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ORIGINAL RESEARCH ARTICLE

Association of Blood Pressure Classification Using the 2017 American College of Cardiology/ American Heart Association Blood Pressure Guideline With Risk of Heart Failure and Atrial Fibrillation

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BACKGROUND: Heart failure (HF) and atrial fibrillation (AF) are growing in prevalence worldwide. Few studies have assessed to what extent stage 1 hypertension in the 2017 American College of Cardiology/American Heart Association blood pressure (BP) guidelines is associated with incident HF and AF.

METHODS: Analyses were conducted with a nationwide health claims database collected in the JMDC Claims Database between 2005 and 2018 (n=2 196 437; mean age, 44.0±10.9 years; 58.4% men). No participants were taking antihypertensive medication or had a known history of cardiovascular disease. Each participant was categorized as having normal BP (systolic BP <120 mm Hg and diastolic BP <80 mm Hg; n=1 155 885), elevated BP (systolic BP 120–129 mm Hg and diastolic BP <80 mm Hg; n=337 390), stage 1 hypertension (systolic BP 130–139 mm Hg or diastolic BP 80–89 mm Hg; n=459 820), or stage 2 hypertension (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg; n=243 342). Using Cox proportional hazards models, we identified associations between BP groups and HF/AF events. We also calculated the population attributable fractions to estimate the proportion of HF and AF events that would be preventable if participants with stage 1 and stage 2 hypertension were to have normal BP.

RESULTS: Over a mean follow-up of 1112±854 days, 28 056 incident HF and 7774 incident AF events occurred. After multivariable adjustment, hazard ratios for HF and AF events were 1.10 (95% CI, 1.05–1.15) and 1.07 (95% CI, 0.99–1.17), respectively, for elevated BP; 1.30 (95% CI, 1.26–1.35) and 1.21 (95% CI, 1.13–1.29), respectively, for stage 1 hypertension; and 2.05 (95% CI, 1.97–2.13) and 1.52 (95% CI, 1.41–1.64), respectively, for stage 2 hypertension versus normal BP. Population attributable fractions for HF associated with stage 1 and stage 2 hypertension were 23.2% (95% CI, 20.3%–26.0%) and 51.2% (95% CI, 49.2%–53.1%), respectively. The population attributable fractions for AF associated with stage 1 and stage 2 hypertension were 17.4% (95% CI, 11.5%–22.9%) and 34.3% (95% CI, 29.1%–39.2%), respectively.

CONCLUSIONS: Both stage 1 hypertension and stage 2 hypertension were associated with a greater incidence of HF and AF in the general population. The American College of Cardiology/American Heart Association BP classification system may help identify adults at higher risk for HF and AF events.

Key Words: atrial fibrillation ■ epidemiology ■ guidelines as topic ■ heart failure ■ hypertension

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Clinical Perspective

What Is New?

- Among adults not taking antihypertensive medications and with no prevalent history of cardiovascular disease, stage 1 hypertension and stage 2 hypertension according to the 2017 American College of Cardiology/American Heart Association Blood Pressure guidelines were associated with a higher incidence of heart failure and atrial fibrillation.
- The population attributable fractions for heart failure associated with stage 1 and stage 2 hypertension were 23.2% (95% CI, 20.3%–26.0%) and 51.2% (95% CI, 49.2%–53.1%), respectively. The population attributable fractions for atrial fibrillation associated with stage 1 and stage 2 hypertension were 17.4% (95% CI, 11.5%–22.9%) and 34.3% (95% CI, 29.1%–39.2%), respectively.

What Are the Clinical Implications?

- The blood pressure categorization based on the 2017 American College of Cardiology/American Heart Association Blood Pressure guidelines may improve risk stratification for identifying adults at high risk for heart failure and atrial fibrillation events.

Nonstandard Abbreviations and Acronyms

ACC	American College of Cardiology
AF	atrial fibrillation
AHA	American Heart Association
AP	angina pectoris
BP	blood pressure
CVD	cardiovascular disease
DBP	diastolic blood pressure
HF	heart failure
ICD-10	*International Classification of Diseases, 10th Revision*
MI	myocardial infarction
PAF	population attributable fraction
SBP	systolic blood pressure
SPRINT	Systolic Blood Pressure Intervention Trial

Heart failure (HF) and atrial fibrillation (AF) are increasing in prevalence worldwide. The prevalence of HF is predicted to increase by 46% from 2012 to 2030, resulting in >8 million people ≥18 years of age with HF, and the prevalence of AF has been estimated to rise from 5.2 million in 2010 to 12.1 million in 2030 in the United States.[1] Prevention of HF and AF is therefore an urgent public health issue.

High blood pressure (BP) is a major risk factor for and a preventable cause of HF and AF.[1–3] The 2017 American College of Cardiology (ACC)/American Heart Association (AHA) BP guideline defined stage 1 hypertension as systolic BP (SBP) of 130 to 139 mm Hg or diastolic BP (DBP) of 80 to 89 mm Hg.[4] This new definition lowered the BP threshold for hypertension from SBP/DBP ≥140/90 mm Hg to SBP/DBP ≥130/80 mm Hg. Previous studies reported the association between stage 1 hypertension using this definition and coronary artery disease, stroke, and HF.[5–7] However, little is known about whether stage 1 hypertension versus normal BP is specifically associated with a higher risk for HF and AF. Furthermore, the proportion of HF and AF that would be prevented if individuals with stage 1 hypertension were to have their BP normalized has not been reported.

Using data from a nationwide health claims database,[8] we assessed (1) whether adults with stage 1 hypertension were at higher risk for incident HF and AF events compared with those with normal BP (SBP <120 mm Hg and DBP <80 mm Hg) and (2) the proportion of incident HF and AF that would potentially be preventable when stage 1 hypertension could be lowered to normal BP with the use of the population attributable fraction (PAF).

METHODS

This database is available for anyone who purchases it from the JMDC Inc (Tokyo, Japan; https://www.jmdc.co.jp/en/index).

Study Population

This study is a retrospective observational analysis using the JMDC Claims Database between January 2005 and August 2018 (n=2 943 563).[8–13] The JMDC Claims Database includes individual health insurance claims from >60 insurers. The JMDC Claims Database includes workplace employees' annual health checkup data, including demographics, medical history, medications, hospital claims with *International Classification of Diseases, 10th Revision* (ICD-10) coding, and death information. Of the records of 2 943 563 individuals, we excluded the records of 415 406 individuals who were missing data for BP or antihypertensive medication use. Compared with participants with available data on BP and antihypertensive medication use, individuals missing BP or antihypertensive medication use data were younger and more likely to be male (Table I in the Data Supplement). We further excluded individuals taking antihypertensive medications (n=246 870), those <20 years of age (n=22 198), and those with history of myocardial infarction (MI), angina pectoris (AP), coronary revascularization, HF, stroke, AF, or hemodialysis (n=622 652) at baseline, leaving a final analytic sample of 2 196 437 participants. However, because the number of individuals taking antihypertensive medications was substantial, in a sensitivity analysis, we added participants taking antihypertensive medication to the stage 2 hypertension group.

Ethics

We conducted this study according to the ethics guidelines of our institution (approval by the Ethical Committee of the University of Tokyo: 2018-10862) and in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived because all data from the JMDC Claims Database were deidentified.

BP and Other Measurements

In the Japanese health checkup system, BP was measured according to the recommended protocol of the Japanese Ministry of Health, Labor, and Welfare[14] by health care professionals using a standard sphygmomanometer or an automated device on the right arm after participants had rested for 5 minutes in a seated position (see the Data Supplement). The measurements were performed 2 times at an interval of ≥1 minute, and the average of 2 measurements on a single occasion was used for analyses. Participants were categorized as having normal BP, elevated BP, stage 1 hypertension, or stage 2 hypertension. The normal BP group included participants with untreated SBP <120 mm Hg and untreated DBP <80 mm Hg. The elevated BP group included participants with untreated SBP 120 to 129 mm Hg and untreated DBP <80 mm Hg. The stage 1 hypertension group included participants with untreated SBP 130 to 139 mm Hg or untreated DBP 80 to 89 mm Hg. The stage 2 hypertension group included participants with untreated SBP ≥140 mm Hg or untreated DBP ≥90 mm Hg. Other data, including body mass index, waist circumference, history of diabetes, dyslipidemia, and cardiovascular disease (CVD), and fasting laboratory values, were collected with the use of standardized protocols across study centers. Information on cigarette smoking (current or noncurrent) and alcohol consumption (every day or not every day) was self-reported. Obesity was defined as body mass index ≥25 kg/m^2.[15] High waist circumference was defined as waist circumference ≥85 cm for men and ≥90 cm for women.[16] Diabetes was defined as fasting glucose ≥126 mg/dL or use of glucose-lowering medications. Dyslipidemia was defined as low-density lipoprotein cholesterol ≥140 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, triglycerides ≥150 mg/dL, or use of lipid-lowering medications.

Outcomes

Outcomes were collected between January 2005 and August 2018. The primary outcomes included HF (*ICD-10*: I500, I501, I509, I110) and AF (*ICD-10*: I480, I481, I482, I483, I484, I489). The secondary outcomes included MI (*ICD-10*: I210, I211, I212, I213, I214, I219), AP (*ICD-10*: I200, I201, I208, I209), and stroke (*ICD-10*: I630, I631, I632, I633, I634, I635, I636, I638, I639, I600, I601, I602, I603, I604, I605, I606, I607, I608, I609, I610, I611, I613, I614, I615, I616, I619, I629), as described in previous studies.[8,17] Each CVD event was analyzed separately. For example, if a participant had an MI and then had a stroke a month later, both the MI and stroke events were counted as separate outcomes. The secondary outcomes also included composite CVD events, including HF, AF, MI, AP, and stroke; if a participant had >1 event, the first event was counted as the outcome.

Statistical Analysis

Descriptive statistics are reported as means (SDs), medians (interquartile ranges) for skewed variables, and proportions when appropriate. A *P* value for trend of each variable was calculated with the Jonckheere-Terpstra trend test for continuous variables and χ^2 test for categorical variables. The cumulative incidences of each CVD event and composite CVD events according to BP groups were calculated with the Kaplan-Meier method and the log-rank test. We conducted Cox regression analyses to assess the association of BP groups with subsequent risk for outcomes. We also assessed SBP and DBP levels as continuous variables and their associations with CVD outcomes. Hazard ratios were calculated in an unadjusted model and after adjustment for potential confounders, including age, sex, obesity, high waist circumference, diabetes, dyslipidemia, cigarette smoking, and alcohol consumption. Covariates were selected a priori because they have been shown to be associated with BP and CVD events.[8,17] PAF represents the proportion of cases of a disease in a population that can be attributed to a risk factor. The PAF was calculated as the proportional reduction in population disease or mortality that would occur if exposure to a risk factor were reduced to an ideal scenario. We calculated the PAF with corresponding 95% CI using the STATA command punafcc,[18,19] which calculates CIs for PAFs and population unattributable fractions in survival studies. It estimates the log of the mean rate ratio (eg, HF events) between 2 scenarios, a baseline scenario (scenario 0; ie, stage 1 or 2 hypertension) and a fantasy scenario (scenario 1) in which stage 1 or 2 hypertension is assumed to be reduced to normal BP, and any other variables (ie, same covariates, including age, sex, obesity, high waist circumference, diabetes, dyslipidemia, cigarette smoking, and alcohol consumption) in the model are assumed to remain the same. This ratio is known as the population unattributable fraction and is subtracted from 1 to derive the PAF. We performed 5 sensitivity analyses. First, we used multiple imputation for missing data, as previously described.[8,20] Assuming that missing data for covariates occurred independently of missing measures of BP, we imputed missing data for covariates using the chained equation method with 20 iterations as described by Aloisio et al.[21] Hazard ratio and SEs were obtained with the Rubin rules.[22] Second, we adjusted for glucose and lipid parameters as continuous variables instead of categorial variables. Third, we added into the stage 2 hypertension group 192 370 participants ≥20 years of age taking antihypertensive medication who also had no history of CVD. Fourth, to refine the BP groups by requiring 2 BP readings for classification of BP stage, we included 818 478 participants who had BP measured on 2 consecutive occasions (ie, at baseline and within the first year of follow-up). Fifth, in this study, death could be regarded as a competing risk with HF and AF events. Because our study objective was to evaluate whether stage 1 hypertension is associated with the incidence of HF and AF, we performed the cause-specific Cox proportional hazard modeling as a competing-risk analysis.[23,24] A value of $P<0.05$ was considered statistically significant. Statistical analyses were performed with SPSS software version 25 (IBM Corp, Armonk, NY) and STATA version 16 (StataCorp LLC, College Station, TX).

RESULTS

Using BP measurements at baseline, we categorized the 2 196 437 participants as having normal BP (n=1 155,885), elevated BP (n=337 390), stage 1 hypertension (n=459 820), or stage 2 hypertension (n=243 342). Participants with elevated BP, stage 1 hypertension, and stage 2 hypertension were older and more likely to be men than their counterparts with normal BP (Table). At baseline, participants in the elevated BP and stage 1 and stage 2 hypertension groups had higher body mass index, waist circumference, plasma glucose, hemoglobin A_{1c}, and serum low-density lipoprotein cholesterol and triglyceride levels and lower serum high-density lipoprotein cholesterol levels compared with the normal BP group. Cigarette smoking and alcohol consumption were more common in participants in the elevated BP and stage 1 and stage 2 hypertension groups compared with the normal BP group.

During a mean follow-up of 1112±854 days, 28 056 HF and 7774 AF events occurred. The cumulative incidence of HF and AF events was lowest in the normal BP group, followed by the elevated BP group, the stage 1 hypertension group, and the stage 2 hypertension group (Figure 1). The event rates for HF and AF events were lowest in the normal BP group (2.99 and 0.78, respectively, per 1000 person-years), followed by the elevated BP group (3.56 and 1.04, respectively, per 1000 person-years), the stage 1 hypertension group (5.00 and 1.54, respectively, per 1000 person-years), and the stage 2 hypertension group (9.53 and 2.41, respectively, per 1000 person-years). In an unadjusted model, elevated BP, stage 1 hypertension, and stage 2 hypertension were associated with a significantly higher risk of HF and AF events compared with normal BP. After multivariable adjustment, the hazard ratios for HF and AF events were 1.10 (95% CI, 1.05–1.15) and 1.07 (95% CI, 0.99–1.17), respectively, for elevated BP; 1.30 (95% CI, 1.26–1.35) and 1.21 (95% CI, 1.13–1.29), respectively, for stage 1 hypertension; and 2.05 (95% CI, 1.97–2.13) and 1.52 (95% CI, 1.41–1.64), respectively, for stage 2 hypertension (Figure 2). We assessed the proportional hazards assumptions by graphically checking log-log plots and

Table. Clinical Characteristics of Study Population

Characteristic	Missing, n	Normal BP (n=1 155 885)	Elevated BP (n=337 390)	Stage 1 hypertension (n=459 820)	Stage 2 hypertension (n=243 342)	*P* for trend
Age, y	0	41.9±10.5	43.2±11.6	46.6±10.3	49.9±9.8	<0.001
20–29, n (%)	0	170 478 (14.7)	51 481 (15.3)	31 811 (6.9)	7962 (3.3)	
30–39, n (%)	0	240 296 (20.8)	60 815 (18.0)	60 535 (13.2)	20 056 (8.2)	
40–49, n (%)	0	476 131 (41.2)	125 466 (37.2)	185 091 (40.3)	87 101 (35.8)	
50–59, n (%)	0	206 146 (17.8)	68 978 (20.4)	129 545 (28.2)	84 356 (34.7)	
≥60, n (%)	0	62 834 (5.4)	30 650 (9.1)	52 838 (11.5)	43 867 (18.0)	
Male sex, n (%)	0	551 583 (47.7)	226 180 (67.0)	329 298 (71.6)	176 274 (72.4)	<0.001
Body mass index, kg/m²	956	21.5±3.0	23.0±3.4	23.7±3.7	24.8±4.2	<0.001
Obesity, n (%)	956	137 291 (11.9)	82 189 (24.4)	146 682 (31.9)	102 358 (42.1)	<0.001
Waist circumference, cm	214 178	77.4±8.5	81.5±9.2	83.6±9.6	86.2±10.5	<0.001
High waist circumference, n (%)	214 178	150 450 (14.7)	84 558 (28.7)	161 205 (37.7)	110 564 (47.4)	<0.001
SBP, mm Hg	0	106.6±8.3	123.9±2.8	128.0±7.3	146.4±13.0	<0.001
DBP, mm Hg	0	65.2±7.3	72.1±5.4	81.4±5.1	92.4±9.1	<0.001
Diabetes, n (%)	452 573	16 589 (1.8)	9443 (3.7)	19 103 (5.2)	16 345 (8.5)	<0.001
Dyslipidemia, n (%)	79 524	320 893 (29.0)	128 582 (40.0)	217 497 (48.5)	135 033 (56.3)	<0.001
Cigarette smoking, n (%)	16 770	284 848 (24.8)	97 347 (29.1)	135 321 (29.6)	72 329 (29.9)	<0.001
Alcohol consumption, n (%)	281 396	170 085 (16.8)	64 715 (21.9)	117 435 (29.5)	72 559 (34.9)	<0.001
Laboratory data						
Glucose, mg/dL	457 595	90.6±12.7	93.9±15.9	96.6±18.5	101.1±22.9	<0.001
HbA_{1c}, %	423 011	5.4±0.5	5.5±0.6	5.6±0.6	5.7±0.8	<0.001
Low-density lipoprotein cholesterol, mg/dL	79 699	115.3±30.5	120.8±31.5	125.5±32.0	129.2±33.3	<0.001
High-density lipoprotein cholesterol, mg/dL	73 778	65.6±16.3	62.4±16.4	61.6±16.6	61.2±17.1	<0.001
Triglycerides, mg/dL	74 263	71 (52–103)	86 (60–128)	97 (67–146)	109 (75–165)	<0.001

Data are reported as means (SDs), medians (interquartile ranges) for skewed variables, and proportions (percentage) as appropriate. A *P* value for trend of each variable was calculated with the Jonckheere-Terpstra trend test for continuous variables and χ^2 test for categorical variables. Participants were categorized as having normal BP (untreated SBP <120 mm Hg and DBP <80 mm Hg), elevated BP (untreated SBP 120–129 mm Hg and DBP <80 mm Hg), stage 1 hypertension (untreated SBP 130–139 mm Hg or DBP 80–89 mm Hg), or stage 2 hypertension (untreated SBP ≥140 mm Hg or DBP ≥90 mm Hg). BP indicates blood pressure; DBP, diastolic blood pressure; HbA_{1c}, hemoglobin A_{1c}; and SBP, systolic blood pressure.

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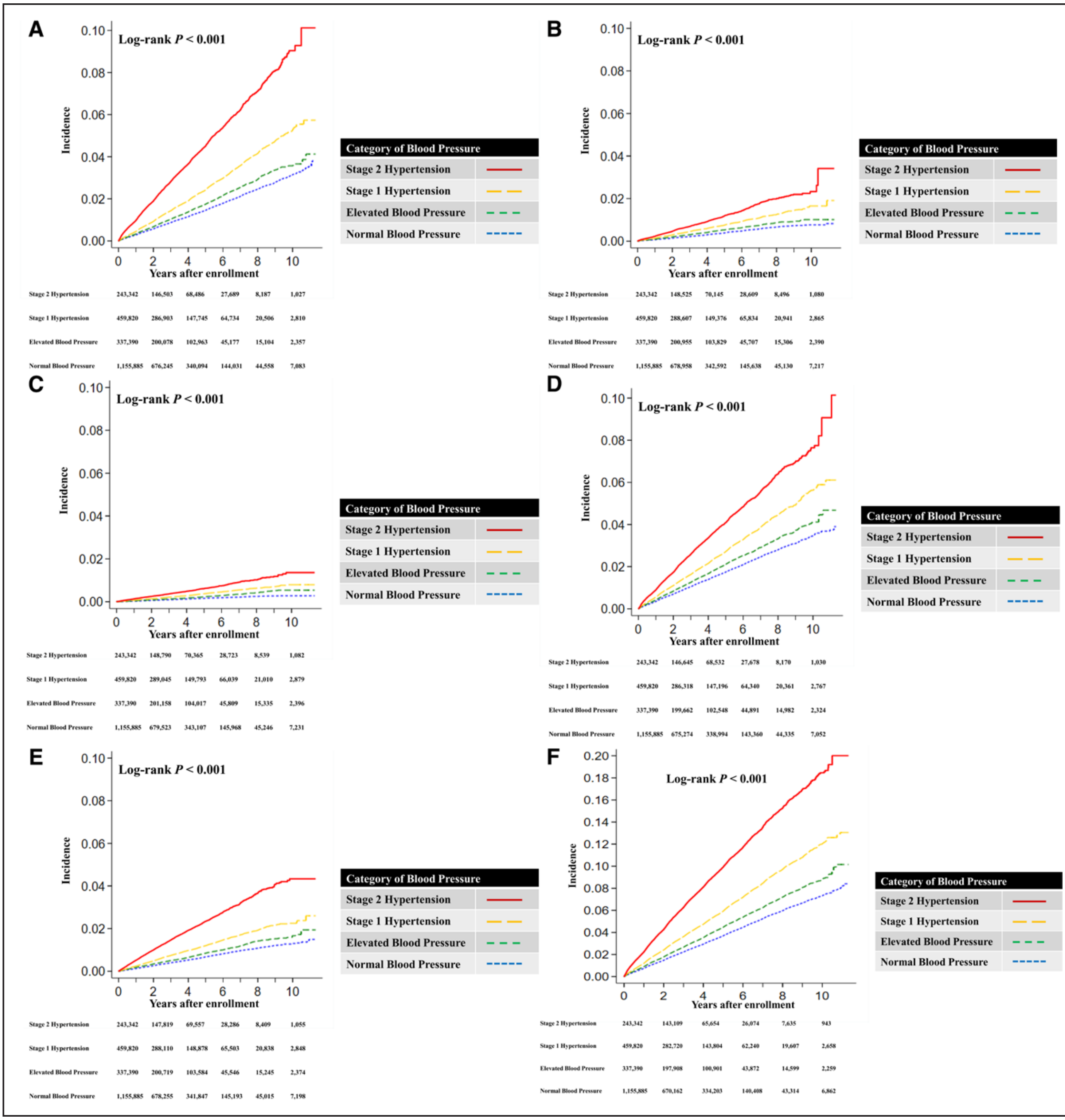
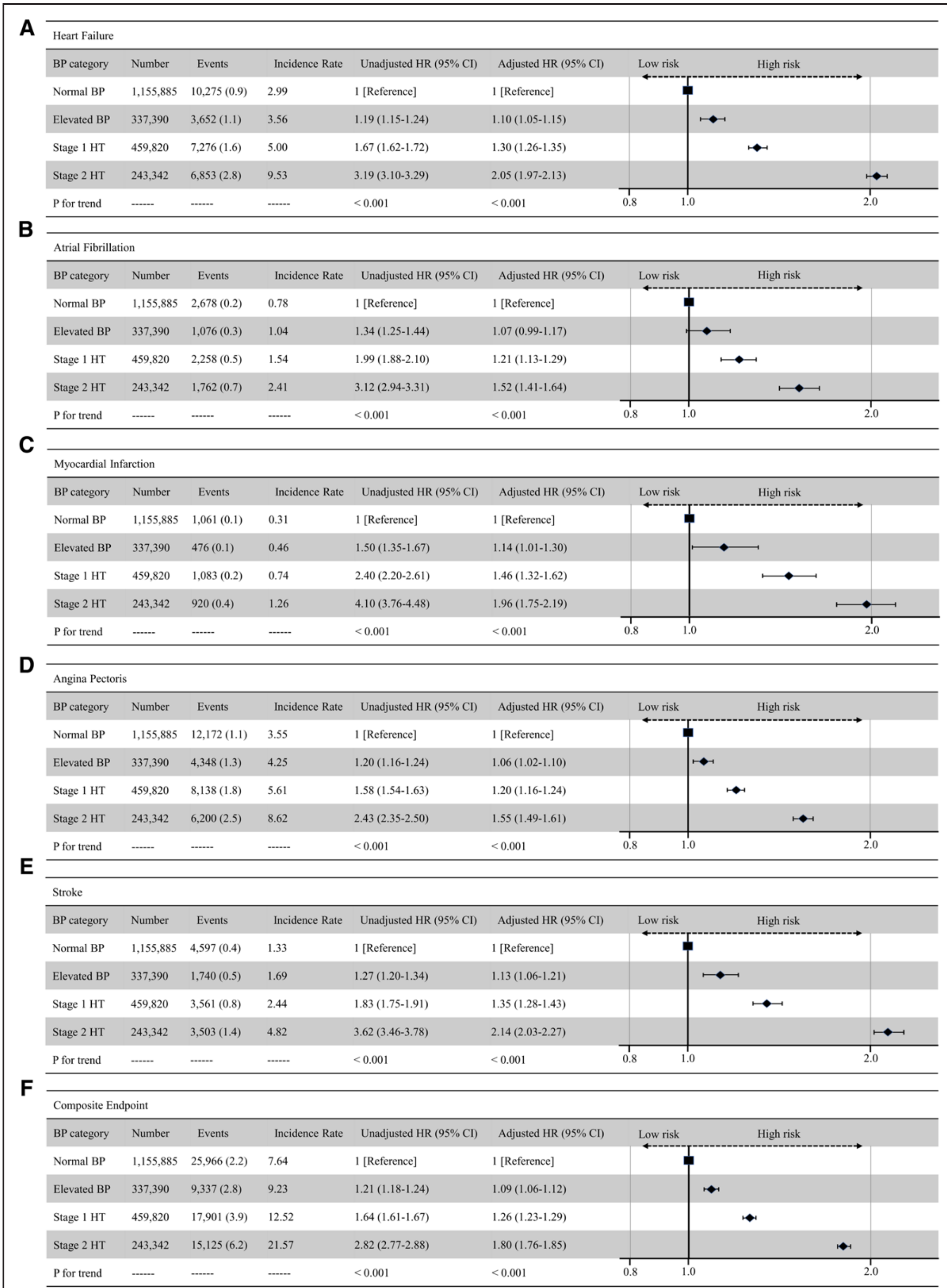


Figure 1. Kaplan-Meier curves.

The cumulative probability of heart failure (**A**), atrial fibrillation (**B**), myocardial infarction (**C**), angina pectoris (**D**), stroke (**E**), and composite end point (**F**) by blood pressure (BP) groups was calculated with the Kaplan-Meier method. Log-rank test was used to calculate *P* values, and the values were all <0.001. Participants were categorized as having normal BP (untreated systolic BP [SBP] <120 mm Hg and diastolic BP [DBP] <80 mm Hg), elevated BP (untreated SBP 120–129 mm Hg and DBP <80 mm Hg), stage 1 hypertension (untreated SBP 130–139 mm Hg or DBP 80–89 mm Hg), or stage 2 hypertension (untreated SBP ≥140 mm Hg or DBP ≥90 mm Hg).

did not find any obvious violation of the assumption. Each 1 SD higher SBP (per 15.9 mm Hg) and DBP (per 11.6 mm Hg) were associated with a higher risk for HF and AF events (Table II in the Data Supplement). The PAFs for HF associated with stage 1 hypertension and stage 2 hypertension were 23.2% (95% CI, 20.3%–26.0%) and 51.2% (95% CI, 49.2%–53.1%), respectively. The PAFs for AF associated with stage 1 hypertension and stage 2 hypertension were 17.4% (95% CI, 11.5%–22.9%) and 34.3% (95% CI, 29.1%–39.2%), respectively.

During the follow-up, 3540 MI, 30 858 AP, and 13 401 stroke events occurred. The cumulative incidence of MI, AP, stroke, and composite CVD events was highest in the stage 2 hypertension group, followed by the stage 1 hypertension group, elevated BP group, and normal BP group (Figure 1). In adjusted models, elevated BP, stage



A

Heart Failure

BP category	Number	Events	Incidence Rate	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Normal BP	1,155,885	10,275 (0.9)	2.99	1 [Reference]	1 [Reference]
Elevated BP	337,390	3,652 (1.1)	3.56	1.19 (1.15-1.24)	1.10 (1.05-1.15)
Stage 1 HT	459,820	7,276 (1.6)	5.00	1.67 (1.62-1.72)	1.30 (1.26-1.35)
Stage 2 HT	243,342	6,853 (2.8)	9.53	3.19 (3.10-3.29)	2.05 (1.97-2.13)
P for trend	------	------	------	< 0.001	< 0.001

B

Atrial Fibrillation

BP category	Number	Events	Incidence Rate	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Normal BP	1,155,885	2,678 (0.2)	0.78	1 [Reference]	1 [Reference]
Elevated BP	337,390	1,076 (0.3)	1.04	1.34 (1.25-1.44)	1.07 (0.99-1.17)
Stage 1 HT	459,820	2,258 (0.5)	1.54	1.99 (1.88-2.10)	1.21 (1.13-1.29)
Stage 2 HT	243,342	1,762 (0.7)	2.41	3.12 (2.94-3.31)	1.52 (1.41-1.64)
P for trend	------	------	------	< 0.001	< 0.001

C

Myocardial Infarction

BP category	Number	Events	Incidence Rate	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Normal BP	1,155,885	1,061 (0.1)	0.31	1 [Reference]	1 [Reference]
Elevated BP	337,390	476 (0.1)	0.46	1.50 (1.35-1.67)	1.14 (1.01-1.30)
Stage 1 HT	459,820	1,083 (0.2)	0.74	2.40 (2.20-2.61)	1.46 (1.32-1.62)
Stage 2 HT	243,342	920 (0.4)	1.26	4.10 (3.76-4.48)	1.96 (1.75-2.19)
P for trend	------	------	------	< 0.001	< 0.001

D

Angina Pectoris

BP category	Number	Events	Incidence Rate	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Normal BP	1,155,885	12,172 (1.1)	3.55	1 [Reference]	1 [Reference]
Elevated BP	337,390	4,348 (1.3)	4.25	1.20 (1.16-1.24)	1.06 (1.02-1.10)
Stage 1 HT	459,820	8,138 (1.8)	5.61	1.58 (1.54-1.63)	1.20 (1.16-1.24)
Stage 2 HT	243,342	6,200 (2.5)	8.62	2.43 (2.35-2.50)	1.55 (1.49-1.61)
P for trend	------	------	------	< 0.001	< 0.001

E

Stroke

BP category	Number	Events	Incidence Rate	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Normal BP	1,155,885	4,597 (0.4)	1.33	1 [Reference]	1 [Reference]
Elevated BP	337,390	1,740 (0.5)	1.69	1.27 (1.20-1.34)	1.13 (1.06-1.21)
Stage 1 HT	459,820	3,561 (0.8)	2.44	1.83 (1.75-1.91)	1.35 (1.28-1.43)
Stage 2 HT	243,342	3,503 (1.4)	4.82	3.62 (3.46-3.78)	2.14 (2.03-2.27)
P for trend	------	------	------	< 0.001	< 0.001

F

Composite Endpoint

BP category	Number	Events	Incidence Rate	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Normal BP	1,155,885	25,966 (2.2)	7.64	1 [Reference]	1 [Reference]
Elevated BP	337,390	9,337 (2.8)	9.23	1.21 (1.18-1.24)	1.09 (1.06-1.12)
Stage 1 HT	459,820	17,901 (3.9)	12.52	1.64 (1.61-1.67)	1.26 (1.23-1.29)
Stage 2 HT	243,342	15,125 (6.2)	21.57	2.82 (2.77-2.88)	1.80 (1.76-1.85)
P for trend	------	------	------	< 0.001	< 0.001

Figure 2. Frequency of events, corresponding incidence rates, and hazard ratios (HRs) for cardiovascular disease (CVD) events.
The incidence rate was per 1000 person-years. Participants were categorized as having normal blood pressure (BP; untreated systolic BP [SBP] <120 mm Hg and diastolic BP [DBP] <80 mm Hg), elevated BP (untreated SBP 120–129 mm Hg and DBP <80 mm Hg), stage 1 hypertension (HT; untreated SBP 130–139 mm Hg or DBP 80–89 mm Hg), or stage 2 hypertension (untreated SBP ≥140 mm Hg or DBP ≥90 mm Hg). Adjusted models include adjustments for age, sex, obesity, high waist circumference, diabetes, dyslipidemia, cigarette smoking, and alcohol consumption. Event rates for heart failure (HF; **A**) and atrial fibrillation (AF; **B**) events were lowest in the normal BP group (2.99 and 0.78, respectively, per 1000 person-years), followed by the elevated BP group (3.56 and 1.04, respectively, per 1000 person-years), (*Continued*)

Figure 2 Continued. the stage 1 hypertension group (5.00 and 1.54, respectively, per 1000 person-years), and the stage 2 hypertension group (9.53 and 2.41, respectively, per 1000 person-years). In an unadjusted model, elevated BP, stage 1 hypertension, and stage 2 hypertension were associated with a significantly higher risk of HF and AF events compared with normal BP. After multivariable adjustment, the HRs for HF and AF events were 1.10 (95% CI, 1.05–1.15) and 1.07 (95% CI, 0.99–1.17), respectively, for elevated BP; 1.30 (95% CI, 1.26–1.35) and 1.21 (95% CI, 1.13–1.29), respectively, for stage 1 hypertension; and 2.05 (95% CI, 1.97–2.13) and 1.52 (95% CI, 1.41–1.64), respectively, for stage 2 hypertension. In adjusted models, elevated BP, stage 1 hypertension, and stage 2 hypertension vs normal BP were each associated with a significantly higher risk for myocardial infarction (**C**), angina pectoris (**D**), stroke (**E**), and composite CVD events (**F**), respectively.

1 hypertension, and stage 2 hypertension versus normal BP were each associated with a significantly higher risk for MI, AP, stroke, and composite CVD events (Figure 2). We assessed the proportional hazards assumptions by graphically checking log-log plots and did not find any obvious violation of the assumption. Each 1 SD higher SBP and DBP were associated with a higher risk for MI, AP, stroke, and composite CVD events (Table II in the Data Supplement). The PAFs for MI associated with stage 1 hypertension and stage 2 hypertension were 31.4% (95% CI, 24.0%–38.0%) and 48.9% (95% CI, 42.8%–54.4%), respectively. The PAFs for AP associated with stage 1 hypertension and stage 2 hypertension were 16.8% (95% CI, 13.9%–19.6%) and 35.5% (95% CI, 32.9%–38.0%), respectively. The PAFs for stroke associated with stage 1 hypertension and stage 2 hypertension were 26.2% (95% CI, 22.2%–30.0%) and 53.3% (95% CI, 50.6%–55.9%), respectively. Last, the PAFs for composite CVD end point associated with stage 1 hypertension and stage 2 hypertension were 20.6% (95% CI, 18.7%–22.4%) and 44.5% (95% CI, 43.1%–46.0%), respectively.

Sensitivity Analyses

We imputed missing data for covariates (left column in the Table). Results with versus without multiple imputation for missing covariates were similar in terms of the point estimates for elevated BP, stage 1 hypertension, and stage 2 hypertension (Table III in the Data Supplement). When we adjusted for glucose and lipid parameters as continuous variables instead of categorial variables, results were similar in terms of the point estimates for elevated BP, stage 1 hypertension, and stage 2 hypertension for each CVD event (Table IV in the Data Supplement). The point estimates for each CVD event associated with stage 2 hypertension when participants taking antihypertensive medication were included versus not included were similar (Table V in the Data Supplement). We analyzed the relationship between the BP category according to the average of 2 BP measurements and the incidence of CVD from the time point 1 year after the 1st BP evaluation. As Table VI in the Data Supplement shows, the results of this sensitivity analysis were also consistent with our main results, and stage 1 hypertension was associated with higher incidence of HF and AF. We calculated cause-specific hazard ratios to account for the competing risk of death as shown in Table VII in the Data Supplement. The results with and without using competing-risk models were similar in terms of the point estimates for risks of CVD events for each BP group.

DISCUSSION

The present analyses using a nationwide epidemiological database, including a general population of >2 million adults without a history of CVD, demonstrated that stage 1 hypertension and stage 2 hypertension, as defined by the 2017 ACC/AHA BP guideline, were associated with a higher risk for subsequent HF, AF, MI, AP, and stroke. Elevated BP was also associated with a higher risk for subsequent HF, MI, AP, and stroke. PAFs for HF, AF, MI, AP, and stroke associated with stage 1 hypertension were 23.2%, 17.4%, 31.4%, 16.8%, and 26.2%, respectively. PAFs for HF, AF, MI, AP, and stroke associated with stage 2 hypertension were 51.2%, 34.3%, 48.9%, 35.5%, and 53.3%, respectively.

Lowering the BP threshold for the diagnosis of hypertension by 10 mm Hg in the 2017 ACC/AHA BP guideline was a bold revision with major medical and public health implications. Clinical evidence supporting the validity of the 2017 ACC/AHA BP guideline is still accruing. From this perspective, our results using a large-scale epidemiological database and showing the association between stage 1 hypertension and higher incidence of HF, AF, and other CVDs support the validity of this decision.

Individuals with elevated BP or stage 1 hypertension are at high risk for developing stage 2 hypertension,[25] and those with stage 1 hypertension who experienced an increase in SBP/DBP to ≥140/90 mm Hg have a 3-fold higher incidence of CVD events compared with those who maintain SBP/DBP <130/<80 mm Hg.[26] In this regard, 3 previous randomized clinical trials have suggested the efficacy of pharmacological treatment in the prevention of stage 2 hypertension among individuals with elevated BP or stage 1 hypertension.[27–29]

In the PREVER-Prevention trial (Prevention of Hypertension in Patients With Prehypertension), low doses of a thiazide-type diuretic combined with a potassium-sparing agent prevented the incidence of stage 2 hypertension by almost 50% among individuals with elevated BP or stage 1 hypertension.[27] Left ventricular mass assessed through Sokolow-Lyon voltage and voltage-duration product decreased to a greater extent in participants allocated to the intervention group compared with the placebo group. These results suggest that preventing progression to stage 2 hypertension could reduce the burden of high BP among individuals with elevated BP or stage 1 hypertension, which may lead to a reduced lifetime risk of CVD. Similarly, TROPHY (Trial of Preventing Hypertension) showed that treatment with angiotensin receptor blocker for subjects with stage 1 hypertension was well tolerated and reduced the risk of the development of hypertension.[28] Furthermore, the PHARAO study (Prevention of Hypertension With the Angiotensin Converting Enzyme Inhibitor Ramipril in Patients With High-Normal Blood Pressure) demonstrated that treatment with an angiotensin-converting enzyme inhibitor for subjects with high-normal office BP could lower the risk of progression to manifest hypertension compared with a control group.[29]

The optimal treatment strategy may vary depending on the CVD risk of each individual. The 2017 ACC/AHA BP guideline recommends the combination of nonpharmacological and pharmacological interventions for preventing HF events among adults with stage 1 hypertension who also have an estimated 10-year atherosclerotic CVD risk of ≥10%, prevalent CVD, diabetes, or chronic kidney disease.

SPRINT (Systolic Blood Pressure Intervention Trial),[30] which is a major driver for the revisions in the 2017 ACC/AHA BP guideline, suggested that, among individuals at high risk for CVD events but without diabetes (baseline mean SBP/DBP 140/78 mm Hg), targeting SBP to <120 mm Hg instead of <140 mm Hg resulted in a 36% lower rate of acute decompensated HF.[31] Even so, it remains unclear how BP measurements in the SPRINT study collected in a highly controlled research setting correspond to BP measurements commonly obtained in a typical clinic setting. Furthermore, the SPRINT study included individuals at high risk for CVD events. Thus, it is unclear whether lowering the cutoff value of hypertension from 140/90 to 130/80 mm Hg would yield similar improvements in real-world clinical settings and among individuals with low CVD risk.

Given the relationship between stage 1 hypertension and a higher incidence of HF and AF in our study population, which included mainly subjects with relatively low CVD risk, an optimal management strategy is needed even among subjects with stage 1 hypertension and low CVD risk. For this reason, we need to consider the amount of time required to accumulate a sufficient number of HF and AF events among a sample population of adults with stage 1 hypertension with low CVD risk. Therefore, studies to evaluate left ventricular hypertrophy, which often precedes the development of HF and AF,[32] as a primary outcome would be an initial step toward providing evidence that pharmacological treatment is essential for subjects with elevated BP or stage 1 hypertension.

Strengths of this study include a large general population, the fact that participants were not taking antihypertensive medications at baseline, and high retention of participants. The JMDC data set includes medical and pharmacy claims data combined with annual health checkup data from employees' health insurance programs in an anonymous format. Of note, clinical follow-up data obtained from claim records are also included in the JMDC database. Therefore, the JMDC database is theoretically capable of tracking all of an individual's clinical information (such as diagnosis of HF and AF using *ICD-10* codes) even if the patient sees different medical providers as long as the individual has the same insurance coverage.

This study has several limitations. BP measured at a single occasion was used for BP classification, which might not fully reflect a person's BP phenotype. However, when we defined BP groups using the average of BP on 2 occasions (ie, at baseline and within the first year of follow-up), the association remained between stage 1 and stage 2 hypertension and a higher risk for HF and AF. The Japanese Ministry of Health, Labor, and Welfare requests health care professionals who engage in the Japanese health checkup system to follow the recommended protocol for BP measurements. However, in a real-world setting on a nationwide scale, adherence to the protocol might be limited. BP levels measured in routine clinical practice are generally higher than BP measurements in a highly controlled research setting, which might overestimate the true BP levels in routine clinical practice and underestimate the true associations between BP levels and CVD events.[33] In this health claims database, diseases were identified according to diagnostic codes. However, uncertainty remains about the accuracy of the diagnoses for HF, AF, MI, AP, and stroke. Of the records of 2 943 563 individuals collected between January 2005 and August 2018, we excluded 415 406 (14.1%) individuals missing data for BP and antihypertensive medication use, and characteristics of those included versus not included in the present study differed. The JMDC Claims Database included an employed, working-age population. Accordingly, mainly young and middle-aged adults were included in the present study, and the prevalence of diabetes was low.[34] Therefore, a "healthy worker" bias might be present in this population. Further investigation is needed to determine whether our results can be generalizable to other populations of different ethnicities, races, educational levels, and incomes. Detection bias may cause overestimation or underestimation of true correlation between high BP and HF/AF events. For example, AF was more likely to be diagnosed among the stage 1 and stage 2 hypertension group because those individuals use medical services more frequently compared with the normal BP group, which itself might influence the likelihood of disease detection. Possible residual confounding, including sodium intake and psychological factors, may affect the BP–CVD event associations.[35,36]

ORIGINAL RESEARCH ARTICLE

Conclusions

Stage 1 hypertension and stage 2 hypertension, as defined by the 2017 AHA/ACC BP guideline, were associated with higher risk of HF, AF, and other CVDs compared with normal BP in a large general population without known history of CVD. The ACC/AHA BP classification system may help identify adults at higher risk for HF and AF events.

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Supplemental Materials

Supplementary Data
Data Supplement Tables I–VII

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