Blood Pressure and Risk of Cardiovascular Events in Patients on Chronic Hemodialysis

The CRIC Study (Chronic Renal Insufficiency Cohort)

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See Editorial Commentary, pp 255–256

Abstract—We recently reported a linear association between higher systolic blood pressure (SBP) and risk of mortality in hemodialysis patients when SBP is measured outside of the dialysis unit (out-of-dialysis-unit-SBP), despite there being a U-shaped association between SBP measured at the dialysis unit (dialysis-unit-SBP) with risk of mortality. Here, we explored the relationship between SBP with cardiovascular events, which has important treatment implications but has not been well elucidated. Among 383 hemodialysis participants enrolled in the prospective CRIC study (Chronic Renal Insufficiency Cohort), multivariable splines and Cox models were used to study the association between SBP and adjudicated cardiovascular events (heart failure, myocardial infarction, ischemic stroke, and peripheral artery disease), controlling for differences in demographics, cardiovascular disease risk factors, and dialysis parameters. Dialysis-unit-SBP and out-of-dialysis-unit-SBP were modestly correlated (r=0.34; P<0.001). We noted a U-shaped association of dialysis-unit-SBP and risk of cardiovascular events, with the nadir risk between 140 and 170 mm Hg. In contrast, there was a linear stepwise association between out-of-dialysis-unit-SBP with risk of cardiovascular events. Participants with out-of-dialysis-unit-SBP ≥128 mm Hg (top 2 quartiles) had >2-fold increased risk of cardiovascular events compared with those with out-of-dialysis-unit-SBP ≤112 mm Hg (3rd SBP quartile: adjusted hazard ratio, 2.08 [95% confidence interval, 1.12–3.87] and fourth SBP quartile: adjusted hazard ratio, 2.76 [95% confidence interval, 1.42–5.33]). In conclusion, among hemodialysis patients, although there is a U-shaped (paradoxical) association of dialysis-unit-SBP and risk of cardiovascular disease, there is a linear association of out-of-dialysis-unit-SBP with risk of cardiovascular disease. Out-of-dialysis-unit blood pressure provides key information and may be an important therapeutic target. **(*Hypertension*. 2017;70:435-443. DOI: 10.1161/HYPERTENSIONAHA.117.09091.)** • **Online Data Supplement**

Key Words: blood pressure ■ dialysis ■ heart failure ■ renal dialysis ■ stroke

Among patients on maintenance hemodialysis, prior observational studies have consistently noted a U-shaped association between level of systolic blood pressure (SBP) measured in the dialysis unit and risk of all-cause mortality.[1–12] Hemodialysis patients with SBP <140 mm Hg measured before the dialysis treatment (predialysis SBP) experience higher risk of mortality than those with SBP >140 mm Hg.[3,4,12,13] Moreover, patients with predialysis SBP of 150 to 179 mm Hg seem to be at similar, if not lower, adjusted risk for all-cause mortality compared with those with predialysis SBP of 140 to 149 mm Hg, even accounting for case-mix.[3,14] In the absence of robust randomized controlled trial data, these reverse epidemiology and paradoxical blood pressure (BP) observational data have led to uncertainty among practitioners on how to manage BP in hemodialysis patients.[3,4,13,15]

Recently, we confirmed the paradoxical U-shaped association between dialysis-unit-SBP and risk of all-cause mortality in a multicenter cohort of incident hemodialysis patients

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but reported that there was a linear, stepwise, independent association between higher level of SBP measured outside of the dialysis unit, at 1 sitting in a single day, and higher risk of mortality[12]—an association similar to that observed in the general population. However, whether these same associations also apply for cardiovascular disease (CVD), which remains the leading cause of morbidity and mortality in hemodialysis patients, has not been well described. A better understanding of the association of BP with cardiovascular events would guide treatment in this high-risk patient population, particularly in the absence of clinical trials.

In this study, we examined the association between SBP measured in the dialysis unit (measured before starting dialysis) and outside of the dialysis unit (at a research study visit) and risk of cardiovascular events. We also examined the association of other BP components: diastolic BP (DBP) and pulse pressure (PP) with cardiovascular events. We hypothesized that there would be a linear association with risk of cardiovascular events with BP measured outside of the dialysis unit and a U-shaped association with BP measured at the dialysis unit.

Methods

Study Population

We studied participants of the CRIC study (Chronic Renal Insufficiency Cohort). The CRIC study is a National Institutes of Health–sponsored multicenter prospective observational cohort[16–18] study, which initially enrolled 3939 participants 21 to 74 years of age with chronic kidney disease with estimated glomerular filtration rate 20 to 70 mL/min per 1.73 m^2 by the Modification in Diet in Renal Disease equation between 2003 and 2008.[19] Exclusion criteria included New York Heart Association class III or IV heart failure (HF) and severe liver disease. Study participants have been followed annually through in-person visits and interim 6-month telephone calls. A subset of enrolled CRIC participants have had progression of their chronic kidney disease and have initiated hemodialysis. Informed consent was obtained from each participating site.

We studied 377 CRIC participants who initiated chronic hemodialysis by March 31, 2013, and had measures of both dialysis-unit and out-of-dialysis-unit-BP available. Consistent with our prior study,[12,20] we included only participants who had at least one CRIC study visit when their glomerular filtration rate was <30 mL/min per 1.73 m^2 before starting hemodialysis.

Predictors

We examined 3 BP components: SBP (primary exposure), DBP, and PP (calculated from SBP minus DBP; secondary exposures), all in mm Hg and modeled in quartiles.

Dialysis-Unit-BP

For CRIC participants who started maintenance hemodialysis, study personnel obtained records from each patient's dialysis unit ≈6 months after hemodialysis initiation and abstracted information on BP measurements recorded at the start of each hemodialysis session. The mean of the BP measurements obtained from these dialysis unit records obtained during 1 week was used to define dialysis-unit-BP in our study.[12]

Out-of-Dialysis-Unit-BP

We used mean BP obtained at the first in-person CRIC research study visit after initiation of maintenance hemodialysis. BP was measured by centrally trained staff using a standardized method.[12,21] Per the CRIC protocol, BP measurement is performed in a quiet, standardized setting. Participants abstain from caffeine, smoking, and exercise at least one and a half hour before and until completion of the BP measurement. The Tycos Classic Hand Aneroid sphygmomanometer is the standard equipment for all BP measurements at CRIC clinical visits. The mean of 3 seated resting BP readings was used to define out-of-dialysis-unit-BP.

Outcomes

Our primary outcome was time to adjudicated cardiovascular events, which occurred after ascertainment of both dialysis-unit and out-of-dialysis-unit-BP. Cardiovascular events included HF, myocardial infarction (MI), ischemic stroke, and peripheral artery disease (PAD) events identified through March 31, 2013.[22] Participants were censored at death or end of study period. Deaths were identified from report from next of kin, retrieval of death certificates or obituaries, review of hospital records, and the Social Security Death Master File.

Study participants were queried every 6 months during alternating in-person and telephone visits about whether they were hospitalized, experienced a possible cardiovascular event, or underwent a selected set of diagnostic tests/procedures. *International Classification of Diseases, Ninth Revision* discharge codes were obtained for all hospitalizations, and relevant medical records were retrieved for review by at least 2 physicians to ascertain events of HF, MI, and stroke. Trained study staff reviewed medical records classified with *International Classification of Diseases, Ninth Revision* codes that suggest a PAD event.[23,24]

HF events were determined based on clinical symptoms, radiographic evidence of pulmonary edema, physical examination of the heart and lungs, central venous hemodynamic monitoring data, and echocardiographic imaging in hospitalized patients based on the Framingham and ALLHAT (antihypertensive and lipid-lowering treatment to prevent heart attack trial) criteria.[25,26] Diagnosis of probable or definite MI was based on symptoms consistent with acute ischemia, cardiac biomarker levels, and electrocardiograms as recommended by a consensus statement on the universal definition of MI.[27] Two neurologists reviewed all hospitalizations suggestive of stroke. Outcomes included both probable and definite ischemic stroke. The latter was determined based on autopsy findings or sudden onset of neurological symptoms supported with computed tomography or magnetic resonance imaging demonstration of infarction in a territory where an injury or infarction would be expected to create those symptoms. The former was defined as sudden or rapid onset of 1 major or 2 minor neurological signs or symptoms lasting for >24 hours or until the patient died with no evidence of hemorrhage or infarction on computed tomography or magnetic resonance imaging performed within 24 hours of the onset of symptoms.[28] Ascertainment of PAD was based on nurse-abstracted hospital records indicating that amputation, bypass procedure, angioplasty, or surgical/vascular procedure for abdominal aortic aneurysm or noncoronary arteries took place.[23]

Multiple events during the same hospitalization were only counted as 1 event (because we used a composite outcome).

Covariates

History of CVD was determined by self-report (at baseline) and occurrence of an adjudicated cardiovascular event during CRIC follow-up (ie, occurred between enrollment into CRIC and ascertainment of BP in this study). Medication use was ascertained by self-report. For analyses based on out-of-dialysis-unit-BP, covariates were obtained from the same CRIC study visit as the out-of-dialysis-unit-BP measurement. For the analyses based on dialysis-unit-BP, covariates were obtained from the closest study visit before the dialysis-unit-BP measurement. Selected measurements taken during routine clinical care abstracted from dialysis-unit records included dose of dialysis (Kt/V), serum albumin and hemoglobin level, and mean intradialytic weight gain during 1 week.[12]

Statistical Methods

We compared characteristics across quartiles of out-of-dialysis-unit-SBP using ANOVA tests for continuous variables and χ^2 tests for categorical variables. The start time for each patient for all time-to-event analyses was the latter of the date of dialysis-unit-BP measurement or the date of the out-of-dialysis-unit-BP measurement. Participants were censored if they disenrolled from CRIC, if they died, or at

the end of follow-up (on March 31, 2013). We examined the association of each BP component measured in the dialysis-unit and out-of-dialysis-unit with risk of adjudicated cardiovascular events. We first explored the association between SBP and cardiovascular events using adjusted penalized smoothing splines with $N^{0.2}$ evenly spaced knots (at the quintiles of the marginal distribution of the independent variable) among the inner 99% distribution of SBP in Cox models.[29–31] This allowed us to display the relationship of SBP and CVD without making assumptions about the shape of the relationship.[12] We then performed multivariable Cox proportional hazard modeling SBP in quartiles. We first adjusted for demographics; next, we adjusted for CVD risk factors (tobacco use, body mass index, diabetes mellitus, and history of CVD); and finally, we additionally adjusted for dialysis-related variables (Kt/V, serum albumin and hemoglobin level).[12]

In secondary analyses, we repeated our models examining dialysis-unit and out-of- dialysis-unit-DBP and PP measurements as predictors of cardiovascular events.

In a sensitivity analysis, we adjusted for the number of self-reported BP medication classes prescribed. In a second sensitivity analysis, we excluded PAD as part of our composite outcome because PAD is not always considered a hard outcome in CVD trials.

Results

Study Participants

Among 377 eligible participants who initiated maintenance hemodialysis during follow-up, those with higher levels of out-of-dialysis-unit-SBP were more likely to have higher DBP and were more likely to be current smokers (Table 1). Of the out-of-dialysis-unit-BP measures, 82.5% of were performed on the right arm and 17.5% on the left arm. The mean (±SD) of each of the 3 SBP readings was the following: SBP #1, 132 (±36); SBP #2, 131 (±25); and SBP #3, 131 (±26) mm Hg. The mean (SD) of each of the 3 DBP readings was the following: DBP #1, 67 (±14); DBP #2, 66 (±13); and DBP #3, 66 (±14) mm Hg.

Correlation Between Dialysis-Unit-BP and Out-of-Dialysis-Unit-BP

The median time between dialysis-unit-BP and out-of-dialysis-unit-BP measures was 101 (interquartile range, 36–195) days. Overall, there was a modest correlation between level of dialysis-unit-SBP and out-of-dialysis-unit-SBP (correlation coefficient=0.34; $P<0.001$; Figure 1A). Only 39% (148/377) of participants were matched by categories of dialysis-unit-SBP and out-of-dialysis-unit-SBP (Table 2). The correlation between dialysis-unit measures of DBP and PP with out-of-dialysis-unit measures were also modest (Figure 1B and 1C).

Dialysis-Unit-SBP and Risk of Cardiovascular Events

There were a total of 113 first cardiovascular events observed during a mean (±SD) follow-up time of 2.4 (±1.71) years. The types of cardiovascular events were as follows: 59 HF events, 19 MI events, 8 strokes, 18 PAD events, 7 with MI and HF during the same hospitalization, 1 with MI and PAD during the same hospitalization, and 1 with MI, stroke, and PAD during the same hospitalization.

Table 1. Characteristics of Study Participants by Quartiles of Out-of-Dialysis-Unit-Systolic Blood Pressure (N=377)

Characteristics	Q1 (SBP 70–112 mm Hg) N=93	Q2 (SBP 113–127 mm Hg) N=95	Q3 (SBP 128–145 mm Hg) N=93	Q4 (SBP 146–238 mm Hg) N=96	*P* Value
Age, y; mean±SD	59±12	59±11	61±10	61±11	0.2
Women, %	40	43	41	42	1.0
Race/ethnicity, %					0.1
Non-Hispanic white	18	21	20	7	
Non-Hispanic black	63	63	67	75	
Hispanic	13	13	13	15	
Other	6	3	0	3	
Systolic blood pressure, mm Hg; mean±SD	102±8	121±4	137±5	165±18	<0.0001
Diastolic blood pressure, mm Hg; mean±SD	57±9	64±11	69±13	74±14	<0.0001
Pulse pressure, mm Hg; mean±SD	44±11	56±12	68±14	91±18	<0.0001
Body mass index, kg/m^2; mean±SD	31±8	32±8	30±8	30±7	0.1
Hypertension, %	99	97	99	100	0.3
Diabetes mellitus, %	65	68	76	72	0.3
Current smoker, %	4	14	14	18	0.04
History of CVD, %	55	60	60	66	0.5
Dialysis vintage, d; median (IQR)	206 (115–314)	205 (113–319)	232 (123–340)	205 (107–299)	0.7
Kt/V, mean±SD	1.58±0.36	1.56±0.34	1.53±0.34	1.53±0.30	0.8
Serum albumin, mg/dL; mean±SD	3.9±0.8	3.8±0.4	3.8±0.4	3.8±0.4	0.2
Hemoglobin, g/L; mean±SD	11.7±1.3	11.6±1.9	11.7±1.3	12.0±2.7	0.6

CVD indicates cardiovascular disease; IQR, interquartile range; and SBP, systolic blood pressure.

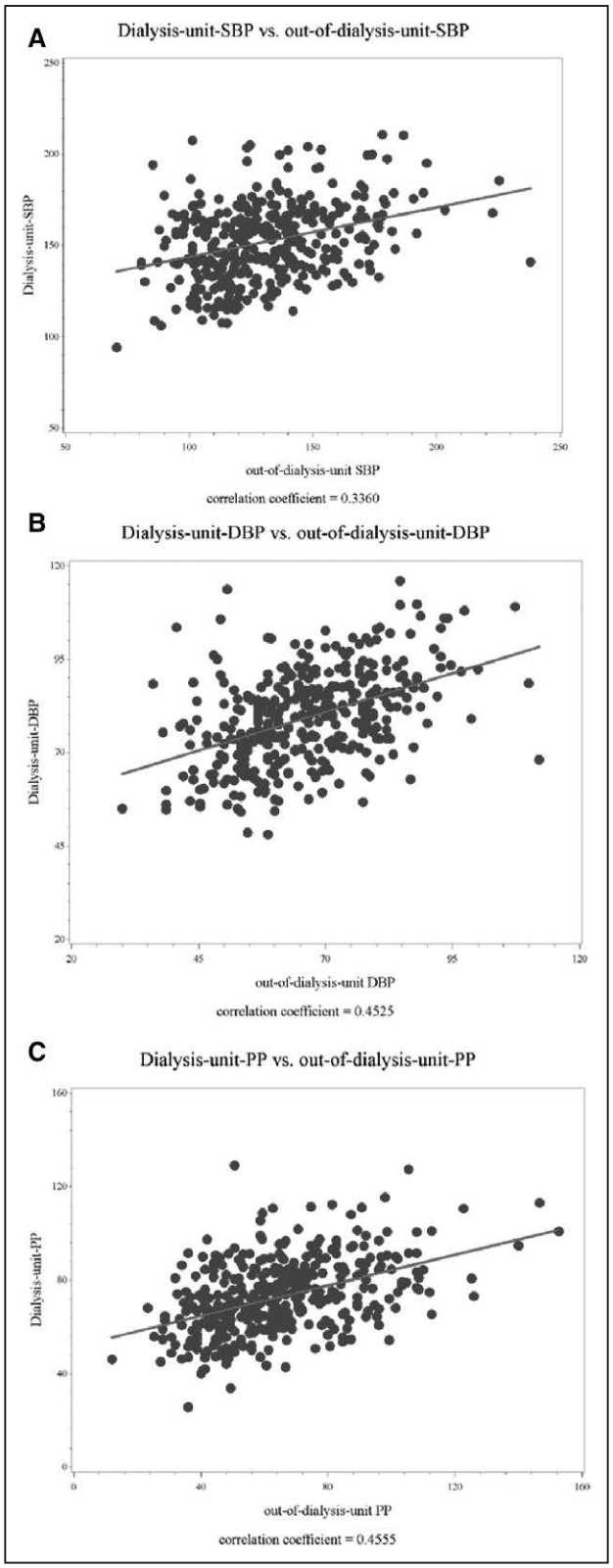

Figure 1. A, Correlation between dialysis-unit-systolic blood pressure (SBP) and out-of-dialysis-unit-SBP (N=377). **B**, Correlation between dialysis-unit-diastolic blood pressure (DBP) and out-of-dialysis-unit-DBP (N=377). **C**, Correlation between dialysis-unit-pulse pressure (PP) and out-of-dialysis-unit-PP (N=377).

Table 2. Correlation Between Categories of Dialysis-Unit-Systolic Blood Pressure and Out-of-Dialysis-Unit-Systolic Blood Pressure (N=377)*

Dialysis-Unit-SBP, mm Hg	Out-of-Dialysis-Unit-SBP		
	<120 mm Hg	120–140 mm Hg	>140 mm Hg
<120	19	2	1
120–140	40	26	20
>140	74	92	103

SBP indicates systolic blood pressure.
*Cell contents represent number of participants in each category.

Multivariable splines demonstrated a U-shaped association of dialysis-unit-SBP and risk of cardiovascular events, with the nadir being between 150 and 170 mm Hg (Figure 2). Compared with the second quartile, there was not a statistically significant association between the lowest or highest quartiles of dialysis-unit-SBP with risk of cardiovascular events in unadjusted or multivariable models (Table 3).

Out-of-Dialysis-Unit-SBP and Risk of Cardiovascular Events

In contrast, multivariable splines showed a linear direct association of out-of-dialysis-unit-SBP with cardiovascular events (Figure 3). Unadjusted rates (per 100 person-years) of cardiovascular events increased across increasing quartiles of

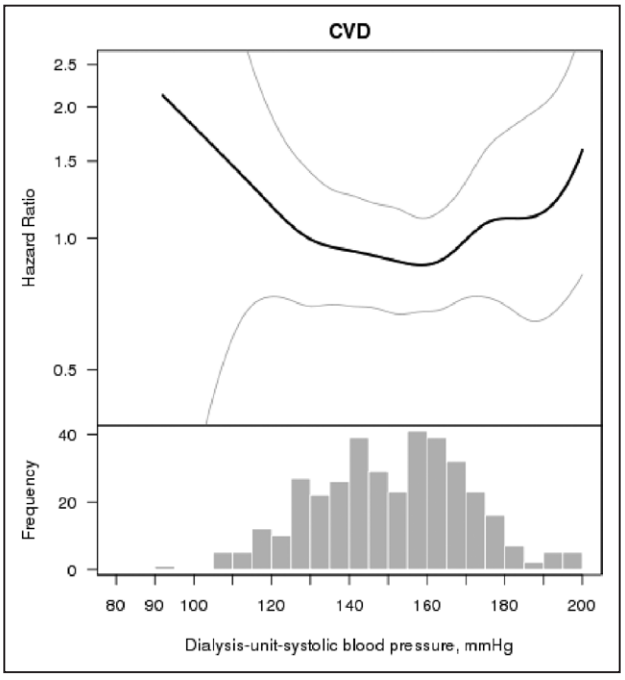

Figure 2. Multivariable association of dialysis-unit-systolic blood pressure with cardiovascular events (N=377). The smooth spline estimates the hazard ratio of cardiovascular events, according to systolic blood pressure (SBP; mm Hg) measured in the dialysis unit among CRIC study (chronic renal insufficiency cohort) participants. All analyses are adjusted for age, sex, race/ethnicity, tobacco use, body mass index, diabetes mellitus, history of cardiovascular disease (CVD), Kt/V, serum albumin, and hemoglobin level. Dotted lines represent 95% confidence intervals. Below each spline is the histogram of the distribution of SBP to indicate the range of the majority of the data.

Table 3. Association Between Systolic Blood Pressure and Risk of Cardiovascular Events (N=377)

Blood Pressure Measure	CVD Events		Unadjusted		Model 1: Adjusted for Age, Sex, and Race/ Ethnicity		Model 2: Additionally Adjusted for Patient Characteristics*		Model 3: Additionally Adjusted for Patient Characteristics+Dialysis Variables†	
Dialysis-unit-SBP, mm Hg	No. of events	Rate (per 100 py)	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Q1 (94–137)	26	11.98	1.00 (0.59–1.72)	1.0	0.93 (0.54–1.60)	0.8	0.86 (0.49–1.51)	0.6	0.75 (0.44–1.39)	0.4
Q2 (138–152)	27	11.85	Ref		Ref		Ref		Ref	
Q3 (153–165)	26	10.53	0.89 (0.52–1.53)	0.7	0.93 (0.54–1.59)	0.8	0.81 (0.47–1.41)	0.5	0.65 (0.36–1.18)	0.2
Q4 (166–211)	34	16.24	1.37 (0.82–2.27)	0.2	1.45 (0.87–2.41)	0.2	1.40 (0.83–2.35)	0.2	1.06 (0.60–1.85)	0.9
Out-of-dialysis-unit-SBP, mm Hg										
Q1 (70–112)	21	8.11	Ref		Ref		Ref		Ref	
Q2 (113–127)	25	10.79	1.32 (0.74–2.35)	0.4	1.27 (0.71–2.28)	0.4	1.20 (0.66–2.17)	0.6	1.33 (0.71–2.50)	0.4
Q3 (128–145)	33	15.13	1.84 (1.07–3.19)	0.03	1.69 (0.98–2.93)	0.06	1.77 (1.01–3.11)	0.047	2.14 (1.17–3.90)	0.01
Q4 (146–238)	34	17.68	2.14 (1.24–3.69)	0.006	2.24 (1.29–3.89)	0.004	2.44 (1.38–4.29)	0.002	2.90 (1.55–5.42)	<0.001

CI indicates confidence interval; CVD, cardiovascular disease; HR, hazard ratio; and SBP, systolic blood pressure.

*Patient characteristics include age, sex, race/ethnicity, tobacco use, BMI, diabetes mellitus, and history of cardiovascular disease (covariates taken from same visit/ closest prior visit of SBP reading).

†Dialysis variables: Kt/V, serum albumin, and hemoglobin level.

out-of-dialysis-unit-SBP (Table 3). There was a graded association between higher out-of-dialysis-unit-SBP and risk of CVD in unadjusted models and in models adjusting for patient demographic characteristics and comorbidity (Table 3).

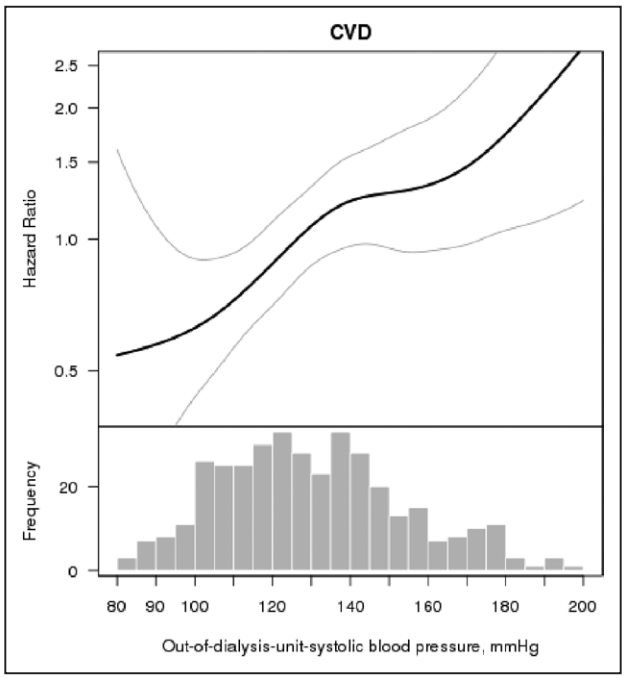

Figure 3. Multivariable association of out-of-dialysis-unit-systolic blood pressure with cardiovascular events (N=377). The smooth spline estimates the hazard ratio of cardiovascular events, according to systolic blood pressure (SBP; mm Hg) measured outside the dialysis unit (at a CRIC study [chronic renal insufficiency cohort] visit) among CRIC participants. All analyses are adjusted for age, sex, race/ethnicity, tobacco use, body mass index, diabetes mellitus, history of cardiovascular disease (CVD), Kt/V, serum albumin, and hemoglobin level. Dotted lines represent 95% confidence intervals. Below each spline is the histogram of the distribution of SBP to indicate the range of the majority of the data.

Participants with out-of-dialysis-unit-SBP ≥128 mm Hg had >2-fold increased risk of cardiovascular events compared with those with out-of-dialysis-unit-SBP ≤112 mm Hg (Table 3).

Sensitivity Analyses

In a sensitivity analysis, similar associations of dialysis-unit and out-of-dialysis-unit-SBP with cardiovascular events were observed after additional adjustment for number of BP medication classes (Table S1 in the online-only Data Supplement).

In a second sensitivity analysis, we did not include PAD as part of our composite outcome and repeat our models. With this exclusion, results were similar to the main analysis (Table S2).

Dialysis-Unit and Out-of-Dialysis-Unit-DBP and Risk of Cardiovascular Events

Crude rates of cardiovascular events were highest in those in the lowest and highest quartiles of dialysis-unit-DBP (Table S3). Multivariable splines suggested a U-shaped association between dialysis-unit-DBP and risk of CVD, which was not observed with out-of-dialysis-unit-DBP (Figure S1A and S1B). In adjusted models examining quartiles of DBP, there was a statistically significant association between low and high dialysis-unit-DBP with cardiovascular events (ie, a U-shape). No association was noted with quartiles of out-of-dialysis-unit-DBP in either unadjusted or adjusted analyses (Table S1).

Dialysis-Unit and Out-of-Dialysis-Unit-PP and Risk of Cardiovascular Events

Multivariable splines suggested a J-shaped association between dialysis-unit-PP and CVD risk (Figure S2A). There was no statistically significant association between quartiles of dialysis-unit-PP with risk of CVD in either unadjusted or adjusted analyses (Table S2). In contrast, there was a strong linear association of out-of-dialysis-unit-PP with risk of cardiovascular events (Figure S2B), with >2-fold increased risk

of cardiovascular events for participants in the top versus bottom quartile of out-of-dialysis-unit-PP (Table S4).

Discussion

In this multicenter prospective research cohort of maintenance hemodialysis patients, we found a U-shaped association between dialysis-unit-SBP and risk of cardiovascular events, with the lowest risk of cardiovascular events at the range of 150 to 170 mm Hg. However, among these same participants, there was a strong linear and positive association between out-of-dialysis-unit-SBP and risk of cardiovascular events.[12] Our results add important observational data on BP in hemodialysis patients, particularly given the relative paucity of clinical trials in this patient population. Unlike most of the prior literature on BP and outcomes in hemodialysis patients, which have focused all-cause mortality, we studied cardiovascular events, which has important implications in the care of these patients.

The small body of prior literature on BP and CVD in hemodialysis patients includes 2 articles, which reported no association of dialysis-unit-SBP with risk of cardiovascular events[32,33] and another, which reported a J-shaped association.[34] Some of these studies were limited by not having out-of-dialysis-BP measures.[34] The study by Alborzi et al[33] studied 150 hemodialysis patients at a single center and reported that although there was no association of predialysis SBP with CVD death, there was a significant association of home BP with CVD death. Home BP was ascertained using several weeks of home BP recordings; which contrasts with our study, which relied on SBP readings from a single visit. Furthermore, Alborzi et al did not examine CVD events (only CVD death) and included primarily black participants. The same research group led by Agarwal found that out-of-dialysis-unit-SBP among hemodialysis patients was a stronger correlate than dialysis-unit-SBP with subclinical CVD—as assessed by left ventricular hypertrophy—but did not ascertain clinical cardiovascular events.[35] Out-of-dialysis-unit-BP was assessed here via 44-hour interdialytic ambulatory BP monitoring or average of 3 daily home measurements obtained during 1 week.[35] Thus, our study makes a unique contribution by linking higher out-of-dialysis-unit-BP measured at 1 sitting with greater risk of clinically important cardiovascular events.

These data add to the body of evidence that out-of-dialysis-unit-SBP should be measured and potentially targeted for treatment in hemodialysis patients to improve outcomes.[1,36] Shifting treatment targets from dialysis-unit to out-of-dialysis-unit SBP represents a potential way to address the current therapeutic dilemma faced by practitioners who care for hemodialysis patients. These challenges have been brought on, in part, by the paradoxical BP and reverse epidemiology literature, which suggests lowering of SBP to <140 mm Hg would be associated with harm (or no benefit) in hemodialysis patients.[1,3–6,12,13,15]

Our data suggest that it is not necessary to perform ambulatory BP monitoring (or multiple home BP measurements) to gather important prognostic information. This opens up the possibility that BP measured at a single clinical encounter—for example, when the patient is in the office of an internist or cardiologist—may help guide treatment to improve outcomes in hemodialysis patients. However, because most clinical counter office BPs are a single measurement and do not adhere to standardized protocols, further studies are needed.

Currently in clinical practice, many primary care providers, cardiologists, and other specialists often defer treatment of BP to the nephrologist; yet non-nephrologists actually observe out-of- dialysis-unit-BP readings, whereas most nephrologists typically have access only to dialysis-unit-BP readings. Notably, we found significant disparities in participants who would meet criteria for BP treatment depending on which BP measure was used. Only 39% (103/269) of participants (Table 2) with dialysis-unit-SBP >140 mm Hg had out-of-dialysis-unit-SBP also >140 mm Hg. Relying only on measurement of dialysis-unit-SBP may be leading to overtreatment of BP, contributing to intradialytic hypotension, and other adverse consequences, such as myocardial stunning. These data should also be considered in the design of future clinical trials of BP control in hemodialysis patients, which have traditionally only targeted dialysis-unit-BP.[37–39]

In terms of the other BP components, we also observed a U-shaped association between dialysis-unit-DBP and risk of cardiovascular events. This finding is consistent with prior reports of dialysis-unit-DBP and mortality.[40–42] Lower DBP may result from increased arterial stiffening and may lead to decreased coronary perfusion and left ventricular hypertrophy, thus, contributing to greater risk of cardiovascular events. Because there was no association of out-of-dialysis-unit-DBP with cardiovascular events, neither dialysis-unit-DBP nor out-of-dialysis-unit-DBP seem to be appropriate BP treatment targets.

For PP, there have been prior reports that higher dialysis-unit-PP in hemodialysis patients was associated with greater risk of all-cause mortality[43,44] and of CVD.[32] Our study adds to this prior body of literature by reporting that out-of-dialysis-unit-PP was more consistently associated with cardiovascular events compared with dialysis-unit-PP. Although currently there are no medications that specifically target PP—a marker of arterial stiffness—a recent clinical trial of hemodialysis patients reported that atenolol was superior to lisinopril in improving arterial stiffness.[45] Thus, understanding the relationship of various BP components with outcomes among hemodialysis patients may help in selection of appropriate BP medications as more therapies emerge.

Previous hypotheses to explain the U-shape association between SBP and adverse outcomes have included survival bias, competing risk factors, or neurohormonal state unique to hemodialysis patients.[3,14] However, these other explanations seem unlikely because we observed a linear association between higher SBP and risk of CVD when out-of-dialysis-unit-SBP is measured in the same patients. Instead, we hypothesize the inability to mount an elevated BP in response to fluid accumulated between hemodialysis sessions—reflected in the dialysis-unit-BP documented at the start of each hemodialysis session—is an adverse prognostic marker.[12] Dialysis-unit-BP may reflect mostly the transient effect of interdialytic volume accumulation, rather than being a good overall indication of BP load because it relates to end-organ damage. Regardless of the exact pathophysiologic mechanism, these data strongly suggest that the focus should be on measuring and treating out-of-dialysis-unit-BP, rather than dialysis-unit-BP. Existing guidelines recommend dialysis-unit-SBP as the target of treatment and recommend a BP goal of <140/90 mm Hg recorded

at the start of each hemodialysis session.[46–51] However, our data and data from others[1,33,35] strongly suggest that out-of-dialysis-unit-SBP may be more important when targeting a level of BP for treatment in hemodialysis patients.

Our results are consistent with the few randomized controlled trials of BP lowering in patients on hemodialysis. In a meta-analysis of 8 such trials of end-stage renal disease patients, lowering of dialysis-unit-BP was associated with lower risk of cardiovascular events and CVD mortality.[37,52] Results from these interventional studies are not consistent with the paradoxical BP and reverse epidemiology literature,[1,3–6,12,13,15] which would predict that pharmacological lowering of SBP in range of 140 mm Hg would be associated with harm (or no benefit) in hemodialysis patients.

Our study had several strengths, including a diverse number of hemodialysis participants recruited from multiple sites in the United States. Out-of-dialysis-unit-BP was measured using a standardized protocol by trained research staff. CVD outcomes were ascertained by rigorous adjudication methods. We were able to capture comorbid conditions uniformly using research grade data. We also recognize several limitations. We quantified correlations of dialysis-unit and out-of-dialysis unit-BP readings which were not taken simultaneously. However, our time-to-event analysis was based from the later of the 2 measures for all analyses. We do not have reliable information on the timing of out-of-dialysis-unit-BP measurements relative to hemodialysis treatment sessions although we think the majority of CRIC research study visits did not take place on the same day as a scheduled hemodialysis treatment. Details of changes in BP during the hemodialysis sessions (such as nadir SBP) are not available. We did not analyze changes in antihypertensive use after the initial study visit after end-stage renal disease. We presume there were adjustments in antihypertensive medication over time because these patients were receiving regular clinical care. However, this would not have changed our findings because we are contrasting BP measures in the same study participants, who are thus exposed to the same medications over time. We studied a composite cardiovascular events outcome and had limited power to examine individual types of cardiovascular events because of the overall low number of events. Because of the relatively small sample size, confidence intervals on the U-shaped splines were relatively wide in Figure 2, although the dialysis-unit-SBP clearly did not have a linear association with cardiovascular events in the same manner as the out-of-dialysis-unit-SBP. The CRIC adjudication process adapted validated procedures used in other major CVD studies and did not use end-stage renal disease–specific criteria. However, to our knowledge, end-stage renal disease–specific CVD adjudication processes have not been developed and validated. For HF events, it may be difficult to delineate with certainty the role of volume overload related to missed dialysis or dietary indiscretion or incorrect dry weight estimation. But prior studies using similar or less rigorous case definitions have shown that the syndrome of HF/volume overload in dialysis patients is associated with poor outcomes.[53–56] So this is an important clinical entity regardless of its exact pathophysiology. We were unable to study incident cardiovascular events because majority of participants had prevalent CVD (and were taking antihypertensive medications). However, this largely reflects the hemodialysis population, which has a large burden of preexisting CVD. We did not have concurrent 24-hour ambulatory BP monitoring in these participants, and there were no standardized measurements of BP in the dialysis units.[57–60] We only studied those who volunteered to enroll in this prospective cohort study, and patients with advanced HF were not enrolled into CRIC, which may limit generalizability.

In conclusion, in this multicenter study of hemodialysis patients, there was a U-shaped association between dialysis-unit-SBP and risk of cardiovascular events, with the lowest risk among participants with SBP 150 to 170 mm Hg. Among these same participants, there was a strong linear association between a 1-time reading of higher out-of-dialysis-unit-SBP and risk of cardiovascular events. The findings support the argument that targeting BP measured outside of the dialysis unit may not only be more appropriate than targeting BP measured in the dialysis unit[12] but may be more feasible that perhaps previously realized because BP readings taken at a single setting are associated with important outcomes (without the need for 44-hour ambulatory or weeklong home BP measurements). Although further study on the biological mechanisms to explain the observed associations is needed, the results from our study may inform clinical management of the hemodialysis patient population to improve CVD outcomes and help in the design of future clinical trials of BP reduction in hemodialysis patients.

Perspectives

Among a multicenter, diverse cohort of patients on maintenance hemodialysis, there was a strong, positive, linear association between out-of-dialysis-unit-SBP and a U-shaped association between dialysis-unit-SBP and cardiovascular events was observed. Greater effort to obtain out-of-dialysis unit-SBP in hemodialysis patients should be made, which may help guide clinical management and in the planning of clinical trials of BP control to decrease risk of CVD in this high-risk patient population.

Appendix

The CRIC study investigators are listed as follows: Lawrence J. Appel, Harold I. Feldman, Alan S. Go, Jiang He, John W. Kusek, James P. Lash, Akinlolu Ojo, Mahboob Rahman, and Raymond R. Townsend.

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Disclosures

None.

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Novelty and Significance

What Is New?

- Low and high blood pressure (BP) (eg, U-shape) measured in the dialysis unit in hemodialysis patients is associated with higher risk of cardiovascular events among patients on dialysis.
- When BP is measured outside of the dialysis unit in these same hemodialysis patients, there is a linear association with higher BP and higher risk of cardiovascular events.

What Is Relevant?

- Cardiovascular disease remains the leading cause of morbidity and mortality among patients on dialysis.
- Hypertension is extremely prevalent in patients on dialysis, and there remains uncertainty on how best to manage these high-risk patients.
- This study helps inform clinical management of the high-risk dialysis population and may guide the design of future clinical trials of BP reduction in kidney disease.

Summary

Greater effort to obtain out-of-dialysis unit BP in hemodialysis patients should be made, which may inform clinical practice and future studies to reduce the risk of cardiovascular disease.

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Blood pressure and risk of cardiovascular events in patients on chronic hemodialysis: the CRIC Study

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SUPPLEMENTAL TABLES AND FIGURES

Table S1. Association between systolic blood pressure (SBP) and risk of cardiovascular (CVD) events: sensitivity analysis: adjustment for anti-hypertensive medications (N=377)

Blood pressure measure	**Model 3: Adjusted for patient characteristics + dialysis variables***		**Model 4: Model 3+ adjustment for # of anti-hypertensive medication classes**	
Dialysis-unit SBP (mm Hg)	**HR (95%CI)**	**p value**		
Q1 (94-137)	0.75 (0.44, 1.39)	0.4	0.77 (0.41, 1.42)	0.4
Q2 (138-152)	Ref		Ref	
Q3 (153 -165)	0.65 (0.36, 1.18)	0.2	0.61 (0.33, 1.11)	0.1
Q4 (166-211)	1.06 (0.60, 1.85)	0.9	1.01 (0.58, 1.78)	1.0
Out-of-dialysis-unit SBP (mm Hg)	**HR (95%CI)**	**p value**		
Q1 (71-112)	Ref		Ref	
Q2 (113-127)	1.33 (0.71, 2.50)	0.4	1.45 (0.76, 2.77)	0.3
Q3 (128-145)	2.14 (1.17, 3.90)	0.01	2.28 (1.24, 4.21)	0.009
Q4 (146-238)	2.90 (1.55, 5.42)	0.0009	2.94 (1.54, 5.60)	0.001

*patient characteristics include: age, gender, race/ethnicity, tobacco use, BMI, diabetes, history of cardiovascular disease, Kt/V, serum albumin and hemoglobin level

Table S2. Association between systolic blood pressure (SBP) and risk of cardiovascular (CVD) events (N=377), now excluding peripheral arterial disease as part of the composite outcome

Blood pressure measure	**CVD Events**		**Unadjusted**		**Model 1: Adjusted for age, sex and race/ethnicity**		**Model 2: Adjusted for patient characteristics***		**Model 3: Adjusted for patient characteristics + dialysis variables†**	
Dialysis-unit-SBP (mmHg)	**Number of events**	**Rate (per 100py)**	**HR (95% CI)**	**p value**	**HR (95%CI)**	**p value**	**HR (95%CI)**	**p value**	**HR (95%CI)**	**p value**
Q1 (94-137)	24	11.00	1.09 (0.62, 1.92)	0.8	0.98 (0.55, 1.75)	0.9	0.86 (0.49, 1.51)	0.6	0.80 (0.43, 1.51)	0.8
Q2 (138-152)	24	9.94	Ref		Ref		Ref		Ref	
Q3 (153 -165)	22	8.70	0.87 (0.50, 1.56)	0.6	0.91 (0.51, 1.63)	0.8	0.81 (0.47, 1.41)	0.5	0.66 (0.35, 1.24)	0.2
Q4 (166-211)	29	13.45	1.34 (0.78, 2.30)	0.3	1.40 (0.81, 2.41)	0.2	1.40 (0.83, 2.35)	0.2	1.02 (0.56, 1.86)	0.9
Out-of-dialysis-unit-SBP (mmHg)	**Number of events**	**Rate (per 100py)**	**HR (95% CI)**	**p value**	**HR (95%CI)**	**p value**	**HR (95%CI)**	**p value**	**HR (95%CI)**	**p value**
Q1 (70-112)	19	7.32	Ref		Ref		Ref		Ref	
Q2 (113-127)	19	7.72	1.05 (0.56, 1.98)	0.9	1.02 (0.54, 1.93)	1.0	0.97 (0.51, 1.86)	0.9	0.99 (0.50, 1.95)	1.0
Q3 (128-145)	31	13.75	1.87 (1.06, 3.31)	0.03	1.72 (0.97, 3.05)	0.06	1.79 (1.00, 3.23)	0.051	2.08 (1.12, 3.87)	0.02
Q4 (146-238)	30	15.23	2.04 (1.15, 3.64)	0.015	2.17 (1.21, 3.90)	0.01	2.40 (1.32, 4.37)	0.004	2.76 (1.42, 5.33)	0.0026

*patient characteristics include: age, gender, race/ethnicity, tobacco use, BMI, diabetes, history of cardiovascular disease (covariates taken from same visit/closest prior visit of SBP reading)

†dialysis variables: Kt/V, serum albumin and hemoglobin level

Table S3. Association between diastolic blood pressure (DBP) and risk of cardiovascular (CVD) events (N=377)

Blood pressure measure	**CVD Events**		**Unadjusted**		**Model 1: Adjusted for age, sex and race**		**Model 2: Adjusted for patient characteristics***		**Model 3: Adjusted for patient characteristics + dialysis variables†**	
Dialysis-unit DBP (mmHg)	**Number of events**	**Rate (per 100py)**	**HR (95% CI)**	**p value**	**HR (95%CI)**	**p value**	**HR (95%CI)**	**p value**	**HR (95%CI)**	**p value**
Q1 (48-71)	34	17.95	1.87 (1.09, 3.20)	0.02	1.65 (0.96, 2.84)	0.07	1.68 (0.97, 2.91)	0.06	2.15 (1.18, 3.91)	0.01
Q2 (72-79)	22	9.49	Ref		Ref		Ref		Ref	
Q3 (80-87)	25	10.03	1.06 (0.60, 1.88)	0.8	1.13 (0.63, 2.02)	0.7	1.09 (0.61, 2.97)	0.8	1.11 (0.59, 2.08)	0.8
Q4 (88-116)	32	13.89	1.47 (0.86, 2.54)	0.2	1.89 (1.06, 3.37)	0.03	2.07 (1.15, 3.71)	0.01	2.00 (1.08, 3.69)	0.03
Out-of-dialysis-unit DBP (mmHg)	**Number of events**	**Rate (per 100py)**	**HR (95% CI)**	**p value**	**HR (95%CI)**	**p value**	**HR (95%CI)**	**p value**	**HR (95%CI)**	**p value**
Q1 (30-56)	31	12.72	Ref		Ref		Ref		Ref	
Q2 (57-66)	27	14.11	1.11 (0.66, 1.54)	0.7	1.11 (0.66, 1.87)	0.7	1.10 (0.64, 1.88)	0.7	0.85 (0.48, 1.51)	0.6
Q3 (66-76)	26	11.28	0.90 (0.53, 1.51)	0.7	0.99 (0.58, 1.68)	1.0	0.92 (0.54, 1.59)	0.8	0.88 (0.50, 1.56)	0.7
Q4 (77-112)	29	12.31	0.97 (0.59, 1.62)	0.9	1.28 (0.74, 2.21)	0.4	1.56 (0.89, 2.74)	0.1	1.53 (0.84, 2.80)	0.2

*patient characteristics include: age, gender, race/ethnicity, tobacco use, BMI, diabetes, history of cardiovascular disease (covariates taken from same visit/closest prior visit of SBP reading)

†dialysis variables: Kt/V, serum albumin and hemoglobin level

Table S4. Association between pulse pressure (PP) and risk of cardiovascular (CVD) events (N=377)

Blood pressure measure	CVD Events		Unadjusted		Model 1: Adjusted for age, sex and race		Model 2: Adjusted for patient characteristics*		Model 3: Adjusted for patient characteristics + dialysis variables†	
Dialysis-unit PP (mmHg)	**Number of events**	**Rate (per 100py)**	**HR (95% CI)**	**p value**	**HR (95%CI)**	**p value**	**HR (95%CI)**	**p value**	**HR (95%CI)**	**p value**
Q1 (26-61)	26	11.89	1.08 (0.62, 1.86)	0.8	1.00 (0.58, 1.73)	1.0	1.07 (0.61, 1.88)	0.8	1.29 (0.72, 2.34)	0.4
Q2 (62-71)	26	10.67	Ref		Ref		Ref		Ref	
Q3 (72-83)	24	10.26	0.94 (0.54, 1.64)	0.8	0.83 (0.47,1.46)	0.5	0.77 (0.43, 1.38)	0.4	0.63 (0.34, 1.18)	0.2
Q4 (84-129)	37	18.07	1.64 (0.99, 2.71)	0.06	1.43 (0.85, 2.38)	0.2	1.47 (0.87, 2.51)	0.2	1.42 (0.82, 2.46)	0.2
Out-of-dialysis-unit PP (mmHg)	**Number of events**	**Rate (per 100py)**	**HR (95% CI)**	**p value**	**HR (95%CI)**	**p value**	**HR (95%CI)**	**p value**	**HR (95%CI)**	**p value**
Q1 (12– 47)	20	7.28	Ref		Ref		Ref		Ref	
Q2 (48-62)	27	12.07	1.62 (0.91, 2.90)	0.1	1.53 (0.85, 2.76)	0.2	1.36 (0.74, 2.50)	0.3	1.25 (0.65, 2.42)	0.5
Q3 (63-78)	31	14.57	1.97 (1.12, 3.46)	0.02	1.70 (0.94, 3.07)	0.08	1.71 (0.94, 3.13)	0.08	1.80 (0.94, 3.45)	0.08
Q4 (79-153)	35	18.44	2.46 (1.41, 4.29)	0.002	2.33 (1.30, 4.19)	0.005	2.38 (1.30, 4.36)	0.005	2.56 (1.33, 4.93)	0.005

*patient characteristics include: age, gender, race/ethnicity, tobacco use, BMI, diabetes, history of cardiovascular disease (covariates taken from same visit/closest prior visit of SBP reading)

†dialysis variables: Kt/V, serum albumin and hemoglobin level

SUPPLEMENTAL FIGURES

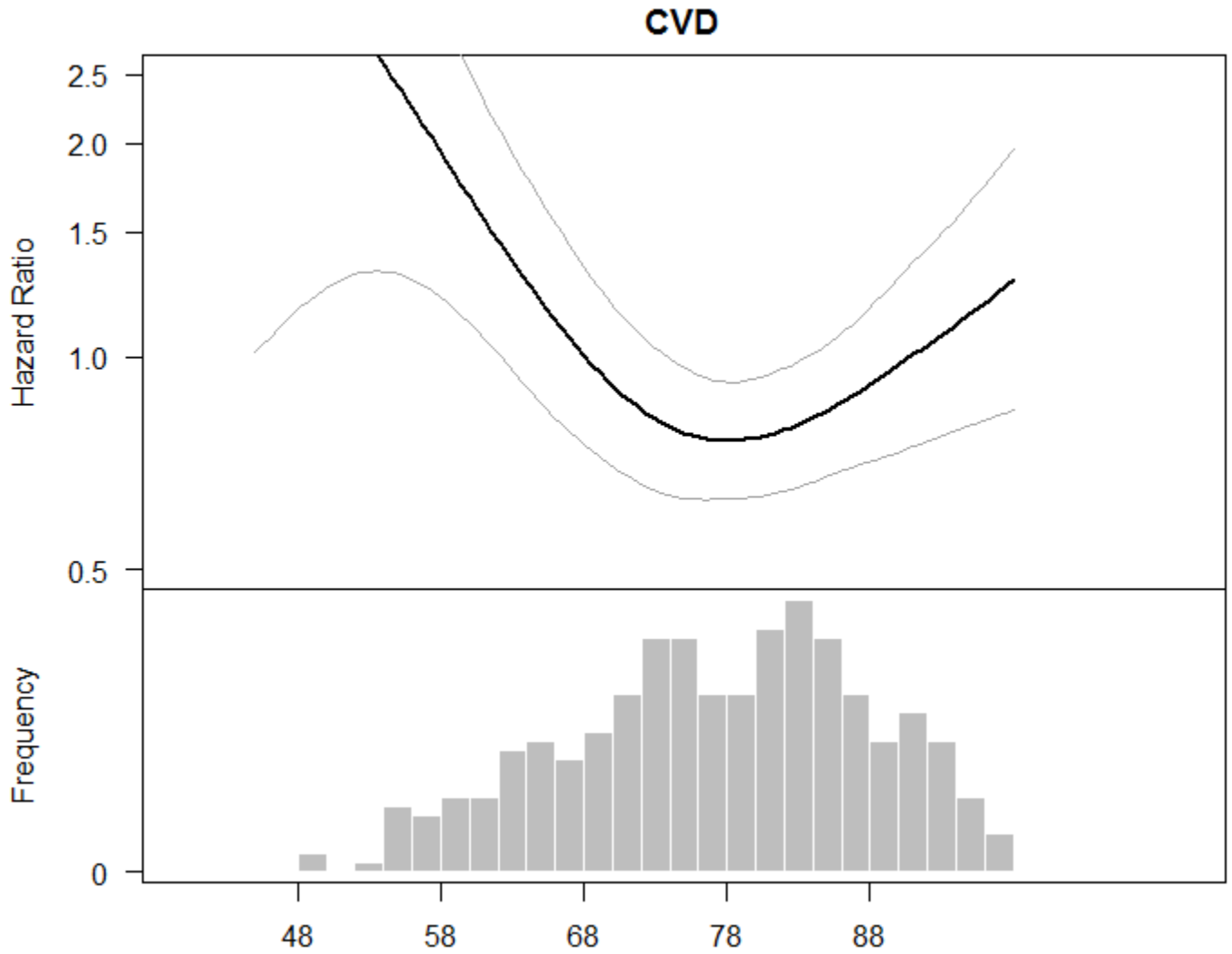

Figure S1a. Multivariable association of dialysis-unit-diastolic blood pressure with cardiovascular (CVD) events (N=377)

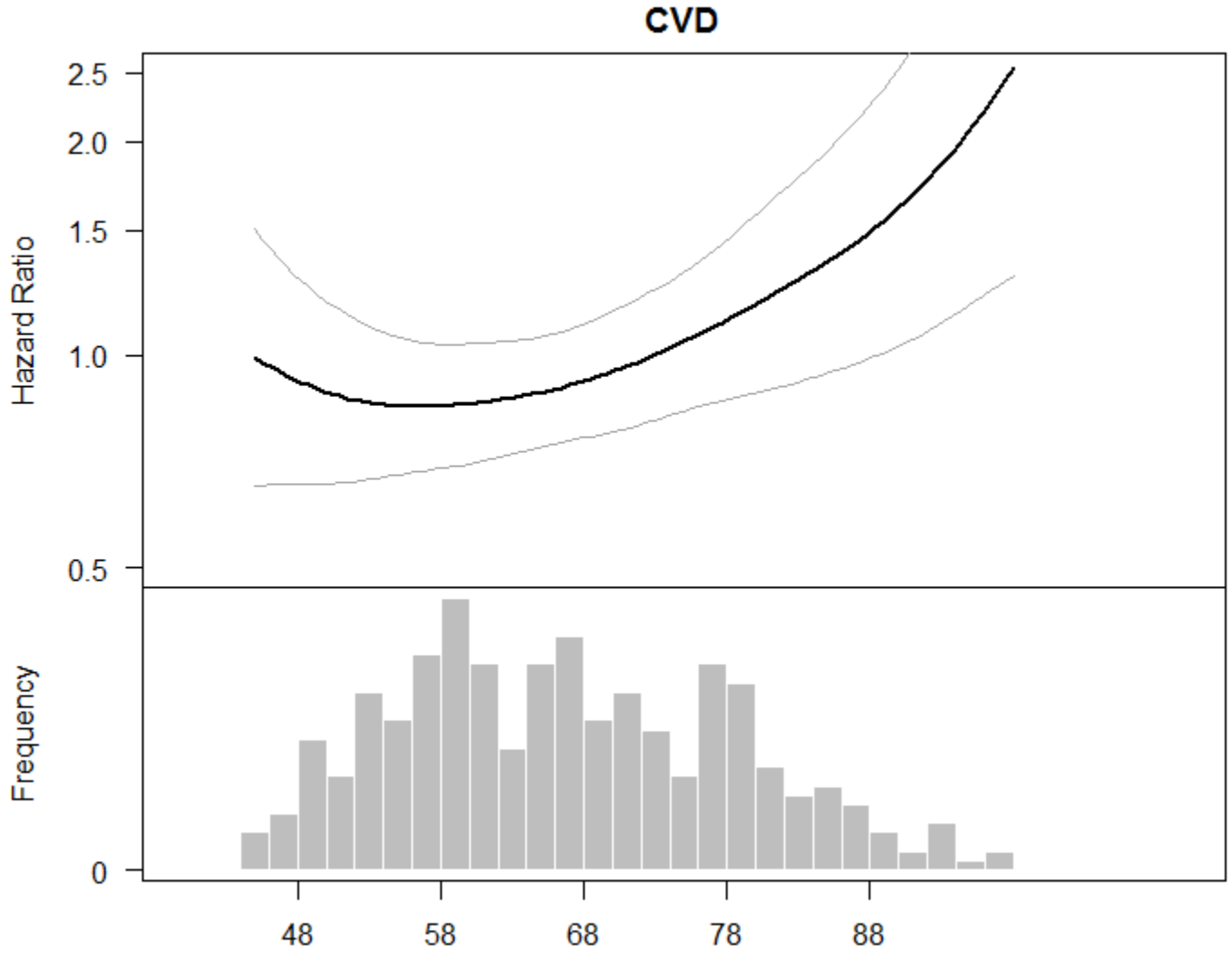
CVD
Hazard Ratio
2.5
2.0
1.5
1.0
0.5
Frequency
0
48
58
68
78
88

Figure S1b. Multivariable association of out-of-dialysis-unit-diastolic blood pressure with cardiovascular (CVD) events (n=377)

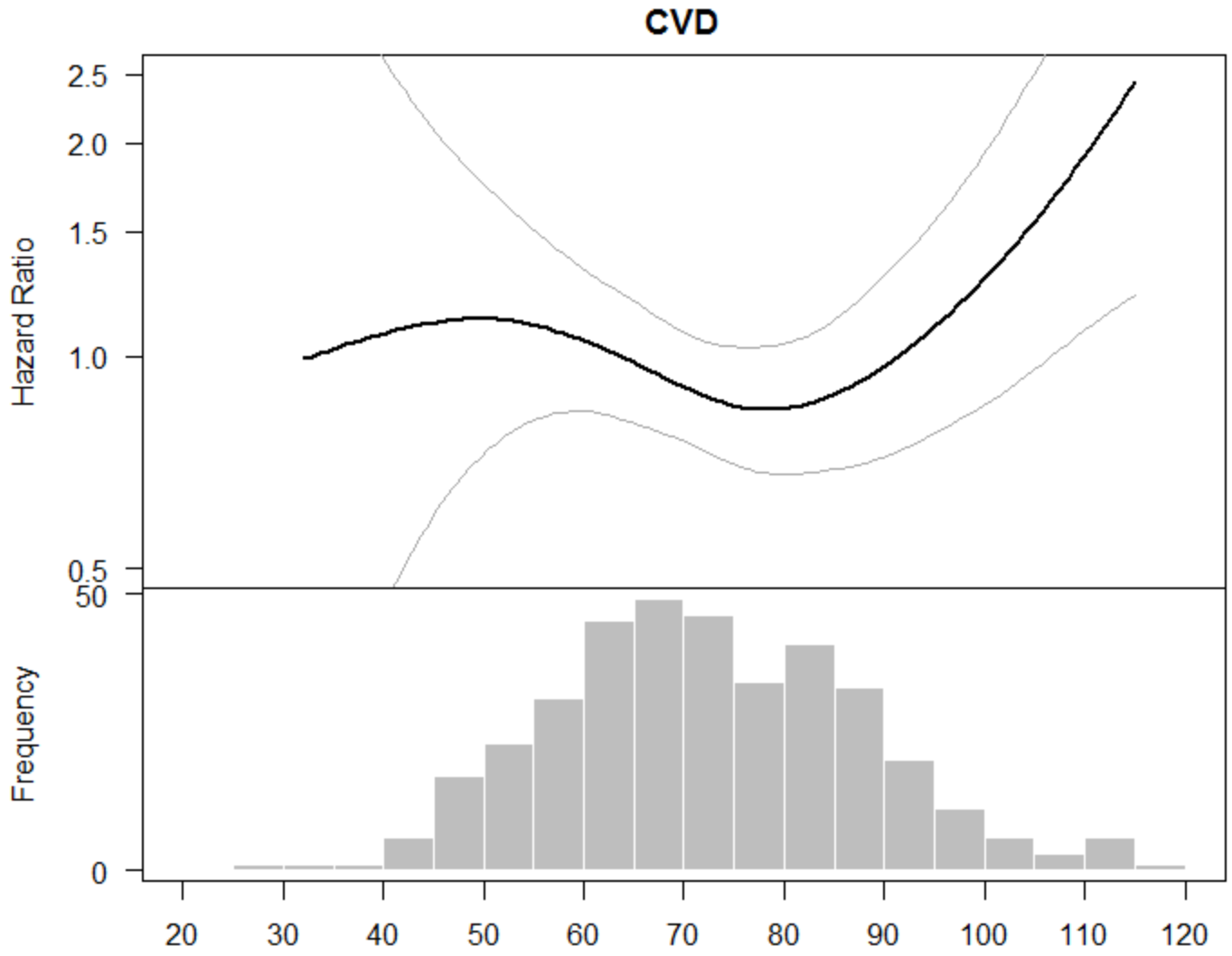

Figure S2a. Multivariable association of dialysis-unit-pulse pressure with cardiovascular (CVD) events (N=377)

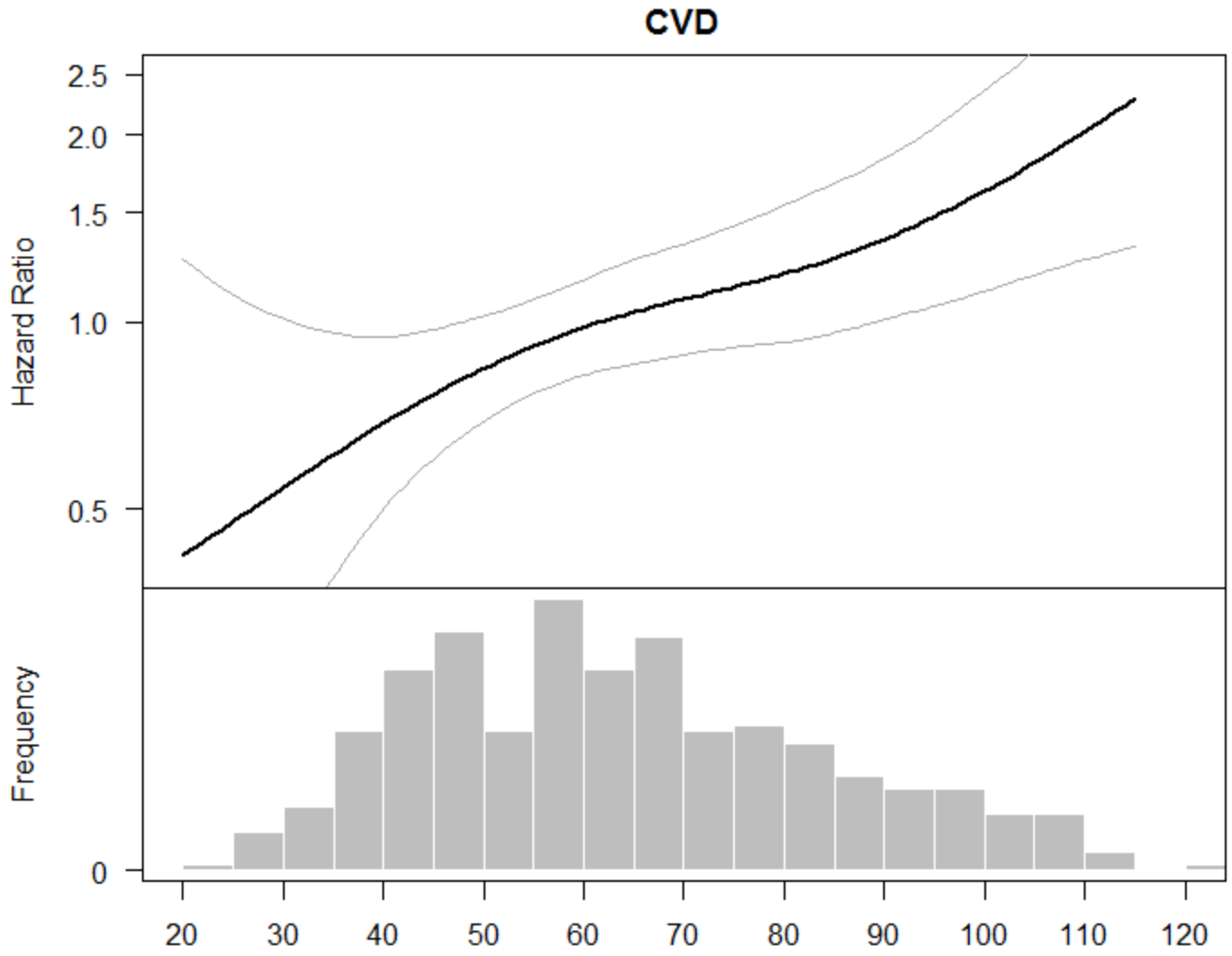

Figure S2b. Multivariable association of out-of-dialysis-unit-pulse pressure with cardiovascular (CVD) events (N=377)