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심혈관계질환 과거력이 없는 50세 이상 대한민국성인의 신규 고혈압 진단을 위한 수정된 혈압 기준: 약 백만 명 한국인에 대한 실제 장기 코호트 연구

Modified Blood Pressure Criteria for Newly Diagnosed Hypertension among Korean Adults ≥50 years without history of Cardiovascular Disease: A Real-World Long-Term Cohort Study of about a Million Koreans

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Modified Blood Pressure Criteria for Newly Diagnosed Hypertension among Korean Adults ≥50 years without history of Cardiovascular Disease: A Real-World Long-Term Cohort Study of about a Million Koreans

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Abstract

Modified Blood Pressure Criteria for Newly Diagnosed Hypertension among Korean Adults ≥50 years without history of Cardiovascular Disease: A Real-World Long-Term Cohort Study of about a Million Koreans

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Background:
The 2017 American College of Cardiology / American Heart Association (ACC/AHA) Hypertension Guidelines lowered the criteria for diagnosing hypertension from 140/90 or higher to 130/80mmHg or higher and suggested a threshold for drug therapy of 10-year cardiovascular disease (CVD) risk ≥10%. However, little is known about the appropriate blood pressure (BP) criteria for newly diagnosed hypertension reflecting the subsequent CVD risk among Korean adults without history of CVD.

Methods:
We analyzed 967,853 adults ≥50 years living in seven major metropolitan areas in Korea and underwent health screening in 2004-2005 without history of anti-hypertensive medication and CVD. After determining BP during 2004-2005, all

participants were followed up for CVD starting from January 2006 to December 2018. Participants were categorized into the 2018 ESC/ESH and 2017 ACC/AHA BP categories. The primary outcome was CVD defined as ≥2 days of hospitalization due to CVD. The risk of CVD according to BP categories was determined by calculating the hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox proportional hazards regression analysis.

Results:

The 10-year CVD incidence of 2017 ACC/AHA stage 1 hypertension group was lower than 10% (7.7 events per 1,000 person-years) and that of stage 2 hypertensive group was about 10% (10.2 events per 1,000 person-years). The CVD risk of 2017 ACC/AHA stage 1 isolated diastolic hypertension (IDH, SBP <130 and DBP 80-89mmHg) was higher than optimal BP (adjusted hazard ratio [aHR], 1.13; 95% confidence interval [CI], 1.11-1.16), but not higher than 2017 ACC/AHA Elevated BP (SBP 120-129 and DBP <80mmHg) (aHR 0.98, 95% CI 0.96-1.01). Compared to IDH participants, isolated systolic hypertension (ISH, SBP 130-139 and DBP <80mmHg) (aHR 1.13, 95% CI 1.09-1.16) and combined systolic/diastolic hypertension (SDH, SBP 130-139 and DBP 80-89mmHg) (aHR 1.15, 95% CI 1.12-1.17) participants had significantly higher CVD risk. In participants >80 years, the CVD risk of 2017 ACC/AHA stage 1 hypertension was not higher than that of optimal BP (aHR, 0.99; 95% CI, 0.82-1.21), but BP category of 140-159/90-99 mmHg was associated with an increased risk of CVD (aHR, 1.23; 95% CI, 1.02-1.50).

Conclusion:

The 10-year CVD incidence of 2017 ACC/AHA stage 1 hypertension group was low. The 2017 ACC/AHA stage 1 hypertension group appeared to be heterogeneous and the CVD risk of 2017 ACC/AHA stage 1 IDH was not higher than Elevated

BP. The criteria for diagnosing hypertension of 140/90mmHg or higher would be appropriate among Korean adults ≥50 years without history of hypertension and CVD.

Keywords : Blood Pressure; Hypertension; Cardiovascular Disease
Student Number : 2018-30799

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Ⅰ. INTRODUCTION

1. Background

The goal of diagnosing and treating hypertension is to prevent subsequent cardiovascular disease (CVD). Therefore, when determining the blood pressure (BP) criteria for the diagnosis of hypertension, the risk of subsequent CVD of the BP category is carefully considered. The American College of Cardiology (ACC) and the American Heart Association (AHA) released a new guideline on hypertension with a new definition of stage 1 hypertension (systolic blood pressure [SBP] 130-139 mmHg or diastolic blood pressure [DBP] 80-89 mmHg) in 2017 (Table 1).[1] However, the 2018 European Society of Cardiology (ESC) and European Society of Hypertension (ESH) guideline for hypertension maintained the traditional diagnostic criteria of more than 140/90 mmHg (Table 2).[2] The prevalence of hypertension increased significantly when 2017 ACC/AHA hypertension guideline was applied. However, the clinical implications of stage 1 hypertension according to 2017 ACC/AHA hypertension guideline has been controversial. And little is known about the appropriate blood pressure (BP) criteria for newly diagnosed hypertension reflecting the subsequent CVD risk among middle-aged and elderly Koreans without history of CVD.

Table 1. 2017 ACC/AHA hypertension guideline BP categories*

BP Category	SBP (mmHg)		DBP (mmHg)
Normal	<120	and	<80
Elevated	120-129	and	<80
Hypertension			
Stage 1	130-139	or	80-89
Stage 2	≥140	or	≥90

*Individuals with SBP and DBP in 2 categories should be designated to the higher BP category.
BP indicates blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions)
Acronyms: ACC, American College of Cardiology; AHA, American Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure

Table 2. 2018 ESC/ESH hypertension guideline BP categories*

BP Category	SBP (mmHg)		DBP (mmHg)
Optimal	<120	and	<80
Normal	120-129	and/or	80-84
High normal	130-139	and/or	85-89
Grade 1 hypertension	140-159	and/or	90-99
Grade 2 hypertension	160-179	and/or	100-109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

*BP category is defined according to seated clinic BP and by the highest level of BP, whether systolic or diastolic.
Isolated systolic hypertension is graded 1, 2, or 3 according to SBP values in the ranges indicated.
Acronyms: ESC, European Society of Cardiology; ESH, European Society of Hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure

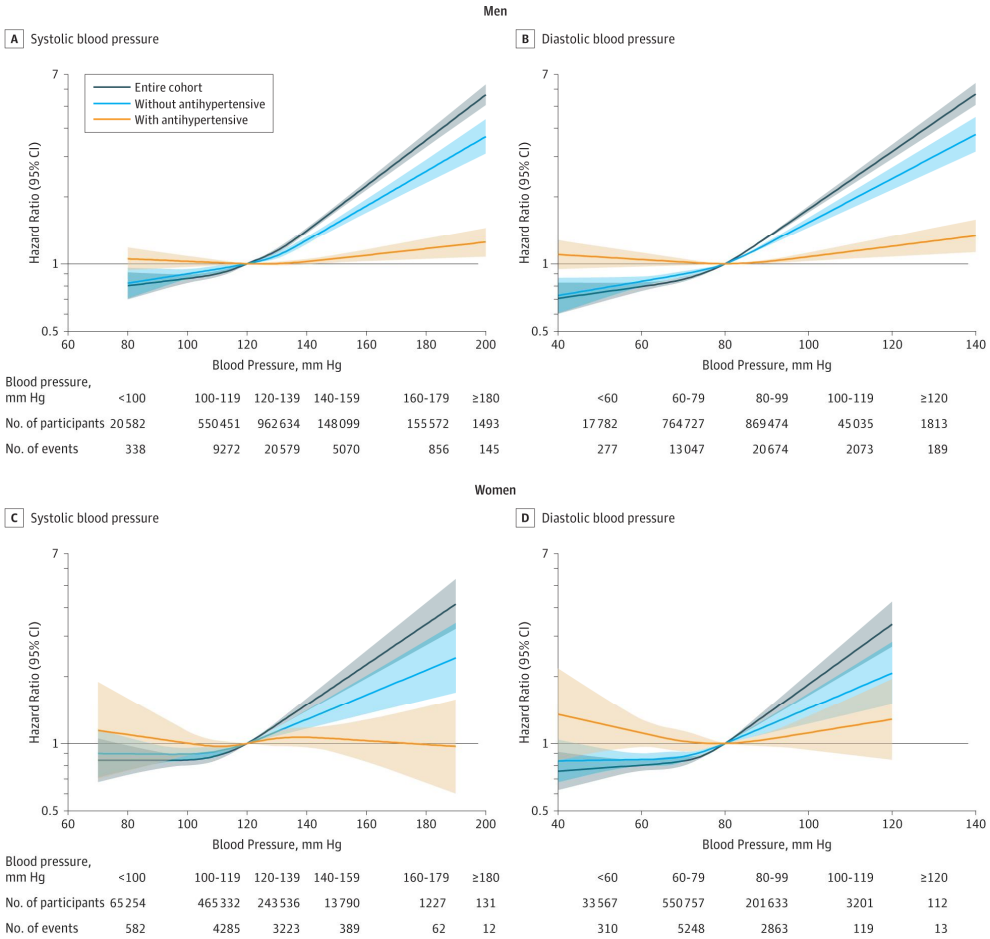
2. Previous literature

1) Cardiovascular risk according to 2018 ESC/ESH and 2017 ACC/AHA hypertension categories

There have been observational studies showing that the risk of cardiovascular disease (CVD) increases in patients with SBP greater than 130 mmHg.[3−5] Moreover, long−term follow−up studies of young adults have shown that 2017 ACC/AHA defined stage 1 hypertension was associated with subsequent CVD events (Figure 1).[6,7] However, there has been controversy over setting the DBP threshold for stage 1 hypertension to 80 mmHg or higher.[8] A cohort study showed that the differences of CVD risk between DBPs of <80 mmHg and 80-89 mmHg mostly disappeared after statistical stratification or adjustment.[9] There has also been additional controversy over the possibility of the J−curve relationship between low DBP and CVD risk.[10−17] Particular attention might be needed because the lower BP targets in the 2017 ACC/AHA hypertension guidelines could result in more hypertension patients being treated to the level of diastolic hypotension.[14,18−21]

When 2017 ACC/AHA defined stage 1 hypertension was divided into subgroups, there has been studies showing different risks of CVD in each subgroup.[8,22] Moreover, among participants aged more than 60 or 65 years, the 2017 ACC/AHA defined stage 1 hypertension was not associated with an increased risk of CVD.[4,23]

Figure 1. Hazard Ratios for Cardiovascular Disease According to Index Blood Pressure Among Young Adults With and Without Stratification According to Antihypertensive Medication Prescription Within the First 5 Years of Follow-up



Solid lines indicate hazard ratios and shaded areas indicate 95% CIs using restricted cubic spline regression. Without antihypertensive medication indicates that patients had not been prescribed antihypertensive medication within the first 5 years of follow-up; with antihypertensive medication indicates that they were prescribed antihypertensive medication within the first 5 years of follow-up. Restricted cubic splines were constructed with 4 knots placed at the fifth, 35th, 65th, and 95th percentiles. Hazard ratios were calculated by Cox proportional hazards regression analysis after adjustments

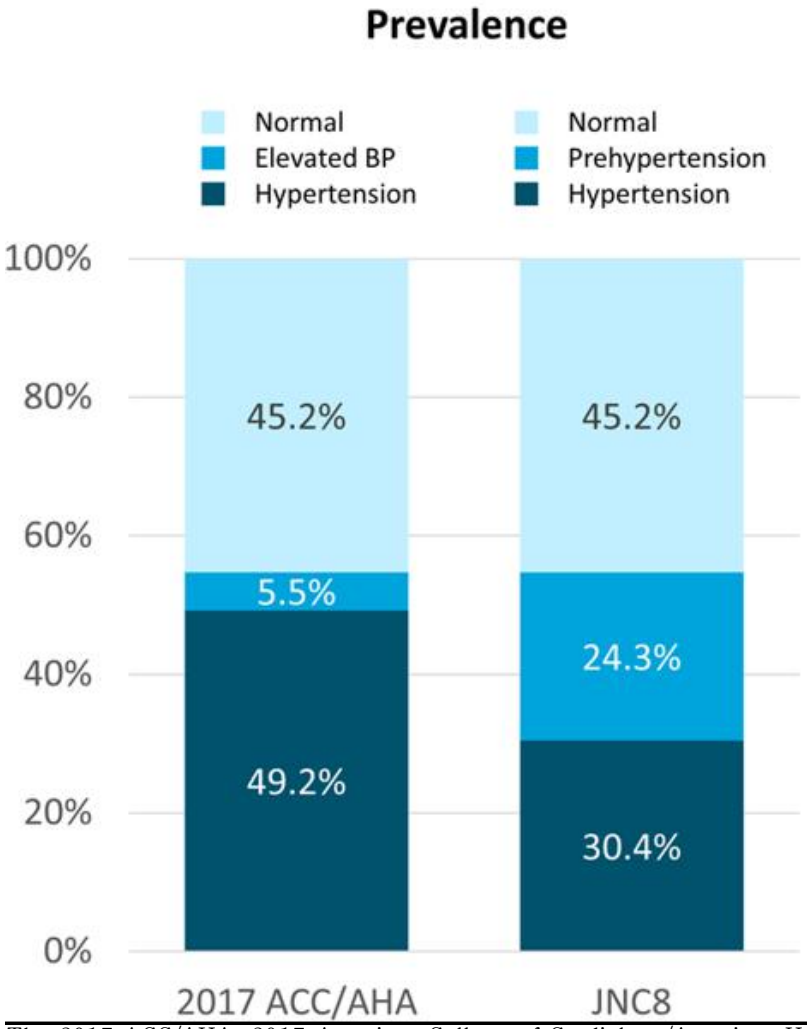
for age, household income, physical activity, smoking, alcohol consumption, body mass index, fasting serum glucose and total cholesterol levels, and Charlson comorbidity index.

2) Prevalence of hypertension according to 2018 ESC/ESH and 2017 ACC/AHA hypertension categories

The 2017 ACC/AHA hypertension guidelines would lead to a significant increase in the prevalence of hypertension. In a cross-sectional study of Korean adults aged 30 years or older, the prevalence of hypertension was about 49% according to the 2017 ACC/AHA hypertension categories versus 30% according to the 2018 ESC/ESH hypertension categories (Figure 2).[24] More than half of the entire population in China and the United States would be diagnosed with hypertension if the 2017 ACC/AHA hypertension guidelines were applied to adults over 45 years of age.[25]

A large cohort of low-risk, hypertensive patients (baseline SBP 140 to 159 mm Hg or DBP 90 to 99 mm Hg) showed that controlled BP <140/90 mm Hg was associated with a low risk of mortality and stroke, with the lowest mortality risk at a SBP range of 120 to <130 mm Hg and DBP range of 70 to <80 mm Hg.[26] However, there was a lack of randomized controlled trials (RCTs) on whether diagnosis according to the 2017 ACC/AHA defined stage 1 hypertension actually would lead to CVD prevention.[27] Moreover, there has been no direct comparison of the clinical significance of the 2018 ESC/ESH and 2017 ACC/AHA hypertension categories for middle-aged and elderly Asians.

Figure 2. The potential impact of implementing the 2017 ACC/AHA guideline for high blood pressure (BP) based on hypertension prevalence in Korean adults aged 30 years or older



The 2017 ACC/AHA: 2017 American College of Cardiology/American Heart Association Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults; JNC8: Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report from the Panel Members Appointed to the Eighth Joint National Committee.

Ⅱ. Purpose

In this nationwide population-based study, we aimed to investigate the CVD risk of 2018 ESC/ESH and 2017 ACC/AHA BP categories and appropriate BP criteria for newly diagnosed hypertension reflecting the subsequent CVD risk among middle-aged and elderly Koreans without history of CVD using the National Health Insurance Service (NHIS) database. The associations between BP categories and CVD were analyzed by age groups. For in-depth analysis, 2017 ACC/AHA defined stage 1 hypertension was analyzed by dividing it into 3 groups as follows; isolated diastolic hypertension (IDH, SBP<130 and DBP 80-89 mmHg), isolated systolic hypertension (ISH, SBP 130-139 and DBP <80 mmHg), and combined systolic/diastolic hypertension (SDH, SBP 130-139 and DBP 80-89 mmHg).

Ⅲ. Methods

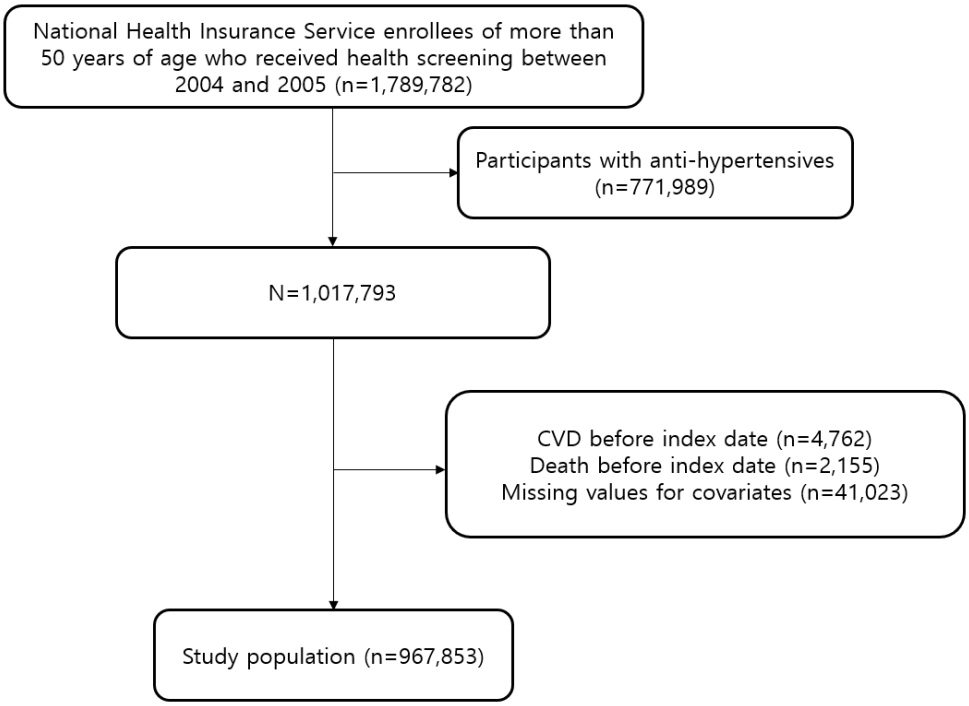
1. Study population

The study population was derived from the Korean National Health Insurance Service (NHIS) database. In South Korea, the NHIS provides mandatory health insurance for all Korean citizens providing nearly all types of health services.[28] Furthermore, the NHIS provides health screening examinations for all enrollees aged 40 years or older, which include a self-reported questionnaire on lifestyle behaviors, anthropometric measurements, and laboratory exams for blood and urine. The NHIS collects information on all insured health services including outpatient and inpatient hospitalizations, health screening examinations, diagnostic and treatment-related procedures, and pharmaceutical prescriptions for claims purposes.[29] From this database, the NHIS provides a part of their data for research purposes. A number of previous large-scale epidemiological studies have used the NHIS database and its validity is described in detail elsewhere.[29] [6]

Among 1,789,782 participants aged 50 years or older without history of CVD within 7 metropolitan areas in South Korea who underwent health examinations in 2004-2005, 771,989 participants had anti-hypertensive medications before the index date of 1 January 2006 and 1,017,793 participants had no history of medication. 4,762 participants with CVD before the index date of 1 January 2006 were excluded. Then, 2,155 participants who died before the index date were removed. Finally, 41,023 participants with missing values for

covariates were excluded, resulting in a final study population of 967,853 participants (Figure 3). After determining BP during 2004−2005, all participants were followed up for CVD or death starting from 1 January 2006 to 31 December 2018.

Figure 3. Flow diagram of the study population



2. Key variables

During the health examination between 2004−2005, BP was measured after participants rested for 2 minutes in sitting position by digital or automatic BP monitors. Participants were categorized into the

2018 ESC/ESH and 2017 ACC/AHA BP categories. The 2018 ESC/ESH BP groups were optimal (SBP <120/80 and DBP <80 mmHg), normal (SBP 120−139 and DBP 80−84 mmHg), high normal (SBP 130−139 and/or DBP 85−89 mmHg), grade 1 hypertension (SBP 140−159 and/or DBP 90−99 mmHg), grade 2 hypertension (SBP 160−179 and/or DBP 100−109 mmHg), and grade 3 hypertension (SBP≥180 and/or DBP≥110 mmHg). The 2017 ACC/AHA BP categories were normal (SBP <120 and <80 mmHg), elevated BP (SBP 120−129 and DBP <80 mmHg), stage 1 hypertension (SBP 130−139 mmHg or DBP 80−89 mmHg), and stage 2 hypertension (SBP≥140 or DBP≥90 mmHg).

Upon admission, the attending physician is required to insert the International Classification of Diseases, Tenth Revision (ICD−10) codes for the primary disease in which the patient was hospitalized for. CVD was defined when a participant was hospitalized for ICD−10 codes for coronary heart disease (CHD) or stroke for 2 or more days. The ICD−10 codes for CHD and stroke were I20 to I25 and I60 to I69, respectively. Multiple previous studies that used the NHIS database had a similar operational definition for CVD.[6] The ICD−10 codes for CVD, CHD, and stroke were adopted from the American Heart Association guidelines.[30]

Upon multivariate Cox proportional hazards regression, potential confounders were adjusted for. Adjusted covariates included age (continuous, years), sex (categorical, men and women), household income (categorical, 1st, 2nd, 3rd, and 4th quartiles), smoking (categorical, no and yes), alcohol intake (categorical, no and yes), physical activity (categorical, no and yes), body mass index (continuous, kg/m2), fasting serum glucose (continuous, mg/dL), total cholesterol

(continuous, mg/dL), and Charlson comorbidity index (continuous). Household income was calculated by the insurance premium and body mass index by dividing the weight in kilograms by height in meters squared.

3. Statistical analysis

Multivariate Cox proportional hazards regression was used to determine the adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for CVD, CHD, and stroke risk according to 2018 ESC/ESH and 2017 ACC/AHA hypertension categories. Stage 1 hypertension was further divided into isolated diastolic stage 1 hypertension (IDH, SBP<130 and DBP 80−89 mmHg), isolated systolic stage 1 hypertension (ISH, SBP 130−139 and DBP <80 mmHg), and combined systolic/diastolic stage 1 hypertension (SDH, SBP 130−139 and DBP 80−89 mmHg). Stratified analysis for the association of BP categories with CVD risk according to subgroups of age was conducted.

Statistical significance was determined as a p value of <0.05 in a two−sided manner. All data collection and statistical analysis were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA).

Ⅳ. Results

1. Baseline characteristics

Table 3 depicts the descriptive characteristics of the study population. A total of 524,146 men and 443,707 women were included in the study population. The number (%) of participants who were optimal, normal, high normal, grade 1, grade 2, and grade 3 hypertension according to the 2018 ESC/ESH categories were 288,444 (29.8), 246,188 (25.4), 201,165 (20.8), 181,557 (18.8), 41,545 (4.3), and 8,954 (0.9), respectively. On the other hand, the number (%) of participants who were normal, elevated BP, stage 1, and stage 2 hypertension according to the 2017 ACC/AHA categories were 288,444 (29.8), 106,464 (11.0), 340,889 (35.2), and 232,056 (24.0), respectively.

Table 3. Descriptive characteristics of the study population.

	Total	Men	Women
Number of people	967,853	524,146	443,707
2018 ESC/ESH, N (%)			
Optimal (<120/<80 mmHg)	288,444 (29.8)	125,665 (24.0)	162,779 (36.7)
Normal (120-129/80-84 mmHg)	246,188 (25.4)	133,441 (25.5)	112,747 (25.4)
High normal (130-139/85-89 mmHg)	201,165 (20.8)	117,252 (22.4)	83,913 (18.9)
Grade 1 hypertension (140-159/90-99 mmHg)	181,557 (18.8)	113,847 (21.7)	67,710 (15.3)
Grade 2 hypertension (160-179/100-109 mmHg)	41,545 (4.3)	27,643 (5.3)	13,902 (3.1)
Grade 3 hypertension (≥180/≥110 mmHg)	8,954 (0.9)	6,298 (1.2)	2,656 (0.6)
2017 ACC/AHA, N (%)			
Normal (<120/<80 mmHg)	288,444 (29.8)	125,656 (24.0)	162,779 (36.7)
Elevated BP (120-129/<80 mmHg)	106,464 (11.0)	52,135 (10.0)	54,329 (12.2)
Stage 1 hypertension (130-139/80-89 mmHg)	340,889 (35.2)	198,558 (37.9)	142,331 (32.1)
Stage 2 hypertension (≥140/≥90 mmHg)	232,056 (24.0)	147,788 (28.2)	84,268 (19.0)
Age, years, mean (SD)	57.9 (6.8)	57.8 (6.7)	57.9 (7.0)
Household income, quartiles, N (%)			
1st (highest)	370,911 (38.3)	211,092 (40.3)	159,819 (36.0)
2nd	219,261 (22.7)	118,541 (22.6)	100,720 (22.7)
3rd	157,713 (16.3)	82,486 (15.7)	75,227 (17.0)
4th (lowest)	219,968 (22.7)	112,027 (21.4)	107,941 (24.3)
Smoking, N (%)			
Never smoker	668,134 (69.0)	240,167 (45.8)	427,967 (96.5)
Past smoker	93,912 (9.7)	89,871 (17.2)	4,041 (0.9)
Current smoker	205,807 (21.3)	194,108 (37.0)	11,699 (2.6)
Alcohol intake, times per week, N (%)			
0	581,512 (60.1)	205,718 (39.3)	375,794 (84.7)
1-2	133,538 (13.8)	93,804 (17.9)	39,734 (9.0)
3-4	146,790 (15.2)	125,820 (24.0)	20,960 (4.7)
5-6	64,230 (6.6)	59,955 (11.4)	4,275 (1.0)
7	41,783 (4.3)	38,839 (7.4)	2,944 (0.7)
Physical activity, times per week, N (%)			
0	451,280 (46.6)	219,129 (41.8)	232,151 (52.3)
1-2	265,236 (27.4)	167,061 (31.9)	98,175 (22.1)
3-4	126,198 (13.0)	71,653 (13.7)	54,545 (12.3)
5-6	33,722 (3.5)	18,360 (3.5)	15,362 (3.5)
7	91,417 (9.5)	47,943 (9.2)	43,474 (9.8)
Body mass index, kg/m^2, mean (SD)	23.6 (2.7)	23.6 (2.7)	23.6 (2.8)
Fasting serum glucose, mg/dl, mean (SD)	97.6 (27.3)	100.1 (30.1)	94.8 (23.2)
Total cholesterol, mg/dl, mean (SD)	202.7 (45.6)	197.9 (44.5)	208.5 (46.3)
Charlson comorbidity index, N (%)			
0	567,819 (58.7)	325,514 (62.1)	242,305 (54.6)
1	238,676 (24.7)	119,241 (22.8)	119,435 (26.9)
≥2	161,358 (16.7)	79,391 (15.2)	81,967 (18.5)

Acronyms: ESC, European Society of Cardiology; ESH, European Society of Hypertension; ACC, American College of Cardiology; AHA, American Heart Association; N, number of people; SD, standard deviation.

Table 4 depicts the descriptive characteristics according to 2017 ACC/AHA hypertension categories and subcategories for stage 1 hypertension. The number (%) of participants who were normal, elevated BP, stage 1 IDH, stage 1 ISH, stage 1 SDH, and stage 2 hypertension according to the 2017 ACC/AHA categories were 288,444 (29.8), 106,464 (11.0), 155,152 (16.0), 51,027 (5.3), 134,710 (13.9), and 232,056 (24.0), respectively.

Table 4. Descriptive characteristics according to 2017 ACC/AHA hypertension categories and subcategories for stage 1 hypertension.

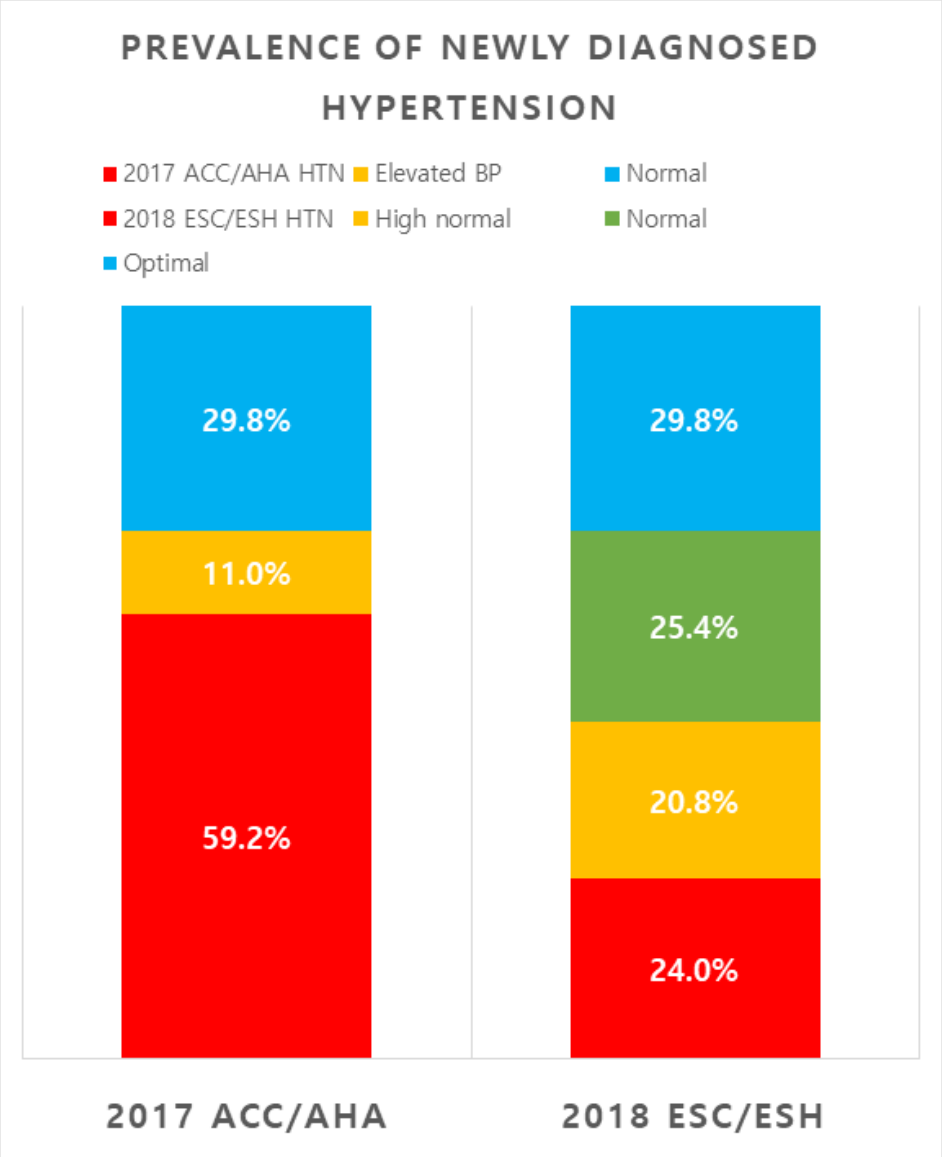
	Normal	Elevated BP	Stage 1 hypertension			Stage 2 hypertension	P value
			IDH	ISH	SDH		
	<120/80 mmHg	120-129/<80 mmHg	<130/80-89 mmHg	130-139/<80 mmHg	130-139/80-89 mmHg	≥140/≥90 mmHg	
Number of people	288,444	106,464	155,152	51,027	134,710	232,056	
SBP, mmHg, mean (SD)	107.3 (7.4)	122.6 (3.0)	119.2 (5.3)	132.6 (3.0)	132.1 (3.0)	143.9 (12.6)	<0.001
SBP (25th percentile, 50th percentile, 75th percentile)	100, 110, 111	120, 121, 125	120, 120, 120	130, 132, 135	130, 130, 135	140, 140, 150	
DBP, mmHg, mean (SD)	67.2 (6.0)	71.4 (4.5)	80.9 (2.1)	72.6 (4.4)	82.0 (2.9)	90.0 (8.3)	<0.001
DBP (25th percentile, 50th percentile, 75th percentile)	61, 70, 70	70, 70, 75	80, 80, 80	70, 72, 76	80, 80, 84	87, 90, 92	
Age, years, mean (SD)	56.9 (6.4)	58.2 (6.9)	56.9 (6.2)	59.9 (7.6)	58.0 (6.8)	59.1 (7.3)	<0.001
Sex, Female, N (%)	162,779 (56.4)	54,329 (51.0)	64,221 (41.4)	25,543 (50.1)	52,567 (39.0)	84,268 (36.3)	<0.001
Household income, quartiles, N (%)							
1st (highest)	118,133 (41.0)	41,127 (38.6)	63,017 (40.6)	18,801 (36.9)	48,746 (36.2)	81,087 (34.9)	<0.001
2nd	64,674 (22.4)	24,693 (23.2)	34,800 (22.4)	11,757 (23.0)	30,740 (22.8)	52,597 (22.7)	
3rd	45,790 (15.9)	17,365 (16.3)	24,007 (15.5)	8,595 (16.8)	22,191 (16.5)	39,765 (17.1)	
4th (lowest)	59,847 (20.8)	23,279 (21.9)	33,328 (21.5)	11,874 (23.3)	33,033 (24.5)	58,607 (25.3)	
Smoking, N (%)							
Never smoker	212,198 (73.6)	76,661 (72.0)	103,567 (66.8)	36,632 (71.8)	89,010 (66.1)	150,066 (64.7)	<0.001
Past smoker	22,195 (7.7)	9,535 (9.0)	16,519 (10.7)	4,565 (9.1)	14,964 (11.1)	26,044 (11.2)	
Current smoker	54,051 (18.7)	20,268 (19.0)	35,066 (22.6)	9,739 (19.1)	30,737 (22.8)	55,946 (24.1)	
Alcohol intake, N (%)							
0	195,168 (67.7)	68,591 (64.4)	89,290 (57.6)	32,503 (63.7)	74,859 (55.6)	121,101 (52.2)	<0.001
1-2	38,565 (13.4)	14,050 (13.2)	23,422 (15.1)	6,215 (12.2)	19,178 (14.2)	32,108 (13.8)	
3-4	34,319 (11.9)	13,982 (13.1)	25,582 (16.5)	6,827 (13.4)	23,485 (17.4)	42,595 (18.4)	
5-6	12,684 (4.4)	5,886 (5.5)	10,605 (6.8)	3,132 (6.1)	10,505 (7.8)	21,418 (9.2)	
7	7,708 (2.7)	3,955 (3.7)	6,253 (4.0)	2,350 (4.6)	6,683 (5.0)	14,834 (6.4)	
Physical activity, N (%)							
0	137,201 (47.6)	49,565 (46.6)	70,601 (45.5)	23,815 (46.7)	61,522 (45.7)	108,576 (46.8)	<0.001
1-2	77,650 (26.9)	28,441 (26.7)	44,561 (28.7)	13,035 (25.6)	38,031 (28.2)	63,418 (27.4)	
3-4	37,915 (13.1)	14,098 (13.2)	20,815 (13.4)	6,660 (13.1)	17,622 (13.1)	29,088 (12.5)	
5-6	10,310 (3.6)	3,908 (3.7)	5,328 (3.4)	1,858 (3.6)	4,641 (3.5)	7,677 (3.3)	
7	25,368 (8.8)	10,452 (9.8)	13,847 (8.9)	5,659 (11.1)	12,894 (9.6)	23,197 (10.0)	
Body mass index, kg/m², mean (SD)	23.0 (2.6)	23.6 (2.7)	23.6 (2.7)	23.8 (2.7)	24.0 (2.8)	24.2 (2.8)	<0.001
Fasting serum glucose, mg/dl, mean (SD)	94.4 (23.7)	97.5 (26.5)	96.7 (26.3)	99.6 (28.4)	99.0 (28.0)	101.1 (31.1)	<0.001
Total cholesterol, mg/dl, mean (SD)	200.0 (43.1)	202.1 (44.6)	202.1 (49.3)	202.9 (40.1)	203.9 (45.9)	205.5 (47.4)	<0.001
Charlson comorbidity index, N (%)							
0	162,160 (56.2)	60,234 (56.6)	91,069 (58.7)	28,752 (56.4)	80,447 (59.7)	145,157 (62.6)	<0.001
1	75,054 (26.0)	27,276 (25.6)	38,264 (24.7)	12,935 (25.4)	32,615 (24.2)	52,532 (22.6)	
≥2	51,230 (17.8)	18,954 (17.8)	25,819 (16.6)	9,340 (18.3)	21,648 (16.1)	34,367 (14.8)	

Acronyms: BP, blood pressure; IDH, isolated diastolic stage 1 hypertension; ISH, isolated systolic stage 1 hypertension; SDH, combined systolic/diastolic stage 1 hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; N, number of people; SD, standard deviation.

2. Prevalence of newly diagnosed hypertension according to 2018 ESC/ESH and 2017 ACC/AHA hypertension categories

The prevalence of newly diagnosed hypertension according to the 2018 ESC/ESH guidelines was 24.0%, but the prevalence of hypertension according to the 2017 ACC/AHA guidelines was 59.2%. The reason for the increased prevalence of newly diagnosed hypertension was due to an increase in 2017 ACC/AHA stage 1 hypertension. 2017 ACC/AHA stage 1 hypertension was diagnosed in 37.9% of men, 32.1% of women and 35.2% of the total (Figure 4, 5).

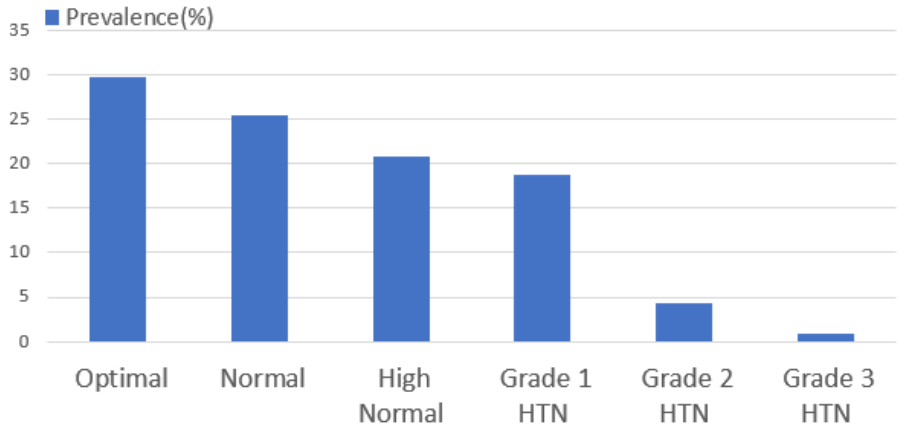
Figure 4. Prevalence of newly diagnosed hypertension according to 2018 ESC/ESH and 2017 ACC/AHA hypertension categories in Korean adults ≥ 50 years living in seven major metropolitan areas



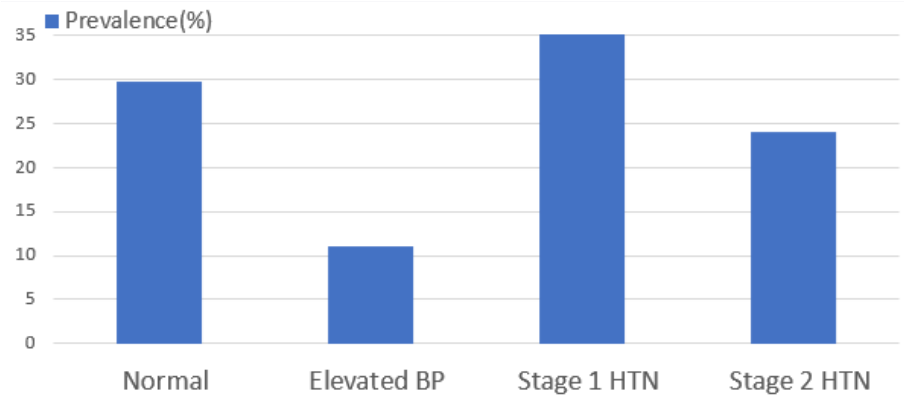
Acronyms: ESC, European Society of Cardiology; ESH, European Society of Hypertension; ACC, American College of Cardiology; AHA, American Heart Association; HTN, Hypertension

Figure 5. Prevalence of newly diagnosed hypertension according to 2018 ESC/ESH and 2017 ACC/AHA hypertension categories in Korean adults ≥50 years living in seven major metropolitan areas

A. Prevalence of newly diagnosed hypertension according to 2018 ESC/ESH



B. Prevalence of newly diagnosed hypertension according to 2017 ACC/AHA



Acronyms: ESC, European Society of Cardiology; ESH, European Society of Hypertension; ACC, American College of Cardiology; AHA, American Heart Association; HTN, Hypertension

3. The association of hypertension categories with CVD, CHD, and stroke risk.

Part I. Analysis of participants had no history of antihypertensive medication before the index date

1) The association of 2018 ESC/ESH and 2017 ACC/AHA hypertension categories with CVD, CHD, and stroke risk.

The association of 2018 ESC/ESH and 2017 ACC/AHA hypertension categories with CVD, CHD, and stroke risk is shown in Table 5, 6, and 7, respectively. Compared to those with optimal BP defined by the 2018 ESC/ESH categories, those with normal (aHR 1.14, 95% CI 1.12−1.17), high normal (aHR 1.28, 95% CI 1.26−1.31), grade 1 hypertension (aHR 1.41, 95% CI 1.38−1.43), grade 2 hypertension (aHR 1.62, 95% CI 1.57−1.67), and grade 3 hypertension (aHR 2.02, 95% CI 1.91−2.13) had higher risk for CVD. Similarly, participants with elevated BP (aHR 1.16, 95% CI 1.13−1.19), stage 1 hypertension (aHR 1.22, 95% CI 1.20−1.24), and stage 2 hypertension (aHR 1.46, 95% CI 1.44−1.49) had higher risk for CVD compared to normal participants according to the 2017 ACC/AHA guidelines (Table 5, Figure 6). Similar risk−increasing associations for both 2018 ESC/ESH and 2017 ACC/AHA BP categories were observed for CHD and stroke.

Table 5. Hazard ratios for cardiovascular disease according to 2018 ESC/ESH and 2017 ACC/AHA hypertension categories.

	Blood pressure, mean (SD)						
	Systolic	Diastolic	Events	Person-years	Incidence	aHR	95% CI
Cardiovascular disease							
2018 ESC/ESH							
Optimal (<120/<80 mmHg)	107.3 (7.4)	67.2 (6.0)	19,691	3,529,741	56	1.00	reference
Normal (120-129/80-84 mmHg)	120.4 (4.8)	76.5 (5.4)	20,732	2,975,718	70	1.14	1.12-1.17
High normal (130-139/85-89 mmHg)	131.5 (4.2)	80.0 (5.5)	20,137	2,399,819	84	1.28	1.26-1.31
Grade 1 hypertension (140-159/90-99 mmHg)	140.0 (8.9)	87.4 (5.9)	20,601	2,132,353	97	1.41	1.38-1.43
Grade 2 hypertension (160-179/100-109 mmHg)	155.1 (11.2)	97.2 (6.7)	5,535	475,135	116	1.62	1.57-1.67
Grade 3 hypertension (≥180/≥110 mmHg)	170.5 (17.4)	109.6 (9.8)	1,445	98,865	146	2.02	1.91-2.13
2017 ACC/AHA							
Normal (<120/<80 mmHg)	107.3 (7.4)	67.2 (6.0)	19,691	3,529,741	56	1.00	reference
Elevated BP (120-129/<80 mmHg)	122.6 (3.0)	71.4 (4.5)	9,235	1,282,673	72	1.16	1.13-1.19
Stage 1 hypertension (130-139/80-89 mmHg)	126.3 (7.8)	80.1 (4.3)	31,634	4,092,863	77	1.22	1.20-1.24
Stage 2 hypertension (≥140/≥90 mmHg)	143.9 (12.6)	90.0 (8.3)	27,581	2,706,353	102	1.46	1.44-1.49

*Operational definition: hospitalization of 2 or more days due to Cardiovascular disease.

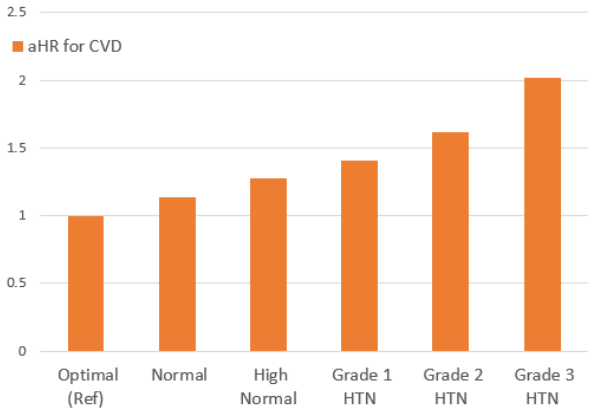
Incidence calculated by the number of events per 10,000 person-years.

Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, and Charlson comorbidity index.

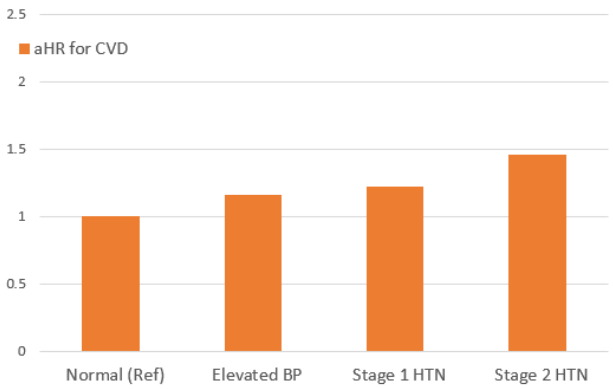
Acronyms: SD, standard deviation; aHR, adjusted hazard ratio; CI, confidence interval; ESC/ESH, European Society of Cardiology/European Society of Hypertension; ACC/AHA, American College of Cardiology/American Heart Association; BP, blood pressure.

Figure 6. Hazard ratios for cardiovascular disease according to 2018 ESC/ESH and 2017 ACC/AHA hypertension categories.

A. 2018 ESC/ESH hypertension categories.



B. 2017 ACC/AHA hypertension categories.



Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, and Charlson comorbidity index.

Acronyms: aHR, adjusted hazard ratio; CVD, cardiovascular disease; ESC/ESH, European Society of Cardiology/European Society of Hypertension; ACC/AHA, American College of Cardiology/American Heart Association; BP, blood pressure.

Figure 7. Kaplan-Meier curves demonstrating the incidence of cardiovascular disease according to 2018 ESC/ESH hypertension categories.

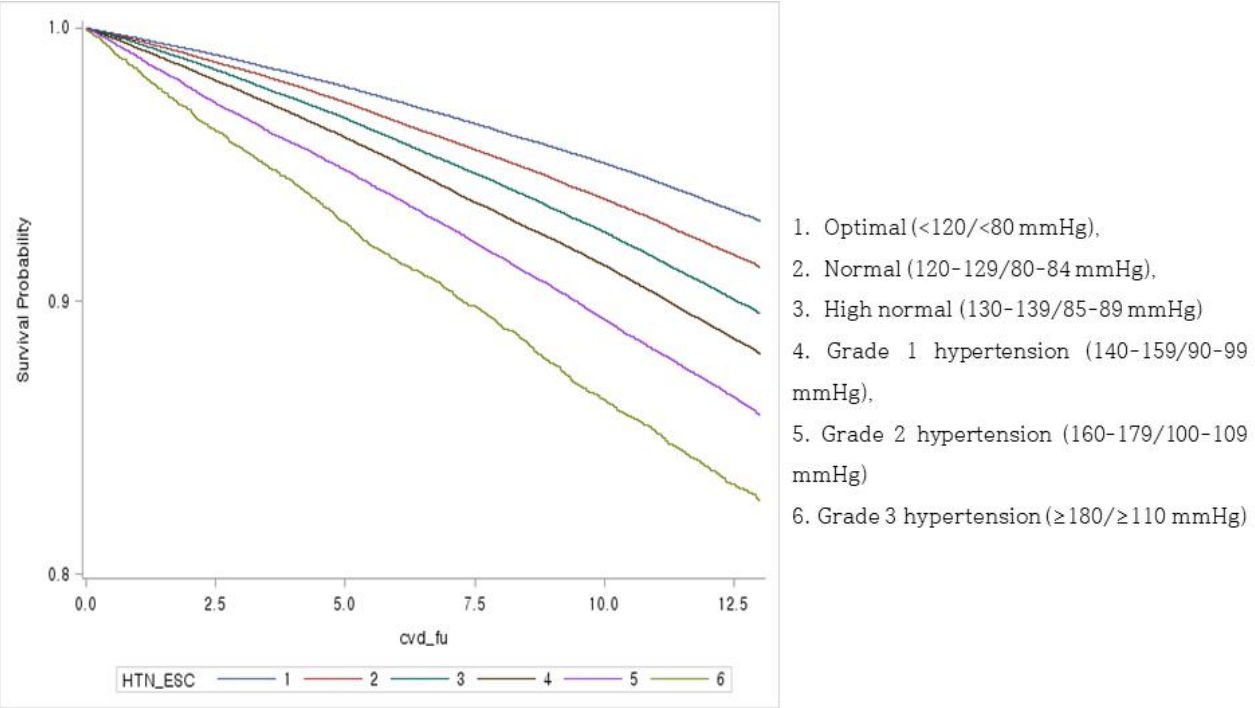
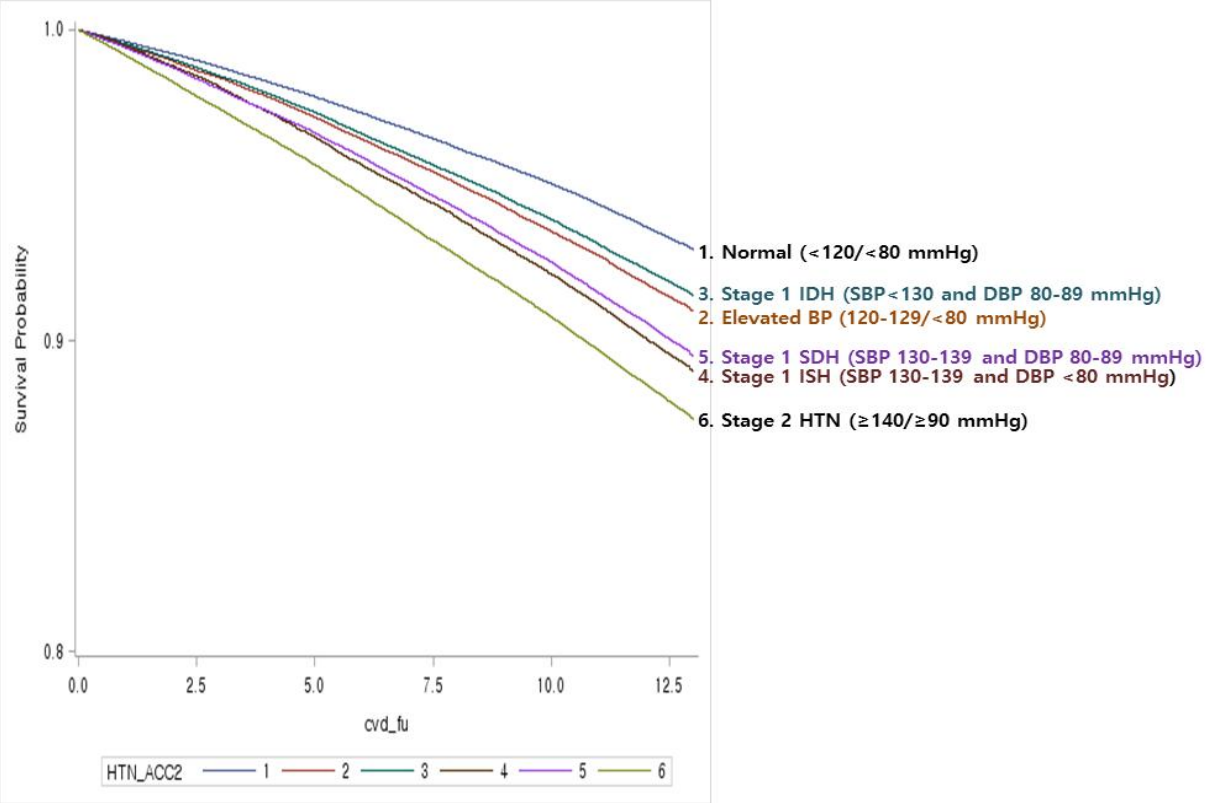


Figure 8. Kaplan-Meier curves demonstrating the incidence of cardiovascular disease according to 2017 ACC/AHA hypertension categories and subcategories for stage 1 hypertension.



Participants with normal (aHR 1.14, 95% CI 1.11−1.17), high normal (aHR 1.22, 95% CI 1.18−1.25), grade 1 hypertension (aHR 1.26, 95% CI 1.23−1.30), grade 2 hypertension (aHR 1.32, 95% CI 1.26−1.38), and grade 3 hypertension (aHR 1.30, 95% CI 1.18−1.43) had higher risk for CHD compared to those with optimal BP defined by the 2018 ESC/ESH categories. Similarly, compared to normal participants according to the 2017 ACC/AHA guidelines, those with elevated BP (aHR 1.17, 95% CI 1.13−1.21), stage 1 hypertension (aHR 1.18, 95% CI 1.15−1.21), and stage 2 hypertension (aHR 1.27, 95% CI 1.24−1.31) had higher risk for CHD (Table 6, Figure 9).

Table 6. Hazard ratios for coronary heart disease according to 2018 ESC/ESH and 2017 ACC/AHA hypertension categories.

	Blood pressure, mean (SD)						
	Systolic	Diastolic	Events	Person-years	Incidence	aHR	95% CI
Coronary heart disease							
2018 ESC/ESH							
Optimal (<120/<80 mmHg)	107.3 (7.4)	67.2 (6.0)	9,621	3,529,741	27	1.00	reference
Normal (120-129/80-84 mmHg)	120.4 (4.8)	76.5 (5.4)	10,279	2,975,718	35	1.14	1.11-1.17
High normal (130-139/85-89 mmHg)	131.5 (4.2)	80.0 (5.5)	9,354	2,399,819	39	1.22	1.18-1.25
Grade 1 hypertension (140-159/90-99 mmHg)	140.0 (8.9)	87.4 (5.9)	9,014	2,132,353	42	1.26	1.23-1.30
Grade 2 hypertension (160-179/100-109 mmHg)	155.1 (11.2)	97.2 (6.7)	2,156	475,135	45	1.32	1.26-1.38
Grade 3 hypertension (≥180/≥110 mmHg)	170.5 (17.4)	109.6 (9.8)	445	98,865	45	1.30	1.18-1.43
2017 ACC/AHA							
Normal (<120/<80 mmHg)	107.3 (7.4)	67.2 (6.0)	9,621	3,529,741	27	1.00	reference
Elevated BP (120-129/<80 mmHg)	122.6 (3.0)	71.4 (4.5)	4,487	1,282,673	35	1.17	1.13-1.21
Stage 1 hypertension (130-139/80-89 mmHg)	126.3 (7.8)	80.1 (4.3)	15,146	4,092,863	37	1.18	1.15-1.21
Stage 2 hypertension (≥140/≥90 mmHg)	143.9 (12.6)	90.0 (8.3)	11,615	2,706,353	43	1.27	1.24-1.31

*Operational definition: hospitalization of 2 or more days due to coronary heart disease.

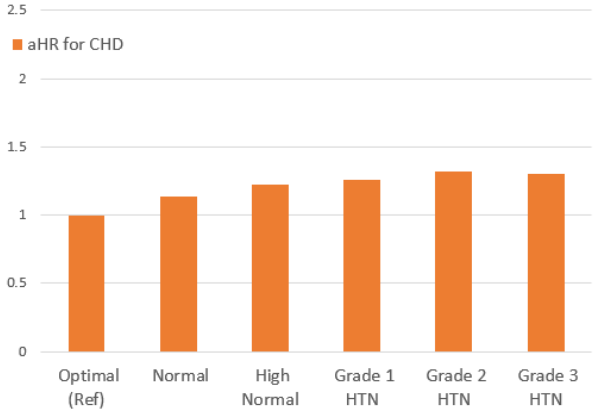
Incidence calculated by the number of events per 10,000 person−years.

Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, and Charlson comorbidity index.

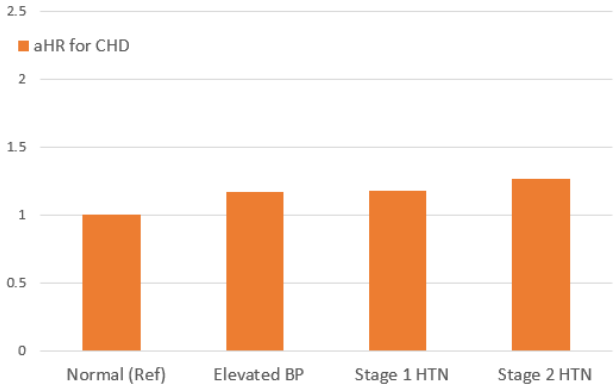
Acronyms: SD, standard deviation; aHR, adjusted hazard ratio; CI, confidence interval; ESC/ESH, European Society of Cardiology/European Society of Hypertension; ACC/AHA, American College of Cardiology/American Heart Association; BP, blood pressure.

Figure 9. Hazard ratios for coronary heart disease according to 2018 ESC/ESH and 2017 ACC/AHA hypertension categories.

A. 2018 ESC/ESH hypertension categories.



B. 2017 ACC/AHA hypertension categories.



Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, and Charlson comorbidity index.

Acronyms: aHR, adjusted hazard ratio; CHD, coronary heart disease; ESC/ESH, European Society of Cardiology/European Society of Hypertension; ACC/AHA, American College of Cardiology/American Heart Association; BP, blood pressure.

Compared to those with optimal BP defined by the 2018 ESC/ESH categories, those with normal (aHR 1.15, 95% CI 1.12−1.18), high normal (aHR 1.36, 95% CI 1.32−1.39), grade 1 hypertension (aHR 1.56, 95% CI 1.51−1.60), grade 2 hypertension (aHR 1.92, 95% CI 1.85−2.00), and grade 3 hypertension (aHR 2.71, 95% CI 2.53−2.89) had higher risk for stroke. Similarly, participants with elevated BP (aHR 1.16, 95% CI 1.12−1.20), stage 1 hypertension (aHR 1.27, 95% CI 1.24−1.30), and stage 2 hypertension (aHR 1.66, 95% CI 1.62−1.70) had higher risk for stroke compared to normal participants according to the 2017 ACC/AHA guidelines (Table 7, Figure 10).

Table 7. Hazard ratios for stroke according to 2018 ESC/ESH and 2017 ACC/AHA hypertension categories.

	Blood pressure, mean (SD)						
	Systolic	Diastolic	Events	Person-years	Incidence	aHR	95% CI
Stroke							
2018 ESC/ESH							
Optimal (<120/<80 mmHg)	107.3 (7.4)	67.2 (6.0)	10,070	3,529,741	29	1.00	reference
Normal (120-129/80-84 mmHg)	120.4 (4.8)	76.5 (5.4)	10,453	2,975,718	35	1.15	1.12-1.18
High normal (130-139/85-89 mmHg)	131.5 (4.2)	80.0 (5.5)	10,783	2,399,819	45	1.36	1.32-1.39
Grade 1 hypertension (140-159/90-99 mmHg)	140.0 (8.9)	87.4 (5.9)	11,587	2,132,353	54	1.56	1.51-1.60
Grade 2 hypertension (160-179/100-109 mmHg)	155.1 (11.2)	97.2 (6.7)	3,379	475,135	71	1.92	1.85-2.00
Grade 3 hypertension (≥180/≥110 mmHg)	170.5 (17.4)	109.6 (9.8)	1,000	98,865	101	2.71	2.53-2.89
2017 ACC/AHA							
Normal (<120/<80 mmHg)	107.3 (7.4)	67.2 (6.0)	10,070	3,529,741	29	1.00	reference
Elevated BP (120-129/<80 mmHg)	122.6 (3.0)	71.4 (4.5)	4,748	1,282,673	37	1.16	1.12-1.20
Stage 1 hypertension (130-139/80-89 mmHg)	126.3 (7.8)	80.1 (4.3)	16,488	4,092,863	40	1.27	1.24-1.30
Stage 2 hypertension (≥140/≥90 mmHg)	143.9 (12.6)	90.0 (8.3)	15,966	2,706,353	59	1.66	1.62-1.70

*Operational definition: hospitalization of 2 or more days due to Stroke.

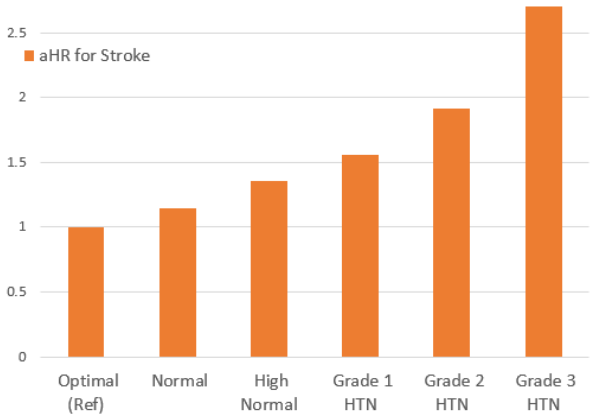
Incidence calculated by the number of events per 10,000 person−years.

Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, and Charlson comorbidity index.

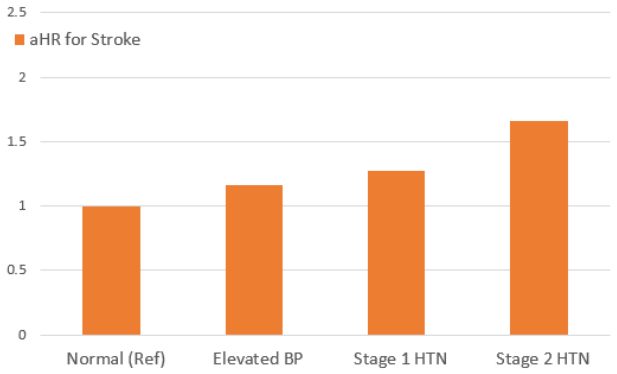
Acronyms: SD, standard deviation; aHR, adjusted hazard ratio; CI, confidence interval; ESC/ESH, European Society of Cardiology/European Society of Hypertension; ACC/AHA, American College of Cardiology/American Heart Association; BP, blood pressure.

Figure 10. Hazard ratios for stroke according to 2018 ESC/ESH and 2017 ACC/AHA hypertension categories.

A. 2018 ESC/ESH hypertension categories.



B. 2017 ACC/AHA hypertension categories.



Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, and Charlson comorbidity index.

Acronyms: aHR, adjusted hazard ratio; ESC/ESH, European Society of Cardiology/European Society of Hypertension; ACC/AHA, American College of Cardiology/American Heart Association; BP, blood pressure.

2) Sensitivity analysis

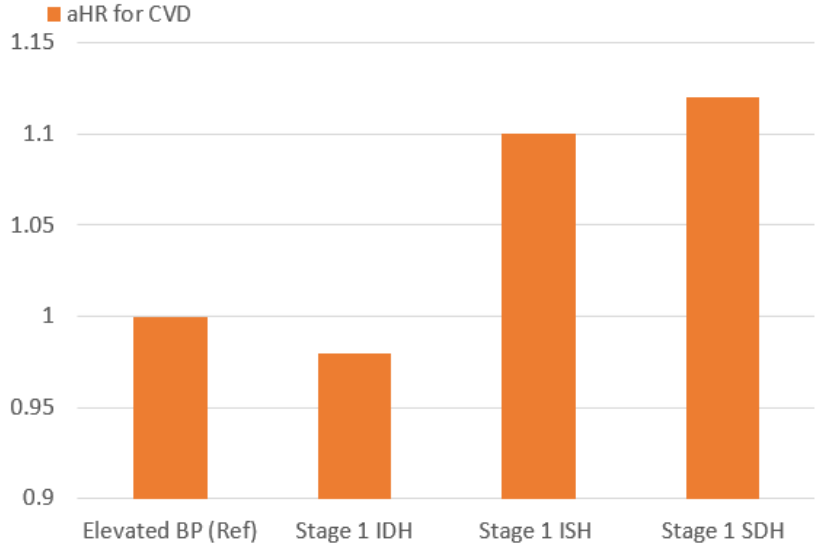
Sensitivity analysis on the association of 2017 ACC/AHA hypertension categories and CVD risk according to subcategories for stage 1 hypertension is depicted in Table 8 and Figure 11. Compared to normal participants, those with elevated BP (aHR 1.15, 95% CI 1.12−1.18) and IDH (aHR 1.13, 95% CI 1.11−1.16) had higher risk for CVD. Compared to elevated BP participants, IDH participants did not have increased risk for CVD (aHR 0.98, 95% CI 0.96−1.01), ISH (aHR 1.10, 95% CI 1.06−1.14) and SDH (aHR 1.12, 95% CI 1.09−1.15) participants had higher CVD risk. Finally, compared to IDH participants, ISH (aHR 1.13, 95% CI 1.09−1.16) and SDH (aHR 1.15, 95% CI 1.12−1.17) participants had significantly higher CVD risk. The associations of stage 1 hypertension subcategories on the risk for CHD and stroke were similar to that from CVD.

Table 8. Sensitivity analysis on the association between 2017 ACC/AHA hypertension categories and cardiovascular disease according to subcategories for stage 1 hypertension.

	Normal	Elevated BP	Stage 1 hypertension		
			IDH	ISH	SDH
	<120/80 mmHg	120-129/<80 mmHg	<130/80-89 mmHg	130-139/<80 mmHg	130-139/80-89 mmHg
Cardiovascular Disease					
Events	19,691	9,235	12,787	5,322	13,525
Person-years	3,529,741	1,282,673	1,880,428	603,762	1,608,673
Incidence	56	72	68	88	84
aHR (95% CI)[a]	1.00 (reference)	1.15 (1.12-1.18)	1.13 (1.11-1.16)	1.26 (1.22-1.30)	1.29 (1.26-1.32)
aHR (95% CI)[b]		1.00 (reference)	0.98 (0.96-1.01)	1.10 (1.06-1.14)	1.12 (1.09-1.15)
aHR (95% CI)[c]			1.00 (reference)	1.13 (1.09-1.16)	1.15 (1.12-1.17)
Coronary heart disease					
Events	9,621	4,487	6,432	2,379	6,335
Person-years	3,529,741	1,282,673	1,880,428	603,762	1,608,673
Incidence	27	35	34	39	39
aHR (95% CI)[a]	1.00 (reference)	1.16 (1.12-1.21)	1.13 (1.09-1.16)	1.21 (1.16-1.27)	1.22 (1.18-1.26)
aHR (95% CI)[b]		1.00 (reference)	0.97 (0.93-1.00)	1.05 (1.00-1.10)	1.05 (1.01-1.09)
aHR (95% CI)[c]			1.00 (reference)	1.09 (1.04-1.15)	1.09 (1.06-1.13)
Stroke					
Events	10,070	4,748	6,355	2,943	7,190
Person-years	3,529,741	1,282,673	1,880,428	603,762	1,608,673
Incidence	29	37	34	49	45
aHR (95% CI)[a]	1.00 (reference)	1.15 (1.11-1.19)	1.15 (1.11-1.18)	1.31 (1.26-1.37)	1.37 (1.33-1.41)
aHR (95% CI)[b]		1.00 (reference)	0.99 (0.96-1.03)	1.15 (1.10-1.20)	1.19 (1.15-1.24)
aHR (95% CI)[c]			1.00 (reference)	1.16 (1.11-1.22)	1.20 (1.16-1.24)

[a]Cardiovascular disease risk calculated with the normal group as the reference group.
[b]Cardiovascular disease risk calculated with the elevated blood pressure group as the reference group.
[c]Cardiovascular disease risk calculated with the isolated diastolic stage 1 hypertension group as the reference group.
Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, and Charlson comorbidity index.
Acronyms: BP, blood pressure; IDH, isolated diastolic stage 1 hypertension; ISH, isolated systolic stage 1 hypertension; SDH, combined systolic/diastolic stage 1 hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation; aHR, adjusted hazard ratio; CI, confidence interval.

Figure 11. Sensitivity analysis on the association between 2017 ACC/AHA hypertension categories and cardiovascular disease according to subcategories for stage 1 hypertension.



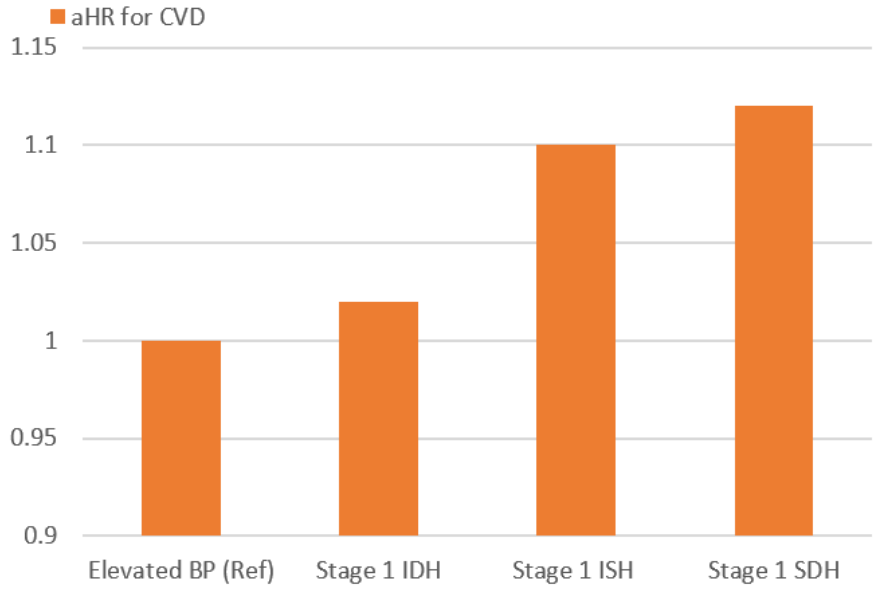
Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, and Charlson comorbidity index.
Acronyms: aHR, adjusted hazard ratio; CVD, cardiovascular disease; ACC/AHA, American College of Cardiology/American Heart Association; BP, blood pressure; Ref, reference; IDH, isolated diastolic stage 1 hypertension; ISH, isolated systolic stage 1 hypertension; SDH, combined systolic/diastolic stage 1 hypertension

77.4% of participants with stage 1 IDH had a diastolic blood pressure of 80 mmHg (Table 9). Therefore, sensitivity analysis was performed except those with DBP of 80 mmHg among participants with stage 1 IDH. Compared to elevated BP participants, IDH participants did not have increased risk for CVD (aHR 1.02, 95% CI 0.98−1.06) (Table 10, Figure 12).

Table 9. Distribution of diastolic blood pressure in stage 1 isolated diastolic hypertension group

DBP (mmHg)	N	%
80	120,072	77.4
81	4,969	3.2
82	5,953	3.8
83	3,941	2.5
84	4,789	3.1
85	6,228	4.0
86	3,080	2.0
87	1,803	1.2
88	2,403	1.6
89	1,914	1.2

Figure 12. Sensitivity analysis on the association between 2017 ACC/AHA hypertension categories and cardiovascular disease according to subcategories for stage 1 hypertension (Excludes participants whose diastolic blood pressure was 80mmHg).



Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, and Charlson comorbidity index.

Acronyms: aHR, adjusted hazard ratio; CVD, cardiovascular disease; ACC/AHA, American College of Cardiology/American Heart Association; BP, blood pressure; Ref, reference; IDH, isolated diastolic stage 1 hypertension; ISH, isolated systolic stage 1 hypertension; SDH, combined systolic/diastolic stage 1 hypertension

Table 10. Sensitivity analysis on the association between 2017 ACC/AHA hypertension categories and cardiovascular disease according to subcategories for stage 1 hypertension (Excludes participants whose diastolic blood pressure was 80mmHg).

	Normal	Elevated BP	Stage 1 hypertension		
			IDH	ISH	SDH
	<120/80 mmHg	120-129/<80 mmHg	<130/80-89 mmHg	130-139/<80 mmHg	130-139/80-89 mmHg
SBP, mmHg, mean (SD)	107.3 (7.4)	122.6 (3.0)	122.3 (5.5)	132.6 (3.0)	132.1 (3.0)
DBP, mmHg, mean (SD)	67.2 (6.0)	71.4 (4.5)	84.2 (2.3)	72.6 (4.4)	82.0 (2.9)
Cardiovascular Disease					
Events	19,691	9,235	2,923	5,322	13,525
Person-years	3,529,741	1,282,673	426,526	603,762	1,608,673
Incidence	56	72	69	88	84
aHR (95% CI)[a]	1.00 (reference)	1.15 (1.12-1.18)	1.18 (1.13-1.22)	1.26 (1.22-1.30)	1.29 (1.26-1.32)
aHR (95% CI)[b]		1.00 (reference)	1.02 (0.98-1.06)	1.10 (1.06-1.14)	1.12 (1.09-1.15)
aHR (95% CI)[c]			1.00 (reference)	1.09 (1.04-1.14)	1.11 (1.06-1.15)
Coronary heart disease					
Events	9,621	4,487	1,463	2,379	6,335
Person-years	3,529,741	1,282,673	426,526	603,762	1,608,673
Incidence	27	35	34	39	39
aHR (95% CI)[a]	1.00 (reference)	1.16 (1.12-1.20)	1.14 (1.08-1.21)	1.21 (1.16-1.27)	1.22 (1.18-1.25)
aHR (95% CI)[b]		1.00 (reference)	0.98 (0.93-1.04)	1.05 (1.00-1.10)	1.05 (1.01-1.09)
aHR (95% CI)[c]			1.00 (reference)	1.08 (1.01-1.15)	1.08 (1.02-1.14)
Stroke					
Events	10,070	4,748	1,460	2,943	7,190
Person-years	3,529,741	1,282,673	426,526	603,762	1,608,673
Incidence	29	37	34	49	45
aHR (95% CI)[a]	1.00 (reference)	1.15 (1.11-1.19)	1.22 (1.15-1.29)	1.32 (1.26-1.37)	1.37 (1.33-1.41)
aHR (95% CI)[b]		1.00 (reference)	1.05 (0.99-1.11)	1.15 (1.10-1.21)	1.19 (1.15-1.24)
aHR (95% CI)[c]			1.00 (reference)	1.11 (1.04-1.18)	1.14 (1.08-1.21)

[a]Cardiovascular disease risk calculated with the normal group as the reference group.
[b]Cardiovascular disease risk calculated with the elevated blood pressure group as the reference group.
[c]Cardiovascular disease risk calculated with the isolated diastolic stage 1 hypertension group as the reference group.
Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, and Charlson comorbidity index.
Acronyms: BP, blood pressure; IDH, isolated diastolic stage 1 hypertension; ISH, isolated systolic stage 1 hypertension; SDH, combined systolic/diastolic stage 1 hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation; aHR, adjusted hazard ratio; CI, confidence interval.

3) Stratified analysis

Table 11 shows the results from the stratified analysis on the risk of CVD according to subgroups of age. For those aged less than 65 years, 2018 ESC/ESH grade 1 hypertension was associated with higher risk for CVD (aHR 1.49, 95% CI 1.46−1.53). Similarly, grade 1 hypertension was associated with higher risk for CVD among participants aged between 65 and 80 years (aHR 1.37, 95% CI 1.32−1.43) and those aged more than 80 years (aHR 1.23, 95% CI 1.02−1.50), respectively. Grade 2 hypertension was associated with higher CVD risk (aHR 1.34, 95% CI 1.04−1.72) among those aged more than 80 years.

The 2017 ACC/AHA stage 1 hypertension was related with the risk of CVD in participants younger than 65 years old (aHR 1.27, 95% CI 1.24−1.29) and those between the ages of 65 and 80 (aHR 1.18, 95% CI 1.14−1.22), respectively. However, among those aged more than 80 years, 2017 ACC/AHA stage 1 hypertension was not associated with the risk of CVD (aHR 0.99, 95% CI 0.82−1.21).

Table 11. Stratified analysis on the association of the 2018 ESC/ESH and 2017 ACC/AHA hypertension categories with cardiovascular disease risk according to subgroups of age.

	Adjusted hazard ratio (95% confidence interval) of cardiovascular disease			
	Age <65 years	**Age 65-80 years**	**Age >80 years**	***p* for interaction**
2018 ESC/ESH				
Optimal (<120/<80 mmHg)	1.00 (reference)	1.00 (reference)	1.00 (reference)	<0.001
Normal (120-129/80-84 mmHg)	1.17 (1.4-1.20)	1.11 (1.07-1.15)	1.11 (0.90-1.36)	
High normal (130-139/85-89 mmHg)	1.35 (1.32-1.38)	1.24 (1.19-1.29)	0.96 (0.78-1.18)	
Grade 1 hypertension (140-159/90-99 mmHg)	1.49 (1.46-1.53)	1.37 (1.32-1.43)	1.23 (1.02-1.50)	
Grade 2 hypertension (160-179/100-109 mmHg)	1.79 (1.72-1.85)	1.51 (1.43-1.60)	1.34 (1.04-1.72)	
Grade 3 hypertension (≥180/≥110 mmHg)	2.16 (2.02-2.30)	2.00 (1.81-2.20)	1.53 (1.03-2.26)	
2017 ACC/AHA				
Normal (<120/<80 mmHg)	1.00 (reference)	1.00 (reference)	1.00 (reference)	<0.001
Elevated BP (120-129/<80 mmHg)	1.19 (1.16-1.22)	1.15 (1.10-1.21)	1.13 (0.89-1.44)	
Stage 1 hypertension (130-139/80-89 mmHg)	1.27 (1.24-1.29)	1.18 (1.14-1.22)	0.99 (0.82-1.21)	
Stage 2 hypertension (≥140/≥90 mmHg)	1.56 (1.53-1.60)	1.42 (1.37-1.48)	1.28 (1.06-1.53)	

Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, and Charlson comorbidity index.

Acronyms: ESC/ESH, European Society of Cardiology/European Society of Hypertension; ACC/AHA, American College of Cardiology/American Heart Association; BP, blood pressure.

Table 12. Stratified analysis on the association of the 2018 ESC/ESH hypertension categories with cardiovascular disease risk according to subgroups of age and fasting serum glucose.

	Adjusted hazard ratio (95% confidence interval)					
	Optimal	Normal	High-normal	Hypertension		
				Grade 1	Grade 2	Grade 3
	<120/<80 mmHg	120-129/80-84 mmHg	130-139/85-89 mmHg	140-159/90-99 mmHg	160-179/100-109 mmHg	≥180/≥110 mmHg
Age, years						
<60	1.00 (reference)	1.13 (1.09-1.16)	1.28 (1.24-1.33)	1.44 (1.40-1.49)	1.78 (1.69-1.87)	2.28 (2.10-2.47)
≥60	1.00 (reference)	1.13 (1.11-1.16)	1.30 (1.26-1.33)	1.46 (1.42-1.50)	1.78 (1.72-1.84)	2.30 (2.17-2.44)
Fasting serum glucose, mg/dL						
<126	1.00 (reference)	1.12 (1.10-1.14)	1.26 (1.23-1.28)	1.39 (1.37-1.42)	1.67 (1.62-1.72)	2.12 (2.01-2.23)
≥126	1.00 (reference)	1.06 (0.99-1.13)	1.13 (1.06-1.20)	1.24 (1.17-1.32)	1.44 (1.33-1.56)	1.90 (1.68-2.15)

Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, and Charlson comorbidity index.

Acronyms: ESC/ESH, European Society of Cardiology/European Society of Hypertension

Table 13. Stratified analysis on the association of the 2017 ACC/AHA hypertension categories with cardiovascular disease risk according to subgroups of age and fasting serum glucose.

	Adjusted hazard ratio (95% confidence interval)			
	Normal	Elevated BP	Hypertension	
			Stage 1	Stage 2
	<120/<80 mmHg	120-129/<80 mmHg	130-139/80-89 mmHg	≥140/≥90 mmHg
Age, years				
<60	1.00 (reference)	1.14 (1.10-1.19)	1.21 (1.18-1.24)	1.53 (1.48-1.57)
≥60	1.00 (reference)	1.16 (1.12-1.20)	1.23 (1.20-1.26)	1.55 (1.51-1.59)
Fasting serum glucose, mg/dL				
<126	1.00 (reference)	1.13 (1.10-1.16)	1.20 (1.18-1.22)	1.47 (1.44-1.50)
≥126	1.00 (reference)	1.07 (0.99-1.15)	1.10 (1.04-1.16)	1.31 (1.24-1.38)

Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, and Charlson comorbidity index.

Acronyms: ACC/AHA, American College of Cardiology/American Heart Association; BP, blood pressure.

Part II. Analysis of participants with and without history of antihypertensive medication before the index date

Among 1,323,379 participants aged 50 years or older without history of CVD within 7 metropolitan areas in South Korea who underwent health examinations in 2004−2005, 420,162 participants had anti−hypertensive medications before the index date of 1 January 2006 and 901,217 participants had no history of medication. After determining BP during 2004−2005, all participants were followed up for CVD or death starting from 1 January 2006 to 31 December 2018.

The association of 2018 ESC/ESH hypertension categories with CVD, CHD, and stroke risk were shown in Table 14, 15, and 16.

Among total participants, compared to those with optimal BP defined by the 2018 ESC/ESH categories, those with normal (aHR 1.11, 95% CI 1.09−1.13), high normal (aHR 1.21, 95% CI 1.19−1.23), grade 1 hypertension (aHR 1.29, 95% CI 1.27−1.31), grade 2 hypertension (aHR 1.43, 95% CI 1.40−1.46), and grade 3 hypertension (aHR 1.62, 95% CI 1.57−1.67) had higher risk for CVD (Table 14).

Among participants without history of antihypertensive medication before the index date, compared to those with optimal BP defined by the 2018 ESC/ESH categories, those with normal (aHR 1.12, 95% CI 1.09−1.14), high normal (aHR 1.25, 95% CI 1.22−1.27), grade 1 hypertension (aHR 1.38, 95% CI 1.36−1.41), grade 2 hypertension (aHR 1.64, 95% CI 1.60−1.69), and grade 3 hypertension (aHR 2.08, 95% CI 1.99−2.19) had higher risk for CVD (Table 15).

Among participants with history of antihypertensive medication before the index date, those with normal (aHR 1.02, 95% CI 0.99−1.05), high normal (aHR 1.06, 95% CI 1.02−1.09), grade 1 hypertension (aHR 1.08, 95% CI 1.05−1.11), grade 2 hypertension (aHR 1.16, 95% CI 1.13−1.20), and grade 3 hypertension (aHR 1.27, 95% CI 1.22−1.32) had higher risk for CVD compared to those with optimal BP defined by the 2018 ESC/ESH categories (Table 16).

Table 14. Hazard ratios for cardiovascular disease according to 2018 ESC/ESH hypertension categories: Results with additional adjustment for history of antihypertensive medication before the index date

		Optimal	Normal	High normal	Grade 1 hypertension	Grade 2 hypertension	Grade 3 hypertension	
		SBP<120 and DBP<80 mmHg	SBP 120−129 or DBP 80-84 mmHg	SBP130−139 or DBP 85−89 mmHg	SBP 140−159 or DBP 90−99 mmHg	SBP 160−179 or DBP 100−109 mmHg	SBP≥180 or DBP≥110 mmHg	p for trend
Total	Number of people	289,243	289,944	274,512	334,426	106,087	29,167	
	SBP, mmHg, mean (SD)	107.6 (7.4)	120.7 (4.6)	131.7 (4.0)	141.7 (8.6)	157.8 (10.6)	175.2 (16.7)	
	DBP, mmHg, mean (SD)	67.2 (6.0)	76.3 (5.5)	79.6 (5.7)	86.9 (6.3)	96.2 (7.2)	108.4 (11.1)	
	Cardiovascular disease							<0.001
	Events, N (%)	25,509 (8.8)	30.437 (10.6)	34,313 (12.5)	46,989 (14.1)	17,431 (16.4)	5,397 (18.5)	
	aHR	1.00	1.11	1.21	1.29	1.43	1.62	
	95% CI	reference	1.09−1.13	1.19−1.23	1.27−1.31	1.40−1.46	1.57−1.67	
	Coronary heart disease							<0.001
	Events, N (%)	12,516 (4.3)	14,992 (5.2)	16,259 (5.9)	21,712 (6.5)	7,448 (7.0)	2,101 (7.2)	
	aHR	1.00	1.1	1.16	1.2	1.23	1.28	
	95% CI	reference	1.07−1.12	1.13−1.19	1.17−1.23	1.20−1.27	1.22−1.34	
	Stroke							<0.001
	Events, N (%)	14,427 (5.0)	17,206 (6.0)	20,292 (7.4)	28,643 (8.6)	11,292 (10.6)	3,750 (12.9)	
	aHR	1.00	1.11	1.26	1.38	1.61	1.94	
	95% CI	reference	1.09−1.14	1.23−1.29	1.35−1.41	1.57−1.65	1.87−2.02	

Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, Charlson comorbidity index, and antihypertensive medication before the index date.
Acronyms: ESC/ESH, European Society of Cardiology/European Society of Hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure

Table 15. Hazard ratios for cardiovascular disease according to 2018 ESC/ESH hypertension categories: Analysis of participants without history of antihypertensive medication before the index date

		Optimal	Normal	High normal	Grade 1 hypertension	Grade 2 hypertension	Grade 3 hypertension	
		SBP<120 and DBP<80 mmHg	SBP 120−129 or DBP 80-84 mmHg	SBP130−139 or DBP 85−89 mmHg	SBP 140−159 or DBP 90−99 mmHg	SBP 160−179 or DBP 100−109 mmHg	SBP≥180 or DBP≥110 mmHg	p for trend
Without anti−hypertensives	Number of people	245,130	222,173	187,540	191,009	45,096	10,269	
	SBP, mmHg, mean (SD)	107.4 (7.4)	120.5 (4.7)	131.6 (4.1)	140.6 (8.8)	156.3 (11.0)	172.6 (17.1)	
	DBP, mmHg, mean (SD)	67.1 (6.0)	76.3 (5.5)	79.6 (5.6)	87.1 (6.1)	96.6 (6.9)	108.9 (10.4)	
	Cardiovascular disease							<0.001
	Events, N (%)	18,916 (7.7)	20,223 (9.1)	20,098 (10.7)	23,077 (12.1)	6,578 (14.6)	1,848 (18.0)	
	aHR	1.00	1.12	1.25	1.38	1.64	2.08	
	95% CI	reference	1.09−1.14	1.22−1.27	1.36−1.41	1.60−1.69	1.99−2.19	
	Coronary heart disease							<0.001
	Events, N (%)	9,279 (3.8)	9,861 (4.4)	9,404 (5.0)	10,323 (5.4)	2,682 (6.0)	630 (6.1)	
	aHR	1.00	1.09	1.19	1.26	1.39	1.49	
	95% CI	reference	1.06−1.12	1.15−1.22	1.22−1.29	1.33−1.45	1.37−1.61	
	Stroke							<0.001
	Events, N (%)	10,600 (4.3)	11,353 (5.1)	11,801 (6.3)	14,138 (7.4)	4,332 (9.6)	1,342 (13.1)	
	aHR	1.00	1.13	1.3	1.5	1.87	2.59	
	95% CI	reference	1.10−1.16	1.27−1.34	1.46−1.54	1.80−1.94	2.45−2.74	

Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, and Charlson comorbidity index.

Acronyms: ESC/ESH, European Society of Cardiology/European Society of Hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure

Table 16. Hazard ratios for cardiovascular disease according to 2018 ESC/ESH hypertension categories: Analysis of participants with history of antihypertensive medication before the index date

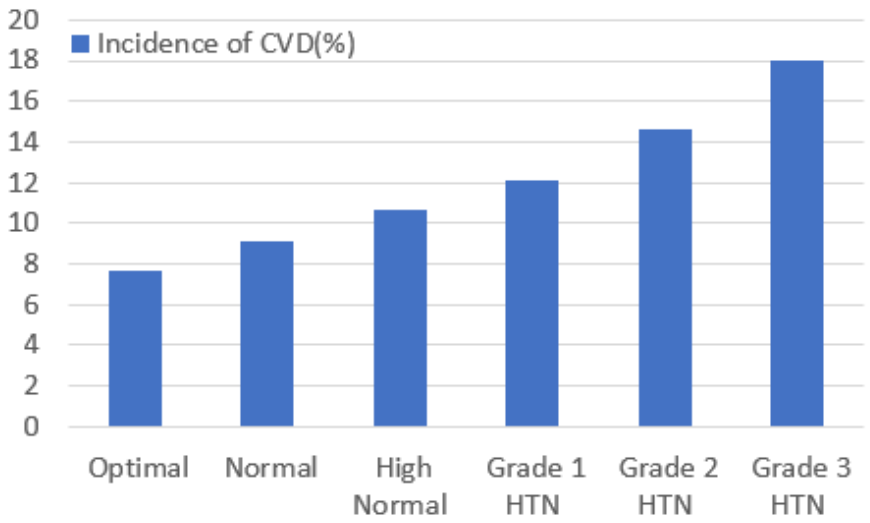
		Optimal	Normal	High normal	Grade 1 hypertension	Grade 2 hypertension	Grade 3 hypertension	
		SBP<120 and DBP<80 mmHg	SBP 120−129 or DBP 80-84 mmHg	SBP130−139 or DBP 85−89 mmHg	SBP 140−159 or DBP 90−99 mmHg	SBP 160−179 or DBP 100−109 mmHg	SBP≥180 or DBP≥110 mmHg	p for trend
With anti−hypertensives	Number of people	44,113	65,771	86,972	143,417	60,991	18,898	
	SBP, mmHg, mean (SD)	108.9 (7.0)	121.1 (4.4)	132.1 (3.9)	143.1 (8.2)	158.9 (10.1)	176.7 (16.3)	
	DBP, mmHg, mean (SD)	67.8 (6.0)	76.1 (5.7)	79.5 (5.8)	86.7 (6.5)	95.9 (7.4)	108.1 (11.5)	
	Cardiovascular disease							<0.001
	Events, N (%)	6,593 (15.0)	10,214 (15.5)	14,215 (16.3)	23,912 (16.7)	10,853 (17.8)	3,549 (18.8)	
	aHR	1.00	1.02	1.06	1.08	1.16	1.27	
	95% CI	reference	0.99−1.05	1.02−1.09	1.05−1.11	1.13−1.20	1.22−1.32	
	Coronary heart disease							0.013
	Events, N (%)	3,237 (7.3)	5,131 (7.8)	6,855 (7.9)	11,389 (7.9)	4,766 (7.8)	1,471 (7.8)	
	aHR	1.00	1.04	1.04	1.05	1.05	1.09	
	95% CI	reference	0.99−1.08	0.99−1.08	1.01−1.09	1.00−1.10	1.02−1.15	
	Stroke							<0.001
	Events, N (%)	3,827 (8.7)	5,853 (8.9)	8,491 (9.8)	14,505 (10.1)	6,960 (11.4)	2,408 (12.7)	
	aHR	1.00	1.01	1.08	1.13	1.28	1.47	
	95% CI	reference	0.97−1.05	1.04−1.13	1.09−1.17	1.23−1.33	1.39−1.54	

Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, and Charlson comorbidity index.

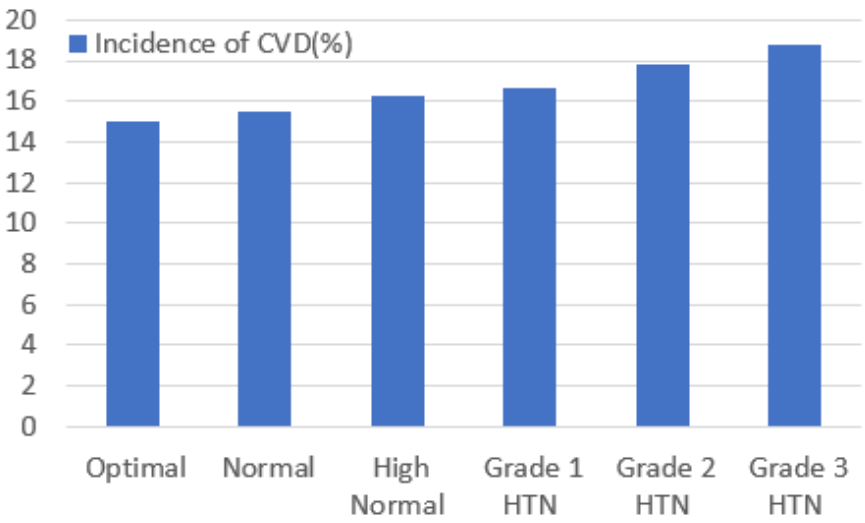
Acronyms: ESC/ESH, European Society of Cardiology/European Society of Hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure

Figure 13. Incidences of cardiovascular disease according to 2018 ESC/ESH hypertension categories: Analysis of participants with and without history of antihypertensive medication before the index date.

A. Without history of antihypertensive medication



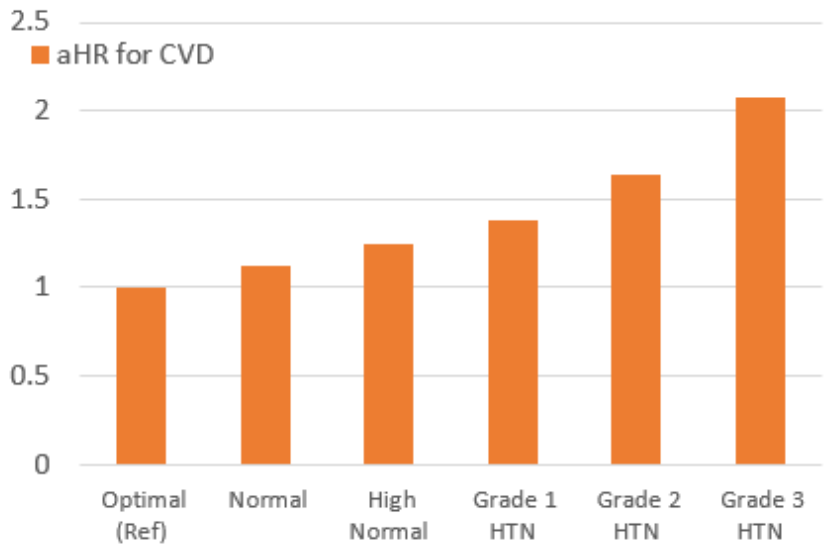
B. With history of antihypertensive medication



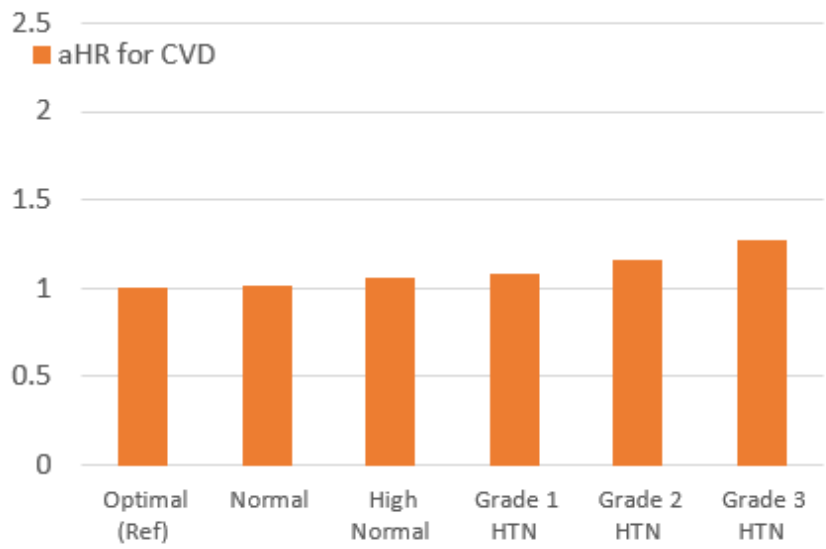
Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, and Charlson comorbidity index.
Acronyms: CVD, cardiovascular disease; ESC/ESH, European Society of Cardiology/European Society of Hypertension

Figure 14. Hazard ratios for cardiovascular disease according to 2018 ESC/ESH hypertension categories: Analysis of participants with and without history of antihypertensive medication before the index date.

A. Without history of antihypertensive medication



B. With history of antihypertensive medication



Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, and Charlson comorbidity index.

Acronyms: aHR, adjusted hazard ratio; CVD, cardiovascular disease; ESC/ESH, European Society of Cardiology/European Society of Hypertension

Part III. Stratified analysis for the risk of cardiovascular disease according to prescription of antihypertensives within the first 5 years of follow-up in participants without history of antihypertensive medication before the index date

Among participants had no history of medication before the index date of 1 January 2006, stratified analysis for the risk of cardiovascular disease was done according to prescription of antihypertensives within the first 5 years of follow-up. Participants with cardiovascular disease events within the first 5 years of follow-up were excluded. After determining BP during 2004-2005, all participants were followed up for CVD or death starting from 1 January 2006 to 31 December 2018.

Of the total study subjects, 37.1%, had history of antihypertensive medication within the first 5 years of follow-up. The descriptive characteristics of the study population are described in the Table 17.

The association of 2018 ESC/ESH and 2017 ACC/AHA hypertension categories with CVD, CHD, and stroke risk were shown in Table 18, 19, and 20.

Table 17. Descriptive characteristics according to prescription of anti-hypertensives within the first 5 years of follow-up.

	Without anti-hypertensives	With anti-hypertensives	P value
Number of people	608,971	358,882	
2018 ESC/ESH, N (%)			
Optimal (<120/<80 mmHg)	212,056 (34.8)	76,388 (21.3)	<0.001
Normal (120-129/80-84 mmHg)	167,106 (27.4)	79,082 (22.0)	
High normal (130-139/85-89 mmHg)	120.252 (19.8)	80,913 (22.6)	
Grade 1 hypertension (140-159/90-99 mmHg)	91,365 (15.0)	90,192 (25.1)	
Grade 2 hypertension (160-179/100-109 mmHg)	15,450 (2.5)	26,095 (7.3)	
Grade 3 hypertension (≥180/≥110 mmHg)	2,742 (0.5)	6,212 (1.7)	
2017 ACC/AHA, N (%)			
Normal (<120/<80 mmHg)	212,056 (34.8)	76,388 (21.3)	<0.001
Elevated BP (120-129/<80 mmHg)	71,900 (11.8)	34,563 (9.6)	
Stage 1 hypertension (130-139/80-89 mmHg)	215,458 (35.4)	125,431 (35.0)	
Stage 2 hypertension (≥140/≥90 mmHg)	109,557 (18.0)	122,499 (34.1)	
Age, years, mean (SD)	57.1 (6.5)	59.2 (7.2)	<0.001
Sex, Female, N (%)	274,889 (45.1)	168,818 (47.0)	<0.001
Household income, quartiles, N (%)			
1st (highest)	238,966 (39.2)	131,945 (36.8)	<0.001
2nd	136,372 (22.4)	82,889 (23.1)	
3rd	98,202 (16.1)	59,511 (16.6)	
4th (lowest)	135,431 (22.2)	84,537 (23.6)	
Smoking, N (%)			
Never smoker	417,281 (68.5)	250,853 (69.9)	<0.001
Past smoker	58,972 (9.7)	34,940 (9.7)	
Current smoker	132,718 (21.8)	73,089 (20.4)	
Alcohol intake, times per week, N (%)			
0	363,732 (59.7)	217,780 (60.7)	<0.001
1-2	87,283 (14.3)	46,255 (12.9)	
3-4	93,771 (15.4)	53,019 (14.8)	
5-6	39,459 (6.5)	24,771 (6.9)	
7	24,726 (4.1)	17,057 (4.8)	
Physical activity, times per week, N (%)			
0	281,031 (46.2)	170,249 (47.4)	<0.001
1-2	171,278 (28.1)	93,958 (26.2)	
3-4	80,532 (13.2)	45,666 (12.7)	
5-6	21,519 (3.5)	12,203 (3.4)	
7	54,611 (9.0)	36,806 (10.3)	
Body mass index, kg/m², mean (SD)	23.4 (2.7)	24.0 (2.8)	<0.001
Fasting serum glucose, mg/dl, mean (SD)	96.4 (25.1)	99.8 (30.5)	<0.001
Total cholesterol, mg/dl, mean (SD)	201.9 (46.0)	204.2 (44.9)	<0.001
Charlson comorbidity index, N (%)			
0	377,400 (62.0)	190,419 (53.1)	<0.001
1	142,950 (23.5)	95,726 (26.7)	
≥2	88,621 (14.6)	72,737 (20.3)	

Acronyms: ESC, European Society of Cardiology; ESH, European Society of Hypertension; ACC, American College of Cardiology; AHA, American Heart Association; N, number of people; SD, standard deviation.

Among participants without prescription of antihypertensives within the first 5 years of follow-up, those with normal (aHR 1.11, 95% CI 1.08-1.15), high normal (aHR 1.24, 95% CI 1.21-1.28), grade 1 hypertension (aHR 1.39, 95% CI 1.35-1.44), grade 2 hypertension (aHR 1.66, 95% CI 1.57-1.76), and grade 3 hypertension (aHR 2.19, 95% CI 1.96-2.45) had higher risk for CVD compared to those with optimal BP defined by the 2018 ESC/ESH categories (Table 18, Figure 15).

Among participants with prescription of antihypertensives within the first 5 years of follow-up, compared to those with optimal BP defined by the 2018 ESC/ESH categories, those with normal (aHR 0.97, 95% CI 0.92-1.02), high normal (aHR 0.96, 95% CI 0.92-1.01), grade 1 hypertension (aHR 0.96, 95% CI 0.92-1.01), grade 2 hypertension (aHR 1.00, 95% CI 0.95-1.07), and grade 3 hypertension (aHR 1.07, 95% CI 0.97-1.18) had higher risk for CVD (Table 18, Figure 15).

Table 18. Stratified analysis for the risk of cardiovascular disease according to prescription of antihypertensives within the first 5 years of follow-up.

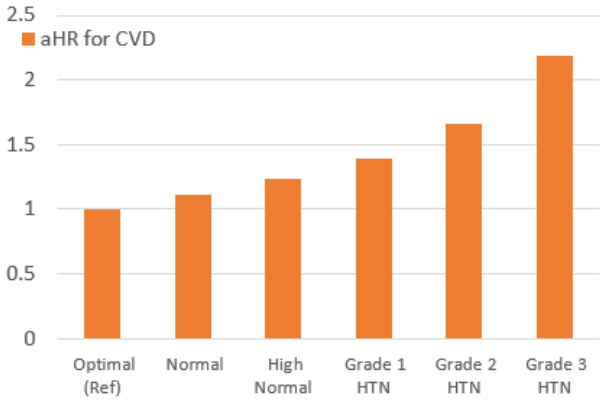
	Without antihypertensives		With antihypertensives	
	aHR	95% CI	aHR	95% CI
Cardiovascular disease				
2018 ESC/ESH				
Optimal	1.00	reference	1.00	reference
Normal	1.11	1.08-1.15	0.97	0.92-1.02
High normal	1.24	1.21-1.28	0.96	0.92-1.01
Grade 1 hypertension	1.39	1.35-1.44	0.96	0.92-1.01
Grade 2 hypertension	1.66	1.57-1.76	1.00	0.95-1.07
Grade 3 hypertension	2.19	1.96-2.45	1.07	0.97-1.18
2017 ACC/AHA				
Normal	1.00	reference	1.00	reference
Elevated BP	1.13	1.09-1.18	1.00	0.95-1.07
Stage 1 hypertension	1.18	1.15-1.21	0.96	0.91-1.00
Stage 2 hypertension	1.45	1.41-1.49	0.98	0.94-1.02

Participants with cardiovascular disease events within the first 5 years of follow-up were excluded.
Without anti-hypertensives: participants not prescribed anti-hypertensives within the first 5 years of follow-up.
With anti-hypertensives: participants prescribed anti-hypertensives within the first 5 years of follow-up.
Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, and Charlson comorbidity index.

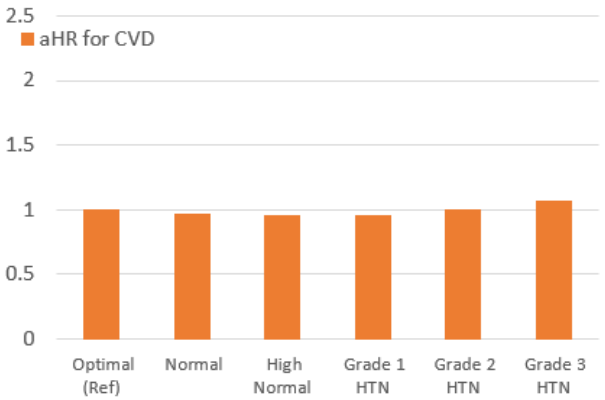
Acronyms: aHR, adjusted hazard ratio; CI, confidence interval; ESC/ESH, European Society of Cardiology/European Society of Hypertension; ACC/AHA, American College of Cardiology/American Heart Association; BP, blood pressure.

Figure 15. Stratified analysis for the risk of cardiovascular disease according to prescription of anti-hypertensives within the first 5 years of follow-up.

A. Without history of antihypertensive medication



B. With history of antihypertensive medication



Participants with cardiovascular disease events within the first 5 years of follow-up were excluded.
Without anti-hypertensives: participants not prescribed anti-hypertensives within the first 5 years of follow-up.
With anti-hypertensives: participants prescribed anti-hypertensives within the first 5 years of follow-up.
Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, and Charlson comorbidity index.
Acronyms: aHR, adjusted hazard ratio; CVD, cardiovascular disease, HTN, hypertension

Similar associations for both 2018 ESC/ESH and 2017 ACC/AHA BP categories were observed for CHD and stroke.

Among participants without prescription of antihypertensives within the first 5 years of follow-up, those with normal (aHR 1.06, 95% CI 1.02-1.11), high normal (aHR 1.17, 95% CI 1.11-1.23), grade 1 hypertension (aHR 1.21, 95% CI 1.15-1.27), grade 2 hypertension (aHR 1.34, 95% CI 1.22-1.46), and grade 3 hypertension (aHR 1.54, 95% CI 1.27-1.87) had higher risk for CHD compared to those with optimal BP defined by the 2018 ESC/ESH categories (Table 19, Figure 16).

Among participants with prescription of antihypertensives within the first 5 years of follow-up, compared to those with optimal BP defined by the 2018 ESC/ESH categories, those with normal (aHR 0.99, 95% CI 0.93-1.07), high normal (aHR 0.96, 95% CI 0.89-1.03), grade 1 hypertension (aHR 0.93, 95% CI 0.87-1.00), grade 2 hypertension (aHR 0.91, 95% CI 0.83-1.00), and grade 3 hypertension (aHR 0.85, 95% CI 0.73-1.00) had higher risk for CHD (Table 19, Figure 16).

Table 19. Stratified analysis for the risk of coronary heart disease according to prescription of antihypertensives within the first 5 years of follow-up.

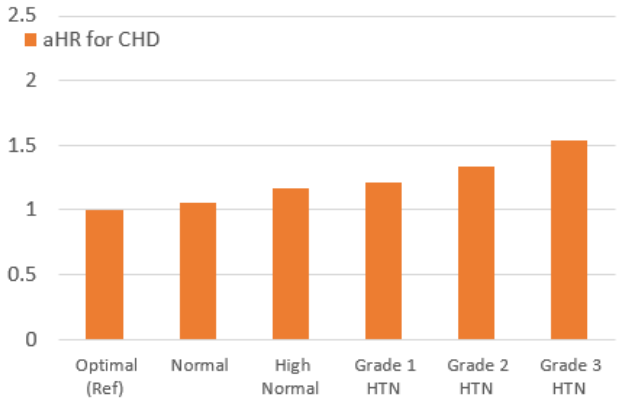
	Without antihypertensives		With antihypertensives	
	aHR	95% CI	aHR	95% CI
Coronary heart disease				
2018 ESC/ESH				
Optimal	1.00	reference	1.00	reference
Normal	1.06	1.02-1.11	0.99	0.93-1.07
High normal	1.17	1.11-1.23	0.96	0.89-1.03
Grade 1 hypertension	1.21	1.15-1.27	0.93	0.87-1.00
Grade 2 hypertension	1.34	1.22-1.46	0.91	0.83-1.00
Grade 3 hypertension	1.54	1.27-1.87	0.85	0.73-1.00
2017 ACC/AHA				
Normal	1.00	reference	1.00	reference
Elevated BP	1.11	1.05-1.18	1.02	0.93-1.13
Stage 1 hypertension	1.11	1.06-1.16	0.96	0.90-1.03
Stage 2 hypertension	1.23	1.18-1.29	0.92	0.86-0.98

Participants with cardiovascular disease events within the first 5 years of follow-up were excluded.
Without anti-hypertensives: participants not prescribed anti-hypertensives within the first 5 years of follow-up.
With anti-hypertensives: participants prescribed anti-hypertensives within the first 5 years of follow-up.
Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex,

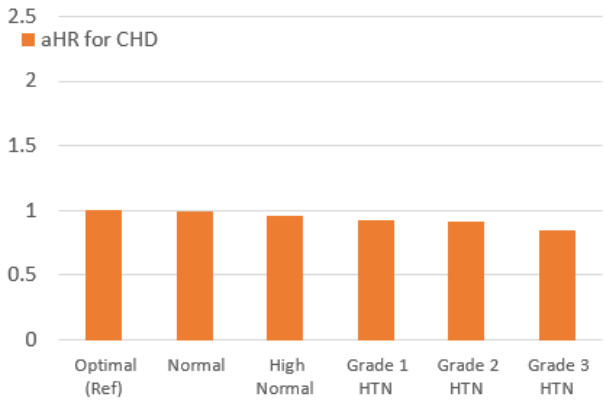
household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, and Charlson comorbidity index.
Acronyms: aHR, adjusted hazard ratio; CI, confidence interval; ESC/ESH, European Society of Cardiology/European Society of Hypertension; ACC/AHA, American College of Cardiology/American Heart Association; BP, blood pressure.

Figure 16. Stratified analysis for the risk of coronary heart disease according to prescription of antihypertensives within the first 5 years of follow-up.

A. Without history of antihypertensive medication



B. With history of antihypertensive medication



Participants with cardiovascular disease events within the first 5 years of follow-up were excluded.
Without anti-hypertensives: participants not prescribed anti-hypertensives within the first 5 years of follow-up.
With anti-hypertensives: participants prescribed anti-hypertensives within the first 5 years of follow-up.
Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, and Charlson comorbidity index.
Acronyms: aHR, adjusted hazard ratio; CHD, coronary heart disease; HTN, hypertension

Among participants without prescription of antihypertensives within the first 5 years of follow-up, those with normal (aHR 1.14, 95% CI 1.10-1.19), high normal (aHR 1.31, 95% CI 1.26-1.37), grade 1 hypertension (aHR 1.55, 95% CI 1.49-1.62), grade 2 hypertension (aHR 1.95, 95% CI 1.82-2.09), and grade 3 hypertension (aHR 2.74, 95% CI 2.40-3.11) had higher risk for stroke compared to those with optimal BP defined by the 2018 ESC/ESH categories (Table 20, Figure 17).

Among participants with prescription of antihypertensives within the first 5 years of follow-up, compared to those with optimal BP defined by the 2018 ESC/ESH categories, those with normal (aHR 0.97, 95% CI 0.90-1.03), high normal (aHR 0.97, 95% CI 0.91-1.04), grade 1 hypertension (aHR 1.01, 95% CI 0.95-1.08), grade 2 hypertension (aHR 1.09, 95% CI 1.01-1.18), and grade 3 hypertension (aHR 1.27, 95% CI 1.13-1.42) had higher risk for stroke (Table 20, Figure 17).

Table 20. Stratified analysis for the risk of stroke according to prescription of antihypertensives within the first 5 years of follow-up.

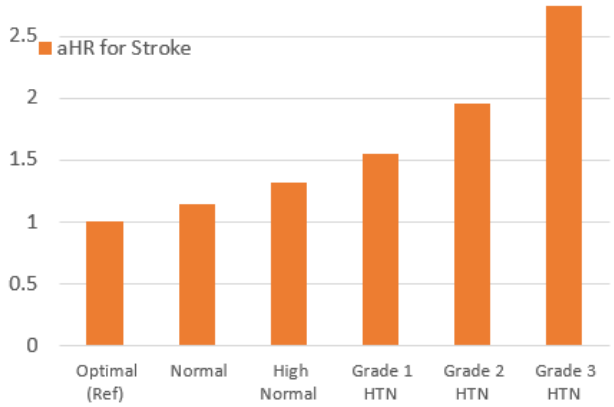
	Without antihypertensives		With antihypertensives	
	aHR	95% CI	aHR	95% CI
Stroke				
2018 ESC/ESH				
Optimal	1.00	reference	1.00	reference
Normal	1.14	1.10-1.19	0.97	0.90-1.03
High normal	1.31	1.26-1.37	0.97	0.91-1.04
Grade 1 hypertension	1.55	1.49-1.62	1.01	0.95-1.08
Grade 2 hypertension	1.95	1.82-2.09	1.09	1.01-1.18
Grade 3 hypertension	2.74	2.40-3.11	1.27	1.13-1.42
2017 ACC/AHA				
Normal	1.00	reference	1.00	reference
Elevated BP	1.14	1.09-1.20	1.00	0.93-1.09
Stage 1 hypertension	1.24	1.19-1.29	0.96	0.90-1.02
Stage 2 hypertension	1.63	1.57-1.70	1.04	0.98-1.10

Participants with cardiovascular disease events within the first 5 years of follow-up were excluded.
Without anti-hypertensives: participants not prescribed anti-hypertensives within the first 5 years of follow-up.
With anti-hypertensives: participants prescribed anti-hypertensives within the first 5 years of follow-up.
Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, and Charlson comorbidity index.
Acronyms: aHR, adjusted hazard ratio; CI, confidence interval; ESC/ESH, European Society of Cardiology/European

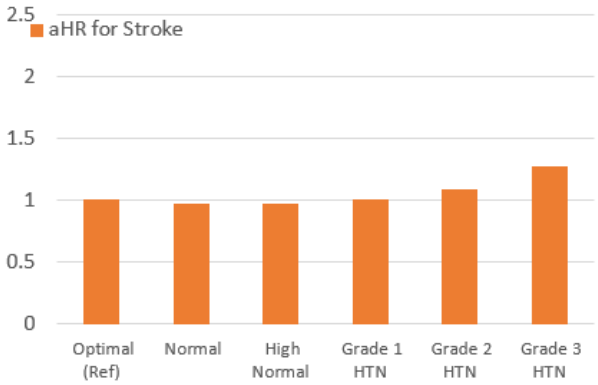
Society of Hypertension; ACC/AHA, American College of Cardiology/American Heart Association; BP, blood pressure.

Figure 17. Stratified analysis for the risk of stroke according to prescription of antihypertensives within the first 5 years of follow-up.

A. Without history of antihypertensive medication



B. With history of antihypertensive medication



Participants with cardiovascular disease events within the first 5 years of follow-up were excluded.
Without anti-hypertensives: participants not prescribed anti-hypertensives within the first 5 years of follow-up.
With anti-hypertensives: participants prescribed anti-hypertensives within the first 5 years of follow-up.
Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, and Charlson comorbidity index.
Acronyms: aHR, adjusted hazard ratio; HTN, hypertension

Part Ⅳ. Detailed Analysis for the Risk of Cardiovascular Disease According to Index Blood Pressure Among Adults With and Without History of Antihypertensive Medication Within the First 5 Years of Follow-up in Participants Without History of Antihypertensive Medication Before the Index Date

Among participants had no history of medication before the index date of 1 January 2006, detailed analysis for the risk of CVD according to index BP was done according to prescription of antihypertensives within the first 5 years of follow-up. Participants with cardiovascular disease events within the first 5 years of follow-up were excluded. After determining BP during 2004-2005, all participants were followed up for CVD or death starting from 1 January 2006 to 31 December 2018.

Among participants without prescription of antihypertensives within the first 5 years of follow-up, those with SBP 130-139 mmHg (aHR 1.24, 95% CI 1.21-1.28), SBP 140-149 mmHg (aHR 1.35, 95% CI 1.30-1.40), SBP 160-169 mmHg (aHR 1.68, 95% CI 1.56-1.82), and SBP 180-189 mmHg (aHR 2.91, 95% CI 2.40-2.53) had higher risk for CVD compared to those with SBP 110-119 mmHg (Table 21, Figure 18).

Among participants with prescription of antihypertensives within the first 5 years of follow-up, compared to those with SBP 110-119 mmHg, those with SBP 130-139 mmHg (aHR 1.07, 95% CI 1.04-1.10), SBP 140-149 mmHg (aHR 1.06, 95% CI 1.03-1.10), SBP 160-169 mmHg (aHR 1.13, 95% CI 1.08-1.19), and SBP 180-189 mmHg

(aHR 1.32, 95% CI 1.18-1.47) had higher risk for CVD (Table 21, Figure 19).

Among participants without prescription of antihypertensives within the first 5 years of follow-up, it showed consistently increased risk of CVD with increased index SBP. No statistically significant J-curve phenomenon was observed.

Among participants without prescription of antihypertensives within the first 5 years of follow-up, those with DBP 80-89 mmHg (aHR 1.12, 95% CI 1.09-1.15), DBP 90-99 mmHg (aHR 1.30, 95% CI 1.26-1.35), and DBP 100-109 mmHg (aHR 1.57, 95% CI 1.47-1.66) had higher risk for CVD compared to those with DBP 70-79 mmHg (Table 21, Figure 20).

Among participants with prescription of antihypertensives within the first 5 years of follow-up, compared to those with DBP 70-79 mmHg, those with DBP 80-89 mmHg (aHR 1.02, 95% CI 0.99-1.04), DBP 90-99 mmHg (aHR 1.01, 95% CI 0.99-1.04), and DBP 100-109 mmHg (aHR 1.04, 95% CI 0.99-1.08) didn't have statistically significantly higher risk for CVD (Table 21, Figure 21).

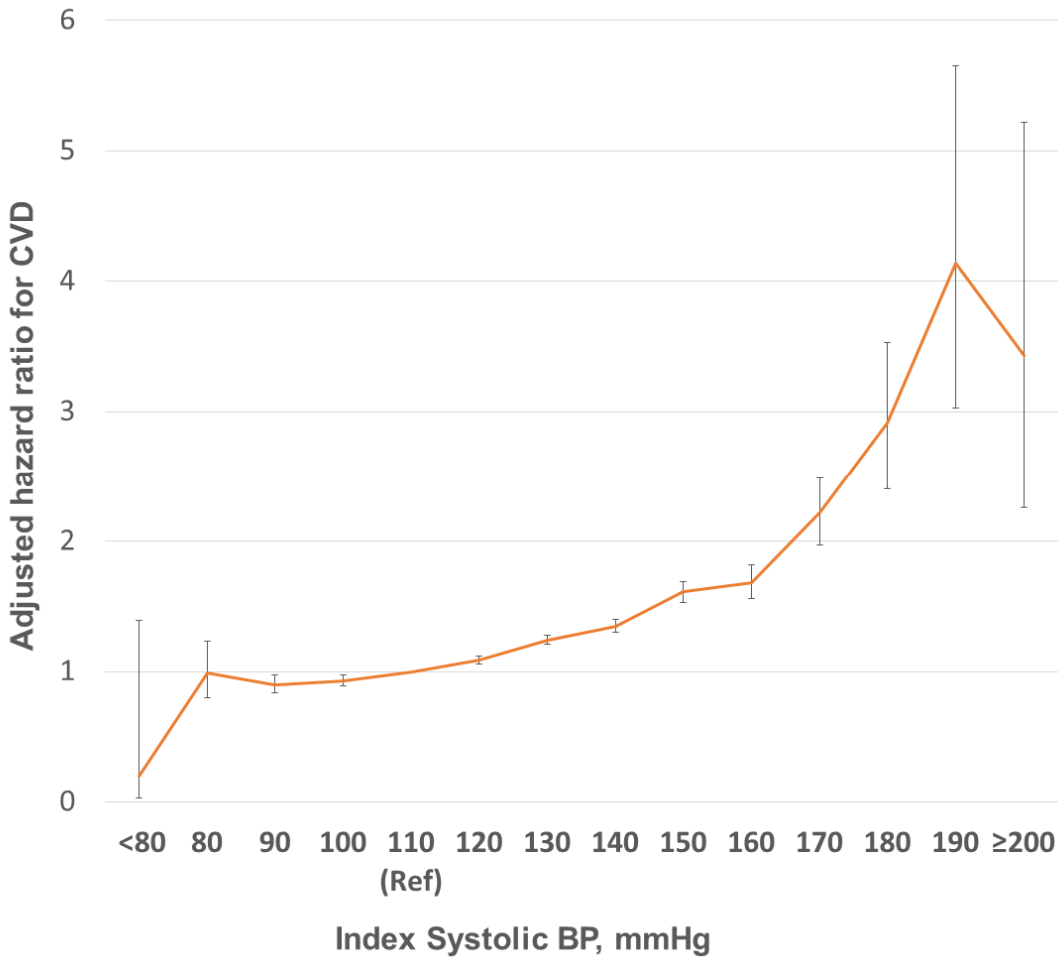
The J-curve phenomenon was not observed even in DBP.

Table 21. Hazard Ratios for Cardiovascular Disease According to Index Blood Pressure Among Adults With and Without History of Antihypertensive Medication Within the First 5 Years of Follow-up in Participants Without History of Antihypertensive Medication Before the Index Date

	Adjusted hazard ratio (95% confidence interval)		
BP groups	**Total**	**Without antihypertensives**	**With antihypertensives**
Systolic BP, mmHg			
<80	0.82 (0.41-1.65)	0.20 (0.03-1.39)	1.54 (0.74-3.24)
80-89	1.01 (0.86-1.18)	0.99 (0.80-1.23)	1.10 (0.87-1.39)
90-99	0.87 (0.83-0.92)	0.90 (0.84-0.97)	0.91 (0.84-0.99)
100-109	0.94 (0.91-0.97)	0.93 (0.89-0.97)	1.00 (0.96-1.05)
110-119	1.00 (reference)	1.00 (reference)	1.00 (reference)
120-129	1.12 (1.10-1.15)	1.09 (1.06-1.12)	1.08 (1.04-1.11)
130-139	1.26 (1.23-1.28)	1.24 (1.21-1.28)	1.07 (1.04-1.10)
140-149	1.36 (1.33-1.39)	1.35 (1.30-1.40)	1.06 (1.03-1.10)
150-159	1.53 (1.49-1.58)	1.61 (1.53-1.69)	1.11 (1.07-1.16)
160-169	1.60 (1.54-1.67)	1.68 (1.56-1.82)	1.13 (1.08-1.19)
170-179	1.89 (1.78-2.01)	2.22 (1.97-2.49)	1.28 (1.19-1.37)
180-189	2.08 (1.89-2.29)	2.91 (2.40-2.53)	1.32 (1.18-1.47)
190-199	2.53 (2.16-2.96)	4.14 (3.03-5.65)	1.52 (1.27-1.83)
≥200	3.38 (2.84-4.02)	3.43 (2.26-5.22)	2.28(1.88-2.76)
Diastolic BP, mmHg			
<50	0.78 (0.59-1.03)	0.75 (0.51-1.13)	0.85 (0.58-1.25)
50-59	0.90 (0.85-0.95)	0.93 (0.86-1.01)	0.96 (0.88-1.05)
60-69	0.92 (0.90-0.94)	0.94 (0.91-0.97)	0.97 (0.93-0.99)
70-79	1.00 (reference)	1.00 (reference)	1.00 (reference)
80-89	1.12 (1.10-1.14)	1.12 (1.09-1.15)	1.02 (0.99-1.04)
90-99	1.27 (1.24-1.29)	1.30 (1.26-1.35)	1.01 (0.99-1.04)
100-109	1.44 (1.39-1.49)	1.57 (1.47-1.66)	1.04 (0.99-1.08)
110-119	1.65 (1.54-1.77)	1.99 (1.74-2.27)	1.12 (0.93-1.33)
120-129	1.72 (1.48-2.00)	2.37 (1.79-3.14)	1.11 (0.93-1.33)
130-139	2.57 (1.92-3.45)	2.44 (1.16-5.12)	1.76 (1.28-2.43)
≥140	3.71 (2.50-5.48)	2.69 (1.01-7.16)	2.86 (1.86-4.38)

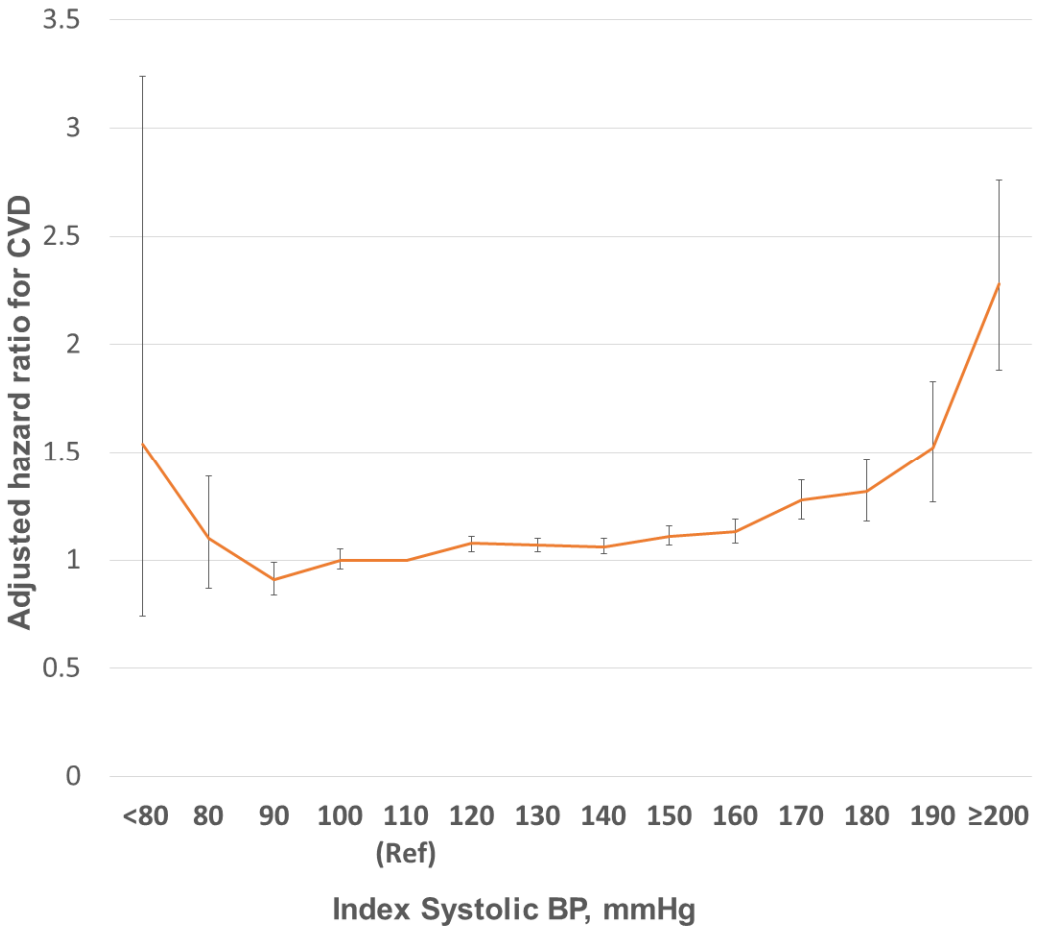
Participants with cardiovascular disease events within the first 5 years of follow-up were excluded.
Without anti-hypertensives: participants not prescribed anti-hypertensives within the first 5 years of follow-up.
With anti-hypertensives: participants prescribed anti-hypertensives within the first 5 years of follow-up.
Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, and Charlson comorbidity index.

Figure 18. Hazard Ratios for Cardiovascular Disease According to Index Systolic Blood Pressure Among Participants Without history of antihypertensive medication within the first 5 years of follow-up.



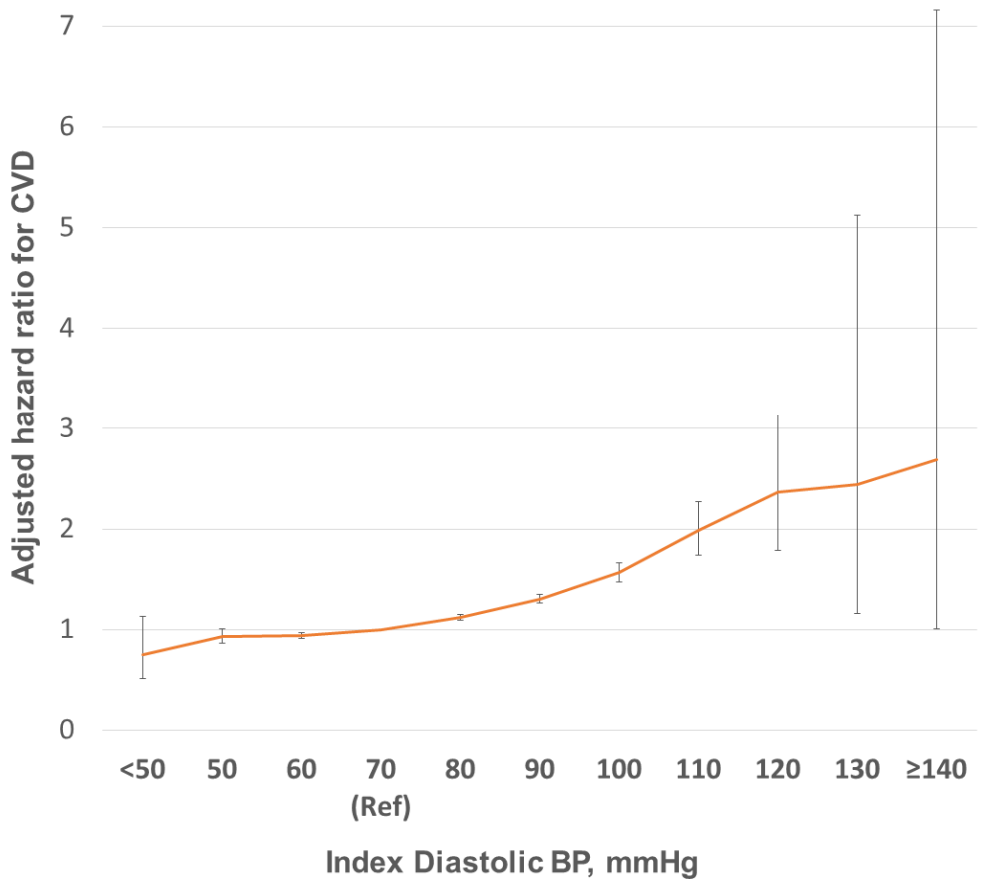
Participants with cardiovascular disease events within the first 5 years of follow-up were excluded.
Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, and Charlson comorbidity index.
Acronyms: CVD, cardiovascular disease

Figure 19. Hazard Ratios for Cardiovascular Disease According to Index Systolic Blood Pressure Among Participants With history of antihypertensive medication within the first 5 years of follow-up.



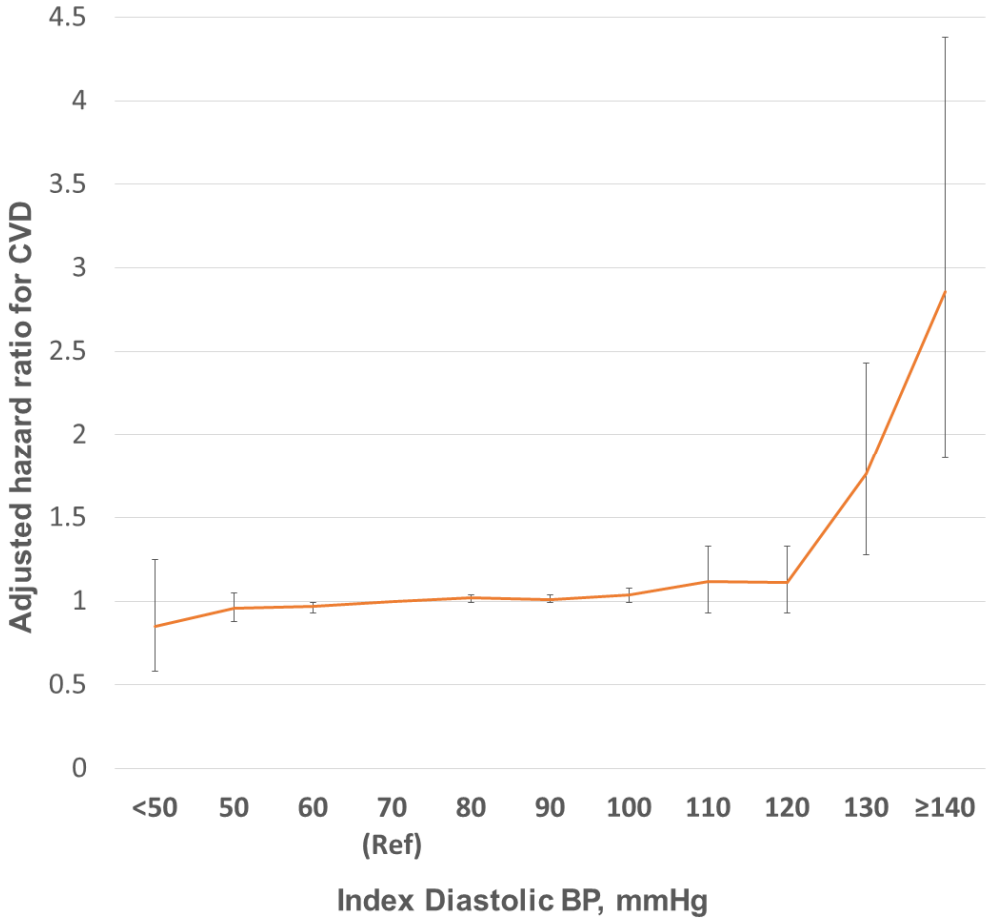
Participants with cardiovascular disease events within the first 5 years of follow-up were excluded.
Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, and Charlson comorbidity index.
Acronyms: CVD, cardiovascular disease

Figure 20. Hazard Ratios for Cardiovascular Disease According to Index Diastolic Blood Pressure Among Participants not prescribed anti-hypertensives within the first 5 years of follow-up.



Participants with cardiovascular disease events within the first 5 years of follow-up were excluded.
Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, and Charlson comorbidity index.
Acronyms: CVD, cardiovascular disease

Figure 21. Hazard Ratios for Cardiovascular Disease According to Index Diastolic Blood Pressure Among Participants With history of antihypertensive medication within the first 5 years of follow-up.



Participants with cardiovascular disease events within the first 5 years of follow-up were excluded.
Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, and Charlson comorbidity index.
Acronyms: CVD, cardiovascular disease

Ⅴ. Discussion

In this population-based study of about a million middle-aged and elderly Koreans, we have shown that the 10-year CVD incidence of 2017 ACC/AHA stage 1 hypertension group was lower than 10% (7.7 events per 1,000 person-years) and that of stage 2 hypertensive group was about 10% (10.2 events per 1,000 person-years). The 2017 ACC/AHA stage 1 hypertension group appeared to be heterogeneous and the CVD risk of the 2017 ACC/AHA stage 1 IDH group (SBP < 130 and DBP 80-89 mmHg) was not different from that of the 2017 ACC/AHA Elevated BP group (SBP 120-129 and DBP < 80 mmHg). No statistically significant J-curve phenomenon was observed. In participants aged more than 80 years, the CVD risk of the 2017 ACC/AHA stage 1 hypertension group was not higher than that of optimal BP group, but BP category of 140-159/90-99 mmHg was associated with an increased risk of CVD. The criteria for diagnosing hypertension of 140/90 mmHg or higher would be appropriate among Korean adults ≥50 years without history of hypertension and CVD.

1. Prevalence of newly diagnosed hypertension

If the 2017 ACC/AHA definition of hypertension is applied, the prevalence of hypertension increases dramatically. In a cross-sectional study of Korean adults aged 30 years or older, the prevalence of hypertension was about 49% according to the 2017 ACC/AHA hypertension categories versus 30% according to the 2018 ESC/ESH

hypertension categories.[24] More than half of the entire population in China and the United States would be diagnosed with hypertension if the 2017 ACC/AHA hypertension guidelines were applied to adults over 45 years of age.[25] This study showed similar results. Both 2018 ESC/ESH normal and high normal groups could be classified as 2017 ACC/AHA stage 1 hypertension because the DBP criteria are 80-84 mmHg or 85-89 mmHg. According to the 2017 ACC/AHA criteria, 34.6% of adults aged 50 years or older were diagnosed with stage 1 hypertension, and the prevalence of hypertension increased from 26.6% in 2018 ESC/ESH hypertension category to 61.3% in 2017 ACC/AHA hypertension category.

2. Hypertension categories and 10-year CVD incidence

The 10-year CVD incidence of 2017 ACC/AHA stage 1 hypertension group was lower than 10% and that of stage 2 hypertensive group was about 10%. The relatively low incidence of CVD was presumed to be because the study population was a low-risk subject with no history of hypertension and CVD. The 2017 ACC/AHA hypertension guidelines recommended antihypertensive drug treatment for adults with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of 10% or higher and a BP of 130/80 mmHg or higher.[1] This recommendation was not based on randomized controlled trial (RCT) results, but was based on expert opinion. There has been a lack of evidence as to whether diagnosing 2017 ACC/AHA stage 1 hypertension in middle-aged and elderly Koreans without a history of hypertension and CVD might be beneficial. Therefore,

diagnosing stage 1 hypertension based on 2017 ACC/AHA hypertension guidelines has the potential for overdiagnosis among Korean adults ≥50 years without history of hypertension and CVD.

3. Hypertension categories and CVD risk

This study showed that the 2018 ESC/ESH hypertension categories, rather than the 2017 ACC/AHA hypertension categories, were more closely associated with subsequent CVD risk in middle-aged and elderly adults. The results of observational studies on the clinical significance of 2017 ACC/AHA stage 1 hypertension were controversial. Some observational studies have shown that the risk of CVD increased in patients with SBP greater than 130 mmHg.[3-5] A prospective cohort study using the Korean Health and Genome Study (KHGS) data have shown that SBP ≥130 mmHg was significantly associated with increased risk of CVD, CVD death, and total deaths compared to SBP <120 mmHg. However, participants with DBP 80-89 mmHg did not have a significantly higher CVD risk than those with DBP <80 mmHg. [31] A Korean cohort study using the National Health Insurance Services-Health Screening (NHIS-HEALS) data (290,600 subjects, median follow-up duration 6.7 years) showed that the differences of CVD risk between DBPs of <80 mmHg and 80-89 mmHg mostly disappeared after statistical stratification or adjustment.[9] This analysis appears to suggest that the DBP component of ≥80 mmHg, which is part of the diagnostic criteria of stage 1 hypertension, may be disproportionately low. The German MONICA/KORA prospective study (11,603 participants, follow-up period of 10 years) showed that the risk of CVD mortality in

the 2017 ACC/AHA stage 1 hypertension group was not significantly higher (aHR 0.93, 95% CI 0.61−1.44, P = 0.76) than in the optimal BP group.[32]

4. Subcategories of stage 1 hypertension and CVD risk

In order to find the possible cause of those controversy, we conducted further sensitivity analysis. A previous study suggested that the 2017 ACC/AHA stage 1 hypertension might be a heterogeneous group. [22] The 2017 ACC/AHA stage 1 hypertension group was classified into the following three groups: IDH, ISH, and SDH. The IDH group, which accounts for more than one−third of stage 1 hypertension patients, had similar cardiovascular risk as the 2017 ACC/AHA elevated BP group. Compared with the IDH group, the SDH group had a higher risk of CVD (aHR 1.13, 95% CI, 1.10−1.16) despite being classified in the same stage 1 hypertension group. Moreover, the mean SBP of the IDH group was less than 120 mmHg. Therefore, the 2017 ACC/AHA stage 1 hypertension group was a heterogeneous group, and care should be taken upon diagnosing hypertension, especially when the patient has SBP <130 mmHg. Additional research is needed on the clinical significance and within−group heterogeneity of 2017 ACC/AHA defined stage 1 hypertension.

A large−scale study analyzing the effects of diastolic and systolic blood pressure on CVD risk showed that both systolic and diastolic blood pressure independently affected the risk of CVD regardless of the definition of hypertension (≥140/90 mm Hg or ≥

130/80 mm Hg).[33] However, there has been controversy over the risk of CVD in isolated systolic and isolated diastolic hypertension. [34-40] A long-term follow-up study of the nationally representative subjects in the United States showed that the 2017 ACC/AHA stage 1 IDH was not associated with an increased risk of CVD.[41] In a large long-term follow-up study of Korean young adult, the 2017 ACC/AHA stage 1 IDH was associated with an increased risk of CVD than normal BP. The risk of CVD in stage 1 IDH and stage 1 ISH was similar, but lower than the CVD risk of stage 1 SDH.[8] The difference in these results is thought to be due to the difference in age group of the study population.

5. Hypertension categories and CVD risk among middle-aged, elderly, and very elderly

A meta-analysis of the effects of intensive BP control in adults aged 60 years or older showed that aggressive BP control is associated with higher risk for adverse effects, such as hypotension and syncope.[42] The SPRINT study also showed more serious adverse events such as hypotension, syncope, electrolyte abnormalities, and acute kidney injury in the intensive-treatment group than in the standard-treatment group.[43] A bivariate analysis of RCTs comparing intensive versus standard BP control that reported both major adverse cardiac events (MACE) and serious adverse events (SAE) endpoints, including the Valsartan in Elderly Isolated Systolic Hypertension (VALISH) study, the Action to Control Cardiovascular Risk in Diabetes

(ACCORD) BP trial, the Secondary Prevention of Small Subcortical Strokes (SPS3) trial, and the SPRINT study, was published. The pooled analysis of these RCTs suggested that intensive BP control did not have a net clinical benefit when weighing the benefit of MACE prevention against the risk of SAE over standard BP control.[44] In the case of hypertension medication among those within the lower range of BP criteria, the harm due to the adverse effect may be greater than the benefit.[45] Until definitive studies will be published, it is advisable to consider adopting 2018 ESC/ESH hypertension guidelines that better reflect the risk of CVD among Asian middle-aged and elderly people.

Interestingly, in participants >80 years, the CVD risk of the 2017 ACC/AHA stage 1 hypertension group was not higher than that of optimal BP group. Other cohort studies also showed that among participants aged more than 60 or 65 years, the 2017 ACC/AHA defined stage 1 hypertension was not associated with an increased risk of CVD.[4] [23] These findings suggest that there has been a lack of evidence in applying the 2017 ACC/AHA hypertension guidelines to the elderly.

6. No J-curve phenomenon antihypertensive medication among Korean adults ≥50 years without history of hypertension and CVD.

This study showed consistently increased risk of CVD with increased index SBP among participants without prescription of

antihypertensives within the first 5 years of follow-up. No statistically significant J-curve phenomenon was observed. There has been controversy over the possibility of the J-curve relationship between low DBP and CVD risk.[10-17] Particular attention might be needed because the lower BP targets in the 2017 ACC/AHA hypertension guidelines could result in more hypertension patients being treated to the level of diastolic hypotension.[14,18-21] A large-scale cohort study of Korean low-risk hypertensive patients showed that SBP <120 mmHg and DBP <80 mmHg were associated with an increased risk of myocardial infarction.[19] A study of more than 1 million Koreans reported a J-curve relationship between SBP and vascular mortality. SBP below 90 mmHg was associated with death from vascular disease, especially from ischemic heart disease.[16] According to a cohort study that classified Koreans by risk factors (hypertension, diabetes, hyperlipidemia, proteinuria, and smoking), patients with three or more risk factors had a higher risk of all-cause mortality than high-risk patients with normal BP (120 to 129 mmHg).[17] The reasons why the J-curve phenomenon was not observed in this study were those that did not consider death, and this study was conducted in a relatively low risk group without history of anti-hypertensive medication.

7. Modified BP criteria for newly diagnosed hypertension among Korean adults ≥50 years without history of CVD

The 2018 Korean Society of Hypertension guidelines presented the following BP classification (Table 22).[46]

Table 22. 2018 Korean hypertension guideline BP categories

BP Category	Systolic blood pressure (mmHg)		Diastolic blood pressure (mmHg)
Normal blood pressure[a]	< 120	And	< 80
Elevated blood pressure	120-129	And	< 80
Prehypertension	130-139	Or	80-89
Hypertension Grade 1	140-159	Or	90-99
Hypertension Grade 2	≥160	Or	≥100
Isolated systolic hypertension	≥140	And	< 90

[a]Blood pressure with minimal risk for cardiovascular events

However, this classification was not based on the results of a recent large-scale study of Korean adults. Therefore, it needed to be verified through a recent large-scale cohort study of Koreans.

A summary of the results of our long-term follow-up study on Korean Adults ≥50 years without history of CVD is as follows (Table 23). The hazard ratios for CVD in the group with DBP 80-89 mmHg and DBP 90-99 mmHg were 1.12 (95% CI 1.10-1.14) and 1.27 (95% CI 1.24-1.29), respectively, compared to those with DBP 70-79 mmHg. The 10-year CVD incidence of 2017 ACC/AHA stage 1 hypertension group was lower than 10% (7.7 events per 1,000 person-years) and that of stage 2 hypertensive group was about 10% (10.2 events per 1,000 person-years). The HOPE-3 (Heart Outcomes Prevention Evaluation-3) trial was an RCT that validates the CVD preventive effect of anti-hypertensive medications in adults ≥55 years who had no history of CVD and had moderate CVD risk.[47] As a result of the HOPE-3 study, in the case of baseline SBP 131.6-143.5 mmHg, there was no CVD prevention effect of anti-hypertensive drugs, and only in the group of baseline SBP

>143.5mmHg, there was CVD prevention effect. Considering these points, it would be reasonable to define 140/90 mmHg or higher as hypertension among Korean Adults ≥50 years without history of CVD (Table 24). The hazard ratio for CVD in the group with SBP 120−129 mmHg (aHR 1.12, 95% CI 1.10−1.15) was similar to that of those with DBP 80−89 mmHg (aHR 1.12, 95% CI 1.10−1.14). And the 10−year CVD incidence of 'SBP 120−129 and DBP <90 mmHg' BP category was about 7%. Therefore, it was proposed to name the category with 'SBP 120−129 and DBP <90 mmHg' as 'High normal'.

Table 23. A summary of hazard ratios for cardiovascular disease according to 2017 ACC/AHA and 2018 ESC/ESH hypertension categories

2017 ACC/AHA	Normal (<120/80)	Elevated BP (120–129/<80)	Stage 1 hypertension			Stage 2 HTN (≥140/≥90)		
			IDH (<130/80–89)	ISH (130–139/<80)	SDH (130–139/80–89)			
CVD Incidence	5.6	7.2	6.8	8.8	8.4	10.2		
CVD aHR (95% CI)	1.00 (reference)	1.15 (1.12–1.18)	1.13 (1.11–1.16)	1.26 (1.22–1.30)	1.29 (1.26–1.32)	1.46 (1.44–1.49)		
2018 ESC/ESH	Optimal (<120/80)	Normal (120–129/80–84)		High normal (130–139/85–89)		Grade 1 HTN (140–159/90–99)	Grade 2 HTN (160–179/100–109)	Grade 3 HTN (≥180/≥110)
CVD Incidence	5.6	7.0		8.4		9.7	11.6	14.6
CVD aHR (95% CI)	1 (reference)	1.14 (1.12–1.17)		1.28 (1.26–1.31)		1.41 (1.38–1.43)	1.62 (1.57–1.67)	2.02 (1.91–2.13)

Incidence calculated by the number of events per 1,000 person-years

Adjusted hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, sex, household income, smoking, alcohol intake, physical activity, body mass index, fasting serum glucose, total cholesterol, and Charlson comorbidity index.

Acronyms: HTN, hypertension; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; SDH, combined systolic/diastolic hypertension; SD, standard deviation; aHR, adjusted hazard ratio; CI, confidence interval; ESC/ESH, European Society of Cardiology/European Society of Hypertension; ACC/AHA, American College of Cardiology/American Heart Association; BP, blood pressure; CVD, Cardiovascular Disease

Table 24. Modified Blood Pressure Criteria for Newly Diagnosed Hypertension among Korean Adults ≥50 years without history of Cardiovascular Disease

			Stage 1 hypertension					
2017 ACC/AHA	Normal (<120/80)	Elevated BP (120–129/<80)	IDH (<130/80–89)	ISH (130–139/<80)	SDH (130–139/80–89)	Stage 2 HTN (≥140/≥90)		
2018 ESC/ESH	Optimal (<120/80)	Normal (120–129/80–84)		High normal (130–139/85–89)		Grade 1 HTN (140–159/90–99)	Grade 2 HTN (160–179/100–109)	Grade 3 HTN (≥180/≥110)
Modified Blood Pressure Criteria for Newly Diagnosed Hypertension among Korean Adults ≥50 years without history of CVD								
Age 50–80 years	Normal (<120/80) 정상혈압	High normal (120–129/<90) 주의혈압		Pre-HTN (130–139/<90) 고혈압전단계		Grade 1 HTN (140–159/90–99) 1기 고혈압	Grade 2 HTN (≥160/≥100) 2기 고혈압	
Age >80 years	Normal (<140/<90) 정상혈압					Grade 1 HTN (140–159/90–99) 1기 고혈압	Grade 2 HTN (≥160/≥100) 2기 고혈압	

Acronyms: HTN, hypertension; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; SDH, combined systolic/diastolic hypertension; SD, standard deviation; aHR, adjusted hazard ratio; CI, confidence interval; ESC/ESH, European Society of Cardiology/European Society of Hypertension; ACC/AHA, American College of Cardiology/American Heart Association; BP, blood pressure; CVD, Cardiovascular Disease

8. Limitation and Strength

A number of limitations must be considered when interpreting the results from our study. First, there is a methodological limitation in BP measurements. The hypertension guidelines recommend that BP be measured repeatedly and averaged, but BP measurements in our study were conducted only once. Second, the subjects of this study were limited to citizens of seven metropolitan areas in South Korea. Therefore, results may differ among those within other countries or with different ethnicities. Third, CVD event in this study was defined based on a claims data. Therefore, there may be limitations due to claims data and additional validation studies may be required. However, a study validating the diagnosis of acute myocardial infarction in Korean national medical health insurance claims data showed more than 70% accuracy.[48] Fourth, since this study's analysis was based on baseline BP, we could not consider changes in BP after the index date. Moreover, this study did not take into account medications that could affect CVD incidence. Fifth, the participants' death data were not available for this study. Therefore, there was a limit that CVD death without CVD hospitalization could not be considered. Last, this study was a retrospective observation study, therefore, the causal relationship is unclear and prospective intervention studies are required. Despite these limitations, there are also several strengths. The current study is a large long-term follow-up cohort study of about a million subjects. This study considered many potential confounding factors such as sociodemographic, comorbidities, and health behaviors.

Ⅵ. Conclusion

In this real-world long-term cohort study of about a million Koreans ≥50 years without CVD, the 10-year CVD incidence of 2017 ACC/AHA stage 1 hypertension group was lower than 10% and that of stage 2 hypertensive group was about 10%. The 2017 ACC/AHA stage 1 hypertension group appeared to be heterogeneous and the CVD risk of 2017 ACC/AHA stage 1 IDH was not higher than Elevated BP. In participants aged more than 80 years, the CVD risk of the 2017 ACC/AHA stage 1 hypertension group was not higher than that of optimal BP group, but BP category of 140-159/90-99 mmHg was associated with an increased risk of CVD. The criteria for diagnosing hypertension of 140/90 mmHg or higher would be appropriate among Korean adults ≥50 years without history of hypertension and CVD.

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국 문 요 약

연구 배경

2017년 미국심장학회/미국심장협회 (ACC/AHA) 고혈압 지침은 고혈압 진단 기준을 140/90 이상에서 130/80mmHg 이상으로 낮추었고 stage 1 고혈압 약물치료의 역치를 10년 심혈관계질환 (CVD) 위험도 10% 이상으로 권고하였다. 그러나 CVD 과거력이 없는 대한민국 중년과 노인에서 향후의 CVD 위험도를 반영한 적절한 신규 고혈압 진단 기준에 관한 연구는 부족하다.

연구 방법

국민건강보험공단 맞춤형 코호트에서 전국 7대 도시에 거주하고 50세 이상이면서 과거 고혈압 약물 복용력과 CVD 과거력이 없고 2004-2005년 공단검진을 받은 967,853명의 성인을 대상으로 분석하였다. 2004-2005년 공단검진 시에 측정한 혈압을 2018년 ESC/ESH 고혈압 지침 및 2017년 ACC/AHA 고혈압 지침 혈압 범주를 기준으로 분류하였고, 2006년 1월부터 2018년 12월까지 CVD 발생을 추적 관찰하였다. 일차결과변수인 CVD 발생은 CVD에 의한 2일 이상의 입원으로 정의하였다. 혈압 범주에 따른 CVD 발생 위험은 Cox 비례 위험 회귀 분석을 사용하여 위험 비율 (HR)과 95% 신뢰구간 (CI)을 계산하여 결정되었다.

연구 결과

2017 ACC/AHA stage 1 고혈압 군의 10년 CVD 발생률은 10% 미만이었고 (7.7 events per 1,000 person-years), stage 2 고혈압 군은 약 10% 정도였다 (10.2 events per 1,000 person-years). 2017 ACC/AHA

stage 1 단독 이완기 고혈압 (IDH, SBP <130 and DBP 80-89mmHg) 군의 CVD 발생 위험은 정상혈압 군보다는 높았지만 (adjusted hazard ratio [aHR], 1.13; 95% confidence interval [CI], 1.11-1.16), 2017 ACC/AHA Elevated BP (SBP 120-129 and DBP <80mmHg)군 보다는 높지 않았다 (adjusted hazard ratio [aHR], 0.98; 95% confidence interval [CI], 0.96-1.01). IDH 군과 비교했을 때, 단독 수축기 고혈압 (ISH, SBP 130-139 and DBP <80mmHg) 군의 CVD 발생 위험 (aHR 1.13, 95% CI 1.09-1.16)과 수축기 이완기 고혈압 (SDH, SBP 130-139 and DBP 80-89mmHg) 군의 CVD 발생 위험 (aHR 1.15, 95% CI 1.12-1.17)이 높았다. 80세가 넘는 초고령자에서 2018 ESC/ESH optimal BP 군과 비교했을 때, 2017 ACC/AHA stage 1 고혈압 군의 CVD 발생 위험은 크지 않았지만 (aHR, 0.99; 95% CI, 0.82-1.21), 혈압 범주 140-159/90-99mmHg인 군의 CVD 발생 위험은 컸다 (aHR, 1.23; 95% CI, 1.02-1.50).

연구 결론

2017 ACC/AHA stage 1 고혈압 군의 10년 CVD 발생률은 낮았다. 2017 ACC/AHA stage 1 고혈압 군은 이질적으로 보였고, stage 1 IDH 군의 CVD 위험도는 Elevated BP 군과 차이가 없었다. 과거 고혈압 약물 복용력과 CVD 과거력이 없는 대한민국 50세 이상의 성인에서 고혈압 진단 기준은 140/90mmHg 이상이 적합할 것으로 추정된다.

주요어: 혈압; 고혈압; 심혈관계질환

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