Blood Pressure and Visit-to-Visit Blood Pressure Variability Among Individuals With Primary Proteinuric Glomerulopathies

Christine B. Sethna, Kevin E.C. Meyers, Laura H. Mariani, Kevin J. Psoter, Crystal A. Gadegbeku, Keisha L. Gibson, Tarak Srivastava, Matthias Kretzler, Tammy M. Brady

Abstract—Hypertension and blood pressure variability (BPV; SD and average real variability) in primary proteinuric glomerulopathies are not well described. Data were from 433 participants in the NEPTUNE (Nephrotic Syndrome Study Network). Hypertensive BP status was defined as previous history of hypertension or BP ≥140/90 mm Hg for adults/≥95th percentile for children at baseline. BPV was measured in participants with ≥3 visits in the first year. Two-hundred ninety-six adults (43 years [interquartile range, 32–57.8 years], 61.5% male) and 147 children (11 years [interquartile range, 5–14 years], 57.8% male) were evaluated. At baseline, 64.8% of adults and 46.9% of children were hypertensive. Histological diagnosis was associated with hypertensive status in adults (P=0.036). In adults, hypertensive status was associated with lower hazard of complete remission (hazard ratio, 0.36; 95% confidence interval, 0.19–0.68) and greater hazard of achieving the composite end point (end-stage renal disease or estimated glomerular filtration rate decline >40%; hazard ratio, 4.1; 95% confidence interval, 1.4–12). Greater systolic and diastolic SD and average real variability were also associated with greater hazard of reaching the composite end point in adults (all P<0.01). In children, greater BPV was an independent predictor of composite end point (determined by systolic SD and average real variability) and complete remission (determined by systolic and diastolic average real variability; all P<0.05). Hypertensive status was common among adults and children enrolled in NEPTUNE. Differences in hypertensive status prevalence, BPV, and treatment were found by age and histological diagnosis. In addition, hypertensive status and greater BPV were associated with poorer clinical outcomes. **(*Hypertension*. 2017;70:315-323. DOI: 10.1161/HYPERTENSIONAHA.117.09475.)** ● **Online Data Supplement**

Key Words: adult ■ blood pressure ■ hypertension ■ nephrotic syndrome ■ prevalence

Nephrotic syndrome is recognized as a significant cardiovascular disease (CVD) risk factor, associated with hypertension and accelerated atherosclerosis. In fact, the American Heart Association classifies nephrotic syndrome in children as a Tier II CVD risk factor.[1] Primary glomerular diseases such as membranous nephropathy, focal segmental glomerulosclerosis (FSGS), and minimal change disease (MCD) often become manifest in individuals when nephrotic syndrome develops, and treatment focuses on decreasing proteinuria and inducing remission. The clinical course of these diseases can include periods of remission and relapse of nephrotic syndrome. Hypertension and CVD are comorbid conditions associated with these entities.

While not completely understood, there are several possible pathophysiologic mechanisms for the development of elevated blood pressure (BP) and hypertension among individuals with primary proteinuric glomerulopathies. Proposed causes include renin–angiotensin–aldosterone system (RAAS) activation, sodium retention, and volume expansion either because of RAAS activation or secondary to a sodium-handling defect.[2] Elevated BP is also caused by medication side effects of corticosteroids and calcineurin inhibitors (CNIs) that are commonly used in the treatment of individuals with proteinuric disease. Despite the increased risk for CVD morbidity and mortality among these individuals, the prevalence of hypertension, antihypertensive treatment patterns, and relationship of hypertension to clinical outcomes in these specific glomerular diseases have not been well described.

Independent of adequate BP control, visit-to-visit BP variability (BPV), defined as the degree of variation between discrete BP readings at separate time points, has been shown to predict cardiovascular morbidity and mortality in the general population and in patients with chronic kidney disease.[3–6] In addition, greater visit-to-visit BPV has been associated

Received March 29, 2017; first decision April 13, 2017; revision accepted May 25, 2017.

From the Cohen Children's Medical Center of New York (C.B.S.); The Children's Hospital of Philadelphia, PA (K.E.C.M.); University of Michigan, Ann Arbor (L.H.M., M.K.); Arbor Research, MI (L.H.M.); Johns Hopkins School of Medicine, Baltimore, MD (K.J.P., T.M.B.); Temple University, Philadelphia, PA (C.A.G.); University of North Carolina, Chapel Hill (K.L.G.); and Children's Mercy Hospital, Kansas City, MO (T.S.).

The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.117.09475/-/DC1.

Reprint requests to Christine B. Sethna, Division of Nephrology, Cohen Children's Medical Center of New York, 269-01 76th Ave, New Hyde Park, NY 11040. E-mail csethna@northwell.edu

with worse proteinuria and renal function.[7,8] The relationship between visit-to-visit BPV and renal outcomes in proteinuric glomerular disease is unknown.

To characterize CVD risk factors and antihypertensive treatment patterns among a contemporary cohort of adults and children with primary glomerular diseases that can present with nephrotic syndrome, we studied individuals enrolled in the NEPTUNE (Nephrotic Syndrome Study Network). The goals of this study were (1) to define the prevalence and management of hypertensive BP status in patients with primary proteinuric glomerulopathies across age groups and histological diagnoses and (2) to determine whether hypertensive BP status and BPV were associated with adverse renal outcomes.

Materials and Methods

NEPTUNE (Nephrotic Syndrome Study Network)

The design of the NEPTUNE study has been previously described in detail.[9] In brief, NEPTUNE is a multicenter observational cohort study of children and adults with glomerular diseases that cause nephrotic syndrome. Participants of any age with ≥500 mg/d of proteinuria on a 24-hour urine sample or with a urine protein/creatinine ratio ≥0.5 g/g on a spot urine specimen were enrolled at the time of a clinically indicated kidney biopsy at 21 sites in North America. Patients with kidney manifestations of systemic disease, prior solid organ transplant, or life expectancy <6 months were excluded. There were 470 participants enrolled between July 1, 2010 and May 1, 2016. Participants were assigned to the following disease cohorts based on histological confirmation by core pathologists: MCD, FSGS, membranous nephropathy, or other glomerulopathy, which included IgA nephropathy.[10] Study visits consisted of data and biosample collection at baseline, every 4 months during the first year, and then every 6 months for a total of 5 years. The study protocol was approved by the Institutional Review Board at each participating site, and informed consent/assent was obtained from each participant.

BP Measurements

Casual BP measurements were obtained in triplicate at each study visit using a calibrated oscillometric device. BP was measured in the right arm with the participant in a seated position after 5 minutes of rest. The average of the last 2 readings was used. Participants were classified as hypertensive BP status (HTN) if either of the following criteria were met: (1) a clinical diagnosis of hypertension was recorded in their medical record or (2) their average baseline BP was in the hypertensive range for age. Among the subset of individuals categorized as HTN who had a previous clinical diagnosis of hypertension, those with an average baseline BP either ≥95th percentile for age, sex, and height[11] for children or ≥140 mm Hg systolic or ≥90 mm Hg diastolic[12] for adults were consider to be hypertensive uncontrolled. Those with a clinical diagnosis of hypertension with BPs below these thresholds were considered hypertensive controlled. To allow for comparison across adults and children, a systolic and diastolic BP index was calculated: average measured BP was divided by 140 or 90 as applicable in adults or by the sex-, age-, and height-specific 95th percentile BP in children. Although BP index has not been used previously in adult studies, BP index is a common approach to standardize BP among individuals of different age, sex, and size in the pediatric literature.[13–15] BP index ≥1 indicates BP in the hypertensive range, and every 0.1 U increase represents a 10% increase in BP above hypertensive range.

Visit-to-visit BPV was calculated using BP measurements obtained during the first year of the study in participants with ≥3 separate visits with a documented BP measurement. We chose to examine 2 metrics of systolic and diastolic BPV: (1) SD which measures overall variability and (2) average real variability (ARV) which measures variability between consecutive visits and was calculated as the mean difference in BP between visits.[16]

CVD Risk Factors, Covariate, and Outcome Measurements

Clinical and demographic characteristics, including immunosuppressive and antihypertensive medication use, urine protein/creatinine ratio, serum creatinine, and self-reported smoking status, were collected from the participants. Children <18 years old were categorized into the pediatric group; all others were categorized as adults. Weight status was classified into normal, overweight, and obese categories based on reference data for body mass index in adults or body mass index percentile in children.[17] The presence of edema was documented by a clinician at each study visit. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease–Epidemiology (CKD-Epi) formula for participants ≥18 years and the modified Schwartz formula for participants <18 years.[18,19]

Renal outcomes that were pre-determined by NEPTUNE included complete remission ever, composite end point, and eGFR slope. Complete remission ever was defined as urine protein/creatinine ratio ≤0.3 at any study visit. The composite end point was defined as development of end-stage renal disease (ESRD) or eGFR decline by ≥40% by the time of the last follow-up. The eGFR slope of the least-squares regression line was calculated for each person using the first and last serum creatinine measured at least 8 months apart, reported as mL min^{-1} y^{-1}.

Statistical Analysis

NEPTUNE participants with BP recorded at the baseline visit were included in this analysis. Adult and pediatric patients were considered separately and then compared. Descriptive statistics were used to describe the demographic and clinical characteristics among the full cohort, stratified by age and histological subgroups based on χ^2/Fisher exact tests or the Wilcoxon rank-sum/Kruskal–Wallis test for categorical and continuous variables, respectively. Multivariable logistic regression was used to evaluate the association of disease cohort and odds of having HTN for both adults and children adjusting for age, sex, race, weight status (overweight/obese versus not), edema (yes/no), steroid use (yes/no), CNI use (yes/no), eGFR, and smoking status (yes/no; adults only).

To evaluate the association of renal outcomes (eGFR slope, composite end point, and complete remission ever) with HTN and BPV, regression models were used adjusting for age, sex, race, disease cohort, and follow-up time (model 1). A second model (model 2) included those variables from model 1 in addition to smoking status, CNI/steroid use, RAAS use, weight status, edema, cholesterol, and baseline systolic BP index and baseline eGFR. Multiple linear regression based on generalized estimating equations to account for the correlation of individual-level clinical visits was used to determine the relationship between HTN and BPV with eGFR slope. Finally, pooled logistic regression models with a complementary log–log link were used to evaluate the association of HTN and BPV with time to complete remission ever and the composite end point. Results of these analyses are presented as hazard ratios with corresponding 95% confidence interval (CI). The time-to-event analysis started with the baseline visit. The entire follow-up period was used to analyze outcomes where HTN was the primary exposure of interest, whereas a minimum of 2 visits after year 1 in participants was included in the outcome analysis for BPV only. All analyses were conducted using SPSS, version 24 (IBM Inc) and R version 3.3.2.[20] A 2-sided *P* value of ≤0.05 was considered statistically significant.

Results

Patient Population

There were 443 participants with baseline BP, including 296 adults and 147 children enrolled in NEPTUNE as of May 1, 2016. Cross-sectional baseline demographic and clinical characteristics of the study cohort stratified by age group are summarized in Table 1. There was a significantly greater proportion of black race and lower prevalence of obese/

Table 1. Demographics and BP of the NEPTUNE (Nephrotic Syndrome Study Network) Cohort at Baseline

Characteristics, n (%) or Median (IQR)	Adult, n=296	Pediatric, n=147	*P* Value
Age, y	43 (32–57.8)	11 (5–14)	<0.0001
Male	182 (61.5%)	85 (57.8%)	0.46
Black	61 (21.3%)	61 (43.9%)	<0.0001
Hispanic	62 (20.9%)	33 (22.4%)	0.82
BMI, kg/m^2	28.4 (24.8–33.2)	20.8 (17.7–24.9)	<0.0001
Obese/overweight	217 (73.3%)	84 (57.1%)	0.003
Edema	133 (44.9%)	55 (37.4%)	0.13
Smoker	31 (10.5%)	1 (0.7%)	0.001
Disease duration, mo	12 (0–24)	12 (0–12)	0.73
Follow-up time, mo	24.5 (12–37)	24 (12–36)	0.49
Cohort: MCD	40 (13.2%)	69 (46.9%)	<0.0001
MN	71 (24%)	2 (1.4%)	
FSGS	98 (33.1%)	49 (33.3%)	
IgA	48 (16.2%)	8 (5.4%)	
Other*	39 (13.2%)	19 (12.9%)	
Hypertensive BP status†	192 (64.8%)	69 (46.9%)	<0.0001
Hypertensive uncontrolled†	69 (23.3%)	61 (41.5%)	<0.0001
SBP, mm Hg	124 (113–137)	109 (101–118)	<0.0001
DBP, mm Hg	77.5 (69–85)	68 (61–77)	<0.0001
SBP index‡	0.89 (0.81–0.98)	0.92 (0.87–1.0)	<0.0001
DBP index‡	0.86 (0.77–0.94)	0.90 (0.81–1.0)	<0.0001
SBP SD, mm Hg	10 (6.6–14.7)	7.3 (4.5–10.2)	<0.0001
DBP SD, mm Hg	6.5 (4.3–9.7)	7.1 (4.2–10.7)	0.34
SBP ARV, mm Hg	11.7 (7–18)	8.0 (5.5–11.8)	<0.0001
DBP ARV, mm Hg	8 (5–11.3)	8 (5.5–12.2)	0.38
No antihypertensive medication	36 (12.1%)	64 (43.5%)	<0.001
1 antihypertensive medication	93 (31.4%)	64 (43.5%)	
2 antihypertensive medications	101 (34.1%)	15 (10.2%)	
≥3 antihypertensive medications	66 (22.2%)	4 (2.7%)	
Steroid use	74 (25%)	102 (69.4%)	<0.0001
CNI use	9 (3%)	39 (26.5%)	<0.0001
eGFR, mL min^{-1} 1.73 m^{-}2	69.5 (42.6–96.3)	100.4 (82–118.3)	<0.0001
UPC, g/g	2.3 (0.86–4.1)	1.2 (0.22–4.1)	0.005

ARV indicates average real variability; BMI, body mass index; BP, blood pressure at baseline; CNI, calcineurin inhibitor; DBP, diastolic BP; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; IQR, interquartile range; MCD, minimal change disease; MN, membranous nephropathy; SBP, systolic BP; and UPC, urine protein:creatinine ratio.

*Other glomerulopathy cohort included diagnoses of membranoproliferative glomerulonephritis, thin basement membrane, complement 1Q, complement 3 glomerulopathy, crescentic glomerulonephritis, mesangial, glomerulosclerosis, membranous with nodular diabetes mellitus, nodular glomerulosclerosis, thrombotic microangiopathy, and indeterminate.

†Hypertensive BP status defined as previous clinical diagnosis of hypertension or an elevated BP for age at the baseline visit; hypertensive uncontrolled defined as previous diagnosis of hypertension and elevated BP at the baseline visit.

‡BP index: BP was divided by 140 or 90 in adults or by the 95th percentile BP in children; an index ≥1 is indicative of a BP in the hypertensive range.

overweight in the pediatric group. Diagnosis differed by age group; there was a higher proportion of membranous nephropathy in adults and a higher proportion of MCD in children. Children had a significantly higher eGFR and lower urine protein/creatinine ratio than adults. The pediatric group also had a significantly greater proportion of participants

treated with steroids and CNI than the adult group. For the entire cohort, the median follow-up time was 24 months (interquartile range, 12–37 months) with a median of 4 visits (interquartile range, 2–7 visits; 13.8% with 3 visits, 11% with 4 visits, 10% with 5 visits, 9.6% with 6 visits, and 27.9% with ≥7 visits). There was no difference in mean follow-up time between age groups.

Hypertensive BP Status

At baseline, 261 participants (58.9%) had a previous clinical diagnosis of hypertension (n=207) or had baseline BP in the hypertensive range (n=54) and were classified as HTN. Children were disproportionately more likely to be categorized as HTN based on baseline BP than by previous clinical diagnosis of hypertension, 59.4% (n=41/69) versus 40.6% (n=28/69), *P*=0.001, respectively. Although HTN was more prevalent among adults than children, children were more likely to be categorized as hypertensive uncontrolled (Table 1).

Comparing by disease cohort, there was a significant difference in prevalence of HTN across the disease groups in adults but not in children (Table 2). Disease cohort was significantly associated with HTN after adjustment for age, sex, race, weight status, edema, steroids, CNI, eGFR, and smoking (adults) in adults (*P*=0.036) but not in children (*P*=0.9). For adults, the odds of HTN were 5.5× greater in IgA and 3.8× greater in FSGS compared with MCD (Table 3).

Table 2. BP, BP Variability, and Hypertension Risk Factors by Disease Cohort

Characteristics, n (%) or Median (IQR)	MCD	MN	FSGS	IgA	*P* Value
Adult	n=40	n=71	n=98	n=48	
Hypertensive BP status*	16 (40%)	46 (64.8%)	73 (74.5%)	34 (70.8%)	0.004
Hypertensive uncontrolled*	4 (7.1%)	9 (16.1%)	26 (46.4%)	10 (17.9%)	0.1
SBP, mm Hg	121 (107.3–129)	121 (113–135)	125 (115–137.3)	126 (115.3–139.5)	0.33
DBP, mm Hg	74.5 (65–81.8)	77 (69–84)	80 (69.8–88)	78 (73–85.8)	0.11
SBP SD, mm Hg	7.1 (4.9–12.4)	11.1 (7.1–16.4)	11 (6.9–15.8)	8.8 (6.9–12.2)	0.19
DBP SD, mm Hg	7 (3.4–8.9)	6.5 (4.2–9.4)	7.1 (5.2–9.7)	6.3 (4.3–10.8)	0.47
SBP ARV, mm Hg	9 (5.3–17)	13.5 (7.2–18)	12.8 (8.3–20.8)	11.2 (7.3–17.4)	0.52
DBP ARV, mm Hg	6.3 (2.7–10)	7.7 (4.3–10.8)	8.6 (5.9–12.5)	7.2 (5.3–13.8)	0.11
Steroid use	19 (47.5%)	10 (14.1%)	16 (16.4%)	17 (35.4%)	0.001
CNI use	3 (7.5%)	4 (5.6%)	0 (0%)	0 (0%)	0.13
eGFR, mL min^{-1} 1.73 $m^{-}2$)	85.9 (45.9–107)	81.4 (65.2–98.2)	52 (33.9–82.4)	62.2 (36.9–95.3)	<0.0001
UPC, g/g	0.78 (0.1–3.3)	4.3 (2.5–7.2)	2.2 (0.97–3.5)	1.4 (0.6–3.0)	<0.0001
Pediatric	n=69	n=2	n=49	n=8	
Hypertensive BP status*	31 (44.9%)	1 (50%)	23 (46.9%)	5 (62.5%)	0.91
Hypertensive uncontrolled*	9 (45%)	1 (50%)	6 (12.2%)	2 (10%)	0.5
SBP (mm Hg)†	107 (100–116)	121.5	112 (102–118.5)	124.5 (105–133)	0.13
DBP (mm Hg)†	66 (60–74.5)	77.5	71 (61–77)	70 (63.8–80.3)	0.56
SBP index	0.92 (0.87–1.0)	0.97	0.90 (0.85–0.99)	1.0 (0.93–1.1)	0.6
DBP index	0.91 (0.80–1.0)	0.96	0.90 (0.79–1.0)	0.88 (0.84–1.0)	0.84
SBP SD (mm Hg)	6.4 (3.6–9.4)	9.6	7.1 (5–10.4)	8.3 (5.6–12.7)	0.41
DBP SD mm Hg)	6.5 (4.2–9.9)	8.9	7.1 (4.1–12.5)	7 (3–9.4)	0.78
SBP ARV (mm Hg)	7 (4–11)	9.5	9 (6–11.9)	9.1 (6.6–11.8)	0.28
DBP ARV (mm Hg)	98 (5–11.2)	9	8.4 (6–14.4)	7.8 (3.9–9.1)	0.49
Steroid use	49 (71%)	1 (50%)	34 (69.4%)	3 (37.5%)	0.02
CNI use	18 (26.1%)	1 (50%)	16 (32.7%)	2 (25%)	0.4
eGFR, mL min^{-1} 1.73 $m^{-}2$	110.4 (92–133)	118.3	89.5 (77–110.7)	65.6 (55.8–98.9)	<0.0001
UPC, g/g	0.39 (0.1–4.2)	2.3	2.4 (0.68–5.9)	1.2 (0.17–5.0)	0.34

ARV indicates average real variability; BP, blood pressure at baseline; CNI, calcineurin inhibitor; DBP, diastolic BP; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; IQR, interquartile range; MCD, minimal change disease; MN, membranous nephropathy; SBP, systolic BP; and UPC, urine protein:creatinine ratio.

*Hypertensive BP status defined as previous diagnosis of hypertension or elevated BP for age at the baseline visit; hypertensive uncontrolled defined as previous diagnosis of hypertension and elevated BP at the baseline visit.

†SBP/DBP index: BP was divided by the 95th percentile BP in children.

Table 3. Adjusted ORs of Baseline Hypertensive Blood Pressure Status by Disease Cohort

Disease Cohort	Adult		Pediatric	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
MCD	Ref		Ref	
MN	1.8 (0.62–5)	0.29	…	…
FSGS	3.8 (1.4–10.9)	0.01	0.86 (0.35–2.1)	0.73
IgA	5.5 (1.7–18)	0.005	1.8 (0.3–10)	0.53
Other	2.3 (0.68–7.5)	0.18	0.7 (0.2–2.5)	0.59

Model adjusted for age, sex, race, weight status, edema, steroids, calcineurin inhibitors, estimated glomerular filtration rate, and smoking (adults). MN excluded from the pediatric cohort. CI indicates confidence interval; FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease; MN, membranous nephropathy; and OR, odds ratio.

Treatment Patterns

Antihypertensive treatment by age group is shown in Table S1 in the online-only Data Supplement. In contrast to adults, children more frequently were not treated with antihypertensive medications (43.5% versus 12.1%) at baseline ($P<0.001$). Overall, RAAS blockade (65.1%) was most common followed by diuretics (35.7%) and calcium channel blockers (22.2%). A greater proportion of adults were taking each class of antihypertensive medication when compared with children (all $P<0.05$).

Blood Pressure Variability

There were 378 (85.3%) participants with ≥3 BP readings over separate visits during the first year of participation in NEPTUNE from which visit-to-visit BPV was calculated. Adults had significantly greater systolic SD and ARV compared with children (Table 1). There was no significant difference in these parameters by disease cohort (Table 2).

Variables were assessed in regression models to examine determinants of BPV in adults and children. In adults, black race (β=2.8; 95% CI, 0.65–4.9; $P=0.01$) and baseline systolic BP (β=0.08; 95% CI, 0.03–0.13; $P=0.004$) were significantly associated with systolic SD in the multivariable model adjusting for age, sex, race, weight status, and edema. Black race was also associated with systolic ARV in adults (β=3.6; 95% CI, 0.67–6.6; $P=0.02$). In children, baseline systolic BP was directly related to systolic SD (β=0.23; 95% CI, 0.15–0.3; $P<0.0001$) and systolic ARV (β=0.2; 95% CI, 0.12–0.3; $P<0.0001$). Disease cohort, antihypertensive medication class, immunosuppression, weight status, and edema were not associated with BPV in adults or children.

Hypertensive BP Status and BPV with Outcomes

Overall, after a median of 2 years of follow-up, there were 212 complete remission ever events (129/296 in adults and 83/147 in children) and 91 composite end point events (69/296 in adults and 22/147 in children).

In adults, HTN was significantly associated with a lower hazard of complete remission ever ($P<0.001$) in models 1 and 2 (Table 4; Figure S1). HTN was also associated with a 4.1× greater hazard of reaching the composite end point only in the more parsimonious model 1 (Figure). There was no

Table 4. Association of Hypertensive Blood Pressure Status at Baseline and Blood Pressure Variability Over the First Year with Clinical Outcomes in Adults Enrolled in NEPTUNE (Nephrotic Syndrome Study Network)

Outcome	β	95% CI	*P* Value
eGFR slope, mL min^{-1} y^{-1}			
HTN			
Model 1	−0.92	(−3.28 to 1.45)	0.45
Model 2	2.07	(−2.51 to 6.65)	0.38
SBP SD			
Model 1	0.06	(−0.1 to 0.22)	0.44
Model 2	0.08	(−0.08 to 0.23)	0.35
DBP SD			
Model 1	0.00	(−0.22 to 0.21)	0.98
Model 2	0.01	(−0.2 to 0.23)	0.91
SBP ARV			
Model 1	0.04	(−0.09 to 0.18)	0.52
Model 2	0.05	(−0.08 to 0.19)	0.43
DBP ARV			
Model 1	−0.06	(−0.24 to 0.13)	0.55
Model 2	−0.05	(−0.23 to 0.13)	0.61
Complete remission ever (UPC <0.3)	HR	95% CI	*P* value
HTN			
Model 1	0.36	(0.19 to 0.68)	<0.001
Model 2	0.48	(0.29 to 0.80)	<0.001
SBP SD			
Model 1	1.01	(0.98 to 1.04)	0.41
Model 2	1.03	(0.99 to 1.07)	0.10
DBP SD			
Model 1	1.01	(0.98 to 1.03)	0.55
Model 2	1.02	(0.99 to 1.05)	0.13
SBP ARV			
Model 1	1.00	(0.96 to 1.04)	0.92
Model 2	1.01	(0.96 to 1.07)	1.01
DBP ARV			
Model 1	0.98	(0.94 to 1.01)	0.19
Model 2	0.99	(0.94 to 1.03)	0.55
Composite end point (ESRD or eGFR decline <40%)			
HTN			
Model 1	4.11	(1.41 to 12.02)	0.01
Model 2	1.40	(0.71 to 2.76)	0.33
SBP SD*			
Model 1	1.05	(1.02 to 1.09)	<0.001
DBP SD*			
Model 1	1.04	(1.01 to 1.07)	0.01

(*Continued*)

Table 4. Continued

Outcome	β	95% CI	*P* Value
SBP ARV*			
Model 1	1.10	(1.02 to 1.18)	0.01
DBP ARV*			
Model 1	1.08	(1.04 to 1.12)	<0.001

Model 1 includes age at baseline, sex, race, disease cohort, and follow-up time. Model 2 includes model 1+smoking status, calcineurin inhibitor/steroid use, renin–angiotensin–aldosterone system use, weight status, edema, cholesterol, SBP index, and eGFR. ARV indicates average real variability; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HR, hazard ratio; HTN, hypertensive blood pressure status; SBP, systolic blood pressure; and UPC, urine protein creatinine.

*Model 2 failed to converge (ie, there was no maximum to the maximum likelihood function because there were variables in which there were no observations for exposure levels among the cases and controls.)

association of baseline HTN with eGFR slope. Greater systolic and diastolic BPVs were associated with a greater hazard of reaching the composite end point (Table 4). For each 1 U increase in systolic SD, there was a 5% increase in the occurrence of the composite end point (model 1). For systolic ARV, there was a 10% increase in composite end point for each 1 U increase (model 1).

In children, HTN trended toward lower hazard of complete remission ever in model 1, but failed to reach statistical significance (Table 5). HTN was not associated with eGFR slope or composite end point in children. Greater systolic SD and ARV were associated with a greater hazard of reaching the composite end point in model 1. Systolic and diastolic ARV were also associated with a lower hazard of complete remission ever in children (Table 5).

Discussion

In this large cohort of adults and children with primary proteinuric glomerulopathies, nearly 60% of participants had HTN at enrollment. Although HTN was more prevalent among adults, children were more often categorized as having uncontrolled BP. Treatment with antihypertensive medication was common, although less so in children compared with adults. Of the various antihypertensive classes, RAAS blockade was the most commonly prescribed, with two thirds of the population overall treated with these agents. In adults, HTN was associated with lower odds of complete remission ever and greater hazard of reaching the composite end point of ESRD or eGFR decline by ≥40%. Adults had significantly greater BPV as determined by systolic SD and ARV when compared with children, and these measures, along with diastolic SD and ARV, were associated with a greater hazard of reaching the composite end point in adults. In children, BPV was also associated with greater hazard of reaching the composite end point (as determined by systolic SD and ARV) and with a lower hazard of reaching complete remission ever (as determined by systolic and diastolic ARV).

Although nephrotic syndrome is known to be associated with increased cardiovascular risk, there is little information on the prevalence of hypertension and antihypertensive treatment patterns in adults and children with primary proteinuric glomerulopathies associated with nephrotic syndrome. We found that HTN was more common in adults than in children. In agreement with our findings, a smaller study of individuals with FSGS also described a substantial hypertension prevalence: 76% in adults and 44% in children.[21] In other smaller studies of children, hypertension before corticosteroid therapy was reported to be uncommon in MCD but was found in 20% to 50% of children with FSGS at the time of diagnosis.[22,23] Prevalence rates of hypertension as determined by 24-hour ambulatory BP monitoring vary in the literature, ranging from 14% to 89%.[24–26] Our finding of a higher prevalence of HTN in adults compared with children could possibly be explained by the higher baseline prevalence of essential hypertension found in the general adult population and lower eGFR in adults compared with children in this cohort. Surprisingly, we found that disease cohort was not associated with HTN in children, whereas FSGS and IgA were determinants of HTN in adults. This finding in children could possibly be explained by the almost universal use of steroid/CNI treatment in children regardless of disease cohort. In addition, we observed that BP was treated more aggressively in adults than in children. As expected, RAAS blockade was the most used class of antihypertensive medications, likely owing its antiproteinuric effects.

There is also a paucity of data on the relationship of hypertension with clinical outcomes in primary proteinuric glomerulopathies. Our findings support our hypothesis that HTN is associated with worse clinical outcomes in adults with proteinuric glomerulopathies. We demonstrate that adult hypertensive BP status is associated both with the development of ESRD and with a decline in eGFR of ≥40%. Data from the CRIC (Chronic Renal Insufficiency Cohort) support that hypertension is associated with progression of renal disease and ESRD; however, the cohort includes various causes of kidney disease.[27] The scant reports on primary glomerulopathies are conflicting. Moranne et al[28] reported that baseline hypertension was not predictive of ESRD in those of primary glomerulonephritis, whereas Chou et al[29] showed that baseline hypertension in IgA nephropathy (but not in membranous nephropathy or FSGS) was associated with progression to ESRD. Interestingly, Zagury et al[23] showed that hypertension was associated with increased risk for developing ESRD in children with steroid-resistant nephrotic syndrome. Although this is in contrast to our findings, where we did not find HTN to be associated with poorer outcomes in children, it should be noted that the article by Zagury et al[23] was not an adjusted analyses and was limited to children with steroid resistance.

BPV is emerging as an important CVD risk factor, with evidence suggesting that it is associated with clinical outcomes.[3–6] Recent literature suggests that visit-to-visit BPV also has promise in predicting renal outcomes. In the ALLHAT study (Anti-Lipid Lowering Heart Attack Trial) of 21 245 hypertensive adults, greater visit-to-visit BPV was associated with incident ESRD and ≥50% decline in eGFR independent of mean BP.[5] Yano et al[30] described the association of long-term visit-to-visit BPV with the development of chronic kidney disease in a large Japanese population. A smaller study

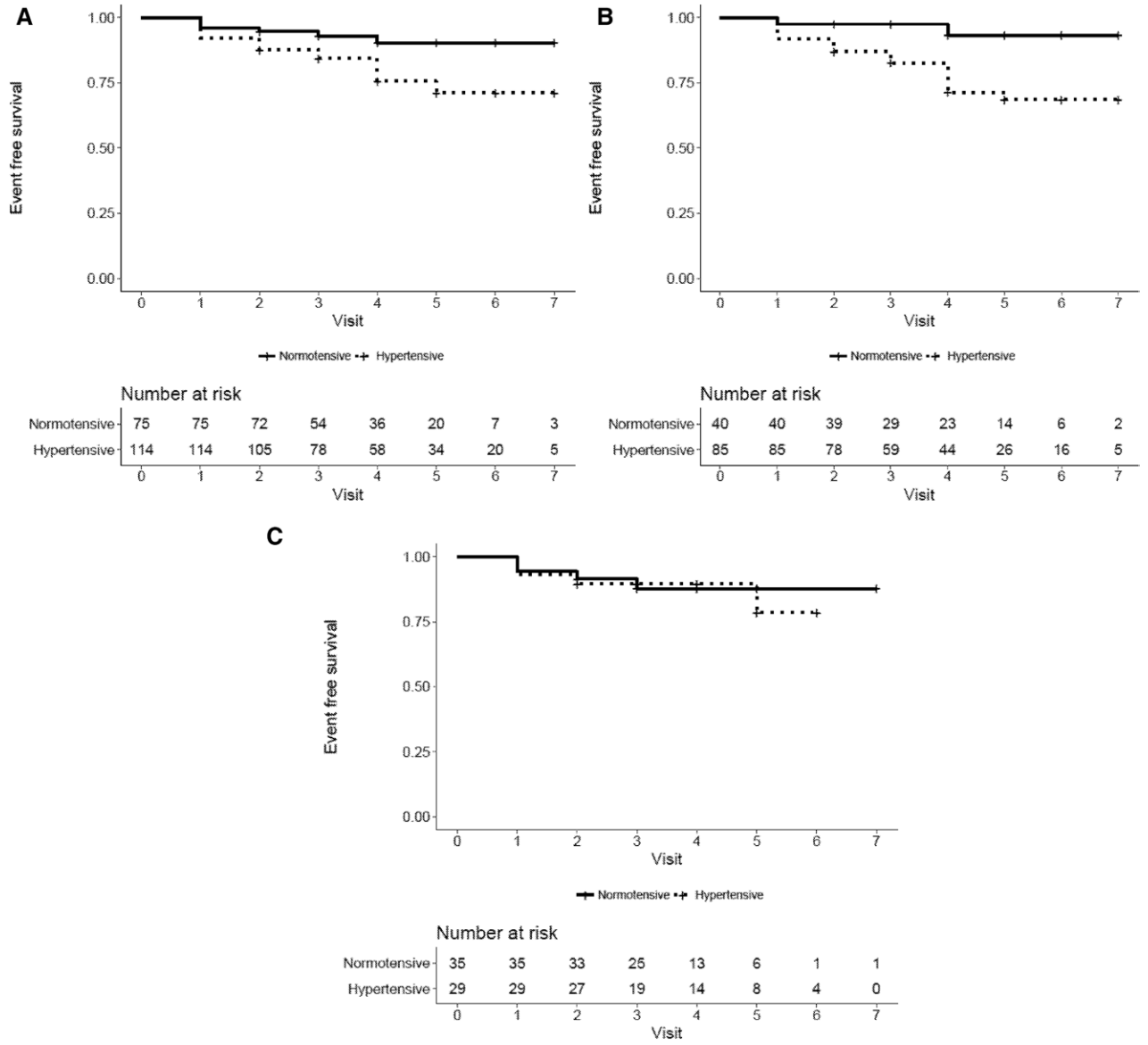

Figure. Kaplan–Meier plot of hypertensive blood pressure status and composite end point (end-stage renal disease or glomerular filtration rate decline 40%; **A**) overall (*P*=0.02) and among **(B)** adults (*P*=0.02) and **(C)** children (*P*=0.84) in the NEPTUNE (Nephrotic Syndrome Study Network) cohort.

also in Japan demonstrated that increased visit-to-visit BPV was associated with albuminuria.[7] In this study, we provide evidence that this association of BPV to renal outcomes can be extended to primary glomerulopathy populations throughout the lifespan. Our findings also demonstrate that adults have significantly greater systolic SD and ARV compared with children, which is not surprising given that BPV has been shown to increase with mean BP and age.[31] Interestingly, disease cohort, clinical characteristics (weight and edema), and treatment (antihypertensive medication class and immunosuppressive medications) were not associated with BPV in adults or children.

There are limitations to this study that should be taken into consideration. Ideally, hypertension is defined by the measurement of elevated BP from at least 2 (adults) or 3 (children) separate office visits.[11,12] Guidelines further recommend that auscultation is the preferred method of BP measurement over oscillometry.[11] The use of 24-hour ambulatory BP monitoring is also increasingly recommended for the diagnosis of hypertension.[32] In this study, we used previous medical history and the average of 2 seated oscillometric BPs from the baseline visit to determine hypertensive BP status. As a result, our findings may be subject to BP misclassification. However, if normotensive patients were mislabeled as HTN, we would expect to find weaker associations of HTN with outcomes. Although available, longitudinal measurements of BP in this cohort were not used to define hypertension because of the confounding of antihypertensive medication use over time that could have potentially affected BP. This is particularly relevant for this patient population because many are likely prescribed RAAS blockade for treatment of proteinuria. Second, although this

Table 5. Association of Hypertensive Blood Pressure Status at Baseline and Blood Pressure Variability over the First Year with Clinical Outcomes in Children Enrolled in NEPTUNE (Nephrotic Syndrome Study Network)

Outcome	β	95% CI	*P* Value
eGFR slope, mL min^{-1} y^{-1}			
HTN			
Model 1	−0.17	(−2.95 to 2.62)	0.91
Model 2	2.07	(−2.51 to 6.65)	0.38
SBP SD			
Model 1	−0.41	(−1.12 to 0.31)	0.27
Model 2	−0.58	(−1.4 to 0.24)	0.17
DBP SD			
Model 1	−0.34	(−1.17 to 0.49)	0.43
Model 2	−0.36	(−0.96 to 0.1)	0.11
SBP ARV			
Model 1	−0.32	(−0.84 to 0.2)	0.23
Model 2	−0.43	(−1.27 to 0.54)	0.44
DBP ARV			
Model 1	−0.41	(−0.95 to 0.14)	0.14
Model 2	−0.37	(−0.91 to 0.17)	0.18
Complete remission ever (UPC < 0.3)*	HR	95% CI	*P* value
HTN			
Model 1	0.51	(0.26 to 1.01)	0.05
SBP SD			
Model 1	0.96	(0.91 to 1.01)	0.11
DBP SD			
Model 1	1.00	(0.95 to 1.04)	0.89
SBP ARV			
Model 1	0.92	(0.87 to 0.98)	0.01
DBP ARV			
Model 1	0.95	(0.90 to 1.00)	0.04
Composite end point (ESRD or eGFR decline <40%)*			
HTN			
Model 1	1.23	(0.42 to 3.59)	0.71
SBP SD			
Model 1	1.10	(1.03 to 1.09)	<0.001
DBP SD			
Model 1	1.05	(0.99 to 1.12)	0.09
SBP ARV			
Model 1	1.10	(1.02 to 1.18)	0.01
DBP ARV			
Model 1	1.03	(0.97 to 1.09)	0.30

Model 1 includes age at baseline, sex, race, disease cohort, and follow-up time. Model 2 includes model 1+calcineurin inhibitor/steroid use, renin–angiotensin–aldosterone system use, weight status, edema, cholesterol, SBP index, and eGFR. ARV indicates average real variability; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HTN, hypertensive blood pressure status; SBP, systolic blood pressure; and UPC, urine protein creatinine.

*Model 2 failed to converge (ie, there was no maximum to the maximum likelihood function because there were variables in which there were no observations for exposure levels among the cases and controls.)

study focuses on the association of baseline hypertension and BPV with outcomes, the relationship between BP, proteinuria cause, and renal outcomes may not necessarily be causal, especially given the observational nature of the study. However, the renal outcomes evaluated were restricted to a period after the measurement of BPV. An additional limitation is that treatment with antihypertensive medications was not stable throughout the study duration; therefore, greater BPV in these patients could be a reflection of changes in BP control caused by medications (ie, patients with higher BP at study initiation could potentially be those who experienced the greatest fall in BP over time, which in turn affects BPV). It should be noted though that baseline BP and use of RAAS blockade were adjusted for in the regression models for renal outcomes. Last, all the NEPTUNE sites are academic centers where practices of BP management may differ from nonacademic institutions, thereby possibly affecting the generalizability of our results.

Perspectives

In summary, HTN is common among the adults and children with primary proteinuric glomerular diseases enrolled in NEPTUNE. There were significant differences in the prevalence of HTN, BPV, and treatment by age and disease cohort. HTN and greater BPV were associated with poorer renal outcomes, which may have clinical implications. These observations highlight the importance of further research, including clinical trials, to determine the impact of improved BP control on renal and CVD outcomes among individuals with primary proteinuric glomerular disease.

Acknowledgment

We acknowledge the participating sites in NEPTUNE (Nephrotic Syndrome Study Network).

Sources of Funding

The NEPTUNE (Nephrotic Syndrome Study Network Consortium), U54-DK-083912, is a part of the National Institutes of Health (NIH) Rare Disease Clinical Research Network (RDCRN), supported through a collaboration between the Office of Rare Diseases Research (ORDR), National Center for Advancing Translational Sciences, and the National Institute of Diabetes, Digestive, and Kidney Diseases. Additional funding or programmatic support for this project has also been provided by the University of Michigan, the NephCure Kidney International, and the Halpin Foundation.

Disclosures

None.

References

1. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics*. 2011;128(suppl 5):S213–S256. doi: 10.1542/peds.2009-2107C.
2. Ray EC, Rondon-Berrios H, Boyd CR, Kleyman TR. Sodium retention and volume expansion in nephrotic syndrome: implications for hypertension. *Adv Chronic Kidney Dis*. 2015;22:179–184. doi: 10.1053/j.ackd.2014.11.006.
3. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, Sever PS, Poulter NR. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet*. 2010;375:895–905. doi: 10.1016/S0140-6736(10)60308-X.

4. Mallamaci F, Minutolo R, Leonardis D, D'Arrigo G, Tripepi G, Rapisarda F, Cicchetti T, Maimone I, Enia G, Postorino M, Santoro D, Fuiano G, De Nicola L, Conte G, Zoccali C. Long-term visit-to-visit office blood pressure variability increases the risk of adverse cardiovascular outcomes in patients with chronic kidney disease. *Kidney Int*. 2013;84:381–389. doi: 10.1038/ki.2013.132.
5. Whittle J, Lynch AI, Tanner RM, Simpson LM, Davis BR, Rahman M, Whelton PK, Oparil S, Muntner P. Visit-to-visit variability of BP and CKD outcomes: results from the ALLHAT. *Clin J Am Soc Nephrol*. 2016;11:471–480. doi: 10.2215/CJN.04660415.
6. Diaz KM, Tanner RM, Falzon L, Levitan EB, Reynolds K, Shimbo D, Muntner P. Visit-to-visit variability of blood pressure and cardiovascular disease and all-cause mortality: a systematic review and meta-analysis. *Hypertension*. 2014;64:965–982. doi: 10.1161/HYPERTENSIONAHA.114.03903.
7. Kawai T, Ohishi M, Kamide K, Onishi M, Takeya Y, Tatara Y, Oguro R, Yamamoto K, Sugimoto K, Rakugi H. The impact of visit-to-visit variability in blood pressure on renal function. *Hypertens Res*. 2012;35:239–243. doi: 10.1038/hr.2011.170.
8. Okada T, Matsumoto H, Nagaoka Y, Nakao T. Association of home blood pressure variability with progression of chronic kidney disease. *Blood Press Monit*. 2012;17:1–7. doi: 10.1097/MBP.0b013e32834f7125.
9. Gadegbeku CA, Gipson DS, Holzman LB, et al. Design of the Nephrotic Syndrome Study Network (NEPTUNE) to evaluate primary glomerular nephropathy by a multidisciplinary approach. *Kidney Int*. 2013;83:749–756. doi: 10.1038/ki.2012.428.
10. Barisoni L, Nast CC, Jennette JC, et al. Digital pathology evaluation in the multicenter Nephrotic Syndrome Study Network (NEPTUNE). *Clin J Am Soc Nephrol*. 2013;8:1449–1459. doi: 10.2215/CJN.08370812.
11. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114:555–576.
12. Armstrong C; Joint National Committee. JNC8 guidelines for the management of hypertension in adults. *Am Fam Physician*. 2014;90:503–504.
13. Soergel M, Kirschstein M, Busch C, Danne T, Gellermann J, Holl R, Krull F, Reichert H, Reusz GS, Rascher W. Oscillometric twenty-four-hour ambulatory blood pressure values in healthy children and adolescents: a multicenter trial including 1141 subjects. *J Pediatr*. 1997;130:178–184.
14. Sorof JM, Cardwell G, Franco K, Portman RJ. Ambulatory blood pressure and left ventricular mass index in hypertensive children. *Hypertension*. 2002;39:903–908.
15. Flynn J, Zhang Y, Solar-Yohay S, Shi V. Clinical and demographic characteristics of children with hypertension. *Hypertension*. 2012;60:1047–1054. doi: 10.1161/HYPERTENSIONAHA.112.197525.
16. Levitan EB, Kaciroti N, Oparil S, Julius S, Muntner P. Relationships between metrics of visit-to-visit variability of blood pressure. *J Hum Hypertens*. 2013;27:589–593. doi: 10.1038/jhh.2013.19.
17. Center for Disease Control. Body Mass Index Calculator; 2016. https://www.cdc.gov/healthyweight/assessing/bmi/index.html.
18. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF III, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612. doi: 10.7326/0003-4819-150-9-200905050-00006.
19. Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol*. 2009;20:629–637. doi: 10.1681/ASN.2008030287.
20. R Development Core Team. *R: A Language and Environment for Statistical Computing* [computer program]. Vienna, Austria: the R Foundation for Stistical Computing; 2011. ISBN: 3-900051-07-0. http://www.R-project.org/.
21. Newman WJ, Tisher CC, McCoy RC, Gunnells JC, Krueger RP, Clapp JR, Robinson RR. Focal glomerular sclerosis: contrasting clinical patterns in children and adults. *Medicine*. 1976;55:67–87.
22. Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. A report of the International Study of Kidney Disease in Children. *Kidney Int*. 1978;13:159–165.
23. Zagury A, Oliveira AL, Montalvão JA, Novaes RH, Sá VM, Moraes CA, Tavares Mde S. Steroid-resistant idiopathic nephrotic syndrome in children: long-term follow-up and risk factors for end-stage renal disease. *J Bras Nefrol*. 2013;35:191–199. doi: 10.5935/0101-2800.20130031.
24. Xu ZQ, Yi ZW, Dang XQ, Wu XC, He XJ. [Relationship of 24-hour ambulatory blood pressure and rennin-angiotensin-aldosterone system in children with primary nephrotic syndrome]. *Zhongguo Dang Dai Er Ke Za Zhi*. 2010;12:788–792.
25. Sarkar S, Sinha A, Lakshmy R, Agarwala A, Saxena A, Hari P, Bagga A. Ambulatory blood pressure monitoring in frequently relapsing nephrotic syndrome. *Indian J Pediatr*. 2017;84:31–35. doi: 10.1007/s12098-016-2207-y.
26. Candan C, Canpolat N, Gökalp S, Yıldız N, Turhan P, Taşdemir M, Sever L, Çalışkan S. Subclinical cardiovascular disease and its association with risk factors in children with steroid-resistant nephrotic syndrome. *Pediatr Nephrol*. 2014;29:95–102. doi: 10.1007/s00467-013-2608-3.
27. Grams ME, Yang W, Rebholz CM, et al. Risks of adverse events in advanced CKD: the Chronic Renal Insufficiency Cohort (CRIC) Study [published online ahead of print March 30, 2017]. *Am J Kidney Dis*. doi: 10.1053/j.ajkd.2017.01.050. http://www.ajkd.org/article/S0272-6386(17)30543-7/fulltext.
28. Moranne O, Watier L, Rossert J, Stengel B; GN-Progress Study Group. Primary glomerulonephritis: an update on renal survival and determinants of progression. *QJM*. 2008;101:215–224. doi: 10.1093/qjmed/hcm142.
29. Chou YH, Lien YC, Hu FC, Lin WC, Kao CC, Lai CF, Chiang WC, Lin SL, Tsai TJ, Wu KD, Chen YM. Clinical outcomes and predictors for ESRD and mortality in primary GN. *Clin J Am Soc Nephrol*. 2012;7:1401–1408. doi: 10.2215/CJN.04500511.
30. Yano Y, Fujimoto S, Kramer H, et al. Long-term blood pressure variability, new-onset diabetes mellitus, and new-onset chronic kidney disease in the Japanese general population. *Hypertension*. 2015;66:30–36. doi: 10.1161/HYPERTENSIONAHA.115.05472.
31. Mancia G PG, Di Rienzo M, Zanchetti A. Blood pressure variability. In: Zanchetti A, Mancia G, eds. *Handbook of Hypertension*. Amsterdam, The Netherlands: Elsevier; 1997:117–169.
32. Flynn JT, Daniels SR, Hayman LL, Maahs DM, McCrindle BW, Mitsnefes M, Zachariah JP, Urbina EM; American Heart Association Atherosclerosis, Hypertension and Obesity in Youth Committee of the Council on Cardiovascular Disease in the Young. Update: ambulatory blood pressure monitoring in children and adolescents: a scientific statement from the American Heart Association. *Hypertension*. 2014;63:1116–1135. doi: 10.1161/HYP.0000000000000007.

Novelty and Significance

What Is New?

- Nephrotic syndrome is recognized as a significant cardiovascular disease risk factor; however, the prevalence of hypertension and blood pressure (BP) variability in primary glomerulopathies associated with nephrotic syndrome have not been well described.
- The relationship of BP and BP variability with renal outcomes in primary proteinuric glomerular diseases is not known.

What Is Relevant?

- This study describes hypertension and BP variability in adults and children with primary proteinuric glomerulopathies.

Summary

In adults and children with primary glomerulopathies associated with nephrotic syndrome, nearly 60% of participants had HTN at enrollment. Differences in hypertensive status prevalence, BP variability, and treatment were found by age and histological diagnosis. Hypertensive status and greater BP variability were associated with poorer clinical outcomes.