were followed for up to 11 years after cohort entry.

Results The median times at risk were 3.15 years, 3.53 years, and 2.76 years for adults age 65–70, 71–80, and >80 years, respectively. Mortality during follow-up was 19.6% for those age 65–70 years, 33.4% for those age 71–80 years, and 55.7% for those age >80 years. The relationship between SBP and mortality varied as a function of age. The risk of death was highest for patients with the lowest SBP in all age groups. Only among adults age 65–70 years was an SBP >140 mmHg associated with a higher risk of death compared with the referent category. Patterns of age modification of the relationship between SBP and mortality were consistent in all sensitivity analyses.

Conclusions In a cohort of older adults, the relationship between SBP and mortality varied systematically with age. A relationship between higher SBP and mortality was present only for younger members of this cohort and not for those older than 70. These results raise the question of whether the relative benefits and harms of lowering BP to recommended targets for older adults with CKD may vary as a function of age.


Introduction

BP control has long been a cornerstone of care for patients with CKD, and more stringent BP targets than those used for the general population have historically been recommended for patients with kidney disease. The recent 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults recommends a BP target of <140/90 mmHg for adults younger than age 60 years and adults of all ages with CKD, along with a target of <150/90 mmHg for adults older than age 60 years who do not have CKD (1). Liberalization of systolic BP (SBP) target recommendations from 140 to 150 mmHg in adults aged ≥60 years was driven primarily by the absence of data to suggest that lowering SBP to <140 mmHg resulted in fewer deaths or cardiovascular events at older ages (2). Recent guidelines for BP control developed by the Kidney Disease Improving Global Outcomes (KDIGO) also recommend a target of <140/90 mmHg for all patients with CKD and further suggest a target of <130/80 mmHg for the subset of patients with proteinuria; these recommendations are intended to apply to both older and younger adults with CKD (3). Other guideline groups continue to recommend lower BP targets (<130/80 mmHg) for patients with specific comorbidities (diabetes) or when target organ damage is present (4,5). Enthusiasm for these relatively lower BP targets in patients with CKD is not supported by strong evidence and is driven largely by concerns about high cardiovascular event rates in patients with CKD, by early observational data showing a decreased risk of renal disease progression when patients with CKD received some versus no BP control, and by trial data that support the safety—if not benefit—of treating lower BP targets (6–10).

Knowledge of the benefits and harms of pursuing relatively lower BP targets for patients with CKD is especially lacking for older adults. Approximately one in every two adults with CKD in the general population is over age 70 years (11). Evidence for a favorable effect of BP reduction on mortality, cardiovascular events, and stroke in older adults in the general population has been demonstrated only with targeting an SBP<160 mmHg—a target that is substantially higher than those currently recommended for patients with CKD (12–14). Further, trials supporting the safety of an SBP<130 mmHg for patients with CKD did not enroll participants over age 70 years (6–8).

We previously described an increase in mortality associated with lower baseline SBP values (<130 mmHg) among older adults with CKD, although this observational...
study did not examine mortality rates across the spectrum of BP levels or among older adults with CKD of different ages (15). Kovesdy et al. recently described a nonlinear relationship (J-curve effect) between BP and mortality in a national retrospective cohort of veterans with CKD. This study described a higher mortality risk among those with extremes of BP—both >160/100 mmHg and <120/80 mmHg—compared with the referent group (120–139/80–89 mmHg) (16). In stratified analyses, a nonlinear relationship between BP and mortality was present in older cohort members but did not seem to be present in those under age 70 years—among whom there was a linear relationship between BP and mortality. Here we evaluate the possibility that the relationship between BP and mortality may vary by age among older adults with CKD.

Methods

Study Design and Setting

We conducted a retrospective cohort study of adults age 65 years and older with stages 3–5 predialysis CKD receiving care within the Kaiser Permanente Northwest (KPNW) health maintenance organization, which provides care for 450,000 patients in the metropolitan area of Vancouver; Washington; and Portland, Oregon. The KPNW patient care system has used a single electronic medical record system since 1997 (Epicare). This study was approved by the institutional review boards of Oregon Health and Science University and KPNW.

Cohort Identification

Members of KPNW from 2000 to 2010 were eligible for inclusion if they were age 65 years and older at the time of cohort entry, had stages 3–5 predialysis CKD (defined as two eGFR values of <60 ml/min per 1.73 m² ≥90 days and ≤730 days apart during the 2-year baseline period before cohort entry), and had at least two recorded outpatient BP measurements during the 2-year baseline period before cohort entry (Figure 1). The index date for cohort entry was the date of the second outpatient BP measurement; this BP measurement had to occur after the second eGFR to ensure that all participants met criteria for CKD before cohort inclusion. GFR was estimated using the CKD-Epidemiology Collaboration formula.

Figure 1. | Cohort development diagram. This flow chart outlines the delineation of our cohort from the Kaiser Permanente Northwest (KPNW) health maintenance organization population using our inclusion and exclusion criteria. The baseline period was the 2 years before the qualifying second systolic BP (SBP). Of note, patients within KPNW have the opportunity to opt out of future research when they enter the health maintenance organization. Patients who have requested this designation are entered into the KPNW Center for Health Research exclusion database and are not included within our cohort. *Probable errors in medical records included patients with SBP but no diastolic BP (n=4) and patients for whom date of cardiovascular hospitalization followed date of death (n=24). eGFR was calculated using the CKD-Epidemiology Collaboration formula.
the CKD-Epidemiology Collaboration formula (17). Age at cohort entry was the patient’s age at index date. To ascertain baseline medication information, we required that patients have 2 years of continuous pharmacy benefits at KPNW before the index date. To limit our cohort to patients most likely to be receiving antihypertensive therapy to achieve their documented baseline SBP, we excluded individuals who had neither a diagnosis of hypertension during the 2-year baseline period or any antihypertensive medication use in the 3 months before cohort entry. We excluded individuals whose two baseline SBP values differed by ≥50 mmHg or who had any history of RRT (dialysis or transplantation, as documented in an internal KPNW dialysis registry). Patients were censored at the time of initiation of RRT, disenrollment, or the end of follow-up.

Additional Patient-Level Data

Patient data for the 2-year period before cohort entry were used to ascertain key baseline characteristics. Previously diagnosed conditions were identified using International Classification of Diseases, 9th Edition (ICD-9) diagnostic codes (Supplemental Table 1). Tobacco use was ascertained according to documentation in the outpatient medical record of tobacco use during the 2-year baseline period. Patients were considered to have proteinuria if they had a positive dipstick finding (1+, 2+, 3+) in the absence of leukocyte esterase positivity or an albumin-to-creatinine ratio >30 mg/mg; if more than one measure was present, the value closest to and after the index date was used. Only variables with <15% missing values were included in our analyses.

Outcome Identification

Patients were followed for up to 11 years from the time of cohort entry through December 31, 2010, for ascertainment of all-cause mortality using the KPNW enrollment database, which has been internally reviewed and found to be >90% consistent with statewide death records.

Statistical Analyses

We used Cox proportional hazards regression to analyze all-cause mortality as a function of baseline SBP and age group at cohort entry. Patients were categorized into one of five groups on the basis of their baseline SBP (SBP ≤120, 121–130, 131–140, 141–150, and >150 mmHg); patients with an SBP of 131–140 mmHg served as the referent. The second documented outpatient SBP value defined each patient’s baseline SBP group assignment. Our primary analysis included evaluation by age at cohort entry (65–70, 71–80, and >80 years) and SBP. Given the limited number of events to support age-stratified analyses, we adopted a parsimonious approach to model building guided by anticipated clinical relevance and ease of ascertaining of variables in real-world clinical settings. Adjustment variables included sex, body mass index, baseline diastolic BP (DBP), and comorbidities (heart failure; diabetes; tobacco use; and a composite variable including coronary artery disease, peripheral vascular disease, and cerebrovascular disease). Violations of the proportional hazards assumption were accommodated using stratification. We examined two-way interactions between eGFR and mortality and SBP and mortality and the three-way interaction between SBP, eGFR, and mortality; a P value of <0.05 was considered to represent a statistically significant difference.

We conducted sensitivity analyses stratified by eGFR (≤44 versus 45–59 ml/min per 1.73 m²) and sex. The second documented eGFR value defined a participant’s baseline eGFR group. To evaluate the potential role of confounding by the presence of heart failure, we repeated the primary analysis after excluding those with a diagnosis of heart failure. We conducted a supplementary analysis evaluating the relationship between DBP and mortality.

Results

Our cohort included 21,015 individuals (Figure 1). The prevalence of most chronic conditions (cardiovascular disease, heart failure, peripheral vascular disease, and stroke) was highest among those with lower SBP, and the percentage of women increased with increasing SBP (Table 1). Those with the highest baseline SBP were more likely to have proteinuria, while the prevalence of diabetes and use of antihypertensive medications at baseline was relatively similar across BP groups. The median times at risk (the time between index date and either death or censoring) for adults age 65–70, 71–80, and >80 years were 3.15 years (25th percentile, 1.39 years; 75th percentile, 5.47 years), 3.53 years (25th percentile, 1.53 years; 75th percentile, 6.4 years), and 2.76 years (25th percentile, 1.17 years; 75th percentile, 4.8 years), respectively. Mortality rates during follow-up were 38.7% for the overall cohort, 19.6% for those age 65–70 years, 33.4% for those age 71–80 years, and 55.7% for those age >80 years.

In both unadjusted and adjusted analyses, the relationship between SBP and mortality varied with age (P for interaction=0.003). At all ages, patients with the lowest SBP had a higher risk of death than those in the referent category (SBP, 131–140 mmHg) (Table 2). Among the youngest cohort members (age 65–70 years), there was a U-shaped relationship between SBP and mortality with elevated mortality risk compared with the referent group for both those with baseline SBP <130 mmHg and >140 mmHg. Among those older than age 70 years, risk of death was higher at SBP<130 mmHg (with the greatest risk in the lowest SBP group [≤120 mmHg]) but was no higher for those with SBP>140 mmHg compared with the referent group. (Figure 2)

Results were broadly consistent in terms of the directionality of hazard ratios at all levels of eGFR, although some results did not reach statistical significance in stratified analyses. We did not detect clinically meaningful interactions between level of eGFR and SBP (P=0.17) or level of eGFR, age, and SBP (P=0.06) (Supplemental Table 2). Results were also broadly consistent in men and women for all combinations of age, sex, and SBP with the exception of the youngest cohort members (age 65–70 years) with the highest SBP (>150 mmHg). In this age group, men with an SBP in this range had a higher risk of death compared with the referent, whereas the risk was indeterminate for women; the higher risk of death among men age 65–70 years with SBP>150 mmHg was significant (95% confidence interval did not cross 1), and the magnitude of risk appeared greater than that for women (hazard ratio, 1.74 versus 1.19) (Supplemental
Table 3). A sensitivity analysis that excluded participants with a prior diagnosis of heart failure yielded results that were consistent with the primary analysis (Supplemental Table 4). A supplementary analysis examining the relationship between DBP groups and mortality showed a higher risk of death among those with a DBP ≤ 60 mmHg and a lower risk of death among those with a DBP > 80 mmHg compared with the referent group (DBP of 61–80 mmHg). This relationship did not vary meaningfully across age groups (Supplemental Table 5).

Discussion
In a cohort of older adults with CKD and hypertension, the relationship between SBP and mortality varied as a function of age. Among the youngest members of this cohort (age 65–70 years), there was a U-shaped relationship between baseline SBP and mortality, similar to that described for more broadly defined populations with CKD and in very elderly adults in the general population (16,18–20). However, a U-shaped relationship between SBP and mortality was not present among older members of this cohort, for
whom mortality rates were similar at all levels of SBP>130 mmHg examined in this analysis. These findings add to a growing body of literature highlighting an important knowledge gap about the relative benefits and harms of treating to currently recommended BP targets for older adults with CKD (15,16).

Improved understanding of the benefits or harms of treating to SBP targets in the 140–160 mmHg range is of particular importance for older adults with CKD because a large number have baseline BPs in this range (21). In our cohort, 32.7% of patients had baseline SBP above the target of 140 mmHg at cohort entry, including 14.5% with an SBP between 141–150 mmHg and 9% with an SBP between 151–160 mmHg. Older adults with certain patterns of comorbidities may have a heightened risk of decreased organ perfusion and orthostasis with lower BPs, or may already struggle with the sometimes complex medication regimens needed to achieve aggressive BP lowering. Particularly in frail older adults, less stringent targets may also have a favorable effect on other potentially important outcomes, such as fall risk and treatment burden, polypharmacy, and adverse effects (22–25). The paucity of information regarding the sequelae of BP lowering for older adults with CKD with SBPs in the 141–160 mmHg range leaves patients and providers uncertain of the wisdom of following current guidelines in this area.

Although we anticipated that there might be differences in the relationship of SBP with mortality among patients

<table>
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<tr>
<th>Table 2. Cox proportional hazards analysis to evaluate the relationship between mortality and systolic BP by age</th>
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<tr>
<td><strong>Age Group</strong></td>
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<tr>
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<tr>
<td>65–70 yr (n=4164)</td>
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<td>71–80 yr (n=9278)</td>
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This analysis adjusts for heart failure, cardiovascular disease, tobacco use, and level of eGFR and stratifies on diabetes, sex, body mass index, and diastolic BP. Stratification was used to accommodate violations in the proportional hazards principle. The cardiovascular disease variable is a composite variable that includes coronary artery disease, peripheral vascular disease, and stroke. The diastolic BP is incorporated as a tiered variable using initial diastolic BP to categorize patients as having diastolic BP ≤60, 61–80, 81–90, and >90 mmHg. Body mass index is incorporated as a tiered variable (<18.5, 18.5–24.9, 25–29.9, ≥30 kg/m²). Tobacco use is incorporated as a dichotomous variable (yes/no) for tobacco use in the 2 years before index date. 95% CI, 95% confidence interval.

**Figure 2.** Graphical representation of hazard ratios for mortality by age and systolic blood pressure. Hazard for mortality by age group and systolic blood pressure (SBP). This figure shows the adjusted hazard ratios for mortality by age group in adults with an eGFR<60 ml/min per 1.73 m². This analysis is adjusted for heart failure, cardiovascular disease, tobacco use, and level of eGFR and stratifies on diabetes, sex, body mass index, and diastolic blood pressure. Error bars represent 95% confidence intervals around the hazard ratios.
with differing levels of eGFR, results were broadly consistent among patients with moderate and more severe reductions in renal function. While hazard ratios indicate that the magnitude of the association of the lowest SBP (≤120 mmHg) with mortality may be greater in adults with more severe reductions in eGFR (eGFR≤44 ml/min per 1.73 m²) than for those with more moderate reductions (45–59 ml/min per 1.73 m²), the direction of the association was the same, interaction tests did not reach statistical significance, and we suspect the clinical relevance of observed differences to be limited.

In contrast with SBP, the relationship between DBP and mortality was linear, with higher risk of death at lower DBP; this relationship was consistent across age groups. Observed differences across age groups in the relationship between SBP and mortality among members of this cohort did not appear to be explained by differences in DBP as these persisted after adjustment for DBP. Diastolic hypertension was less common to be explained by differences in DBP than systolic hypertension among members of this cohort: Only 6% had a DBP >140 mmHg while 27% had isolated systolic hypertension (SBP >140 mmHg with DBP <90 mmHg). Thus, for members of this cohort, differences in mortality by DBP seem to raise fewer questions about currently recommended treatment targets than differences in mortality by SBP. Nevertheless, because most BP agents decrease both SBP and DBP, BP treatment in patients with isolated systolic hypertension often does involve trade-offs between the potential benefits of lowering SBP and potential harms of lowering DBP (16,26). This may be a particularly relevant consideration in older adults with CKD, given the high frequency of isolated systolic hypertension in this population.

The retrospective nature of our study does increase the risk of residual confounding. The concern for confounding is most pronounced with regard to the lowest SBP group, for whom lower BP may be a marker for poor cardiac function. To help address this possibility, we performed a sensitivity analysis that excluded patients with a prior diagnostic code for heart failure, the results of which were broadly similar to our original analysis (Supplemental Table 4). Importantly, exclusion of patients with a diagnosis of heart failure did not completely mitigate the risk associated with lower SBP values, suggesting that very low BPs are associated with mortality for older adults even in the absence of a heart failure diagnosis.

The relatively small size of the cohort and low event rate during follow-up limited our ability to include all possible confounders in adjusted analyses and limited the precision of estimates in stratified analyses; specifically, our data could not support finer stratification at higher SBP (>150 mmHg). Thus, we can neither exclude nor support the possibility that a nonlinear relationship may exist between BP and mortality at levels of SBP above the 150 mmHg SBP cutpoint examined here.

This study is intentionally limited to patients with a history of hypertension, identified either via ICD-9 code or use of antihypertensive medications because our goal was to perform a study that might help guide treatment choices for patients being treated for hypertension. In an earlier study we noted that lower BP readings were not associated with a higher risk of death in patients without a prior diagnosis of hypertension (15). As such, these results should not be extrapolated to patients whose BP is low in the absence of antihypertensive therapy.

In a cohort of older adults with CKD and hypertension the relationship between SBP and mortality varied systematically by age. Among the oldest members of this cohort, mortality rates were no higher for those with SBPs >140 mmHg than for those with SBPs of 131–140 mmHg. These findings add to a growing body of work questioning the appropriateness of currently recommended BP targets in patients with CKD and highlight the potential for heterogeneity in treatment responses among older adults with this condition.

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Preliminary results from this study were presented as an abstract/poster at the American Society of Nephrology meeting in 2012 as “The Relationship between Blood Pressure and Mortality in Older Adults with Chronic Kidney Disease is Modified by Age and Renal Function.”

Disclosures

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