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Pre-ESRD Visit-to-Visit Systolic Blood Pressure Variability and Post-ESRD Mortality in Incident Dialysis Patients

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Abstract

Objectives—Higher systolic blood pressure (SBP) visit-to-visit variability (SBPV) has been associated with increased risk of adverse events in patients with chronic kidney disease (CKD), but the association of SBPV in advanced non-dialysis dependent CKD (NDD-CKD) with mortality after the transition to end-stage renal disease (ESRD) remains unknown.

Methods—Among 17,729 US veterans transitioning to dialysis between 10/2007–9/2011, we assessed SBPV calculated from the standard deviation of at least three intra-individual outpatient SBP values during the last year prior to dialysis transition ("prelude period"). Outcomes included factors associated with higher prelude SBPV and post-transition all-cause, cardiovascular, and infection-related mortality, assessed using multivariable linear regression and Cox and competing risk regressions, respectively, adjusted for demographics, comorbidities, medications, cardiovascular medication adherence, SBP, body mass index, estimated glomerular filtration rate, and type of vascular access.

Results—Modifiable clinical factors associated with higher prelude SBPV included higher SBP, use of antihypertensive medications and erythropoiesis-stimulating agents, inadequate cardiovascular medication adherence, and catheter use. After multivariable adjustment, higher

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prelude SBPV was significantly associated with higher post-ESRD all-cause and infection-related mortality, but not cardiovascular mortality (hazard/subhazard ratios [95% CI] for the highest (vs. lowest) quartile of SBPV, 1.08 [1.01–1.16], 1.02 [0.89–1.15], and 1.41 [1.10–1.80] for all-cause, cardiovascular, and infection-related mortality, respectively).

Conclusions—High pre-ESRD SBPV is potentially modifiable and associated with higher all-cause and infection-related mortality following dialysis initiation. Further studies are needed to test whether modification of pre-ESRD SBPV can improve clinical outcomes in incident ESRD patients.

Keywords

systolic blood pressure; variability; mortality; cardiovascular disease; chronic kidney disease; end-stage renal disease

INTRODUCTION

A growing number of studies have reported that visit-to-visit variability in systolic blood pressure (SBPV) is independently associated with adverse clinical outcomes such as all-cause and cardiovascular mortality,[1–6] coronary heart disease,[7–9] heart failure,[10] and stroke,[11–13] mostly in patients with hypertension or in those with end-stage renal disease (ESRD) on hemodialysis. Over the course of chronic kidney disease (CKD) progression, patients with CKD develop a wide variety of cardiovascular complications such as endothelial dysfunction,[14] arterial stiffness,[15] and left ventricular diastolic dysfunction,[16] all of which are also associated with high SBPV;[17–19] and indeed, some recent studies have shown similar associations of SBPV with outcomes among patients with non-dialysis dependent CKD (NDD-CKD).[20–25] These studies, however, have primarily focused on patients with CKD stage 3 or 4; and thus it remains unknown if these associations apply to those with advanced NDD-CKD transitioning to ESRD, a unique patient population who experience the highest mortality immediately after the transition to dialysis and suffer from an exceptionally high health and economic burden.[26]

Given the peculiar risk profile and the pervasive nature of hypertension in this vulnerable population during the transition period,[27] the question whether high SBPV in advanced NDD-CKD holds prognostic significance on post-transition mortality is of paramount relevance. With this background in mind, we hypothesized that advanced NDD-CKD patients with higher SBPV are at greater risk of mortality following dialysis initiation. To test this hypothesis, we investigated the association of SBPV in the pre-ESRD transition period with post-ESRD all-cause, cardiovascular, and infection-related mortality, using a large nationally representative cohort of US veterans with advanced NDD-CKD transitioning to dialysis.

METHODS

Study Population

We analyzed longitudinal data from the Transition of Care in CKD (TC-CKD) study, a retrospective cohort study examining US veterans with advanced NDD-CKD transitioning to

dialysis from October 1, 2007 through September 30, 2011.[28–30] A total of 52,172 US veterans were identified from the US Renal Data System (USRDS)[26] as a source population. The algorithm for the cohort definition is shown in Supplemental Figure 1. In the present study, we used all SBP values measured during outpatient clinical encounters in any Veterans Affairs (VA) facility; therefore, patients without any outpatient systolic blood pressure (SBP) measurements at a VA facility were excluded (n = 19,533). We also excluded those who had less than three outpatient SBP measurements recorded on different days within one year prior to dialysis initiation (i.e., one-year "prelude period") (n = 14,645) and who were missing follow-up data (n = 265), resulting in a study population of 17,729 patients.

Exposure Variable

The primary exposure of interest was SBPV over the one-year prelude period. SBPV was defined as the standard deviation (SD) of the intra-individual outpatient SBP values in each patient measured during the same prelude period. We categorized the SBPV values into quartiles (<11.6, 11.6-<15.7, 15.7-<20.4, and ≥20.4 mmHg), using the lowest SBPV quartile as reference.

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 initiation. Information about comorbidities was extracted from the VA Inpatient and Outpatient Medical SAS Datasets,[31] 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 and Medicaid Services (CMS) data. The Charlson Comorbidity Index score was calculated using the Deyo modification for administrative datasets, without including kidney disease.[32] Cardiovascular disease was defined as the presence of diagnostic codes for angina, coronary artery disease, myocardial infarction, or cerebrovascular disease. Medication data were collected from both CMS Data (Medicare Part D) and VA pharmacy dispensation records.[33] Patients who received at least one dispensation of medications within the one-year prelude 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 one-year prelude period, capped at 100%.[30] Laboratory data were obtained from VA research databases as previously described,[34, 35] and their baseline values were defined as the average of each covariate during the one-year prelude period preceding dialysis initiation. Estimated glomerular filtration rate (eGFR) was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation.[36]

Outcome Assessment

The co-primary outcomes of interest were all-cause, cardiovascular, and infection-related mortality after dialysis initiation. The start of the follow-up period was the date of dialysis initiation, and patients were followed up until death or other censoring events including kidney transplantation, loss of follow-up, or the last date of available follow-up (December 27, 2012 and October 6, 2011 for all-cause and cause-specific mortality, respectively).[28–

30] All-cause mortality data, censoring events, and associated dates were obtained from VA and USRDS data sources.[26] Cause-specific mortality data were obtained from USRDS.

Statistical analysis

Baseline patient characteristics were summarized according to SBPV categories, and presented as number (percent) for categorical variables and the mean ± standard deviation (SD) for continuous variables with a normal distribution or median (25th, 75th percentiles) for those with a skewed distribution. Differences across categories were assessed using analysis of variance and chi-squared tests for continuous and categorical variables, respectively. We performed multivariable linear regression to identify factors independently associated with SBPV. Based on a priori knowledge and their availability in this study, the following explanatory variables were included: sociodemographics (age, sex, race, and marital status), comorbidities (diabetes mellitus, cardiovascular disease, congestive heart failure [CHF], peripheral vascular disease, lung disease, liver disease, and Charlson comorbidity index), SBP, body mass index [BMI], vascular access type, medications (angiotensin-converting enzyme inhibitors [ACEIs]/angiotensin receptor blockers [ARBs], β-blockers, calcium channel blockers [CCBs], diuretics, vasodilators, statins, and erythropoietin stimulating agents [ESAs]), cardiovascular medication adherence, and laboratory parameters (serum albumin, blood hemoglobin, and eGFR). Variance inflation factors were calculated to examine substantial multicollinearity among these parameters, and values >5.0 were considered to indicate collinearity. The association between SBPV and mortality was estimated using Cox proportional hazards models for all-cause death and Fine and Gray competing risks regression for cause-specific deaths by treating deaths from other causes as competing events.[37] Models were incrementally adjusted for the following potential confounders based on theoretical considerations: model 1 unadjusted; model 2 adjusted for age, sex, race/ethnicity, and marital status; model 3 additionally accounted for comorbidities (hypertension, diabetes mellitus, cardiovascular disease, CHF, peripheral vascular disease, lung disease, liver disease, and Charlson comorbidity index), and SBP, BMI, and eGFR levels averaged over the one-year prelude period; and model 4 additionally included medications, cardiovascular medication adherence, and type of vascular access (arteriovenous fistula, arteriovenous graft, or catheter).

We conducted several sensitivity analyses to evaluate the robustness of our main findings. SBPV was also defined as the coefficient of variation of the intra-individual outpatient SBP values (i.e., SD/mean SBP), and the associations of the relative SBPV index (in quartiles) with outcomes were evaluated. The associations between SBPV and mortality were examined in subgroups of patients stratified by age, race, BMI, SBP, eGFR, and presence/absence of select comorbidities. 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 SBPV-mortality associations in the group of 15,615 patients with available albumin and hemoglobin measurements as an additional model (model 5).

Compared to patients in the main cohort (n = 17,729), those who were excluded from the source cohort (n = 34,443) were older (71.6 versus 67.8 years) and were less likely to be

male (92.5% versus 98.1%), African-American (20.5% versus 31.4%), and diabetic (49.4% versus 73.0%). Of the variables included in multivariable models, data points were missing for race (0.2%), BMI (<0.01%), eGFR (0.7%), vascular access type (7.5%), serum albumin (3.3%), and blood hemoglobin (2.3%). Information about cause of death was also missing in 4,337 of the 9,064 (52.2%) who died in our study population. Compared to patients with missing cause of death, those without missing cause of death were less likely to be African-American (21.6% versus 25.6%) and had a slightly higher prevalence of cardiovascular disease (57.1% versus 53.3%), CHF (66.7% versus 63.0%), and chronic pulmonary disease (56.3% versus 51.1%) (Supplemental Table 1). Of the 17,729 patients in our study population, 16,275 (91.8%) had complete data available for the main adjusted multivariable model (model 4). Due to the relatively low proportion of missingness, missing data was not imputed. The reported *P* values are two-sided and reported as significant at <0.05 for all analyses. All analyses were conducted using STATA/MP Version 14 (STATA Corporation, College Station, TX). The study was approved by the Institutional Review Boards of the Memphis and Long Beach VA Medical Centers, with exemption from informed consent.

RESULTS

Baseline Characteristics

Overall, the mean±SD age at baseline was 67.8±11.2 years; 98.1% were male; 31.4% were African-American; and 73.0% were diabetic. The median (25th, 75th percentiles) eGFR level was 15.7 (11.9, 22.2) mL/min/1.73m^2. During the one-year prelude period, patients had a median (25th, 75th percentiles) of 10 (5, 16) outpatient SBP measurements. The mean ±SD prelude SBPV was 16.4±7.0 mmHg. Baseline characteristics in the overall cohort and stratified by SBPV quartiles are presented in Table 1. Compared to patients with lower SBPV, those with higher SBPV were younger; were more likely to be African-American and unmarried; had higher systolic and diastolic BPs; and had a higher prevalence of hypertension, diabetes, cardiovascular disease, and peripheral vascular disease. They were also more likely to use antihypertensive medications; were less likely to adhere to cardiovascular medications; and had lower serum albumin, blood hemoglobin, and eGFR levels.

Factors associated with prelude SBPV

Table 2 shows the association of SBPV with baseline patient characteristics. After multivariable adjustment, higher SBP, presence of comorbidities such as diabetes, cardiovascular disease, and peripheral vascular disease, catheter use, and use of ACEIs/ARBs, β-blockers, vasodilators, and ESAs were associated with higher SBPV. In contrast, older age, married status, higher BMI, adequate cardiovascular medication adherence, and higher serum albumin were associated with lower SBPV.

Association of Pre-ESRD SBPV with Post-ESRD All-Cause Mortality

There were 9,064 all-cause deaths during a median follow-up of 2.0 years (25th, 75th percentiles, 1.1, 3.1 years; total time at risk, 37,969 patient-years) following dialysis initiation (crude incidence rate, 238.7 per 1000 patient-years; 95% confidence interval [CI], 233.9–243.7). Figure 1 shows the unadjusted- and multivariable-adjusted hazard ratios

(HRs) associated with pre-ESRD SBPV quartiles. In the crude model, SBPV quartiles were inversely associated with all-cause mortality, with significantly lower death risks seen in higher SBPV quartiles. After multivariable adjustment, the association between SBPV and all-cause mortality was substantially attenuated and remained statistically significant only for the highest SBPV category (adjusted HRs [95% CI] for SBPV quartiles 2 through 4 [vs. quartile 1], 0.99 [0.93–1.05], 0.98 [0.92–1.04], and 1.08 [1.01–1.16], respectively, in model 4; Figure 1). The association remained essentially unchanged when SBPV was quantified as coefficient of variation of SBP (Supplemental Figure 2).

In subgroup analyses, higher SBPV was associated with higher all-cause mortality across most subgroups (Figure 2). Statistically significant interactions were present for BMI, diabetes, and CHF, with greater contributions of higher SBPV to all-cause mortality among patients with BMI <30 kg/m^2, those without diabetes, and those without CHF. Results were similar after additional adjustment for serum albumin and blood hemoglobin levels, albeit without reaching statistical significance (Supplemental Table 2).

Association of Pre-ESRD SBPV with Post-ESRD Cardiovascular and Infection-Related Mortality

During a median follow-up of 1.3 years (25th, 75th percentiles, 0.5, 2.3 years) following dialysis initiation, 2,363 and 574 deaths occurred from cardiovascular and infection-related causes, respectively, and 1,790 deaths occurred from other causes. In our crude model, SBPV quartiles were inversely associated with cardiovascular mortality, with significantly lower death risks seen in higher SBPV quartiles. This association was considerably attenuated and no longer significant after multivariable adjustment (adjusted SHRs [95% CI] for SBPV quartiles 2 through 4 [vs. quartile 1], 0.97 [0.86–1.09], 0.91 [0.80–1.03], and 1.02 [0.89–1.15], respectively, in model 4; Figure 3). In contrast, higher SBPV quartiles were associated with higher infection-related mortality in all models (adjusted SHRs [95% CI] for SBPV quartiles 2 through 4 [vs. quartile 1], 1.08 [0.85–1.38], 1.02 [0.78–1.32], and 1.41 [1.10–1.80], respectively, in model 4; Figure 3). The associations were largely similar for SBPV defined as coefficient of variation of SBP (Supplemental Figure 3).

In subgroup analyses, the pattern of association between SBPV and cardiovascular mortality was qualitatively similar to that with all-cause mortality, while the association with infection-related mortality was generally consistent across selected subgroups (Supplemental Figure 4). The associations were robust to additional adjustment for serum albumin and blood hemoglobin levels (Supplemental Table 3).

DISCUSSION

In this large national cohort of 17,729 US veterans with advanced NDD-CKD transitioning to dialysis, we found that higher SBPV was associated with higher all-cause and infection-related mortality, but not cardiovascular mortality, following dialysis initiation. During the one-year prelude period, we also found that higher SBP, history of diabetes, cardiovascular disease, and peripheral vascular disease, use of antihypertensive medications and ESAs, inadequate cardiovascular medication adherence, and catheter use were all associated with higher SBPV.

Although the concept that SBPV has a prognostic value for cardiovascular events is not new, [38–40] there has been limited evidence for its effect on outcomes among NDD-CKD population. In recent years, some observational studies have demonstrated its independent associations with all-cause mortality and cardiovascular and renal events in patients with NDD-CKD;[20–25] however, these studies consisted mostly of patients with CKD stage 3 or 4 and included a relatively small number of patients with advanced NDD-CKD. More importantly, all but one of these studies have examined the association of SBPV with outcomes that occurred before ESRD transition, presumably due to the lack of large databases linking pre-ESRD transition data to post-ESRD registries. In one retrospective cohort study of 374 elderly patients with NDD-CKD and hypertension, Iorio et al.[20] investigated the carry-over effect of SBPV on mortality after dialysis initiation by extending the observation of 34 out of 374 patients (9.0%) who initiated dialysis, but failed to show an association due to not detecting any fatal events over a mean follow-up of six months after dialysis initiation. In the present study, we therefore extended the previous observations to a large and unique cohort of patients with advanced NDD-CKD transitioning to dialysis, and for the first time demonstrated the prognostic impact of pre-ESRD SBPV with post-ESRD outcomes, including not only all-cause mortality but also cardiovascular and infection-related mortality.

Several potential explanations have been proposed for the mechanisms underlying higher SBPV, such as endothelial dysfunction,[17] increased arterial stiffness,[41, 42] disturbed baroreflex regulation of BP,[43] use of certain types of antihypertensive medications,[44] low medication adherence,[45] and social and lifestyle factors.[46] Increased SBPV can in turn cause greater stress on blood vessels and induce endothelial dysfunction and subclinical inflammation, serving as a potential direct mediator of early target-organ damage.[47, 48] In line with these plausible mechanisms linking SBPV to adverse outcomes, we identified both non-modifiable and modifiable factors associated with higher SBPV, including history of diabetes, cardiovascular disease, and peripheral vascular disease as non-modifiable factors; and higher SBP, use of antihypertensive medications and ESAs, low cardiovascular medication adherence and dialysis catheter use as vascular access as modifiable risk factors. When we accounted for all of these factors in the mortality risk estimates, the association of pre-ESRD SBPV with post-ESRD mortality, particularly with all-cause and cardiovascular mortality, was substantially modified; which may in turn support their potential involvement as underlying pathophysiological mechanisms in the SBPV-mortality relationship. Contrary to expectation, however, we found a weak U-shaped but not statistically significant association between pre-ESRD SBPV and post-ESRD cardiovascular mortality. This seemingly counterintuitive observation might be partly explained by survivorship bias in this unique study population, such that patients who had severely suffered from the above-mentioned cardiovascular complications and had higher SBPV may have died before reaching ESRD. Notably, there was an inverse association of pre-ESRD SBPV with post-ESRD mortality in the unadjusted model, which was substantially confounded by patient characteristics such as younger age and higher SBP (recently reported to be associated with lower post-ESRD mortality in the same study population.[49]) Nonetheless, it is important to note that a similar weak U-shaped association has also been reported between SBPV and fatal coronary heart disease or nonfatal myocardial infarction in a high-risk hypertensive

population.[50] In this context, it is of particular interest that higher pre-ESRD SBPV was consistently associated with higher post-ESRD infection-related mortality. Considering the increased risk of infection in later stages of CKD, it is plausible that higher SBPV in patients with advanced NDD-CKD reflects non-fatal infectious events accompanied by hypotensive episodes during the prelude period, which could be harbingers of future deaths from infectious causes.

SBPV is a complex construct which is not readily available in daily clinical practice, but given the considerable uncertainty about the optimal approach to BP management in advanced NDD-CKD patients, there are several potential clinical and prognostic implications from our study. First, physicians need to be aware of the post-ESRD death risk, particularly infection-related death risk, associated with high pre-ESRD SBPV. Given the independent associations of pre-ESRD SBPV with some potentially modifiable clinical factors such as SBP, use of antihypertensive medications and ESAs, cardiovascular medication adherence, and catheter use, SBPV could become a treatment target through interventions aimed at these characteristics. The effect of such interventions on patient outcomes will have to be tested in future studies.

Our study has several limitations that should be acknowledged. First, this study was observational, and hence, the results do not allow us to infer causality but merely associations. Second, our cohort consisted of predominantly male US veterans, and only 1.9% of the main cohort were women; thus, the results may not apply to women or patients from other geographical areas. Also of note, the majority of patients (73%) in our study population were diabetic. Third, the effect of longitudinal changes in SBPV and other potential confounders such as cardiovascular medications over the post-ESRD follow-up period was not accounted for; therefore, it is possible that such time-dependent factors might affect the observed associations. However, the obtained results with the use of fixed pre-ESRD baseline covariates would still be of value, providing potential prognostic implications for post-ESRD outcomes in patients with advanced NDD-CKD. Fourth, we examined only SBPV but not diastolic BP variability separately; however, some previous studies have demonstrated poor associations of visit-to-visit diastolic BP variability with clinical outcomes both in NDD-CKD patients[22] and in the general population.[2] Finally, as with all observational studies, we cannot eliminate the possibility of unmeasured confounders such as proteinuria.

In conclusion, in this large national cohort of US veterans with advanced NDD-CKD transitioning to dialysis, a greater pre-ESRD SBPV, a potentially modifiable risk factor, was independently associated with higher all-cause and infection-related mortality after dialysis initiation. Our findings suggest the prognostic importance of pre-ESRD SBPV on post-ESRD outcomes and the need for careful consideration to high SBPV in CKD patients during the transition period. Further studies are needed to test whether modification of pre-ESRD SBPV can improve clinical outcomes among incident ESRD patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

CHF	congestive heart failure
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
NDD-CKD	non-dialysis dependent chronic kidney disease
SBPV	systolic blood pressure visit-to-visit variability

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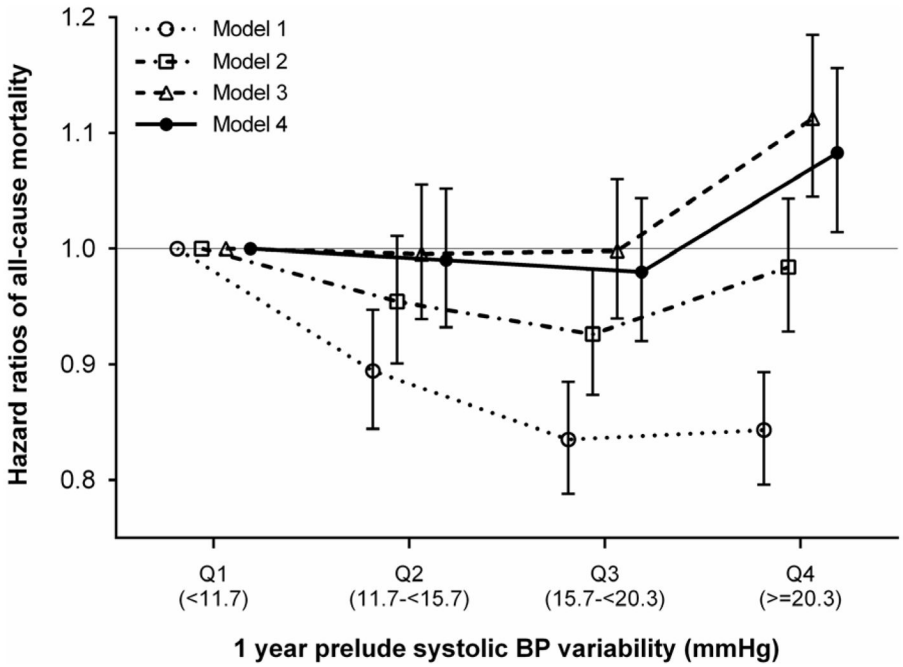

Figure 1. Association of prelude SBPV with all-cause mortality after dialysis initiation

Models are as follows: 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 comorbidities (hypertension, cardiovascular disease, congestive heart failure, peripheral vascular disease, lung disease, diabetes mellitus, liver disease, and Charlson comorbidity index) and systolic BP, BMI, and eGFR averaged over the one-year prelude period; and model 4 is adjusted for the variables in model 3 plus medications (ACEIs/ARBs, β-blockers, calcium channel blockers, vasodilators, diuretics, statins, and ESAs), cardiovascular medication adherence, and type of vascular access (arteriovenous fistula, arteriovenous graft, or catheter).

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; ESA, erythropoietin stimulating agent; SBPV, systolic blood pressure variability

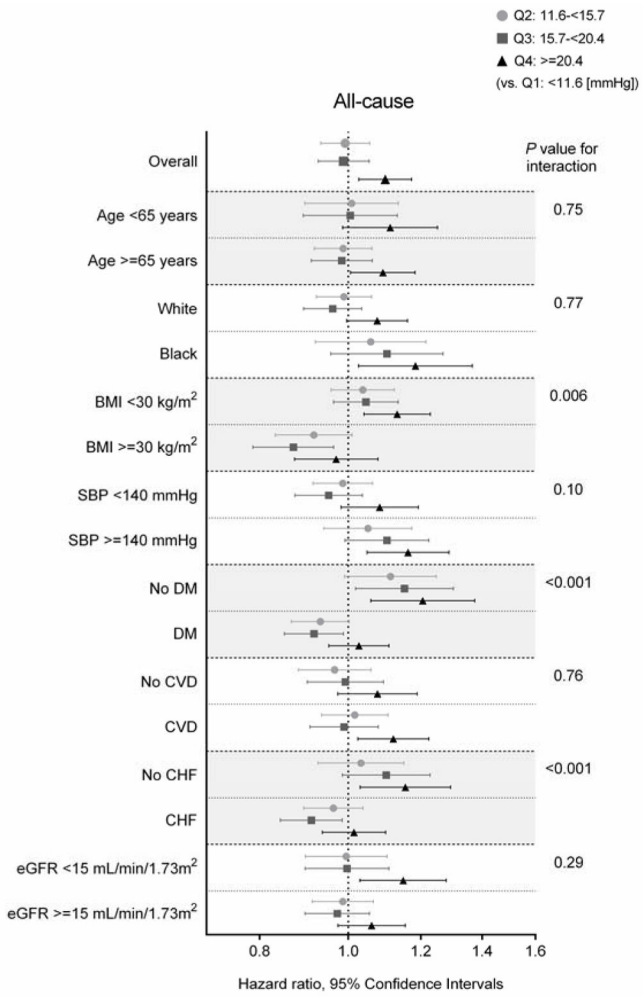

Figure 2. Adjusted hazard ratios (95% CIs) of all-cause mortality after dialysis initiation associated with prelude SBPV quartiles in selected subgroups

Model is adjusted for age, sex, race/ethnicity, marital status, comorbidities (hypertension, cardiovascular disease, congestive heart failure, peripheral vascular disease, lung disease, diabetes mellitus, liver disease, and Charlson comorbidity index), systolic BP, BMI, and eGFR averaged over the one-year prelude period, medications (ACEIs/ARBs, β-blockers, calcium channel blockers, vasodilators, diuretics, statins, and ESAs), cardiovascular medication adherence, and type of vascular access (arteriovenous fistula, arteriovenous graft, or catheter).

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CHF, congestive heart failure; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESA, erythropoietin stimulating agent; SBPV, systolic blood pressure variability

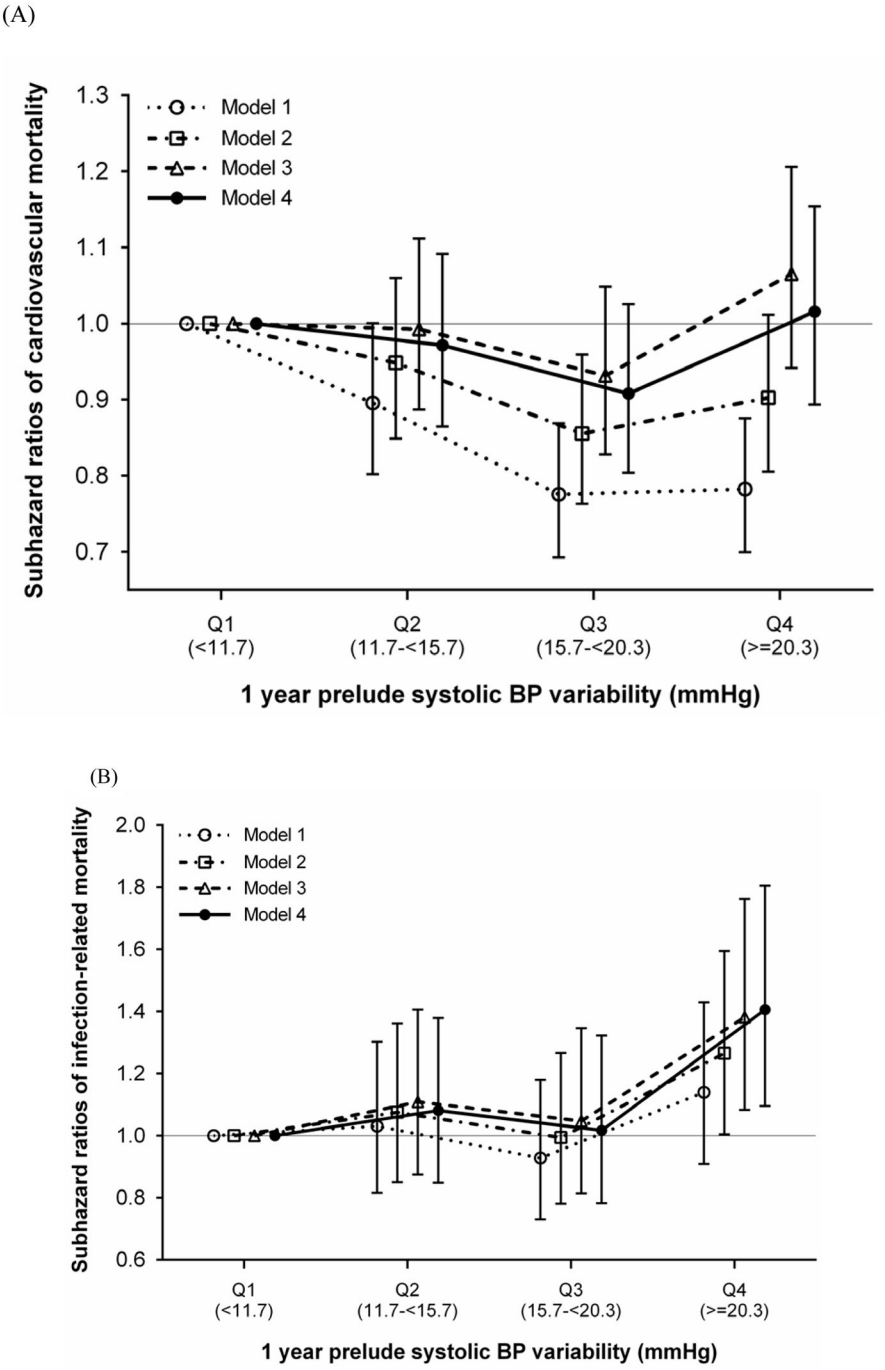

Figure 3. Association of prelude SBPV with (A) cardiovascular and (B) infection-related mortality after dialysis initiation

Models are as follows: 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 comorbidities (hypertension, cardiovascular disease, congestive heart failure, peripheral vascular disease, lung disease, diabetes mellitus, liver disease, and Charlson comorbidity index) and systolic BP, BMI, and eGFR averaged over the one-year prelude period; and model 4 is adjusted for the variables in model 3 plus medications (ACEIs/ARBs, β-blockers,

calcium channel blockers, vasodilators, diuretics, statins, and ESAs), cardiovascular medication adherence, and type of vascular access (arteriovenous fistula, arteriovenous graft, or catheter).

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; ESA, erythropoietin stimulating agent; SBPV, systolic blood pressure variability

Table 1

Baseline patient characteristics according to quartiles of prelude SBPV

	All	Quartile of SBPV (mmHg)				*P*
		Q1 (lowest) <11.6	Q2 11.6 to <15.7	Q3 15.7 to <20.4	Q4 (highest) ≥20.4	
	(*N* = 17,729)	(*n* = 4,433)	(*n* = 4,432)	(*n* = 4,431)	(*n* = 4,433)	
Age (years)	67.8±11.2	69.5±11.6	68.1±11.3	67.3±10.9	66.2±11.0	<0.001
Sex (male)	17,388 (98.1)	4,361 (98.4)	4,349 (98.1)	4,350 (98.2)	4,328 (97.6)	0.071
Race (African-American)	5,559 (31.4)	1,076 (24.3)	1,372 (31.0)	1,486 (33.5)	1,625 (36.7)	<0.001
Marital status (married)	9,204 (51.9)	2,540 (57.3)	2,332 (52.6)	2,223 (50.2)	2,109 (47.6)	<0.001
Systolic BP (mmHg)	141.2±16.1	133.5±15.1	138.2±14.6	143.3±14.3	149.9±15.4	<0.001
Diastolic BP (mmHg)	73.7±10.6	71.1±10.4	72.8±10.1	74.1±10.2	77.0±10.9	<0.001
Body mass index (kg/m^2)	29.9±6.6	30.0±6.5	30.4±6.6	30.1±6.6	29.2±6.4	<0.001
Hypertension	17,327 (97.7)	4,237 (95.6)	4,329 (97.7)	4,367 (98.6)	4,394 (99.1)	<0.001
Diabetes mellitus	12,941 (73.0)	2,921 (65.9)	3,177 (71.7)	3,382 (76.3)	3,461 (78.1)	<0.001
Cardiovascular disease *	8,315 (46.9)	2,012 (45.4)	2,023 (45.6)	2,150 (48.5)	2,130 (48.0)	0.003
Congestive heart failure	9,930 (56.0)	2,455 (55.4)	2,471 (55.8)	2,519 (56.8)	2,485 (56.1)	0.55
Peripheral vascular disease	7,354 (41.5)	1,773 (40.0)	1,795 (40.5)	1,914 (43.2)	1,872 (42.2)	0.007
Chronic pulmonary disease	8,136 (45.9)	2,098 (47.3)	2,098 (47.3)	2,050 (46.3)	1,890 (42.6)	<0.001
Liver disease	2,393 (13.5)	595 (13.4)	616 (13.9)	587 (13.2)	595 (13.4)	0.83
Malignancies	4,401 (24.8)	1,189 (26.8)	1,212 (27.3)	1,057 (23.9)	943 (21.3)	<0.001
AIDS/HIV	244 (1.4)	70 (1.6)	60 (1.4)	60 (1.4)	54 (1.2)	0.53
Charlson Comorbidity Index	5.0 (3.0, 7.0)	5.0 (3.0, 7.0)	5.0 (3.0, 7.0)	5.0 (3.0, 7.0)	5.0 (3.0, 7.0)	<0.001
Vascular access type (catheter)	12,345 (69.6)	3,086 (69.6)	3,027 (68.3)	2,994 (67.6)	3,238 (73.0)	<0.001
Medications						
ACEIs/ARBs	11,238 (63.4)	2,454 (55.4)	2,793 (63.0)	2,936 (66.3)	3,055 (68.9)	<0.001
β-blockers	14,036 (79.2)	3,161 (71.3)	3,448 (77.8)	3,679 (83.0)	3,748 (84.5)	<0.001
Calcium channel blockers	13,047 (73.6)	2,799 (63.1)	3,158 (71.3)	3,459 (78.1)	3,631 (81.9)	<0.001
Diuretics	14,854 (83.8)	3,428 (77.3)	3,725 (84.0)	3,862 (87.2)	3,839 (86.6)	<0.001
Vasodilators	1,075 (6.1)	126 (2.8)	198 (4.5)	307 (6.9)	444 (10.0)	<0.001
Statins	12,772 (72.0)	3,027 (68.3)	3,189 (72.0)	3,295 (74.4)	3,261 (73.6)	<0.001

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	All	Quartile of SBPV (mmHg)				*P*
		Q1 (lowest) <11.6	Q2 11.6 to <15.7	Q3 15.7 to <20.4	Q4 (highest) ≥20.4	
	(*N* = 17,729)	(*n* = 4,433)	(*n* = 4,432)	(*n* = 4,431)	(*n* = 4,433)	
Vitamin D analogs	6,391 (36.0)	1,453 (32.8)	1,679 (37.9)	1,713 (38.7)	1,546 (34.9)	<0.001
ESAs	6,762 (38.1)	1,231 (27.8)	1,698 (38.3)	1,946 (43.9)	1,887 (42.6)	<0.001
CV medication adherence (>80%)	13,793 (77.8)	3,640 (82.1)	3,561 (80.3)	3,407 (76.9)	3,185 (71.8)	<0.001
Laboratory parameters†						
Serum albumin (g/dL)	3.4±0.6	3.5±0.6	3.4±0.6	3.4±0.6	3.3±0.6	<0.001
Blood hemoglobin (g/dL)	10.9±1.4	11.1±1.5	10.9±1.4	10.8±1.3	10.7±1.3	<0.001
eGFR (mL/min/1.73m^2)	15.7 (11.9, 22.2)	16.3 (11.9, 24.7)	15.7 (11.9, 22.5)	15.4 (11.8, 21.2)	15.6 (12.0, 21.0)	<0.001

Data are presented as number (percentage), mean ± standard deviation, or median (25th, 75th percentiles).

*Cardiovascular disease include coronary artery disease, angina, myocardial infarction, or cerebrovascular disease.

†All laboratory results averaged over the one-year prelude period.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESA, erythropoietin stimulating agent; SBPV, systolic blood pressure variability

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Table 2

Factors associated with prelude SBPV

Characteristics	Coefficient*	(95% CI)	*P* value
Age (per 1 year)	−0.03	(−0.04 to −0.02)	<0.001
Sex (male vs. women)	0.63	(−0.06 to 1.31)	0.072
Race (African-American vs. white)	−0.01	(−0.23 to 0.21)	0.91
Marital status (married vs. non-married)	−0.44	(−0.64 to −0.25)	<0.001
Systolic BP (per 1 mmHg)	0.15	(0.14 to 0.16)	<0.001
Body mass index (per 1 kg/m^2)	−0.10	(−0.11 to −0.08)	<0.001
Comorbidities (yes vs. no)			
Diabetes mellitus	0.64	(0.38 to 0.90)	<0.001
Cardiovascular disease†	0.44	(0.23 to 0.66)	<0.001
Congestive heart failure	0.08	(−0.14 to 0.30)	0.49
Peripheral vascular disease	0.39	(0.18 to 0.60)	<0.001
Chronic pulmonary disease	0.07	(−0.14 to 0.28)	0.53
Liver disease	−0.10	(−0.39 to 0.20)	0.52
Charlson Comorbidity Index (per 1 unit)	−0.02	(−0.08 to 0.03)	0.37
Vascular access type (catheter vs. others)	0.34	(0.13 to 0.56)	<0.001
Medications (yes vs. no)			
ACEIs/ARBs	0.65	(0.44 to 0.85)	<0.001
β-blockers	0.88	(0.64 to 1.13)	<0.001
Calcium channel blockers	0.19	(−0.05 to 0.42)	0.12
Diuretics	0.27	(−0.02 to 0.55)	0.067
Vasodilators	0.96	(0.56 to 1.36)	<0.001
Statins	0.15	(−0.08 to 0.37)	0.21
ESAs	0.74	(0.53 to 0.95)	<0.001
CV medication adherence (>80% vs. ≤80%)	−0.80	(−1.02 to −0.57)	<0.001
Laboratory parameters‡			
Serum albumin (per 1 g/dL)	−0.82	(−1.00 to −0.65)	<0.001
Blood hemoglobin (per 1 g/dL)	0.008	(−0.07 to 0.08)	0.84
eGFR (per 1 mL/min/1.73m^2)	0.002	(−0.006 to 0.01)	0.53

[*] Coefficient for multivariable linear regression models. Value of coefficient represents change in SBPV (mmHg) per 1 unit change in each factor. Positive and negative numbers indicate higher and lower BPV per 1 unit change in factors, respectively. The variance inflation factors of these parameters were all less than 5.

[†] Cardiovascular disease include coronary artery disease, angina, myocardial infarction, or cerebrovascular disease.

[‡] All laboratory results averaged over the one-year prelude period.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; eGFR, estimated glomerular filtration rate; ESA, erythropoietin stimulating agent; SBPV, systolic blood pressure variability