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Association Between Systolic and Diastolic Blood Pressure Variability and the Risk of End-Stage Renal Disease

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Abstract—Recent data suggest that visit-to-visit variability of blood pressure (BP) is associated with cardiovascular events. We evaluated the role of BP variability as a determinant of end-stage renal disease (ESRD). Using nationally representative data from the Korean National Health Insurance System, 8 199 089 subjects had been enrolled during 2009 to 2010 who were free of ESRD and underwent ≥3 health examinations during 2005 to 2010 were followed to the end of 2017. BP variability was measured using the coefficient of variation, SD, and variability independent of the mean. The primary outcome was the development of ESRD, defined as a combination of the relevant disease code and the initiation of renal replacement therapy. The χ^2 test, *t* test, and log-rank test were used in the statistical analysis. There were 16 567 cases of ESRD during a median follow-up of 7.89±0.88 years. The highest quartile of systolic or diastolic BP showed a higher incident rate of ESRD compared with the other 3 quartiles. It was augmented in patients with the highest quartile of both systolic and diastolic BP variabilities. Among patients with the highest quartile of systolic and diastolic BP variabilities, the uncontrolled hypertension group (>140/90 mm Hg) taking antihypertensive medication showed the highest incidence rate of ESRD. These results were consistent when modeling variability of BP using coefficient of variation, SD, and variability independent of the mean and in various sensitivity analyses. Systolic and diastolic BP variabilities were independently associated with an increased incidence of ESRD, and it was augmented when both variabilities were present together. (***Hypertension*****. 2019;74:880-887. DOI: 10.1161/HYPERTENSIONAHA.119.13422.)** ● **Online Data Supplement**

Key Words: adult ■ blood pressure ■ hypertension ■ kidney failure, chronic ■ variability

The intraindividual variability in various physiological measures has been of increasing interest in recent years, and high systolic blood pressure (SBP) variability has been associated with adverse outcomes.[1–3] Asayama et al[4] reported that a higher SBP level predicted cardiovascular complication without contribution of variability. Therefore, the influence of SBP variability on cardiovascular risk over and above mean SBP remains controversial. Chronic kidney disease (CKD) is a growing public health problem. More than 10% of the United States adult population is estimated to have stages 1 to 4 CKD.[5] The estimated prevalence of CKD in Korea is 8.2%,[6] and its prevalence is increasing worldwide with the growing prevalence of diabetes mellitus (DM) and hypertension.[7] CKD has substantial importance because it is considered as a strong risk factor for cardiovascular morbidity and mortality. Targeting modifiable factors has been frequently recommended as a first-line strategy for reducing the risks of kidney disease progression and cardiovascular disease in patients with CKD. Hypertension is one of the most independent risk factors for end-stage renal disease (ESRD) to date in diabetic and nondiabetic patients with CKD.[8–10] Visit-to-visit blood pressure (BP) variability predicts the risk of ESRD, independent of the achieved SBP.[1] However, previous studies on BP variability have important limitations such as mainly SBP variability, being restricted to specific or high-risk populations, or assessing only selected outcomes.[1,11,12] To better understand the role of BP variability as a determinant of incident ESRD in the broader and general population, we analyzed nationally representative data from the Korean National Health Insurance System.

Methods

Because of the confidentiality of the data used for this study and strict privacy policy from the data holder that the data can be kept among the designated research personnel only, the data cannot be provided to other else, whether or not the data are made anonymous.

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Table 1. Baseline Characteristics of Subjects According to the BP Variability Measure As CV

Group	S&DQ1-3 (N=5 108 019)	DQ4 (N=1 040 977)	SQ4 (N=1 040 001)	S&DQ4 (N=1 010 092)	*P* Value
Sex, male (%)	3 144 640 (61.56)	610 488 (58.65)	536 712 (51.61)	518 454 (51.33)	<0.0001
Age	47.63±13.4	48.29±14.01	49.38±14.18	50.22±14.21	<0.0001
Current smoker	2 231 241 (43.68)	434 237 (41.71)	384 354 (36.96)	373 636 (36.99)	<0.0001
Drinker-2 level	2 606 008 (51.02)	509 986 (48.99)	461 673 (44.39)	447 507 (44.3)	<0.0001
Physical activity-regular	1 029 475 (20.15)	204 101 (19.61)	197 504 (18.99)	188 747 (18.69)	<0.0001
Income low	796 314 (15.59)	173 464 (16.66)	180 053 (17.31)	185 689 (18.38)	<0.0001
Diabetes mellitus	430 793 (8.43)	88 483 (8.5)	90 044 (8.66)	91 517 (9.06)	<0.0001
HTN	1 280 548 (25.07)	296 768 (28.51)	260 992 (25.1)	315 001 (31.19)	<0.0001
Dyslipidemia	803 419 (15.73)	162 374 (15.6)	161 592 (15.54)	167 304 (16.56)	<0.0001
CKD (eGFR<60)	330 705 (6.47)	67 216 (6.46)	69 364 (6.67)	70 028 (6.93)	<0.0001
eGFR	86.75±40.83	87.49±43.14	86.83±39.06	86.85±39.35	<0.0001
Proteinuria					<0.0001
Negative	4 893 706 (95.8)	994 740 (95.56)	994 939 (95.67)	963 151 (95.35)	
Trace	106 354 (2.08)	22 570 (2.17)	21 982 (2.11)	22 101 (2.19)	
1+	73 101 (1.43)	15 912 (1.53)	15 361 (1.48)	16 503 (1.63)	
2+	27 174 (0.53)	5982 (0.57)	5942 (0.57)	6301 (0.62)	
3+	6466 (0.13)	1469 (0.14)	1481 (0.14)	1699 (0.17)	
4+	1218 (0.02)	304 (0.03)	296 (0.03)	337 (0.03)	
BMI	23.85±3.09	23.76±3.14	23.46±3.13	23.52±3.18	<0.0001
Glucose	97.04±21.53	96.82±21.48	96.71±21.79	97.03±22.37	<0.0001
Total cholesterol	195.85±35.66	195.28±36.04	195.13±36.16	195.35±36.66	<0.0001
SBP	123.18±13.05	122.74±13.97	120.34±17.39	120.78±18.32	<0.0001
DBP	77.04±8.68	75.78±11.89	74.99±9.15	75.36±12.46	<0.0001
HTN medication	929 270 (18.19)	175 744 (16.88)	174 931 (16.82)	193 427 (19.15)	<0.0001
SBP_SD	6.9±3.28	8.17±3.36	14.61±4.24	16.68±5.5	<0.0001
SBP_CV	5.56±2.45	6.58±2.4	12.03±2.6	13.59±3.6	<0.0001
SBP_VIM	6.79±2.94	8.04±2.82	14.97±2.87	16.76±4.07	<0.0001
DBP_SD	4.87±2.31	10.76±2.46	5.73±2.19	11.88±3.27	<0.0001
DBP_CV	6.31±2.88	14.09±2.64	7.6±2.67	15.59±3.59	<0.0001
DBP_VIM	4.83±2.21	10.8±2.02	5.83±2.04	11.96±2.73	<0.0001
F/U duration	7.91±0.84	7.87±0.9	7.85±0.93	7.83±0.99	<0.0001

BMI indicates body mass index; CKD, chronic kidney disease; CV, coefficient of variation; DBP, diastolic blood pressure; DQ4, only diastolic highest quartile group; eGFR, estimated glomerular filtration nrate; F/U, follow-up; HTN, hypertension; S&DQ1-3, both systolic and diastolic lower quartile group; SBP, systolic blood pressure; SQ4, only systolic highest quartile group, S&DQ4, both systolic and diastolic highest quartile group; and VIM, variability independent of the mean.

Study Design and Database

The Korean National Health Insurance Service comprises a complete set of health information pertaining to 50 million Koreans, which includes an eligibility database, a medical treatment database, a health examination database, and a medical care institution database.[13–15] The National Health Insurance Corporation is the single insurer, managed by the Korean government, to which ≈97% of the Korean population subscribes. Enrolees in the National Health Insurance Corporation are recommended to undergo a standardized medical examination at least every 2 years. Among 17 539 992 subjects who underwent health examinations in 2009 to 2010 (index year), 8 376 860 subjects underwent ≥3 health examinations from January 1, 2005 to December 31, 2010. We excluded 165 191 subjects with missing data for at least 1 variable. To avoid confounders by preexisting diseases and minimize the possible effects of reverse causality, those who had a history of ESRD before the index year were also excluded (n=6 089). Ultimately, the study population consisted of 8 199 089 subjects (Figure S1 in the online-only Data Supplement).

This study was approved by the Chonnam National University Hospital (study approval number: CNUH-EXP-2018–234) and National Health Insurance Service (NHIS-2019-1-119), and it was conducted according to the principles of the Declaration of Helsinki. The need for written informed consent was waived by our review board.

Measurements and Definitions

In the Korean National Health Insurance Service, the equipment used to measure BP varies between sites. However, most people received their medical examinations in the same hospital near their residence, and most BP measurements were performed using the same equipment in each individual. BP was measured by trained clinicians. SBP and diastolic BP (DBP) were measured, and the sitting brachial BP was the average of the 2 measurements taken after the subject had been seated for 5 minutes with an arm in the appropriate position. Body mass index was calculated as the subject's weight in kilograms divided by the square of the subject's height in meters. Information on current smoking and alcohol consumption was obtained by a questionnaire. Regular exercise was defined as physical activity that was performed at least 5× per week. Income level was dichotomised at the lower 10%. Blood samples for the measurement of serum glucose and total cholesterol levels were drawn after an overnight fast. Proteinuria was tested by the dipstick method and defined as negative, trace, and 1+ to 4+. Comorbidities were identified using information gathered in the 1 year before the index date and included DM (*International Classification of Diseases, Tenth Revision [ICD-10]* code E11-E14), hypertension (*ICD-10* codes I10, I11, I12, I13, and I15), and dyslipidemia (*ICD-10* code E78).

Definition of BP Variability

We used the mean SBP and DBP measured at each visit to calculate the SDs in SBP and DBP over the various visits. Three indices of variability were used: SD, coefficient of variation, which was obtained by dividing the SD by the average BP level,[16] and variability independent of the mean (VIM). The VIM was calculated as 100×SD/mean β, where β is the regression coefficient, based on the natural logarithm of the SD divided by the natural logarithm of the mean.[17] We also analyzed BP variability based on BP measurements taken 3×, 4×, and 5×. SBP or DBP variability was divided into quartiles (SBP, SQ1-SQ4; DBP, and DQ1-DQ4). High variability of SBP (SQ4) or DBP (DQ4) was defined as values in the highest quartile for each parameter, and it was compared with that of the lower 3 quartiles (Q1-3) as the reference group.

Study Outcomes and Follow-Up

The study population was followed from baseline to the date of ESRD diagnosis or until December 31, 2017, whichever came first. The primary end point was incident ESRD, which was defined using a combination of ICD-10 codes (N18-19, Z49, Z94.0, and Z99.2) and a special code (V code) that was assigned in the initiation of renal replacement therapy (hemodialysis, V001; peritoneal dialysis [PD], V003) and kidney transplantation (V005) during hospitalization. All medical expenses for dialysis are reimbursed using the Korean Health Insurance Review and Assessment Service database. These patients are also registered as special medical aid beneficiaries. Therefore, we were able to identify every patient with ESRD in the entire South Korean population and to analyze the data for all patients with ESRD who started dialysis. Codes for treatment or medical expense claims included V005 for kidney transplantation, V001 for hemodialysis, and V003 for PD. We excluded individuals without previous CKD who had a transplant or dialysis code on the same date as an acute renal failure code. Subjects on continuous renal replacement therapy or acute peritoneal dialysis were also excluded.

Statistical Analysis

We report the mean±SD with intervals for continuous variables and the numbers (with percentages) for categorical variables. Participants were classified into 4 groups according to the SBP and DBP variability quartile. Baseline characteristics were compared among the ESRD and other groups using the χ^2 and *t*-tests. To identify the risk of ESRD by the quartile of BP variability, we calculated the hazard ratios (HRs) with 95% CIs and analyzed these data using the Cox proportional hazard regression model. All subjects were divided into 4 quartiles, Q1-Q4, based on the coefficient of variation, VIM, and SD off SBP and DBP. We analyzed associations between BP variability and ESRD development using 4 models. Model 1: adjusted for age, sex. Model 2: adjusted for model 1 plus smoking, alcohol, physical activity, income, body mass index. Model 3: adjusted for model 2 plus DM, dyslipidemia, hypertension, antihypertensive medication, glomerular filtration rate, proteinuria, average SBP. Model 4: adjusted for model 3 plus average diastolic blood pressure. The cumulative ESRD incidence was estimated by constructing Kaplan-Meier curves for the entire 8-year follow-up period, and we used the log-rank test to examine differences in ESRD development by the quartile of BP variability. Because an event of mortality could compete with our outcome of interest, we also performed competing risk analysis using a subdistribution hazard model.[18,19] Sensitivity analyses were also performed and excluded subjects with end points

Table 2. Baseline Characteristics of Subjects According to the Incident ESRD

Group	No ESRD (N=8 182 522)	ESRD (N=16 567)	*P* Value
Sex, male (%)	4 798 896 (58.65)	11 398 (68.8)	<0.0001
Age	48.23±13.7	60.87±12.89	<0.0001
Current smoker	3 415 976 (41.75)	7492 (45.22)	<0.0001
Drinker-2 level	4 019 493 (49.12)	5681 (34.29)	<0.0001
Physical activity-regular	1 616 358 (19.75)	3469 (20.94)	0.0001
Income-low	1 332 067 (16.28)	3453 (20.84)	<0.0001
Diabetes mellitus	693 562 (8.48)	7275 (43.91)	<0.0001
HTN	2 140 460 (26.16)	12 849 (77.56)	<0.0001
dyslipidemia	1 287 847 (15.74)	6842 (41.3)	<0.0001
CKD (GFR<60)	527 812 (6.45)	9501 (57.35)	<0.0001
GFR	86.93±40.72	56.87±35.79	<0.0001
Proteinuria			<0.0001
Negative	172 230 (2.1)	777 (4.69)	
Trace	118 757 (1.45)	2120 (12.8)	
1+	42 638 (0.52)	2761 (16.67)	
2+	9628 (0.12)	1487 (8.98)	
3+	1821 (0.02)	334 (2.02)	
4+	693 562 (8.48)	7275 (43.91)	
BMI	23.74±3.12	24.21±3.24	<0.0001
Glucose	96.93±21.54	119.35±51.42	<0.0001
Total cholesterol	195.63±35.87	194.66±44.72	0.0081
SBP	122.45±14.54	132.2±17.68	<0.0001
DBP	76.4±9.76	79.54±10.92	<0.0001
HTN medication	1 461 538 (17.86)	11 834 (71.43)	<0.0001
SBP_SD	9.24±5.3	12.55±7.32	<0.0001
SBP_CV	7.5±4.07	9.38±5.2	<0.0001
SBP_VIM	9.21±4.95	10.83±5.94	<0.0001
DBP_SD	6.59±3.69	8.09±4.59	<0.0001
DBP_CV	8.6±4.67	10.04±5.54	<0.0001
DBP_VIM	6.59±3.58	7.66±4.22	<0.0001
F/U duration	7.89±0.86	4.65±2.27	<0.0001

BMI indicates body mass index; CKD, chronic kidney disease; CV, coefficient of variation; DBP, diastolic blood pressure; ESRD, end-stage renal disease; F/U, follow-up; GFR, glomerular filtration rate; HTN, hypertension; SBP, systolic blood pressure; and VIM, variability independent of the mean

Table 3. Hazard Ratios and 95% CIs of ESRD by Quartiles of BP Variability Measured Using VIM

VIM	Total (n)	Events (n)	IR	HR (95% CI)					
				Model 1	Model 2	Model 3	Model 4	Model 3 (Competing Risk)	Model 4 (Competing Risk)
Systolic BP variability									
Q1	2 050 390	3679	0.23	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Q2	2 043 961	3682	0.23	1.05 (1.00–1.10)	1.05 (1.00–1.10)	0.10 (0.95–1.04)	0.99 (0.95–1.04)	0.99 (0.95–1.04)	0.99 (0.95–1.04)
Q3	2 054 645	4026	0.25	1.09 (1.05–1.14)	1.10 (1.05–1.15)	1.08 (1.04–1.13)	1.08 (1.03–1.13)	1.08 (1.03–1.13)	1.08 (1.03–1.12)
Q4	2 050 093	5180	0.32	1.28 (1.23–1.34)	1.29 (1.24–1.34)	1.40 (1.34–1.46)	1.39 (1.32–1.44)	1.38 (1.32–1.44)	1.36 (1.30–1.42)
P Value for trend				<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Diastolic BP variability									
Q1	2 049 794	3638	0.23	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Q2	2 051 660	3928	0.24	1.07 (1.02–1.12)	1.07 (1.02–1.12)	1.06 (1.02–1.11)	1.05 (1.00–1.10)	1.06 (1.02–1.11)	1.05 (1.00–1.10)
Q3	2 046 566	3914	0.24	1.11 (1.06–1.17)	1.12 (1.07–1.17)	1.07 (1.02–1.12)	1.07 (1.02–1.12)	1.06 (1.02–1.11)	1.07 (1.02–1.12)
Q4	2 051 069	5087	0.32	1.29 (1.24–1.35)	1.29 (1.24–1.35)	1.35 (1.30–1.41)	1.34 (1.28–1.40)	1.33 (1.28–1.39)	1.34 (1.28–1.40)
P Value for trend				<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Systolic and diastolic highest quartile BP variability									
S&DQ1-3	5 108 019	9106	0.23	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
DQ4	1 040 977	2281	0.28	1.16 (1.11–1.21)	1.16 (1.11–1.21)	1.22 (1.17–1.28)	1.25 (1.19–1.31)	1.22 (1.17–1.28)	1.25 (1.19–1.31)
SQ4	1 040 001	2374	0.29	1.16 (1.11–1.22)	1.17 (1.12–1.22)	1.31 (1.26–1.38)	1.31 (1.25–1.37)	1.31 (1.26–1.38)	1.31 (1.25–1.37)
S&DQ4	1 010 092	2806	0.35	1.35 (1.29–1.41)	1.36 (1.30–1.42)	1.47 (1.41–1.54)	1.46 (1.40–1.53)	1.47 (1.41–1.54)	1.46 (1.40–1.53)
P vaue for trend				<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Model 1: adjusted for age, sex. Model 2: adjusted for model 1 plus smoking, alcohol, physical activity, income, body mass index. Model 3: adjusted for model 2 plus diabetes mellitus, dyslipidemia, hypertension, antihypertensive medication, glomerular filtration rate, proteinuria, average systolic blood pressure. Model 4: adjusted for model 3 plus average diastolic blood pressure. BP indicates blood pressure; DQ4, only diastolic highest quartile group; ESRD, end-stage renal disease; IR, incidence rate (per 1000 person-years); Q1-Q4, quartile of blood pressure; S&DQ1-3, both systolic and diastolic lower quartile group; S&DQ4, both systolic and diastolic highest quartile group; SQ4, only systolic highest quartile group; and VIM, variability independent of the mean.

occurring within 1 and 2 years of follow-up. A $P<0.05$ was considered to reflect statistical significance. SAS version 9.3 software and SAS survey procedures (SAS Institute, Inc, Cary, NC) were used for all statistical analyses.

Results

Baseline Characteristics

The characteristics of participants classified by quartiles of VIM of SBP and DBP are presented in Table 1. Subjects in the highest quartiles of SBP and DBP variability (S&DQ4 group) were older, more likely to be women, have a low income, exercise less, and have a higher prevalence of comorbid conditions (Table 1). The mean SBP/DBP level in all 4 groups was ≈122/76 mm Hg. Baseline levels of the estimated glomerular filtration rate (eGFR) were comparable among the groups. The proportion of subjects with proteinuria increased gradually from the subjects with lower quartiles to the highest SBP and DBP variability. *P* for trend were <0.0001 for all variables because of the large size of the study population. Baseline coefficient of variation, SD, and VIM of BP were significantly higher in subjects with incident ESRD than in those without ESRD, although the baseline and mean SBP and DBP levels were higher according to the occurrence of ESRD (Table 2).

BP Variability and the Risk of ESRD

During a median (5%–95%) 7.89 (7.01–8.77) years of follow-up after the BP variability assessment period, 16 567 (0.20%; 0.26/1000 person-years) participants developed ESRD. The incidence rate was higher in the SBP or DBP VIM Q4 group compared with the other groups (Table 3). Furthermore, the SBP and DBP VIM Q4 group showed a higher incidence rate than the SBP Q4 or DBP Q4 group

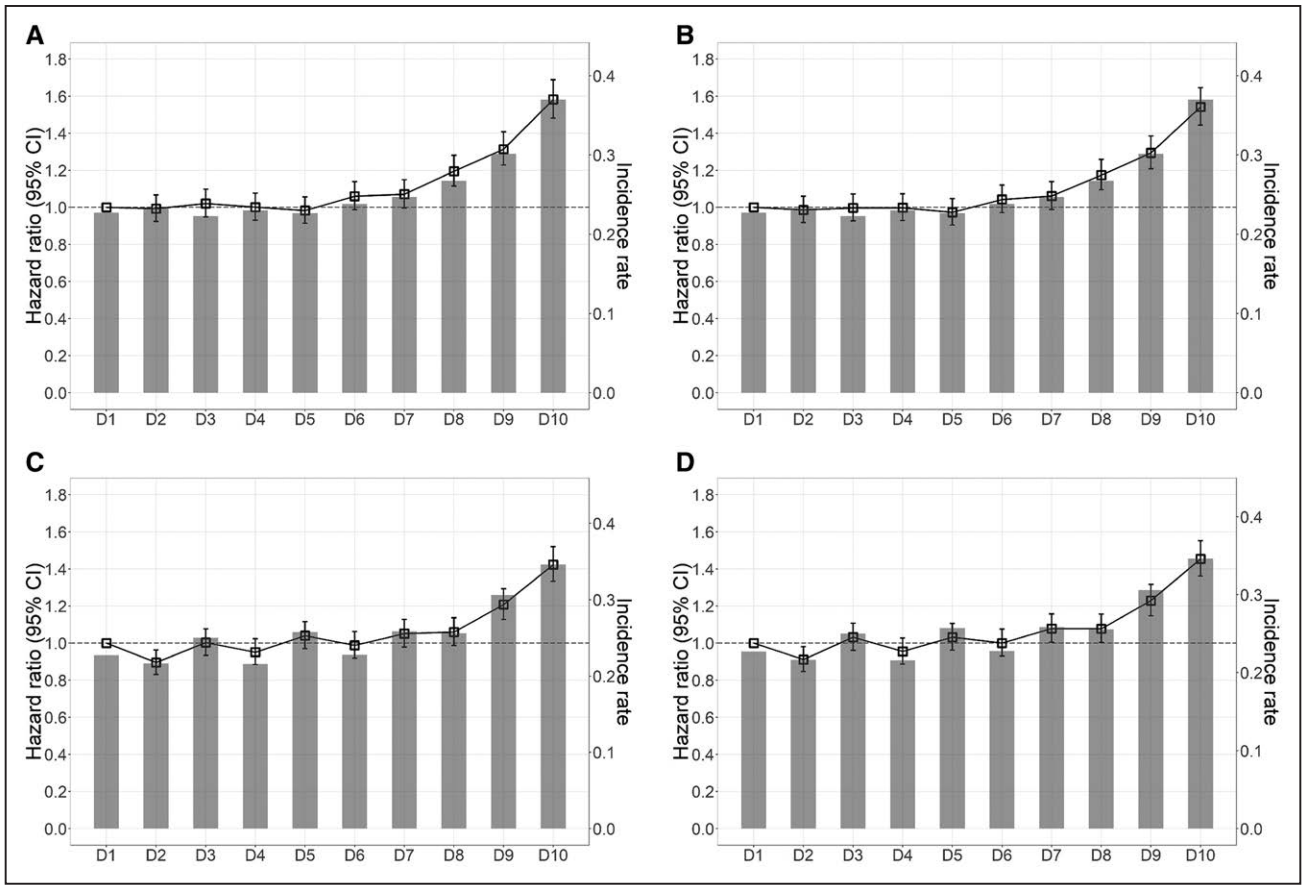

Figure 1. Incidence rates, hazard ratios, and 95% CIs of end-stage renal disease by deciles of systolic blood pressure (SBP; **A** and **B**) and diastolic blood pressure (DBP; **C** and **D**) variability. Adjusted for age, sex, current smoker, alcohol consumption, regular exercise, income, body mass index, diabetes mellitus, dyslipidemia, antihypertensive agents, glomerular filtration rate, proteinuria, average systolic BP (**A** and **C**). Adjusted for age, sex, current smoker, alcohol consumption, regular exercise, income, body mass index, diabetes mellitus, dyslipidemia, antihypertensive agents, glomerular filtration rate, proteinuria, average diastolic BP (**B** and **D**).

alone (Table 3). After adjusting for age, sex, body mass index, alcohol consumption, smoking, regular exercise, income, and SBP, the HRs for incident ESRD were 1.43 (95% CI, 1.37–1.50) for the fourth quartile versus the first quartile of VIM of SBP and 1.40 (95% CI, 1.34–1.50) for the fourth quartile versus the first quartile of VIM of DBP (Table 3; Figure 1). After considering both VIMs of SBP and DBP, the association between BP variability and incident ESRD was augmented significantly (HR [95% CI]: SQ4, 1.33 [1.27–1.40]; DQ4, 1.28 [1.20–1.32]; S&DQ4, 1.53 [1.50–1.63]; Table 2). Competing risk analysis including mortality as a competing risk showed similar results (Table 3, Tables S1 and S2). Increasing BP measurement times showed a higher association with the incidence rate and HR of ESRD and BP variability (Table S3). BP variability as measured by coefficient of variation (Table S1) or SD (Table S2) was also an independent predictor of ESRD, even after full multivariable adjustment. Among the patients taking antihypertensive medication, the incident rate of ESRD according to BP variability was investigated based on 140/90 mm Hg. The HR for ESRD was higher in patients with SBP and DBP variabilities in the uncontrolled hypertension group (1.67 [95% CI, 1.54–1.82]) than in the well-controlled hypertension group (1.30 [95% CI, 1.22–1.39]; Table 4).

Subgroup Analyses

Analyses stratified by age, antihypertensive agents, sex, DM, hypertension, and CKD were performed (Figure 2). The Q4 group of BP variability (SQ4) remained predictive of ESRD in all studied subgroups compared with the Q1-Q3 groups in both SBP (Figure 2A and 2B) and DBP variabilities (Figure 2C and 2D). Higher adjusted HRs of incident ESRD were observed in the subgroups such as young age (<55 years), male sex, no antihypertensive medication, DM, and hypertension. To account for the possible influence of previous renal function on incident ESRD, we performed a subgroup analysis based on the presence of a low eGFR defined as baseline eGFR <60 mL/min per 1.73 m^2. The associations between BP variability and ESRD were consistent in subjects with or without low GFR, even in the eGFR <45 subgroup.

Sensitivity Analyses

To account for the possibility of reverse causation, sensitivity analysis was performed and excluded subjects with the occurrence of end points within 1 and 2 years of follow-up. Similar to the original analysis, incrementally higher incidence rate and HR of ESRD were noted with higher SBP and DBP variability (Table S4). The results of the 1-year follow-up showed nearly identical findings (data not shown).

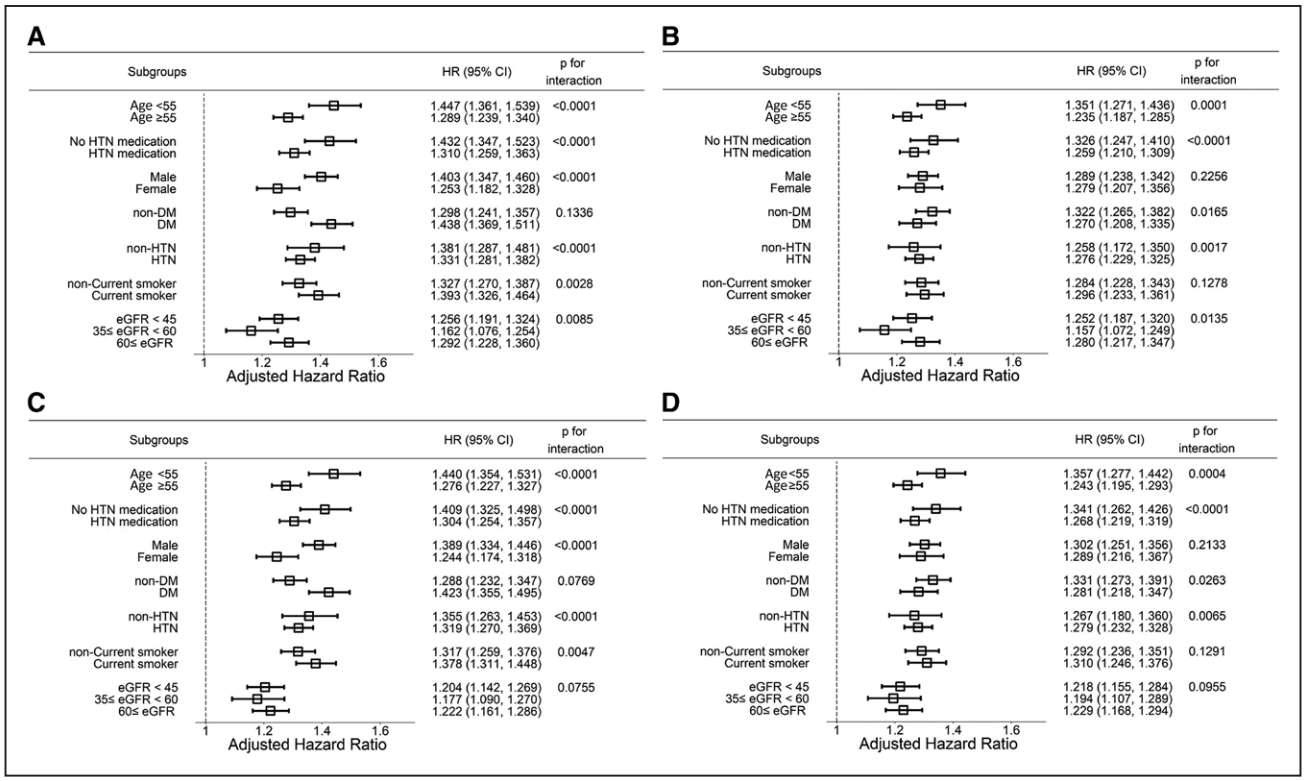

Figure 2. Subgroup analysis. Hazard ratios (HRs) and 95% CIs of end-stage renal disease in the highest quartile vs lower 3 quartiles of systolic blood pressure (SBP; **A** and **B**) and diastolic blood pressure (DBP; **C** and **D**) variability in subgroups. Adjusted for age, sex, current smoker, alcohol consumption, regular exercise, income, body mass index, diabetes mellitus, dyslipidemia, antihypertensive agents, glomerular filtration rate, proteinuria, average SBP (**A** and **C**). Adjusted for age, sex, current smoker, alcohol consumption, regular exercise, income, body mass index, diabetes mellitus, dyslipidemia, antihypertensive agents, glomerular filtration rate, proteinuria, average DBP (**B** and **D**). DM indicates diabetes mellitus; HTN, hypertension; and eGFR, estimated glomerular filtration rate.

Discussion

Herein, we demonstrated that both long-term SBP and DBP variability were associated with a higher risk for ESRD development during a 7.88-year follow-up period. Not only the SBP variability but also the DBP variability showed an association with the ESRD risk. Moreover, patients with the highest quartile of SBP and DBP variability showed the highest risk of ESRD. The association persisted after multivariable adjustment for important potential confounders.

In the last few decades, interest has been focused on BP variability, and consistent results of the association with BP variability and cardiovascular outcome[20–22] and dementia have been shown.[23] However, the association between BP variability and CKD progression remains only SBP variability and renal outcome.[1,11,12]

The mechanisms underlying the altered BP variability and CKD progression are incompletely understood. Several factors or mechanisms have been proposed to explain the altered circadian rhythm,[24] and those factors also affect glomerular injury. Kawai et al[25] reported that visit-to-visit variability in BP was associated with renal vascular resistance, which was a useful marker for renal function and albuminuria. Eto et al[26] suggested that increased BP variability, independently of average BP level, impairs endothelial function by inhibiting nitric oxide production, enhances neointimal formation, and thereby may contribute to atherogenesis in an animal model. In the setting of increased BP variability, increased sympathetic nerve activity plays an important role in the progression of hypertension and kidney disease.[27] In addition, chronic sympathetic nerve hyperactivity can damage renal blood vessels by inducing smooth muscle and fibroblast proliferation in the vessel wall,[28] reduce nitric oxide bioavailability,[29,30] resulting in intrarenal vasoconstriction, decrease blood flow, and worsen renal injury.[31] These results reinforce the role of increased BP variability as an important marker of the progression of renal diseases.

Our study evaluated > 10 million people and demonstrated a greater impact of SBP and DBP variability in subjects without a previous hypertension history. It showed that both increased long-term SBP and DBP variabilities can worsen CKD progression regardless of the BP levels or presence of antihypertensive medications. Herein, subjects in the higher BP variability group (Q4) were more likely to have albuminuria than those with lower BP variability (Q1-Q3). After controlling for baseline eGFR and proteinuria as confounders, we found a consistent association between BP variability and incident ESRD. Moreover, the sensitivity analysis that excluded subjects with outcomes occurring in the first 2 years of follow-up revealed similar results. The rate of progression to ESRD was higher in the uncontrolled BP patients (>140/90 mm Hg) with high BP variability (Q4) than in the well-controlled patients (≤140/90 mm Hg). This result is not surprising but predictable. Numerous studies have shown that higher BP is correlated with CKD progression,[32,33] and controlled

Table 4. Hazard Ratios and 95% CIs of ESRD by Quartiles of BP Variability in Patients Taking Antihypertensive Medication

VIM	Total (n)	Events (n)	IR	HR (95% CI)			
				Model 1	Model 2	Model 3	Model 4
Well-controlled patients (≤140/90)							
S&DQ1-3	625 362	4162	0.86	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
DQ4	115 483	981	1.10	1.26 (1.17–1.35)	1.26 (1.17–1.35)	1.24 (1.16–1.33)	1.26 (1.16–1.38)
SQ4	117 801	959	1.06	1.22 (1.14–1.31)	1.21 (1.12–1.30)	1.21 (1.13–1.30)	1.58 (1.45–1.72)
S&DQ4	140 012	1263	1.17	1.38 (1.29–1.46)	1.36 (1.27–1.44)	1.34 (1.25–1.42)	1.78 (1.63–1.93)
P Value for trend				<0.0001	<0.0001	<0.0001	<0.0001
Uncontrolled patients (systolic BP >140 or diastolic BP >90)							
S&DQ1-3	303 908	2473	1.05	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
DQ4	60 261	626	1.35	1.26 (1.16–1.38)	1.25 (1.15–1.37)	1.25 (1.16–1.34)	1.27 (1.16–1.39)
SQ4	57 130	684	1.57	1.46 (1.34–1.59)	1.44 (1.32–1.57)	1.22 (1.33-1.30)	1.48 (1.36–1.61)
S&DQ4	53 415	686	1.68	1.63 (1.50–1.78)	1.60 (1.47–1.74)	1.37 (1.28–1.45)	1.63 (1.49–1.77)
P Value for trend				<0.0001	<0.0001	<0.0001	<0.0001

Model 1: adjusted for age, sex. Model 2: adjusted for model 1 plus smoking, alcohol, physical activity, income, body mass index. Model 3: adjusted for model 2 plus diabetes mellitus, dyslipidemia, hypertension, antihypertensive medication, glomerular filtration rate, proteinuria, average systolic blood pressure. Model 4: adjusted for model 3 plus average diastolic blood pressure. BP indicates blood pressure; DQ4, only diastolic highest quartile group; ESRD, end-stage renal disease; IR, incidence rate (per 1000 person-years); Q1-Q4, quartile of blood pressure; S&DQ1-3, both systolic and diastolic lower quartile group; S&DQ4, both systolic and diastolic highest quartile group; SQ4, only systolic highest quartile group; and VIM, variability independent of the mean.

BP below the target range is associated with a reduced risk of progression of mortality.[34] This subanalysis data suggest that well-controlled hypertension with antihypertensive medication is important and that clinicians should be concerned about variability of SBP and DBP independent of the antihypertensive medication. Although the prospective association between BP variability and the incidence of ESRD was significant and independent of other risk factors, the potential for reverse causality is of concern.

Study Limitations

The first limitation of our study is an observational study; therefore, the association found between BP variability and renal end points may not be causal. As aforementioned, reverse causality is plausible because people with more significant renal disease (or proteinuria) might have greater BP variability. However, to minimize the possible effects of reverse causality, subjects with preexisting ESRD were excluded. The sensitivity analysis that excluded subjects with ESRD occurring in the first 2 years of follow-up also showed similar results. Second, the causes of renal disease were not identifiable in our study. Third, we defined proteinuria by dipstick testing results and did not quantify the proteinuria. Fourth, the study population consisted of Korean men and women; hence, it is uncertain whether these findings can be generalized to other ethnic groups. Fifth, different BP devices and no standardized protocols were used in each center, and this could be a source of extra variability. Last, there is no consensus on the ideal statistical measure of visit-to-visit BP variability.

Perspectives

This is the first study of the relationship between DBP variability and ESRD development in a large general population that used a well-established and validated longitudinal national database for around 8 years. Our study demonstrated a greater impact of both SBP and DBP variabilities on controlled and uncontrolled groups. We can assume that the fluctuation of BP level per se, not the medication or underlying diseases, could have affected the outcome. Although the precise mechanism is unclear, a more uniform and less variable BP might be important for preventing progression to ESRD.

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Disclosures

None.

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Novelty and Significance

What Is New?

- This is the first study of the relationship between diastolic blood pressure variability and end-stage renal disease development in a large general population that used a well-established and validated longitudinal national database for around 8 years.
- Our study demonstrated a greater impact of both systolic blood pressure and diastolic blood pressure variabilities on controlled and uncontrolled groups. We can assume that the fluctuation of blood pressure level per se, not the medication or underlying diseases, could have affected the outcome.

What Is Relevant?

- Our findings suggest that highest systolic and diastolic blood pressure variability increases the risk of end-stage renal disease synergistically in the general population.

Summary

Systolic and diastolic blood pressure variabilities were independently associated with an increased incidence of end-stage renal disease in general population, and it was augmented when both variabilities were present together.