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ORIGINAL INVESTIGATIONS

On-Treatment Blood Pressure and Cardiovascular Outcomes in Adults With Hypertension and Left Ventricular Hypertrophy

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ABSTRACT

BACKGROUND Benefits of intensive blood pressure lowering on health outcomes have been demonstrated in high-risk patients. However, little is known about such benefits in patients with left ventricular hypertrophy (LVH).

OBJECTIVES This study sought to investigate the association of on-treatment blood pressure with cardiovascular disease (CVD) risk in adults with hypertension and LVH.

METHODS From a nationwide health examination database, this study identified 95,545 participants aged 40-79 years who were taking antihypertensive medication and had LVH on baseline electrocardiography. Using Cox models, HRs and 95% CIs for CVD events were calculated according to systolic blood pressure (SBP) or diastolic blood pressure (DBP).

RESULTS Over a median follow-up of 11.5 years, 12,035 new CVD events occurred. An SBP of <130 mm Hg and DBP of <80 mm Hg were associated with the lowest risk for CVD events in cubic spline models. When the group with SBP of 120-129 mm Hg was the reference, multivariable-adjusted HRs were 1.31 (95% CI: 1.24-1.38) in the ≥140 mm Hg group, 1.08 (95% CI: 1.02-1.15) in the 130-139 mm Hg group, and 1.03 (95% CI: 0.93-1.15) in the <120 mm Hg group. Likewise, when the group with DBP of 70-79 mm Hg was the reference, multivariable-adjusted HRs were 1.30 (95% CI: 1.24-1.37) in the ≥90 mm Hg group, 1.06 (95% CI: 1.01-1.12) in the 80-89 mm Hg group, and 1.08 (95% CI: 0.96 to 1.20) in the <70 mm Hg group.

CONCLUSIONS In adults with hypertension and LVH, the risk for CVD events was the lowest at SBP <130 mm Hg and DBP <80 mm Hg. Further randomized trials are warranted to establish optimal blood pressure–lowering strategies for these patients. (J Am Coll Cardiol 2021;78:1485-1495) © 2021 by the American College of Cardiology Foundation.

In the SPRINT (Systolic Blood Pressure Intervention Trial), intensive blood pressure (BP) lowering (target systolic blood pressure [SBP] <120 mm Hg) resulted in lower rates of cardiovascular disease (CVD) events compared with standard BP lowering (target SBP <140 mm Hg) (1,2). Accordingly, current hypertension guidelines recommend a strict BP goal, in most cases, below 130/80 mm Hg (3,4). However, several studies indicated that excessive BP lowering can also increase

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ABBREVIATIONS AND ACRONYMS

BP = blood pressure

CVD = cardiovascular disease

DBP = diastolic blood pressure

ECG = electrocardiography

HF = heart failure

ICD-10 = International Classification of Disease-10th Revision

LVH = left ventricular hypertrophy

MI = myocardial infarction

NHIS = National Health Insurance Service

SBP = systolic blood pressure

CVD events in high-risk patients or those with established CVD (5-10); consequently, the 2018 European Society of Cardiology/European Society of Hypertension guidelines incorporated a lower limit for BP control of 120/70 mm Hg (4).

Left ventricular hypertrophy (LVH), a marker of cardiac end-organ damage, is a specific disease entity that has been consistently under-represented in landmark trials—7.4% in the SPRINT and 5.4% in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study (1,11). Intensive BP lowering in patients with LVH can lead to the regression of myocardial hypertrophy and subsequently exert beneficial effects on CVD outcomes. On the contrary, because of the increased myocardial compressive pressure on coronary arteries and impaired left ventricular filling in LVH (12), excessive BP lowering might hinder adequate myocardial perfusion and elevate the risk of CVD events (13).

Using a nationwide health examination and claims database, we investigated the association between on-treatment BP and cardiovascular outcomes in adults with hypertension and LVH.

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METHODS

DATA SOURCE. We used a nationwide anonymized database provided by the National Health Insurance Service (NHIS), which includes medical claim records for the entire South Korean population. The NHIS is the single provider of universal health care coverage in South Korea. The NHIS database contains sociodemographic details, reimbursement claims with the International Classification of Disease-10th Revision (ICD-10) coding, general health check-up results, and death information. This data source was described in previous studies (14,15). This study complied with the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board of Yonsei University Health System, Seoul, Korea (#Y-2019-0081). Written informed consent was waived, as this is a retrospective study of deidentified administrative data.

STUDY POPULATION. A total of 12,041,906 adults aged 40-79 years underwent routine NHIS health examinations including electrocardiography (ECG) between 2004 and 2008. If a participant had multiple examinations during this period, the last record was used as the baseline. Among 11,673,788 participants with complete covariable information, we identified 160,774 participants who had been treated for hypertension ≥1 year and had ECG findings of LVH on or before the baseline examination in the absence of possible causes for nonhypertensive LVH (eg, mitral regurgitation, aortic stenosis/regurgitation, or hypertrophic cardiomyopathy) or major intraventricular conduction delay (eg, complete left or right bundle branch block, Wolff-Parkinson-White syndrome, major nonspecific conduction delay, or pacemaker implantation) (16-20). Identification of antihypertensive treatment and its regimen in claims data followed the protocol developed by the Korean Society of Hypertension (21). After excluding participants with <2 BP-measuring visits (n = 35,626), with prior records of CVD (n = 28,896), or with <1 year of follow-up (n = 707), a final analytical sample of 95,545 participants resulted (Supplemental Figure 1).

KEY VARIABLES. Clinical and biochemical measurements and questionnaire-based lifestyle information were collected during routine biennial health examinations provided to all Korean adults by the NHIS. Health examination facilities are designated and overseen for quality control according to relevant national laws and regulations. Details of health examinations are described elsewhere (22). The main exposure was on-treatment BP, averaged from all available examinations after initial antihypertensive treatment through December 31, 2008 (median: 3 visits [range: 2-6 visits]; the last of these visits was the baseline for the main time-to-event analyses) (Supplemental Figure 2A). BP was measured by trained medical staff using auscultatory or oscillometric methods. The BP measurement protocol recommended at least 5 minutes of rest in a seated position followed by 2 measurements averaged in a 5-minute interval (23). The presence of electrocardiographic LVH was confirmed by trained physicians in each health examination center. Other collected variables included body mass index, fasting glucose, total cholesterol, tobacco use, alcohol consumption, and exercise frequency. Use of lipid- or glucose-lowering drugs (24,25) and Charlson comorbidity index (26) were determined from insurance claims data during a 2-year look-back period.

OUTCOMES. The primary outcome was a composite CVD event, defined as the first hospitalization for myocardial infarction (MI) (ICD-10: I21-I23), stroke (ICD-10: I60-I64), or heart failure (HF) (ICD-10: I50), or a CVD-related death (ICD-10: I00-I99) (15,27,28) recorded through December 31, 2019. The accuracy of the hospitalization codes has previously been validated (29). If a participant had >1 event during the follow-up period, the first event was counted as the outcome. Secondary outcomes were MI, stroke, and

HF hospitalization, assessed separately; if a participant had more than one type of event, the first occurrence of each type of event was counted as an outcome. Participants who did not have any event were censored at the date of death, last follow-up, or December 31, 2019, whichever came first. Death was ascertained by linkage to the national registry via resident registration numbers.

STATISTICAL ANALYSIS. Baseline characteristics were reported as mean ± SD, median (interquartile range), or n (%) as appropriate. Incidence rates of CVD events were calculated as the number of events per 1,000 person-years of follow-up. HRs and adjusted cumulative incidence of CVD events were calculated using Cox proportional hazards models. All analyses were done separately for SBP and diastolic blood pressure (DBP). For categorical analyses of BP, the following cutoffs were used—for SBP, <120 mm Hg, 120-129 mm Hg, 130-139 mm Hg, and ≥140 mm Hg; for DBP, <70 mm Hg, 70-79 mm Hg, 80-89 mm Hg, and ≥90 mm Hg. For continuous analyses of BP, restricted cubic spline terms were used with reference SBP of 130 mm Hg and DBP of 80 mm Hg and 4 knots at the 5th, 35th, 65th, and 95th percentiles. The proportionality of hazards was confirmed via graphical inspection of log-minus-log plots and Schoenfeld residuals. HRs were adjusted for age, sex, household income quartile, Charlson comorbidity index, antihypertensive class, lipid-lowering drug use, diabetes, tobacco smoking, alcohol consumption, exercise frequency, body mass index, and total cholesterol. Covariables were selected a priori on the basis of their possible associations with BP and CVD (30,31).

The following sensitivity analyses were conducted. First, the main analyses were further stratified by sex, hypercholesterolemia, diabetes, or monotherapy versus combination therapy. Second, to further minimize the possibility of reverse causation or residual confounding, the analyses were restricted to participants with: 1) 1-year lag period (ie, without outcome events) after the baseline (n = 94,742); or 2) no significant underlying comorbidity (Charlson comorbidity index ≤1; n = 58,537). Third, to account for the changes in BP over time, we used time-varying Cox models with a time-updated average BP during follow-up (median: 8 visits [range: 2-16 visits]) as the main exposure (Supplemental Figure 2B). Fourth, we repeated our main analyses using Fine-Gray models instead of Cox models to account for a competing risk of noncardiovascular death. Fifth, we explored the association of BP with incident adverse events (a composite of hypotension, syncope, electrolyte abnormality, or acute kidney injury) at BP levels below 130/80 mm Hg. Analyses were performed using SAS version 9.4 (SAS Institute Inc) and R version 3.5.3 (R Foundation for Statistical Computing).

RESULTS

BASELINE CHARACTERISTICS. Of the 95,545 participants who had LVH on baseline ECG (median age: 62 years; 63.6% men), 4,405 (4.6%), 17,239 (18.0%), 30,560 (32.0%), and 43,341 (45.4%) had an SBP of <120 mm Hg, 120-129 mm Hg, 130-139 mm Hg, and ≥140 mm Hg, respectively; 2,315 (2.4%), 20,180 (21.1%), 46,597 (48.8%), and 26,453 (27.7%) had a DBP of <70 mm Hg, 70-79 mm Hg, 80-89 mm Hg, and ≥90 mm Hg, respectively. Participants were generally older in higher SBP groups but younger in higher DBP groups. Participants with higher SBP or DBP levels had lower household income and Charlson comorbidity index; were more likely to be on combination antihypertensive therapy; used lipid-lowering drug less frequently; were more frequent drinkers; exercised less frequently; and had higher body mass index, total cholesterol, and fasting glucose levels compared with those with lower SBP or DBP levels (**Table 1**).

PRIMARY ANALYSES. During a median follow-up of 11.5 years, 12,035 new CVD events were recorded. In the SBP <120 mm Hg, 120-129 mm Hg, 130-139 mm Hg, and ≥140 mm Hg groups, 442, 1,709, 3,406, and 6,478 events occurred, respectively; in the DBP <70 mm Hg, 70-79 mm Hg, 80-89 mm Hg, and ≥90 mm Hg groups, 353, 2,519, 5,577, and 3,586 events occurred, respectively. Using the group with SBP 120-129 mm Hg as the reference, multivariable-adjusted HRs were 1.31 (95% CI: 1.24-1.38) in the ≥140 mm Hg group, 1.08 (95% CI: 1.02-1.15) in the 130-139 mm Hg group, and 1.03 (95% CI: 0.93-1.15) in the <120 mm Hg group. Likewise, using the group with DBP 70-79 mm Hg as the reference, multivariable-adjusted HRs were 1.30 (95% CI: 1.24-1.37) in the ≥90 mm Hg group, 1.06 (95% CI: 1.01-1.12) in the 80-89 mm Hg group, and 1.08 (95% CI: 0.96-1.20) in the <70 mm Hg group (**Figure 1,** Supplemental Table 1). The adjusted cumulative incidence of CVD events was also the highest in the SBP ≥140 mm Hg group, followed by the 130-139 mm Hg group, and then by both 120-129 mm Hg and <120 mm Hg groups (**Figure 2A**). Similarly, the adjusted cumulative incidence of CVD events was the highest in the DBP ≥90 mm Hg group, followed by the 80-89 mm Hg group, and then by both 70-79 mm Hg and <70 mm Hg groups (**Figure 2B**).

In restricted cubic spline analyses, the risk for CVD events was the lowest at SBP <130 mm Hg, whereas

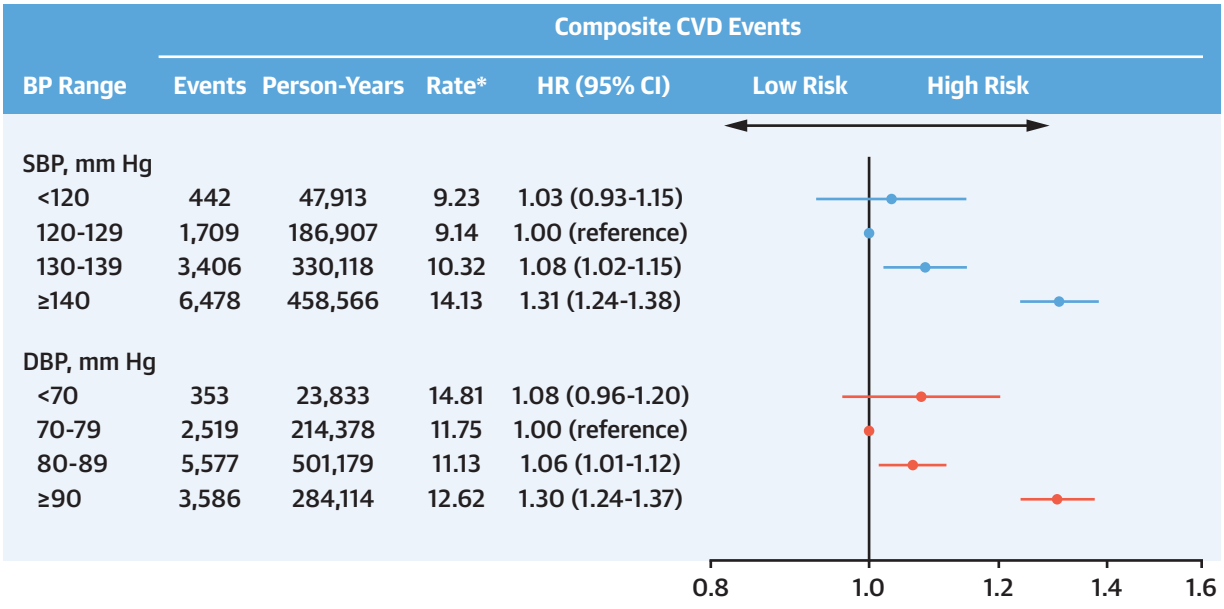
TABLE 1 Baseline Characteristics by BP Range

	By SBP, mm Hg				By DBP, mm Hg			
	<120 (n = 4,405)	120-129 (n = 17,239)	130-139 (n = 30,560)	≥140 (n = 43,341)	<70 (n = 2,315)	70-79 (n = 20,180)	80-89 (n = 46,597)	≥90 (n = 26,453)
Age, y	59 (53-68)	60 (53-68)	60 (54-68)	63 (56-70)	68 (60-72)	64 (56-70)	61 (54-68)	60 (52-68)
Sex								
Female	1,718 (39.0)	5,972 (34.6)	10,365 (33.9)	16,745 (38.6)	1,126 (48.6)	8,304 (41.1)	16,512 (35.4)	8,858 (33.5)
Male	2,687 (61.0)	11,267 (65.4)	20,195 (66.1)	26,596 (61.4)	1,189 (51.4)	11,876 (58.9)	30,085 (64.6)	17,595 (66.5)
Household income quartile[a]								
Q4, highest	1,948 (44.2)	7,421 (43.0)	12,698 (41.6)	15,983 (36.9)	1,014 (43.8)	8,349 (41.4)	18,687 (40.1)	10,000 (37.8)
Q3	1,002 (22.7)	3,917 (22.7)	7,119 (23.3)	10,469 (24.2)	495 (21.4)	4,659 (23.1)	10,974 (23.6)	6,379 (24.1)
Q2	671 (15.2)	2,789 (16.2)	4,936 (16.2)	7,891 (18.2)	341 (14.7)	3,255 (16.1)	7,835 (16.8)	4,856 (18.4)
Q1, lowest	784 (17.8)	3,112 (18.1)	5,807 (19.0)	8,998 (20.8)	465 (20.1)	3,917 (19.4)	9,101 (19.5)	5,218 (19.7)
Charlson comorbidity index								
0	1,646 (37.4)	6,736 (39.1)	12,363 (40.5)	17,936 (41.4)	776 (33.5)	7,474 (37.0)	18,962 (40.7)	11,469 (43.4)
1	968 (22.0)	3,505 (20.3)	6,299 (20.6)	9,084 (21.0)	574 (24.8)	4,452 (22.1)	9,672 (20.8)	5,158 (19.5)
2	868 (19.7)	3,476 (20.2)	5,821 (19.0)	8,058 (18.6)	417 (18.0)	3,835 (19.0)	8,868 (19.0)	5,103 (19.3)
≥3	923 (21.0)	3,522 (20.4)	6,077 (19.9)	8,263 (19.1)	548 (23.7)	4,419 (21.9)	9,095 (19.5)	4,723 (17.9)
Number of antihypertensive class								
1	1,968 (44.7)	7,418 (43.0)	13,168 (43.1)	17,374 (40.1)	1,018 (44.0)	8,687 (43.0)	19,855 (42.6)	10,368 (39.2)
2	1,708 (38.8)	6,744 (39.1)	11,876 (38.9)	16,809 (38.8)	862 (37.2)	7,863 (39.0)	18,119 (38.9)	10,293 (38.9)
≥3	729 (16.5)	3,077 (17.8)	5,516 (18.0)	9,158 (21.1)	435 (18.8)	3,630 (18.0)	8,623 (18.5)	5,792 (21.9)
Antihypertensive class[b]								
Renin-angiotensin blocker	1,790 (40.6)	6,510 (37.8)	10,762 (35.2)	15,204 (35.1)	880 (38.0)	7,375 (36.5)	16,271 (34.9)	9,740 (36.8)
Calcium-channel blocker	2,576 (58.5)	11,128 (64.6)	20,886 (68.3)	30,486 (70.3)	1,458 (63.0)	13,181 (65.3)	31,966 (68.6)	18,471 (69.8)
Diuretic	1,655 (37.6)	6,693 (38.8)	11,687 (38.2)	17,863 (41.2)	889 (38.4)	7,734 (38.3)	18,241 (39.1)	11,034 (41.7)
Beta-blocker	1,506 (34.2)	5,723 (33.2)	9,873 (32.3)	15,096 (34.8)	792 (34.2)	6,835 (33.9)	15,256 (32.7)	9,315 (35.2)
Other	77 (1.7)	293 (1.7)	646 (2.1)	1,029 (2.4)	57 (2.5)	448 (2.2)	991 (2.1)	549 (2.1)
Lipid-lowering drug use	1,246 (28.3)	4,599 (26.7)	7,529 (24.6)	9,956 (23.0)	691 (29.8)	5,480 (27.2)	11,232 (24.1)	5,927 (22.4)
Diabetes	855 (19.4)	3,333 (19.3)	6,295 (20.6)	10,044 (23.2)	618 (26.7)	4,594 (22.8)	9,769 (21.0)	5,546 (21.0)
Tobacco smoking								
Never	2,972 (67.5)	11,673 (67.7)	21,174 (69.3)	31,522 (72.7)	1,726 (74.6)	14,467 (71.7)	32,758 (70.3)	18,390 (69.5)
Past	526 (11.9)	2,268 (13.2)	3,922 (12.8)	4,871 (11.2)	225 (9.7)	2,313 (11.5)	5,806 (12.5)	3,243 (12.3)
Current	907 (20.6)	3,298 (19.1)	5,464 (17.9)	6,948 (16.0)	364 (15.7)	3,400 (16.8)	8,033 (17.2)	4,820 (18.2)
Alcohol consumption								
None	2,531 (57.5)	9,167 (53.2)	16,028 (52.4)	23,940 (55.2)	1,551 (67.0)	12,043 (59.7)	24,924 (53.5)	13,148 (49.7)
1-2 times/wk	1,394 (31.6)	5,949 (34.5)	10,404 (34.0)	13,040 (30.1)	542 (23.4)	5,827 (28.9)	15,306 (32.8)	9,112 (34.4)
≥3 times/wk	480 (10.9)	2,123 (12.3)	4,128 (13.5)	6,361 (14.7)	222 (9.6)	2,310 (11.4)	6,367 (13.7)	4,193 (15.9)
Exercise frequency								
None	1,946 (44.2)	7,629 (44.3)	13,771 (45.1)	21,190 (48.9)	1,097 (47.4)	9,387 (46.5)	21,642 (46.4)	12,410 (46.9)
1-2 times/wk	1,200 (27.2)	4,709 (27.3)	8,229 (26.9)	10,623 (24.5)	502 (21.7)	4,978 (24.7)	12,092 (26.0)	7,189 (27.2)
≥3 times/wk	1,259 (28.6)	4,901 (28.4)	8,560 (28.0)	11,528 (26.6)	716 (30.9)	5,815 (28.8)	12,863 (27.6)	6,854 (25.9)
SBP, mm Hg	114.7 ± 4.2	125.2 ± 2.9	134.5 ± 2.9	150.2 ± 9.3	122.3 ± 11.6	129.2 ± 10.0	137.7 ± 9.5	150.4 ± 11.6
DBP, mm Hg	73.0 ± 5.4	78.8 ± 5.2	83.4 ± 5.5	89.9 ± 7.6	66.4 ± 2.7	75.8 ± 2.7	84.3 ± 2.9	95.0 ± 5.2
Body mass index, kg/m^2	24.1 ± 2.8	24.4 ± 2.8	24.6 ± 2.9	24.8 ± 3.0	23.9 ± 2.9	24.3 ± 2.8	24.6 ± 2.9	24.9 ± 3.0
Total cholesterol, mg/dL	192.8 ± 36.3	194.6 ± 37.2	196.5 ± 36.7	199.3 ± 38.3	191.3 ± 38.3	194.6 ± 37.2	197.2 ± 37.2	200.0 ± 38.2
Fasting glucose, mg/dL	102.2 ± 27.6	103.0 ± 27.5	104.4 ± 27.9	107.1 ± 31.9	103.7 ± 27.3	104.4 ± 29.1	105.0 ± 29.0	106.6 ± 31.7

Values are median (interquartile range), n (%), or mean ± SD. [a]Household income categorized based on quartiles among the entire Korean population. [b]Counted with duplicates for combination therapy. BP = blood pressure; DBP = diastolic blood pressure; Q1 = quartile 1; SBP = systolic blood pressure.

the CVD risk increased log-linearly with SBP at ≥130 mm Hg. Likewise, the risk for CVD events was the lowest at DBP <80 mm Hg, whereas the CVD risk increased log-linearly with DBP at ≥80 mm Hg (Figure 3). As for secondary outcomes, the associations of SBP with CVD risk were generally consistent across all outcomes at ≥130 mm Hg. SBP <130 mm Hg was not associated with additional reductions in the risk for stroke or HF but was marginally associated with a reduced risk for MI (Figure 4, upper panel). Similarly, the associations of DBP with CVD risk were generally consistent across all secondary outcomes at ≥80 mm Hg. DBP <80 mm Hg was not associated with additional reductions in the risk for MI or stroke

FIGURE 1 **BP Range and CVD Risk**



The results were adjusted for age, sex, household income quartile, Charlson comorbidity index, antihypertensive class, lipid-lowering drug use, diabetes, tobacco smoking, alcohol consumption, exercise frequency, body mass index, and total cholesterol. *Incidence rate calculated as the number of events per 1,000 person-years. BP = blood pressure; CVD = cardiovascular disease; DBP = diastolic blood pressure; SBP = systolic blood pressure.

but was marginally associated with an elevated risk for HF (**Figure 4**, lower panel).

SENSITIVITY ANALYSES. First, when stratified by hypercholesterolemia, diabetes, or monotherapy versus combination therapy, the association of SBP or DBP with CVD risk was generally consistent across all subgroups. However, when stratified by sex, the associations diverged at SBP ≥160 mm Hg or DBP <80 mm Hg (Supplemental Figure 3). Second, when a lag period of 1 year or exclusion of participants with severe comorbidity was imposed to minimize reverse causality, the results remained consistent with those of the main analyses (Supplemental Figure 4). Third, when using time-updated average BP during follow-up as a time-varying exposure, the associations of BP with CVD events were generally similar to those from the main analyses (Supplemental Figure 5). Fourth, the main findings seen in Cox models were replicated in Fine-Gray models, which accounted for a competing risk of noncardiovascular death (Supplemental Figure 6). Fifth, lower SBP below 130 mm Hg was associated with a higher risk of adverse events (a composite of hypotension, syncope, electrolyte abnormality, or acute kidney injury); lower DBP below 80 mm Hg was not significantly associated with adverse events (Supplemental Figure 7).

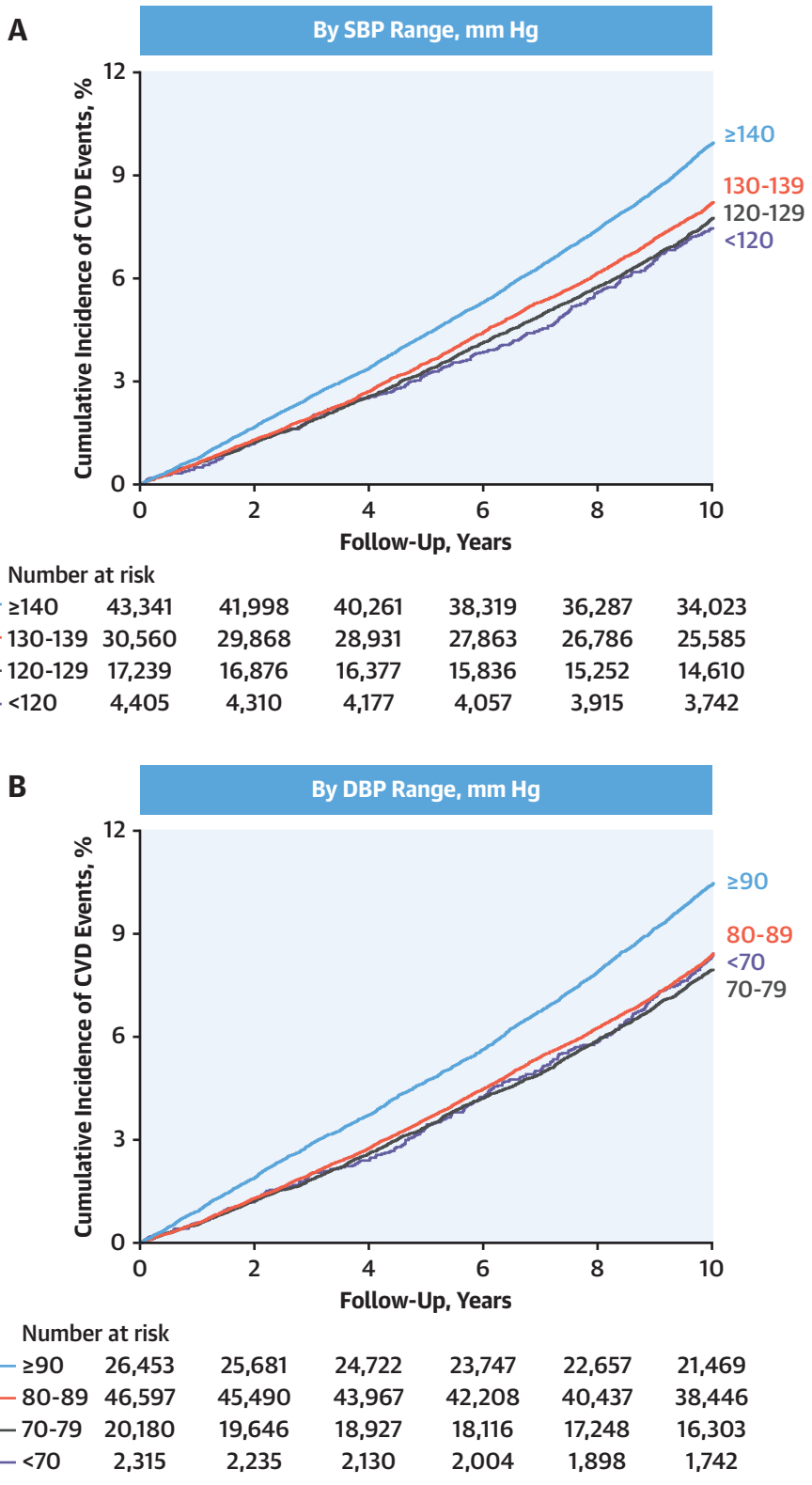
DISCUSSION

In this nationwide study of Korean adults with hypertension and LVH, the risk for CVD events was the lowest at SBP <130 mm Hg or DBP <80 mm Hg without evidence of J-curve association. In comparison, SBP ≥130 mm Hg or DBP ≥80 mm Hg was associated with a higher CVD risk (**Central Illustration**). The results were generally consistent across all outcomes, subgroups, and sensitivity analyses.

LVH is a maladaptive response of cardiomyocytes to chronic pressure overload. Intensive BP control could halt or reverse this process and subsequently exert beneficial effects on CVD outcomes (20). However, given that hypertrophied myocardium demands more oxygen and intramyocardial coronary arteries are compressed more strenuously in LVH (12), excessive BP lowering might also hinder adequate coronary perfusion and lead to myocardial ischemia in patients with LVH. Our findings indicate that the benefits of intensive BP lowering may outweigh, or at least balance with, the potential harms of myocardial hypoperfusion such that the lowest CVD risk can be achieved at BP <130/80 mm Hg.

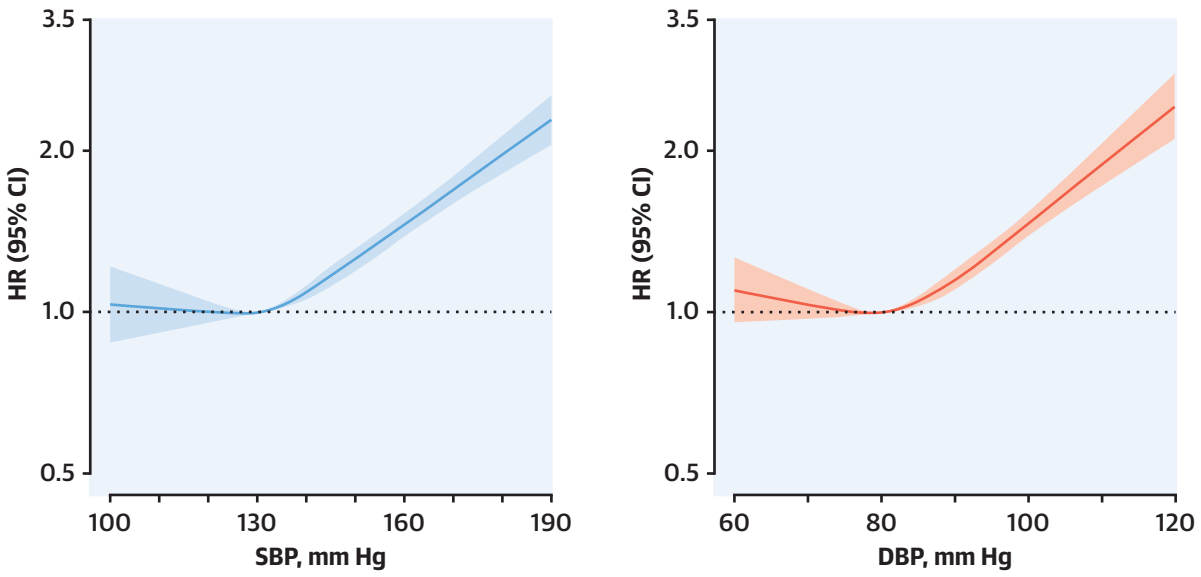
Recent post hoc analyses of the ONTARGET (Ongoing Telmisartan Alone and in Combination With

FIGURE 2 Cumulative Incidence of CVD Events According to BP Range



The results for **(A)** SBP and **(B)** DBP were adjusted for age, sex, household income quartile, Charlson comorbidity index, antihypertensive class, lipid-lowering drug use, diabetes, tobacco smoking, alcohol consumption, exercise frequency, body mass index, and total cholesterol. Abbreviations as in Figure 1.

FIGURE 3 BP and CVD Risk



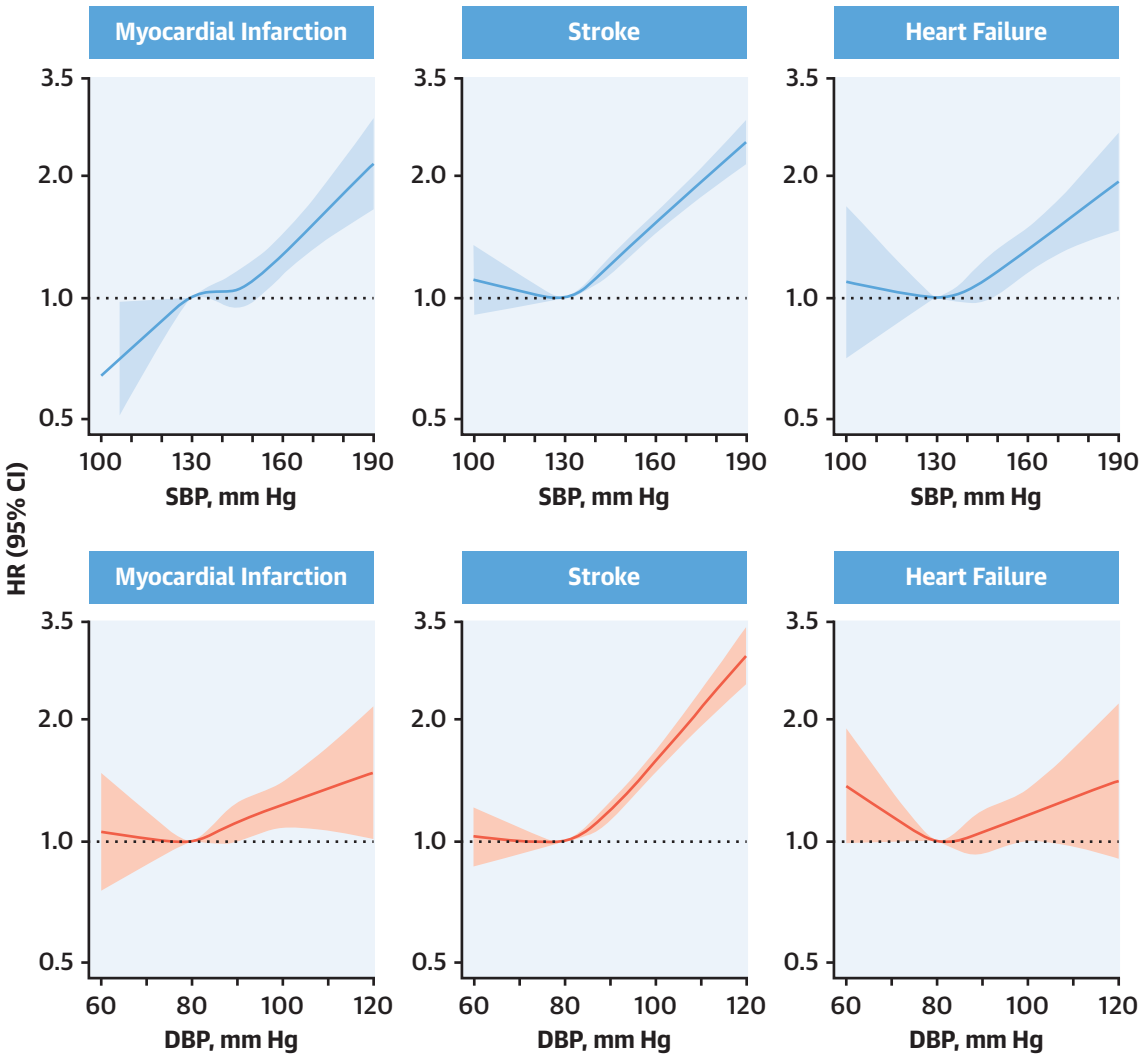
Solid lines and shaded areas denote HRs and 95% CIs, respectively. The results were adjusted for age, sex, household income quartile, Charlson comorbidity index, antihypertensive class, lipid-lowering drug use, diabetes, tobacco smoking, alcohol consumption, exercise frequency, body mass index, and total cholesterol. Abbreviations as in **Figure 1**.

Ramipril Global Endpoint Trial) and TRANSCEND (Telmisartan Randomised Assessment Study in ACE Intolerant Participants With Cardiovascular Disease) trials identified that achieved SBP of 120-139 mm Hg or DBP of 70-79 mm Hg was associated with the lowest risk for CVD events in patients with coronary artery disease, peripheral artery disease, stroke, or diabetes with target organ damage (5,6). Although the BP levels for the lowest CVD risk varied, the results were generally similar in patients with acute coronary syndrome (8), HF (9), and old age (10). However, no study has investigated the optimal BP levels in adults with hypertension and LVH. The present study adds to the published data by demonstrating, exclusively in patients with LVH, that on-treatment SBP and DBP levels associated with the lowest CVD risk are <130 mm Hg and <80 mm Hg, respectively.

Our findings support intensive BP-lowering strategies for patients with hypertension and LVH by reassuring log-linear associations of on-treatment SBP and DBP with CVD risk without definite J-curve phenomena found in some observational studies. In particular, SBP of 120-129 mm Hg and DBP of 70-79 mm Hg were each associated with a lower CVD risk than were SBP of 130-139 mm Hg and DBP of 80-89 mm Hg, respectively. However, no additional risk difference was observed at SBP <120 mm Hg and DBP <70 mm Hg in comparison with SBP of 120-129 mm Hg and DBP of 70-79 mm Hg, respectively. These findings seem plausible as myocardial hypoperfusion, which is of specific concern in LVH (12,13), can offset the benefits of intensive BP lowering at very low BP levels. On the other hand, people with frailty, significant comorbidities, or previous CVD events—hence at high CVD risk—can exhibit low BP; such possible reverse causation or residual confounding may also have masked the benefits of intensive BP lowering. Furthermore, the fact that arterial stiffening lowers DBP and imparts a higher risk for CVD leaves low DBP-CVD association even more prone to reverse causation (32,33). The sex differences in low DBP-CVD association observed in the present study may also be partly attributable to the arterial stiffening, given that it starts earlier and remains more significant in men than in women until their 60s-70s (34,35).

Current international guidelines for hypertension recommend target SBP of <130 mm Hg and DBP of <80 mm Hg in patients with LVH (3,4). This is an extrapolation of findings from the SPRINT and ACCORD trials (1,11), in which participants with electrocardiographic LVH represented only a small proportion of total study participants (7.4% and 5.4%, respectively). Although multiple previous studies have shown that intensive BP lowering results in higher rates of LVH regression (20,36,37), data were scarce regarding overall cardiovascular benefits of

FIGURE 4 **BP and Risk of Secondary Outcomes**



Solid lines and shaded areas denote HRs and 95% CIs, respectively. The results were adjusted for age, sex, household income quartile, Charlson comorbidity index, antihypertensive class, lipid-lowering drug use, diabetes, tobacco smoking, alcohol consumption, exercise frequency, body mass index, and total cholesterol. Abbreviations as in Figure 1.

intensive BP lowering specifically in adults with hypertension and LVH. The present study fills this knowledge gap by identifying the association between on-treatment BP and CVD risk in individuals with LVH, further supporting the current guidelines' BP treatment goal of <130/80 mm Hg in this patient group.

STUDY STRENGTHS. This study has several distinguishing points. To our knowledge, this is the first study to elucidate the association of on-treatment BP with CVD risk exclusively in individuals with LVH. The use of a nationwide database covering the entire Korean population allowed a large sample of hypertensives with LVH, a long follow-up period, and an adequate number of outcome events. Especially, median follow-up period of 11.5 years and the number of events >12,000 are the figures rarely achieved in randomized controlled trials. A multitude of sensitivity analyses also added robustness to our findings.

STUDY LIMITATIONS. First, because of the retrospective, nonrandomized nature of the study, a causal relationship between BP and CVD risk could not be established. Despite adjustment for a wide range of covariates and a multitude of sensitivity analyses, possibilities of residual confounding and

CENTRAL ILLUSTRATION **On-Treatment Blood Pressure and Cardiovascular Outcomes in Left Ventricular Hypertrophy**

Study Population

95,545 adults with hypertension and LVH

Inclusion
- Antihypertensive treatment for >1 year
- At least 2 BP-measuring visits

Exclusion
- Valvular heart disease (eg, MR, AS, AR)
- Hypertrophic cardiomyopathy
- Ventricular conduction delay (eg, LBBB/RBBB, WPW syndrome)
- Previous CVD history
- Follow-up <1 year

Main Exposure

Average on-treatment BP (median 3 BP-measuring visits)

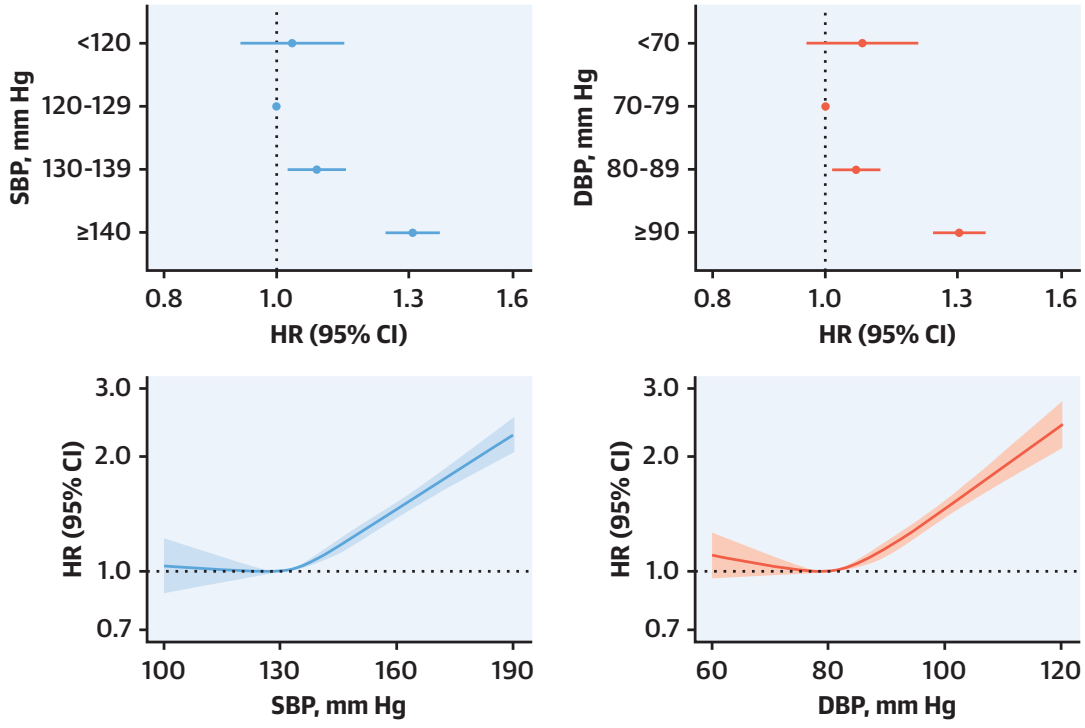
On-treatment BP
- Average of BPs from all visits between initial antihypertensive treatment and baseline examination

Primary Outcome

12,035 CVD events over 11.5 years

Composite CVD events
- Myocardial infarction
- Stroke
- Heart failure hospitalization
- CVD-related death

Main Findings



Lee, H.-H. et al. J Am Coll Cardiol. 2021;78(15):1485-1495.

Solid lines and shaded areas in main findings denote adjusted HRs and 95% CIs, respectively. AR = aortic regurgitation; AS = aortic stenosis; BP = blood pressure; CVD = cardiovascular disease; DBP = diastolic blood pressure; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; MR = mitral regurgitation; RBBB = right bundle branch block; SBP = systolic blood pressure; WPW = Wolff-Parkinson-White.

bias still exist. Second, the diagnostic accuracy of LVH remains to be validated; because our study was based on administrative health data, the diagnostic criteria for LVH could not be prespecified and was left to the discretion of each health examination center. Moreover, although the ECG criteria for LVH have been reported to show high specificity (>90%) in the Asian population (38,39), there might have been some false-positive LVHs, especially among young or thin individuals. We, however, did try to enhance the diagnostic accuracy of LVH by excluding participants with possible causes of non-hypertensive LVH or major intraventricular conduction delay that can impair the validity of ECG diagnosis (16-20). Third, the persistence or regression of LVH during the follow-up period was not assessed in our study. Given that the regression of LVH during antihypertensive therapy is associated with better cardiovascular outcomes than persistent LVH (40), further studies should verify whether the observed association between BP and outcome holds for both regressed and persistent LVH. Fourth, the current study participants' baseline BP levels, assessed by averaging BPs from all visits after initial antihypertensive treatment and on or before baseline examination, may not have fully reflected a person's on-treatment BP status. However, we repeated our analyses using time-updated average BP during follow-up, which yielded consistent results. Last, our results were derived from Korean adults with LVH and should be interpreted cautiously when applied to other populations.

CONCLUSIONS

In adults with hypertension and LVH, on-treatment BP showed a log-linear association with the risk of CVD events. In particular, SBP of 120-129 mm Hg and DBP of 70-79 mm Hg were each associated with a lower CVD risk in comparison with SBP of 130-139 mm Hg and DBP of 80-89 mm Hg, respectively. However, BP levels <120/<70 mm Hg were not associated with additional reductions in CVD risk. Further randomized trials are warranted to establish optimal BP-lowering strategies for patients with hypertension and LVH.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Intensive BP control (BP <130/80 mm Hg) may reduce the risk of cardiovascular events in adults with hypertension LVH.

TRANSLATIONAL OUTLOOK: Whether the relationship between BP lowering and risk reduction holds at levels <130/80 mm Hg in patients with LVH needs further investigation.

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KEY WORDS cardiovascular risk, hypertension, left ventricular hypertrophy, optimal blood pressure

APPENDIX For supplemental figures and a table, please see the online version of this paper.