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Original Article

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Association of low blood pressure with increased mortality in patients with moderate to severe chronic kidney disease

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Abstract

Background. Blood pressure shows an inverse association with mortality in patients with chronic kidney disease (CKD) on dialysis. It is unclear if the same phenomenon exists in patients with CKD not yet on dialysis.

Methods. We examined the association of systolic (SBP) and diastolic (DBP) blood pressure with all-cause mortality in a historical prospective cohort of 860 patients (age 68.1 ± 10.1 years, 99.1% male, 24.4% black) with estimated glomerular filtration rate (GFR) <60 ml/min/1.73 m^2. We used Cox models to adjust for the effects of age, race, diabetes mellitus, atherosclerotic cardiovascular disease (ASCVD), congestive heart failure, smoking, antihypertensive medications, body mass index, GFR, albumin, cholesterol, haemoglobin and proteinuria. To examine the role of comorbidities, we performed subgroup analyses based on prevalent ASCVD status and level of estimated GFR.

Results. Higher SBP and higher DBP were both associated with lower mortality [adjusted hazard ratio (95% confidence interval) for SBP 133–154, 155–170 and >170 mmHg, compared with <133 mmHg, respectively: 0.61 (0.44–0.85), 0.62 (0.45–0.87) and 0.68 (0.49–0.96); and for DBP 65–75, 76–86 and >86 mmHg, compared with <65 mmHg: 0.85 (0.62–1.18), 0.72 (0.52–1.00) and 0.60 (0.41–0.86)]. The same association was present for both SBP and DBP only in subgroups with GFR ≤30 ml/min/1.73 m^2 and for DBP only in the subgroup with ASCVD.

Conclusions. Lower blood pressure is associated with higher mortality in patients with moderate to severe CKD, but interactions with kidney function and with ASCVD suggest that blood pressure may play a surrogate rather than a causative role in this association.

Keywords: cardiovascular disease; chronic kidney disease; diastolic blood pressure; glomerular filtration rate; mortality; systolic blood pressure

Introduction

Although high blood pressure is associated with increased risk of cardiovascular disease and death in the general population [1–3], low blood pressure has been shown to be paradoxically associated with increased mortality in patients with chronic kidney disease (CKD) on dialysis [4–9]. The underlying mechanism for this counterintuitive phenomenon is unclear. Given the strong association between lower blood pressure and greater survival in the general population, it has been suggested that in dialysis patients low blood pressure could be a surrogate marker of certain comorbidities that develop gradually over the course of progressive CKD [10,11]. The association of blood pressure with mortality has not been studied yet in patients with moderate and severe CKD, but who are not yet on dialysis. It is, thus, unclear if the same paradoxical association is present in this population and if yes, at what level of severity of CKD. We analysed the association of systolic (SBP) and diastolic blood pressure (DBP) with all-cause mortality in a cohort of 860 US veterans with moderate to severe CKD [Stage 3–5, according to the National Kidney Foundation Kidney/Dialysis Outcomes Quality Initiative (K/DOQI) guidelines [12] not yet on dialysis. We examined the role of decreased kidney function and prevalent atherosclerotic cardiovascular disease (ASCVD) to test the hypothesis that the inverse association between blood pressure and mortality seen in dialysis patients develops gradually during the course

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of CKD and that low blood pressure is a surrogate marker of cardiovascular disease in this patient population.

Subjects and methods

Patients

We examined patients enrolled in the Nephrology Clinic at Salem Veterans Affairs Medical Center (VAMC) between 1 January 1990 and 31 December 2004. Nine hundred and sixty patients with CKD not yet on dialysis were identified. After estimation of glomerular filtration rate (GFR) by the abbreviated Modification of Diet in Renal Disease Study equation [13], patients' CKD severity was classified according to K/DOQI guidelines [12]. Patients with CKD Stage 1 and 2 ($n = 99$) were excluded. Of the 861 patients with CKD Stage 3–5, one patient had no blood pressure measurement available and was excluded. The final cohort consisted of 860 patients.

Data collection

We used blood pressure measurements recorded at the first encounter with the patients in the nephrology clinic. These measurements were performed by trained nephrology nurses according to established protocols, using appropriately sized blood pressure cuffs, with patients in the sitting position and after 10 min of rest. Other baseline data were collected from paper and electronic records and included demographic and anthropometric information, prevalent comorbidities, use of antihypertensive medications [angiotensin-converting enzyme inhibitors (ACEI)/angiotensin II-receptor blockers (ARB), beta-blockers and other antihypertensives] and laboratory measures [serum creatinine, albumin, haemoglobin and total cholesterol concentrations and the magnitude of proteinuria (24 h urine protein or ratio of spot urine protein and creatinine)]. Echocardiograms performed prior to the baseline evaluations were used to estimate congestive heart failure (CHF), defined as an ejection fraction of <50%. Body mass index (BMI) was calculated as the weight (kg) divided by the square of the height (m). Diabetes mellitus (DM) was defined as the presence of a fasting glucose level of >126 mg/dl or anti-diabetic therapy. ASCVD was defined as a previous history of cardiovascular (including prior history of angina, myocardial infarction or coronary artery bypass grafting), cerebrovascular (including prior history of transient ischaemic attack, stroke or carotid end-arterectomy) or peripheral vascular disease (including prior history of claudication or peripheral arterial bypass grafting).

Outcomes

Patients were followed until they expired or were lost to follow-up, or until 15 May 2005. A patient was considered lost to follow-up if no contact with the medical centre could be documented for >6 months. Forty-two patients (4.9%) were lost to follow-up and all their characteristics were similar to the overall groups'. The main outcome measure was all-cause mortality, with the recording of deaths both before and [in the case of patients who advanced to end-stage renal disease (ESRD)] after dialysis. Deaths were recorded from the US Department of Veterans Affairs computerized centralized patient record system (CPRS), which utilizes a combination of sources, including national databases, direct notifications from family members and obituaries to ascertain events. No data were available on cause of death. The initiation of dialysis (haemodialysis or peritoneal dialysis, with pertinent dates) was captured from local medical records, including Form 2729.

Statistical analysis

Descriptive statistics were performed and variables with skewed distribution were transformed to their natural logarithm. Missing data points were imputed for proteinuria (4.6% missing), blood cholesterol (1.8% missing) and serum albumin (1.7% missing) using multivariable linear regression to calculate missing values, with all other patient characteristics entered as independent variables. Given the large number of missing data points for BMI (24.3%), we categorized this variable by using quartiles and adding a 'missing' category as a fifth category. Similarly, CHF (41.3% missing) and smoking status (6.8% missing) were analysed as categorical variables and entering a third, 'missing' category.

Survival modelling. The starting time for survival analysis was the date of the initial encounter and the outcome measure was all-cause mortality. Patients lost to follow-up were censored at the date of the last documented encounter. Event rates were calculated using the person-years approach. The association of categorized SBP and DBP with all-cause mortality was analysed using Kaplan–Meier plots and the log-rank test. Multivariable Cox models were used to adjust for the effects of age, race, DM, ASCVD, BMI, CHF, smoking, use of ACEI/ARB, beta-blockers or other antihypertensives, estimated GFR, serum albumin, blood cholesterol, haemoglobin and 24 h urine protein. Adjustment for the effect of dialysis initiation in patients who reached ESRD was done by entering this as a time-dependent covariate in the multivariable Cox models. Non-linear associations were explored by use of quadratic terms. Subgroup analyses were performed after categorizing patients by estimated GFR level and presence or absence of prevalent ASCVD. We tested the proportionality assumption using plots and interaction terms with time. *P*-values of <0.05 were considered significant. Statistical analyses were performed using STATA statistical software version 8.0 (STATA Corporation, College Station, TX, USA). The study protocol was approved by the Research and Development Committee at the Salem VAMC.

Results

Baseline characteristics divided by levels of SBP are shown in Table 1. Patients with SBP <133 mmHg were less likely to be black and to be on antihypertensive medications, more likely to have ASCVD and CHF, and had higher estimated GFR, lower cholesterol and lower proteinuria (Table 1). Table 2 shows the distribution of event rates (deaths and dialysis) by quartiles of SBP and DBP, indicating higher death rates in the lowest quartiles of SBP and DBP and higher rates of initiating dialysis in the highest quartiles of SBP and

Table 1. Baseline characteristics of individuals stratified by categories of SBP

	SBP (mmHg)				*P*-value
	<133	133–154	155–170	>170	
Number (%)	217 (25.2)	238 (27.7)	211 (24.5)	194 (22.5)	
Age (years)	68.3 ± 10.5	67.3 ± 12.0	68.7 ± 9.7	68.3 ± 9.7	0.5
Gender (male)	213 (98.1)	238 (100)	209 (99.0)	192 (98.9)	0.1
Race White	182 (83.9)	182 (76.5)	156 (73.9)	130 (67.0)	0.001
Black	35 (16.1)	56 (23.5)	56 (26.0)	64 (32.9)	
DM	110 (50.7)	130 (54.6)	104 (49.2)	111 (57.2)	0.3
ASCVD	146 (67.3)	149 (62.6)	115 (54.5)	117 (60.3)	0.05
EF >50%	67 (51.5)	84 (61.2)	85 (71.4)	79 (68.7)	0.007
35–50%	25 (19.2)	26 (18.3)	21 (17.6)	20 (17.3)	
<35%	38 (29.2)	29 (20.4)	13 (10.9)	16 (13.9)	
Use of ACEI/ARB	177 (73.1)	215 (76.2)	186 (69.9)	201 (78.5)	0.1
Use of beta-blockers	156 (64.4)	165 (58.5)	154 (57.8)	170 (66.4)	0.1
Use of other antihypertensives	171 (70.6)	221 (78.3)	226 (84.9)	225 (87.8)	<0.001
BMI (kg/m^2)	28.5 ± 5.9	28.7 ± 4.8	28.9 ± 5.9	28.7 ± 5.7	0.9
Active smoking	50 (25.6)	57 (25.2)	50 (25.6)	61 (32.9)	0.2
Estimated GFR (ml/min/1.73 m^2)	32.9 ± 10.3	34.3 ± 11.8	32.2 ± 11.8	31.1 ± 11.5	0.03
Albumin (g/dl)	3.5 ± 0.5	3.6 ± 0.4	3.6 ± 0.4	3.5 ± 0.4	0.3
Haemoglobin (g/dl)	12.4 ± 1.9	12.7 ± 2.0	12.3 ± 1.6	12.3 ± 1.6	0.1
Cholesterol (mg/dl)[a]	176.8 (170.0–183.9)	185.0 (178.6–191.5)	189.7 (183.1–196.5)	196.6 (189.8–203.6)	0.0008
Urinary protein (mg/24 h)[a]	454.8 (370.3–558.7)	710.4 (581.1–868.0)	910.8 (750.3–1105)	1365.9 (1091.2–1709.8)	<0.0001

EF, ejection fraction.
Comparisons are made by analysis of variance, Fisher's exact test or chi^2 test.
Data are presented as means ± SD, number (% of total) or [a]geometric mean (95% CI).

Table 2. Distribution of events, by quartiles of SBP and DBP

	Death rate (95% CI)	Dialysis initiation rate (95% CI)
Overall	122.8 (110.6–136.2)	56.7 (49.2–65.2)
SBP (mmHg)		
<133 (n = 217)	145.6 (117.4–180.6)	33.3 (22.7–49.0)
134–155 (n = 238)	104.8 (85.0–129.1)	48.5 (36.4–64.5)
156–170 (n = 211)	116.1 (94.2–143.1)	66.0 (50.9–85.6)
>170 (n = 194)	133.7 (109.5–163.1)	77.6 (60.7–99.2)
DBP (mmHg)		
<64 (n = 233)	167.0 (135.7–205.6)	36.4 (25.0–53.2)
65–75 (n = 197)	145.3 (116.7–180.9)	44.7 (33.9–66.4)
75–86 (n = 230)	114.9 (94.9–139.1)	63.3 (49.7–80.6)
>86 (n = 200)	91.5 (73.7–113.6)	71.5 (56.3–90.8)

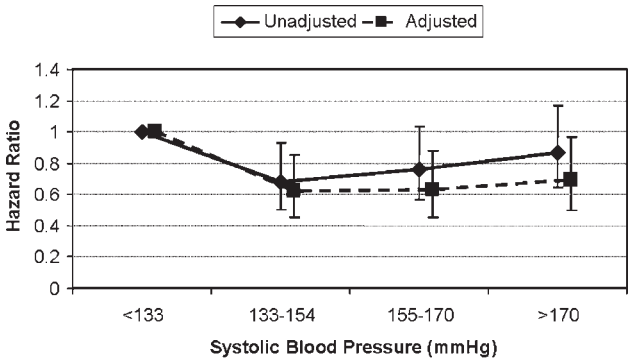

Fig. 1. Hazard ratio (95% CI) of all-cause mortality in the overall patient population, associated with different levels of SBP, unadjusted and after adjustment for age, race, DM, ASCVD, CHF, smoking status, BMI, use of antihypertensive medications, estimated GFR, serum albumin, blood cholesterol, haemoglobin and 24 h urine protein. The group with SBP <133 mmHg served as reference.

DBP. Figure 1 shows the hazard ratio [95% confidence interval (CI)] for all-cause mortality associated with SBP 133–154, 155–170 and >170 mmHg, compared with <133 mmHg overall, unadjusted and after adjustment for age, race, DM, ASCVD, CHF, smoking, BMI, use of ACEI/ARB, beta-blockers or other antihypertensives, and levels of estimated GFR, albumin, cholesterol, haemoglobin and proteinuria. Mortality was highest in the SBP <133 mmHg group and lowest in the SBP 133–154 mmHg group. Introduction of a quadratic term for SBP confirmed the presence of a U-shaped association with mortality ($P = 0.009$ for the quadratic term in the multivariable model). Table 3 shows the multivariable Cox model describing the association of categorized SBP with all-cause mortality. Older age, DM, ASCVD, ejection fraction <35%, active smoking, lower estimated GFR, lower serum albumin, lower proteinuria and being on dialysis were also associated with higher mortality. Figure 2 shows the hazard ratio (95% CI) for all-cause mortality associated with DBP 65–75, 76–86 and >86 mmHg, compared with <65 mmHg overall, unadjusted and after adjustments. Mortality was highest in the DBP <65 mmHg group, with higher DBP quartiles showing significantly lower mortality rates in a linear fashion ($P_{\text{trend}} = 0.005$ in the adjusted model). In a multivariable Cox model analysing DBP as a continuous variable, a 10 mmHg higher DBP was associated with a hazard ratio (95% CI) for all-cause mortality of 0.87 (0.80–0.94; $P = 0.002$). Figures 3A and 3B show the adjusted hazard ratios for all-cause mortality by quartiles of SBP (Figure 3A) and DBP (Figure 3B), in subgroups with and without prevalent ASCVD. DBP was inversely associated with mortality in the

Table 3. Associations with all-cause mortality in a multivariable Cox model

	Hazard ratio	SE	95% CI		*P*-value
SBP (Referent: SBP <133 mmHg)					
134–154 mmHg	0.62	0.10	0.45	0.85	0.003
155–170 mmHg	0.63	0.11	0.45	0.87	0.006
>170 mmHg	0.69	0.12	0.49	0.96	0.029
Age (1 year)	1.04	0.01	1.03	1.06	<0.001
Black race (Referent: white race)	0.88	0.12	0.68	1.15	0.351
DM	1.29	0.16	1.00	1.65	0.047
ASCVD	1.50	0.20	1.16	1.95	0.002
Ejection Fraction (Referent: EF >50%)					
35–50%	1.30	0.24	0.91	1.86	0.15
<35%	2.01	0.34	1.44	2.79	<0.001
Missing EF	1.15	0.15	0.88	1.49	0.311
Use of ACEI/ARB	1.03	0.12	0.81	1.30	0.836
Use of beta-blockers	0.98	0.12	0.77	1.24	0.847
Use of other antihypertensives	1.09	0.15	0.83	1.43	0.539
BBI (Referent: BMI < 25 kg/m^2)					
25–27.9 kg/m^2	0.96	0.20	0.64	1.45	0.849
28–32 kg/m^2	0.97	0.21	0.63	1.48	0.881
>32 kg/m^2	1.03	0.23	0.67	1.59	0.89
Missing BMI	3.43	0.60	2.43	4.84	<0.001
Active smoking					
Active smoking	1.31	0.17	1.02	1.70	0.038
Missing smoking status	0.98	0.19	0.68	1.43	0.921
Estimated GFR (1 ml/min/1.73 m^2)	0.98	0.01	0.97	0.99	0.001
Haemoglobin (1 g/dl)	1.00	0.04	0.94	1.08	0.907
Albumin (1 g/dl)	0.43	0.06	0.33	0.55	<0.001
Cholesterol (1 ln-unit)	0.74	0.16	0.49	1.12	0.151
24 h urine protein (1 ln-unit)	0.87	0.04	0.79	0.95	0.003
Dialysis	1.97	0.31	1.45	2.68	<0.001

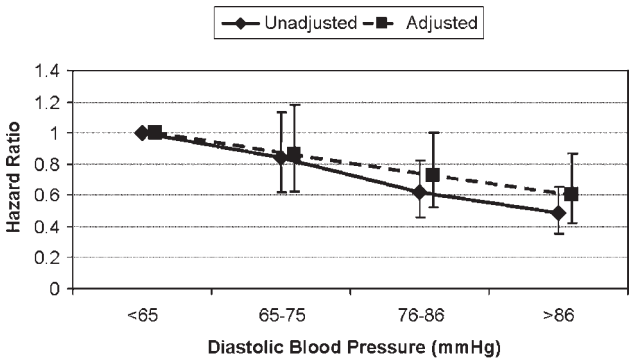

Fig. 2. Hazard ratio (95% CI) of all-cause mortality in the overall patient population, associated with different levels of DBP, unadjusted and after adjustment for age, race, DM, ASCVD, CHF, smoking status, BMI, use of antihypertensive medications, estimated GFR, serum albumin, blood cholesterol, haemoglobin and 24 h urine protein. The group with DBP <65 mmHg served as reference.

subgroup with prevalent ASCVD ($P_{trend} = 0.002$), but not in patients without ASCVD ($P_{trend} = 0.5$). A similar tendency was apparent with SBP, but the associations were not statistically significant. Figures 4A and 4B show the adjusted hazard ratios for all-cause mortality by quartiles of SBP (Figure 4A) and DBP (Figure 4B) in subgroups divided by different levels of estimated GFR, relative to the groups with estimated GFR <20 ml/min/1.73 m^2 and the lowest quartiles of SBP and DBP. The lowest quartiles of both SBP and DBP were associated with significantly higher mortality within the groups with estimated GFR <20 ml/min/1.73 m^2 [hazard ratio (95% CI) for SBP >170 *vs* <133 mmHg: 0.39 (0.16–0.90); and for DBP >86 *vs* <65 mmHg: 0.27 (0.11–0.67)] and 20–30 ml/min/1.73 m^2 [0.38 (0.19–0.74) and 0.47 (0.23–0.99)], but not within the groups with estimated GFR 30–40 ml/min/1.73 m^2 [0.97 (0.46–2.04) and 0.45 (0.18–1.09)] and >40 ml/min/1.73 m^2 [1.86 (0.71–4.82) and 0.5 (0.2–1.28)].

Discussion

We examined the association of SBP and DBP with all-cause mortality in a historical prospective cohort of patients with moderate to severe CKD. We found that both SBP and DBP were inversely associated with mortality overall, but that there were significant interactions with prevalent ASCVD (for DBP) and with lower GFR, indicating that a low blood pressure may not be an independent risk factor for mortality, but rather a surrogate marker of ASCVD and low GFR-associated comorbidities.

The association of lower blood pressure with increased mortality has been described repeatedly in patients with Stage 5 CKD on dialysis [4–9] and the phenomenon has been termed 'reverse epidemiology' [14] or 'risk factor paradox' [5] to contrast it with the well-established and strong direct association between higher blood pressure and increased mortality found in the general population [1–3]. Some of the explanations offered to explain this phenomenon included differences in the neurohormonal status in obese and hypertensive individuals [15], an interaction between endotoxin and lipoproteins [16], reverse causation [17], survival bias and the presence of competitive risk factors [18] and the modifying effect of chronic inflammation on traditional risk factors for ASCVD [19]. In patients with CKD, gradual loss of kidney function is associated with the development of several abnormalities, such as anaemia [20,21], malnutrition and inflammation [22], elevation in homocysteine level [23] and abnormalities in bone and mineral metabolism [24]. It is possible that during the course of CKD such alterations result in increased burden of uraemia and cardiovascular disease [25] and a concomitant decline in blood pressure as a result of worsening ischaemic heart disease and CHF [26] or as a result of uraemia-associated autonomic neuropathy. The higher mortality associated with lower blood pressure in CKD would then be the result of the mortality associated with the already present cardiovascular disease outweighing the mortality risk associated with higher blood pressure, as opposed to a cause–effect relationship between

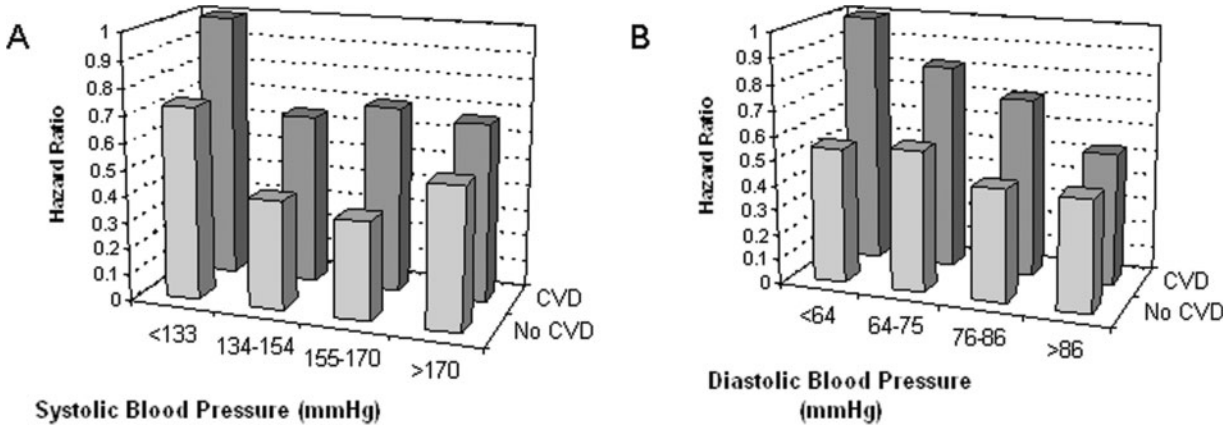

Fig. 3. Adjusted hazard ratios of all-cause mortality in subgroups with and without prevalent ASCVD, associated with different levels of SBP (**A**) and DBP (**B**). Adjustments were made for age, race, DM, CHF, smoking status, BMI, use of antihypertensive medications, estimated GFR, serum albumin, blood cholesterol, haemoglobin and 24 h urine protein. The groups with prevalent ASCVD in the lowest quartile of SBP or DBP served as reference.

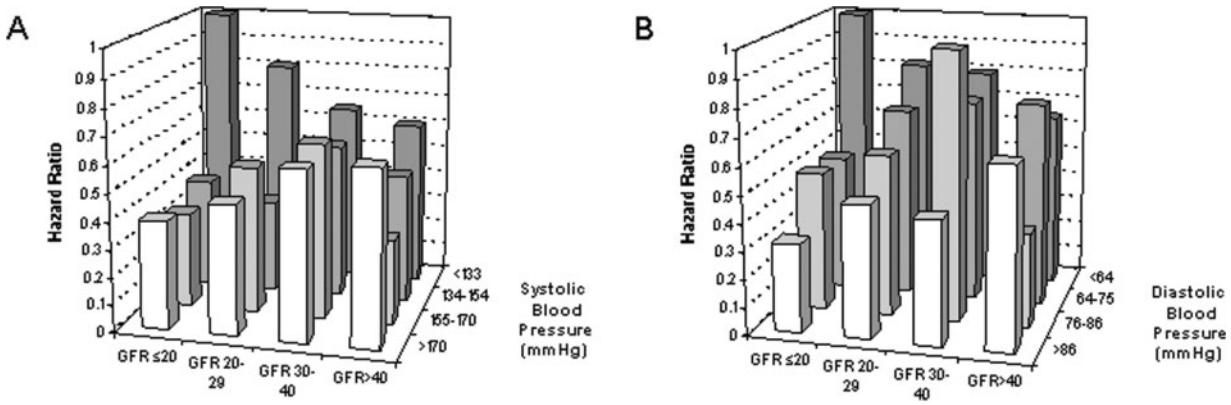

Fig. 4. Adjusted hazard ratios of all-cause mortality in subgroups with different levels of estimated GFR, associated with different levels of SBP (**A**) and DBP (**B**). Adjustments were made for age, race, DM, ASCVD, CHF, smoking status, BMI, use of antihypertensive medications, estimated GFR, serum albumin, blood cholesterol, haemoglobin and 24 h urine protein. The groups with estimated GFR $<20\,\text{ml/min/1.73}\,\text{m}^2$ in the lowest quartile of SBP or DBP served as reference.

mortality and lower blood pressure [10]. We also postulate that the above-mentioned pathological processes would develop gradually during the course of advancing CKD; hence, the inverse association between low blood pressure and mortality may only manifest itself during later stages of the disease. Our findings support these hypotheses, since the inverse association between blood pressure and mortality was only present in patients with estimated GFR $<30\,\text{ml/min/1.73}\,\text{m}^2$ and (in the case of DBP) in those with prevalent ASCVD.

Our study has several shortcomings that need to be stressed. Our cohort consisted almost exclusively of men from a single medical centre; hence, our findings may not be applicable to women or patients from other geographic areas. Since this was an observational study, no cause–effect relationships can be established from it, but associations can be described. While we tried to account for several potential confounding risk factors, residual and/or unknown confounders may still be present. We defined ASCVD historically, but without confirmatory ascertainment. This approach might have underestimated the true prevalence of ASCVD, which might have been even higher than the 60.5% that we found in the study population. Finally, we used a single blood pressure measurement; thus, the effects of longitudinal changes in this parameter could not be accounted for.

Perspective

We describe an inverse association between blood pressure and all-cause mortality in patients with moderate to severe CKD. This association was explained by the presence of more advanced CKD and prevalent ASCVD, suggesting that the paradoxical association found in our study may not be a causal relationship. Similar findings have been described by Liu *et al.* [27] for blood cholesterol level, which, as blood pressure, shows an inverse association with mortality in dialysis patients, but this relationship was limited to individuals with elevated C-reactive protein level. These findings suggest that therapeutic interventions targeting traditional risk factors for ASCVD in

patients with CKD should be considered, even though it is unclear yet if such interventions will prove to be effective in improving mortality or morbidity. The ideal blood pressure levels pertinent to mortality in patients with CKD need to be established based on clinical trials and not observational studies. We, thus, caution against over-interpretation of observational studies and compromising treatment of hypertension in this patient population.

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Conflict of interest statement. None declared.

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