



Blood Pressure Before Initiation of Maintenance Dialysis and Subsequent Mortality

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Background: Mortality is extremely high immediately after the transition to dialysis therapy, but the association of blood pressure (BP) before dialysis therapy initiation with mortality after dialysis therapy initiation remains unknown.

Study Design: Observational study.

Setting & Participants: 17,729 US veterans transitioning to dialysis therapy in October 2007 to September 2011, with a median follow-up of 2.0 years.

Predictor: Systolic (SBP) and diastolic BP (DBP) averaged over the last 1-year predialysis transition period as 6 (<120 to ≥160 mm Hg in 10–mm Hg increments) and 5 (<60 to ≥90 mm Hg in 10–mm Hg increments) categories, respectively, and as continuous measures.

Outcomes & Measurements: Postdialysis all-cause mortality, assessed over different follow-up periods (ie, <3, 3–<6, 6–<12, and ≥12 months after dialysis therapy initiation) using Cox regressions adjusted for demographics, comorbid conditions, medications, cardiovascular medication adherence, body mass index, estimated glomerular filtration rate, and type of vascular access.

Results: Mean predialysis SBP and DBP were 141.2 ± 16.1 (SD) and 73.7 ± 10.6 mm Hg, respectively. There was a reverse J-shaped association of SBP with all-cause mortality, with significantly higher mortality seen with SBP < 140 mm Hg. Mortality risks associated with lower SBP were greatest in the first 3 months after dialysis therapy initiation, with multivariable-adjusted HRs of 2.40 (95% CI, 1.96–2.93), 1.99 (95% CI, 1.66–2.40), 1.35 (95% CI, 1.13–1.62), 0.98 (95% CI, 0.78–1.22), and 0.76 (95% CI, 0.57–1.00) for SBP <120, 120 to <130, 130 to <140, 150 to <160, and ≥160 (vs 140–<150) mm Hg, respectively. No consistent association was observed between predialysis DBP and postdialysis mortality.

Limitations: Results cannot be inferred to show causality and may not be generalizable to women or the general US population.

Conclusions: Lower predialysis SBP is associated with higher all-cause mortality in the immediate postdialysis period. Predialysis DBP showed no consistent association with postdialysis mortality. Further studies are needed to clarify ideal predialysis SBP levels among incident dialysis patients as a potential means to improve the excessively high early dialysis mortality.

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Despite numerous advances in our understanding of chronic kidney disease (CKD) progression, the incidence of end-stage renal disease remains exceedingly high.^{1,2} Furthermore, patients with advanced non–dialysis-dependent CKD (NDD-CKD)

transitioning to end-stage renal disease have the highest mortality within the first few months after the transition to dialysis therapy and have an exceptionally high health and economic burden.¹ It is therefore of paramount importance to focus on this vulnerable

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population and identify modifiable risk factors and interventions during the period preceding the transition to dialysis therapy that could ameliorate their adverse clinical outcomes.

Hypertension is a well-known risk factor for cardiovascular disease and death in the general population,^{3,4} whereas paradoxically, low blood pressure (BP) has been associated with higher mortality in dialysis patients, a phenomenon referred to as “reverse epidemiology” or “risk factor paradox.”⁵⁻⁹ Among patients with NDD-CKD and hypertension, some observational studies have indicated a J-shaped association between systolic BP (SBP) and mortality,¹⁰⁻¹⁴ suggesting the unique contribution of SBP to the risk for mortality in patients with different levels of kidney function. Current clinical guidelines recommend a target BP < 140/90 or <130/80 mm Hg for patients with CKD, depending on their age, severity of albuminuria, and comorbid conditions,^{15,16} but there is a paucity of evidence on the association between BP and mortality in patients with advanced NDD-CKD, particularly among those in the transition period from advanced NDD-CKD to maintenance dialysis therapy. To address this knowledge gap, we aimed to investigate the associations of SBP and diastolic BP (DBP) in the predialysis transition period with postdialysis all-cause mortality, using a large nationally representative cohort of US veterans transitioning to dialysis therapy.

METHODS

Study Population

We analyzed longitudinal data from the Transition of Care in CKD (TC-CKD) study, a retrospective cohort study examining US veterans transitioning to chronic kidney failure requiring renal replacement therapy from October 1, 2007, through September 30, 2011.¹⁷⁻¹⁹ A total of 52,172 US veterans were identified from the US Renal Data System (USRDS)¹ as a source population. The algorithm for the cohort definition is shown in Fig S1 (provided as online supplementary material). In the present study, we used only outpatient BP measurements available from US Department of Veterans Affairs (VA) medical centers, given the potential fluctuation of BP among hospitalized patients. Therefore, patients without outpatient BP measurements at a VA medical center were excluded (n = 19,533). We also excluded those who did not have at least 3 outpatient BP measurements within 1 year prior to dialysis therapy initiation (ie, 1-year predialysis period; n = 14,645), those who initiated renal replacement therapy with pre-emptive kidney transplantations (n = 163), or those who were missing follow-up data (n = 102), resulting in a study population of 17,729 patients.

Exposure Variable

The primary exposures of interest were SBP and DBP averaged over the 1-year predialysis period. SBP and DBP were measured by trained staff using a standardized method. We divided the averaged SBP and DBP values into 6 and 5 categories, respectively (SBP, <120 to \geq 160 mm Hg in 10-mm Hg increments; DBP, <60 to \geq 90 mm Hg in 10-mm Hg increments). The SBP and DBP categories of 140 to <150 and 70 to <80 mm Hg,

respectively, were used as references in all analyses under the assumption that mortality risks are the lowest in these groups. SBP and DBP were also treated as continuous variables to examine nonlinear associations by using fractional polynomials.

Covariates

Data from the USRDS Patient and Medical Evidence files were used to determine patients' baseline demographic characteristics and type of vascular access at the time of dialysis therapy initiation. Information about comorbid conditions at the time of dialysis therapy initiation was extracted from the VA Inpatient and Outpatient Medical SAS Datasets,²⁰ using the *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnostic and procedure codes and *Current Procedural Terminology* codes, as well as from VA/Centers for Medicare & Medicaid Services (CMS) data. We calculated the Charlson Comorbidity Index score using the Deyo modification for administrative data sets, without including kidney disease.²¹ Cardiovascular disease was defined as the presence of diagnostic codes for coronary artery disease, angina, myocardial infarction, or cerebrovascular disease. Medication data were collected from both CMS data (Medicare Part D) and VA pharmacy dispensation records.²² Patients who received at least 1 dispensation of medications within the 1-year predialysis period were recorded as having been treated with these medications. Cardiovascular medication adherence was defined as the proportion of days covered by a drug during the 1-year predialysis period, capped at 100%.¹⁹ Laboratory data were obtained from VA research databases as previously described,^{23,24} and their baseline values were defined as the average of each covariate during the 1-year predialysis period preceding dialysis therapy initiation. Using serum creatinine and demographic data, estimated glomerular filtration rate (eGFR) was calculated with the CKD-EPI (CKD Epidemiology Collaboration) creatinine equation.²⁵ The last eGFR before dialysis therapy initiation was obtained from USRDS Form 2728. The eGFR slope was calculated from an ordinary least squares regression model using all available outpatient eGFR measurements within the 1-year predialysis period and stratified into 4 a priori categories for the analyses as follows: < -10, -10 to < -5, -5 to < 0, and \geq 0 mL/min/1.73 m².¹⁷

Outcome Assessment

The primary outcome of interest was all-cause mortality after dialysis therapy initiation. All-cause mortality data, censoring events, and associated dates were obtained from VA and USRDS data sources.¹ The start of the follow-up period was the date of dialysis therapy initiation, and patients were followed up until death or other censoring events, including kidney transplantation, loss of follow-up, or December 27, 2012.¹⁷⁻¹⁹

Statistical Analysis

Baseline patient characteristics were summarized according to SBP categories and presented as number and percentage for categorical variables and mean \pm standard deviation for continuous variables with a normal distribution or median and interquartile range (IQR) for those with a skewed distribution. Differences across categories were assessed using analysis of variance and χ^2 tests for continuous and categorical variables, respectively. The association of SBP and DBP with all-cause mortality was estimated using Cox proportional hazards models. The proportionality assumption was tested by plotting $\log[-\log(\text{survival rate})]$ against $\log(\text{survival time})$ and by scaled Schoenfeld residuals. There was a violation in the proportionality assumption for the primary exposure variables; hence, hazard ratios (HRs) were presented for 4 discrete periods (ie, <3, 3-<6, 6-<12, and \geq 12 months after dialysis therapy initiation) to accommodate the

violation. Given the exceptionally high mortality during the immediate posttransition period, we selected the first 3 months as the primary time window for our main analyses. Models were incrementally adjusted for the following potential confounders based on theoretical considerations and their availability in this study: model 1, unadjusted; model 2, adjusted for age, sex, race/ethnicity, and marital status; model 3 additionally accounted for comorbid conditions (cardiovascular disease, congestive heart failure [CHF], peripheral vascular disease, lung disease, diabetes mellitus, liver disease, and Charlson Comorbidity Index), body mass index (BMI; and SBP for the associations with predialysis DBP) averaged over the 1-year predialysis period, eGFR slope, and last eGFR before dialysis therapy initiation; and model 4 additionally included medications (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β -blockers, calcium channel blockers, vasodilators, diuretics, statins, and erythropoiesis-stimulating agents), cardiovascular medication adherence, and type of vascular access (arteriovenous fistula, arteriovenous graft, or catheter). We used fractional polynomial regression models to examine nonlinear associations of SBP and DBP with mortality,²⁶ in which SBP and DBP were treated as continuous variables.

We conducted several sensitivity analyses to evaluate the robustness of our main findings. Associations of SBP and DBP with outcomes were examined in subgroups of patients stratified by age, race, BMI, eGFR, and presence/absence of select comorbid conditions using 3 SBP and DBP categories (SBP, <130, 130-150, and \geq 150 mm Hg; DBP, <70, 70-80, and \geq 80 mm Hg). Potential interactions were formally tested by including relevant interaction terms. We also investigated whether accounting for serum albumin and blood hemoglobin levels further attenuates the associations of SBP and DBP with mortality in the group of 14,573 patients with available albumin and hemoglobin measurements as an additional model (model 5). In addition, we repeated our main analyses by including patients with 1 or 2 outpatient BP measurements.

Compared with patients in the main cohort ($n = 17,729$), those who were excluded from the source cohort ($n = 34,443$) were older (71.6 vs 67.8 years) and less likely to be men (92.5% vs 98.1%) and African American (20.5% vs 31.4%). Of variables included in multivariable models, data points were missing for race (0.2%), vascular access type (7.5%), BMI (<0.01%), eGFR slope (10.5%), last eGFR (2.0%), serum albumin level (3.3%), and blood hemoglobin level (2.3%). Of the 17,729 patients in our study population, 15,719 (88.7%) had complete data available for the main adjusted multivariable model (model 4). Due to the relatively low proportion of missingness, missing data were not imputed. Reported P values are 2 sided and reported as significant at <0.05 for all analyses. All analyses were conducted using STATA/MP, version 14 (STATA Corp). The study was approved by the institutional review boards of the Memphis (protocol number 555872) and Long Beach VA Medical Centers (protocol number MIRB1282), with exemption from informed consent.

RESULTS

Baseline Characteristics

Patients' baseline characteristics in the overall cohort and stratified by SBP categories are presented in Table 1. Overall mean age at baseline was 67.8 ± 11.2 years, 98.1% were men, 31.4% were African American, and 73.0% had diabetes. The median last eGFR before dialysis therapy initiation was 11.0 (IQR, 8.1-14.7) mL/min/1.73 m². During

the 1-year predialysis period, there were a median of 10 (IQR, 5-16) outpatient BP measurements per patient, and mean SBP and DBP were 141.2 ± 16.1 and 73.7 ± 10.6 mm Hg, respectively. Compared with patients with lower SBPs, those with higher SBPs were younger; were more likely to be African American; and had a higher prevalence of diabetes and lower prevalence of other comorbid conditions. They were also more likely to be prescribed antihypertensive medications; were less likely to adhere to cardiovascular medications; and had lower serum albumin, blood hemoglobin, and eGFR levels.

Association of Predialysis SBP With Postdialysis All-Cause Mortality

During a median follow-up of 2.0 (IQR, 1.1-3.1) years following dialysis therapy initiation (total time at risk, 37,969 patient-years), 9,064 all-cause deaths occurred (crude incidence rate, 238.7 [95% CI, 233.9-243.7] per 1,000 patient-years). Among 9,064 all-cause deaths, 1,515 deaths occurred in the first 3 months after dialysis therapy initiation, followed by 1,097, 1,529, and 4,923 deaths in 3 to less than 6, 6 to less than 12, and 12 or more months, respectively. Table 2 shows unadjusted and multivariable-adjusted HRs in the first 3 months after dialysis therapy initiation associated with predialysis SBP categories. In the crude model, SBP categories were inversely associated with all-cause mortality, with significantly higher death risk seen in SBP categories of <140 (vs 140-150) mm Hg (Table 2). After adjustment for potential confounders, the association between SBP and mortality was attenuated but remained statistically significant (adjusted HRs of SBP < 120, 120-130, and 130-140 [vs 140-150] mm Hg are 2.40 [95% CI, 1.96-2.93], 1.99 [95% CI, 1.66-2.40], and 1.35 [95% CI, 1.13-1.62], respectively, in model 4). SBP categories \geq 150 mm Hg were associated with lower risk for mortality without reaching statistical significance (adjusted HRs of SBP of 150-160 and \geq 160 [vs 140-150] mm Hg are 0.98 [95% CI, 0.78-1.22] and 0.76 [95% CI, 0.57-1.00], respectively, in model 4; Table 2). Similar associations were observed in different follow-up periods after the first 3 months of dialysis therapy initiation, with the highest death risk seen in patients with SBPs < 120 mm Hg (adjusted HRs of SBP < 120 [vs 140-150] mm Hg of 1.71 [95% CI, 1.34-2.18], 2.16 [95% CI, 1.75-2.65], and 1.24 [95% CI, 1.08-1.42] for 3-6, 6-12, and \geq 12 months, respectively, in model 4; Table S1).

Figure 1 shows the multivariable-adjusted association of SBP with mortality in the first 3 months after dialysis therapy initiation using fractional polynomials. There was a reverse J-shaped association, with significantly higher death risk seen in patients

Table 1. Baseline Patient Characteristics Overall and According to Predialysis SBP

	SBP, mm Hg						
	Total (N = 17,729)	<120 (n = 1,497)	120-<130 (n = 2,560)	130-<140 (n = 4,380)	140-<150 (n = 4,376)	150-<160 (n = 2,856)	≥160 (n = 2,060)
SBP, mm Hg	141.2 ± 16.1	112.2 ± 6.4	125.4 ± 2.8	135.2 ± 2.9	144.7 ± 2.9	154.4 ± 2.8	169.3 ± 9.0
Diastolic BP, mm Hg	73.7 ± 10.6	63.6 ± 7.0	68.1 ± 8.1	71.7 ± 8.7	74.7 ± 8.8	78.3 ± 9.7	84.3 ± 11.5
Age, y	67.8 ± 11.2	70.8 ± 10.7	69.5 ± 11.3	68.5 ± 11.3	67.4 ± 11.2	65.9 ± 11.0	65.3 ± 10.9
Male sex	17,388 (98.1)	1,475 (98.5)	2,511 (98.1)	4,309 (98.4)	4,297 (98.2)	2,800 (98.0)	1,996 (96.9)
African American race	5,559 (31.4)	279 (18.6)	590 (23.0)	1,183 (27.0)	1,426 (32.6)	1,119 (39.2)	962 (46.7)
Married marital status	9,204 (51.9)	836 (55.8)	1,347 (52.6)	2,426 (55.4)	2,233 (51.0)	1,434 (50.2)	928 (45.0)
BMI, kg/m ²	29.9 ± 6.6	29.3 ± 6.8	29.7 ± 6.6	30.1 ± 6.5	30.1 ± 6.5	30.1 ± 6.7	29.8 ± 6.5
Diabetes mellitus	12,941 (73.0)	966 (64.5)	1,726 (67.4)	3,073 (70.2)	3,292 (75.2)	2,239 (78.4)	1,645 (79.9)
Cardiovascular disease ^a	8,315 (46.9)	817 (54.6)	1,281 (50.0)	2,073 (47.3)	1,992 (45.5)	1,266 (44.3)	886 (43.0)
Congestive heart failure	9,930 (56.0)	1,037 (69.3)	1,456 (56.9)	2,425 (55.4)	2,376 (54.3)	1,549 (54.2)	1,087 (52.8)
Peripheral vascular disease	7,354 (41.5)	659 (44.0)	1,148 (44.8)	1,889 (43.1)	1,825 (41.7)	1,123 (39.3)	710 (34.5)
Chronic pulmonary disease	8,136 (45.9)	902 (60.3)	1,317 (51.4)	2,072 (47.3)	1,908 (43.6)	1,178 (41.2)	759 (36.8)
Liver disease	2,393 (13.5)	280 (18.7)	368 (14.4)	558 (12.7)	571 (13.0)	389 (13.6)	227 (11.0)
Malignancies	4,401 (24.8)	435 (29.1)	745 (29.1)	1,176 (26.8)	1,050 (24.0)	623 (21.8)	372 (18.1)
Charlson Comorbidity Index score	5 [3-7]	5 [3-7]	5 [3-7]	5 [3-7]	5 [3-7]	5 [3-6]	5 [3-6]
Catheter vascular access type	12,345 (69.6)	1,210 (80.8)	1,835 (71.7)	2,886 (65.9)	2,867 (65.5)	1,971 (69.0)	1,576 (76.5)
Medications							
ACE inhibitors/ARBs	11,238 (63.4)	887 (59.3)	1,524 (59.5)	2,721 (62.1)	2,753 (62.9)	1,929 (67.5)	1,424 (69.1)
β-Blockers	14,036 (79.2)	1,117 (74.6)	1,906 (74.5)	3,401 (77.6)	3,520 (80.4)	2,373 (83.1)	1,719 (83.4)
Calcium channel blockers	13,047 (73.6)	492 (32.9)	1,472 (57.5)	3,263 (74.5)	3,567 (81.5)	2,482 (86.9)	1,771 (86.0)
Diuretics	14,854 (83.8)	1,207 (80.6)	1,993 (77.9)	3,600 (82.2)	3,719 (85.0)	2,534 (88.7)	1,801 (87.4)
Vasodilators	1,075 (6.1)	11 (0.7)	48 (1.9)	156 (3.6)	273 (6.2)	285 (10.0)	302 (14.7)
Statins	12,772 (72.0)	1,012 (67.6)	1,823 (71.2)	3,273 (74.7)	3,210 (73.4)	2,039 (71.4)	1,415 (68.7)
Vitamin D analogues	6,391 (36.0)	373 (24.9)	864 (33.8)	1,711 (39.1)	1,700 (38.8)	1,075 (37.6)	668 (32.4)
ESAs	6,762 (38.1)	398 (26.6)	816 (31.9)	1,687 (38.5)	1,847 (42.2)	1,256 (44.0)	758 (36.8)
CV medication adherence > 80%	13,793 (77.8)	1,214 (81.1)	2,092 (81.7)	3,527 (80.5)	3,399 (77.7)	2,116 (74.1)	1,445 (70.1)
Laboratory parameters ^b							
Serum albumin, g/dL	3.4 ± 0.6	3.4 ± 0.6	3.4 ± 0.6	3.4 ± 0.6	3.4 ± 0.6	3.3 ± 0.6	3.2 ± 0.6
Blood hemoglobin, g/dL	10.9 ± 1.4	11.1 ± 1.6	11.1 ± 1.5	11.0 ± 1.4	10.8 ± 1.3	10.7 ± 1.3	10.5 ± 1.4
Mean eGFR, mL/min/1.73 m ²	15.7 [11.9-22.2]	22.3 [15.4-33.2]	17.8 [13.1-27.7]	15.6 [12.0-22.4]	14.9 [11.5-19.8]	14.8 [11.2-19.6]	14.4 [10.8-19.3]
First eGFR predialysis, ^c mL/min/1.73 m ²	19.8 [14.4-29.6]	27.3 [18.2-45.0]	21.6 [15.2-36.1]	19.1 [14.3-28.7]	19.0 [14.0-26.7]	19.1 [14.0-27.4]	19.0 [13.8-27.6]
Last eGFR, mL/min/1.73 m ²	11.0 [8.1-14.7]	13.3 [9.3-19.0]	12.0 [8.5-16.3]	11.2 [8.3-14.9]	10.7 [8.0-14.1]	10.1 [7.6-13.5]	10.0 [7.3-13.4]

(Continued)

Table 1 (Cont'd). Baseline Patient Characteristics Overall and According to Predialysis SBP

	SBP, mm Hg					
	<120 (n = 1,497)	120-<130 (n = 2,560)	130-<140 (n = 4,380)	140-<150 (n = 4,376)	150-<160 (n = 2,856)	≥160 (n = 2,060)
Total (N = 17,729)						
eGFR slope						
<-10 mL/min/1.73 m ² per y	6,604 (41.6)	845 (37.6)	1,379 (35.1)	1,621 (40.6)	1,241 (47.7)	961 (53.0)
-10 to <-5 mL/min/1.73 m ² per y	3,836 (24.2)	455 (20.2)	1,018 (25.9)	1,089 (27.3)	640 (24.6)	434 (23.9)
-5 to <0 mL/min/1.73 m ² per y	3,313 (20.9)	517 (23.0)	959 (24.4)	859 (21.5)	489 (18.8)	265 (14.6)
≥0 mL/min/1.73 m ² per y	2,116 (13.3)	432 (19.2)	574 (14.6)	423 (10.6)	229 (8.8)	153 (8.4)

Note: Values for categorical variables are given as percentages; values for continuous variables, as mean ± standard deviation or median [interquartile range]. All P values for comparing differences across categories were statistically significant.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent; SBP, systolic blood pressure.

^aCV disease includes coronary artery disease, angina, myocardial infarction, or cerebrovascular disease.

^bAll laboratory results except for last eGFR were averaged over the 1-year predialysis period.

^cFirst eGFR during the 1-year predialysis period.

with lower SBPs (Fig 1). When comparing adjusted HRs across different follow-up periods, the mortality risk associated with lower SBP was highest in the first 3 months after dialysis therapy initiation (Figs 1 and S2). In subgroup analyses, compared with SBP of 130 to <150 mm Hg, lower SBP (<130 mm Hg) was associated with higher mortality overall and across all subgroups; higher SBP (≥150 mm Hg) was associated with lower mortality in the first 3 months after dialysis therapy initiation (Fig 2). A similar pattern of association between SBP and mortality was observed in the 3- to less than 6-month and 6- to less than 12-month periods after dialysis therapy initiation (Fig S3). In contrast, among patients who survived the first 12 months after dialysis therapy initiation, both lower and higher predialysis SBPs were associated with higher mortality overall and in most examined subgroups. Statistically significant interactions were present for BMI, CHF, and eGFR, with greater contributions of lower SBP to mortality among patients with BMI ≥ 30 kg/m², those with CHF, and those with a last eGFR ≥ 10 mL/min/1.73 m² (Fig S3). Results were consistent after further adjustment for serum albumin and blood hemoglobin levels and even after including patients with 1 or 2 outpatient SBP measurements (Table S2; Fig S4).

Association of Predialysis DBP With Postdialysis All-Cause Mortality

Table 3 shows unadjusted and multivariable-adjusted HRs for all-cause mortality in the first 3 months after dialysis therapy initiation associated with predialysis DBP categories. In the crude model, DBP categories were inversely associated with mortality, with the highest risk seen in the DBP category of <60 mm Hg (Table 3). The association of DBP categories with mortality was substantially attenuated after multivariable adjustment and no longer statistically significant (adjusted HRs of DBP < 60, 60-<70, 80-<90, and ≥90 [vs 70-<80] mm Hg are 0.96 [95% CI, 0.78-1.17], 1.03 [95% CI, 0.89-1.19], 0.90 [95% CI, 0.73-1.12], and 1.05 [95% CI, 0.71-1.53], respectively, in model 4; Table 3). As shown in Fig 3, the multivariable-adjusted association between DBP and mortality was slightly J-shaped, without statistical significance. There was no consistent association of DBP with mortality in different follow-up periods (Table S3; Fig S5).

In subgroup analyses, the pattern of associations between DBP and mortality was qualitatively similar in selected subgroups across different follow-up periods (Fig S6). Associations were similar after further adjustment for serum albumin and blood hemoglobin levels and after including patients with 1 or 2 outpatient DBP measurements (Table S4; Fig S7).

Table 2. Adjusted Hazard Ratios for All-Cause Mortality in the First 3 Months After Dialysis Initiation by Categories of Predialysis SBP

	SBP < 120 (n = 1,497)	SBP 120-<130 (n = 2,560)	SBP 130-<140 (n = 4,380)	SBP 140-<150 (n = 4,376)	SBP 150-<160 (n = 2,856)	SBP ≥ 160 (n = 2,060)
Events	318 (21.2)	350 (13.7)	364 (8.3)	245 (5.8)	149 (5.2)	89 (4.3)
Hazard ratio						
Model 1	4.17 (3.53-4.93)	2.56 (2.17-3.01)	1.51 (1.28-1.77)	1.00 (reference)	0.93 (0.76-1.14)	0.77 (0.60-0.98)
Model 2	3.58 (3.02-4.23)	2.32 (1.97-2.73)	1.44 (1.22-1.69)	1.00 (reference)	1.00 (0.81-1.23)	0.86 (0.67-1.09)
Model 3	2.85 (2.37-3.43)	2.19 (1.83-2.61)	1.37 (1.15-1.63)	1.00 (reference)	0.97 (0.78-1.21)	0.80 (0.61-1.05)
Model 4	2.40 (1.96-2.93)	1.99 (1.66-2.40)	1.35 (1.13-1.62)	1.00 (reference)	0.98 (0.78-1.22)	0.76 (0.57-1.00)

Note: Data are presented as number (percentage) or hazard ratio (95% confidence interval). Model 1 is unadjusted; model 2 is adjusted for age, sex, race/ethnicity, and marital status; model 3 is adjusted for variables in model 2 plus comorbid conditions (cardiovascular disease, congestive heart failure, peripheral vascular disease, lung disease, diabetes mellitus, liver disease, and Charlson Comorbidity Index score), body mass index averaged over the 1-year predialysis period, eGFR slope, and last eGFR before dialysis therapy initiation; and model 4 is adjusted for variables in model 3 plus medications (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β -blockers, calcium channel blockers, vasodilators, diuretics, statins, and erythropoiesis-stimulating agents), cardiovascular medication adherence, and type of vascular access (arteriovenous fistula, arteriovenous graft, or catheter).

Abbreviations: eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure (in mm Hg).

DISCUSSION

In this large national cohort of US veterans transitioning to dialysis therapy, we found a reverse J-shaped association of SBP over the 1-year predialysis period with all-cause mortality following dialysis therapy initiation, independent of demographics, comorbid conditions, BMI, eGFR,

medications, cardiovascular medication adherence, and type of vascular access. We also found that patients with predialysis SBPs < 140 mm Hg had significantly higher death risks after dialysis therapy initiation. These associations were most robust for mortality within the immediate 3 months following the dialysis transition. In contrast, predialysis DBP showed no consistent association with postdialysis mortality.

Several epidemiologic studies have repeatedly demonstrated that lower SBP is associated with higher mortality risk in dialysis patients,⁵⁻⁹ which has also been termed reverse epidemiology²⁷ or risk factor paradox²⁸ to contrast it with the well-established association of higher SBP with greater mortality risk in the general population.^{3,4} Previous studies have also described a J-shaped association of SBP with all-cause mortality in patients with NDD-CKD,¹⁰⁻¹³ suggesting that the pattern seen in dialysis patients may also be present in NDD-CKD and probably becomes manifest when patients reach late stages of CKD.²⁹ Regarding the SBP-mortality association in later stages of CKD, a few observational studies have offered seemingly conflicting evidence, some suggesting a J-shaped association,^{11,12} while one other showing no association between SBP and mortality.³⁰ More recently, using extended follow-up data from the MDRD (Modification of Diet in Renal Disease) Study and the African American Study of Kidney Disease and Hypertension trial, Ku et al^{31,32} have shown an association of strict BP control (mean arterial pressure \leq 92 [vs 102-107] mm Hg) with lower mortality risk in patients with moderate to advanced NDD-CKD. However, these studies enrolled relatively small numbers of individuals with advanced NDD-CKD, including patients who did—as well as those who did not—reach end-stage renal disease. In this study, we therefore

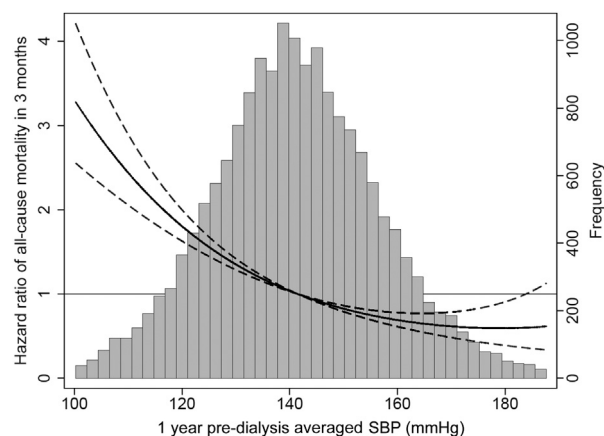


Figure 1. Association of predialysis systolic blood pressure (SBP) with all-cause mortality in the first 3 months after dialysis therapy initiation. Solid and dashed lines represent hazard ratio and 95% confidence interval, respectively. A hazard reference ratio of 1 (solid horizontal line) and a histogram of observed SBP values are overlaid. The x-axis shows SBPs, trimmed at 0.5% and 99.5%. Model is adjusted for age, sex, race/ethnicity, marital status, comorbid conditions (cardiovascular disease, congestive heart failure, peripheral vascular disease, lung disease, diabetes mellitus, liver disease, and Charlson Comorbidity Index score), body mass index averaged over the 1-year predialysis period, estimated glomerular filtration rate (eGFR) slope, last eGFR before dialysis therapy initiation, medications (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β -blockers, calcium channel blockers, vasodilators, diuretics, statins, and erythropoiesis-stimulating agents), cardiovascular medication adherence, and type of vascular access (arteriovenous fistula, arteriovenous graft, or catheter).

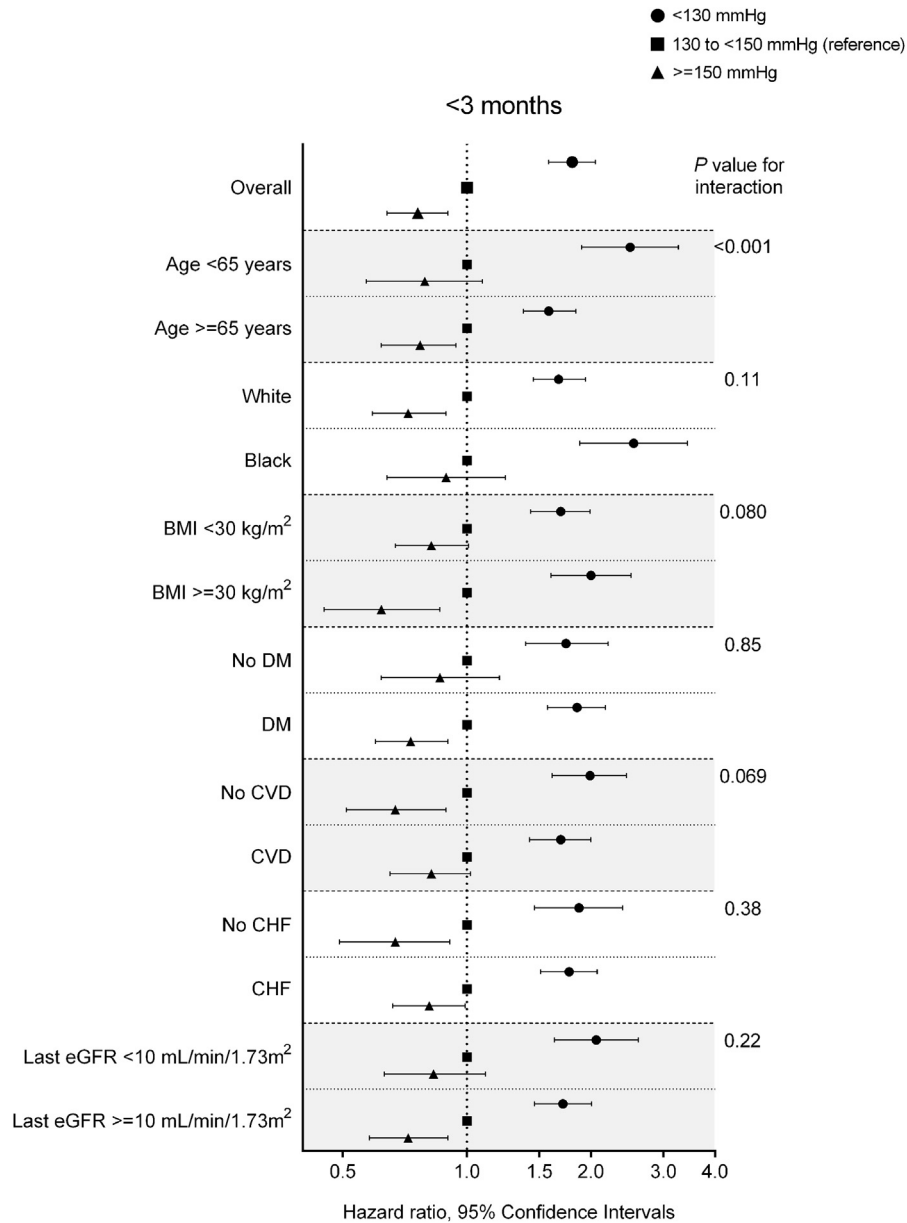


Figure 2. Adjusted hazard ratios (95% confidence intervals) of all-cause mortality in the first 3 months after dialysis therapy initiation associated with predialysis systolic blood pressure categories in selected subgroups. Model is adjusted for age, sex, race/ethnicity, marital status, comorbid conditions (cardiovascular disease [CVD], congestive heart failure [CHF], peripheral vascular disease, lung disease, diabetes mellitus [DM], liver disease, and Charlson Comorbidity Index score), body mass index (BMI) averaged over the 1-year predialysis period, estimated glomerular filtration rate (eGFR) slope, last eGFR before dialysis therapy initiation, medications (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β -blockers, calcium channel blockers, vasodilators, diuretics, statins, and erythropoiesis-stimulating agents), cardiovascular medication adherence, and type of vascular access (arteriovenous fistula, arteriovenous graft, or catheter).

extended these observations to a large and unique cohort of patients, all of whom transitioned to dialysis therapy, and for the first time investigated the associations of SBP and DBP in the immediate predialysis transition period with mortality after dialysis therapy initiation.

Several potential explanations have been suggested for the underlying mechanisms of the observed

reverse J-shaped association with all-cause mortality. Over the course of CKD progression, patients with CKD develop a wide variety of comorbid conditions, such as ischemic heart disease and CHF.^{33,34} Patients with advanced NDD-CKD have an exceptionally high burden of such conditions, and low SBP may be a marker of more severe underlying comorbid conditions, which could therefore confound the association

Table 3. Adjusted Hazard Ratios for All-Cause Mortality in the First 3 Months After Dialysis Initiation by Categories of Predialysis DBP

	DBP < 60 (n = 1,517)	DBP 60-<70 (n = 5,269)	DBP 70-<80 (n = 6,152)	DBP 80-<90 (n = 3,574)	DBP ≥ 90 (n = 1,217)
Events	250 (16.5)	608 (11.5)	442 (7.2)	171 (4.8)	44 (3.6)
Hazard ratio					
Model 1	2.43 (2.08-2.84)	1.64 (1.45-1.86)	1.00 (reference)	0.66 (0.55-0.78)	0.49 (0.36-0.67)
Model 2	1.72 (1.46-2.02)	1.32 (1.16-1.49)	1.00 (reference)	0.85 (0.71-1.01)	0.82 (0.59-1.12)
Model 3	0.90 (0.74-1.09)	0.96 (0.84-1.11)	1.00 (reference)	1.01 (0.83-1.24)	1.25 (0.86-1.81)
Model 4	0.96 (0.78-1.17)	1.03 (0.89-1.19)	1.00 (reference)	0.90 (0.73-1.12)	1.05 (0.71-1.53)

Note: Data are presented as number (percentage) or hazard ratio (95% confidence interval). Model 1 is unadjusted; model 2 is adjusted for age, sex, race/ethnicity, and marital status; model 3 is adjusted for the variables in model 2 plus comorbid conditions (cardiovascular disease, congestive heart failure, peripheral vascular disease, lung disease, diabetes mellitus, liver disease, and Charlson Comorbidity Index score), systolic blood pressure and body mass index averaged over the 1-year predialysis period, eGFR slope, and last eGFR before dialysis therapy initiation; and model 4 is adjusted for the variables in model 3 plus medications (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β -blockers, calcium channel blockers, vasodilators, diuretics, statins, and erythropoiesis-stimulating agents), cardiovascular medication adherence, and type of vascular access (arteriovenous fistula, arteriovenous graft, or catheter).

Abbreviations: DBP, diastolic blood pressure (in mm Hg); eGFR, estimated glomerular filtration rate.

between BP and mortality. However, low SBP could also be a direct mediator of the effects of severe comorbid conditions on clinical outcomes by causing compromised blood flow to vital organs, which could explain the higher mortality observed in our study. Furthermore, cardiovascular drug overdose (regardless of whether it was for cardio- or renoprotection)

and/or ultrafiltration procedures during the hemodialysis treatment (particularly for those with low predialysis SBPs)³⁵ could possibly play contributory roles in the associations seen in our study.

Our findings support the hypothesis that the effect of higher SBP, a conventional cardiovascular risk factor affecting relatively long-term outcomes, on future mortality might be outweighed by the short-term effects of lower SBP accompanied by the mentioned pathophysiologic processes intrinsic to this population; hence, the observation that the reverse J-shaped association was more evident for short-term mortality immediately after the dialysis transition. It is also important to note that we observed notable interactions in a few subgroups of patients who survived the first 12 months after dialysis therapy initiation. In this particular population, the contribution of higher SBP (>150 mm Hg) to higher all-cause mortality was more evident in patients without CHF. The inverse association of SBP with all-cause mortality seen in patients with CHF during this long-term period is generally consistent with what has been described in the general CHF population.³⁶ It is thus possible that low SBP in some patients with advanced NDD-CKD is preceded by cardiovascular (ie, CHF) and diabetic (ie, autonomic neuropathy) consequences, and its role in the outcomes of these patients may require special consideration, particularly if they survive the first 12 months after dialysis therapy initiation.

Given the considerable uncertainty about the optimal approach to BP management in patients with advanced NDD-CKD, our study may have several clinical implications. First, physicians should be aware of the marked immediate postdialysis death risk associated with low predialysis SBP in patients with advanced NDD-CKD transitioning to dialysis therapy. Notwithstanding considerations about

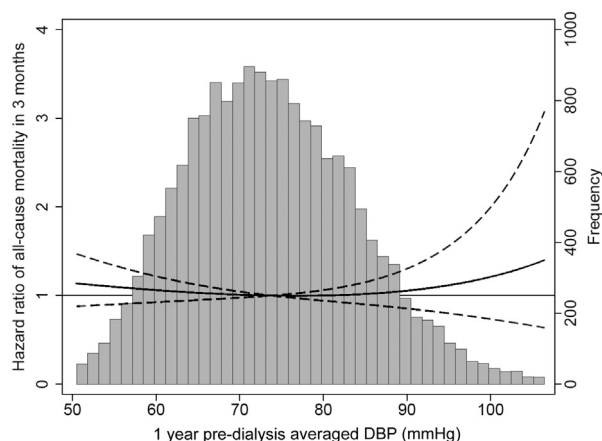


Figure 3. Association of predialysis diastolic blood pressure (DBP) with all-cause mortality in the first 3 months after dialysis therapy initiation. Solid and dashed lines represent hazard ratio and 95% confidence interval, respectively. A hazard reference ratio of 1 (solid horizontal line) and a histogram of observed DBP values are overlaid. The x-axis shows DBP levels, trimmed at 0.5% and 99.5%. Model is adjusted for age, sex, race/ethnicity, marital status, comorbid conditions (cardiovascular disease, congestive heart failure, peripheral vascular disease, lung disease, diabetes mellitus, liver disease, and Charlson Comorbidity Index score), systolic blood pressure and body mass index averaged over the 1-year predialysis period, estimated glomerular filtration rate (eGFR) slope, last eGFR before dialysis therapy initiation, medications (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β -blockers, calcium channel blockers, vasodilators, diuretics, statins, and erythropoiesis-stimulating agents), cardiovascular medication adherence, and type of vascular access (arteriovenous fistula, arteriovenous graft, or catheter).

causality (or lack thereof), a low predialysis SBP could thus be used as a predictor of higher early posttransition mortality and could therefore be useful when counseling patients or planning dialysis preparations (eg, vascular access placement). If we allow for the possibility that the SBP-mortality relationship may be causal, our findings suggest caution when implementing BP-lowering strategies based on current hypertension treatment guidelines that recommend a target BP < 140/90 or < 130/80 mm Hg without specifying a desirable lower limit for the target BP.^{15,16} Optimal SBPs and the effect of antihypertensive medications to lower elevated SBPs toward such levels toward improving clinical outcomes in this unique population deserve future prospective studies, including controlled clinical trials.

This study needs to be interpreted with acknowledgment of several limitations. First, because this was an observational study, only associations, not cause-effect relationships, can be established. Most important, we cannot conclude that the mortality risk associated with various SBPs in our study is equal to the risk imparted by the same SBPs when they occur as a result of antihypertensive interventions in clinical practice. Therefore, it must be emphasized that our current findings should not divert clinicians' efforts from lowering elevated SBP to prevent cardiovascular complications and kidney disease progression in patients with NDD-CKD. Second, most of our patients were male US veterans; hence, results may not apply to women or patients from other geographic areas. Also of note, all patients in this cohort survived to the point of initiating dialysis therapy and were anchored on that time point. Third, the effect of longitudinal changes in BP and other confounders such as cardiovascular medications over the postdialysis follow-up period were not accounted for; thus, it is possible that such time-dependent factors might affect the observed risk estimates. However, given the nature of this study, which examined the impact of predialysis SBP and DBP on postdialysis outcomes, the results obtained with the use of fixed baseline covariates would still be of value, with important clinical implications for patients with CKD in the transition period. Finally, as with all observational studies, we were not able to eliminate the possibility of unmeasured confounders such as proteinuria.

In conclusion, in this large national cohort of US veterans transitioning to dialysis therapy, we found a reverse J-shaped association of predialysis SBP with all-cause mortality following dialysis therapy initiation, with significantly higher death risk seen with SBPs < 140 mm Hg, but found no consistent association with predialysis DBP. Our findings suggest that

pretransition low SBP could be a useful predictor of early posttransition mortality, and also that physicians should be cautious when substantially lowering SBP below the currently established targets in this unique patient population. Future clinical trials are needed to clarify the ideal predialysis SBP and determine whether active interventions targeting predialysis SBP could be applied to improve the high early mortality seen among incident dialysis patients.

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Contributions: Research idea: KS, CPK; study design: KS, MZM, PKP, FT, JLL, VAR, MS, CMR, ES, JJS, KY, KK-Z, CPK; data acquisition: KS, MZM, PKP, JLL, VAR, MS, ES, CPK; data analysis/interpretation: KS, PKP, KK-Z, CPK; supervision or mentorship: KY, KK-Z, CPK. 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. CPK and KS take responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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SUPPLEMENTARY MATERIAL

Table S1: Adjusted HRs for all-cause mortality 3-<6, 6-<12, and \geq 12 mo after initiation, by predialysis SBP category.

Table S2: Adjusted HRs for all-cause mortality in 4 periods after initiation, by predialysis SBP category, with adjustment for lab data.

Table S3: Adjusted HRs for all-cause mortality 3-<6, 6-<12, and \geq 12 months after initiation, by predialysis DBP category.

Table S4: Adjusted HRs for all-cause mortality in 4 periods after initiation, by predialysis DBP category, with adjustment for lab data.

Figure S1: Flow chart of study population.

Figure S2: Association of predialysis SBP with all-cause mortality 3-<6, 6-<12, and \geq 12 mo after initiation.

Figure S3: Adjusted HRs of all-cause mortality 3-<6, 6-<12, and \geq 12 mo after initiation, by predialysis SBP category; selected subgroups.

Figure S4: Association of predialysis SBP with all-cause mortality <3, 3-<6, 6-<12, and \geq 12 mo after initiation in patients with \geq 1 SBP.

Figure S5: Association of predialysis DBP with all-cause mortality 3-<6, 6-<12, and \geq 12 mo after dialysis initiation.

Figure S6: Adjusted HRs of all-cause mortality <3, 3-<6, 6-<12, and \geq 12 mo after initiation, by predialysis DBP category; selected subgroups.

Figure S7: Association of predialysis DBP with all-cause mortality in <3, 3-<6, 6-<12, and \geq 12 mo after initiation in patients with \geq 1 DBP.

Note: The supplementary material accompanying this article (<http://dx.doi.org/10.1053/j.ajkd.2016.12.020>) is available at www.ajkd.org

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