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ORIGINAL RESEARCH

Blood Pressure and Cardiovascular Outcomes in Adults With Diabetes and Chronic Kidney Disease

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BACKGROUND: Current hypertension guidelines recommend intensive blood pressure (BP) targets (eg, <130/80 mm Hg) for patients with diabetes and chronic kidney disease. However, data supporting these recommendations are limited.

METHODS: From Korean nationwide health screening and claims data, we identified 373 966 adults with both diabetes and chronic kidney disease who (1) underwent a baseline health examination in 2009 to 2013; (2) had ≥3 BP-measuring visits during a 5-year look-back period; and (3) did not have prior cardiovascular disease (CVD). The mean of all BPs measured throughout the look-back period was used for the analysis. The primary outcome was CVD event, defined as a composite of myocardial infarction, stroke, heart failure, or death from CVD.

RESULTS: Over a median follow-up of 10.2 years, 40 781 CVD events occurred. When using systolic BP 130 to <140 mm Hg as the reference, multivariable-adjusted hazard ratios (HRs) for CVD event in the systolic BP ≥150, 140 to <150, 120 to <130, and <120 mm Hg groups were 1.34 (95% CI, 1.29–1.39), 1.11 (95% CI, 1.08–1.14), 0.89 (95% CI, 0.87–0.91), and 0.77 (95% CI, 0.74–0.80), respectively. When using diastolic BP 80 to <90 mm Hg as the reference, HRs in the diastolic BP ≥100, 90 to <100, 70 to <80, and <70 mm Hg groups were 1.70 (95% CI, 1.56–1.85), 1.19 (95% CI, 1.15–1.24), 0.88 (95% CI, 0.86–0.90), and 0.83 (95% CI, 0.80–0.87), respectively. Systolic BP <130 mm Hg and diastolic BP <80 mm Hg were each associated with reduced CVD risk in a log-linear pattern.

CONCLUSIONS: Among patients with diabetes and chronic kidney disease, SBP <130 mm Hg and diastolic BP <80 mm Hg were associated with reduced risk of CVD.

Key Words: blood pressure ■ cardiovascular disease ■ chronic kidney disease ■ diabetes ■ target

Chronic kidney disease (CKD) is a global health concern, with its prevalence surpassing 9% worldwide.[1] Diabetes is the leading cause of CKD and coexists in over one fourth of patients with the condition.[2] Given that diabetes and CKD are major risk factors for cardiovascular disease (CVD), patients with both diabetes and CKD are expected to have an exceedingly high risk of CVD.[3] Previous studies have indicated that the incidence rate of CVD in these individuals can be as high as 5 to 6 events per 100 person-years.[4,5] Therefore, the prevention of CVD in this high-risk population is a key public health priority.

Hypertension is common among adults with CKD and contributes substantially to the development of CVD.[6,7] Current hypertension guidelines recommend intensive blood pressure (BP) targets for patients

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CLINICAL PERSPECTIVE

What Is New?

- In this study of Korean adults with diabetes and chronic kidney disease, systolic blood pressure <130 mm Hg and diastolic blood pressure <80 mm Hg were each associated with a reduced risk of cardiovascular disease.

What Are the Clinical Implications?

- Our findings support current guideline recommendations for intensive blood pressure lowering in patients with both diabetes and chronic kidney disease.

Nonstandard Abbreviation and Acronym

NHIS	National Health Insurance Service

with CKD regardless of their diabetes status: systolic BP (SBP)/diastolic BP (DBP) <130/80 mm Hg in the 2017 American College of Cardiology/American Heart Association guideline,[8] SBP 120 to 129 mm Hg in the 2024 European Society of Cardiology guideline,[9] and SBP <120 mm Hg in the 2021 Kidney Disease: Improving Global Outcomes guideline.[10] Patients with diabetes and CKD, however, have been underrepresented in major randomized trials and meta-analyses supporting these recommendations, comprising <10% of participants in most of the studies.[11–16] Thus, uncertainty remains about the benefits of intensive BP lowering in this high-risk population.

To address such a gap in evidence, we examined the association of BP with cardiovascular outcomes among adults with diabetes and CKD.

METHODS

Because of the sensitive nature of the database, requests from qualified researchers to access the data may be sent to the National Health Insurance Service at https://nhiss.nhis.or.kr.

Data Source

The National Health Insurance Service (NHIS) is the sole provider of universal health insurance in South Korea. The NHIS database contains deidentified information on sociodemographics, health insurance reimbursement claims, and vital status of the entire South Korean population.[17] The database also incorporates the results of routine biennial health examinations provided by the NHIS to all Korean adults.[18] Additional details of the NHIS database and health examination have been previously reported.[17,18]

This study complied with the Declaration of Helsinki; the study protocol was approved by the Institutional Review Board of Severance Hospital, Seoul, Korea (4–2022-0871). Written informed consent was waived, as the study was based on anonymized administrative data.

Study Population

We identified 2 206 500 patients with CKD who (1) were aged 20 to 79 years; (2) underwent health examinations between January 1, 2009, and December 31, 2013—which was designated as the baseline; and (3) had at least 3 BP-measuring visits within 5 years preceding and including the baseline. CKD was defined as estimated glomerular filtration rate (eGFR) of <60 mL/min per 1.73 m^2 or urine dipstick protein of trace or ≥1+ at baseline.[19,20] Of 2 206 500 patients with CKD, 2 102 871 had complete information on key variables. Among them, 529 288 were identified as having concomitant diabetes, defined as fasting glucose of ≥126 mg/dL, the presence of diagnosis code for diabetes (*International Classification of Diseases, Tenth Revision* [*ICD-10*]: E10-E14), or the use of glucose-lowering drug. After excluding 32 313 participants with eGFR <15 mL/min per 1.73 m^2; 1934 who underwent maintenance dialysis or kidney transplantation; 118 517 with prior myocardial infarction (MI), stroke, or heart failure; and 2558 with <1 year of follow-up, a final analytical sample included 373 966 patients with diabetes and CKD (Figure S1).

BP and Use of BP-Lowering Drugs

BP was measured by trained health care personnel using the auscultatory or oscillometric method; the standardized protocol recommended 5 minutes of seated rest followed by 2 consecutive BP readings averaged over a 5-minute interval.[21] We collected data on all BP measurements and health insurance claims for BP-lowering drug prescriptions over the look-back period of 5 years preceding and including the baseline (median [range] BP records, 3 [3–6]). In the primary analysis, the baseline BP was determined as the mean of all BPs measured throughout the look-back period (Figure S2A). In the secondary analysis, 3 different measures of BP burden >130/80 mm Hg—separately for SBP and DBP—were assessed over the look-back period (Figure S2C): (1) cumulative BP load, defined as the area under the curve above 130 mm Hg (for SBP) or 80 mm Hg (for DBP) divided by the total area under the curve (expressed in percentage); (2) time-weighted BP load, defined as the area under the curve above 130 mm Hg (for SBP) or 80 mm Hg (for DBP) divided by the total observation time; and (3) time above target BP, defined as the time during which

BP was above 130 mm Hg (for SBP) or 80 mm Hg (for DBP) divided by the total observation time (expressed in percentage) (Figure S3).[22,23]

Key Variables

During the baseline health examination, physical activity,[24] tobacco smoking, and alcohol consumption were self-reported by participants via standardized questionnaires; height and weight were measured by trained health care personnel; and fasting glucose, total cholesterol, triglyceride, high-density lipoprotein cholesterol, serum creatinine, and urine protein were measured by each health screening institution, as overseen by the Korean Association of Laboratory Quality Control and the NHIS.[18] eGFR was calculated using the 2009 CKD Epidemiology Collaboration equation.[25] The use of glucose- or lipid-lowering drugs and Charlson comorbidity index[26] were ascertained from insurance claims data during a look-back period of 2 years.

Outcomes

The primary outcome was CVD event, defined as a composite of MI, stroke, heart failure, or death from CVD. The secondary outcomes included a composite of kidney disease progression (decline in eGFR of ≥50%, end-stage kidney disease, or death from kidney disease) or death from CVD, kidney disease progression, and individual components of CVD event and kidney disease progression (Table S1). Participants were followed up from the baseline to the occurrence of an outcome event, death, or December 31, 2021, whichever came earliest (Figure S2). For health claims-based outcomes (eg, MI, stroke), patients without any corresponding claims until the end of follow-up were considered not to have experienced the outcome event. For health examination-based outcomes (eg, decline in eGFR of ≥50%), patients were additionally censored at their last available health examination. The Statistics Korea mortality database was linked with the study cohort to determine underlying causes of death.

Statistical Analysis

All analyses were conducted separately for SBP and DBP. Baseline characteristics were reported as median [interquartile range] or number (%) as appropriate. Cumulative incidence of CVD event was estimated using subdistribution cumulative incidence function, which accounted for the competing risk of death from non-CVD.[27,28] Incidence rate was calculated as the number of outcome events per 1000 person-years of follow-up. Hazard ratios (HRs) and 95% CIs of the outcomes were assessed using cause-specific Cox proportional hazards models, in which participants were censored at competing death events.[28,29] The models were adjusted for age at baseline, sex, household income quartile, residential area, tobacco smoking, alcohol consumption, physical activity, body mass index, Charlson comorbidity index, BP-lowering drug use, glucose-lowering drug class (insulin, metformin, sulfonylurea, dipeptidyl peptidase-4 inhibitor, α-glucosidase inhibitor, others), lipid-lowering drug use, fasting glucose, total cholesterol, triglyceride, high-density lipoprotein -cholesterol, eGFR, and urine dipstick protein. Covariables were selected a priori considering their possible associations with BP and study outcomes.[30] The proportionality of hazards was confirmed via graphical inspection of log-minus-log plots and Schoenfeld residuals.

The primary analysis assessed the risk of the outcomes according to the baseline BP (Figure S2A). In categorical analysis, participants were classified according to BP range as follows—for SBP, <120 mm Hg, 120 to <130 mm Hg, 130 to <140 mm Hg, 140 to <150 mm Hg, and ≥150 mm Hg; for DBP, <70 mm Hg, 70 to <80 mm Hg, 80 to <90 mm Hg, 90 to <100 mm Hg, and ≥100 mm Hg. Participants were also classified based on joint categories of SBP and DBP (<130 mm Hg, 130 to <140 mm Hg, and ≥140 mm Hg; <80 mm Hg, 80 to <90 mm Hg, and ≥90 mm Hg; respectively). In continuous analysis, restricted cubic spline terms of BP were used with the reference of 130 mm Hg and 80 mm Hg for SBP and DBP, respectively; 4 knots were positioned at the 5th, 35th, 65th, and 95th percentiles. As sensitivity analyses, we (1) stratified the study participants by sociodemographic, lifestyle, and clinical factors; (2) redefined CKD as eGFR of <60 mL/min per 1.73 m^2 or urine dipstick protein of ≥1+; (3) used time-updated BP as the exposure (Figure S2B); and (4) limited the participants to those with DBP <80 mm Hg for the SBP analysis and to those with SBP <130 mm Hg for the DBP analysis.

The secondary analysis assessed the risk of CVD event according to the BP burden (Figure S2C). For each parameter (ie, cumulative BP load, time-weighted BP load, and time above target BP), restricted cubic spline terms were used with the reference of 0; 4 knots were positioned at the 5th, 35th, 65th, and 95th percentiles. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics

The study included 373 966 patients with diabetes and CKD (median age, 62 years; 40.8% female). Participants in the higher SBP groups were older, had lower household income, resided more frequently in rural areas, reported heavier alcohol consumption,

had higher body mass index, were more commonly on BP-lowering drugs, and exhibited higher levels of fasting glucose, total cholesterol, triglyceride, and urine dipstick protein (Table). Baseline characteristics of the participants by DBP range are provided in Table S2.

Primary Analysis

Over a median follow-up of 10.2 years, a total of 40 781 incident CVD events occurred, corresponding to an incidence rate of 11.4 (95% CI, 11.3–11.5) per 1000 person-years. The cumulative incidence of CVD event was lower with decreasing SBP ranges (Figure 1A) and DBP ranges (Figure 1B), with cumulative incidence curves diverging from the start of follow-up. Compared with the SBP 130 to <140 mm Hg group, the multivariable-adjusted HRs (95% CIs) for CVD event in the SBP ≥150 mm Hg, 140 to <150 mm Hg, 120 to <130 mm Hg, and <120 mm Hg groups were 1.34 (1.29–1.39), 1.11 (1.08–1.14), 0.89 (0.87–0.91), and 0.77 (0.74–0.80), respectively. Compared with the DBP 80 to <90 mm Hg group, the HRs (95% CIs) in the DBP ≥100 mm Hg, 90 to <100 mm Hg, 70 to <80 mm Hg, and <70 mm Hg groups were 1.70 (1.56–1.85), 1.19 (1.15–1.24), 0.88 (0.86–0.90), and 0.83 (0.80–0.87), respectively (Figure 2, Table S3). The risk of CVD event according to the joint categories of SBP and DBP is presented in Figure S4. Following a log-linear pattern, SBP ≥130 mm Hg and DBP ≥80 mm Hg were each associated with an increased risk of CVD event, whereas SBP <130 mm Hg and DBP <80 mm Hg were each associated with a decreased risk of CVD event (Figure 3).The overall incidence rates of the secondary outcomes per 1000 person-years were 8.8 (95% CI: 8.7–8.9) for kidney disease progression or death from CVD, 5.7 (95% CI: 5.7–5.8) for kidney disease progression, 2.2 (95% CI: 2.2–2.3) for MI, 6.8 (95% CI: 6.7–6.9) for stroke, 1.5 (95% CI: 1.5–1.6) for heart failure, 2.8 (95% CI: 2.7–2.8) for death from CVD, 2.9 (95% CI: 2.9–3.0) for decline in eGFR of ≥50%, 4.5 (95% CI: 4.4–4.6) for end-stage kidney disease, and 0.6 (95% CI: 0.6–0.6) for death from kidney disease. SBP ≥130 mm Hg and DBP ≥80 mm Hg were associated with elevated risks of all secondary outcomes, including the composite of kidney disease progression or death from CVD. SBP <130 mm Hg was associated with reduced risks of all secondary outcomes except heart failure. DBP <80 mm Hg was associated with reduced risks of the composite of kidney disease progression or death from CVD, kidney disease progression, stroke, and decline in eGFR of ≥50% (Figures S5 and S6).

Sensitivity Analysis

First, SBP <130 mm Hg and DBP <80 mm Hg were each associated with a lower risk of CVD event in all strata classified by age, sex, household income, residential area, current smoking, alcohol consumption, physical activity, body mass index, Charlson comorbidity index, BP-, glucose-, or lipid-lowering drug use, fasting glucose, eGFR, or urine dipstick protein (Figures S7 and Figure S8; Tables S4 and S5). Second, redefining CKD as eGFR of <60 mL/min per 1.73 m^2 or urine dipstick protein of ≥1+ did not essentially alter our main findings (Figure S9). Third, the associations of SBP and DBP with the risk of CVD event remained consistent when using time-updated BP as the exposure (Figure S10). Finally, SBP <130 mm Hg was associated with a lower risk of CVD event among those with DBP <80 mm Hg (Figure S11A), whereas DBP <80 mm Hg was associated with a lower risk of CVD event among those with SBP <130 mm Hg (Figure S11B).

Secondary Analysis

For both SBP and DBP, higher levels of cumulative BP load, time-weighted BP load, and time above target BP (ie, 130 mm Hg for SBP and 80 mm Hg for DBP) were all associated with an increased risk of CVD event in a dose-dependent manner (Figure 4).

DISCUSSION

In this nationwide study of nearly 400 000 Korean adults with diabetes and CKD, SBP <130 mm Hg and DBP <80 mm Hg were both associated with a decreased CVD risk. The findings were consistent for kidney outcomes and across multiple sensitivity analyses. In the secondary analysis, a higher BP burden above 130/80 mm Hg was associated with an increased CVD risk.

Our findings of reduced CVD risk at SBP <130 mm Hg and DBP <80 mm Hg among patients with diabetes and CKD are in line with and lend support to current BP guidelines. The 2017 American College of Cardiology/American Heart Association guideline recommends a target BP of <130/80 mm Hg for all adults with hypertension, regardless of their CKD or diabetes status[8]; the 2021 Kidney Disease: Improving Global Outcomes guideline advocates a target SBP of <120 mm Hg—using standardized office BP measurement—for patients with CKD and diabetes[10]; and the 2024 European Society of Cardiology guideline proposes a target SBP of 120 to 129 mm Hg for individuals with either diabetes or CKD.[9] Although these recommendations are based on findings from multiple large randomized trials and meta-analyses, patients with concomitant CKD and diabetes have been underrepresented in the majority of this evidence base.[11–16] For instance, the SPRINT (Systolic Blood Pressure Intervention Trial) did not include any patients with diabetes, and only 28% of the participants had eGFR <60 mL/min per 1.73 m^2.[11] The ACCORD BP (Action to Control Cardiovascular Risk in Diabetes Blood Pressure) trial did include patients with diabetes

Table. Baseline Characteristics of the Participants

Variable	Overall (N=373 966)	By SBP range, mm Hg				
		<120 (N=69 717)	120 to <130 (N=117 703)	130 to <140 (N=111 041)	140 to <150 (N=52 572)	≥150 (N=22 933)
Age, y	62 [53–70]	58 [50–66]	62 [52–68]	64 [54–70]	65 [56–71]	66 [56–72]
Sex						
Female	152 483 (40.8)	33 511 (48.1)	46 392 (39.4)	42 707 (38.5)	20 853 (39.7)	9020 (39.3)
Male	221 483 (59.2)	36 206 (51.9)	71 311 (60.6)	68 334 (61.5)	31 719 (60.3)	13 913 (60.7)
Household income*						
Q4, highest	140 591 (37.6)	27 099 (38.9)	45 512 (38.7)	41 432 (37.3)	18 859 (35.9)	7689 (33.5)
Q3	92 260 (24.7)	16 992 (24.4)	28 780 (24.5)	27 545 (24.8)	13 062 (24.8)	5881 (25.6)
Q2	63 619 (17.0)	11 823 (17.0)	19 656 (16.7)	18 651 (16.8)	9286 (17.7)	4203 (18.3)
Q1, lowest	77 496 (20.7)	13 803 (19.8)	23 755 (20.2)	23 413 (21.1)	11 365 (21.6)	5160 (22.5)
Residential area						
Metropolitan	167 187 (44.7)	32 726 (46.9)	52 972 (45.0)	48 891 (44.0)	22 679 (43.1)	9919 (43.3)
Urban	160 060 (42.8)	29 605 (42.5)	50 509 (42.9)	47 730 (43.0)	22 502 (42.8)	9714 (42.4)
Rural	46 719 (12.5)	7386 (10.6)	14 222 (12.1)	14 420 (13.0)	7391 (14.1)	3300 (14.4)
Tobacco smoking						
Never	218 929 (58.5)	42 393 (60.8)	66 752 (56.7)	64 075 (57.7)	31 648 (60.2)	14 061 (61.3)
Past	77 042 (20.6)	12 218 (17.5)	24 850 (21.1)	24 315 (21.9)	11 161 (21.2)	4498 (19.6)
Current	77 995 (20.9)	15 106 (21.7)	26 101 (22.2)	22 651 (20.4)	9763 (18.6)	4374 (19.1)
Alcohol consumption						
None	224 269 (60.0)	45 848 (65.8)	70 383 (59.8)	64 563 (58.1)	30 467 (58.0)	13 008 (56.7)
1–2 times/wk	91 276 (24.4)	16 646 (23.9)	30 202 (25.7)	27 166 (24.5)	12 024 (22.9)	5238 (22.8)
≥3 times/wk	58 421 (15.6)	7223 (10.4)	17 118 (14.5)	19 312 (17.4)	10 081 (19.2)	4687 (20.4)
Physical activity						
None	187 348 (50.1)	34 089 (48.9)	57 245 (48.6)	55 839 (50.3)	27 655 (52.6)	12 520 (54.6)
1–2 times/wk	81 128 (21.7)	16 107 (23.1)	26 666 (22.7)	23 558 (21.2)	10 457 (19.9)	4340 (18.9)
≥3 times/wk	105 490 (28.2)	19 521 (28.0)	33 792 (28.7)	31 644 (28.5)	14 460 (27.5)	6073 (26.5)
Body mass index, kg/m^2	24.9 [22.9–27.0]	23.8 [21.9–25.8]	24.8 [22.9–26.8]	25.2 [23.3–27.3]	25.4 [23.4–27.6]	25.5 [23.4–27.8]
Charlson comorbidity index†						
0	138 147 (36.9)	25 219 (36.2)	42 374 (36.0)	40 707 (36.7)	20 208 (38.4)	9639 (42.0)
1	68 895 (18.4)	13 101 (18.8)	21 645 (18.4)	20 501 (18.5)	9587 (18.2)	4061 (17.7)
2	84 628 (22.6)	15 531 (22.3)	26 954 (22.9)	25 508 (23.0)	11 754 (22.4)	4881 (21.3)
≥3	82 296 (22.0)	15 866 (22.8)	26 730 (22.7)	24 325 (21.9)	11 023 (21.0)	4352 (19.0)
BP-lowering drug use						
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	190 183 (50.9)	20 027 (28.7)	53 554 (45.5)	64 607 (58.2)	35 312 (67.2)	16 683 (72.7)
Calcium channel blocker	181 870 (48.6)	14 849 (21.3)	48 615 (41.3)	64 080 (57.7)	36 640 (69.7)	17 686 (77.1)
Diuretic	154 512 (41.3)	13 944 (20.0)	41 545 (35.3)	53 583 (48.3)	30 538 (58.1)	14 902 (65.0)
β-blocker	95 536 (25.5)	8927 (12.8)	24 875 (21.1)	32 488 (29.3)	19 070 (36.3)	10 176 (44.4)
K-sparing diuretic	10 937 (2.9)	1467 (2.1)	3065 (2.6)	3500 (3.2)	1925 (3.7)	980 (4.3)
Others	12 137 (3.2)	1215 (1.7)	3317 (2.8)	4063 (3.7)	2365 (4.5)	1177 (5.1)
None	104 728 (28.0)	33 485 (48.0)	38 361 (32.6)	23 310 (21.0)	7084 (13.5)	2488 (10.8)
Glucose-lowering drug use						
Insulin	40 248 (10.8)	7709 (11.1)	12 762 (10.8)	11 498 (10.4)	5758 (11.0)	2521 (11.0)
Metformin	146 208 (39.1)	24 824 (35.6)	46 720 (39.7)	44 586 (40.2)	21 148 (40.2)	8930 (38.9)

(*Continued*)

Table. Continued

Variable	Overall (N=373 966)	By SBP range, mm Hg				
		<120 (N=69 717)	120 to <130 (N=117 703)	130 to <140 (N=111 041)	140 to <150 (N=52 572)	≥150 (N=22 933)
Sulfonylurea	128 503 (34.4)	19 894 (28.5)	39 493 (33.6)	40 160 (36.2)	20 027 (38.1)	8929 (38.9)
Dipeptidyl peptidase-4 inhibitor	29 148 (7.8)	5969 (8.6)	9891 (8.4)	8412 (7.6)	3566 (6.8)	1310 (5.7)
α-glucosidase inhibitor	29 095 (7.8)	4901 (7.0)	9084 (7.7)	8797 (7.9)	4360 (8.3)	1953 (8.5)
Others‡	17 998 (4.8)	3229 (4.6)	5842 (5.0)	5292 (4.8)	2554 (4.9)	1081 (4.7)
Lipid-lowering drug use	152 703 (40.8)	26 029 (37.3)	49 202 (41.8)	46 853 (42.2)	21 671 (41.2)	8948 (39.0)
SBP, mm Hg§	130 [122–138]	115 [111–117]	125 [123–127]	134 [132–137]	143 [141–146]	155 [152–160]
DBP, mm Hg§	80 [75–84]	72 [68–75]	78 [75–81]	82 [79–85]	86 [82–90]	91 [87–96]
Fasting glucose, mg/dL	125 [101–151]	118 [96–145]	125 [100–150]	126 [102–151]	128 [105–154]	131 [108–160]
Total cholesterol, mg/dL	194 [167–223]	192 [166–220]	193 [167–222]	194 [168–223]	196 [169–225]	199 [172–229]
Triglyceride, mg/dL	141 [98–209]	123 [85–180]	140 [98–206]	146 [102–216]	151 [105–224]	158 [110–238]
High-density lipoprotein cholesterol, mg/dL	49 [42–59]	50 [42–60]	49 [42–58]	49 [42–59]	49 [42–59]	50 [42–59]
Estimated glomerular filtration rate, mL/min per 1.73 m^2¶	59.7 [54.5–86.8]	64.0 [55.5–90.0]	59.7 [54.9–87.5]	59.7 [54.2–85.6]	59.2 [53.8–84.7]	59.6 [53.2–84.7]
15 to <30	3644 (1.0)	493 (0.7)	948 (0.8)	1096 (1.0)	670 (1.3)	437 (1.9)
30 to <45	22 012 (5.9)	3141 (4.5)	6324 (5.4)	6898 (6.2)	3801 (7.2)	1848 (8.1)
45 to <60	165 494 (44.3)	29 859 (42.8)	52 441 (44.6)	49 765 (44.8)	23 869 (45.4)	9560 (41.7)
≥60	182 816 (48.9)	36 224 (52.0)	57 990 (49.3)	53 282 (48.0)	24 232 (46.1)	11 088 (48.3)
Urine dipstick protein						
-	167 394 (44.8)	30 378 (43.6)	53 321 (45.3)	50 348 (45.3)	23 940 (45.5)	9407 (41.0)
±	89 717 (24.0)	19 776 (28.4)	29 241 (24.8)	25 380 (22.9)	10 922 (20.8)	4398 (19.2)
1+	75 146 (20.1)	13 422 (19.3)	23 328 (19.8)	22 392 (20.2)	10 776 (20.5)	5228 (22.8)
2+	31 103 (8.3)	4677 (6.7)	9057 (7.7)	9568 (8.6)	5059 (9.6)	2742 (12.0)
≥3+	10 606 (2.8)	1464 (2.1)	2756 (2.3)	3353 (3.0)	1875 (3.6)	1158 (5.0)

Values as median [interquartile range] or number (%). BP indicates blood pressure; DBP, diastolic blood pressure; Q, quartile; and SBP, systolic blood pressure.

*Categorized based on quartiles among the entire Korean population.

†Excluding kidney diseases and diabetes.

‡Including sodium-glucose cotransporter-2 inhibitor, glucagon-like peptide-1 receptor agonist, thiazolidinedione, and meglitinide.

§Determined as the mean of all BPs measured throughout the 5-year look-back period.

¶Calculated by the 2009 Chronic Kidney Disease Epidemiology Collaboration equation.

but excluded those with serum creatinine >1.5 mg/dL.[12] The prevalence of diabetes and eGFR <60 mL/min per 1.73 m^2 was as low as 19% and 2%, respectively, in the STEP (Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients) trial,[13] and 39% and 6%, respectively, in the ESPRIT (Effects of Intensive Systolic Blood Pressure Lowering Treatment in Reducing Risk of Vascular Events) trial.[14] Among 358 533 participants in a meta-analysis of 51 trials by the Blood Pressure Lowering Treatment Trialists' Collaboration, only 6980 (2%) were clearly identified as having both CKD and diabetes.[15] Finally, the prevalence of CKD at baseline was 7.6% in the recent BPROAD (Blood Pressure Control Target in Diabetes) trial.[16] The present study bridges this gap in representation by examining the association between BP and CVD risk exclusively among patients with CKD and comorbid diabetes.

Although the CVD benefits of intensive SBP lowering have been demonstrated in diverse populations,[11,13,31] the benefits of intensive DBP lowering remain unclear. The present study has shown that DBP <80 mm Hg is associated with a decreased CVD risk in adults with diabetes and CKD, contradicting some prior reports that very low DBP levels (eg, <70 mm Hg) may increase CVD risk.[32,33] This discrepancy may be partly explained by our definition of baseline BP, which reflects an individual's overall exposure to BP during the 5 years preceding baseline. This approach may have helped reduce the influence of reverse causality and thereby avoid a spurious J-curve association between DBP and CVD risk.[34] Collectively, our findings suggest that DBP lowering is safe and may help further reduce the risk of CVD when combined with intensive SBP lowering.

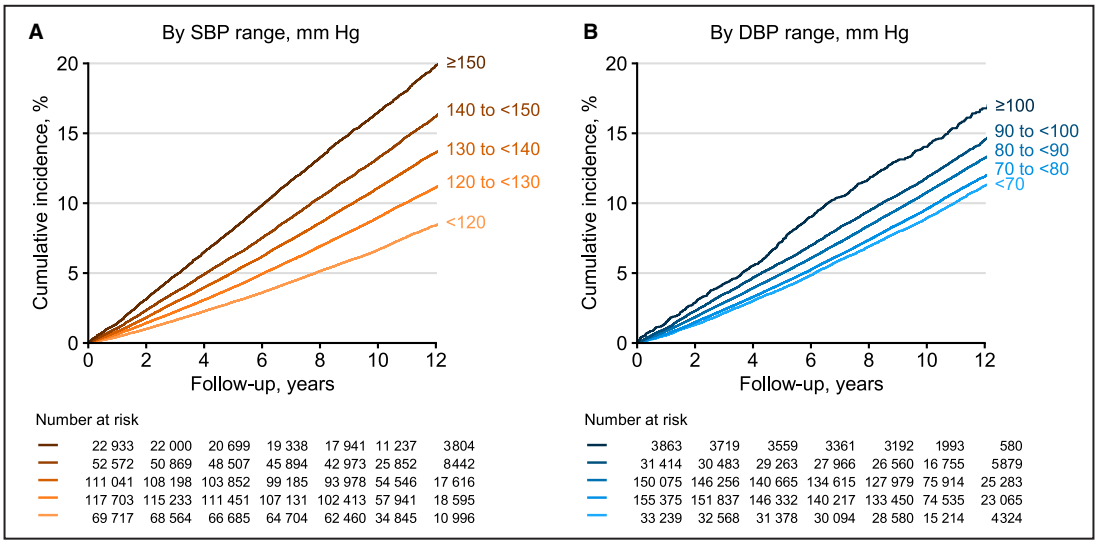

Figure 1. Cumulative incidence of cardiovascular disease event according to blood pressure range.
A, By SBP range. **B**, By DBP range. DBP indicates diastolic blood pressure; and SBP, systolic blood pressure.

A number of previous studies have illustrated the CVD implications of cumulative BP exposure, as opposed to single-point BP measurement, in the general population and among individuals with diabetes.[22,23,35] Our investigation extends the literature and indicates that a higher burden of BP above 130/80 mm Hg—assessed as cumulative BP load, time-weighted BP load, or time above target BP—is associated with an elevated risk of CVD among patients with diabetes and CKD. The observed dose–response relationship between BP burden and CVD risk also highlights the significance of not only lowering BP but also maintaining it below 130/80 mm Hg over time to minimize BP burden and subsequently reduce CVD risk.

Concerns have been raised about the possible adverse effects of intensive BP lowering on kidney function. In both the SPRINT (among participants without CKD) and ACCORD BP trials, the risk of eGFR decline

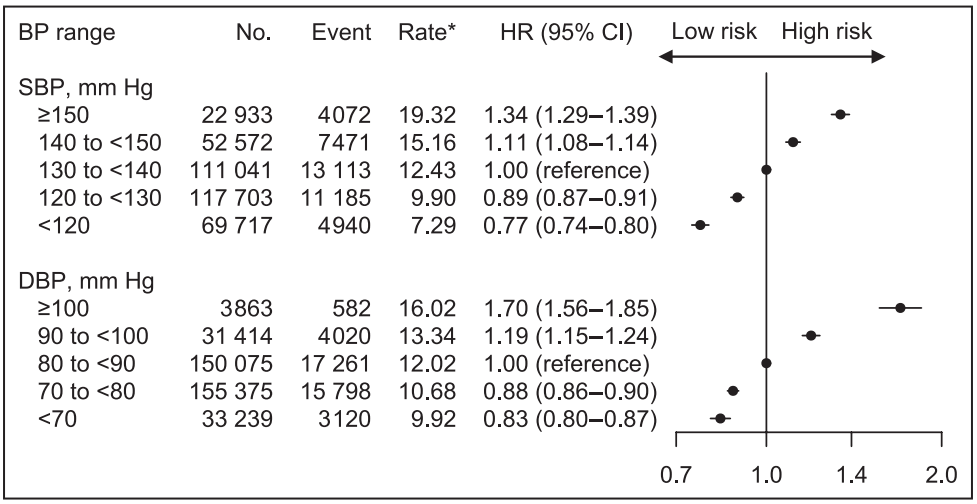

Figure 2. Risk of cardiovascular disease event according to blood pressure range.
P for trend <0.001 for both SBP and DBP. HRs were adjusted for age, sex, household income quartile, residential area, tobacco smoking, alcohol consumption, physical activity, body mass index, Charlson comorbidity index, BP-lowering drug use, glucose-lowering drug class (insulin, metformin, sulfonylurea, dipeptidyl peptidase-4 inhibitor, α-glucosidase inhibitor, others), lipid-lowering drug use, fasting glucose, total cholesterol, triglyceride, high-density lipoprotein cholesterol, estimated glomerular filtration rate, and urine dipstick protein. *Incidence rate per 1000 person-years. BP indicates blood pressure; DBP, diastolic blood pressure; HR, hazard ratio; SBP, systolic blood pressure.

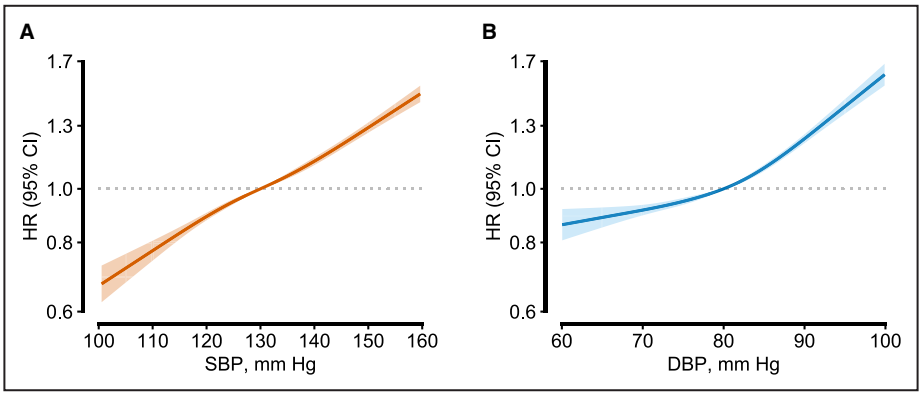

Figure 3. Risk of cardiovascular disease event according to blood pressure.
A, By SBP. **B**, By DBP. Solid lines and shades denote HRs and 95% CIs, respectively. HRs were adjusted for age, sex, household income quartile, residential area, tobacco smoking, alcohol consumption, physical activity, body mass index, Charlson comorbidity index, blood pressure-lowering drug use, glucose-lowering drug class (insulin, metformin, sulfonylurea, dipeptidyl peptidase-4 inhibitor, α-glucosidase inhibitor, others), lipid-lowering drug use, fasting glucose, total cholesterol, triglyceride, high-density lipoprotein cholesterol, estimated glomerular filtration rate, and urine dipstick protein. DBP indicates diastolic blood pressure; HR, hazard ratio; and SBP, systolic blood pressure.

was higher in the intensive treatment group than in the standard treatment group.[11,12] These findings, however, were not replicated in the present study, where SBP <130 mm Hg and DBP <80 mm Hg were both associated with decreased risks of kidney disease progression and decline in eGFR of ≥50%. This discrepancy may be attributable to the observational nature of our study, which did not involve any interventional BP lowering as in the SPRINT or ACCORD BP trials. Our exclusive focus on individuals with diabetes and CKD could also have contributed to the observed reduction in the risk of adverse kidney events at lower BP levels. Indeed, intensive lowering of mean BP to <92 mm Hg was associated with a reduced risk of kidney function decline among patients with CKD and moderate to heavy proteinuria in both the MDRD (Modification of Diet in Renal Disease) and the AASK (African American Study of Kidney Disease and Hypertension) trials.[36,37] The present study adds to the growing body of evidence indicating that intensive BP lowering may exert kidney-protective effects in certain subgroups of CKD.

Study Strengths and Limitations

This study has several strengths. It provides some of the first data on the association of BP with CVD risk specifically in concomitant CKD and diabetes, a condition historically underrepresented in major trials and observational studies. The use of national-scale health screening results linked to the universal single-payer health insurance database enabled us to identify nearly all patients with CKD and diabetes in Korea. Various analytical approaches, including the examination of BP burden, also helped enhance the robustness of our findings.

This study also has some limitations. First, adherence to the BP measurement protocol could have been limited in this nationwide health screening program. However, our use of the mean of all BPs measured during the look-back period is expected to have reduced the effects of potential measurement errors. Second, we cannot exclude the possibility of residual confounding. Unadjusted confounders, such as BP-lowering drug classes, could have influenced our results. Future randomized trials should determine the effect of intensive BP lowering on CVD risk in patients with diabetes and CKD. Third, although our definition of baseline BP reflects the participants' long-term BP management status up to the baseline, it does not account for changes in antihypertensive therapy (eg, initiation, intensification, or cessation) during the look-back or follow-up periods. Moreover, the number of BP measurements during the look-back period was low (median, 3), reflecting the biennial nature of the NHIS health examination.[18] Fourth, defining diabetes and CVD event using health claims information may have introduced some degree of misclassification. However, the diagnosis codes for MI and stroke have demonstrated positive predictive values above 90% in the NHIS database,[38] supporting their validity in a setting where adjudication of clinical end points is not feasible. Lastly, the results of our study may not be applicable to patients with end-stage kidney disease. Whether the findings can be extrapolated to these individuals should be explored in further studies.

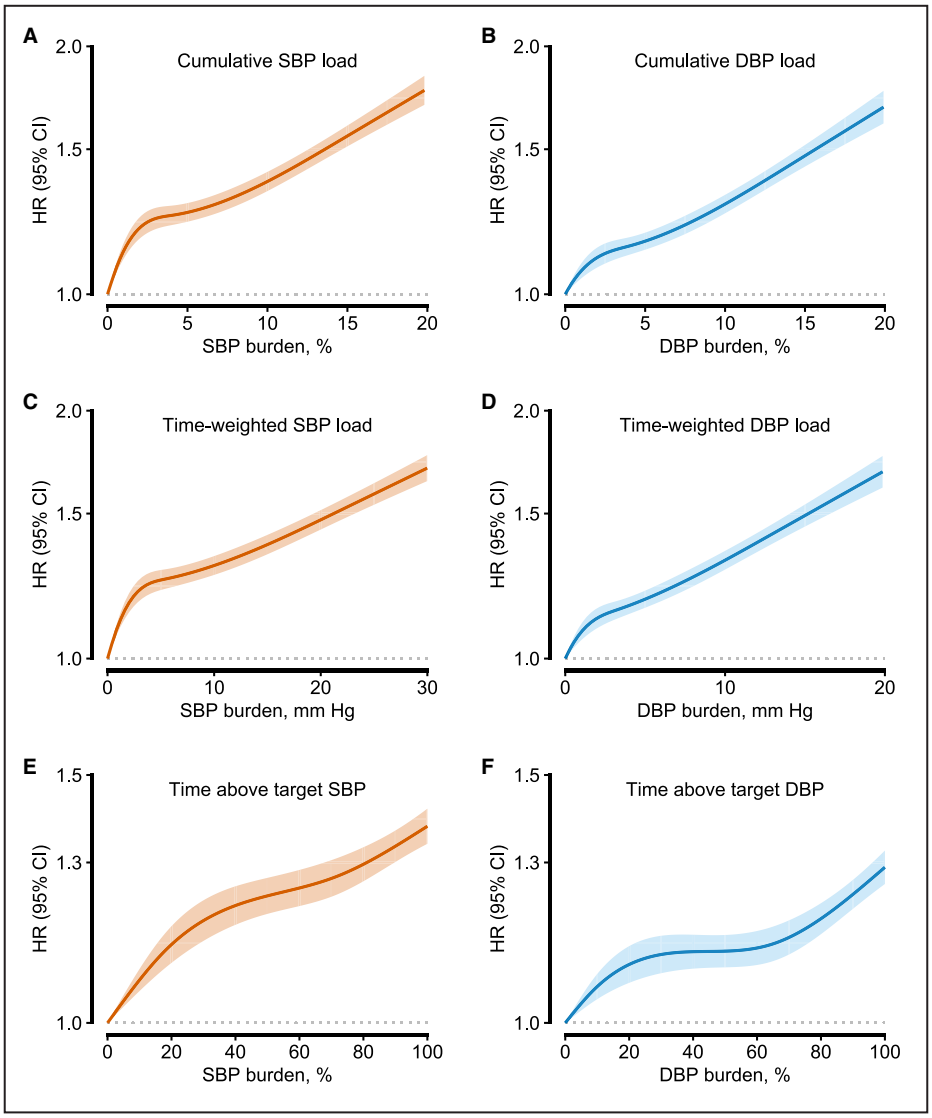

Figure 4. Risk of cardiovascular disease event according to blood pressure burden. **A, B**, By cumulative SBP and DBP load, respectively. **C, D**, By time-weighted SBP and DBP load, respectively. **E, F**, By time >SBP ≥130 mm Hg and DBP ≥80 mm Hg, respectively. Solid lines and shades denote HRs and 95% CIs, respectively. HRs were adjusted for age, sex, household income quartile, residential area, tobacco smoking, alcohol consumption, physical activity, body mass index, Charlson comorbidity index, blood pressure-lowering drug use, glucose-lowering drug class (insulin, metformin, sulfonylurea, dipeptidyl peptidase-4 inhibitor, α-glucosidase inhibitor, others), lipid-lowering drug use, fasting glucose, total cholesterol, triglyceride, high-density lipoprotein cholesterol, estimated glomerular filtration rate, and urine dipstick protein. DBP indicates diastolic blood pressure; HR, hazard ratio; and SBP, systolic blood pressure.

CONCLUSIONS

The optimal BP target for adults with diabetes and CKD remains unknown. In the current study, SBP <130 mm Hg and DBP <80 mm Hg were each associated with a reduced risk of CVD in these individuals. The risks of kidney outcomes, including the composite of kidney disease progression or death from CVD, also showed similar patterns. These findings support an intensive BP target (ie, <130/80 mm Hg) for patients with diabetes and CKD.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S5
Figures S1–S11

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