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

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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 m^2 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 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 pressure under 60 mm Hg was associated in contrast with all-cause mortality and non-cardiovascular/non-malignancy-related deaths.

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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 suggest 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 (GFR),[4] and most patients with chronic kidney disease (CKD) have concomitant hypertension. The ideal blood pressure target for the CKD population (with and without diabetes) has been a matter of debate. Several observational studies have examined the associations between blood pressure (BP) parameters (systolic BP [SBP], diastolic BP [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] On the contrary, some studies have noted that both lower SBP and DBP are associated with higher mortality.[7,9] In contrast to these observational data, recent clinical trial evidence from the Systolic Blood Pressure Intervention Trial (SPRINT) 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 estimated GFR [eGFR] of <60 ml/min/1.73 m^2), 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 differ across various BP strata. Therefore, we examined the associations of SBP and DBP with categories of cause-specific mortality (cardiovascular, malignancy-related, and non-cardiovascular- or nonmalignancy-related deaths) among a large CKD population.

RESULTS

Patient characteristics

Our study population comprised 45,412 patients with CKD stage 3 or 4 (Supplementary Figure S1). The mean age was 72.6 ± 11.4 years, 45.7% were men, and 13.8% were black. Mean SBP was 131 ± 20 mm Hg, and mean DBP was 72.6 ± 11.3 mm Hg. Mean body mass index of the study cohort was 29.9 ± 6.6 kg/m^2. Prevalences 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 m^2. 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 patients (29.3%) died; cause of death was available for 13,154 (98.6%) of those. Of these, 4824 (36.6%) died of cardiovascular causes, 3315 (25.2%) due to malignancy, and 4737 (36.0%) due to other causes. Supplementary Tables S1 and S2 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 of 130 to 139 mm Hg, SBPs < 100, 100 to 110, and 110 to 119 mm Hg were associated with higher overall mortality and higher subdistribution hazards for cardiovascular mortality; SBPs < 100 and 100 to 109 mm Hg were also associated with increased mortality from noncardiovascular- or nonmalignancy-related causes (Table 3). SBPs ≥ 160 and 150 to 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 2 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, DBPs < 50 and 50 to 59 mm Hg (vs. 70–79 mm Hg) were associated with higher hazards of all-cause mortality, and higher subhazards of noncardiovascular- or nonmalignancy-related death (Table 4). DBP ≥ 90 mm Hg (vs. 70–79 mm Hg) was associated with higher subhazards of cardiovascular mortality but lower risk of noncardiovascular- or nonmalignancy-related death. Figure 3 shows the associations between DBP (as a continuous measure) and all-cause death. Figure 2 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 (Supplementary Tables S3 and S4).

Adjusting for proteinuria. Results from the test for 2-way interaction between SBP groups, DBP groups, and proteinuria on all-cause mortality were not significant. In the analysis restricted to those who had proteinuria data (n = 21,015), inclusion of proteinuria in the multivariable model yielded results similar to those of the primary analyses (Supplementary Table S5 and S6).

Adjusting for both SBP and DBP group. When we evaluated the associations between SBP group and mortality while adjusting for DBP group, results were mostly similar to those of our main analysis, except that the lower SBP categories were not associated with noncardiovascular- or nonmalignancy-related death (Supplementary Table S7). When we evaluated the associations between DBP group and mortality while adjusting for SBP group, results were mostly similar to those of our primary analysis (Supplementary Table S8).

Interactions with SBP

Results of the test for 2-way interaction between SBP groups and history of diabetes and number of anti-hypertensive medications on overall mortality were not significant. The interaction with age >65 years (P < 0.001) was significant, suggesting the increased mortality risk associated with very low BP was strongest among patients ≤65 years (Supplementary Table S9). The interaction with history of congestive heart failure (P < 0.01) was also significant, suggesting stronger hazards associated with low BP among those with versus without heart failure, and a significantly stronger hazard of death associated with higher BP only among those without congestive heart failure (CHF) (data not shown). The interaction between CKD stage and SBP group was significant, and 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 (Supplementary Table S10). In stratified analysis, higher SBP categories were not significantly associated with increased mortality for any CKD stage.

Interactions with DBP

The 2-way interactions between DBP categories and diabetes, CKD stage, and number of antihypertensive medications on overall mortality were not significant. The interaction with age > 65 years (P < 0.001) was significant, suggesting that the increased mortality risk associated with low DBP was stronger in younger versus older patients (Supplementary Table S11).