Journal of the American Heart Association

ORIGINAL RESEARCH

Short-Term Systolic Blood Pressure Variability and Kidney Disease Progression in Patients With Chronic Kidney Disease: Results From C-STRIDE

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BACKGROUND: It is unclear whether short-term blood pressure variability is associated with renal outcomes in patients with chronic kidney disease.

METHODS AND RESULTS: This study analyzed data from participants in the C-STRIDE (Chinese Cohort Study of Chronic Kidney Disease) who had chronic kidney disease stages 1 to 4. Short-term blood pressure variability was measured by calculating the weighted SD (w-SD) of systolic blood pressure (SBP). Renal outcomes were defined as dialysis initiation and/or transplantation. Risk factors associated with w-SD of SBP were evaluated by linear regression. Associations of short-term SBP variability with renal outcomes were evaluated by Cox regression. In total, 1421 patients with chronic kidney disease were included in this study (mean age, 49.4±13.6 years; 56.2% men; estimated glomerular filtration rate, 50.5±29.3 mL/min per 1.73 m^2; proteinuria, 0.9 [0.3–2.0] g/d). Mean w-SD of SBP was 12.6±4.4 mm Hg. w-SD of SBP was independently associated with older age, 24-hour SBP, blood pressure circadian pattern, and angiotensin II receptor blocker treatment. During a median follow-up of 4.9 years, 237 patients developed renal outcomes (37.01 per 1000 patient-years). The incidence rate increased across the quartiles of w-SD (log-rank P=0.005). w-SD of SBP was associated with an increased risk of renal outcomes, both as a continuous variable (hazard ratio [HR], 1.47; 95% CI, 1.09–1.99) and as a categorical variable (quartile 4 versus quartile 1: HR, 1.60; 95% CI, 1.08–2.36), independent of 24-hour SBP, daytime SBP, and nighttime SBP.

CONCLUSIONS: Short-term SBP was independently associated with the risk of dialysis initiation and/or transplantation in patients with chronic kidney disease.

Key Words: ambulatory blood pressure monitoring ■ chronic kidney disease ■ renal replacement therapy ■ short-term blood pressure variability

Chronic kidney disease (CKD) is an important public health burden worldwide.[1,2] Hypertension, both as a common cause and comorbidity of CKD, is highly prevalent in patients with CKD, resulting in the development and progression of kidney disease. There is considerable evidence that hypertension control is important for the management of patients with CKD, although real-world management of these patients remains unsatisfactory.[3–5] Ambulatory blood pressure (ABP) monitoring (ABPM), an automated monitoring method to detect blood pressure (BP) values during a daily cycle under nonmedical conditions, performs better than traditional clinic BP (CBP) measurement in the assessment of BP control status and prediction of long-term prognosis.[6,7]

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Supplementary Materials for this article are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.015359

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For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Our study demonstrated that short-term systolic blood pressure variability was associated with higher risk of renal outcomes, irrespective of the 24-hour, diurnal, and nocturnal systolic blood pressure.

What Are the Clinical Implications?

- Our study brings new evidence to the potential role of short-term blood pressure variability in chronic kidney disease progression, which might affect the evaluation and management of hypertension in patients with chronic kidney disease once verified in future studies.

Nonstandard Abbreviations and Acronyms

ABPM	ambulatory blood pressure monitoring
BP	blood pressure
BPV	blood pressure variability
CBP	clinic blood pressure
CKD	chronic kidney disease
C-STRIDE	Chinese Cohort Study of Chronic Kidney Disease
CVD	cardiovascular disease
eGFR	estimated glomerular filtration rate
HR	hazard ratio
SBP	systolic blood pressure
w-SD	weighted SD

The use of ABPM has led to increasing awareness of short-term BP variability (BPV), which indicates the intraindividual fluctuation in BP levels during a 24-hour period. This component of BP adds a layer of complexity in the evaluation and management of hypertension. Studies in general populations and patients with primary hypertension have shown that short-term BPV is associated with organ damage and cardiovascular events, independent of average 24-hour ABP and CBP, respectively.[8–12] The results of cross-sectional studies have suggested that short-term BPV is higher in patients with CKD than in individuals without CKD; in addition, BPV progressively increased with deterioration of renal function.[13,14] Furthermore, short-term BPV has been associated with organ damage in patients with CKD, suggesting that it has a pathophysiological role in CKD development. However, a recent prospective cohort study from Italy did not demonstrate an association between short-term BPV and CKD progression.[15,16] Therefore, it remains unclear whether short-term BPV is useful for risk stratification in patients with CKD.

To better understand associations of short-term BPV with renal outcomes, we analyzed data from C-STRIDE (Chinese Cohort Study of Chronic Kidney Disease) to evaluate associations of short-term BPV with dialysis initiation and/or transplantation and to identify clinical determinants of short-term BPV in patients with CKD.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

This was a multicenter, prospective cohort study of patients with CKD stages 1 to 4 from C-STRIDE. The design and methods of C-STRIDE have been described in detail elsewhere.[17,18] From November 2011 to December 2016, a total of 3700 participants from 39 clinical centers in 22 provinces of China were enrolled in C-STRIDE. The basic characteristics of the participants in C-STRIDE are listed in Table S1. Among the enrolled patients, 2114 had undergone ABPM; 693 were excluded because of missing data regarding SD values in ABPM records. Finally, 1421 patients were included in the present analysis (Figure 1). The patients included in the current analysis had a distribution of baseline characteristics comparable to those of patients who were excluded (Table S1). The study protocol was approved by the ethics committee of Peking University First Hospital and was in compliance with the tenets of the Declaration of Helsinki. All participants provided written informed consent before enrollment in the study.

BP Measurements

CBP was measured with mercury sphygmomanometers in patients in the sitting position, 3 times at 1-minute intervals, by an experienced nurse. Participants were advised to avoid ingestion of spicy foods or stimulant drinks (eg, coffee or tea), to avoid smoking and strenuous exercise for at least 90 minutes before the BP examination, and to rest for at least 5 minutes before the BP examination. CBP values were recorded as the mean of the 3 readings.

ABP was measured using equipment that belonged to each participating center. The type and manufacturer of the equipment were not specified before the study, but the equipment was required to be approved for clinical use by the State Food and Drug Administration of China. Diurnal and nocturnal BPs were arbitrarily defined as 7 AM to 10 PM and

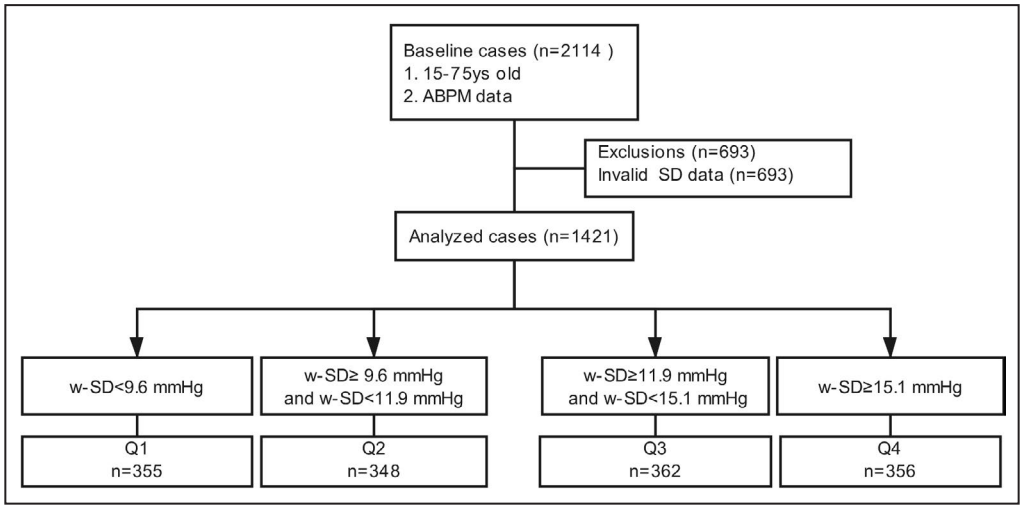

Figure 1. Flowchart of patient enrollment.
ABPM indicates ambulatory blood pressure monitoring; Q, quartile; w-SD, weighted SD of systolic blood pressure.

10 PM to 7 AM, respectively. ABP was recorded at 15-minute intervals during the day and at 30-minute intervals during the night. Diurnal BP was the mean value of 15 hours (7 AM–10 PM), while nocturnal BP was the mean value of 9 hours (10 PM–7 AM). Valid measurements were regarded as successful documentation of at least 70% of BP readings taken during a 24-hour period. Both CBP and ABP measurements were taken from the nondominant arm with an appropriate cuff size based on arm circumference at the time of enrollment.

Short-Term Systolic BPV Definition

Weighted SD (w-SD) was used in the present study to assess short-term systolic BPV. w-SD was defined as the mean SD of diurnal and nocturnal systolic BP (SBP), weighted for the duration of the daytime and nighttime interval, respectively.[19] The w-SD was calculated as the following formula: w-SD=(diurnal SD×15 hours+nocturnal SD×9 hours)/24 hours. Diurnal and nocturnal SDs of SBP were derived directly by ABPM within each individual collection period and recorded as mean values.

Outcomes

Renal outcomes were defined as dialysis initiation and/or transplantation. Patients were followed up at 3-month intervals, either by phone calls or routine clinical visits. Follow-up was terminated at the occurrence of death, loss to follow-up, or a predefined end date (December 31, 2017).

Covariate Definition

Smoking was defined as currently smoking or any history of smoking. Diabetes mellitus was defined as fasting plasma glucose ≥7.0 mmol/L, a self-reported history of diabetes mellitus, or current use of anti-diabetes mellitus medication. Body mass index was calculated by the following formula: body mass index=weight (kg)/height^2 (m^2). Anemia was defined as hemoglobin level <100 g/L. Dyslipidemia was defined as the presence of at least 1 of following observations: serum total cholesterol level ≥200 mg/dL (5.2 mmol/L per L), triglycerides level ≥150 mg/dL (1.7 mmol/L per L), low-density lipoprotein cholesterol level ≥130 mg/dL (3.4 mmol/L per L), high-density lipoprotein cholesterol level <40 mg/dL (1.0 mmol/L per L), or current use of lipid-lowering drugs. Dipper status was defined as the ratio of nighttime SBP/daytime SBP ≤0.9. Cardiovascular disease (CVD) history was defined as the past occurrence of myocardial infarction, hospital admission for congestive heart failure, or severe cardiac arrhythmia incidents (eg, resuscitated cardiac arrest, ventricular fibrillation, sustained ventricular tachycardia, paroxysmal ventricular tachycardia, atrial fibrillation or flutter, severe bradycardia, or heart block). The glomerular filtration rate was estimated from serum creatinine measurements and demographic characteristics, in accordance with the Chronic Kidney Disease Epidemiology Collaboration equation.[20] Patients were classified into 4 stages according to the estimated glomerular filtration rate (eGFR): CKD stage 1 (≥90 mL/min per 1.73 m^2), CKD stage 2 (60–89 mL/min per 1.73 m^2), CKD stage 3 (30–59 mL/min per 1.73 m^2), and CKD stage 4 (15–29 mL/min per 1.73 m^2).[21]

Statistical Analysis

Continuous variables with normal Gaussian distribution are expressed as means±SDs, while variables with non-normal distributions are expressed

Table 1. Baseline Demographic and Clinical Characteristics of Patients Stratified by Quartiles of w-SD

	Total	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
	(N=1421)	(n=355)	(n=348)	(n=362)	(n=356)	*P* Value
Age, y	49.4±13.6	43.5±13.3	48.5±13.6	51.7±12.8	53.7±12.6	<0.001
Men, No. (%)	798 (56)	186 (52)	203 (58)	215 (59)	194 (55)	0.20
Smokers, No. (%)	473 (34)	104 (30)	121 (35)	124 (35)	124 (35)	0.32
DM, No. (%)	285 (25)	50 (18)	65 (25)	72 (24)	98 (31)	0.005
History of CVD, No. (%)	144 (10)	21 (6)	35 (10)	37 (10)	51 (14)	0.003
Causes of CKD, No. (%)						<0.001
DKD	180 (12.9)	27 (7.7)	36 (10.6)	46 (13.0)	71 (20.1)	
Glomerulonephritis	835 (59.6)	251 (71.5)	209 (61.3)	194 (54.6)	181 (51.2)	
Other	385 (27.5)	73 (20.8)	96 (28.2)	115 (32.4)	101 (28.6)	
BMI, kg/m^2	24.7±3.9	23.8±3.9	24. 8±3.9	25.2±3.8	24.8±3.8	<0.001
Serum albumin, g/L	39.3±7.0	38.9±7.4	39.3±6.8	38.9±7.3	39.9±6.4	0.26
FBG, mmol/L	5.03 (4.53–5.65)	4.95 (4.51–5.65)	4.96 (4.47–5.61)	4.96 (4.46–5.53)	5.13 (4.71–5.81)	0.035
Hemoglobin, g/L	126.0±22.2	126.6±21.8	127.4±23.0	126.0±22.5	123.9±21.5	0.19
Triglycerides, mmol/L	1.73 (1.20–2.38)	1.66 (1.09–2.18)	1.76 (1.21–2.46)	1.73 (1.17–2.43)	1.75 (1.24–2.31)	0.09
TC, mmol/L	4.68 (3.81–5.53)	4.64 (3.78–5.50)	4.49 (3.76–5.34)	4.71 (3.94–5.58)	4.74 (4.00–5.64)	0.21
HDL-C, mmol/L	1.09 (0.91–1.31)	1.05 (0.93–1.26)	1.05 (0.87–1.25)	1.09 (0.89–1.33)	1.12 (0.94–1.36)	0.01
LDL-C, mmol/L	2.60 (2.07–3.23)	2.62 (1.99–3.23)	2.52 (2.02–3.12)	2.68 (2.07–3.26)	2.59 (2.20–3.28)	0.29
24-h Proteinuria, g/d	0.87 (0.33–1.98)	0.73 (0.31–1.74)	0.86 (0.33–2.06)	0.87 (0.29–1.95)	0.77 (0.28–1.88)	0.21
Creatinine, μmol/L	144.7 (101.0–202.0)	126.0 (84.0–182.8)	140.9 (97.3–203.8)	148.0 (108.0–205.5)	157.5 (119.3–206.5)	<0.001
eGFR, mL/min per 1.73 m^2	50.5±29.3	59.6±32.9	51.1±29.4	48.6±27.7	42.8±24.2	<0.001
CKD stage, No. %						<0.001
1	192 (13)	81 (22)	44 (13)	44 (12)	23 (7)	
2	241 (17)	75 (21)	64 (18)	54 (15)	48 (14)	
3	569 (40)	112 (32)	138 (40)	156 (43)	163 (46)	
4	419 (30)	87 (25)	102 (29)	108 (30)	122 (34)	

Values are expressed as mean±SD or 95% CI unless otherwise indicated. Missing data: smokers 22, diabetes mellitus (DM) 270, history of cardiovascular disease (CVD) 8, body mass index (BMI) 178, serum albumin 285, fasting blood glucose (FBG) 315, hemoglobin 60, triglycerides 341, total cholesterol (TC) 342, high-density lipoprotein cholesterol (HDL-C) 372, low-density lipoprotein cholesterol (LDL-C) 372, and 24-hour proteinuria 65. CKD indicates chronic kidney disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; and w-SD, weighted SD of systolic blood pressure.

as medians and interquartile ranges. Categorical variables are expressed as frequencies and proportions. According to their distributions, 1-way ANOVA or Kruskal–Wallis test were used to compare differences among groups for continuous variables, while chi-square test and Fisher exact test were used to compare differences among groups for categorical variables. Univariate and multivariate linear regression analyses were performed to analyze the potential determinant(s) of w-SD. Variables with significance in univariate analysis were included in multivariate analysis.

The incidence rates of renal outcomes were calculated as numbers of outcomes per 1000 patient-years. Survival curves of individual quartiles of w-SD were calculated by Kaplan–Meier methods. Log-rank tests were used to compare outcome rates among each quartile.

A multivariable Cox proportional hazards regression model was used to investigate associations between w-SD and renal outcomes. Four models were constructed. Model 1 was adjusted for age (continuous) and sex (male versus female), body mass index (continuous), smoking (yes versus no), history of CVD (yes versus no), antihypertensive therapy (yes versus no), diabetes mellitus (yes versus no), albumin level (continuous), anemia (yes versus no), dyslipidemia (yes versus no), log-transformed proteinuria level (continuous), dipper status (yes versus no), and eGFR (continuous). To further assess whether the associations were independent of BP value, w-SD was additionally adjusted for 24-hour SBP in model 2, daytime SBP in model 3, and nighttime SBP in model 4. Hazard ratios (HRs) and 95% CIs were reported. For Cox regression analysis, in order to reduce the loss of sample, missing values were filled with means for continuous variables with normal distributions and with medians for continuous variables with non-normal distribution, while categorical variables were filled with a separate category. The proportional

hazards assumption was tested by assessing the log-log plot of survival and using Schoenfeld residuals. No violations were found for any of the covariates. Sensitivity analyses were performed in patients with complete data. Data were analyzed using SPSS Statistics version 22.0 (IBM). A 2-sided $P<0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

Table 1 shows the main demographic and clinical features of the 1421 enrolled patients, stratified by quartiles of w-SD. The mean age of the cohort was 49.4±13.6 years, with 56.2% men. Notably, 33.8% of patients were smokers, while 24.8% of patients exhibited diabetes mellitus and 12.7% had a history of CVD. Of the patients, 13.5% were classified as having stage 1 CKD, 17% were classified as having stage 2 CKD, 40% were classified as having stage 3 CKD, and 29.5% were classified as having stage 4 CKD. Patients in the highest quartile of w-SD were older, with a higher prevalence of diabetes mellitus and history of CVD and lowest eGFR. No difference in terms of proteinuria was detected across w-SD quartiles ($P=0.21$).

The overall w-SD of SBP was 12.6±4.4 mm Hg: diurnal SD of SBP was 13.4±5.4 mm Hg and nocturnal SD of SBP was 11.4±4.6 mm Hg. Clinic and ambulatory 24-hour, diurnal, and nocturnal BP, as well as diurnal and nocturnal SD of SBP, and the proportion of dippers increased across quartiles of w-SD (Table 2). Consistent with these findings, the proportions of patients with 24-hour, diurnal, and nocturnal BP at target levels progressively decreased from the lowest quartile to the highest quartile (Table 2). When compared with nondipper patients, dipper patients had higher w-SD (13.9±4.9 versus 12.2±4.1 mm Hg, $P<0.001$) and higher diurnal SD of SBP (15.3±6.3 versus 12.7±4.8 mm Hg, $P<0.001$), whereas nocturnal SD of SBP did not significantly differ (11.6±4.7 versus 11.3±4.6 mm Hg, $P=0.23$).

Factors Associated With w-SD

w-SD was positively associated with age, body mass index, diabetes mellitus, history of CVD, 24-hour SBP, dipper status, and antihypertensive therapy (ie, with angiotensin II receptor blocker, calcium antagonist, or β-blocker medication), whereas it was negatively associated with cause of CKD (glomerulonephritis versus diabetic kidney disease) and eGFR in univariate analysis. After multivariable adjustment, w-SD remained

Table 2. Clinic and Ambulatory BP Parameters of Patients Stratified by Quartiles of w-SD

	Total	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
	(N=1421)	(n=355)	(n=348)	(n=362)	(n=356)	*P* Value
Clinic SBP, mm Hg	129.2±17.3	123.9±15.0	128.5±15.6	131.8±17.1	133.1±20.1	<0.001
Clinic DBP, mm Hg	80.5±10.6	78.2±10.4	80.5±9.5	81.3±11.1	82.1±11.1	<0.001
CBP <140/90 mm Hg, No. (%)	884 (76)	263 (87)	227 (77)	210 (71)	184 (70)	<0.001
24-h SBP, mm Hg	128.7±17.3	120.7±15.4	125.5±15.1	131.0±16.0	137.2±18.3	<0.001
24-h DBP, mm Hg	78.9±10.8	76.3±10.6	78.3±10.2	80.0±11.4	81.1±10.4	<0.001
24-h BP <130/80 mm Hg, No. (%)	616 (44)	210 (60)	159 (46)	136 (38)	111 (31)	<0.001
Daytime SBP, mm Hg	130.6±17.3	122.0±15.4	127.4±14.8	132.8±15.7	140.0±18.0	<0.001
Daytime DBP, mm Hg	80.5±10.9	77.7±10.8	79.7±10.1	81.5±11.3	82.7±10.3	<0.001
Daytime BP <135/85 mm Hg, No. (%)	773 (55)	251 (71)	209 (60)	178 (49)	135 (38)	<0.001
Nighttime SBP, mm Hg	123.3±18.9	115.6±15.8	120.6±16.1	126.6±18.8	130.1±21.1	<0.001
Nighttime DBP, mm Hg	74.9±11.8	72.4±11.5	73.7±10.8	76.4±12.8	76.9±11.5	<0.001
Nighttime BP <120/70 mm Hg, No. (%)	400 (28)	133 (38)	101 (29)	94 (26)	72 (20)	<0.001
Dipper, No. (%)	372 (26)	70 (20)	76 (22)	89 (25)	137 (39)	<0.001
w-SD, mm Hg	12.6±4.4	8.0±1.2	10.5±0.6	13.3±1.0	18.7±3.3	<0.001
Diurnal SD, mm Hg	13.4±5.4	8.3±1.8	10.9±1.5	13.9±2.2	20.4±4.9	<0.001
Nocturnal SD, mm Hg	11.4±4.6	7.5±2.3	10.0±2.6	12.2±3.3	15.9±4.8	<0.001
Antihypertensive treatment, No. (%)	918 (65)	213 (61)	227 (65)	253 (70)	225 (63)	<0.001

Values are expressed as mean±SD unless otherwise indicated. Missing counts: clinic systolic blood pressure (SBP) 262, clinic diastolic blood pressure (DBP) 261, 24-hour SBP 4, 24-hour average DPB 4, daytime SBP 3, daytime DBP 2, nighttime DBP 5, dipper 3, and antihypertensive treatment 244. BP indicates blood pressure; CBP, clinic blood pressure; and w-SD, weighted SD of systolic blood pressure.

significantly associated with age, 24-hour SBP, dipper status, and angiotensin II receptor blocker therapy; the association with eGFR was lost (Table 3). Proteinuria was not associated with w-SD in unadjusted or adjusted analysis.

Outcome Analysis

During a median follow-up of 4.9 years (interquartile range, 4.0–5.6 years), 237 patients initiated dialysis and/or received transplantation, corresponding to an outcome rate of 37.01 per 1000 patient-years. Cox regression analysis showed that w-SD, when expressed as a continuous variable, was associated with 47% greater risk of renal outcomes (HR, 1.47; 95% CI, 1.09–1.99) for each 10-mm Hg increase after adjustment for demographic and traditional risk factors. The HR remained statistically significant after further adjustments for 24-hour SBP, daytime SBP, and nighttime SBP (Table 4). In addition, diurnal SD of SBP was independently associated with renal outcomes (HR, 1.36; 95% CI, 1.08–1.72), whereas nocturnal SD of SBP was not (HR, 1.18; 95% CI, 0.89–1.55) (Table S2).

The incidence rate increased across the quartiles of w-SD (quartile 1, 27.74; quartile 2, 32.74; quartile 3, 37.30; quartile 4, 50.47 per 1000 patient-years, log-rank *P*=0.005) (Figure 2). Multivariable Cox regression analysis showed that w-SD in categorical form was associated with an increased risk of renal outcomes (quartile 4 versus quartile 1: HR, 1.85; 95% CI, 1.28–2.66 in unadjusted model and HR, 1.60; 95% CI, 1.08–2.36 in model 1). The findings remained largely unchanged after further adjustments for 24-hour SBP, daytime SBP, and nighttime SBP (Table 5). The sensitivity analyses showed consistent results (Tables S3 and S4).

Table 3. Univariate and Multivariate Liner Regression Analysis of w-SD

	Univariate		Multivariate*	
	B	*P* Value	*B*	*P* Value
Age	0.085	<0.001	0.06	<0.001
Sex (male vs female)	0.044	0.851		
BMI	0.089	0.005	0.003	0.93
Smoking (yes vs no)	0.29	0.239		
DM (yes vs no)	0.985	0.001	−0.48	0.21
CVD history (yes vs no)	1.582	<0.001	0.31	0.35
Causes of CKD (glomerulonephritis vs DKD)	−1.967	<0.001	−0.078	0.87
Anemia (yes vs no)	0.052	0.888		
Dyslipidemia (yes vs no)	0.255	0.549		
eGFR	−0.027	<0.001	−0.005	0.25
Log-transformed 24-h proteinuria	−0.29	0.168		
24-h SBP	0.089	<0.001	0.076	<0.001
Dipper	1.724	<0.001	1.92	<0.001
Antihypertensive therapy				
ACEI (yes vs no)	−0.432	0.12		
ARB (yes vs no)	0.869	<0.001	0.658	0.002
CCB (yes vs no)	1.72	<0.001	0.129	0.599
α-Blocker (yes vs no)	0.723	0.254		
β-blocker (yes vs no)	1.309	<0.001	0.312	0.233
Diuretic (yes vs no)	1.029	0.023	−0.218	0.599

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CKD, chronic kidney disease; CVD, cardiovascular disease; DKD, diabetic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; and w-SD, weighted SD of systolic blood pressure.

*Variables included in the multivariate analysis were those with significance in univariate analysis.

DISCUSSION

In the present study, we investigated associations between short-term systolic BPV and renal outcomes, as well as clinical factors associated with BPV, in a large prospective cohort of patients with CKD. Older age, 24-hour SBP, dipper status, and angiotensin II receptor blocker therapy were significantly associated with short-term systolic BPV. Short-term systolic BPV was independently associated with the risk of renal outcomes, irrespective of 24-hour, diurnal, and nocturnal SBP. This finding indicates a potential role for short-term SBP fluctuation in the risk of end-stage renal disease in patients with CKD.

BP fluctuation during a 24-hour cycle is a complex physiologic phenomenon, which is regarded as short-term BPV. Many mechanisms have been proposed to explain an increase in short-term BPV (eg, emotional, environmental, behavioral, or neurohumoral factors, as well as increased arterial stiffness); however, the specific mechanism remains unknown.[22] Notably, interactions of these mechanisms with BPV suggest a potential pathophysiologic association between short-term BPV and target organ damage. For instance, Ozkayar et al[23] identified an association between local activation of the renal renin–angiotensin system and an increase in BPV in patients with hypertension. Aoki et al[24] found that wide BPV aggravates preglomerular arteriolosclerosis through a local angiotensin-mediated mechanism in spontaneously hypertensive rats. In addition, sympathetic activation is a major contributor to BPV. Overactivation of the sympathetic nervous system is known to be involved in the development and progression of CVD and CKD, either

Table 4. Multivariate Cox Regression Analysis of the Association of Continuous w-SD With Renal Outcome

	Unadjusted	Model 1	Model 2	Model 3	Model 4
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
w-SD (per 10 mm Hg)	1.45 (1.11–1.88)	1.47 (1.09–1.99)	1.45 (1.04–2.02)	1.45 (1.04–2.02)	1.46 (1.05–2.03)
24-h SBP (per 10 mm Hg)	1.29 (1.22–1.38)	…	0.97 (0.89–1.06)	…	…
Daytime SBP (per 10 mm Hg)	1.29 (1.21–1.37)	…	…	1.01 (0.93–1.09)	…
Nighttime SBP (per 10 mm Hg)	1.27 (1.20–1.35)	…	…	…	1.01 (0.93–1.09)
Age	1.00 (0.99–1.01)	0.97 (0.96–0.98)	0.97 (0.96–0.98)	0.97 (0.96–0.98)	0.97 (0.96–0.98)
Sex (male vs female)	1.32 (1.01–1.71)	1.74 (1.21–2.51)	1.74 (1.20–2.50)	1.74 (1.20–2.50)	1.74 (1.20–2.51)
BMI	0.96 (0.93–1.00)	0.99 (0.95–1.02)	0.98 (0.95–1.02)	0.98 (0.95–1.02)	0.99 (0.95–1.02)
Smoker	1.45 (1.12–1.88)	1.08 (0.76–1.52	1.08 (0.76–1.52)	1.08 (0.76–1.52)	1.08 (0.76–1.52)
DM	1.98 (1.48–2.64)	1.28 (0.91–1.79)	1.27 (0.91–1.79)	1.27 (0.91–1.79)	1.27 (0.91–1.79)
History of CVD	1.17 (0.82–1.68)	0.98 (0.66–1.45)	0.98 (0.66–1.45)	0.98 (0.66–1.45)	0.98 (0.66–1.45)
Antihypertensive treatment	2.30 (1.50–3.51)	1.31 (0.84–2.05)	1.31 (0.84–2.04)	1.31 (0.84–2.04)	1.31 (0.84–2.04)
Dyslipidemia	1.02 (0.63–1.64)	0.95 (0.57–1.57)	0.94 (0.57–1.57)	0.94 (0.57–1.57)	0.94 (0.57–1.57)
Serum albumin	0.95 (0.94–0.97)	0.96 (0.94–0.99)	0.96 (0.94–0.99)	0.96 (0.94–0.99)	0.96 (0.94–0.99)
Anemia	3.84 (2.89–5.11)	1.92 (1.39–2.64)	1.92 (1.39–2.64)	1.92 (1.39–2.64)	1.92 (1.39–2.64)
Log-transformed 24-h proteinuria	4.43 (3.42–5.75)	2.11 (1.50–2.95)	2.10 (1.49–2.94)	2.10 (1.49–2.94)	2.10 (1.49–2.95)
eGFR	0.93 (0.92–0.94)	0.93 (0.92–0.94)	0.93 (0.92–0.94)	0.93 (0.92–0.94)	0.93 (0.92–0.94)
Dipper	0.71 (0.52–0.97)	0.91 (0.67–1.28)	0.91 (0.65–1.27)	0.91 (0.65–1.27)	0.92 (0.65–1.31)

Model 1: adjusted for age and sex, smoking, body mass index (BMI), diabetes mellitus (DM), history of cardiovascular disease (CVD), antihypertensive treatment, serum albumin, anemia, dyslipidemia, dipper, log-transformed 24-hour proteinuria, and estimated glomerular filtration rate (eGFR). Model 2: model 1+24-hour systolic blood pressure (SBP). Model 3: model 1+daytime SBP. Model 4: model 1+nighttime SBP. HR indicates hazard ratio; and w-SD, weighted SD of systolic blood pressure.

directly or through interactions with the angiotensin system.[25,26] Therefore, short-term BPV has emerged as a potential clinical index with pathophysiological relevance.

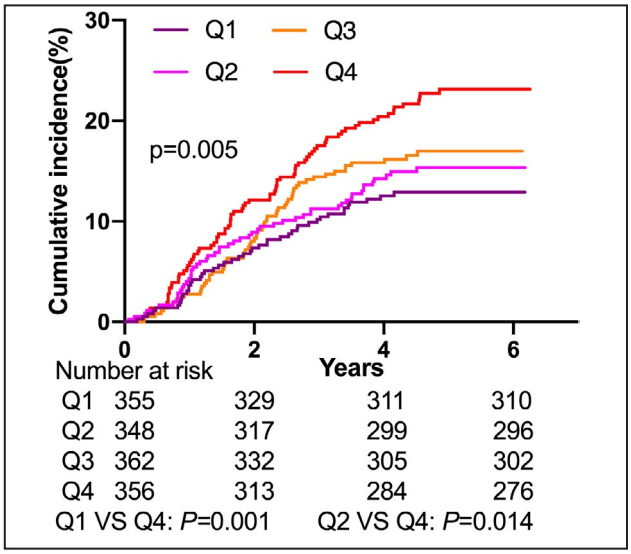

Figure 2. Kaplan–Meier hazard curve for renal outcomes by patients with quartiles of weighted SD of systolic blood pressure (w-SD).
Q1 indicates patients with w-SD <9.6 mm Hg; Q2, patients with w-SD ≥9.6 mm Hg and w-SD <11.9 mm Hg; Q3, patients with w-SD ≥11.9 mm Hg and w-SD <15.1 mm Hg; and Q4, patients with w-SD ≥15.1 mm Hg.

There is growing evidence that short-term BPV is associated with an increased risk of target organ damage and cardiovascular events in the general population and patients with hypertension in a manner independent of mean BP values, which supports its role as a potential cardiovascular risk factor, rather than a limited physiologic response.[8–12] With respect to kidney function, the Jackson Heart Study showed that short-term BPV was significantly higher in patients with CKD than in patients without CKD.[13] A larger study of 16 546 participants from the Spanish ABPM Registry database[14] confirmed that short-term BPV was higher in patients with hypertension with CKD than in patients with hypertension without CKD. In addition, that study revealed a tendency for higher short-term BPV with progression of CKD. In the present study, we observed that eGFR decreased as w-SD increased from quartile 1 to quartile 4. Furthermore, short-term BPV alone has been associated with left ventricular hypertrophy and renal arteriolar hyalinosis in patients with CKD.[27] The results from the present study and the prior cross-sectional studies suggest that short-term BPV might have potential pathophysiological relevance with respect to CKD progression. However, to the best of our knowledge, there have been minimal longitudinal cohort data regarding the relationship between short-term BPV and renal outcome. Recently, one study from Italy, which enrolled 465 nondialysis patients with CKD, showed that short-term BPV did

Table 5. Multivariate Cox Regression Analysis of the Association of Categorized w-SD With Renal Outcome

	Unadjusted	Model 1	Model 2	Model 3	Model 4
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
w-SD					
Quartile 1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quartile 2	1.19 (0.80–1.78)	1.26 (0.84–1.89)	1.26 (0.84–1.90)	1.25 (0.83–1.88)	1.25 (0.83–1.88)
Quartile 3	1.33 (0.90–1.96)	1.16 (0.78–1.73)	1.18 (0.79–1.77)	1.13 (0.75–1.70)	1.13 (0.75–1.71)
Quartile 4	1.85 (1.28–2.66)	1.60 (1.08–2.36)	1.64 (1.10–2.45)	1.55 (1.03–2.33)	1.56 (1.04–2.33)
24-h SBP (per 10 mm Hg)	1.29 (1.22–1.38)	…	0.98 (0.90–1.07)	…	…
Daytime SBP (per 10 mm Hg)	1.29 (1.21–1.37)	…	…	1.02 (0.94–1.10)	…
Nighttime SBP (per 10 mm Hg)	1.27 (1.20–1.35)	…	…	…	1.02 (0.94–1.10)
Age	1.00 (0.99–1.01)	0.97 (0.96–0.99)	0.97 (0.96–0.98)	0.97 (0.96–0.99)	0.97 (0.96–0.99)
Sex (male vs female)	1.32 (1.01–1.71)	1.74 (1.21–2.50)	1.75 (1.21–2.53)	1.73 (1.20–2.49)	1.73 (1.20–2.50)
BMI	0.96 (0.93–1.00)	0.99 (0.95–1.02)	0.97 (0.95–1.02)	0.98 (0.95–1.02)	0.98 (0.95–1.02)
Smoker	1.45 (1.12–1.88)	1.07 (0.76–1.51)	1.07 (0.77–1.52)	1.07 (0.75–1.51)	1.07 (0.75–1.51)
DM	1.98 (1.48–2.64)	1.32 (0.94–1.85)	1.33 (0.95–1.87)	1.31 (0.94–1.84)	1.30 (0.93–1.83)
History of CVD	1.17 (0.82–1.68)	0.97 (0.66–1.44)	0.97 (0.66–1.44)	0.97 (0.65–1.44)	0.97 (0.65–1.43)
Antihypertensive treatment	2.30 (1.50–3.51)	1.32 (0.85–2.06)	1.33 (0.85–2.07)	1.32 (0.85–2.06)	1.32 (0.84–2.05)
Dyslipidemia	1.02 (0.63–1.64)	0.92 (0.56–1.54)	0.93 (0.56–1.55)	0.92 (0.55–1.53)	0.92 (0.55–1.53)
Serum albumin	0.95 (0.94–0.97)	0.96 (0.94–0.99)	0.96 (0.94–0.99)	0.97 (0.94–0.99)	0.97 (0.94–0.99)
Anemia	3.84 (2.89–5.11)	1.94 (1.41–2.68)	1.94 (1.41–2.67)	1.94 (1.41–2.67)	1.94 (1.41–2.67)
Log-transformed 24-h proteinuria	4.43 (3.42–5.75)	2.10 (1.49–2.94)	2.11 (1.50–2.96)	2.08 (1.48–2.92)	2.08 (1.48–2.92)
eGFR	0.93 (0.92–0.94)	0.93 (0.92–0.94)	0.93 (0.92–0.94)	0.93 (0.92–0.94)	0.93 (0.92–0.94)
Dipper	0.71 (0.52–0.97)	0.92 (0.67–1.28)	0.91 (0.66–1.27)	0.91 (0.65–1.27)	0.94 (0.66–1.33)

Model 1: adjusted for age and sex, smoking, body mass index (BMI), diabetes mellitus (DM), history of cardiovascular disease (CVD), antihypertensive treatment, serum albumin, anemia, dyslipidemia, dipper, log-transformed 24-hour proteinuria, and estimated glomerular filtration rate (eGFR). Model 2: model 1+24-hour systolic blood pressure (SBP). Model 3: model 1+daytime SBP. Model 4: model 1+nighttime SBP. HR indicates hazard ratio; quartile 1, patients with weighted SD of SBP (w-SD) <9.6 mm Hg; quartile 2, patients with w-SD ≥9.6 mm Hg and w-SD<11.6 mm Hg; quartile 3, patients with w-SD ≥11.6 mm Hg and w-SD <15.1 mm Hg; and quartile 4, patients with w-SD≥15.1 mm Hg.

not predict the risk of rapid CKD progression, defined as dialysis or transplantation or at least 50% decline in eGFR.[15] Considering these findings, we analyzed data from our CKD cohort study with a follow-up design to determine whether short-term BPV is implicated in the progression of CKD. w-SD was selected as an indicator for short-term BPV in the present study, based on its ability to reduce the confounding effects of day-night BP fluctuations.[19] Renal outcomes were defined as dialysis initiation and/or transplantation. We found that w-SD, both as a continuous variable and as a categorical variable, was positively associated with renal outcomes in the present study. The discrepant results between the Italian study and the present study might be related to different patient characteristics in each cohort, such as participant ethnicity and baseline characteristics (eg, age, eGFR, proteinuria, and history of CVD), as well as causes of CKD. For instance, most participants in the Italian cohort exhibited hypertensive nephropathy, while most of our patients exhibited chronic glomerulonephritis. However, because of its large sample size and long follow-up period, we consider our results to be strong support for the notion that short-term BPV can serve as an independent predictor of CKD progression. Meanwhile, the current study is an observational cohort study. The causal relationship still could not be fully derived based on the nature of the current study, although important risk factors for end-stage renal disease such as age and eGFR have been adjusted. Further studies are needed to validate the association and identify the underlying mechanisms.

In this study, we also analyzed clinical factors that were associated with short-term BPV. The observed associations between dipper status and w-SD, as well as between angiotensin II receptor blocker treatment and w-SD, were novel and potentially useful. The proportion of dipper patients progressively increased with the quartiles of w-SD in the present study. Increased salt excretion during the night, overactivation of the

sympathetic and renin–angiotensin systems during the night, and sleeping disturbance are common symptoms in patients with CKD.[28,29] These factors, either alone or in combination, reduce the occurrence of nocturnal BP dipping, which might lead to reduction of short-term BPV. In the present study, nondippers had lower w-SD compared with dippers. This appears to be paradoxical, because nondipper status was presumed to be associated with renal progression in patients with CKD. However, BP rhythm is not necessarily associated with BP values. We noticed that the hypertension burden, in addition to the proportion of dipper patients, also increased with the quartiles of w-SD in the present study. Several recent studies have shown that the hypertension burden, rather than the BP rhythm alone, was implicated in renal outcomes in patients with CKD.[30,31]With respect to antihypertensive drug therapy, the unique pharmacokinetics and pharmacodynamics of each drug class, as well as the timing of administration, may also contribute to BP fluctuation.[32]

Our study had a few notable strengths. First, the source of the data, C-STRIDE, was a large, multicenter, prospective cohort study of participants with various CKD causes and comorbidities, which was generally representative of Chinese patients with CKD. Second, individuals were followed up regularly to ascertain the occurrence of end point events (ie, outcomes). However, our analysis also had several limitations. First, some of the participants were excluded from this analysis because of incomplete ABPM data necessary to calculate w-SD, which may have contributed to selection bias. However, the enrolled patients were younger, included a low proportion of smokers, and had a high level of albumin, a low level of serum lipids, and low clinic SBP, compared with patients who were excluded, which meant lower risk of CKD progression. Second, although our multivariable analyses included careful adjustment for covariates, we could not exclude the possibility of residual confounding by other unrecorded covariates that were not identified. Third, a single instance of ABPM was performed for each enrolled patient without longitudinal measurement. The differing sampling rates between diurnal and nocturnal with overall 70% successful recordings may presumably allow for more unsuccessful measurement during sleep. All of these might have introduced bias into the calculation of w-SD. Finally, only Chinese patients with CKD were included in the analysis, which reduces the generalizability of our findings. Because of these limitations, our findings should be confirmed in additional independent studies.

CONCLUSIONS

Our findings suggest that short-term systolic BPV was significantly associated with renal outcomes, independent of mean SBP level, in patients with CKD. If these results are confirmed in future studies, evaluations and interventions regarding short-term BPV should be included in the management of patients with CKD. Such changes may slow the progression of renal disease in these patients.

APPENDIX

C-STRIDE Collaborators

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ARTICLE INFORMATION

Received January 5, 2020; accepted April 28, 2020.

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Acknowledgments

The authors would like to express gratitude to every participant and member of the C-STRIDE group for their collaboration. We thank Ryan Chastain-Gross, PhD, from Liwen Bianji, Edanz Group China (www.liwenbianji.cn/ac), for editing the English text of a draft of this article.

Sources of Funding

The study is supported by grants from the Research Special Fund for Public Welfare Industry of Health from the National Health and Family Planning Commission of the People's Republic of China (No. 201002010); the National Key Technology R&D Program of the Ministry of Science and Technology (No. 2011BAI10B01); and the Establishment of Early Diagnosis Pathway and Model for Evaluating Progression of Chronic Kidney Disease (No. D131100004713007) from the Beijing Science and Technology Committee.

Disclosures

None.

Supplementary Materials

Tables S1–S4

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SUPPLEMENTAL MATERIAL

Table S1. Comparison of baseline characteristics between included and excluded participants in the current study.

	Total (N=3700)	Excluded cases (N=2279)	Included cases (N=1421)	*P*
Age, years	49.94±14.30	50.3±14.7	49.3±13.6	0.04
Male, n(%)	2154(58.22%)	1356(59.5%)	798(56.2%)	0.05
Smokers, n(%)	1230(37.79%)	757(40.8%)	473(33.8%)	<0.001
DM, n(%)	772(24.07%)	487(23.7%)	285(24.7%)	0.52
CVD history, n(%)	345(9.32%)	201(8.8%)	144(10.1%)	0.18
Causes of CKD				0.08
DKD	457(13.97%)	277(14.8%)	180(12.9%)	
GN	1973(60.30%)	1138(60.8%)	835(59.7%)	
Others	842(25.73%)	457(24.5%)	385(27.4%)	
BMI, kg/m^2	24.56±3.62	24.5±3.5	24.7±3.9	0.35
ALB, g/L	38.7±7.3	38.4±7.5	39.3±7.0	0.001
FBG, mmol/L	5.0(4.5, 5.7)	5.0(4.5, 5.8)	5.0(4.5, 5.7)	0.94
HGB, g/L	126.7±22.9	127.3±23.3	126.0±22.2	0.12
TG, mmol/L	1.8(1.2, 2.5)	1.8(1.2, 2.6)	1.7(1.2, 2.4)	0.02
TC, mmol/L	4.7(3.9, 5.7)	4.8(4.0, 5.9)	4.7(3.8, 5.5)	0.002
HDLC, mmol/L	1.1(0.9, 1.3)	1.1(0.9, 1.3)	1.1(0.9, 1.3)	0.30
LDLC, mmol/L	2.6(2.1, 3.3)	2.6(2.1, 3.3)	2.6(2.1, 3.2)	0.31
eGFR, mL/min/1.73 m^2	49.84±30.26	49.4±30.8	50.5±29.3	0.26
CKD stages				0.54
1	494(13.35%)	302(13.2%)	192(13%)	

2	595(16.08%)	352(15.4%)	241(17.1%)	
3	1491(40.29%)	924(40.5%)	569(39.9%)	
4	1120(30.27%)	702(30.8%)	419(30%)	
Clinic SBP	130.4±17.9	131±18.2	129.2±17.3	0.04
Clinic DBP	80.6±10.9	80.6±11.1	80.5±10.6	0.84

DM: diabetes mellitus, CVD: cardiovascular disease, CKD: chronic kidney disease, DKD: diabetic Kidney Disease, GN: glomerulonephritis, BMI: Body mass index, ALB: serum albumin, FBG: fasting blood glucose, HGB: hemoglobin, TG: triglyceride, TC: total cholesterol, HDLC: high-density lipoprotein cholesterol, LDLC: low-density lipoprotein cholesterol, eGFR: estimated glomerular filtration rate.

Missing counts: Smoking 445, BMI 807, ALB 490, HGB 395, TG 732, TC 730, HDLC 835, LDLC 833, FBG-571, Diabetes 493, Causes of CKD 428, clinic SBP 558, clinic DBP 558.

Table S2. Multivariate Cox regression analysis of the association of diurnal and nocturnal SD with renal outcome

	unadjusted HR (95% CI)	Model 1HR (95%CI)	Model 2 HR (95%CI)	Model 3 HR (95%CI)	Model 4 HR (95%CI)
diurnal SD (per 10 mm Hg)	1.32(1.07, 1.63)	1.36(1.08, 1.72)	1.41(1.10, 1.81)	1.34(1.04, 1.73)	1.36(1.05, 1.74)
24h-SBP (per 10 mm Hg)	1.29(1.22, 1.38)	-	0.97(0.89, 1.06)	-	-
D-SBP (per 10 mm Hg)	1.29(1.21, 1.37)	-	-	1.01(0.94, 1.10)	-
N-SBP (per 10 mm Hg)	1.27(1.20, 1.35)	-	-	-	1.01(0.93, 1.09)
nocturnal SD (per 10 mm Hg)	1.29(1.00, 1.68)	1.18(0.89, 1.55)	1.18(0.89, 1.56)	1.14(0.85, 1.51)	1.15(0.86, 1.52)
24h-SBP (per 10 mm Hg)	1.29(1.22, 1.38)	-	1.00(0.92, 1.08)	-	-
D-SBP (per 10 mm Hg)	1.29(1.21, 1.37)	-	-	1.04(0.96, 1.12)	-
N-SBP (per 10 mm Hg)	1.27(1.20, 1.35)	-	-	-	1.03(0.96, 1.11)

Model 1: adjusted for age and gender, smoker, BMI, DM, history of CVD, anti-hypertensive treatment, ALB, anemia, dyslipidemia, dipper, lgUpro and eGFR

Model 2: model 1+ 24-h SBP

Model 3: model 1+ D-SBP

Model 4: model 1+ N-SBP

Table S3. Multivariate Cox regression analysis of the association of continuous w-SD with renal outcome in patients with complete data.

	unadjusted	Model 1	Model 2	Model 3	Model 4
	HR(95%CI)	HR(95%CI)	HR(95%CI)	HR(95%CI)	HR(95%CI)
w-SD (per 10 mm Hg)	1.66(1.17, 2.35)	1.56(1.07, 2.29)	1.61(1.07, 2.42)	1.50(1.00, 2.26)	1.56(1.04, 2.36)
24h-SBP(per 10 mm Hg)	1.28(1.18, 1.39)	-	0.98(0.88, 1.09)	-	-
D-SBP(per 10 mm Hg)	1.29(1.19, 1.40)	-	-	1.03(0.93, 1.13)	-
N-SBP(per 10 mm Hg)	1.24(1.16, 1.34)	-	-	-	1.00(0.91, 1.10)
Age	1.01(0.99, 1.02)	0.97(0.96, 0.99)	0.97(0.96, 0.99)	0.97(0.96, 0.99)	0.97(0.96, 0.99)
Gender(M vs W)	1.15(0.82, 1.61)	1.38(0.84, 2.28)	1.38(0.84, 2.29)	1.38(0.84, 2.28)	1.38(0.84, 2.28)
BMI	0.97(0.92, 1.01)	1.02(0.97, 1.06)	1.02(0.97, 1.06)	1.01(0.97, 1.06)	1.02(0.97, 1.06)
Smoker	1.38(0.99, 1.94)	1.42(0.89, 2.25)	1.42(0.89, 2.25)	1.40(0.88, 2.24)	1.42(0.89, 2.25)
DM	1.78(1.26, 2.52)	1.21(0.81, 1.82)	1.23(0.81, 1.86)	1.20(0.80, 1.81)	1.21(0.80, 1.83)
CVD history	1.27(0.82, 1.97)	0.97(0.60, 1.57)	0.97(0.60, 1.57)	0.96(0.60, 1.56)	0.97(0.60, 1.57)
Antihypertension Treatment	1.98(1.18, 3.33)	1.24(0.72, 2.14)	1.25(0.72, 2.17)	1.23(0.71, 2.12)	1.24(0.72, 2.14)
Dyslipidemia	1.12(0.66, 1.91)	1.39(0.77, 2.50)	1.40(0.78, 2.50)	1.39(0.77, 2.51)	1.39(0.77, 2.50)
ALB	0.95(0.93, 0.97)	0.93(0.91, 0.96)	0.93(0.91, 0.96)	0.93(0.91, 0.96)	0.93(0.91, 0.96)
Anemia	3.40(2.29, 5.04)	1.38(0.88, 2.15)	1.37(0.88, 2.14)	1.37(0.88, 2.14)	1.38(0.88, 2.15)
lgUpro	1.49(1.28, 1.72)	1.02(0.83, 1.25)	1.02(0.83, 1.25)	1.02(0.83, 1.25)	1.02(0.83, 1.25)

eGFR	0.93(0.91, 0.94)	0.92(0.91, 0.94)	0.92(0.91, 0.94)	0.92(0.91, 0.94)	0.92(0.91, 0.94)
Dipper	0.80(0.54, 1.20)	0.96(0.62, 1.49)	0.96(0.62, 1.48)	0.95(0.62, 1.47)	0.96(0.61, 1.51)

w-SD: weighted standard deviation of systolic BP, HR: hazard ratio, CI: confidence interval, 24-h SBP: 24-hour systolic blood pressure, D-SBP: daytime systolic blood pressure, N-SBP: nighttime systolic blood pressure, BMI: body-mass index DM: diabetes mellitus, CVD: cardiovascular disease, ALB: serum albumin, lgUpro: logarithm transformed 24-hour proteinuria, eGFR: estimated glomerular filtration rate

Model 1: adjusted for age and gender, smoker, BMI, DM, history of CVD, anti-hypertensive treatment, ALB, anemia, dyslipidemia, dipper, lgUpro and eGFR

Model 2: model 1+ 24-h SBP

Model 3: model 1+ D-SBP

Model 4: model 1+ N-SBP

Table S4. Multivariate Cox regression analysis of the association of categorized w-SD with renal outcome in patients with complete data

	unadjusted	Model 1	Model 2	Model 3	Model 4
	HR(95%CI)	HR(95%CI)	HR(95%CI)	HR(95%CI)	HR(95%CI)
w-SD					
Q1	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
Q2	1.29(0.75, 2.20)	1.47(0.84, 2.57)	1.47(0.84, 2.57)	1.46(0.84, 2.55)	1.47(0.84, 2.56)
Q3	1.44(0.85, 2.44)	1.39(0.81, 2.40)	1.40(0.81, 2.42)	1.33(0.77, 2.32)	1.37(0.79, 2.40)
Q4	2.10(1.29, 3.44)	1.95(1.14, 3.33)	1.96(1.14, 3.37)	1.86(1.08, 3.21)	1.92(1.11, 3.33)
24h-SBP(per 10 mm Hg)	1.28(1.18, 1.39)	-	1.00(0.90, 1.11)	-	-
D-SBP(per 10 mm Hg)	1.29(1.19, 1.40)	-	-	1.04(0.95, 1.14)	-
N-SBP(per 10 mm Hg)	1.24(1.16, 1.34)	-	-	-	1.01(0.92, 1.11)
Age	1.01(0.99, 1.02)	0.97(0.96, 0.99)	0.97(0.96, 0.99)	0.97(0.96, 0.99)	0.97(0.96, 0.99)
Gender(M vs W)	1.15(0.82, 1.61)	1.41(0.85, 2.33)	1.41(0.85, 2.34)	1.42(0.86, 2.35)	1.41(0.85, 2.34)
BMI	0.97(0.92, 1.01)	1.01(0.97, 1.06)	1.01(0.97, 1.06)	1.01(0.97, 1.06)	1.01(0.97, 1.06)
Smoker	1.38(0.99, 1.94)	1.38(0.87, 2.20)	1.38(0.87, 2.21)	1.36(0.86, 2.18)	1.38(0.87, 2.20)
DM	1.78(1.26, 2.52)	1.25(0.83, 1.87)	1.25(0.83, 1.89)	1.22(0.81, 1.84)	1.24(0.82, 1.87)
CVD history	1.27(0.82, 1.97)	0.95(0.58, 1.53)	0.95(0.58, 1.53)	0.94(0.58, 1.52)	0.94(0.58, 1.53)
Antihypertension Treatment	1.98(1.18, 3.33)	1.22(0.71, 2.10)	1.22(0.70, 2.11)	1.19(0.69, 2.06)	1.21(0.70, 2.09)

Dyslipidemia	1.12(0.66, 1.91)	1.39(0.78, 2.51)	1.40(0.78, 2.51)	1.40(0.78, 2.52)	1.39(0.77, 2.51)
ALB	0.95(0.93, 0.97)	0.93(0.91, 0.96)	0.93(0.91, 0.96)	0.93(0.91, 0.96)	0.93(0.91, 0.96)
Anemia	3.40(2.29, 5.04)	1.40(0.89, 2.19)	1.40(0.89, 2.19)	1.38(0.88, 2.17)	1.39(0.89, 2.18)
lgUpro	1.49(1.28, 1.72)	1.02(0.84, 1.25)	1.02(0.84, 1.25)	1.02(0.83, 1.25)	1.02(0.83, 1.25)
eGFR	0.93(0.91, 0.94)	0.92(0.91, 0.94)	0.92(0.91, 0.94)	0.92(0.91, 0.94)	0.92(0.91, 0.94)
Dipper	0.80(0.54, 1.20)	0.94(0.61, 1.46)	0.94(0.61, 1.46)	0.91(0.59, 1.43)	0.95(0.61, 1.49)

w-SD: weighted standard deviation of systolic BP, Q1: patients with w-SD<9.6 mm Hg, Q2: patients with w-SD≥9.6 mm Hg and w-SD<11.6 mm Hg, Q3: patients with w-SD≥11.6 mm Hg and w-SD<15.1 mm Hg, Q4: patients with w-SD≥15.1 mm Hg, HR: hazard ratio, CI: confidence interval, 24-h SBP: 24-hour systolic blood pressure, D-SBP: daytime systolic blood pressure, N-SBP: nighttime systolic blood pressure, BMI: body-mass index DM: diabetes mellitus, CVD: cardiovascular disease, ALB: serum albumin, lgUpro: logarithm transformed 24-hour proteinuria, eGFR: estimated glomerular filtration rate.

Model 1: adjusted for age and gender, smoker, BMI, DM, history of CVD, anti-hypertensive treatment, ALB, anemia, dyslipidemia, dipper, lgUpro and eGFR

Model 2: model 1+ 24-h SBP, Model 3: model 1+ D-SBP, Model 4: model 1+ N-SBP