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Nephrotic range proteinuria is strongly associated with poor blood pressure control in pediatric chronic kidney disease

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Abstract

Despite the importance of blood pressure (BP) control in chronic kidney disease (CKD), few longitudinal studies on its trends exist for pediatric patients with CKD. Here we longitudinally analyzed casual data in 578 children with CKD and annual BP measurements standardized for age, gender and height. At baseline, 124 children were normotensive, 211 had elevated BP and 243 had controlled hypertension. Linear mixed effects models accounting for informative dropout determined factors associated with BP changes over time and relative sub-hazards (RSH) identified factors associated with the achievement of controlled BP in children with baseline elevated BP. Younger age, black children, higher body mass index, and higher proteinuria at baseline were associated with higher standardized BP levels. Overall average BP decreased during follow-up, but nephrotic range proteinuria, and increased proteinuria and body mass index were risk factors for increasing BP over time. Only 46% of hypertensive patients achieved controlled BP during follow-up; least likely were those with nephrotic range proteinuria (RSH 0.19), black children (RSH 0.42) and children with baseline GFR under 40 ml/min/1.73m^2 (RSH 0.58). Thus, of many coexisting factors, nephrotic range proteinuria was most strongly associated with poor BP control and worsening BP over time. Future research should focus on strategies to reduce proteinuria, as this may improve BP control and slow the progression of CKD.

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Disclosures

None

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Introduction

Hypertension (HTN) is common in patients with chronic kidney disease (CKD). Previously, we demonstrated that 54% of children in the Chronic Kidney Disease in Children (CKiD) observational cohort study had evidence of HTN, and 36% of those on antihypertensive medications had uncontrolled blood pressure (BP) at the time of study entry.[1] Risk factors for elevated BP included black race, shorter duration of CKD and the absence of therapy with an antihypertensive medication. The high prevalence of HTN in this vulnerable population is of concern, since lower BP slows the progression of CKD.[2,3]

Despite the importance of BP control in CKD, few longitudinal data on BP trends exist in either pediatric or adult CKD patients. We do not know if HTN remains stable or worsens over time and we do not understand the long-term contributions of specific clinical factors to changes in BP. This gap in our knowledge limits our ability to predict which patients will remain hypertensive and which children's HTN will be more easily controlled, thereby limiting our management strategies. Given its longitudinal design, the CKiD study offers a unique opportunity to characterize longitudinal BP patterns in children with mild-to-moderate CKD.

In this study, we examined longitudinal casual BP data available from the CKiD cohort. Our specific aims were to: (1) determine clinical and demographic factors associated with longitudinal BP changes in children with CKD; and (2) identify factors associated with the achievement of controlled HTN in children with previously elevated BP.

Results

Cohort Characteristics

Between January 2005 and December 2010, 586 children enrolled in CKiD. Of these, 581 had at least one casual systolic BP (SBP)/diastolic BP (DBP) measurement that could be standardized for age, sex and height (SBPz and DBPz). Three children without self-reported history of HTN data could not be classified by their baseline BP status and were excluded, leaving 578 children available for analysis.

Subjects' baseline characteristics are summarized in Table 1. Subjects had a median age of 11 years, 62% were male, 23% were of black race, and 14% were of Hispanic ethnicity. Twenty-two percent of children were diagnosed with glomerular CKD and the median glomerular filtration rate (GFR) was 44 ml/min/1.73m^2. Use of antihypertensive medications was common (63%).

Of the 578, 124 (21%) were normotensive, 211 (37%) had elevated blood pressure, and 243 (42%) had controlled hypertension. As a group, normotensive children were slightly younger, less likely to have glomerular CKD, and had higher baseline GFRs, lower urine protein-to-creatinine ratio (uP/C; mg/dl:mg/dl), and lower body mass index (BMI) percentiles than those with elevated or controlled BP. Children with elevated BP were disproportionately male, and had the highest average uP/C levels and BMI percentiles of the

three groups. Baseline normotensive patients were the least likely to progress to renal replacement therapy (RRT).

Longitudinal Patterns of Standardized SBP and DBP

Overall, a significant decrease over time in SBPz and DBPz was observed in the cohort. In univariate analysis, overall mean SBPz at baseline was 0.385 standard deviation scores (SDs) (95% confidence interval [CI]: 0.296, 0.473) with an average decrease of 0.038 SDs/year (95% CI: −0.060, −0.015; p=0.001). Factors associated with higher SBPz level included younger age, black race, use of a non-ACE/ARB antihypertensive therapy at baseline, and higher baseline BMI z-score (BMIz) and uP/C.

Additionally, baseline GFR and age significantly modified change in SBPz over follow-up. Specifically, children with baseline GFR ≥40 ml/min/1.73m^2 had an average SBPz decline of 0.052 SDs/year (95% CI: −0.079, −0.025) while children with baseline GFR <40 ml/min/1.73m^2 had little change in their SBPz over time (−0.006 SDs/year, 95% CI: −0.044, 0.032; p=0.04 for difference between GFR ≥40 vs. <40 ml/min/1.73m^2). Likewise, children with baseline age <11 years had an average SBPz decline of 0.067 SDs per year (95% CI: −0.096, −0.038) while children with baseline age ≥11 years had no change in their SBPz over time (−0.003 SDs/year, 95% CI: −0.037, 0. −031; p=0.004 for difference between baseline age ≥11 vs. <11). Other baseline factors that presented as possible (though non-significant) modifiers of SBPz change over time were uP/C ≥2 (p=0.12) and male sex (p=0.06).

Overall, mean DBPz at baseline was 0.529 SDs (95% CI: 0.460, 0.599) and decreased on average 0.051 SDs/year (95% CI: −0.073, −0.030; p<0.001). In univariate analysis, younger baseline age, male sex, black race, higher baseline uP/C, and non-ACE/ARB antihypertensive medication use were associated with higher DBPz level; baseline ACE/ARB use was associated with lower DBPz levels. Sex appeared to modify the expected change in DBPz over follow-up: DBPz for males declined on average 0.081 SDs per year (95% CI: −0.108, −0.053) while it remained relatively unchanged for females (0.006 SDs decline per year, 95% CI: −0.040, 0.027; p<0.001 for difference between males and females). Children with a baseline BMI >95th percentile for age and sex showed larger than expected, though non-significant, increases in DBPz over follow-up (p=0.06).

Results from the multivariable linear mixed model accounting for informative dropout of children who underwent RRT are shown in Table 2. The final models for SBPz and DBPz included male sex, black race and baseline age, BMIz, log (GFR), and log (uP/C) as time-fixed covariates; time-varying covariates included current antihypertensive medication use, current immunosuppressant therapy use, change from baseline of log (GFR), log (uP/C), and BMIz, and time (in years) from baseline.

Baseline factors associated with higher SBPz levels were black race, higher BMIz, higher uP/C, and current use of a non-ACE/ARB antihypertensive. Current use of an immunosuppressant was also associated with higher SBPz, albeit non-significantly (p=0.07). Older age at baseline and current use of ACE/ARB were associated with lower SBPz levels. Specifically, SBPz levels were on average 0.322 SDs higher in black children than non-

black children (p<0.001); *between* individuals, a one unit increase in baseline BMIz was associated with a 0.123 SDs increase in SBPz (p<.001). Also *between* individuals, a two-fold higher baseline uP/C was associated with a 0.094 SDs increase in SBPz (p<0.001). *Within-individual* changes in uP/C and BMIz over time were even more strongly associated with higher SBPz. A two-fold increase in uP/C *within* an individual was associated with an average increase in SBPz of 0.168 SDs over the same time period (p<0.001). A one unit increase in BMIz *within* an individual was associated with an average increase in SBPz of 0.187 SDs over the same time period (p<0.001). Neither baseline GFR nor within-individual changes in GFR over follow-up were associated with SBPz level.

Based on the results of the univariate analysis, five dichotomous baseline factors were included as effect modifiers of time from baseline (i.e., slope of BPz over time) in the multivariate models: baseline age >11 years, male sex, baseline BMI> 95th percentile, baseline GFR <40, and baseline uP/C≥2. In the fully adjusted model, sex and baseline uP/C ≥ 2 were significant modifiers of the estimated change in SBPz over follow-up, while baseline GFR <40 ml/min/1.73m^2 approached significance (p=0.06). The effect of uP/C ≥ 2 (0.114 per year) was approximately three times as large as the effect of GFR < 40 ml/min/1.73m^2 (0.040 per year). Male children showed greater declines in SBPz over follow-up compared to female children (sex difference= −0.044 SDs/year, p=0.03).

The results of the multivariable longitudinal model of DBPz are displayed in the right hand column of Table 2. As with SBPz, black race, higher baseline uP/C, and current use of a non-ACE/ARB antihypertensive were associated with higher DBPz levels; older age at baseline and current use of ACE/ARB were associated with lower DBPz levels. On average, black children had DBPz 0.240 SDs higher than non-black children (p<0.001); *between* individuals, a two-fold increase in uP/C was associated with a 0.082 SD higher DBPz (p<0.001). As with SBPz, changes in uP/C over time *within* individuals were even more strongly associated with DBPz levels than uP/C differences between individuals. A two-fold increase in uP/C *within* an individual over time was associated with an average concomitant increase in DBPz of 0.150 SDs. Of the five potential modifying variables, sex was the only one that modified the relationship of change in DBPz over time: DBPz of male participants decreased over time 0.052 SDs/year more than did the DBPz of female participants.

Achievement of Controlled HTN among Children with Elevated BP

Of the 207 children with baseline elevated BP, 96 (46%) achieved controlled HTN during follow-up, 56 (27%) experienced a RRT event or died (n=2) without controlling HTN, and 55 (27%) had persistently elevated BP throughout follow-up. Estimates of proportional relative sub-hazards (RSH) for achieving normal BP are shown in Table 3. After adjusting for the baseline variables listed in the table, black race, presence of nephrotic range proteinuria and GFR <40 mL/min/1.73m^2 were impeding indicators (RSH <1) of achieving normal BP. Nephrotic range proteinuria presented as the strongest risk factor for failure to control HTN (RSH=0.19 vs. normal range uP/C, 95% CI: 0.04, 0.80), a relationship three times stronger than that for GFR<40 and more than twice as strong as that for black race.

Discussion

Our study provides a unique characterization of longitudinal BP trends in children with mild-to-moderate CKD by using prospectively collected BP data over an extended follow-up period. To our knowledge, no other data regarding longitudinal BP trends in pediatric CKD exist. These data show that regardless of disease etiology or GFR, hypertension is common and difficult to control in pediatric CKD patients. Furthermore we found that certain characteristics associate with worsening blood pressure over time and with a lower likelihood of achieving controlled HTN.

Recognition of the factors that contribute to increasing BP over time may facilitate more targeted monitoring and treatment of BP, potentially slowing CKD progression. In this study, younger age, black race, higher BMIz, and greater proteinuria at baseline were associated with higher standardized BP levels. While overall, average SBPz decreased over follow-up, children with a baseline nephrotic range proteinuria, and those experiencing increases in proteinuria and/or BMI showed no decline or increases in SBPz over follow-up. Further, nephrotic range proteinuria and black race were significant independent predictors for persistently elevated BP.

Although the association between proteinuria and hypertension has been described cross-sectionally by Samuels *et al.*,[4] prior to this study there were no data to suggest that increasing proteinuria associates with worsening blood pressure prospectively. In the study by Samuels *et al*., HTN may have pre-dated the proteinuria and accordingly the data do not discern if proteinuria causes HTN, or if HTN causes proteinuria. From the longitudinal nature of our study, we learned that greater amounts of proteinuria at baseline were associated with higher BP levels and worsening BP over follow-up; additionally, worsening proteinuria over follow-up was one of the strongest predictors of worsening BP. This suggests that proteinuria may contribute to the development of HTN.

Other investigators have also demonstrated that proteinuria may pre-date the development of hypertension. Clausen *et al*.[5] compared the dilatory capacity of the brachial artery in two groups of clinically healthy subjects, one group with elevated urinary albumin excretion and the other group without albuminuria. Both flow-associated dilation of the artery and nitrolingual spray induced dilation were significantly impaired in subjects with elevated urinary albumin excretion ($p=0.04$). Higher SBPs were noted in this group as well (mean SBP: 118 versus 129 mmHg; $p=0.001$), suggesting that proteinuria causes arterial dysfunction, which in turn leads to higher BPs. Likewise, in a study by Flack *et al*., [6] longitudinal BP data from a group of hypertensive adults were analyzed to examine the impact of albuminuria and GFR on attainment of specific BP goals. Similar to our findings, they found that patients with either micro- or macro-albuminuria were less likely than patients without albuminuria to attain SBP goals.

Another novel finding in our study was the relatively minor effect that GFR had on BP over time. Subjects with decreasing GFR over follow-up were no more likely to have worsening BP than subjects with steady or improving GFR. Furthermore, when compared to the effects of nephrotic-range proteinuria, having a baseline GFR <40 affected BP change over follow-

up substantially less. Additionally, estimates from our shared parameter model accounting for informed dropout due to the occurrence of RRT differed only minimally from those of a more conventional linear mixed-effects multivariate model that did not account for informative dropout (data not shown). This suggests that patterns of BP showing increases over time can be found across a wide spectrum of GFR, not just among those with poor renal function at high risk for RRT. A prior CKiD study found that greater GFR declines over the one year prior to ambulatory blood pressure (ABP) assessment were associated with abnormal ABP. However, due to the cross-sectional nature of the ABP data (only one measure per subject), the possibility that abnormal ABP existed prior to the decline in GFR cannot be excluded.[4] By using longitudinal data, our study suggests that declining GFR does not adversely affect BP or the control of HTN. Accordingly, the goal of achieving control of HTN should not be dismissed because a patient is nearing RRT.

We found that younger patients were more likely to have higher SBPz and DBPz. This finding has been reported by other investigators and may be related to either difficulty obtaining accurate BP measurements in young children or recognizing elevated BP in them. Kramer *et al*.[7] reported that among children receiving RRT there was a 2.47 increased odds of HTN in patients <3 years old compared to 13–17 year olds. They also demonstrated that younger patients, although more hypertensive, were less likely to receive antihypertensive medication. An analysis of data from chronic pediatric dialysis patients[8] demonstrated similar findings. Younger age associated with a higher likelihood of HTN, and younger patients were 50% less likely to be prescribed an antihypertensive agent.

We also found that black race associated with higher BPz and with failure to achieve controlled HTN, suggesting that black patients have more resistant HTN or do not receive adequate treatment. Menon *et al*.[9] showed that in order to achieve the same level of BP control with the ACE inhibitor fosinopril, black hypertensive children required higher per body weight dosages than their white counterparts. Since most hypertensive pediatric patients with CKD are prescribed ACE inhibitors[1], under-dosing of these medications in black children may contribute to the greater burden of persistently elevated BP observed among this sub-group of our study.

This study also identifies that the modifiable factor of increasing BMIz predicts worsening blood pressure over time. Although the cross-sectional association between BMI and blood pressure in CKD is well known,[10] our results suggest that the longitudinal course of BP is affected by changes in BMIz as opposed to simply being obese. This indicates that maintenance of BMIz is an important modifiable factor in the trajectory of BP. Further support for these findings are studies in the general pediatric population showing that elevations in BMIz are related to worsening of BP.[11]

There are some limitations to the study. BP is a constantly fluctuating variable and the BP measured at the time of the study visit may not accurately reflect a patient's typical BP. We addressed this limitation – and thus minimized misclassification - in the time to achievement of controlled HTN analysis by requiring two consecutive normal BP measurements (approximately one year apart) to define the occurrence of controlled BP. Another limitation of the study includes our use of anti-hypertensive variables. Although we controlled for the

use of ACE/ARB and other anti-hypertensive medications in our analysis, our study methodologies were not designed to evaluate the effectiveness of different classifications of blood pressure medications. This limits the interpretation of the specific parameters in the analyses associated with the anti-hypertensive medications.

There are several strengths to this study as well. Foremost, despite the multi-center nature of the study, we used a standardized BP protocol across multiple sites, a procedure that has previously shown to be a successful approach to assessing BP in this population.[1] We also determined the associations between patient characteristics and BP based on longitudinal data over an extended follow-up period (median follow-up was greater than 4 years). This data allowed for robust estimates of longitudinal changes in BP and permitted the time ordering of factors and outcomes. Lastly, we used a sophisticated model of informative dropout to minimize bias. These features combine a rich and valid dataset with robust analysis to provide information for the first time regarding longitudinal trends of BP in pediatric CKD.

Methods

Study Population and Design

The CKiD Study is a multicenter observational cohort study of children with mild-to-moderate CKD.[12] The study protocol was approved by the Institutional Review Boards of each participating center and informed consent was obtained from all participants.

Children with estimated GFR 30–90 ml/min/1.73m^2 (calculated by the original Schwartz equation[13]) and between the ages of 1 and 16 years were eligible. Exclusion criteria included prior malignancy, transplantation, or dialysis within the previous three months, and a limited number of other conditions.[12]

Measurements

Blood Pressure Measurement—BP measurements are obtained by auscultation at study enrollment, at a follow-up visit six months later, and annually thereafter. The CKiD Clinical Coordinating Centers provide all sites the same aneroid sphygmomanometer (Mabis MedicKit 5; Mabis Healthcare, Waukegan, IL). Annually, CKiD clinical staff are trained and certified in the auscultatory BP measurement technique and each center's aneroid device is calibrated. Details of the standardized BP measurement technique have been published.[1]

At each study visit, three BP measurements at 30-second intervals are obtained by auscultation of the brachial artery using the first Korotkoff sound for SBP and the fifth Korotkoff sound for DBP. The average of the three BP measurements is recorded as the participant's casual BP for that visit. Casual SBP and DBP measurements were standardized (z-scores and percentiles) for age, sex and height using the National High Blood Pressure Education Program Fourth Report on the diagnosis, evaluation and treatment of high BP in children and adolescents.[14]

Other Variables—Demographic and medical history information is collected at the baseline study visit. For this analysis, the baseline visit was defined as the first annual visit

with available SBPz and DBPz. Variables of interest included age, sex, height, weight, self-reported race/ethnicity, underlying CKD diagnosis, CKD duration, self-reported history of HTN, and current use of antihypertensive medications. Data collected at annual follow-up visits documented changes in height, weight, history of HTN, and use of antihypertensive medications. BMI was calculated at each visit as weight (kg)/height (m) ^{2} and standardized (z-scores and percentiles) for age and sex using standard growth charts for US children.[15]

GFR is determined by plasma iohexol disappearance at the baseline visit, the first annual follow-up visit, and every two years thereafter.[16] Formulae to estimate GFR based on sex, height, serum creatinine, cystatin C and/or blood urea nitrogen (BUN)[17] are used to determine estimated GFR at study visits when an iohexol GFR is not obtained.

First-morning urine samples are collected at each visit to calculate uP/C. All serum, urine and plasma iohexol samples are analyzed at the CKiD central laboratory (University of Rochester, Rochester, NY).

Statistical Analysis

Analysis was restricted to children with one or more standardized casual BP measurements and complete self-reported BP history data at baseline. Each subject was classified at baseline according to his or her BP measurements (SBP and DBP), history of HTN and current antihypertensive medication use. Children with SBP and DBP <90th percentile and <120/80 mmHg, no history of HTN, and no current antihypertensive medication use were classified as *normotensive*; children with a baseline SBP or DBP ≥90th percentile or BP >120/80 mmHg were classified as having *elevated BP*. The remaining children (BP <90th percentile and a history of HTN or on antihypertensive medication) were classified as having *controlled hypertension*.

Baseline characteristics were summarized overall and by baseline BP status using median and interquartile ranges (IQR) for continuous variables and percent and frequency for categorical variables. A difference in a characteristic's level or frequency by baseline BP status was determined by the Kruskal-Wallis test (continuous variables) or Fisher's exact test (categorical variables).

Longitudinal Patterns of Standardized SBP and DBP—To determine factors associated with BPz changes over time, univariate linear mixed effects models with random intercept and slope and an unstructured covariance matrix were used. Baseline risk factors were modeled as main-effect covariates (associations with BPz level) and as effect modifiers of the time from baseline (associations with BPz change) in a single model. Dichotomous variables in the analysis included sex, black race, glomerular CKD, antihypertensive medication use, and immunosuppressant therapy use. Antihypertensive use was subdivided into use of ACE inhibitors or type-1 angiotensin II receptor-blockers with or without other antihypertensive therapy (ACE/ARB) and other types of antihypertensives with no concomitant ACE/ARB use (non-ACE/ARB). Immunosuppressant therapy included corticosteroids and calcineurin inhibitors. Continuous variables were age, GFR, uP/C, and BMIz. Both GFR and uP/C were modeled as log-transformed values. Continuous variables

were dichotomized when included as effect modifiers of change in BPz over time: ≥11 years of age, GFR <40 ml/min/1.73m^2, uP/C ≥2, and BMI >95th percentile.

Baseline variables associated with either longitudinal BPz level or change in the univariate model were included in a multivariable regression analysis. Also included were time-dependent exposures for log (GFR), log (uP/C) and BMIz modeled as the change in value from baseline (n.b., change=0 at the baseline observation). Current antihypertensive use and immunosuppressant use were also modeled as time-varying.

Subjects initiating RRT (dialysis or transplant) during follow-up are not followed in the CKiD study following these events. These subjects tended to contribute a smaller number of BP measurements to the analysis while being some of the sickest individuals in the cohort. To account for their exit from the study in the multivariable analysis, longitudinal BP and time to RRT were modeled jointly using a shared-parameter model for the longitudinal and time-to-event (RRT) data.[18] Based on previous analyses from the CKiD study, we used a parametric log normal model for the time until event data.

Achievement of Controlled HTN among Children with Elevated BP—A time-from-baseline-until-event analysis was performed among subjects with elevated baseline BP to identify factors associated with the outcome of controlled HTN. Controlled HTN in this analysis was defined as having both SBP and DBP measurements < 90th percentile and <120/80 mmHg at *two* consecutive study visits, with the time-from-baseline-until-achievement of controlled HTN determined by the first controlled HTN measurement. Use of competing risks regression models due to Fine and Gray for the competing risks of controlled HTN (event of interest) and progression to RRT or death (competing event) yielded proportional relative sub-hazards.[19]

Analyses were performed using SAS v9.2 statistical software (Copyright 2002–2008, SAS Institute Inc., Cary, NC), with the exception of the Fine and Gray competing risks model which was performed using STATA SE v12.1 (Copyright 1985–2011, Statacorp, College Station, TX). Statistical significance was determined at the $\alpha = 0.05$ level.

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Table 1

Baseline characteristics, overall and by baseline blood pressure status

		Baseline BP Status			
Characteristic[a]	**Overall (N=578)**	**Normotensive (N=124)**	**Controlled (N=243)**	**Elevated (N=211)**	**p**[b]
Age, years	11 [7, 14]	9 [5, 13]	12 [9, 15]	10 [6, 15]	<0.001
Male, %	62% (359)	65% (80)	54% (132)	70% (147)	0.003
Black race, %	23% (134)	20% (25)	21% (50)	28% (59)	0.13
Hispanic ethnicity, %	14% (82)	12% (15)	14% (34)	16% (33)	0.67
Glomerular CKD, %	22% (127)	5% (6)	28% (68)	25% (53)	<0.001
GFR, ml/min/1.73m^2	44 [33, 57]	48 [39, 62]	41 [32, 54]	45 [32, 58]	<0.001
Duration of CKD, years					
non-glomerular	7 [4, 11]	6 [3, 9]	9 [5, 12]	6 [3, 10]	<0.001
glomerular	4 [2, 7]	5 [1, 8]	4 [2, 8]	3 [2, 6]	0.64
Urine Protein/Creatinine	0.46 [0.16, 1.20]	0.32 [0.12, 0.77]	0.51 [0.19, 1.17]	0.57 [0.20, 1.50]	0.001
0.2–2.0	57% (321)	52% (62)	60% (141)	58% (118)	
> 2.0	14% (78)	8% (10)	13% (31)	18% (37)	
BMI percentile	65 [35, 89]	52 [29, 83]	66 [37, 90]	69 [39, 92]	0.006
(85–95]	14% (82)	15% (18)	14% (33)	15% (31)	
>95	17% (94)	8% (10)	18% (44)	20% (40)	
Antihypertensive use, %	63% (362)	0% (0)	95% (232)	62% (130)	n/a
ACE/ARB, %	54% (314)	0% (0)	88% (213)	48% (101)	n/a
Calceneuirin inhibitor, %	2% (10)	0% (0)	2% (4)	3% (6)	0.17
Corticosteroid, %	7% (38)	<1% (1)	8% (20)	8% (17)	0.005
Total Follow-up, years	4.1 [2.1, 5.4]	4.9 [3.1, 5.5]	4.1 [1.7, 5.3]	3.9 [2.0, 5.8]	0.023
Number of BP measures over follow-up					0.02[c]
1–2	13% (75)	7% (9)	14% (35)	15% (31)	
3–4	22% (126)	14% (17)	25% (60)	23% (49)	
5–6	31% (180)	40% (50)	27% (66)	30% (64)	
7+	34% (197)	39% (48)	34% (82)	32% (67)	
Observed progression to RRT or death, %	29% (168)	17% (21)	30% (74)	35% (73)	0.002

Missing data: uP/C, n=19; BMI percentile, n=10; Hispanic ethnicity, n=8; years of CKD, n=10.

[a] At baseline, unless otherwise indicated. Median [interquartile range] for continuous variables; percent (frequency) for categorical variables.

[b] For comparison of the three baseline BP status groups. Based on Fisher's exact test for categorical variables and Kruskal-Wallis test for continuous variables, unless otherwise indicated.

[c] Based on Chi-square test for independence.

Table 2

Multivariate mixed model results estimating the effect of baseline and time-dependent characteristics on blood pressure Z-score level and change over follow-up

	Systolic BP (N=550 subjects; 2282 observations)			Diastolic BP (N=550 subjects; 2282 observations)		
Characteristic	**estimate**	**95% CI**	**p**	**estimate**	**95% CI**	**p**
BP z-score level						
Intercept	0.424			0.547		
baseline age, per 1 year increase	−0.062	(−0.081, −0.043)	<0.001	−0.035	(−0.051, −0.020)	<0.001
male sex	−0.009	(−0.180, 0.162)	0.92	0.115	(−0.021, 0.250)	0.10
Black race	0.322	(0.146, 0.498)	<0.001	0.240	(0.101, 0.379)	<0.001
baseline BMI z-score, per 1 unit increase	0.123	(0.058, 0.187)	<0.001	0.011	(−0.040, 0.062)	0.67
baseline log(GFR/40), per 1 unit increase	−0.011	(−0.238, 0.216)	0.92	−0.097	(−0.275, 0.080)	0.28
baseline log(uP/C/0.5), per 1 unit increase	0.136	(0.072, 0.199)	<0.001	0.118	(0.068, 0.168)	<0.001
Current ACE/ARB use	−0.214	(−0.326, −0.103)	<0.001	−0.266	(−0.363, −0.169)	0.001
Current non-ACE/ARB antihypertensive use	0.199	(0.038, 0.361)	0.02	0.187	(0.042, 0.331)	0.011
Current immunosuppressant use[a]	0.201	(−0.013, 0.415)	0.07	0.149	(−0.037, 0.334)	0.12
log(GFR) change from baseline[b]	0.165	(−0.018, 0.348)	0.08	0.141	(−0.030, 0.312)	0.11
log(uP/C) change from baseline[b]	0.243	(0.192, 0.294)	<0.001	0.216	(0.168, 0.263)	<0.001
BMI z-score change from baseline[b]	0.187	(0.117, 0.257)	<0.001	0.009	(−0.057, 0.074)	0.80
BP z-score change over follow-up						
Years from baseline	−0.054	(−0.095, −0.014)	0.009	−0.012	(−0.052, 0.028)	0.56
× baseline age≥ 11 years[c]	−0.001	(−0.041, 0.038)	0.94	−0.020	(−0.059, 0.018)	0.30
× male[c]	−0.044	(−0.085, −0.003)	0.03	−0.052	(−0.092, −0.011)	0.012
× baseline BMI percentile> 95[c]	0.038	(−0.012, 0.087)	0.13	0.023	(−0.025, 0.071)	0.35
× baseline GFR< 40 ml/min/1.73m^2 [c]	0.040	(−0.001, 0.082)	0.06	−0.015	(−0.056, 0.026)	0.48
× baseline uP/C≥ 2[c]	0.114	(0.034, 0.193)	0.005	0.059	(−0.017, 0.135)	0.13

Abbreviations: BP, blood pressure; BMI, body mass index; GFR, glomerular filtration rate; uP/C, urine protein: creatinine ratio.

[a] Includes use of calcineurin inhibitor and/or corticosteroid

[b] Within-subject changes (time-varying) from baseline value. Estimates are expressed per 1 unit change from the baseline value.

[c] Represents the effect modification of the indicated baseline variable, X, on the change in BP z=score over follow-up. Estimates are changes per year and must be added to the "Years from baseline" estimate to calculate the expected change in BP per year for subjects having the indicated characteristic.

Table 3

Relative proportional sub-hazards for control of elevated BP among 207 children with elevated blood pressure

Baseline Characteristics	Relative Sub-hazard for controlling elevated BP, Estimate (95% CI)
Age, per year	0.95 (0.90, 1.00)
Male	1.11 (0.71, 1.75)
Black race	0.42 (0.22, 0.79)
Glomerular CKD	0.63 (0.20, 1.95)
GFR<40 ml/min/1.73m^2	0.58 (0.34, 0.97)
uP/C	
<0.2	1 (ref.)
[0.2, 2.0]	0.85 (0.55, 1.32)
>2.0	0.19 (0.04, 0.80)
BMI percentile > 95	1.17 (0.61, 2.24)
Antihypertensive use	
None	1 (ref.)
ACE/ARB	0.97 (0.61, 1.53)
Other	0.83 (0.38, 1.81)
Immunosuppressant use	2.22 (0.75, 6.53)

Missing Date: baseline BMI percentile, n=8; baseline uP/C, n=5