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ORIGINAL RESEARCH

Association Between Systolic Blood Pressure Variability and Major Adverse Cardiovascular Events in Korean Patients With Chronic Kidney Disease: Findings From KNOW-CKD

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BACKGROUND: Whether visit-to-visit systolic blood pressure (SBP) variability can predict major adverse cardiovascular events (MACE) in patients with chronic kidney disease is unclear.

METHODS AND RESULTS: We investigated the relationship between SDs of visit-to-visit SBP variability during the first year of enrollment and MACE among 1575 participants from KNOW-CKD (Korean Cohort Study for Outcome in Patients With Chronic Kidney Disease). Participants were categorized into 3 groups according to tertiles of visit-to-visit SBP variability (SD). The study end point was MACE, defined as a composite of nonfatal myocardial infarction, unstable angina, revascularization, nonfatal stroke, hospitalization for heart failure, or cardiac death. During 6748 patient-years of follow-up (median, 4.2 years), MACE occurred in 64 participants (4.1%). Compared with the lowest tertile of visit-to-visit SBP variability (SD), the hazard ratios (HRs) for the middle and the highest tertile were 1.64 (95% CI, 0.80–3.36) and 2.23 (95% CI, 1.12–4.44), respectively, in a multivariable cause-specific hazard model. In addition, the HR associated with each 5-mm Hg increase in visit-to-visit SBP variability (SD) was 1.21 (95% CI, 1.01–1.45). This association was consistent in sensitivity analyses with 2 additional definitions of SBP variability determined by the coefficient of variation and variation independent of the mean. The corresponding HRs for the middle and highest tertiles were 2.11 (95% CI, 1.03–4.35) and 2.28 (95% CI, 1.12–4.63), respectively, in the analysis with the coefficient of variation and 1.76 (95% CI, 0.87–3.57) and 2.04 (95% CI, 1.03–4.03), respectively, with the variation independent of the mean.

CONCLUSIONS: Higher visit-to-visit SBP variability is associated with an increased risk of MACE in patients with chronic kidney disease.

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Key Words: blood pressure variability ■ cardiovascular events ■ chronic kidney disease

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CLINICAL PERSPECTIVE

What Is New?

- In this prospective cohort study including 1575 patients, higher systolic blood pressure variability during the first year of follow-up was associated with major adverse cardiovascular events in patients with chronic kidney disease.
- Analyses with 3 metrics of systolic blood pressure variability consistently showed that greater visit-to-visit systolic blood pressure variability was associated with a higher risk of major adverse cardiovascular events in patients with chronic kidney disease.

What Are the Clinical Implications?

- This study clarified the implication of fluctuations in systolic blood pressure from visit-to-visit in terms of major adverse cardiovascular events and highlights the importance of the long-term maintenance of stable blood pressure.

Nonstandard Abbreviations and Acronyms

CoV	coefficient of variation
CVE	cardiovascular event
KNOW-CKD	Korean Cohort Study for Outcomes in Patients With Chronic Kidney Disease
MACE	major adverse cardiovascular events
SBP	systolic blood pressure
VIM	variation independent of the mean

Hypertension is the most prevalent comorbidity in patients with chronic kidney disease (CKD).[1,2] Uncontrolled high blood pressure (BP) is the leading cause of vascular injury and can lead to end-organ damage, such as coronary artery disease, heart failure, stroke, CKD, and death.[3–6] Thus, in clinical practice, BP control with various interventions is at the forefront of preventing these complications.

To date, the majority of clinical trials or epidemiological studies have sought to find an optimal BP level itself associated with the lowest risk of hypertension-related adverse outcomes.[7,8] Accordingly, most guidelines recommend BP control with specific BP targets.[9–12] Recently, BP variability has received attention because it can have prognostic implications in addition to static BP. There has been emerging evidence that visit-to-visit BP variability is an independent risk factor for the development of incident CKD, cardiovascular events, and death.[13–15] Similar issues on BP variability have also been studied in patients with CKD, but the results have been inconsistent.[16–20] Notably, many patients with CKD show high BP fluctuation, and optimal BP control is difficult to achieve as kidney failure worsens.[21–23] In this regard, in-depth analyses with longitudinal BP measurements from contemporary and unbiased prospective cohorts comprising patients with CKD could be helpful to clarify the clinical meaning of visit-to-visit BP variability. With this background, we studied the association between visit-to-visit BP variability and major adverse cardiovascular events (MACE) among participants in KNOW-CKD (Korean Cohort Study for Outcome in Patients With CKD).

METHODS

Because of ethical issues and data protection regulations, data that support the findings of the present study cannot be made publicly available.

Study Participants and Design

KNOW-CKD is a nationwide, multicenter, and prospective cohort study (ClinicalTrials.gov identifier NCT01630486). We previously described the rationale, design, methods, and protocol summary of the cohort.[24] Nine tertiary-care hospitals across the nation participated and enrolled patients aged 20 to 75 years with CKD stages G1 to G5 without kidney replacement therapy between 2011 and 2016. All participants met the criteria for CKD suggested by the KDIGO (Kidney Disease: Improving Global Outcomes) guideline.[12] The exclusion criteria were as follows: (1) inability or unwillingness to provide written consent; (2) previous maintenance dialysis or organ transplantation; (3) heart failure (New York Heart Association functional class III or IV) or cirrhosis (Child-Pugh class II or III); (4) history of prior or current malignancy; (5) pregnancy; or (6) a single kidney caused by trauma or kidney donation. Among the 2238 participants recruited, we excluded 31 patients who did not have available outcome data and 439 patients who had missing data for BP measurements (n=374) or who had reached the prespecified outcomes (n=65) during the BP variability assessment period from baseline to year 1. We excluded an additional 193 patients who had missing values for other baseline covariates such as body mass index, albumin, low-density lipoprotein cholesterol, intact parathyroid hormone, high-sensitivity C-reactive protein, and urine protein to creatinine ratio. Therefore, 1575 patients were included in the final analysis (Figure S1). The study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the institutional review boards of the participating centers. All participants provided written informed consent.

Data Collection and Measurements

Baseline demographic data and medical history, including age, sex, smoking history, education, economic status, history of various comorbidities, and medications, were recorded at enrollment. Age-adjusted Charlson comorbidity index scores were also calculated at baseline using additional points added for age. Comorbidities were assessed at baseline based on self-reports and a review of medical records, including the current use of medication by trained nurses. We also recorded smoking history, which was classified into 2 categories: never or ever (current or former). Education level was divided into elementary school, middle to high school, and higher than college. Income level was divided into low (<$1250 per month), intermediate ($1250–3750 per month), and high (≥$3750 per month).

Blood samples were obtained after 8 hours of overnight fasting. Baseline laboratory measurements included hemoglobin, blood urea nitrogen, creatinine, total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, albumin, uric acid, calcium, phosphorous, parathyroid hormone, and high-sensitivity C-reactive protein. Serum creatinine was measured using an isotope-dilution mass spectrometry-tractable method, and the glomerular filtration rate was estimated using the CKD Epidemiology Collaboration (CKD-EPI) equation.[25] The spot urine protein to creatinine ratio was used for urinary protein excretion measurement.

Main Exposure of Interest

The exposure of interest was the visit-to-visit systolic BP (SBP) variability. As a measure of visit-to-visit SBP variability, we adopted the SD of 3 SBP readings measured at baseline, 6 months, and 12 months (Figure 1). BP measurements were performed in patients at every clinic visit after 5 minutes of rest in a seated position at the clinic office using an electronic sphygmomanometer. The mean of 3 BP readings was used as the BP value for each visit.[26] The participants were classified according to tertiles of visit-to-visit SBP variability (SD).

Among various metrics of SBP variability, we used visit-to-visit SBP variability (SD) for the primary analysis as the Akaike Information Criterion was lower compared with those of other metrics, suggesting that visit-to-visit SBP variability (SD) was the best fit for the analysis (Suppelmentary data, Table S1).

Study End Point

The primary outcome was MACE, defined as a composite of nonfatal myocardial infarction, unstable angina, revascularization, nonfatal stroke, heart failure, or cardiac death. Survival time was defined as the time from the year 1 visit to the development of the primary outcome. Noncardiac death or kidney failure with replacement therapy that occurred before reaching the primary outcome was regarded as a competing risk. All participants had been under close observation for the occurrence of any adverse events, and participants who reached the study end points were reported by each center. The KNOW-CKD investigators cross-checked all events to ensure accurate information on adverse outcomes. The study observation period ended on March 31, 2020.

Statistical Analysis

Continuous variables are presented as means with SDs for normally distributed data or as medians with interquartile ranges for skewed data. The normality of the parameters was assessed using the Kolmogorov-Smirnov test. Categorical variables are presented as the number of participants with a proportion. To investigate the association between visit-to-visit SBP variability and the primary outcome of interest, we used a cause-specific hazard model. In this model, competing events (noncardiac death or kidney failure with replacement therapy before the occurrence of the primary outcome) or censoring events (loss to follow-up) were censored at the time of death, initiation of renal replacement therapy, or the last visit. We then constructed subdistribution hazard models by Fine and Gray[27] to confirm the findings by cause-specific hazard models. The main difference between 2 competing risk models is that patients experiencing

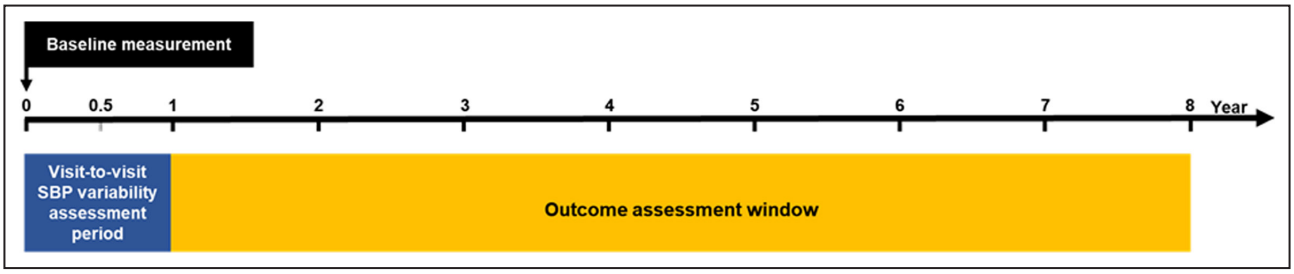

Figure 1. Study design and approach.
SBP indicates systolic blood pressure.

a competing risk event remain in the risk set in the subdistribution hazard model, whereas they are removed in the cause-specific hazard model.[28,29] Incremental adjustments were performed using the following variables. Model 1 represents an unadjusted model. Model 2 was adjusted for age, sex, body mass index, smoking history, diabetes, prior cardiovascular disease, and the average SBP of 3 readings during the first year (from baseline to year 1). We added baseline estimated glomerular filtration rate, serum albumin, low-density lipoprotein cholesterol, intact parathyroid hormone, high-sensitivity C-reactive protein, and urine protein to the creatinine ratio in model 3. In model 4, medications such as the number of antihypertensive drugs and statins were added. All covariates were selected based on the univariate analysis results with a *P* value <0.10 and covariates that are highly relevant to MACE. The results from multivariable hazard models were presented as hazard ratios (HRs) and 95% CIs. Cumulative incidence functions that take competing risk into account were used to derive adjusted cumulative incidence curves for tertiles of visit-to-visit SBP variability. We examined the effect modification of the association of visit-to-visit SBP variability with the primary outcome in prespecified subgroups by age (<60 years and ≥60 years), sex, average SBP (≤130 mm Hg and >130 mm Hg), body mass index (<25 kg/m^2 and ≥25 kg/m^2), diabetes (yes and no), cardiovascular disease (yes and no), estimated glomerular filtration rate (≥60 mL/min per 1.73 m^2 and <60 mL/min per 1.73 m^2), urine protein to creatinine ratio (<0.5 g/gCr and ≥0.5 g/gCr), renin-angiotensin system blocker use (yes and no), calcium channel blocker use (yes and no), and diuretics use (yes and no). For this subgroup analysis, visit-to-visit SBP variability was treated as a continuous variable. To confirm our findings, we performed several sensitivity analyses. First, we used 2 additional definitions of visit-to-visit SBP variability in the first year: the coefficient of variation (CoV), which is the SD divided by the average SBP, and variation independent of the mean (VIM), which is calculated by using a previously described formula.[14] Second, we further performed multiple imputation analysis in 1768 participants who were fit to analysis. To this end, chained equations were applied to fill in the 193 missing values of the baseline covariates. Third, we excluded patients with a history of cardiovascular disease and analyzed the association between visit-to-visit SBP variability (SD) and de novo MACE. Last, we additionally analyzed the association using visit-to-visit SBP variability (SD) with 4 SBP readings between baseline and year 2. Data were analyzed using Stata 15.1 (StataCorp LLC) and R (R Foundation for Statistical Computing), with a *P* value <0.05 considered significant.

RESULTS

Baseline Characteristics

Table 1 presents the baseline characteristics of the 1575 participants according to tertiles of visit-to-visit SBP variability (SD) within the first year of follow-up. The median number of visits per participant was 7 (interquartile range, 5–9). The mean age was 53.6 years (SD, 12.0 years), and 59.8% were men. The median estimated glomerular filtration rate was 48.5 mL/min per 1.73 m^2 (interquartile range, 31.2–76.4 mL/min per 1.73 m^2), and the median random urinary protein to creatinine ratio was 0.4 g/g (interquartile range, 0.1–1.2 g/g). A diagram showing the distribution of visit-to-visit SBP variability (SD) is presented in Figure S2. Overall, participants with a higher visit-to-visit SBP variability (SD) were older and more likely to have diabetes, had higher baseline and average SBP, used more antihypertensive drugs, and had lower kidney function. There were no significant differences in the proportion of patients with prior hypertension and those with renin-angiotensin system blocker use among tertiles.

SBP Variability According to CKD Grades

Table S2 presents 3 metrics of SBP variability according to CKD grades. The mean SBP variability during the first year, presented as SD was 9.54±6.22 mm Hg (CoV: 7.51%±4.77%; VIM: 9.52±6.05). Overall, participants with higher CKD grades were more likely to have greater SBP variability among the 3 metrics of SBP variability, such as SD, CoV, and VIM.

Association of Visit-to-visit SBP Variability (SD) Categories With the Risk of MACE

During 6748 patient-years of follow-up (median, 4.2 years), MACE occurred in 64 participants (4.1%), giving an incidence rate of 9.5 events per 1000 patient-years. Compared with the lowest tertile group with the lowest visit-to-visit SBP variability, the incidence rate of the primary outcome was incrementally higher in the middle and highest tertile groups (Table 2). The cumulative incidence curve also showed a similar pattern (*P*=0.012) (Figure 2).

Next, we investigated the association between visit-to-visit SBP variability (SD) and the risk of MACE using cause-specific hazard models. In the unadjusted model, the HRs for the risk of MACE were 1.89 (95% CI, 0.93–3.85) and 2.88 (95% CI, 1.48–5.62) for the middle and highest tertiles, respectively, compared with the lowest tertile (model 1 in Table 3). The association between visit-to-visit SBP variability (SD) and the primary outcome was maintained after adjusting for demographic factors, comorbidities, and laboratory

Table 1. Baseline Characteristics of the Participants According to Visit-to-visit SBP Variability (SD) for the First Year

	Total N=1575	Visit-to-visit SBP variability (SD), mm Hg		
		Low (≤6.08)	Middle (6.08–11.14)	High (>11.14)
		n=531	n=522	n=522
Age, y	53.6 (12.0)	53.5 (11.8)	52.7 (12.7)	54.8 (11.3)
Men, n (%)	942 (59.8)	314 (59.1)	322 (61.7)	306 (58.6)
BMI, kg/m^2	24.6 (3.3)	24.3 (3.3)	24.6 (3.4)	24.8 (3.3)
Smoking history, n (%)	720 (45.7)	230 (43.3)	236 (45.2)	254 (48.7)
Married, n (%)	1432 (90.9)	488 (91.9)	464 (88.9)	480 (92.0)
Education, n (%)				
Elementary	206 (13.1)	55 (10.4)	56 (10.7)	95 (18.2)
Middle–high school	730 (46.3)	232 (43.7)	231 (44.3)	267 (51.1)
College	639 (40.6)	244 (46.0)	235 (45.0)	160 (30.7)
Income, n (%)*				
High	374 (23.7)	131 (24.7)	132 (25.3)	111 (21.3)
Intermediate	823 (52.3)	301 (56.7)	268 (51.3)	254 (48.7)
Low	335 (21.3)	89 (16.8)	107 (20.5)	139 (26.6)
Baseline SBP, mm Hg	126.9 (15.3)	124.0 (10.6)	126.4 (14.0)	130.4 (19.3)
Baseline DBP, mm Hg	76.7 (10.8)	76.0 (9.2)	77.1 (10.5)	77.1 (12.5)
Average SBP†, mm Hg	126.6 (11.6)	124.0 (10.2)	126.1 (11.4)	129.6 (12.4)
Average DBP†, mm Hg	76.8 (8.4)	76.1 (7.8)	77.0 (8.4)	77.3 (8.9)
eGFR, mL/min per 1.73 m^2	48.5 [31.2–76.4]	51.1 [32.4–82.2]	50.4 [31.8–78.8]	44.2 [29.2–68.1]
Hemoglobin, g/dL	13.0 (2.0)	13.2 (1.9)	13.1 (1.9)	12.7 (2.0)
Albumin, g/dL	4.2 (0.4)	4.3 (0.4)	4.2 (0.4)	4.2 (0.4)
Calcium, mg/dL	9.2 (0.5)	9.2 (0.5)	9.2 (0.5)	9.1 (0.5)
Phosphate, mg/dL	3.6 (0.6)	3.6 (0.6)	3.6 (0.6)	3.7 (0.6)
Total cholesterol, mg/dL	173.7 (37.4)	173.5 (37.3)	174.0 (36.8)	173.5 (38.1)
LDL-C, mg/dL	96.5 (30.5)	96.4 (30.6)	96.8 (31.1)	96.2 (29.9)
HDL-C, mg/dL	49.7 (15.4)	50.3 (14.4)	49.6 (15.7)	49.1 (16.1)
Triglyceride, mg/dL	132 [92–191]	125 [90–190]	138 [91–184]	134 [94–196]
hs-CRP, mg/L	0.6 [0.2–1.6]	0.6 [0.2–1.4]	0.6 [0.2–1.7]	0.7 [0.3–1.7]
Intact PTH, pg/mL	48.7 [32.6–77.1]	48.0 [31.0–74.6]	48.0 [32.0–77.0]	51.0 [34.0–79.0]
UPCR, g/g	0.4 [0.1–1.2]	0.3 [0.1–0.9]	0.4 [0.1–1.2]	0.6 [0.2–1.7]
Primary renal disease, n (%)				
Diabetic nephropathy	362 (23.0)	82 (15.4)	106 (20.3)	174 (33.3)
Hypertension	306 (19.4)	109 (20.5)	106 (20.3)	91 (17.4)
Glomerulonephritis	519 (33.0)	196 (36.9)	172 (33.0)	151 (28.9)
Polycystic kidney disease	283 (18.0)	102 (19.2)	104 (19.9)	77 (14.8)
Others	105 (6.7)	42 (7.9)	34 (6.5)	29 (5.6)
Age-adjusted CCI	3.3 (2.2)	3.0 (2.1)	3.2 (2.2)	3.7 (2.1)
Hypertension, n (%)	1517 (96.3)	512 (96.4)	500 (95.8)	505 (96.7)
Diabetes, n (%)	505 (32.1)	130 (24.5)	145 (27.8)	230 (44.1)
Cardiovascular disease, n (%)	182 (11.6)	52 (9.8)	66 (12.6)	64 (12.3)
No. of antihypertensive drugs	1.9 (1.2)	1.7 (1.1)	1.8 (1.2)	2.0 (1.3)
ARBs/ACEIs, n (%)	1359 (86.3)	453 (85.3)	455 (87.2)	451 (86.4)
β-blockers, n (%)	386 (24.5)	107 (20.2)	137 (26.2)	142 (27.2)
DCCBs, n (%)	644 (40.9)	207 (39.0)	200 (38.3)	237 (45.4)
NDCCBs, n (%)	35 (2.2)	12 (2.3)	9 (1.7)	14 (2.7)

Table 1. (Continued)

	Total N=1575	Visit-to-visit SBP variability (SD), mm Hg		
		Low (≤6.08)	Middle (6.08–11.14)	High (>11.14)
		n=531	n=522	n=522
Diuretics, n (%)	460 (29.2)	137 (25.8)	155 (29.7)	168 (32.2)
Statins, n (%)	822 (52.2)	265 (49.9)	270 (51.7)	287 (55.0)

Data are expressed as mean (SD), median [interquartile range], or count (percentage). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; DBP, diastolic blood pressure; DCCB, dihydropyridine calcium channel blocker; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; NDCCB, nondihydropyridine calcium channel blocker; PTH, parathyroid hormone; SBP, systolic blood pressure; and UPCR, urine protein to creatinine ratio.

*Income data were missing for 2.7% of participants.

†Average blood pressure values calculated from 3 blood pressure readings measured at baseline, 6 months, and 12 months.

parameters (models 2 and 3 in Table 3). Further adjustment of medications did not change the graded relationship between visit-to-visit SBP variability and the risk of MACE. The corresponding HRs for the middle and highest tertiles were 1.64 (95% CI, 0.80–3.36) and 2.23 (95% CI, 1.12–4.44), respectively (model 4 in Table 3). In continuous modeling, a 5-mm Hg increase in visit-to-visit SBP variability (SD) was associated with a 1.21-fold (95% CI, 1.01–1.45) higher risk of MACE (Table 3).

We confirmed this association using an additional competing risk model. The subdistribution HR for the highest tertile of visit-to-visit SBP variability (SD) was 2.21 (95% CI, 1.09–4.50) compared with the lowest tertile (Table S3).

Sensitivity Analysis

In sensitivity analyses, we used different definitions of visit-to-visit SBP variability with the CoV or VIM of 3 SBP readings during the first year of follow-up in the same manner as mentioned above. Baseline characteristics of participants with a higher visit-to-visit SBP variability (CoV or VIM) were similar to those of participants with a higher visit-to-visit SBP variability (SD) (Table S4 and S5). The cumulative incidence curve of CoV and VIM showed a comparable pattern with that of SD (P=0.013 and P=0.028, respectively) (Figure S3). In agreement with the primary analyses with visit-to-visit SBP variability (SD), we found a consistent association between higher SBP variability and an increased risk of MACE. In the analyses with the CoV, the HRs were 2.11 (95% CI, 1.03–4.35)

Table 2. MACE According to the Visit-to-visit SBP Variability (SD)

Outcomes	Overall	Visit-to-visit SBP variability (SD), mm Hg			*P* value*
		Low (≤6.08)	Middle (6.08–11.14)	High (>11.14)	
No. of patients	1575	531	522	522	
Patient-year	6748.2	2381.0	2225.6	2141.6	
MACE					
Events	64	12	21	31	
Events per 1000 patient-year	9.5	5.0	9.4	14.5	0.005
Nonfatal MI, unstable angina, and revascularization					
Events	32	6	9	17	
Events per 1000 patient-year	4.7	2.5	4.0	7.9	0.024
Nonfatal stroke					
Events	19	2	9	8	
Events per 1000 patient-year	2.8	0.8	4.0	3.7	0.079
Hospitalization for heart failure					
Events	3	1	1	1	
Events per 1000 patient-year	0.4	0.4	0.4	0.5	0.997
Death from cardiovascular cause					
Events	10	3	2	5	
Events per 1000 patient-year	1.5	1.3	0.9	2.3	0.453

MACE indicates major adverse cardiovascular events; MI, myocardial infarction; and SBP, systolic blood pressure.

**P* value based on log-rank test.

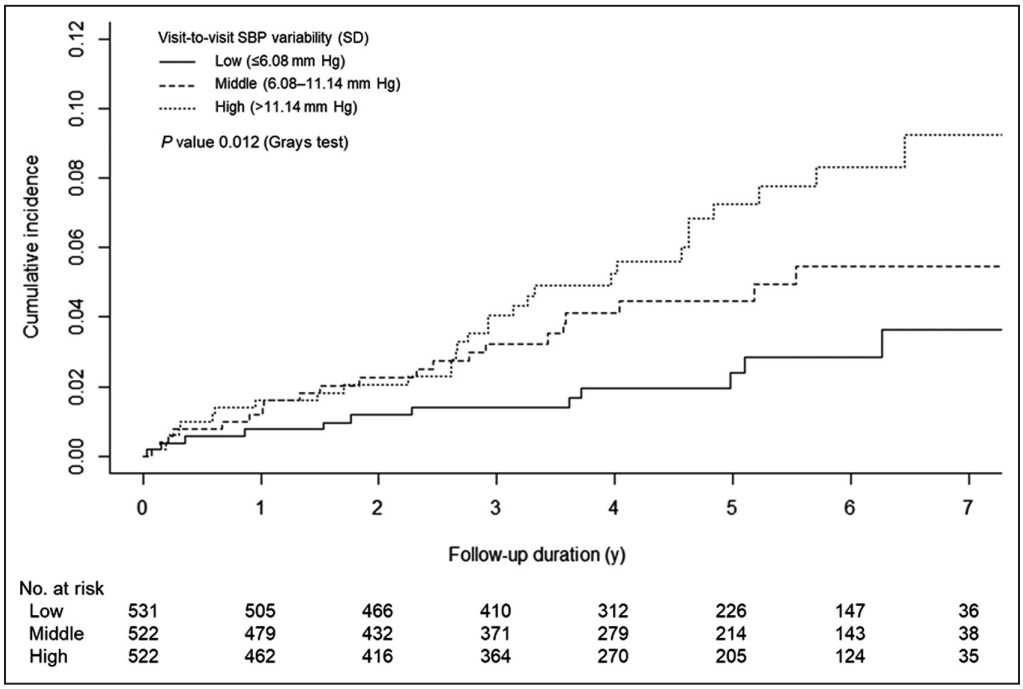

Figure 2. Cumulative incidence function of major adverse cardiovascular events (MACE) according to visit-to-visit systolic blood pressure (SBP) variability (SD) for the first year.
MACE occurred more as the first-year visit-to-visit SBP variability (SD) was higher.

and 2.28 (95% CI, 1.12–4.63) for the middle and highest tertiles, respectively, compared with the lowest tertile (Table S6). Additional analyses using the VIM also showed similar results. The highest tertile of the VIM was associated with a 2.04-fold (95% CI, 1.03–4.03) higher risk of MACE (Table S7). When these metrics were treated as continuous variables, the corresponding HR per 5% CoV increase was 1.28 (95% CI, 1.01–1.61) and that per 5 VIM increase was 1.21 (95% CI, 1.01–1.45) (Table S6 and S7). To prove our findings, we performed additional analyses using a multiple imputation method. After 193 missing values of baseline covariates were imputed, we analyzed 1768 patients and found the consistent association between visit-to-visit SBP variability (SD) and increased risk of MACE (Table S8). Moreover, we evaluated the association between visit-to-visit SBP variability (SD) and de novo MACE excluding patients with prior cardiovascular disease. The results showed that the highest tertile of SD was associated with a significantly higher risk of MACE compared with lowest tertile (HR, 3.10; CI, 1.12–8.56) (Table S9). To substantiate our findings, we used visit-to-visit SBP variability (SD) during the first 2 years and found a graded relationship between this SBP variability (SD) metric and the risk of MACE (Table S10).

Table 3. Cause-specific HRs for MACE According to the Visit-to-visit SBP Variability (SD)

Visit-to-visit SBP variability (SD), mm Hg	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
SBP variability tertiles								
Low (≤6.08)	1.00	…	1.00	…	1.00	…	1.00	…
Middle (6.08–11.14)	1.89 (0.93–3.85)	0.078	1.69 (0.83–3.45)	0.122	1.64 (0.80–3.36)	0.178	1.64 (0.80–3.36)	0.179
High (>11.14)	2.88 (1.48–5.62)	0.002	2.40 (1.22–4.75)	0.012	2.22 (1.12–4.41)	0.023	2.23 (1.12–4.44)	0.022
SBP variability continuous modeling								
Per 5-mm Hg increase	1.28 (1.09–1.50)	0.002	1.23 (1.03–1.48)	0.022	1.20 (1.00–1.44)	0.049	1.21 (1.01–1.45)	0.045

CI indicates confidence interval; HR, hazard ratio; and MACE, major adverse cardiovascular events.
Model 1: unadjusted.
Model 2: adjusted for age, sex, body mass index, smoking history, diabetes, cardiovascular disease, and average systolic blood pressure.
Model 3: Model 2+baseline estimated glomerular filtration rate, serum albumin, low-density lipoprotein cholesterol, intact parathyroid hormone, high-sensitivity C-reactive protein, and urine protein to creatinine ratio.
Model 4: Model 3+number of antihypertensive drugs and statin use.

Subgroup Analyses

To evaluate the effect modification of subgroups on the relationship between visit-to-visit SBP variability (SD) and MACE, we tested the interactions among subgroups according to age, sex, the average SBP during the first year, body mass index, diabetes, cardiovascular disease, estimated glomerular filtration rate, proteinuria, renin-angiotensin system blocker use, calcium channel blocker use, and diuretics use (Figure S4). The *P* values for all of these interactions were >0.05, suggesting a significant relationship between SBP variability and the risk of MACE among the aforementioned subgroups.

DISCUSSION

In this study, a higher visit-to-visit SBP variability was associated with a significantly increased risk of MACE in Korean patients with CKD. We showed this consistent association using 3 measures of visit-to-visit SBP variability: SD, CoV, and VIM. Moreover, this association was not affected by the initial average SBP or baseline kidney function. Our findings highlight the clinical importance of SBP variability and suggest that this BP metric can be used as a predictor of cardiovascular disease in patients with CKD.

In general, interventional randomized controlled trials are considered ideal for testing the effect of BP control on adverse clinical outcomes. Throughout the study period, the BP level should be maintained at a specific target range. However, in real-world practice, BP fluctuations are common, and a constant BP level is often difficult to achieve. This phenomenon is well reflected in observational cohort studies. Thus, many analytical approaches have been developed to account for changes in BP during follow-up, such as time-varying models and marginal structural models. We recently showed that time-updated BPs were more strongly associated with adverse cardiovascular and kidney outcomes than baseline static BP.[4,30,31] In addition to these BP metrics, the clinical significance of BP variability has been examined in various clinical settings. Conventionally, office BP is known to vary from visit to visit and this variation has been reported to be caused by random variation or measurement errors.[22,32,33] For this reason, BP variability has rarely been considered an informative measure for predicting clinical outcomes. However, recent studies revealed that the variability in BP measurements was indeed reproducible and was not merely a random phenomenon.[34–36] Furthermore, BP variability is associated with measures of impaired BP control, such as postural instability and sympathetic overactivity.[14,37] These findings suggest that BP variability can provide additional hemodynamic status of the cardiovascular system and thus provide prognostic information.

Accumulating evidence indicates that increased visit-to-visit BP variability is associated with adverse cardiovascular outcomes independent of the BP level and other conventional cardiovascular risk factors. However, studies on this issue involving patients with CKD are relatively scarce, and the clinical implication of BP variability has not yet been established in these patients. Mallamaci et al[17] first showed a significant association of visit-to-visit SBP variability with death and nonfatal cardiovascular events (CVEs) in an Italian cohort of patients with CKD stages G2 to G5. However, several studies that examined a similar issue showed inconsistent results.[20,35] In particular, Chang et al[35] failed to show a significant association of visit-to-visit BP variability with acute coronary syndrome and ischemic stroke in a large community-based cohort with CKD stages G3 to G4. The reason for these discrepancies is unclear; however, it may be attributed to differences in cohort characteristics, study design, main outcome of interest, and definitions of BP variability. Thus, our findings are noteworthy because we showed a consistent association between visit-to-visit SBP variability and the risk of MACE using different estimates of BP variability in a well-constructed longitudinal CKD cohort.

Although the causality between BP variability and the risk of CVEs is uncertain, several possible mechanisms for this association have been proposed. There is evidence that greater BP variability can contribute to endothelial dysfunction, atherogenesis, atheroma progression, and myocardial inflammation and remodeling.[38–41] In addition, greater BP variability is associated with greater arterial stiffness in a bidirectional manner.[42–44] It is well known that arterial stiffness is closely linked to many CVEs.[45] Such evidence can partly explain the significant association between visit-to-visit SBP variability and MACE in our study.

The strengths of our study are the inclusion of all CKD categories from G1 to G5, rigorous adjustment for potential confounders, and a meticulous statistical approach. The use of both continuous and categorical models with 3 metrics of BP variability, including SD, CoV, and VIM is another strong point because most previous studies used a single metric.

This study has several limitations. First, because of the observational design of the study, residual confounding may remain despite rigorous adjustment. Although our study has many strengths as a prospective cohort study with longitudinal data collection, we could not measure some other important cardiovascular risk factors such as physical activity. In addition, we cannot draw a solid conclusion given the uncertain causality between visit-to-visit SBP variability and MACE. Second, we used office BP at every clinic visit. Unfortunately, our study protocol did not include 24-hour ambulatory BP monitoring,

which can provide more information on diverse BP patterns including day-to-day BP variability. Thus, we could not evaluate the clinical significance of short-term BP variability. However, in a previous study by Mallamaci et al,[20] long-term visit-to-visit SBP variability was more strongly associated with the composite outcome of death or CVE than short-term BP variability determined by 24-hour BP monitoring. Third, BP variability is not easily implemented in clinical practice. However, studies supporting the merits of BP variability may provide insight into the potential hazards of greatly fluctuating BP, which is often encountered in daily practice. Hopefully, more advances in technology that can detect diverse BP patterns at every clinic visit will be made in electronic medical record systems in the future. Fourth, KNOW-CKD enrolled only Korean patients. Therefore, our study results cannot be extrapolated to patients with CKD of other diverse ethnic backgrounds.

In conclusion, our study revealed that visit-to-visit SBP variability was associated with the risk of MACE in the KNOW-CKD cohort. This association was found to be consistent with various metrics of SBP variability. Our findings suggest the limited value of a single BP reading as a prognostic indicator of the future risk of CVEs and emphasize the importance of long-term maintenance of stable BP in patients with CKD.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Appendix S1
Tables S1–S10
Figures S1–S4

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SUPPLEMENTAL MATERIAL

Appendix S1. KNOW-CKD Investigators

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Table S1. The Akaike information criterion (AIC) among the models

	AIC	Δ AIC
Base model	819.36	-
Base model + Visit-to-visit SBP variability (SD)	815.78	-3.58
Base model + Visit-to-visit SBP variability (CoV)	816.33	-3.03
Base model + Visit-to-visit SBP variability (VIM)	817.23	-2.13

The base model includes age, sex, BMI, smoking history, DM, cardiovascular disease, average SBP, baseline eGFR, serum albumin, LDL-C, intact PTH, hs-CRP, UPCR, number of antihypertensive drugs and statin use.

Abbreviations: AIC, Akaike information criterion; BMI, body mass index; CI, confidence interval; CoV, coefficient of variation; hs-CRP, high-sensitivity C-reactive protein; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; PTH, parathyroid hormone; SBP, systolic blood pressure; SD, standard deviation; UPCR, urine protein-to-creatinine ratio; VIM, variation independent of the mean.

Table S2. Visit-to-visit SBP Variability According to CKD Grades

Visit-to-visit SBP variability	Total =1,575	CKD Grade*				P-for-trend
		G1 N=266	G2 N=318	G3 N=631	G4–5 N=360	
SD, mmHg	9.54 (6.22)	8.35 (5.08)	9.04 (5.42)	9.90 (6.81)	10.23 (6.41)	<0.001
CoV, %	7.51 (4.77)	6.67 (4.05)	7.17 (4.20)	7.80 (5.17)	7.94 (4.94)	0.001
VIM	9.52 (6.05)	8.47 (5.18)	9.09 (5.33)	9.88 (6.53)	10.01 (6.26)	0.001

Data are expressed as a mean (SD).

* CKD grades; G1, eGFR ≥90 ml/min/1.73 m^2; G2, eGFR 60-89 ml/min/1.73 m^2; G3, eGFR 30-59 ml/min/1.73 m^2; G4, eGFR 15-29 ml/min/1.73 m^2; G5, eGFR <15 ml/min/1.73 m^2.

Abbreviations: CKD, chronic kidney disease; CoV, coefficient of variation; SD, standard deviation; VIM, variation independent of the mean.

Table S3. Association between Visit-to-visit SBP variability (SD) and MACE Using Fine and Gray Proportional Subdistribution Hazards Models with Non-cardiac Death or Kidney Failure with Replacement Therapy as a Competing Risk

Visit-to-visit SBP Variability (SD) (mmHg)	Model 1		Model 2		Model 3		Model 4	
	SHR (95% CI)	P-value	SHR (95% CI)	P-value	SHR (95% CI)	P-value	SHR (95% CI)	P-value
SBP variability tertiles								
Low (≤6.08)	1.00	-	1.00	-	1.00	-	1.00	-
Middle (6.08–11.14)	1.83 (0.90-3.72)	0.097	1.67 (0.81-3.47)	0.165	1.68 (0.80-3.50)	0.169	1.60 (0.76-3.35)	0.214
High (>11.14)	2.65 (1.36-5.15)	0.004	2.27 (1.13-4.58)	0.022	2.28 (1.12-4.61)	0.023	2.21 (1.09-4.50)	0.029
SBP variability continuous modeling								
per 5 mmHg increase	1.24 (1.09-1.41)	0.001	1.19 (1.01-1.39)	0.035	1.18 (1.01-1.39)	0.041	1.18 (1.01-1.39)	0.041

Model 1: unadjusted.

Model 2: adjusted for age, sex, BMI, smoking history, DM, cardiovascular disease, and average SBP.

Model 3: Model 2 + baseline eGFR, serum albumin, LDL-C, intact PTH, hs-CRP, and UPCR.

Model 4: Model 3 + number of antihypertensive drugs and statin use.

Abbreviations: BMI, body mass index; CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; PTH, parathyroid hormone; SBP, systolic blood pressure; SD, standard deviation; SHR, subdistribution hazard ratio; UPCR, urine protein-to-creatinine ratio.

Table S4. Baseline Characteristics of the Participants According to the Visit-to-visit SBP Variability (CoV) for the First Year

	Total, N=1,575	Visit-to-visit SBP Variability (CoV) (%)		
		Low (≤4.95) N=531	Middle (4.95–8.74) N=519	High (>8.74) N=525
Age, yr	53.6 (12.0)	53.7 (12.0)	52.5 (12.5)	54.6 (11.3)
Male, n(%)	942 (59.8)	315 (59.3)	323 (62.2)	304 (57.9)
BMI, kg/m^2	24.6 (3.3)	24.4 (3.3)	24.6 (3.4)	24.7 (3.3)
Smoking history, n(%)	720 (45.7)	228 (42.9)	237 (45.7)	255 (48.6)
Married, n(%)	1,432 (90.9)	488 (91.9)	460 (88.6)	484 (92.2)
Education, n(%)[a]				
Elementary	206 (13.1)	56 (10.5)	58 (11.2)	92 (17.5)
Middle–High school	730 (46.3)	233 (43.9)	231 (44.5)	266 (50.7)
College	639 (40.6)	242 (45.6)	230 (44.3)	167 (31.8)
Income, n(%)[*]				
High	374 (23.7)	131 (24.7)	135 (26.0)	108 (20.6)
Intermediate	823 (52.3)	297 (55.9)	260 (50.1)	266 (50.7)
Low	335 (21.3)	91 (17.1)	111 (21.4)	133 (25.3)
Baseline SBP, mmHg	126.9 (15.3)	125.5 (11.1)	127.2 (13.8)	128.0 (19.5)
Baseline DBP, mmHg	76.7 (10.8)	76.4 (9.3)	77.7 (10.6)	76.1 (12.3)
Average SBP[†], mmHg	126.6 (11.6)	125.5 (10.5)	127.0 (11.7)	127.3 (12.4)
Average DBP[†], mmHg	76.8 (8.4)	76.6 (8.0)	77.4 (8.4)	76.3 (8.7)
eGFR, mL/min per 1.73m^2	48.5 [31.2-76.4]	51.1 [31.7-81.0]	49.9 [31.5-77.3]	45.6 [30.1-69.8]
Hemoglobin, g/dL	13.0 (2.0)	13.1 (1.9)	13.1 (1.9)	12.7 (2.0)
Albumin, g/dL	4.2 (0.4)	4.3 (0.4)	4.2 (0.4)	4.2 (0.4)
Calcium, mg/dL	9.2 (0.5)	9.2 (0.5)	9.2 (0.5)	9.1 (0.5)
Phosphate, mg/dL	3.6 (0.6)	3.6 (0.6)	3.6 (0.6)	3.7 (0.6)
Total cholesterol, mg/dL	173.7 (37.4)	173.1 (36.1)	175.0 (38.2)	173.0 (37.9)
LDL cholesterol, mg/dL	96.5 (30.5)	96.4 (30.2)	96.5 (31.2)	96.4 (30.2)
HDL cholesterol, mg/dL	49.7 (15.4)	50.3 (14.5)	49.2 (15.1)	49.5 (16.6)
Triglyceride, mg/dL	132 [92-191]	125 [91-190]	140 [92-190]	131 [93-193]
hs-CRP, mg/L	0.6 [0.2-1.6]	0.6 [0.2-1.5]	0.6 [0.2-1.7]	0.6 [0.3-1.7]
PTH, pg/mL	48.7 [32.6-77.1]	48.4 [31.2-74.7]	48.9 [32.6-79.8]	48.7 [34.0-76.5]
UPCR, g/g	0.4 [0.1-1.2]	0.3 [0.1-0.9]	0.4 [0.1-1.2]	0.5 [0.2-1.6]
Primary renal disease, n(%)[a]				
Diabetic nephropathy	362 (23.0)	92 (17.3)	104 (20.0)	166 (31.6)
Hypertension	306 (19.4)	104 (19.6)	109 (21.0)	93 (17.7)
Glomerulonephritis	519 (33.0)	190 (35.8)	165 (31.8)	164 (31.2)
Polycystic kidney disease	283 (18.0)	105 (19.8)	103 (19.8)	75 (14.3)
Others	105 (6.7)	40 (7.5)	38 (7.3)	27 (5.1)
Age adjusted CCI	3.3 (2.2)	3.1 (2.1)	3.2 (2.2)	3.6 (2.1)
Hypertension, n(%)	1,517 (96.3)	514 (96.8)	499 (96.1)	504 (96.0)
Diabetes mellitus, n(%)	505 (32.1)	139 (26.2)	144 (27.7)	222 (42.3)
Cardiovascular disease, n(%)	182 (11.6)	52 (9.8)	67 (12.9)	63 (12.0)
No. of antihypertensive drugs	1.9 (1.2)	1.8 (1.1)	1.9 (1.2)	1.9 (1.3)
ARB/ACEI, n(%)	1,359 (86.3)	457 (86.1)	451 (86.9)	451 (85.9)
β-blockers, n(%)	386 (24.5)	116 (21.8)	138 (26.6)	132 (25.1)
DCCBs, n(%)	644 (40.9)	213 (40.1)	206 (39.7)	225 (42.9)
NDCCBs, n(%)	35 (2.2)	9 (1.7)	12 (2.3)	14 (2.7)
Diuretics, n(%)	460 (29.2)	144 (27.1)	148 (28.5)	168 (32.0)
Statins, n(%)	822 (52.2)	272 (51.2)	261 (50.3)	289 (55.0)

Data are expressed as mean (SD), median [interquartile range], or count (%).

* Income data were missing for 2.7% of participants.

† Average BP values calculated from three BP readings measured at baseline, six months, and 12 months.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CCI, Charlson comorbidity index; CoV, coefficient of variation; hs-CRP, high-sensitivity C-reactive protein; DBP, diastolic blood pressure; DCCB, dihydropyridine calcium channel blocker; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NDCCB, non-dihydropyridine calcium channel blocker; PTH, parathyroid hormone; SBP, systolic blood pressure; UPCR, urinary protein-creatinine ratio.

Table S5. Baseline Characteristics of the Participants According to the Visit-to-visit SBP Variability (VIM) for the First Year

	Total, N=1,575	Visit-to-visit SBP Variability (VIM)		
		Low (≤6.27) N=526	Middle (6.27–11.04) N=524	High (>11.04) N=525
Age, yr	53.6 (12.0)	53.7 (12.2)	52.7 (12.4)	54.5 (11.3)
Male, n(%)	942 (59.8)	314 (59.7)	325 (62.0)	303 (57.7)
BMI, kg/m^2	24.6 (3.3)	24.5 (3.3)	24.6 (3.4)	24.6 (3.3)
Smoking history, n(%)	720 (45.7)	228 (43.3)	236 (45.0)	256 (48.8)
Married, n(%)	1,432 (90.9)	482 (91.6)	467 (89.1)	483 (92.0)
Education, n(%)[a]				
Elementary	206 (13.1)	56 (10.6)	60 (11.5)	90 (17.1)
Middle–High school	730 (46.3)	230 (43.7)	235 (44.8)	265 (50.5)
College	639 (40.6)	240 (45.6)	229 (43.7)	170 (32.4)
Income, n(%)[*]				
High	374 (23.7)	132 (25.1)	134 (25.6)	108 (20.6)
Intermediate	823 (52.3)	290 (55.1)	269 (51.3)	264 (50.3)
Low	335 (21.3)	91 (17.3)	108 (20.6)	136 (25.9)
Baseline SBP, mmHg	126.9 (15.3)	126.3 (11.5)	127.1 (13.9)	127.3 (19.3)
Baseline DBP, mmHg	76.7 (10.8)	77.0 (9.9)	77.5 (10.1)	75.7 (12.2)
Average SBP[†], mmHg	126.6 (11.6)	126.3 (10.8)	126.8 (11.7)	126.6 (12.1)
Average DBP[†], mmHg	76.8 (8.4)	77.1 (8.3)	77.3 (8.2)	76.0 (8.6)
eGFR, mL/min per 1.73m^2	48.5 [31.2-76.4]	52.6 [31.8-82.4]	48.2 [31.4-76.5]	46.1 [30.3-69.8]
Hemoglobin, g/dL	13.0 (2.0)	13.2 (1.9)	13.1 (1.9)	12.7 (2.0)
Albumin, g/dL	4.2 (0.4)	4.3 (0.4)	4.2 (0.4)	4.2 (0.4)
Calcium, mg/dL	9.2 (0.5)	9.2 (0.5)	9.2 (0.5)	9.1 (0.5)
Phosphate, mg/dL	3.6 (0.6)	3.6 (0.6)	3.6 (0.6)	3.7 (0.6)
Total cholesterol, mg/dL	173.7 (37.4)	174.0 (36.0)	174.4 (39.1)	172.7 (37.0)
LDL cholesterol, mg/dL	96.5 (30.5)	97.0 (30.0)	96.0 (31.6)	96.4 (30.0)
HDL cholesterol, mg/dL	49.7 (15.4)	50.3 (14.5)	49.1 (14.9)	49.7 (16.8)
Triglyceride, mg/dL	132 [92-191]	128 [92-190]	139 [91-190]	131 [93-192]
hs-CRP, mg/L	0.6 [0.2-1.6]	0.6 [0.2-1.5]	0.6 [0.2-1.7]	0.6 [0.3-1.6]
PTH, pg/mL	48.7 [32.6-77.1]	49.1 [31.4-75.4]	48.5 [32.1-78.3]	48.5 [33.7-76.5]
UPCR, g/g	0.4 [0.1-1.2]	0.3 [0.1-1.0]	0.4 [0.1-1.2]	0.5 [0.2-1.6]
Primary renal disease, n(%)[a]				
Diabetic nephropathy	362 (23.0)	91 (17.3)	106 (20.2)	165 (31.4)
Hypertension	306 (19.4)	105 (20.0)	108 (20.6)	93 (17.7)
Glomerulonephritis	519 (33.0)	185 (35.2)	169 (32.3)	165 (31.4)
Polycystic kidney disease	283 (18.0)	107 (20.3)	99 (18.9)	77 (14.7)
Others	105 (6.7)	38 (7.2)	42 (8.0)	25 (4.8)
Age adjusted CCI	3.3 (2.2)	3.1 (2.1)	3.2 (2.2)	3.6 (2.2)
Hypertension, n(%)	1,517 (96.3)	509 (96.8)	507 (96.8)	501 (95.4)
Diabetes mellitus, n(%)	505 (32.1)	138 (26.2)	148 (28.2)	219 (41.7)
Cardiovascular disease, n(%)	182 (11.6)	53 (10.1)	68 (13.0)	61 (11.6)
No. of antihypertensive drugs	1.9 (1.2)	1.8 (1.1)	1.9 (1.2)	1.9 (1.3)
ARB/ACEI, n(%)	1,359 (86.3)	451 (85.7)	459 (87.6)	449 (85.5)
β-blockers, n(%)	386 (24.5)	120 (22.8)	134 (25.6)	132 (25.1)
DCCBs, n(%)	644 (40.9)	215 (40.9)	205 (39.1)	224 (42.7)
NDCCBs, n(%)	35 (2.2)	9 (1.7)	12 (2.3)	14 (2.7)
Diuretics, n(%)	460 (29.2)	144 (27.4)	148 (28.2)	168 (32.0)
Statins, n(%)	822 (52.2)	267 (50.8)	269 (51.3)	286 (54.5)

Data are expressed as mean (SD), median [interquartile range], or count (%).

* Income data were missing for 2.7% of participants.

† Average BP values calculated from three BP readings measured at baseline, six months, and 12 months.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CCI, Charlson comorbidity index; hs-CRP, high-sensitivity C-reactive protein; DBP, diastolic blood pressure; DCCB, dihydropyridine calcium channel blocker; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NDCCB, non-dihydropyridine calcium channel blocker; PTH, parathyroid hormone; SBP, systolic blood pressure; UPCR, urinary protein-creatinine ratio; VIM, variation independent of the mean.

Table S6. Cause-specific Hazard Ratios for MACE According to the Visit-to-visit SBP Variability (CoV)

Visit-to-visit SBP Variability (CoV) (%)	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
SBP variability tertiles								
Low (≤4.95)	1.00	-	1.00	-	1.00	-	1.00	-
Middle (4.95–8.74)	2.32 (1.14-4.74)	0.021	2.18 (1.06-4.47)	0.034	2.13 (1.03-4.38)	0.041	2.11 (1.03-4.35)	0.042
High (>8.74)	2.88 (1.44-5.77)	0.003	2.45 (1.21-4.94)	0.012	2.28 (1.12-4.61)	0.022	2.28 (1.12-4.63)	0.022
SBP variability continuous modeling								
per 5% increase	1.38 (1.12-1.70)	0.002	1.32 (1.05-1.65)	0.016	1.27 (1.01-1.60)	0.041	1.28 (1.01-1.61)	0.038

Model 1: unadjusted.

Model 2: adjusted for age, sex, BMI, smoking history, DM, cardiovascular disease, and average SBP.

Model 3: Model 2 + baseline eGFR, serum albumin, LDL-C, intact PTH, hs-CRP, and UPCR.

Model 4: Model 3 + number of antihypertensive drugs and statin use.

Abbreviations: BMI, body mass index; CI, confidence interval; CoV, coefficient of variation; hs-CRP, high-sensitivity C-reactive protein; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; PTH, parathyroid hormone; SBP, systolic blood pressure; UPCR, urine protein-to-creatinine ratio.

Table S7. Cause-specific Hazard Ratios for MACE According to the Visit-to-visit SBP Variability (VIM)

Visit-to-visit SBP Variability (VIM)	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
SBP variability tertiles								
Low (≤6.27)	1.00	-	1.00	-	1.00	-	1.00	-
Middle (6.27–11.04)	1.97 (0.98-3.95)	0.058	1.82 (0.90-3.67)	0.096	1.77 (0.87-3.58)	0.114	1.76 (0.87-3.57)	0.115
High (>11.04)	2.59 (1.32-5.07)	0.006	2.19 (1.11-4.32)	0.024	2.03 (1.03-4.02)	0.042	2.04 (1.03-4.03)	0.041
SBP variability continuous modeling								
per 5 increase	1.29 (1.09-1.51)	0.003	1.25 (1.04-1.49)	0.015	1.21 (1.01-1.44)	0.040	1.21 (1.01-1.45)	0.037

Model 1: unadjusted.

Model 2: adjusted for age, sex, BMI, smoking history, DM, cardiovascular disease, and average SBP.

Model 3: Model 2 + baseline eGFR, serum albumin, LDL-C, intact PTH, hs-CRP, and UPCR.

Model 4: Model 3 + number of antihypertensive drugs and statin use.

Abbreviations: BMI, body mass index; CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; PTH, parathyroid hormone; SBP, systolic blood pressure; UPCR, urine protein-to-creatinine ratio; VIM, variation independent of the mean.

Table S8. Cause-specific Hazard Ratios for MACE According to the Visit-to-visit SBP Variability (SD) among 1,768 Patients Using Multiple Imputation

Visit-to-visit SBP Variability (SD) (mmHg)	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
SBP variability tertiles								
Low (≤6.08)	1.00	-	1.00	-	1.00	-	1.00	-
Middle (6.08–11.27)	1.78 (0.90-3.54)	0.098	1.67 (0.84-3.32)	0.146	1.66 (0.83-3.31)	0.151	1.66 (0.83-3.31)	0.153
High (>11.27)	2.88 (1.52-5.46)	0.001	2.34 (1.22-4.49)	0.011	2.19 (1.14-4.24)	0.019	2.22 (1.15-4.29)	0.018
SBP variability continuous modeling								
per 5 mmHg increase	1.27 (1.09-1.48)	0.003	1.19 (1.01-1.41)	0.040	1.18 (0.99-1.40)	0.058	1.19 (1.00-1.41)	0.045

Model 1: unadjusted.

Model 2: adjusted for age, sex, BMI, smoking history, DM, cardiovascular disease, and average SBP.

Model 3: Model 2 + baseline eGFR, serum albumin, LDL-C, intact PTH, hs-CRP, and UPCR.

Model 4: Model 3 + number of antihypertensive drugs and statin use.

Abbreviations: BMI, body mass index; CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; PTH, parathyroid hormone; SBP, systolic blood pressure; SD, standard deviation; UPCR, urine protein-to-creatinine ratio.

Table S9. Cause-specific Hazard Ratios for de novo MACE According to the Visit-to-visit SBP Variability (SD) among Patients without History of Cardiovascular Disease

Visit-to-visit SBP Variability (SD) (mmHg)	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
SBP variability tertiles								
Low (≤6.03)	1.00	-	1.00	-	1.00	-	1.00	-
Middle (6.03–11.02)	3.03 (1.09-8.42)	0.033	3.08 (1.11-8.59)	0.031	3.06 (1.10-8.55)	0.033	3.02 (1.08-8.42)	0.035
High (>11.02)	4.22 (1.58-11.31)	0.004	3.31 (1.21-9.07)	0.020	3.15 (1.14-8.71)	0.027	3.10 (1.12-8.56)	0.029
SBP variability continuous modeling								
per 5 mmHg increase	1.32 (1.09-1.62)	0.006	1.26 (1.01-1.56)	0.039	1.24 (1.00-1.54)	0.049	1.25 (1.00-1.56)	0.047

Model 1: unadjusted.

Model 2: adjusted for age, sex, BMI, smoking history, DM, and average SBP.

Model 3: Model 2 + baseline eGFR, serum albumin, LDL-C, intact PTH, hs-CRP, and UPCR.

Model 4: Model 3 + number of antihypertensive drugs and statin use.

Abbreviations: BMI, body mass index; CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; PTH, parathyroid hormone; SBP, systolic blood pressure; SD, standard deviation; UPCR, urine protein-to-creatinine ratio.

Table S10. Cause-specific Hazard Ratios for MACE According to the Visit-to-visit SBP Variability (SD) during the First Two Years

Visit-to-visit SBP Variability (SD) (mmHg)	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
SBP variability tertiles								
Low (≤6.85)	1.00	-	1.00	-	1.00	-	1.00	-
Middle (6.85–11.36)	1.64 (0.68-3.96)	0.269	1.74 (0.72-4.23)	0.219	1.76 (0.72-4.28)	0.214	1.74 (0.71-4.25)	0.222
High (>11.36)	3.91 (1.78-8.60)	0.001	3.38 (1.51-7.58)	0.003	3.14 (1.39-7.09)	0.006	3.15 (1.39-7.14)	0.006
SBP variability continuous modeling								
per 5 mmHg increase	1.44 (1.19-1.75)	<0.001	1.36 (1.10-1.68)	0.004	1.30 (1.05-1.61)	0.017	1.32 (1.06-1.64)	0.012

Model 1: unadjusted.

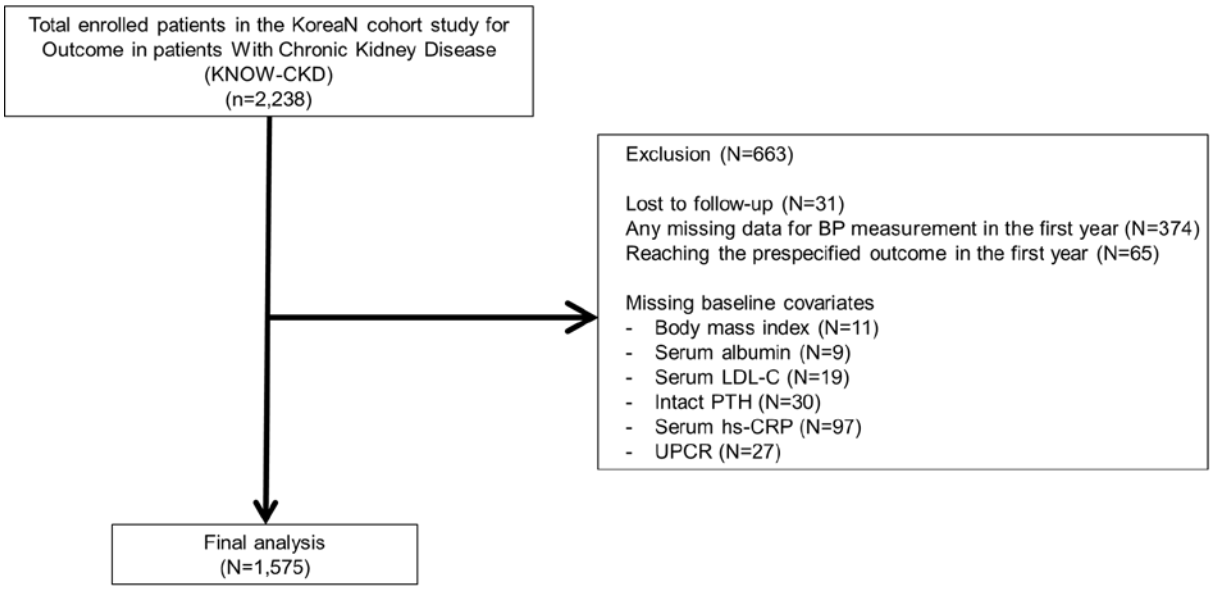
Model 2: adjusted for age, sex, BMI, smoking history, DM, cardiovascular disease, and average SBP.

Model 3: Model 2 + baseline eGFR, serum albumin, LDL-C, intact PTH, hs-CRP, and UPCR.

Model 4: Model 3 + number of antihypertensive drugs and statin use.

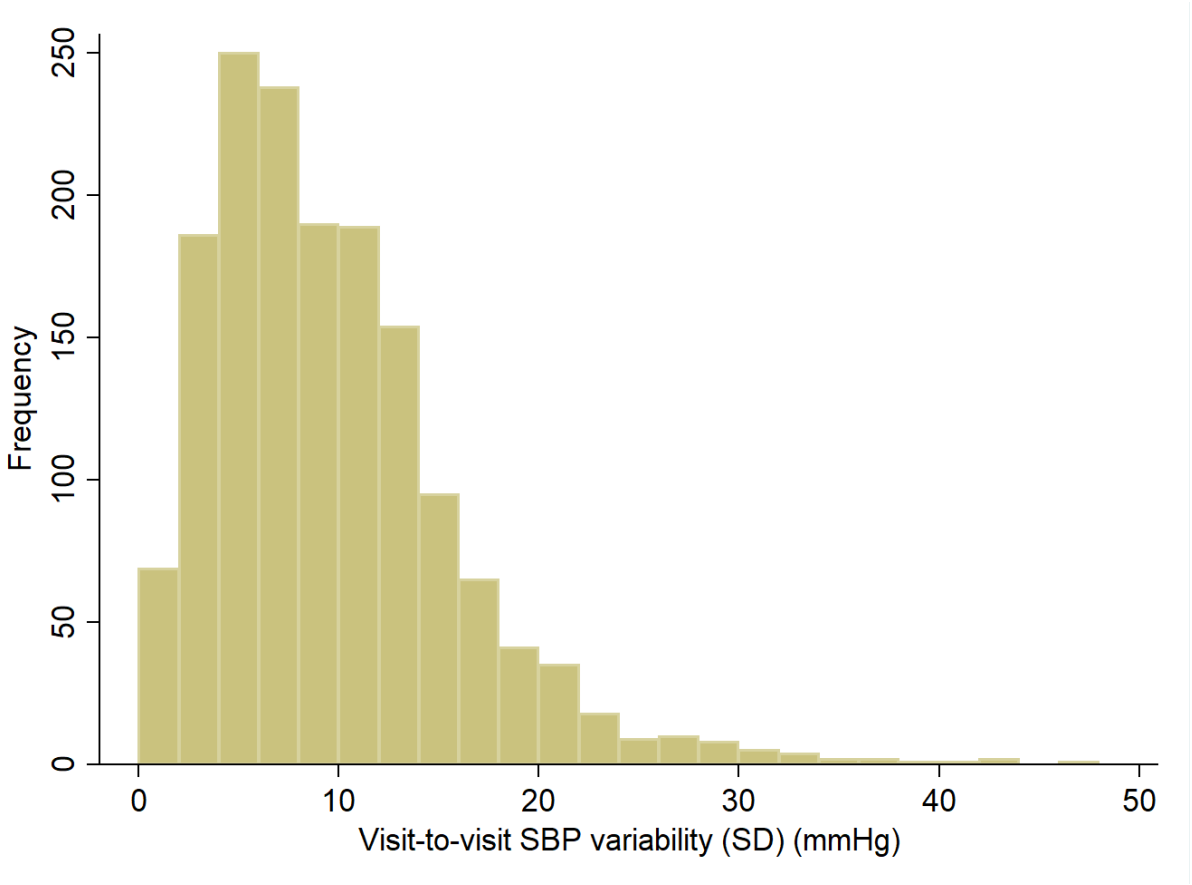
Abbreviations: BMI, body mass index; CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; PTH, parathyroid hormone; SBP, systolic blood pressure; SD, standard deviation; UPCR, urine protein-to-creatinine ratio.

Figure S1. Flow Diagram of Study Cohort



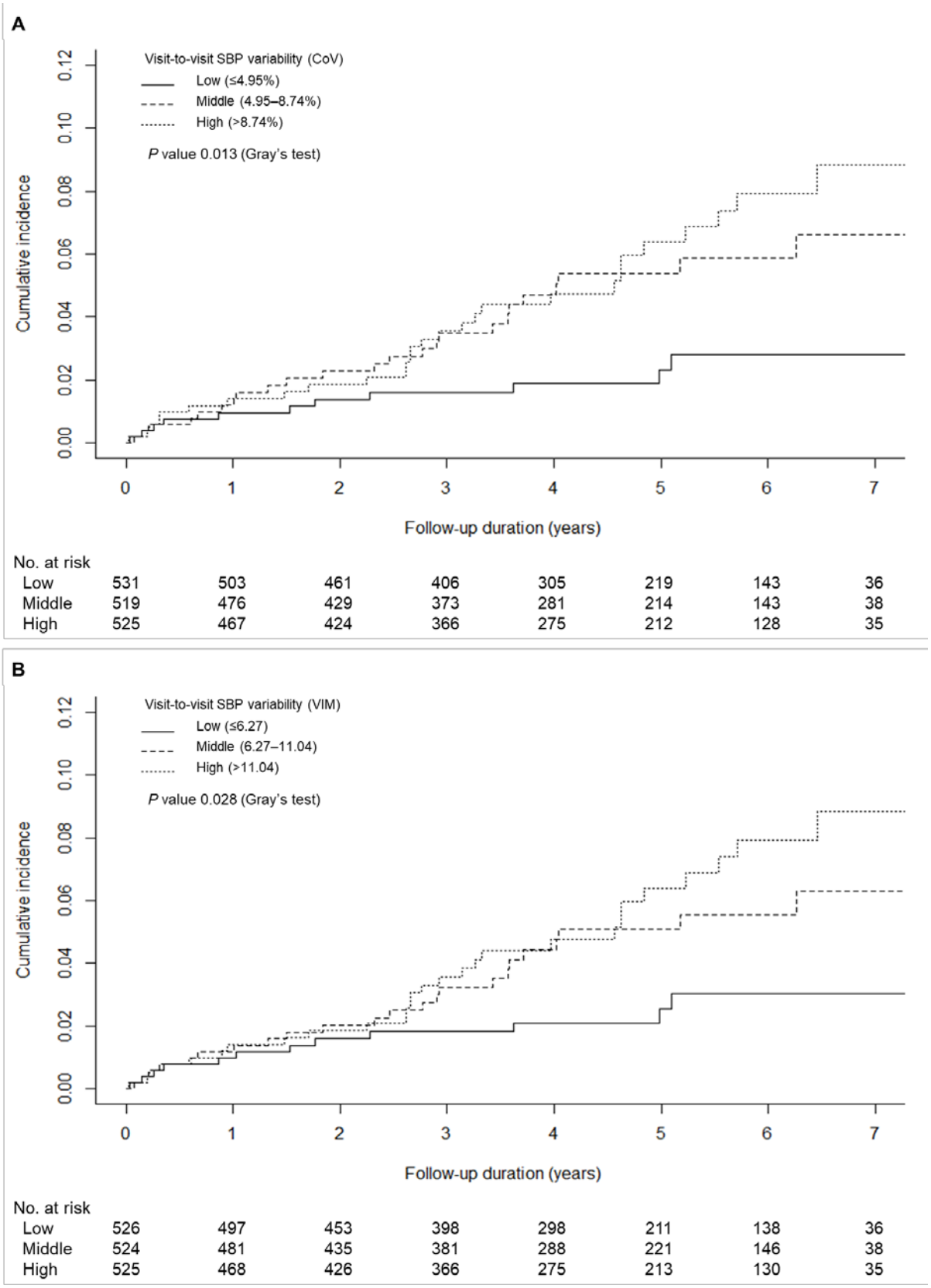
Abbreviations: hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; PTH, parathyroid hormone; UPCR, urine protein-to-creatinine ratio.

Figure S2. Visit-to-visit SBP Variability (SD) Distribution of Study Cohort



Abbreviations: SBP, systolic blood pressure; SD, standard deviation.

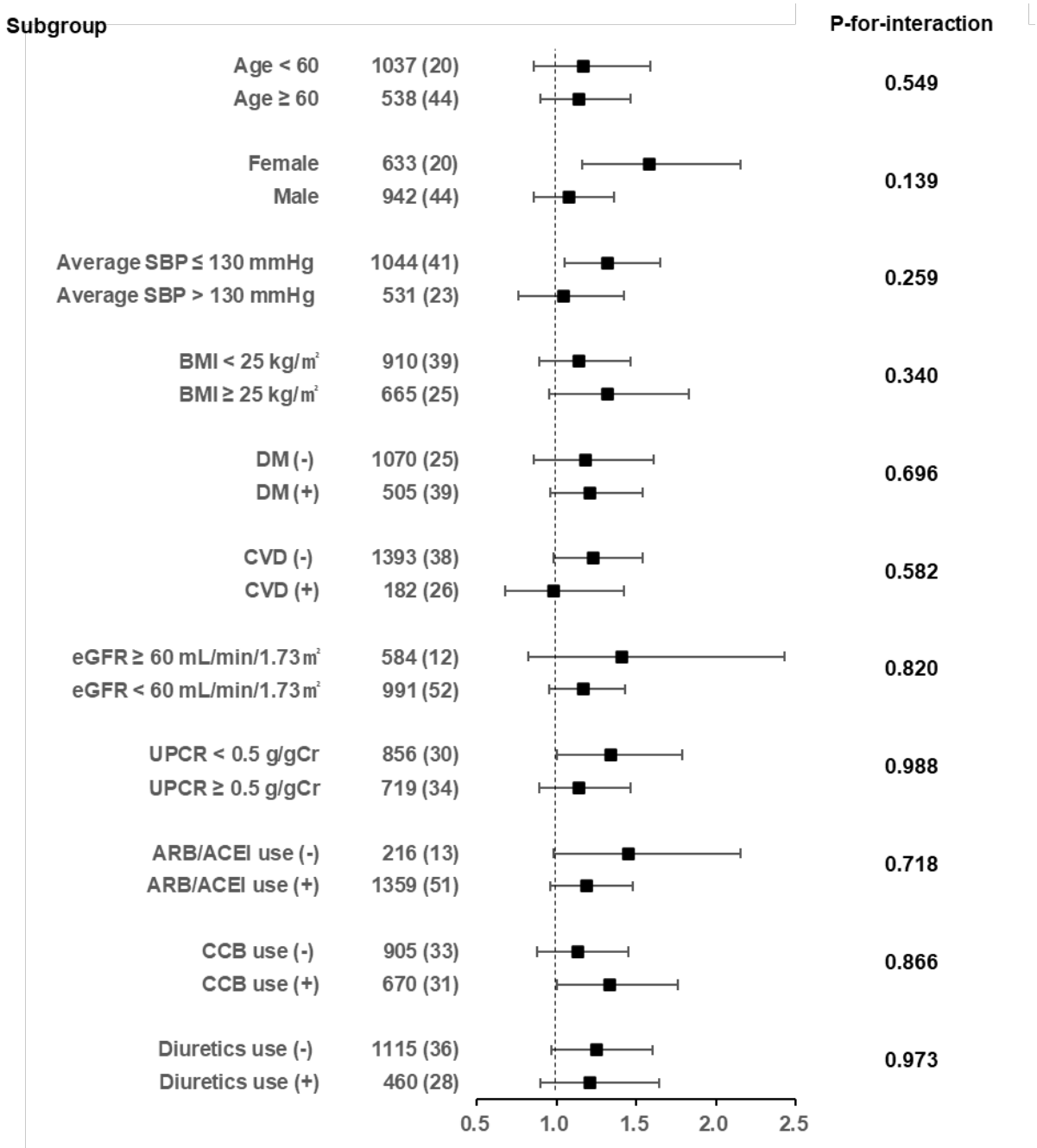
Figure S3. Cumulative Incidence Function of MACE According the Visit-to-visit SBP Variability (CoV and VIM) for the First Year



Major adverse cardiovascular events occurred more as the first year visit-to-visit SBP variability stratified by CoV (A) or VIM (B) was higher.

Abbreviations: CoV, coefficient of variation; MACE, major adverse cardiovascular event; SBP, systolic blood pressure; SD, standard deviation; VIM, variation independent of the mean.

Figure S4. Subgroup Analysis for the Association of the Visit-to-visit SBP Variability (SD) with MACE



Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; MACE, major adverse

cardiovascular event; SBP, systolic blood pressure; SD, standard deviation; UPCR, urinary protein-to-creatinine ratio.