Original Article

Blood pressure and kidney outcomes in patients with severely decreased glomerular filtration rate: a nationwide observational cohort study

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Objectives: To investigate the association between blood pressure (BP) and kidney outcomes in patients with estimated glomerular filtration rate less than 30 ml/min per 1.73 m^2 and different degrees of albuminuria.

Methods: National observational cohort study of 18 071 chronic kidney disease (CKD) stage 4–5 patients in routine nephrology care 2010–2017. The association between both baseline and repeated clinic office BP and eGFR slope and kidney replacement therapy (KRT) was explored using multivariable adjusted joint models. The analyses were stratified on albuminuria at baseline.

Results: The adjusted yearly eGFR slope became increasingly steeper from −0,91 (95% CI −0.83 to −1.05) ml/min per 1.73 m^2 per year in those with SBP less than 120 mmHg at baseline to −2.09 (−1.83 to −2.37) ml/min per 1.73 m^2 in those with BP greater than 160 mmHg. Similarly, eGFR slope was steeper with higher DBP. Lower SBP and DBP was associated with slower eGFR decline in patients with albuminuria grade A3 (>30 mg/mmol) but not consistently in albuminuria A1–A2. Those with diabetes progressed faster and the association between BP and eGFR slope was stronger. In repeated BP measurement analyses, every 10 mmHg higher SBP over time was associated with 39% additional risk of KRT.

Conclusion: In people with eGFR less than 30 ml/min per 1.73 m^2, lower clinic office BP is associated with more favorable kidney outcomes. Our results support lower BP targets also in people with CKD stage 4–5.

Keywords: albuminuria, chronic kidney disease, hypertension, kidney replacement therapy

Abbreviations: ACR, albumin/creatinine ratio; BP, blood pressure; CKD, chronic kidney disease; CKD-EPI, The Chronic Kidney Disease Epidemiology Equation; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease Improving Global Outcome; KRT, kidney replacement therapy; RCT, randomized controlled trials; SPRINT, The Systolic blood Pressure Intervention Trial; SRR-CKD, Swedish Renal Registry – Chronic Kidney Disease

INTRODUCTION

Hypertension is a leading risk factor for death and disability, including stroke, accelerated coronary artery disease, systemic atherosclerosis, heart failure, and chronic kidney disease (CKD) [1]. CKD and hypertension are closely associated with an overlapping and intermingled cause and effect relationship. Decline in kidney function is typically associated with rises in blood pressure (BP), and sustained elevations in BP hasten the progression of kidney function decline [2]. BP control is essential for the care of patients with CKD regardless of the underlying cause [3,4]. Older randomized controlled trials (RCT) and observational data indicate that higher BP is a risk factor for progression of CKD, especially in patients with albuminuria [5–7].

More recently, the Systolic blood Pressure Intervention Trial (SPRINT) investigated the effect of intensive BP control with a lower target (SBP <120 mmHg) in people with cardiovascular risk factors but no diabetes. The results showed lower rates of the primary endpoint (a composite of cardiovascular events and death) in the intensive treatment group.

In people with CKD, two large meta-analyses and subgroup analyses from SPRINT also demonstrated lower cardiovascular event risk in those with an intensive BP treatment target [8,9]. Whether a lower BP target also reduce the risk of kidney outcomes is not clear. In SPRINT, no positive effect was observed on kidney outcomes. Instead, patients randomized to the intensive treatment group had significantly higher rates of acute kidney injury [10].

In two previous trials including only patients with CKD, there was no significant difference in change of the estimated glomerular filtration rate (eGFR) between the standard and more intensive BP-lowering target, except for in those with high albuminuria [11,12]. However, the intensive treatment arm of these trials aimed for higher BP as compared with the more recent BP trials.

Generalizing the benefits of intensive BP targets to those with severely decreased estimated glomerular filtration rate (eGFR <30 ml/min per 1.73 m^2) in CKD stages 4–5 is even more difficult as these patients were excluded in the more recent trials [10,13,14] and observational data is sparse. In a recent KDIGO controversies conference report, it was stated that specific data on BP targets in advanced stage CKD and those with severely increased proteinuria are urgently needed [15]. Furthermore, it is also noted that very little evidence is available to guide management in older adults with nondiabetic CKD [16].

In our investigation, we therefore, aimed to study BP and its association with kidney outcomes in patients with nondialysis CKD stage 4–5 (eGFR <30 ml/min per 1.73 m^2) and different levels of albuminuria, using a nationwide, contemporary cohort under nephrology care.

MATERIALS AND METHODS

Study population

In Sweden, patients attending out-patient nephrology care with an incident estimated glomerular filtration rate (eGFR) less than 45 ml/min per 1.73 m^2 (CKD stage 3b) are eligible to be registered in the Swedish Renal Registry – Chronic Kidney Disease (SRR-CKD) – a quality-control register supported by the Swedish Associations of Local Authorities and Regions [17]. Patients with incident CKD stage 4 (eGFR <30 ml/min per 1.73 m^2) are mandatory to include in the register. Currently, the SRR-CKD includes 98% of all nephrology clinics in Sweden and it has been estimated that greater than 70% of the referred patients with CKD 4–5 are included. For this study, we included patients at least 18 years of age at the first registered eGFR less than 35 ml/min per 1.73 m^2 between 1 January 2010 and 1 January 2018 with an available BP measurement recorded. We chose a threshold of 35 ml/min per 1.73 m^2 in order not to miss any patients who were apparently close to progress to CKD stage 4.

We excluded individuals with a recorded SBP less than 100 mmHg at baseline [$n = 361$ (1.9%), eFigure 1, http://links.lww.com/HJH/B950] as we judged it likely that this level of BP was caused by concomitant comorbidity (e.g. heart failure), and not primarily the result of antihypertensive treatment [18]. We followed all patients until death, dialysis start, kidney transplantation, or end of the observation period (1 January 2018). All patients obtained information about the SRR-CKD and had the possibility to opt-out but specific informed consent for research was not necessary according to the regulations for healthcare quality registers in Sweden. The study protocol was approved by the ethical review committee in Stockholm.

Blood pressure measurements

The clinic office BP was measured at the clinical out-patient visits either through automated oscillometric blood pressure device or manual measurements, whichever method was used regularly at the clinic. The recorded office BPs were measured for the purpose of clinical decision-making and general rules for BP measuring were applied. BP measurement procedures in clinical practice in Sweden states that patients should be seated comfortably with legs uncrossed and back and arm supported for at least 5 min prior to measurement, all general preparations are described in the Supplementary Material, http://links.lww.com/HJH/B950. SBP and DBP at baseline were categorized into a priori defined categories (SBP ≥100 < 120, 120 < 130, 130 < 140, 140 < 160, ≥160 mmHg and DBP < 70, 70 < 80, 80 < 90, ≥90 mmHg).

Outcomes

Our primary outcome was annual decline of eGFR (eGFR slope), and the secondary outcome was the time to kidney replacement therapy (KRT). eGFR was calculated by the Chronic Kidney Disease Epidemiology Equation (CKD-EPI) [15]. Date of death, start of dialysis and kidney transplantation were entered consecutively into the SRR-CKD by the clinics throughout follow-up.

Covariates

We included information from the SRR-CKD on age, sex, BMI, underlying cause of kidney disease defined by the treating nephrologist, information on comorbidity, and medications. Information on routine laboratory values at baseline was also collected, if present. Serum creatinine, hemoglobin, albumin, phosphate, calcium, parathyroid hormone, albuminuria, and c-reactive protein was mandatory to register, if available. Urinary albumin/creatinine ratio (ACR) became mandatory to register in SRR-CKD in 2013, and was therefore, missing to a larger extent in the period before that. ACR was categorized at baseline into no albuminuria (A1) if ACR less than 3 mg/mmol, A2 if ACR was 3 to less than 30 mg/mmol, and A3 if ACR was at least 30 mg/mmol (to convert ACR mg/mmol to mg/g divide by 0.113).

Statistical analysis

Patient characteristics were reported by BP categories at baseline as mean (standard deviations) for normally distributed variables, as medians with interquartile ranges for nonnormally distributed variables, and as proportions for categorical variables. First, using all available eGFR measurements, linear mixed models were used to model the annual decline in eGFR (the R package 'nlme' was used). The association between BP categories at baseline and eGFR decline over time was given by the time–BP interaction parameter. In subsequent models, we investigated the association between BP category at baseline and eGFR decline adjusted for various groups of a priori defined confounders in a step-wise manner [model 1: baseline eGFR + demographics (sex, age group, primary kidney disease); model 2: baseline eGFR + comorbidity (ischemic heart disease, other heart disease/heart failure, cerebrovascular disease, peripheral vascular disease); model 3: baseline eGFR + medication (diuretics, angiotensin converting enzyme or ACE-inhibitor/angiotensin-receptor blockers or

ARB); model 4: baseline eGFR + relevant laboratory values (plasma albumin, calcium, phosphate, hemoglobin); model 5: all of the above, and in a sensitivity analysis additionally C-reactive protein]. Secondly, the association between baseline BP and time to KRT was modelled using Cox regression adjusting for the same sets of confounders as for the linear mixed model analysis (using R package 'survival' and 'rms'). The competing risk of death on KRT initiation was subsequently described using cumulative incidence functions and dealt with using the cause-specific hazards approach [19]. Finally, we combined the above analyses in joint models (the R package 'JMbayes' for the joint models was used). To overcome problems with multiple imputation when using joint models, single imputation was used to deal with missing data (Table 1). In the joint model, we investigated the association between all repeated BP measurements during the entire follow-up and KRT initiation, with adjustments for baseline eGFR, informative censoring, and competing risk of death, and all other confounders as fixed effects at baseline [20]. We then repeated the above-mentioned analyses stratified by ACR at baseline. Subgroup analyses were additionally performed in predefined subgroups of older/younger individuals, men/women, those with diabetes, and a history of cardiovascular disease. A more extensive description of the statistical methods is found in the Supplement, http://links.lww.com/HJH/B950. All analyses were performed in R version 3.4.1 (R Foundation, Vienna, Austria).

RESULTS

Patient characteristics

After exclusions, we identified a total of 18 071 patients in SRR-CKD who fulfilled our eligibility criteria between 2010 and 2017 (eFigure 1, http://links.lww.com/HJH/B950). Median age was 73 years (IQR 64–80), most were men (63%), the predominant primary renal diagnosis was hypertension/nephrosclerosis (28.8%) followed by diabetes nephropathy (22%) (Table 1). Median eGFR was 23.2 ml/min per 1.73 m^2 (IQR 17.5–28.4) at study baseline. Of those with recorded albuminuria at baseline ($n = 8636$), 15% of our cohort had no albuminuria (A1), whereas 32.2 and 51.4% percentage were classified as having A2 and A3, respectively. The characteristics of patients with missing albuminuria are described in eTable 1, http://links.lww.com/HJH/B950. Patients with available albuminuria were more often men, had slightly higher eGFR, had more often diabetes, heart failure and ischemic heart disease, and were more often treated by ACEi/ARB. Median SBP was 140.6 mmHg (IQR 125–152) and DBP was 77.1 mmHg (IQR 70–85) at inclusion. The clinical characteristics

TABLE 1. Clinical characteristics of the chronic kidney disease cohort

Clinical characteristics			Missing (%)
Number		18 071	0.0
Age (years) [median (IQR)]		73 (64–80)	0.0
Women		6762 (37.4%)	0.0
Primary renal disease	Polycystic kidney disease and other hereditary	810 (4.5%)	0.0
	Diabetes nephropathy	3984 (22.0%)	0.0
	Glomerulonephritis	1451 (8.0%)	0.0
	Hypertensive kidney disease	5208 (28.8%)	0.0
	Other specified renal diseases	4290 (23.7%)	0.0
	Unknown	2328 (12.9%)	0.0
Comorbidity	Diabetes mellitus ($n = 16 029$)	5432 (33.9%)	11.3
	Ischemic heart disease ($n = 15 469$)	2282 (14.8%)	14.4
	Chronic heart failure ($n = 15 469$)	1860 (12.0%)	14.4
	Cerebrovascular disease ($n = 15 469$)	891 (5.8%)	14.4
	Peripheral vascular disease ($n = 15 469$)	687 (4.4%)	14.4
Clinical data	eGFR (ml/min per 1.73 m^2) (median, IQR)	23.2 (17.5–28.4)	0.0
	SBP (mmHg)	140.6 (21.0)	0.0
	DBP (mmHg)	77.1 (11.8)	0.0
	BMI (kg/m^2) ($n = 10 861$)	28.2 (5.9)	39.9
	Albumin (g/dl) ($n = 16 969$)	3.6 (0.5)	6.1
	Calcium (mmol/l) ($n = 15 975$)	2.29 (0.16)	11.6
	CRP (mg/l) (median, IQR) ($n = 13 355$)	5 (2–10)	26.1
	Phosphate (mmol/l) ($n = 16 571$)	1.3 (0.3)	8.3
	Hemoglobin (g/dl) ($n = 17 475$)	12.1 (1.61)	3.3
	U-albumin/creatinine ratio (mg/mmol, IQR) ($n = 8636$)	32.7 (5.9–141.8)	52.2
	A1 (<3 mg/mmol)	1367 (15.8%)	
	A2 (3–30 mg/mmol)	2833 (32.2%)	
	A3 (>30 mg/mmol)	4436 (51.4%)	
Medication	Erythropoesis stimulating agents ($n = 16 788$)	3594 (21.4%)	7.1
	Diuretics ($n = 16 788$)	11 054 (65.8%)	7.1
	Statins ($n = 16 788$)	8616 (51.3%)	7.1
	ACEi/ARB ($n = 16 788$)	9890 (58.9%)	7.1

Values for continuous variables are presented as mean (standard deviation) unless indicated, and categorical variables are presented as number (percentage). ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BP, blood pressure; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; IQR, interquartile range. Conversion factors for units: calcium mmol/l to mg/dl divided by 0.2495; phosphate mmol/l to mg/dl divided by 0.3229. UACR mg/mmol to mg/g divide by 0.113.

TABLE 2. Annual decline in estimated glomerular filtration rate by blood pressure category at baseline

SBP (mmHg)	Unadjusted eGFR decline per year (ml/min per 1.73 m² per year) (95% confidence interval)	P value	Adjusted[a] eGFR decline/ year (ml/min per 1.73 m² per year) (95% confidence interval)	P value
≥100 < 120 (n = 3542)	−0.93 (−1.13 to −0.74)	Ref	−0.91 (−0.83 to −1.05)	Ref
120 < 130 (n = 3305)	−1.37 (−1.57 to −1.17)	<0.001	−1.32 (−1.11 to −1.63)	<0.001
130 < 140 (n = 3795)	−1.61 (−1.81 to −1.42)	<0.001	−1.52 (−1.29 to −1.81)	<0.001
140 < 160 (n = 4888)	−1.89 (−2.06 to −1.72)	<0.001	−1.81 (−1.53 to −2.07)	<0.001
≥160 (n = 2541)	−2.14 (−2.39 to −1.89)	<0.001	−2.09 (−1.83 to −2.37)	<0.001
DBP (mmHg)				
<70 (n = 6140)	−1.14 (−1.29; −0.99)	Ref	−1.15 (−1.22; −1.05)	Ref
70 < 80 (n = 6581)	−1.56 (−1.70; −1.42)	<0.001	−1.51 (−1.63; −1.41)	<0.001
80 < 90 (n = 3616)	−1.88 (−2.07; −1.69)	<0.001	−1.76 (−1.91; −1.62)	<0.001
≥90 (n = 1734)	−2.32 (−2.60; −2.05)	<0.001	−2.13 (−2.35; −1.94)	<0.001

[a]On the basis of the multiple imputation model and adjusted for (baseline eGFR, sex, age group, ischemic heart disease, heart failure, cerebrovascular disease, peripheral vascular disease, diabetes, primary renal disease, diuretics, ACE-i, plasma calcium, plasma phosphate, hemoglobin) and accounting for nonrandom drop-out because of death.
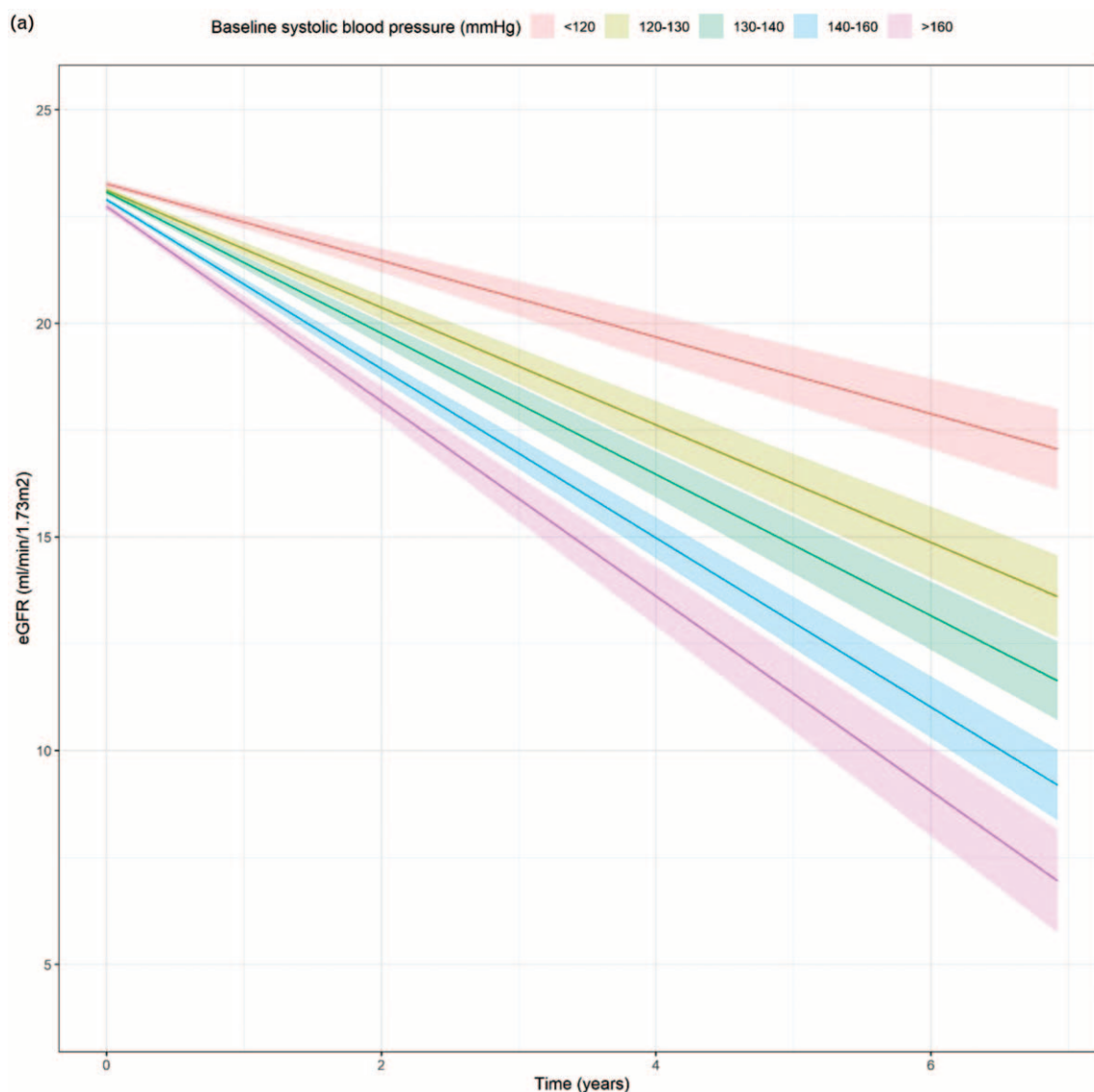

FIGURE 1 Association between baseline achieved SBP (a) and DBP (b) blood pressure on estimated glomerular filtration rate slope. (a) Association between baseline achieved SBP in mmHg on eGFR slope in ml/min per 1.73 m². (b) Association between baseline achieved DBP in mmHg on eGFR slope in ml/min per 1.73 m². (a) Adjusted for baseline eGFR (estimated glomerular filtration rate) albumin, calcium, phosphate, hemoglobin, diabetes, ischemic heart disease, heart failure, cerebrovascular disease, and angiotensin receptor blockers/angiotensin converting enzyme inhibitors. Blood pressure expressed in mmHg. eGFR slope expressed in ml/min per 1.73 m².
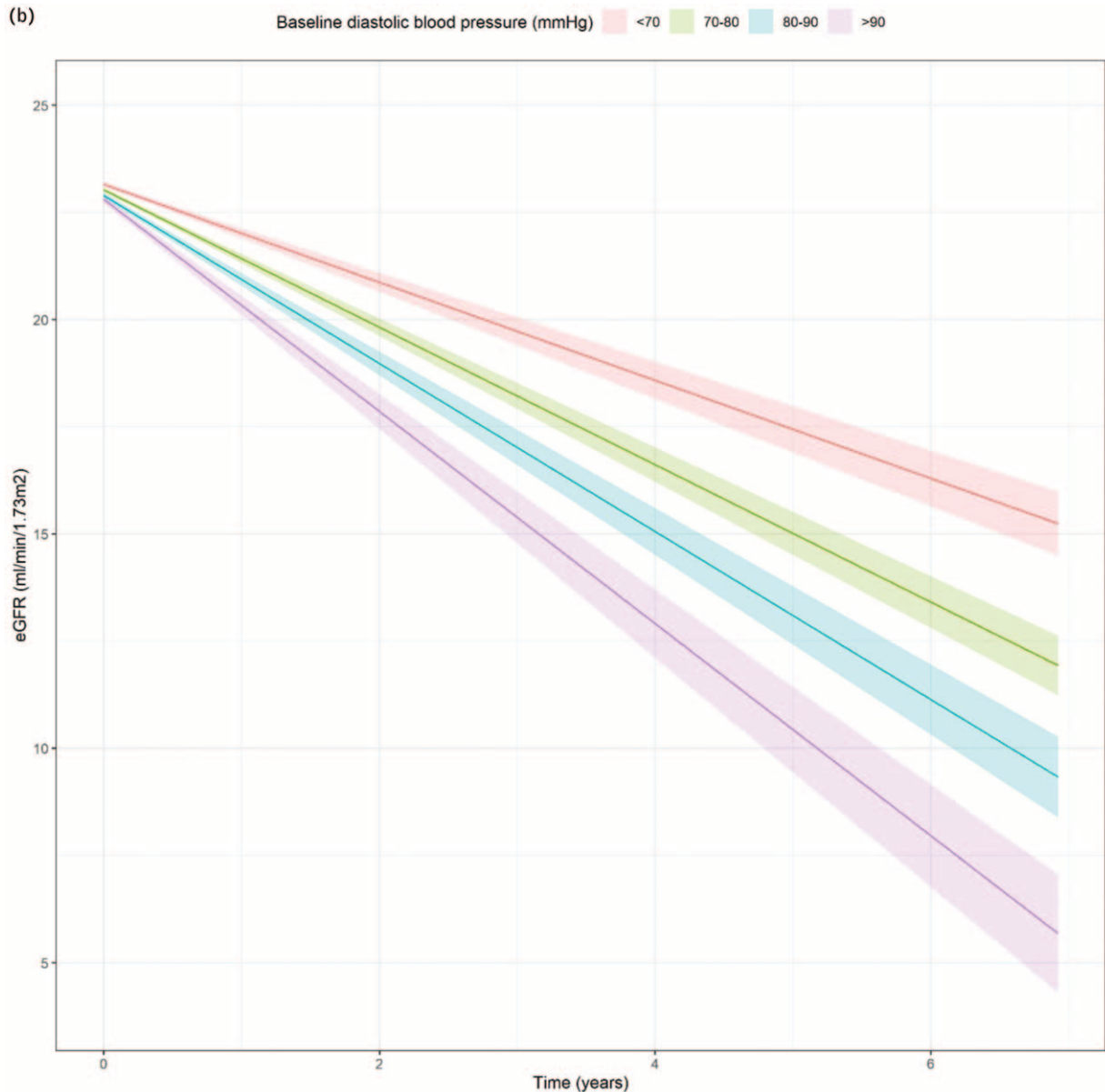
FIGURE 1 (continued)

stratified by different levels of SBP and DBP are presented in eTable 2, http://links.lww.com/HJH/B950 (A and B).

Blood pressure and decline in renal function

The mean annual loss of eGFR was -1.49 (95% confidence interval -1.55 to -1.44) ml/min per 1.73 m^2 per year. The unadjusted eGFR decline per year increased gradually from -0.93 (-1.13 to -0.74) ml/min per 1.73 m^2 per year in those with an achieved SBP less than 120 mmHg at baseline to -2.14 (-2.39 to -1.89) ml/min per 1.73 m^2 in those with achieved BP greater than 160 mmHg (Table 2). Similarly, eGFR decline increased with higher achieved DBP. The differences in eGFR remained after adjustment for confounders in all categories (Fig. 1).

We observed a more rapid eGFR decline with increasing albuminuria (Table 3). Lower achieved SBP and DBP was

associated with slower eGFR decline in patients with albuminuria grade A3 [-1.29 (-1.49 to -1.10) ml/min per 1.73m^2 per year for SBP 100–120 mmHg, -2.01 (-2.18 to -1.83) ml/min per 1.73m^2 per year for SBP 130 > 140 mmHg and -2.22 (-2.41 to -2.04) ml/min per 1.73 m^2 per year for at least 160 mmHg, P trend <0.001). A DBP less than 70 mmHg was associated with slower eGFR decline in patients with albuminuria grade A2 compared with all higher DBP. There was a tendency towards slower eGFR decline in those with lower SBP and albuminuria A1 that did not reach statistical significance. Merging the patients in the A1 and A2 categories did not substantially change the relationship between SBP and eGFR decline but the association between lower DBP and slower eGFR decline was now statistically significant (eTable 3, http://links.lww.com/HJH/B950). The association between SBP and DBP and annual eGFR decline were similar

TABLE 3. Annual decline in estimated glomerular filtration rate by blood pressure category at baseline, and by albuminuria categories

| Blood pressure (mmHg) | Albuminuria categories | | | | | |
| | A1 (<3 mg/mmol) | | A2 (3 < 30 mg/mmol) | | A3 (≥30 mg/mmol) | |
	eGFR decline/year[a] (95% confidence interval)	P value	eGFR decline/year[a] (95% confidence interval)	P value	eGFR decline/year[a] (95% confidence interval)	P value
SBP		P (trend) 0.03		P (trend) 0.0005		P (trend) <0.0001
≥100 < 120	−0.36 (−0.6 to −0.12) (n = 786)	Ref.	−0.63 (−0.81 to −0.45)(n = 1358)	Ref.	−−1.29 (−1.49 to −1.1)(n = 1398)	Ref.
120 < 130	−0.76 (−1.03 to −0.49)(n = 584)	0.03	−0.79 (−0.98 to −0.6) (n = 1191)	0.23	−1.75 (−1.93 to −1.57)(n = 1530)	<0.0001
130 < 140	−0.85 (−1.12 to −0.58)(n = 593)	0.10	−0.97 (−1.15 to −0.79)(n = 1305)	0.01	−2.01 (−2.18− to −1.83)(n = 1897)	<0.0001
140 < 160	−0.81 (−1.08 to −0.54)(n = 586)	0.02	−1.1 (−1.27 to −.92) (n = 1421)	0.00	−2.22 (−2.36 to −2.07)(n = 2881)	<0.0001
≥160	−0.75 (−1.28 to −0.23)(n = 164)	0.18	−1.15 (−1.44 to −0.86)(n = 546)	0.00	−2.22 (−2.41 to −2.04)(n = 1831)	<0.0001
DBP		P (trend) 0.0004		P (trend) <0.0001		P (trend) <0.0001
<70	−0.36 (−0.57; −0.15) (n = 1107)	Ref.	−0.68 (−0.82; −0.53) (n = 2230)	Ref.	−1.60 (−1.75; −1.45)(n = 2803)	Ref.
70 < 80	−0.78 (−0.98; −0.58) (n = 1048)	0.005	−0.94 (−1.09; −0.80) (n = 2100)	0.01	−1.89 (−2.01; −1.76)(n = 3433)	0.003
80 < 90	−1.03 (−1.33; −0.73) (n = 429)	0.0003	−1.10 (−1.30; −0.90) (n = 1062)	0.0007	−2.11 (−2.27; −1.95)(n = 2125)	<0.0001
≥90	−0.81 (−1.32; −0.29) (n = 129)	0.11	−1.26 (−1.55; −0.96) (n = 429)	0.0005	−2.64 (−2.87; −2.42)(n = 1176)	<0.0001

Converting UACR mg/mmol to mg/g divided by 0.113.
[a]On the basis of the multiple imputation model and adjusted for baseline eGFR, sex, age, primary renal disease, comorbidities, drugs, and laboratory values.

in those with missing albuminuria (eTable 4, http://links.lww.com/HJH/B950).

There was a significant interaction between eGFR decline and diabetes mellitus. Those with diabetes mellitus generally progressed faster, and the association between BP and eGFR slope was stronger than in nondiabetic patients (eTable 5, http://links.lww.com/HJH/B950). The association between BP and eGFR decline did not differ in the other predefined subgroups (men/women, and age groups).

Blood pressure and time to kidney replacement therapy initiation

During the observation period, 25% of our cohort started KRT, and 30% died. The median time to KRT was 5.4 years (95% CI 5.2–4.4). The probability of KRT increased with higher BP (Fig. 2a and b).

Patients with higher baseline SBP and DBP had a significantly higher risk of KRT (eTable 6, http://links.lww.com/HJH/B950). The hazard ratio for the association between SBP increased from around 120 mmHg, whereas the risk associated with DBP rose from about 75 mmHg (Fig. 2b). For patients with albuminuria A3, the risk of KRT increased markedly and nonlinearly with rising SBP and DBP. We also observed slightly rising risk curves in those with albuminuria A1 and A2 as SBP and DBP became higher (Fig. 3).

We also analyzed the continuous association between time-updated achieved office BP over time and KRT initiation assuming a linear relationship. In our final model, we observed that every 10 mmHg higher SBP and DBP at any time-point during follow-up was associated with 39 and 28% higher risk of KRT, respectively (Table 4).

DISCUSSION

In this large, nationwide cohort of CKD stage 4–5 patients, we found that lower clinic office BP at baseline and repeatedly over time, was associated with slower eGFR decline and lower KRT risk. SBP was almost linearly associated with KRT incidence. The results of this real-world cohort support the current AHA recommendations of a BP target less than 120/80 mmHg in patients with severely decreased GFR and CKD stage 4–5, and also the recently updated KDIGO recommendations [21]. They also expand findings from previous trials that in people with eGFR less than 30 ml/min per 1.73 m² achieving a lower BP is more important in those with higher levels of albuminuria (A3) and in those with diabetes. At lower levels of albuminuria (A1–A2), the associations were of lesser magnitude and often did not reach statistical significance. There was, however, a tendency towards better outcomes also among these patients.

Guidelines long recommended BP targets less than 140/90 mmHg in most patients [22,23]. A few years ago, SPRINT investigated the effects of intensive BP reductions (<120 mmHg) compared with standard treatment (<140 mmHg) in nondiabetes patients with increased risk of cardiovascular events [10]. Although intensive BP treatment reduced cardiovascular events, it was not associated with improved kidney outcomes (50% reduction in eGFR or dialysis/transplantation). Likewise, meta-analyses of the effects of intensive BP lowering, including SPRINT, show reduced mortality in patients with CKD [24] but not a statistically significant effect on kidney outcomes [25]. However, in most trials, only a small proportion had CKD, and those with more advanced stage CKD or high levels of
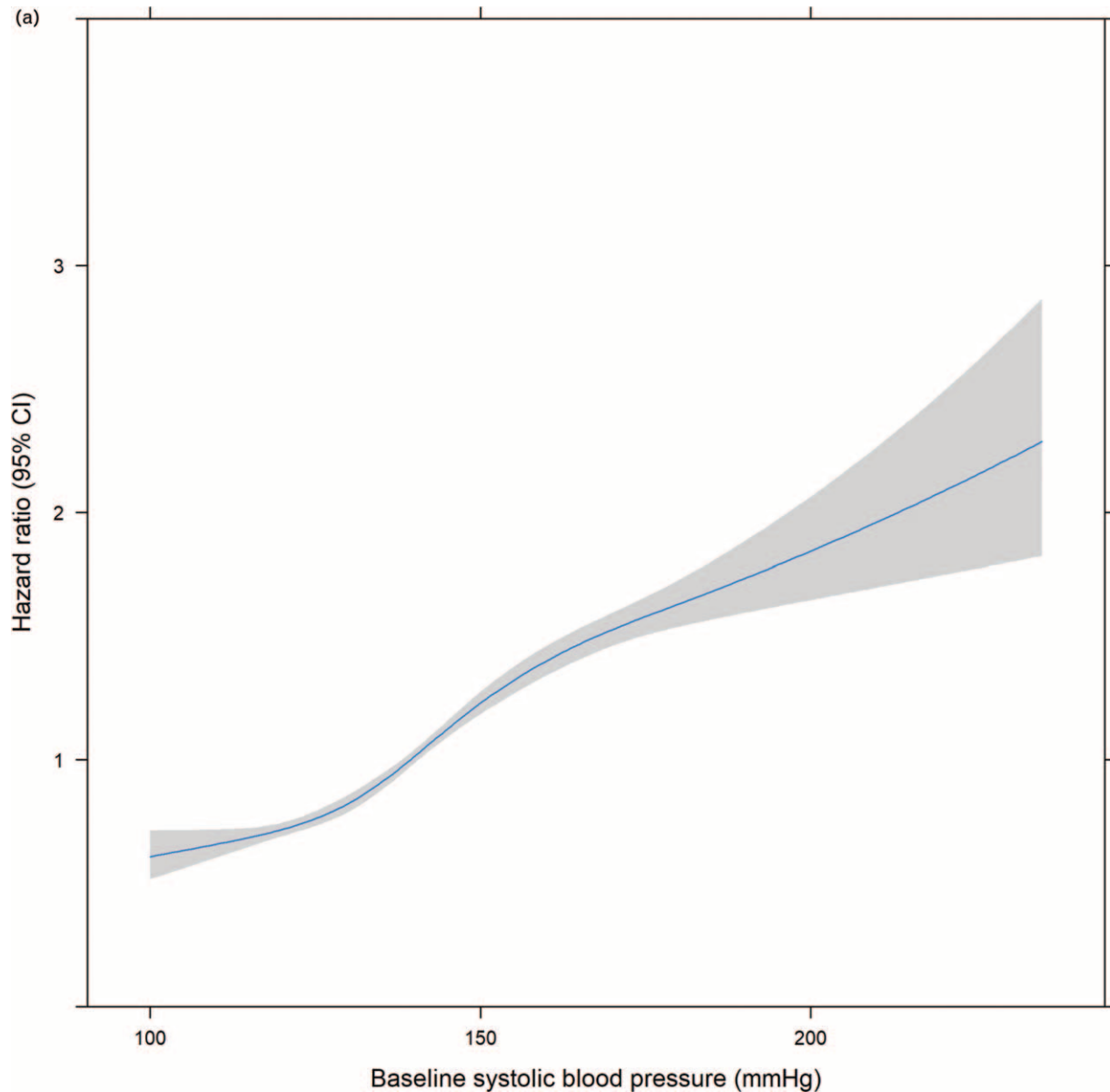
FIGURE 2 Hazard ratios (unadjusted) for the time to kidney replacement therapy initiation by blood pressure [systolic (a), diastolic (b)] at baseline expressed in mmHg.

albuminuria have generally been excluded [26]. This makes generalization to the larger CKD population, especially those with stage 4–5 CKD, uncertain.

A few observational studies have investigated the association between SBP and DBP with end-stage kidney disease (ESKD) or cardiovascular disease risk in patients with CKD [27–29]. Alike our results, higher BP was associated with higher ESKD risk, although not consistently. However, the patients included in most of these studies had higher mean eGFR at inclusion as compared with our patients, they were also younger, had fewer comorbid conditions, were nonreferred, and the majority had low levels of albuminuria indicating less severe CKD compared with our cohort. In summary, these characteristics are not representative of the general CKD population, which on the contrary often represent older adults (>75% of those with CKD stage 3+ are above 75 years of age) with several comorbidities

[30]. Furthermore, neither of these studies considered eGFR slope or the competing risk of death. In patients with advanced stage CKD, this risk is substantial [31].

It has previously been highlighted that the benefits of intensive BP treatment may come at a price for patients in some subgroups; the elderly, those with diabetes and CKD may suffer from increased rates of orthostatic hypotension and more acute kidney injury events [32,33]. Secondary analyses of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and SPRINT show that patients in the intensive BP treatment arms had a higher risk of incident CKD and a post hoc analysis from SPRINT suggested that in patients with CKD, the risk–benefit ratio with intensive BP may even be reversed [33]. However, analyses of tubular markers of participants from both SPRINT and ACCORD indicated that the reason for the worsened eGFR in those in the intensive treatment arm most likely was caused by hemodynamic
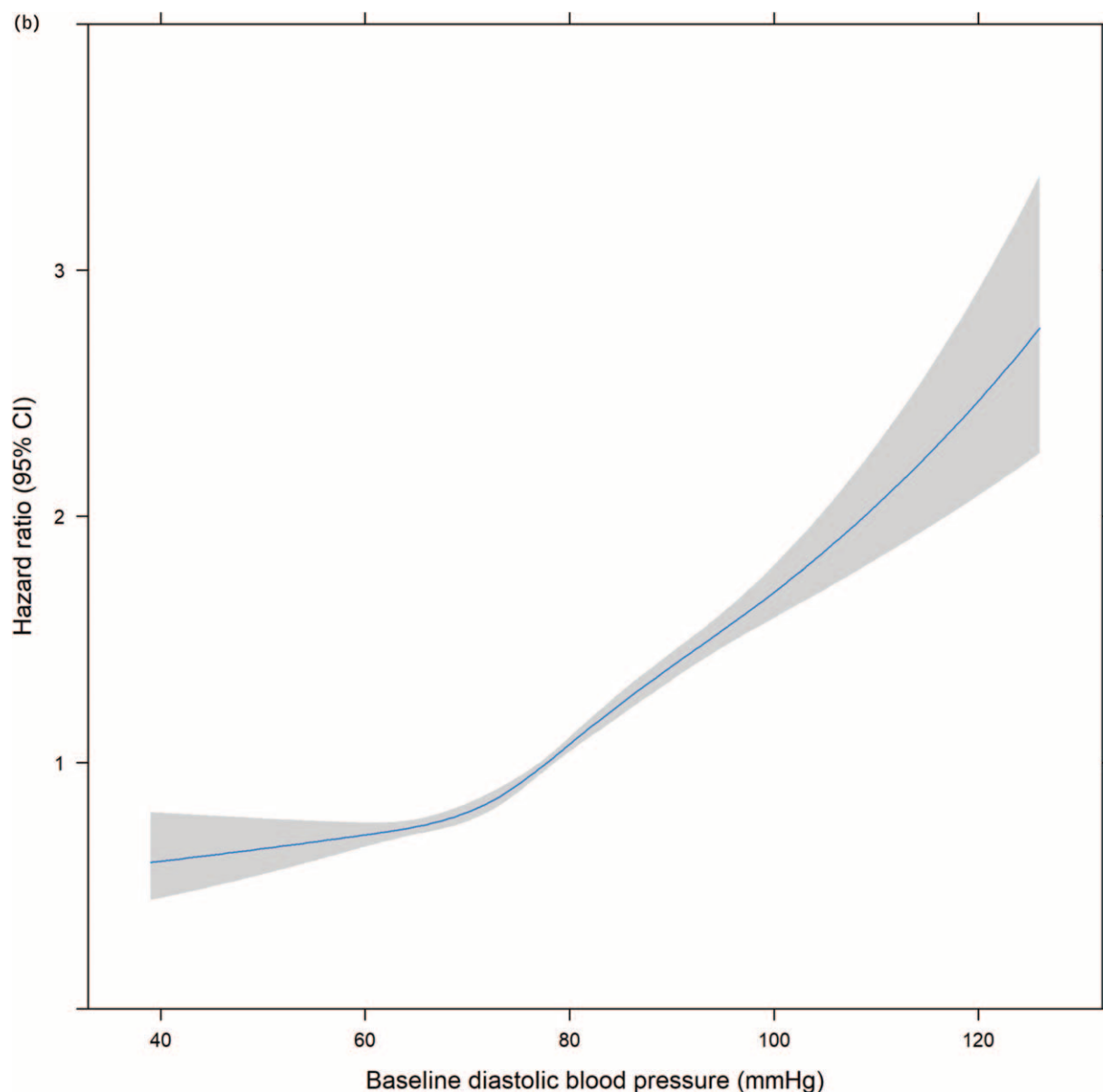
(b)

FIGURE 2 (continued)

changes rather than real kidney damage [24,34]. The above-mentioned safety aspects could call for caution when treating patients with advanced stage CKD, and treatment should be individualized and carefully monitored. In our study, we had no information on acute kidney injury events but as we measured the total eGFR slope during the entire follow-up, acute effects on eGFR would contribute to the overall eGFR decline. Such acute effects on eGFR slope have been observed in the recent sodium-glucose co-transporter 2 trials but still with a total net benefit on eGFR decline [35].

The observed reduced risk association with a lower BP seen in our study should be interpreted in its clinical context. The patients included in our cohort were unselected CKD patients, stage 4–5 but they were all referred, and therefore, carefully monitored. Current clinical guidelines were followed during the study period (at the time of the study follow-up according to KDIGO <130/80 mmHg in most

patients), and thus, the treatment target was not as low as in the latest trials of intensive BP treatment. We do not know why some patients failed to reach below 130 mmHg but from other studies we know that treatment for hypertension is difficult in this group [36]. It is likely that responsiveness to BP treatment is one reason that contributed to the better outcomes in those with lower achieved BPs, thus people with less severe hypertension responded better and this milder disease was also reflected in their risk of CKD progression. We also chose to study the associations adjusting for, rather than stratifying for, type of antihypertensive medication. This was done as the reasons a patient is given a specific combination of antihypertensive medications in CKD stage 4–5 are many, including tolerability, and may be impossible to account for in an observational study. This may also explain the findings of a smaller, and nonconsistent effect in those with albuminuria (A1–A2). Among these patients, there may be
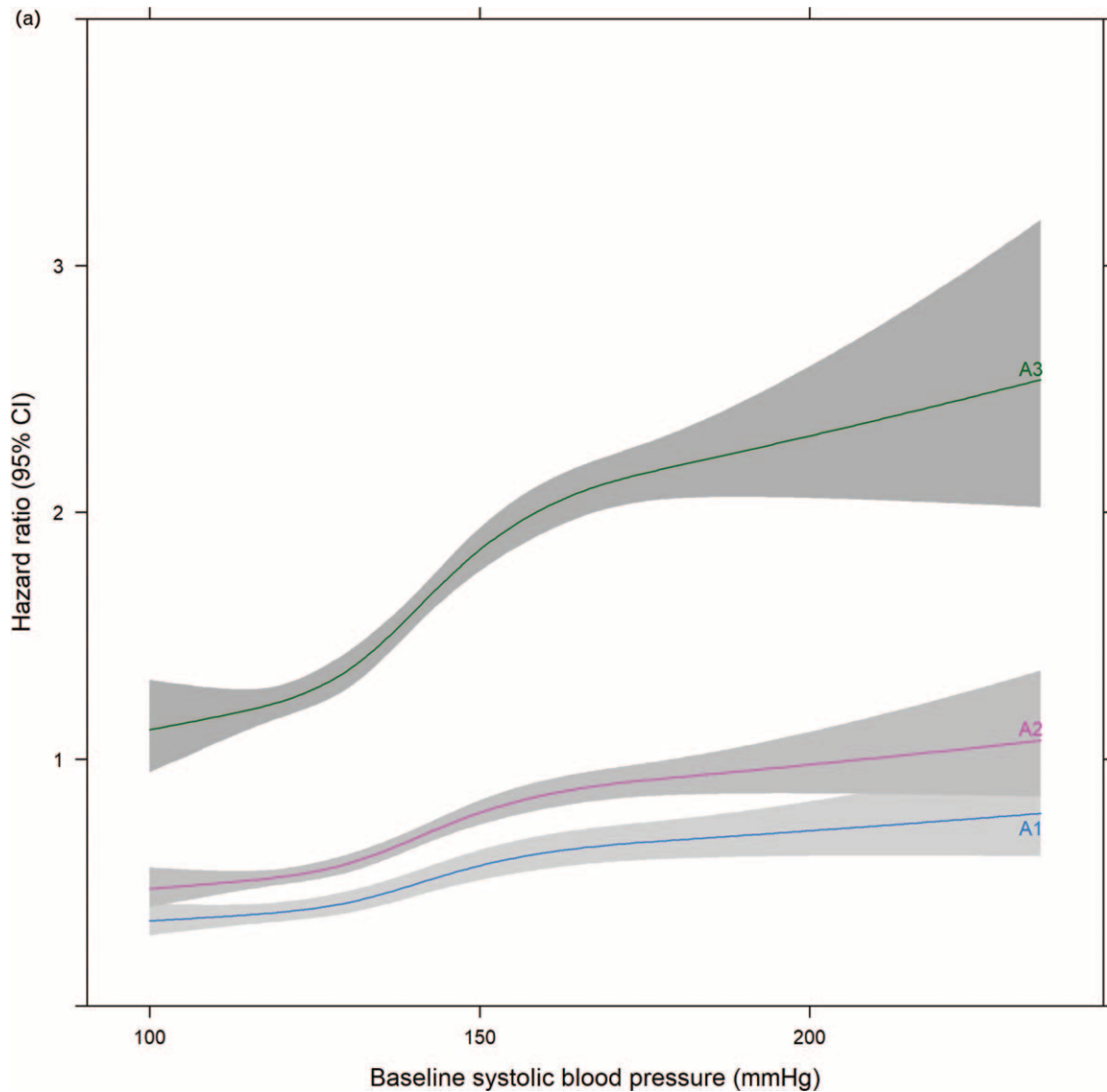
FIGURE 3 Risk of kidney replacement therapy for increasing blood pressure levels (expressed in mmHg) stratified by level of albuminuria categories (expressed in mg/mmol).

both those who (before study inclusion) responded to BP medication or renin–angiotensin inhibition with a reduction in albuminuria, and nonresponders, and these groups may have different underlying risk.

Our study has several strengths. It is the largest cohort study in advanced stage CKD patients so far, with a national representative cohort and virtually no loss to follow-up. As the included patients are older than in most trials and representative of the 'real-world', the results could be generalizable to many referred cohorts. We acknowledge, however, that the patients in our referred cohort may be different from those in primary healthcare, who are often even older and with lower albuminuria. Further strengths are that our study protocol used an incident eGFR threshold for inclusion, minimizing bias from selection and healthy survivors common in prevalent cohorts. We also adjusted for a rich set of confounders and made use of joint models in which we could account for informative censoring because of nonrandom drop out because of death, and study

BP achievement over time in relation to KRT. Furthermore, we also analyzed eGFR slope with consistent results, an outcome recently suggested to improve power in clinical studies of CKD [37]. Our study also has limitations. Firstly, as an observational study it is impossible to infer causality. Previous studies also indicate that cause and effect between BP and CKD is bidirectional. Moreover, the BP was not standardized and although these represents regular clinic office BP, they also reflect how well a patient responds to treatment and patient adherence. We believe, however, that any possible bias resulting from nonstandardized BP measurements in our setting, only would be nondifferential (causing 'noise') and bring the results closer to the null hypothesis. It is likely, though, that the absolute BP measurement levels observed among our patients are different compared with standardized BP recordings. This makes our measurements difficult to compare with those in the trials, although the close to linear association and direction suggested by our results are valid.
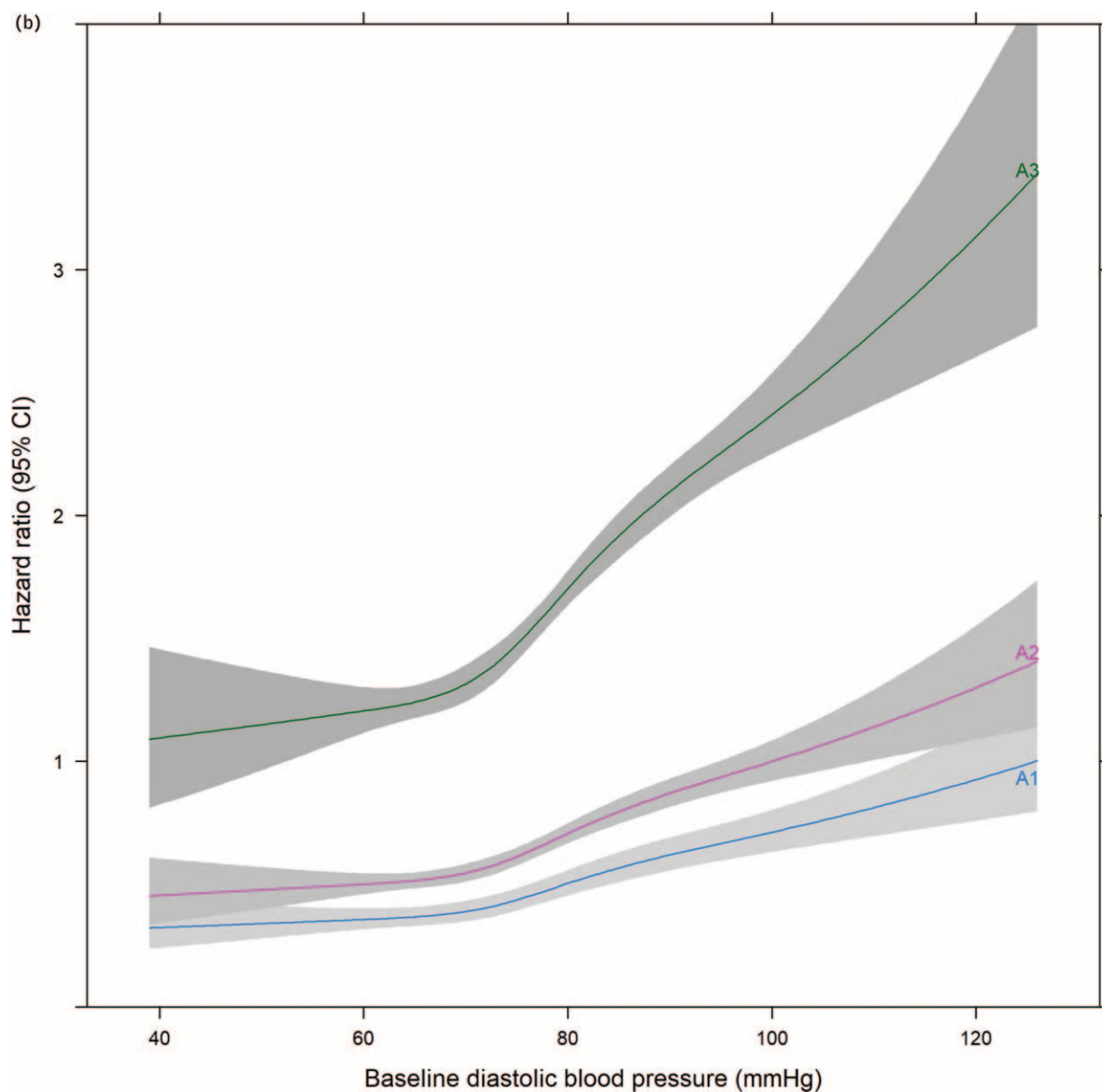
FIGURE 3 (continued)

TABLE 4. Continuous blood pressure over time and its association to kidney replacement therapy initiation

Blood pressure (mmHg)	SBPHR (95% CI) per 10 mmHg higher	DBPHR (95% CI) per 10 mmHg higher
Unadjusted	1.44 (1.41–1.47)	1.63 (1.55–1.70)
Model 1	1.38 (1.34–1.43)	1.24 (1.18–1.29)
Model 2	1.34 (1.31–1.37)	1.81 (1.73–1.91)
Model 3	1.35 (1.32–1.38)	1.65 (1.59–1.69)
Model 4	1.36 (1.32–1.39)	1.73 (1.63–1.82)
Full model	1.38 (1.33–1.42)	1.28 (1.21–1.36)
Full model + CRP	1.39 (1.36–1.41)	1.28 (1.21–1.34)

Model 1: baseline eGFR, sex. age group, primary renal disease.Model 2: baseline eGFR, diabetes, ischemic heart disease, heart failure, cerebrovascular disease, peripheral vascular disease. Model 3: baseline eGFR, diuretics, ACEi/ARB. Model 4: baseline eGFR, albumin, calcium, phosphate, hemoglobin. Full model: all of the above. CRP, C-reactive protein.

There were fewer patients with low levels of albuminuria, which could mean that the study was underpowered to study BP associations in that subgroup. It is also likely that there is some residual confounding as the factors that determine a patient's responsiveness to BP treatment, both in terms of achieved BP and reduction in albuminuria, may not be easily found in observational data. We were, however, able to adjust for most of the most common comorbidities, including BMI and laboratory data. We lacked information on smoking but smoking has, on the other hand, not been associated with KRT incidence in those with advanced stage CKD [38].

In summary, this large observational study of people with CKD 4–5 demonstrated improved kidney outcomes in terms of slower eGFR decline and lower incidence of KRT in patients with lower achieved SBP and DBP. The association was stronger in those with higher levels of albuminuria and in patients with diabetes. Patients with achieved BP levels approaching those in the intensive treatment arm of clinical trials had the most favorable kidney outcomes.

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Conflicts of interest

M.E. reports payment for advisory boards and lectures from Astellas, Astra Zeneca and Vifor Pharma.

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