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Association of optimal blood pressure with mortality in patients taking antihypertensive medications

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Abstract

We investigated the relationship between blood pressure (BP) and mortality in patients taking antihypertensive medications in the Korean using data from the 2007-2015 Korean National Health and Nutrition Examination Surveys. A total of 6601 patients aged 30-74 years were included. Systolic BP (SBP) and diastolic BP (DBP) were both divided into four groups as follows: SBP < 120, 120 ≤ SBP ≤ 129 130 ≤ SBP ≤ 139, and SBP ≥ 140; DBP < 70, 70 ≤ DBP ≤ 79, 80 ≤ DBP ≤ 89, and DBP ≥ 90. The survival rates and hazard ratios were evaluated using Kaplan-Meier curves and multivariable Cox regression analyses. To evaluate the predictability of all-cause mortality according to SBP and/or DBP, we calculated Harrell's concordance-index. The lowest DBP group had a high risk of mortality regardless of the SBP status. The group with DBP < 70 mm Hg and SBP ≥ 140 mm Hg showed the highest mortality. The discriminatory ability calculated using Harrell's C-indexes was greater for the combination of SBP and DBP compared to DBP or SBP alone. These results suggest that it is more effective to simultaneously evaluate the effect of SBP and DBP to predict mortality; clinicians should manage DBP < 70 mm Hg when treating hypertensive patients.

1 | INTRODUCTION

Hypertension is a major risk factor for cardiovascular diseases such as stroke, myocardial infarction (MI), peripheral arterial disease, and heart failure.[1] Controlling blood pressure (BP) with antihypertensive drugs lowers the risk of cardiovascular events and cardiovascular mortality.[2] However, optimal BP management goals have been controversial in many countries. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) guidelines was published in 2003 and sets

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the target BP below 140/90 mm Hg.[3] The JNC8 update in 2014 recommends a BP target < 150/90 mm Hg for people aged ≥ 60 years and maintained a target of 140/90 mm Hg for people < 60 years of age and patients with diabetes or chronic kidney disease.[4] On the other hand, the 2017 American College of Cardiology/American Heart Association (ACC/AHA) Guideline updated the definition of hypertension as SBP/DBP > 130/80 mm Hg compared to a previous standard BP of 140/90 mm Hg.[5] Based on the 2017 ACC/AHA guidelines, the prevalence of hypertension in the Korean population that requires antihypertensive medications was 44.8%, which was significantly increased compared to the JNC7 prevalence of 18.4%.[6] The Systolic Blood Pressure Intervention Trial and a meta-analysis demonstrated that intensive BP lowering reduced cardiovascular outcomes, and those results strongly contributed to changing BP thresholds in the 2017 ACC/AHA guidelines.[5,7] However, another meta-analysis revealed that intensive BP lowering might be harmful in elderly people or people with diabetes.[8] For these reasons, the 2018 European Society of Cardiology/European Society of Hypertension guideline maintained the definition of hypertension as >140/90 mm Hg and recommended antihypertensive medication targeting to <140/90 mm Hg.[9]

BP targets should be determined based on race- and country-specific risk factors. Considering the inconsistency in target BP values, a previous study suggested that the JNC7 target BP of 140/90 mm Hg would be more appropriate than the 2017 ACC/AHA guideline in Korean populations based on all-cause mortality (ACM) and cardiovascular disease mortality.[6] A few studies have been conducted considering new guidelines of ideal BP control and mortality in patients taking antihypertensive medications. Furthermore, most recent investigations assessed the impact of SBP or DBP on clinical outcomes separately as opposed to simultaneously.[10-12]

The goal of this study was to clarify the relationship between ACM and SBP and DBP levels to identify optimal BP targets for patients taking antihypertensive medication. Additionally, we evaluated the possible discriminatory ability of SBP and DBP for ACM in subjects taking antihypertensive medication in a nationwide population-based Korean cohort.

2 | METHODS

2.1 | Study population

This study was conducted using data from the 2007-2015 Korean National Health and Nutrition Examination Survey (KNHANES) cohort provided by the Korea Centers for Disease Control and Prevention. KNHANES is a nationwide cross-sectional survey that represents the health and nutritional status of Koreans.[13] We obtained recent datasets containing any cause of death information. The study period was between January 1, 2007, and December 31, 2015. From a pool of 43 156 participants aged 30-74 years, patients with any of the following criteria were excluded: history of stroke, acute MI, or any type of malignant cancer (n = 2452); death in the registration year (n = 41); no use of any antihypertensive medications (n = 30 134); and missing data of systolic BP (SBP), diastolic BP (DBP), or death (n = 3928). After exclusions, 6601 participants were analyzed (Figure 1).

2.2 | Data collection

A questionnaire was used to assess self-reported cigarette smoking and alcohol consumption. Each participant was classified as a non-smoker, ex-smoker, or current smoker. Alcohol consumption was defined as drinking a certain quantity (≥7 drinks per time for males and ≥5 drinks per time for females) or frequency (≥2 times per week). BP was measured three times by qualified examiners at local examination centers, and the average of the second and third measurements was used.[13] Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters (kg/m^2).

2.3 | Primary outcome

The end point of this study was ACM.

2.4 | Statistical analysis

The study population characteristics are presented as means ± standard deviations and frequencies (percentages). Both SBP and DBP were classified into four groups as follows: SBP < 120, 120 ≤ SBP ≤ 129, 130 ≤ SBP ≤ 139, SBP ≥ 140; DBP < 70, 70 ≤ DBP ≤ 79, 80 ≤ DBP ≤ 89, DBP ≥ 90. Differences between groups were evaluated using one-way analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables.

The survival rates for each group were evaluated using Kaplan-Meier curves and log-rank tests. Incidences per 1000 person-years were calculated for each group. The hazard ratios (HRs) and 95% confidence intervals (CIs) with reference to the highest BP groups (SBP ≥ 140, DBP ≥ 90) were calculated by multivariable Cox regression analyses after adjusting for age, sex, and BMI. To evaluate the predictability of ACM according to SBP, DBP, and both SBP and DBP, we calculated Harrell's concordance (C)-indexes (95% CIs). To calculate the 95% CIs and *P*-values for Harrell's C-index, we used a bootstrap method and resampled 1000 times.

All statistical tests were performed using SAS software, version 9.4 (SAS Institute Inc). All statistical analyses were two-sided, and $P < .05$ was considered statistically significant.

2.5 | Ethics statement

The study was approved by Yonsei University Health System's institutional review board (IRB number: 3-2018-0160), and informed consent was waived.

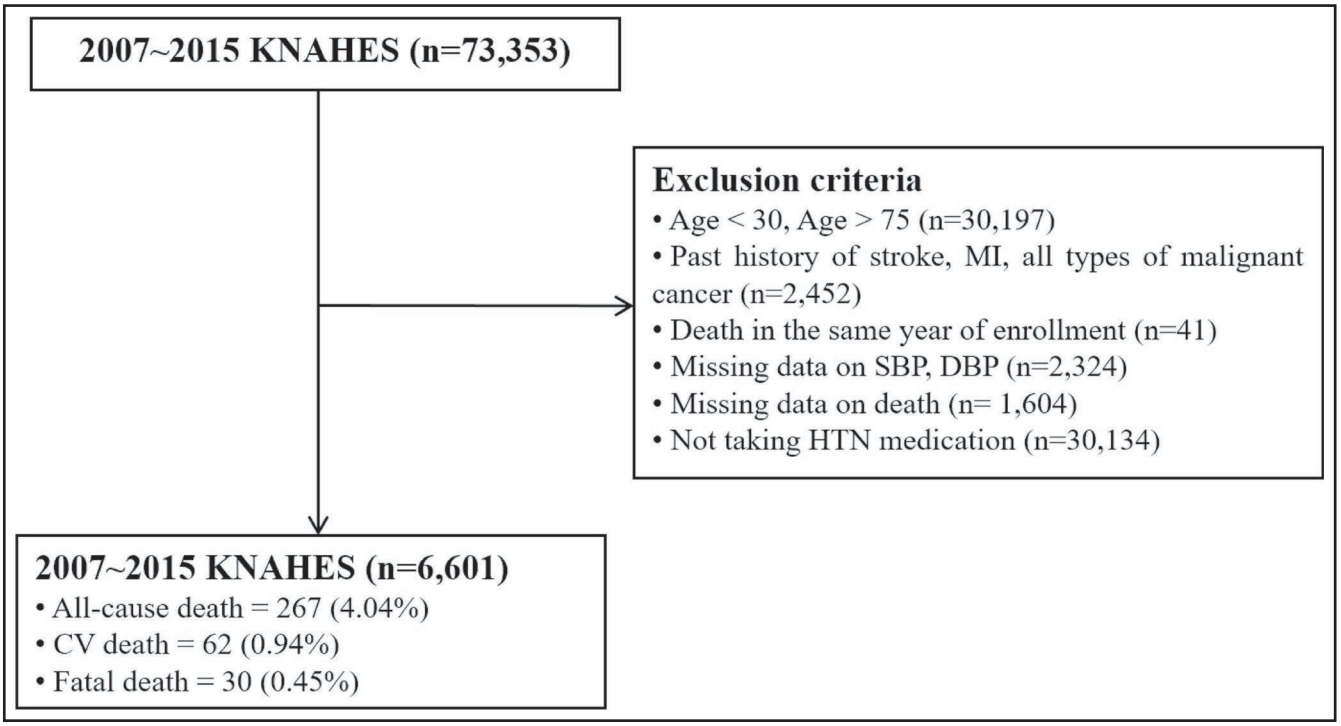


FIGURE 1 Study population flowchart diagram. CV, cardiovascular; DBP, diastolic blood pressure; HTN, hypertension; KNHANES, Korean National Health and Nutrition Examination Survey; MI, myocardial infarction; SBP, systolic blood pressure

3 | RESULTS

We analyzed data from 6601 adults, and 267 persons died during the study period (Figure 1). The study population characteristics according to BP criteria are shown in Table 1. Age showed a positive association with SBP and an inverse association with DBP. Total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol increased with higher SBP and DBP levels.

The cumulative incidence of ACM according to the SBP and DBP categories was assessed using Kaplan-Meier curves and log-rank tests (Figure 2). A total of 2549 ACM events occurred during study period. There were no significant differences when comparing ACM between SBP groups (overall $P = .145$). However, when comparing ACM between DBP groups regardless of SBP, we found that the cumulative incidence of ACM was highest in the lowest DBP group (DBP < 70). Within the group with SBP < 120, Group 1 (DBP < 70) had a greater cumulative incidence of ACM than Group 2 (70 ≤ DBP ≤ 79), Group 3 (80 ≤ DBP ≤ 89), and Group 4 (DBP ≥ 90). Subjects with SBP between 120 and 129 showed a similar pattern, where Group 1 was associated with a higher ACM incidence than Group 3 and 4. In groups with SBP between 130 and 139 and over 140, the cumulative incidence of ACM was also found to be higher in Group 1 than in Group 4. When evaluating cumulative incidences of ACM between DBP groups within a fixed SBP category, we found that overall, the highest cumulative incidences of ACM was associated with subjects with the lowest DBP for any given SBP.

Table 2 presents the unadjusted incidences per 1000 person-years and HRs for ACM based on group after adjusting for age, sex, and BMI. The group with DBP < 70 mm Hg and SBP ≥ 140 mm Hg showed the highest event rates for ACM per 1000 person-years. For DBP analysis within the same SBP group, DBP < 70 had the highest incidence per 1000 person-year except in the SBP < 120 subgroup. There were no significant differences in HRs between SBP groups, whereas the HR (95% CI) of the lowest DBP group was higher [2.439 (1.608-3.700)] than that of other DBP groups. DBP < 70 mm Hg was significantly associated with an increased risk of ACM in the SBP ≥ 130 group. This trend was similar in other groups with the exception of SBP < 120. The HRs (95% CIs) of the lowest DBP group were 3.224 (1.123-9.251) and 2.924 (1.295-6.606) for the 130 ≤ SBP ≤ 139, and 140 ≤ SBP categories, respectively. Similar trend was remained even after additional adjusting of low-density lipoprotein cholesterol (LDL-C) and fasting glucose (Table S1).

Harrell's C-indexes were calculated to determine the possible discriminatory ability of SBP and/or DBP for ACM. DBP showed higher discrimination ability than SBP, but the combination had greater discrimination ability than DBP or SBP alone (Table 3).

Figure 3 shows the classification and regression tree (CART) analysis for considering the combined effects of SBP and DBP on the lowest mortality among patients taking antihypertensive medication. The cutoff DBP levels for predicting mortality were 70 mm Hg in the 120 ≤ SBP < 140 category and 80 mm Hg in the 140 ≤ SBP category.

TABLE 1 Clinical characteristics of the study population

SBP	<120 (n = 1619)	120-129 (n = 1640)	130-139 (n = 1599)	≥140 (n = 1743)	*P*-value
Age (y)	60.8 ± 9.1	60.4 ± 9.4	61.9 ± 8.7	63.5 ± 8.0	<.001
Female sex, n (%)	905 (55.9)	887 (54.1)	909 (56.9)	1093 (62.7)	<.001
BMI, kg/m^2	25.1 ± 3.3	25.4 ± 3.2	25.5 ± 3.3	25.3 ± 3.2	.004
Smokers, n (%)	646 (40.3)	666 (41.0)	616 (38.7)	582 (33.7)	<.001
Alcohol drinkers, n (%)	552 (37.8)	594 (40.1)	556 (38.5)	521 (33.4)	.001
SBP, mm Hg	111.3 ± 6.3	124.5 ± 2.9	134.2 ± 2.9	151.3 ± 11.0	<.001
DBP, mm Hg	72.0 ± 7.9	77.9 ± 8.5	81.4 ± 8.9	85.3 ± 11.1	<.001
Pulse rate	59.0 ± 12.9	56.8 ± 10.9	58.5 ± 12.1	58.5 ± 13.8	.511
Fasting Glucose, mg/dL	107.5 ± 29.1	107.4 ± 27.1	109.2 ± 31.3	109.3 ± 27.5	.107
HbA1c, mg/dL	6.3 ± 1.1	6.3 ± 1.1	6.3 ± 1.1	6.4 ± 1.1	.009
Insulin, mg/dL	11.0 ± 7.5	11.2 ± 8.7	11.3 ± 10.5	11.2 ± 8.8	.931
Total cholesterol, mg/dL	184.7 ± 35.4	187.4 ± 35.1	191.3 ± 37.5	194.8 ± 37.7	<.001
Triglycerides, mg/dL	148.7 ± 94.3	158.5 ± 99.7	164.7 ± 138.9	165.5 ± 123.7	<.001
HDL-C, mg/dL	46.1 ± 11.1	46.7 ± 11.0	47.2 ± 11.5	47.8 ± 11.5	<.001
LDL-C, mg/dL	108.9 ± 33.6	109.0 ± 33.9	111.1 ± 37.1	113.9 ± 37.0	<.001
AST, mg/dL	24.3 ± 11.5	24.9 ± 12.0	25.1 ± 14.5	25.1 ± 13.0	.285
ALT, mg/dL	23.7 ± 16.2	24.7 ± 15.4	24.3 ± 15.4	23.6 ± 14.9	.185
BUN, mg/dL	16.3 ± 5.2	16.2 ± 5.1	16.0 ± 5.4	16.3 ± 5.0	.201
Creatinine, mg/dL	0.9 ± 0.4	0.9 ± 0.4	0.9 ± 0.4	0.9 ± 0.3	.042
WBC, mg/dL	6.3 ± 1.7	6.3 ± 1.7	6.4 ± 1.8	6.4 ± 1.8	.360
DBP	**<70 (n = 1015)**	**70-79 (n = 2267)**	**80-89 (n = 2208)**	**≥90 (n = 1111)**	***P*-value**
Age (y)	66.0 ± 7.1	63.5 ± 7.8	59.9 ± 9.1	57.3 ± 9.3	<.001
Female sex, n (%)	632 (62.3)	1353 (59.7)	1232 (55.8)	577 (51.9)	<.001
BMI, kg/m^2	24.6 ± 3.2	25.2 ± 3.2	25.5 ± 3.2	25.7 ± 3.3	<.001
Smokers, n (%)	367 (36.6)	821 (36.6)	853 (38.9)	469 (42.4)	<.001
Alcohol drinkers, n (%)	263(28.8)	692 (33.8)	823 (41.1)	445 (45.3)	<.001
SBP, mm Hg	119.7 ± 15.7	126.2 ± 13.9	133.1 ± 13.2	145.0 ± 15.2	<.001
DBP, mm Hg	63.5 ± 5.6	74.4 ± 3.0	83.6 ± 3.0	94.8 ± 5.6	<.001
Pulse rate	56.3 ± 10.8	58.9 ± 13.6	57.5 ± 10.8	63.0 ± 15.9	.005
Fasting glucose, mg/dL	114.4 ± 39.1	107.6 ± 25.9	106.9 ± 26.2	107.5 ± 27.8	<.001
HbA1c, mg/dL	6.5 ± 1.2	6.3 ± 1.0	6.3 ± 1.1	6.3 ± 1.1	<.001
Insulin, mg/dL	11.3 ± 12.3	11.0 ± 7.5	11.1 ± 9.3	11.6 ± 8.1	.608
Total cholesterol, mg/dL	182.3 ± 37.1	186.8 ± 35.6	191.7 ± 36.1	197.7 ± 37.5	<.001
Triglycerides, mg/dL	147.2 ± 85.6	149.0 ± 91.6	158.1 ± 99.7	193.6 ± 184.5	<.001
HDL-C, mg/dL	46.0 ± 11.3	46.6 ± 10.8	47.6 ± 11.6	47.2 ± 11.6	.001
LDL-C, mg/dL	106.9 ± 34.5	110.3 ± 33.4	112.4 ± 34.7	111.8 ± 41.4	<.001
AST, mg/dL	24.30 ± 12.9	24.0 ± 9.5	25.1 ± 12.9	26.6 ± 17.2	<.001
ALT, mg/dL	21.6 ± 14.0	22.9 ± 13.2	25.0 ± 16.4	26.8 ± 18.4	<.001
BUN, mg/dL	16.7 ± 6.0	16.4 ± 5.3	16.0 ± 4.8	15.7 ± 4.5	<.001
Creatinine, mg/dL	0.9 ± 0.6	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3	.009
WBC, mg/dL	6.4 ± 1.8	6.3 ± 1.8	6.3 ± 1.7	6.4 ± 1.7	.749

Note: Data are expressed as mean ± standard deviation or frequency (percentage). *P*-values were calculated using one-way ANOVA and chi-square tests.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; WBC, white blood cell.

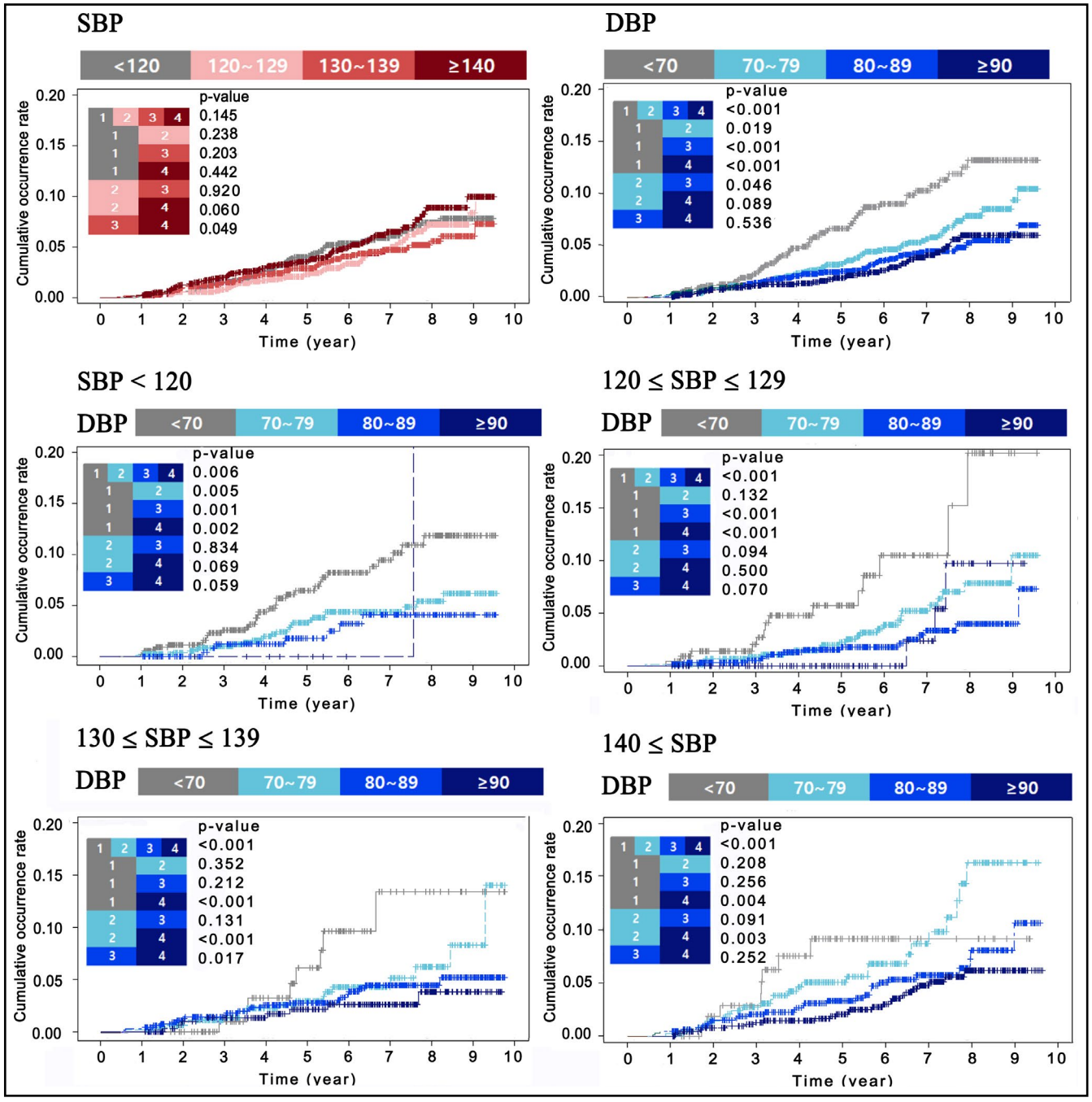


FIGURE 2 Kaplan-Meier curves and log-rank test for ACM according to BP levels. ACM, all-cause mortality; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure

4 | DISCUSSION

It is important to manage hypertension to reduce the risk of cardiovascular morbidity and mortality,[5] but the treatment targets vary among different guidelines.[5,9] Moreover, there is a paucity of studies on optimal BP targets in subjects taking antihypertensive medications. We investigated the optimal SBP and DBP levels to decrease ACM in patients taking antihypertensive medication.

Previous studies demonstrated that mortality was positively associated with the SBP level.[3,14,15] However, we found that the highest cumulative incidences of ACM were associated with subjects with the lowest DBP for any given SBP. There were also no significant differences in ACM according to SBP group in patients taking antihypertensive medication. Similar to our results, an analysis of the ONTARGET and TRASCEND trials showed increased risks of cardiovascular morbidity and mortality in DBP < 70 mm Hg compared with DBP 70-80 mm Hg. However, the study specified the medications (ramipril, telmisartan, and their combinations) and included patients aged ≥ 55 years without symptomatic heart failure at entry, and, with a history of coronary artery disease (CAD), peripheral artery

TABLE 2 HRs and incidences per 1000 per person-years for ACM according to BP group

Groups		n	Events, n (%)	Incidence per 1000 person-years (95% CI)	HR (95% CI)	Pairwise comparison *P*-value		
SBP	<120	1619	66 (4.1)	8.2 (6.2-10.1)	0.9 (0.7-1.3)	.696	.146	.277
	120-129	1640	56 (3.4)	6.6 (4.9-8.3)	0.8 (0.6-1.1)	.128	.724	Ref
	130-139	1599	57 (3.6)	6.6 (4.9-8.3)	0.7 (0.5-1.0)	.055	Ref	
	≥140	1743	88 (5.1)	9.2 (7.3-11.1)	1	Ref		
DBP	<70	1015	63 (6.2)	13.7 (10.3-17.1)	2.4 (1.6-3.7)	<.001	<.001	.001
	70-79	2267	92 (4.1)	8.0(6.4-9.7)	1. 4 (0.9-2.0)	.109	.108	Ref
	80-89	2208	75 (3.4)	6.1 (4.7-7.5)	1.1 (0.7-1.6)	.742	Ref	
	≥90	1111	37 (3.3)	5.8 (3.9-7.6)	1	Ref		
SBP < 120	DBP < 70	544	33 (6.1)	12.9 (8.5-17.3)	0.7 (0.1-5.2)	.718	.024	.013
	70-79	777	25 (3.2)	6.4 (3.9-8.9)	0.4 (0.0-2.7)	.315	.504	Ref
	80-89	285	7 (2.5)	4.5 (1.2-7.9)	0.3 (0.0-2.2)	.217	Ref	
	≥90	13	1 (7.7)	14.8 (14.0-43.5)	1	Ref		
120-129	DBP < 70	222	14 (6.3)	14.9 (7.2-22.7)	3.4 (0.9-12.2)	.064	<.001	.003
	70-79	640	24 (3.8)	7.2 (4.3-10.0)	1.2 (0.3-4.0)	.802	.265	Ref
	80-89	650	15 (2.3)	4.3 (2.1-6.4)	0.8 (0.2-2.8)	.722	Ref	
	≥90	128	3 (2.3)	4.6 (0.6-9.8)	1	Ref		
130-139	DBP < 70	134	8 (6.0.)	13.0 (4.1-22.0)	3.2 (1.1-9.3)	.030	.060	.166
	70-79	480	18 (3.8)	7.6 (4.1-11.1)	1.8 (0.7-4.4)	.210	.549	Ref
	80-89	661	23 (3.5)	6.2 (3.6-8.7)	1.5 (0.6-3.5)	.379	Ref	
	≥90	324	8 (2.5)	4.3 (1.3-7.2)	1	Ref		
≥140	DBP < 70	115	8 (7.0)	16.3 (5.1-27.5)	2.9 (1.3-6.6)	.010	.047	.414
	70-79	370	25 (6.8)	14.0 (8.6-19.5)	2.1 (1.2-3.7)	.011	.090	Ref
	80-89	612	30 (4.9)	8.7 (5.6-11.8)	1.3 (0.8-2.3)	.320	Ref	
	≥90	646	25 (3.9)	6.5 (4.0-9.1)	1	Ref		

Abbreviations: ACM, all-cause mortality; CI, confidence interval; C-index: concordance-index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

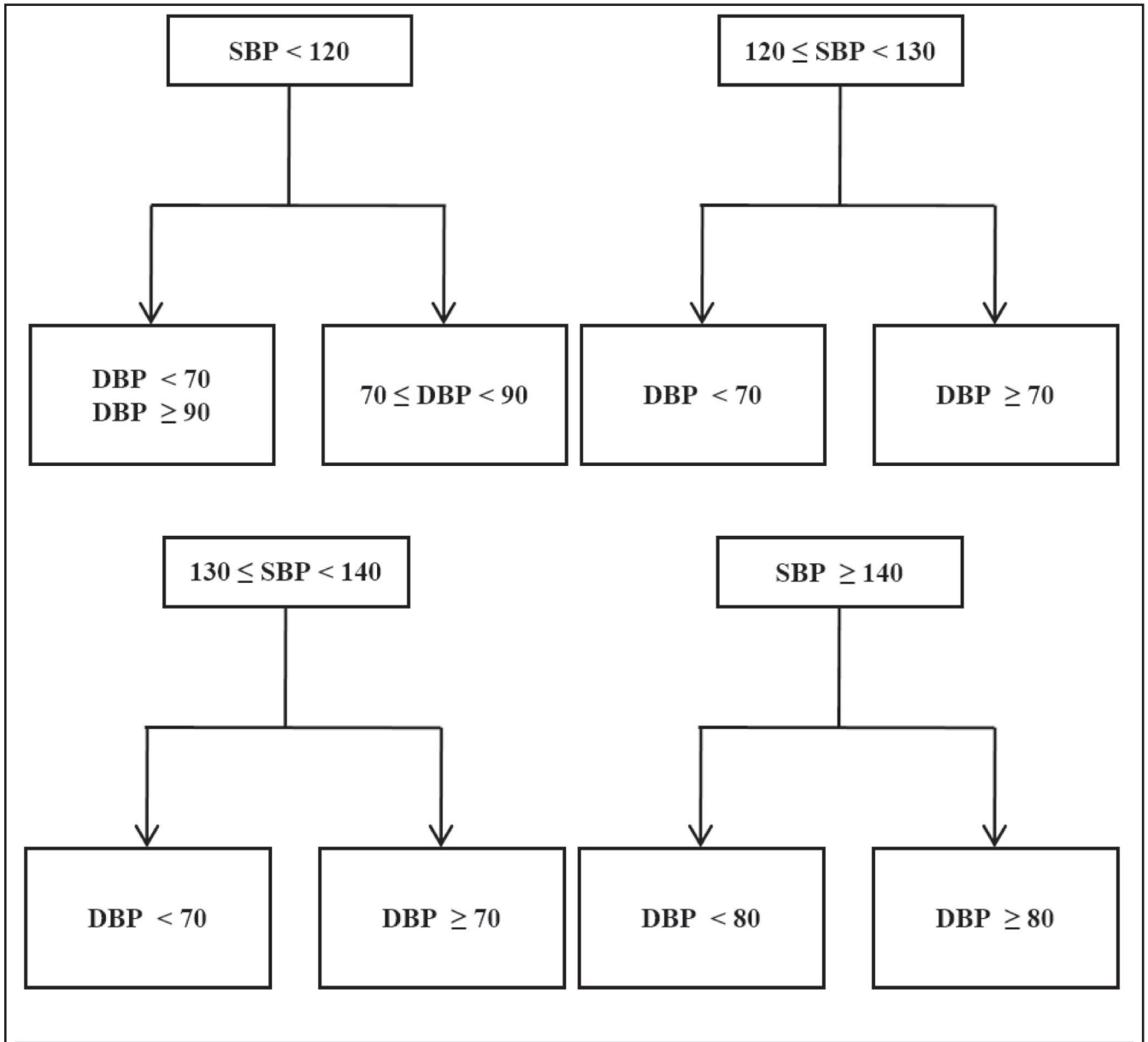
TABLE 3 Discrimination ability for ACM according to SBP and DBP

	C-index (95% CI)	Pairwise comparison *P*-value		
ACM				
SBP	0.519 (0.491-0.551)	Ref		
DBP	0.584 (0.544-0.620)	.030	Ref	
Combination	0.611 (0.580-0.644)	<.001	.024	Ref

Abbreviations: ACM, all-cause mortality; CI, confidence interval; C-index: concordance-index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

disease, transient ischemic attack, stroke, or diabetes mellitus complicated by organ damage.[16] A cohort study of elderly subjects assessed the risk of the cardiovascular outcomes of low DBP induced by antihypertensive medications.[17] The authors found that reducing DBP below 60 mm Hg was associated with shorter survival independent of large artery stiffness and left ventricle (LV) function. Based on this, they suggested an optimal DBP of 70 mm Hg for the elderly and suggested that physicians should also consider DBP in addition to SBP. Our findings also suggest that it is harmful to dramatically reduce DBP.

The mechanisms linking low DBP and higher mortality have not been fully understood, but there are plausible explanations. Coronary blood flow to the LV occurs in diastole. The pressure gradient between the coronary arteries and the right atrium or LV in the diastolic phase is termed coronary perfusion pressure. If it decreases to 40-50 mm Hg, the effective flow becomes nearly zero, which can cause cessation of diastolic coronary arterial blood flow. Additionally, there is an autoregulatory system to compensate for obstructive conditions in the large proximal coronary artery. If it is narrowed by stenotic causes, dilatation of the smaller distal coronary arteries occurs. This "autoregulation" helps ensure constant blood flow to the myocytes. In patients with CAD, a fall in DBP might reduce distal perfusion pressure, which prevents sufficient myocyte perfusion and can aggravate myocardial ischemia. This exacerbation can increase LV filling pressures, perpetuating a vicious cycle by reducing the coronary perfusion pressure (pressure gradient). Left ventricular hypertrophy (LVH) impairs this autoregulatory mechanism. Patients with LVH may have sub-endocardial ischemia even in the absence of stenosis. This can trigger myocardial ischemia



	DBP < 70	70 ≤ DBP < 80	80 ≤ DBP < 90	DBP ≥ 90
SBP < 120	6.46	3.32	2.52	8.33
120 ≤ SBP < 130	6.73	3.9	2.36	2.4
130 ≤ SBP < 140	6.35	3.9	3.61	2.53
SBP ≥ 140	7.48	7.25	5.15	4.03

FIGURE 3 CART analysis of the combined effects of SBP and DBP. CART, classification and regression tree; DBP, diastolic blood pressure; SBP, systolic blood pressure

in patients with impaired coronary blood flow and concurrent LVH, even in a DBP range that is considered physiological.[17-19] Secondly, low DBP and high pulse pressure might be an epiphenomenon of increased arterial stiffness.[17] An increased pulse wave velocity, which is an indicator of arterial stiffness, is highly associated with cardiovascular events.[20] Blacher et al found that a pulse pressure that is 10 mm wider increased the risk of cardiovascular events, irrespective of the SBP level.[21]

Another important finding in our study is that the discrimination ability for ACM using Harrell's C-indexes in patients using antihypertensive medication. DBP has better discriminatory ability than SBP, but the combination of SBP and DBP showed better discriminatory ability than DBP alone in patients taking antihypertensive medications.

Discrepant with our results, Hadaegh et al found that SBP had superior discrimination ability for cardiovascular disease mortality and ACM compared with other BP measures in an Iranian population.[22] However, the study excluded patients receiving antihypertensive medications at baseline. Notably, few studies have considered both SBP and DBP levels.[10-12] Large, longitudinal cohort studies are needed to confirm the influence of each BP measurement or the combined effect of SBP and DBP on mortality in patients taking antihypertensive medications.

This study has several limitations. First, the sample size was small, and the total mortality was just 267 subjects. Among 267 death subjects, cardiovascular death was only 62 (0.94%) and fatal death was 30 (0.45%). This made it difficult to evaluate mortalities attributed to cardiovascular diseases such as MI, hemorrhagic or ischemic stroke, or cardiovascular death. Second, since the data were originally collected using a cross-sectional design from 2007 to 2015 and death information was added newly in 2018 after matching process, it was difficult to reveal the effect of BP control on all-cause mortality. In this regard, the effect of BP on clinical outcomes may be over- or underestimated due to confounding factors. Third, even though BP measurements were performed by qualified examiners using calibrated equipment, the lack of device uniformity and single-visit measurements might have introduced slight variations in our results. Large-scale long-term cohort studies are required and we plan to perform further study. Fourth, the population only included adults from Korea, so the findings might not be applicable to other races or ethnic groups. Fifth, these data do not contain information about the type of antihypertensive agents used. Finally, we could not exclude the possibility of secondary hypertension due to lack of information. Despite these limitations, our study has several strengths. Most previous investigations regarding the relationship between hypertension and mortalities were based on American or European populations.[7,8,10] We used reliable nationwide data representing the health and nutritional status of Koreans. Additionally, various statistical methods were employed to compensate for several biases and enhance the performance of predictive survival models using the combination of SBP and DBP.

5 | CONCLUSIONS

In conclusion, the cumulative incidence of ACM in patients taking antihypertensive medications was highest in the lowest DBP group (DBP < 70) regardless of SBP level. The combination of SBP and DBP has higher discrimination ability for ACM compared to SBP or DBP alone. Appropriate DBP cutoff levels for predicting mortality are 70 mm Hg when 120 ≤ SBP < 140 and 80 mm Hg when 140 ≤ SBP. Therefore, clinical decisions for optimal BP with antihypertensive medications should simultaneously consider SBP and DBP levels and prevent DBP from falling below 70 mm Hg. Additional randomized clinical studies are required to validate these results.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

DHY, DHS, and JWL contributed to conceptualization. HSL contributed to methodology. HSL contributed to software. HSL and DHY contributed to validation. DHS contributed to formal analysis. DHY and DHS contributed to investigation. JWL contributed to resources and data curation. DHY and DHS contributed to writing—original draft preparation. JWL and HJC contributed to writing—review and editing. HSL and DHS contributed to visualization. DHS and JWL contributed to supervision. JWL contributed to project administration. JWL contributed to funding acquisition.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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