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Ideal Blood Pressure in Patients With Atrial Fibrillation

Daehoon Kim, MD,[a,*] Pil-Sung Yang, MD,[b,*] Tae-Hoon Kim, MD,[a,*] Eunsun Jang, MS,[a] Hyejung Shin, MS,[c] Ha Yan Kim, MS,[c] Hee Tae Yu, MD,[a] Jae-Sun Uhm, MD,[a] Jong-Youn Kim, MD,[a] Hui-Nam Pak, MD,[a] Moon-Hyoung Lee, MD,[a] Boyoung Joung, MD,[a,†] Gregory Y.H. Lip, MD[d,†]

ABSTRACT

BACKGROUND The 2017 American College of Cardiology/American Heart Association (ACC/AHA) Guideline for High Blood Pressure in Adults redefined hypertension as systolic blood pressure (BP) ≥130 mm Hg or diastolic BP ≥80 mm Hg. The optimal BP for patients with atrial fibrillation (AF) is uncertain.

OBJECTIVES The goal of this study was to investigate the impacts of the 2017 ACC/AHA guideline and to determine the ideal BP threshold for the management of high BP in patients with AF.

METHODS This study analyzed data for 298,374 Korean adults with oral anticoagulant-naive, nonvalvular AF obtained from the National Health Insurance Service database from 2005 to 2015.

RESULTS According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure guideline, 62.2% of the individuals in our sample had hypertension. After applying the 2017 ACC/AHA guideline, 79.4% had hypertension, including 17.2% with newly redefined hypertension (130 to 139/80 to 89 mm Hg). Those with newly redefined hypertension had greater risks of major cardiovascular events (hazard ratio: 1.07; 95% confidence interval: 1.04 to 1.10; $p < 0.001$), ischemic stroke, intracranial hemorrhage, and heart failure admission, compared with nonhypertensive patients (<130/80 mm Hg). Among patients with AF undergoing hypertension treatment, patients with BP ≥130/80 mm Hg or <120/80 mm Hg were at significantly higher risks of major cardiovascular events than patients with BP of 120 to 129/<80 mm Hg.

CONCLUSIONS Patients with AF and newly redefined hypertension according to the 2017 ACC/AHA guideline were at higher risk of major cardiovascular events, suggesting that the new BP threshold is beneficial for timely diagnosis and intervention. BP of 120 to 129/<80 mm Hg was the optimal BP treatment target for patients with AF undergoing hypertension treatment. (J Am Coll Cardiol 2018;■:■-■) © 2018 by the American College of Cardiology Foundation.

Compared with the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC7), which has been adopted worldwide over the last 10 years, the 2017 American College of Cardiology/American Heart Association (ACC/AHA) Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults proposed a stricter definition of hypertension (systolic blood pressure [SBP] ≥130 mm Hg or

From the [a]Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea; [b]Department of Cardiology, CHA Bundang Medical Center, CHA University, Seongnam, Republic of Korea; [c]Biostatistics Collaboration Unit, Department of Biomedical Systems Informatics, Yonsei University College of Medicine, Seoul, Republic of Korea; and the [d]Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, United Kingdom. This study was supported by a research grant from the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education, Science and Technology (NRF-2017R1A2B3003303) and grants from the Korean Healthcare Technology R&D project funded by the Ministry of Health & Welfare (HI16C0058 and HI15C1200). Dr. Lip has served as a consultant for Bayer/Janssen, Bristol-Myers Squibb/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo; and as a speaker for Bayer, Bristol-Myers Squibb/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. *Drs. D. Kim, Yang, and T.-H. Kim contributed equally to this work and are joint first authors. †Drs. Joung and Lip contributed equally to this work and are joint senior authors.

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ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

AF = atrial fibrillation

AHA = American Heart Association

BP = blood pressure

CI = confidence interval

CVD = cardiovascular disease

DBP = diastolic blood pressure

HR = hazard ratio

NHIS = National Health Insurance Service

SBP = systolic blood pressure

diastolic blood pressure [DBP] ≥80 mm Hg) and treatment thresholds. The ACC/AHA guideline additionally recommended antihypertensive medication for adults at high risk of cardiovascular disease (CVD) with SBP 130 to 139 mm Hg or DBP 80 to 89 mm Hg, and adults ≥65 years of age with SBP 130 to 139 mm Hg (1,2). The 2017 ACC/AHA guideline recommends treating SBP/DBP to <130/80 mm Hg for all adults taking antihypertensive medication (1).

Hypertension is highly prevalent in adults with atrial fibrillation (AF), especially those >60 years of age, and affects ~1 billion adults worldwide (3). Stroke prevention is the principal management priority in patients with AF (4-6). The presence of hypertension in patients with AF is an independent risk factor for stroke, with such individuals at 1.8- to 2-fold increased risk compared with those without hypertension (7,8). However, the optimal blood pressure (BP) treatment threshold and treatment goals for patients with AF and hypertension remain unknown.

Currently, the CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category) score is widely used by most guidelines for stroke prevention in AF (9,10). Hypertension is defined by the CHA_2DS_2-VASc as either a history of hypertension or uncontrolled BP. Therefore, lowering the BP threshold defining hypertension would increase the number of patients with indications for anticoagulation. However, there are few data regarding the clinical outcomes of patients with AF and hypertension that are newly redefined based on the 2017 guideline.

The goal of the present study was to determine the effects of the 2017 ACC/AHA guideline for the management of high BP in patients with AF, compared with the JNC7 guideline, by estimating the prevalence of hypertension under both guidelines and assessing risks of cardiovascular morbidity and mortality for patients with newly redefined hypertension. In addition, we determined optimal BP treatment targets for patients with AF taking antihypertensive medication. To accomplish these goals, we analyzed the entire Korean population cohort data from the Korean National Health Insurance Service (NHIS) database.

METHODS

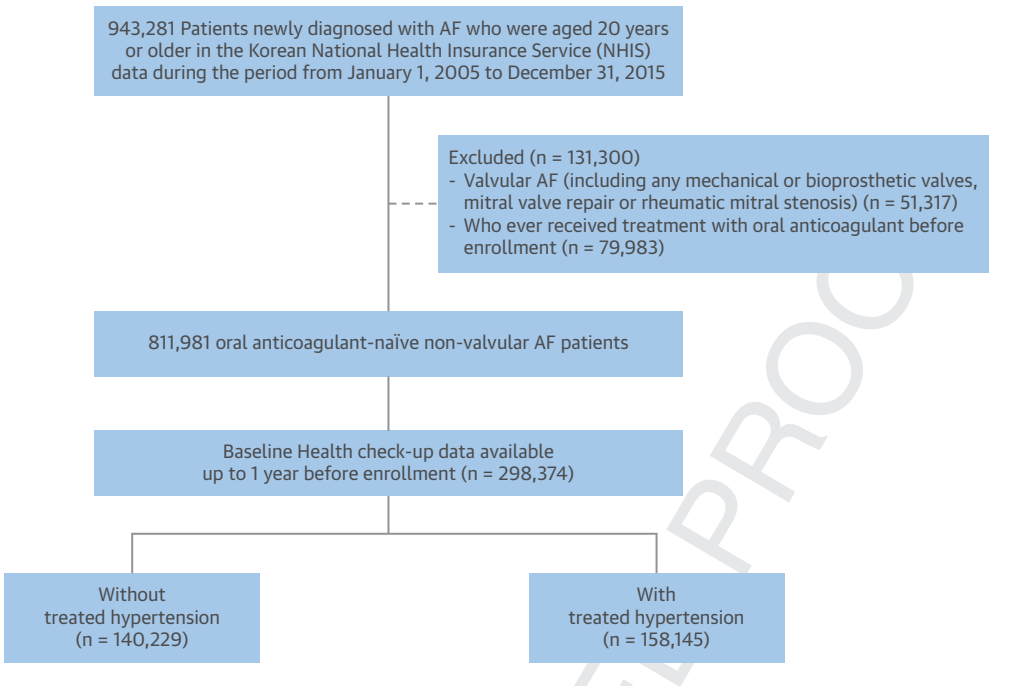
This study is based on the national health claims database (NHIS-2016-4-009) established by the NHIS of Korea. The NHIS is the single insurer managed by the Korean government, and the NHIS database represents the entire Korean population (11). The details of the NHIS database are presented in the Online Methods. This study was approved by the institutional review board of Yonsei University Health System (4-2016-0179), and the requirement for informed consent was waived.

BP MEASUREMENTS. BP measurements were taken at local hospitals and clinics that were certified as medical health examination centers by the Korean National Health Insurance Corporation. After 5 min of rest with the patient in the sitting position, brachial BP was measured by qualified medical personnel at each health examination center. Both automatic oscillometric devices and mercury sphygmomanometers were used for BP measurements, with the choice of device left to the discretion of individual examination centers. The preferred recommendation specified the use of mercury sphygmomanometers until 2015, when the sale of mercury sphygmomanometers was banned. BP was measured repeatedly if the first BP measurement was >120/80 mm Hg.

STUDY POPULATION. Among records representing the entire Korean population in the Korean NHIS database, we identified 943,281 patients ≥20 years of age with incident AF diagnoses during the period from January 1, 2005, to December 31, 2015. AF was diagnosed by using the International Classification of Diseases, 10th Revision, codes (e.g., I48). To ensure diagnostic accuracy, patients were defined as having AF only when AF was the discharge diagnosis or was confirmed at least twice in the outpatient department. The AF diagnosis was previously validated in the NHIS database with a positive predictive value of 94.1% (4,5,12). The index date was the discharge date if the AF diagnosis occurred during a hospitalization. If AF was an outpatient diagnosis, the index date was the date of the first diagnosis in the outpatient department.

Patients meeting the following criteria were excluded: 1) those with valvular AF (with a diagnosis of mitral stenosis or prosthetic heart valves, or with insurance claims for valve replacement or valvuloplasty) (n = 51,317); and 2) those who had ever received treatment with oral anticoagulant agents before the index date (n = 79,983). From the included oral anticoagulant-naive nonvalvular AF cohort (811,981 subjects), we ultimately included 298,374 subjects who underwent baseline health evaluations (including BP measurements) up to 1 year before the index date (**Figure 1**).

FIGURE 1 Flowchart of Study Population Enrollment and Analyses



AF = atrial fibrillation.

DEFINITION OF HYPERTENSION ACCORDING TO OLD AND NEW GUIDELINES. The JNC7 guideline was the standard of care for patients during the time period of the study. We considered patients with a history of treated hypertension at the time of enrollment (defined as the combination of a hypertension diagnosis [I10, I11, I12, I13, and I15] and use of ≥1 antihypertensive drug) as having hypertension that met both the JNC7 criteria and the 2017 ACC/AHA criteria (the ACC/AHA criteria are more inclusive than the JNC7 criteria).

Patients with no history of treated hypertension were categorized according to their measured BP: 1) nonhypertensive, SBP <130 mm Hg and DBP <80 mm Hg; 2) newly redefined hypertension, SBP 130 to 139 mm Hg or DBP 80 to 89 mm Hg, newly diagnosed as hypertension according to the 2017 ACC/AHA guideline compared with the JNC7 guideline; 3) hypertension according to the 2017 ACC/AHA guideline, SBP ≥130 mm Hg or DBP ≥80 mm Hg; and 4) hypertension according to the JNC7 guideline, SBP ≥140 mm Hg or DBP ≥90 mm Hg.

COVARIATES. History of CVD was defined as a previous diagnosis of myocardial infarction, coronary heart disease, stroke, or heart failure. The 10-year predicted CVD risk was calculated by using the pooled cohort risk equations (13). The details of other covariates are described in the Online Methods.

CLINICAL OUTCOME EVENTS AND ASSESSMENTS. The primary clinical outcome was the first occurrence of major cardiovascular events, including ischemic stroke, intracranial hemorrhage, myocardial infarction, and heart failure requiring hospitalization. Secondary outcomes included individual components of the primary composite outcome, all-cause deaths, and serious adverse events (only for patients with treated hypertension). The definitions of clinical outcomes are presented in Online Table 1. Patients were followed up from the index date until the study outcomes occurred, the date of oral anticoagulant initiation (except for all-cause death and heart failure admission), or at the end of follow-up, whichever occurred first.

STATISTICAL ANALYSIS. We estimated the proportion of adults with AF who would meet the definition of hypertension under the JNC7 and 2017 ACC/AHA guidelines. Among participants with no history of treated hypertension, 2 Cox models were used to assess the risk of adverse outcomes for adults defined as having hypertension under each guideline and those with newly redefined hypertension. Nonhypertensive patients comprised the reference group.

Model 1 was adjusted for age, sex, income status, smoking status, body mass index, heart failure, diabetes mellitus, previous ischemic stroke, previous myocardial infarction, previous intracranial hemorrhage, peripheral artery disease, dyslipidemia, chronic kidney disease, and use of antiplatelet agents, statins, and BP modifiable medications listed in Table 1. In model 2, a time-updated Cox regression analysis was performed, adjusting for BP levels and use of antihypertensive medications as time-dependent variables among adults who had a follow-up BP measurement taken after their baseline visits, as well as for all baseline covariates in model 1; we chose this method because BP measurements and the status of BP-lowering medication use may vary over time.

Among patients with AF and treated hypertension, we also investigated event rates and hazard ratios (HRs) for adverse outcomes according to BP control status. Patients were categorized as demonstrating intensive control (<120/80 mm Hg), optimal control (120 to 129/<80 mm Hg), suboptimal control (130 to 139/80 to 89 mm Hg), and poor control (≥140/90 mm Hg) based on their measured BP at baseline. A predictive model was developed to determine the benefit-to-harm ratio of optimal control, compared with suboptimal control, for subgroups stratified according to 10-year CVD risk. The details of the predictive model are described in the Online Methods.

In sensitivity analyses, we first excluded patients with high CVD risk (defined as those with a history of CVD or 10-year predicted CVD risk ≥10%, according to the 2017 ACC/AHA guideline) from those with no treated hypertension history; the goal was to assess the risk of adverse outcomes according to different hypertension definitions in subjects with low CVD risk. Second, among patients with treated hypertension, the risk of adverse outcomes was assessed according to BP control status in patients with low CVD risk. Third, we included patients with a 10-year CVD risk <18.2% among those with treated hypertension, using a cutoff drawn from a recent study by Phillips et al. (14), who suggested that adults with 10-year CVD risk <18.2% would not receive more benefit than harm from intensive treatment.

In supplemental analyses, we assessed the risk of adverse outcomes without censoring at the date of oral anticoagulant initiation. Competing-risk regression was performed by using the Fine-Gray subdistribution hazard model with mortality as competing risk for all outcomes other than all-cause mortality (15). All tests were 2-tailed, with p values <0.05 considered significant. Statistical analyses were conducted by using SAS version 9.3 (SAS Institute, Inc., Cary, North Carolina) and SPSS version 23.0 statistical package (IBM SPSS Statistics, IBM Corporation, Armonk, New York).

RESULTS

BASELINE CHARACTERISTICS. From 2005 to 2015, 20.6% (n = 61,461), 17.2% (n = 51,214), and 9.2% (n = 27,654) of patients with AF and no hypertension treatment history had SBP/DBP levels <130/80 mm Hg, 130 to 139/80 to 89 mm Hg, and ≥140/90 mm Hg, respectively (Table 1). In addition, 53.0% (n = 158,145) of patients with AF had previous hypertension diagnoses and were taking antihypertensive medications. Patients with newly redefined hypertension (130 to 139/80 to 89 mm Hg) were older and more likely to be male, obese, and to have histories of smoking, heart failure, diabetes, ischemic stroke, intracranial hemorrhage, and higher 10-year predicted CVD risk than nonhypertensive patients (<130/80 mm Hg).

HYPERTENSION PREVALENCE AND CHA_2DS_2-VASc SCORES USING DIFFERENT HYPERTENSION GUIDELINES. When different hypertension guidelines were applied to the NHIS AF cohort, 185,799 (62.2%) patients met the definition of hypertension according to the JNC7 guideline. According to the new 2017 ACC/AHA guideline, 237,013 (79.4%) patients with AF had hypertension, after adding 51,214 (17.2%) patients with newly redefined hypertension (Figure 2).

Before and after applying the hypertension definition from the 2017 ACC/AHA guideline, patients with AF were classified according to their CHA_2DS_2-VASc scores as low-risk (0 or 1 point [in female subjects]), intermediate-risk (1 point in male subjects), and high-risk (≥2 points) groups (Online Figure 1). The proportion of low-risk patients decreased from 21.4% to 12.0%, whereas high-risk patients who were recommended to take oral anticoagulant agents increased from 64.4% to 69.8%. The proportion of intermediate-risk patients increased from 14.3% to 18.2%.

ADVERSE OUTCOMES ACCORDING TO DIFFERENT HYPERTENSION DEFINITIONS. Event rates and HRs for clinical outcomes among patients with AF defined as having hypertension under each guideline and those with newly redefined hypertension, compared with nonhypertensive patients, are presented in Figure 3. The mean duration of follow-up was 5.6 ± 3.5 years. In the groups of nonhypertensive, newly redefined hypertension, hypertension according to the 2017 ACC/AHA guideline, and hypertension according to the JNC7 guideline, age- and sex-adjusted

TABLE 1 Baseline Characteristics and Risk Factor Profiles of Adults With AF According to BP Levels and Treated Hypertension History

		Without Treated Hypertension History* (n = 140,229)					
	All Patients With AF (N = 298,374)	Nonhypertensive <130/80 mm Hg (n = 61,461)	Newly Redefined Hypertension 130-139/80-89 mm Hg (n = 51,214)	Hypertension by JNC7 ≥140/90 mm Hg (n = 27,554)	p Value†	With Treated Hypertension History* (n = 158,145)	p Value‡
Age, yrs	64 (54-72)	56 (47-66)	58 (48-68)	67 (58-73)	<0.001	67 (60-74)	<0.001
<65 yrs	155,961 (52.3)	43,399 (70.6)	34,229 (66.8)	15,764 (57.2)	<0.001	62,569 (39.6)	<0.001
≥65 yrs	142,413 (47.7)	18,062 (29.4)	16,985 (33.2)	11,790 (42.8)		95,576 (60.4)	
Male	176,898 (59.3)	36,158 (58.8)	34,753 (67.9)	18,647 (67.7)	<0.001	87,340 (55.2)	<0.001
Systolic BP, mm Hg	127.5 ± 17.0	111.8 ± 9.4	127.0 ± 7.8	145.9 ± 13.6	<0.001	130.6 ± 10.5	<0.001
Diastolic BP, mm Hg	78.4 ± 11.0	68.6 ± 6.1	80.3 ± 4.7	90.7 ± 9.6	<0.001	79.5 ± 11.2	<0.001
Heart failure	62,007 (20.8)	4,357 (7.1)	3,896 (7.6)	2,580 (9.4)	<0.001	51,174 (32.4)	<0.001
Diabetes mellitus	53,074 (17.8)	5,365 (8.7)	4,614 (9.0)	2,625 (9.5)	0.001	40,470 (25.6)	<0.001
Previous ischemic stroke	39,107 (13.1)	3,369 (5.5)	3,050 (6.0)	1,860 (6.8)	<0.001	30,828 (19.5)	<0.001
Previous hemorrhagic stroke	4,301 (1.4)	448 (0.7)	432 (0.8)	273 (1.0)	<0.001	3,148 (2.0)	<0.001
Chronic kidney disease	10,597 (3.6)	724 (1.2)	584 (1.1)	327 (1.2)	0.789	8,962 (5.7)	<0.001
Dyslipidemia	169,589 (56.8)	24,517 (39.9)	20,375 (39.8)	10,337 (37.5)	<0.001	114,360 (72.3)	<0.001
Previous myocardial infarction	19,205 (6.4)	1,486 (2.4)	1,305 (2.5)	716 (2.6)	0.193	15,698 (9.9)	<0.001
Peripheral artery disease	27,540 (9.2)	2,180 (3.5)	1,747 (3.4)	1,007 (3.7)	0.184	22,606 (14.3)	<0.001
Ex-smoker/current smoker	105,509 (35.4)	23,452 (38.7)	21,654 (42.9)	11,023 (40.8)	<0.001	49,380 (31.2)	<0.001
Obesity (BMI ≥30 kg/m^2)	14,237 (4.8)	1,131 (1.8)	1,780 (3.5)	1,379 (5.0)	<0.001	9,947 (6.3)	<0.001
History of CVD	96,016 (32.2)	8,282 (13.5)	7,399 (14.4)	4,595 (16.7)	<0.001	75,740 (47.9)	<0.001
10-yr CVD risk§	10.1 (3.2-16.3)	5.3 (1.0-12.4)	8.4 (2.7-16.3)	12.0 (5.5-20.2)	<0.001	12.5 (6.2-20.6)	<0.001
<10%	95,214 (47.1)	33,828 (63.6)	22,541 (51.4)	8,709 (37.9)	<0.001	30,136 (36.6)	<0.001
10%-20%	80,069 (39.6)	17,355 (32.6)	16,891 (38.6)	10,291 (44.8)		35,532 (43.1)	
>20%	27,075 (13.4)	1,996 (3.8)	4,383 (10.0)	3,959 (17.2)		16,737 (20.3)	
Medication							
Antiplatelet agent	113,181 (37.9)	5,922 (9.6)	4,876 (9.5)	2,731 (9.9)	0.206	99,652 (63.0)	<0.001
Statin	70,380 (23.6)	5,609 (9.1)	4,525 (8.8)	2,022 (7.3)	<0.001	58,224 (36.8)	<0.001
Beta-blocker	101,388 (34.0)	2,066 (3.4)	1,285 (2.5)	455 (1.7)	<0.001	87,144 (55.1)	<0.001
RAS blockade	90,950 (30.5)	204 (0.3)	141 (0.3)	66 (0.2)	<0.001	100,977 (63.9)	<0.001
Calcium-channel blocker	16,989 (5.7)	1,461 (2.4)	1,094 (2.1)	641 (2.3)	0.022	97,275 (61.5)	<0.001
Loop/thiazide diuretics	102,665 (34.4)	1,177 (1.9)	842 (1.6)	388 (1.4)	<0.001	100,258 (63.4)	<0.001
K^+ sparing diuretics	16,989 (5.7)	433 (0.7)	268 (0.5)	114 (0.4)	<0.001	16,174 (10.2)	<0.001

Values are median (interquartile range), n (%), or mean ± SD. *Treated hypertension history was defined as the combination of hypertension diagnosis according to the International Classification of Diseases, 10th Revision, codes (I10, I11, I12, I13, and I15) and use of ≥1 antihypertensive drug. †P value of one-way analyses of variance or chi-square test between 3 groups of patients with atrial fibrillation (AF) without treated hypertension history. ‡P value of one-way analyses of variance or chi-square test between 4 groups (3 groups of patients with AF without treated hypertension history and patients with AF and treated hypertension history). §The predicted 10-year risk was calculated by using the pooled cohort risk equations. Median risk was calculated among adults with no history of cardiovascular disease (CVD).

BMI = body mass index; BP = blood pressure; RAS = renin-angiotensin system.

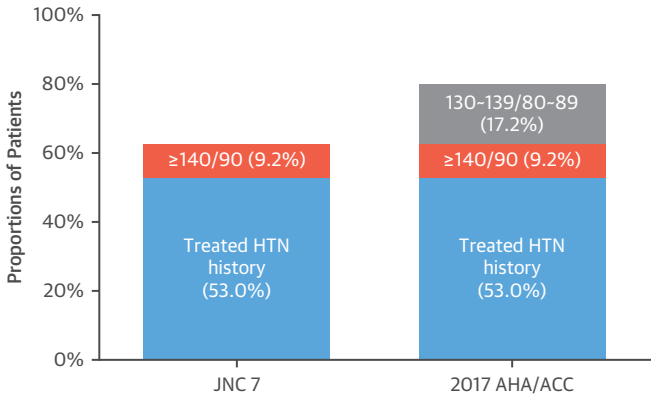
rates for major cardiovascular events were 4.21 (95% confidence interval [CI]: 4.13 to 4.29), 4.41 (95% CI: 4.32 to 4.49), 4.49 (95% CI: 4.42 to 4.56), and 4.67 (95% CI: 4.58 to 4.78) per 100 person-years, respectively.

After multivariable adjustment (model 1) (Figure 3), the newly redefined hypertension group had a greater risk of major cardiovascular events (HR: 1.07; 95% CI: 1.04 to 1.10; p < 0.001) than the nonhypertensive group. This group also had higher risks of ischemic stroke (HR: 1.11; 95% CI: 1.07 to 1.16; p < 0.001), intracranial hemorrhage (HR: 1.11; 95% CI: 1.01 to 1.22; p = 0.041), and heart failure admission (HR: 1.06; 95% CI: 1.01 to 1.11; p = 0.031), but there were no significant differences in all-cause mortality or myocardial infarction.

Of the total 140,229 patients with AF with no history of treated hypertension, 83,961 adults (59.9%) had at least 1 follow-up BP measurement after their baseline visits (model 2) (Figure 4). The mean interval between baseline and follow-up visits was 1.8 ± 0.5 years. After additionally adjusting for time-varying covariates of SBP and DBP and uses of antihypertensive medications at the follow-up visits, the overall results remained consistent, with significantly higher risks of major cardiovascular events, ischemic stroke, intracranial hemorrhage, and heart failure admission in the newly redefined hypertension group, relative to the nonhypertensive group.

ADVERSE OUTCOMES ACCORDING TO BP CONTROL STATUS. Event rates and hazard ratios for clinical

FIGURE 2 Prevalence of HTN Among Patients With AF Meeting the Definition for HTN According to the JNC7 Guideline and the 2017 ACC/AHA Guideline



ACC/AHA = American College of Cardiology/American Heart Association; AF = atrial fibrillation; HTN = hypertension; JNC7 = the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure.

outcomes according to BP control status are shown in Table 2 and the Central Illustration. The mean duration of follow-up was 4.9 ± 3.4 years. The age- and sex-adjusted event rate of major cardiovascular events was lowest in the optimal control group (120 to 129/<80 mm Hg) with 7.99 (95% CI: 7.76 to 8.22) per 100 person-years.

After multivariable adjustment for potentially confounding clinical covariates, the risk of major cardiovascular events was significantly higher both in the suboptimal control group (130 to 139/80 to 89 mm Hg) with an HR of 1.05 (95% CI: 1.01 to 1.08; p = 0.011) and in the poor control group (≥140/90 mm Hg) with an HR of 1.13 (95% CI: 1.09 to 1.16; p < 0.001) compared with the optimal control group as the reference category. The risks of ischemic stroke and heart failure admission were also higher in the suboptimal control and poor control groups than in the optimal control group.

The intensive control group (<120/80 mm Hg) had higher risks of major cardiovascular events (HR: 1.05; 95% CI: 1.01 to 1.09; p = 0.026), all-cause mortality (HR: 1.14; 95% CI: 1.08 to 1.20; p < 0.001), heart failure admission (HR: 1.18; 95% CI: 1.11 to 1.25; p < 0.001), and all-cause serious adverse events (HR: 1.08; 95% CI: 1.02 to 1.14; p = 0.008) than the optimal control group. The event rates and HRs for individual components of serious adverse events according to BP control status are shown in Online Table 2.

The benefit-to-harm ratio of optimal BP control (120 to 129/<80 mm Hg) relative to suboptimal BP control (130 to 139/80 to 89 mm Hg) was >1.0 for all subgroups stratified according to 10-year CVD risk (<10%, 10% to 20%, and >20%), suggesting that patients with AF and treated hypertension would receive greater benefit than harm from optimal BP control regardless of their estimated CVD risk (Figure 5). When stratifying patients with a cutoff of 18.2%, the benefit-to-harm ratio was consistently >1.0 for both subgroups (<18.2% and ≥18.2%) (Online Figure 2).

SENSITIVITY ANALYSIS. In the first sensitivity analysis excluding patients with high CVD risk from the overall 140,229 participants without treated hypertension, we analyzed 65,078 (46.4%) patients with low CVD risk according to the 2017 ACC/AHA guideline (without a history of CVD and 10-year predicted CVD risk <10%) (Online Table 3). The overall findings were consistent with our primary findings, but the risk of heart failure admission was not higher as was reported in the main analysis.

Among 158,145 participants with treated hypertension, we analyzed 30,136 (19.1%) patients with low CVD risk according to the 2017 ACC/AHA guideline (Online Table 4). The overall findings were consistent, revealing that the lowest risk of major cardiovascular events was in the optimal control group. The third sensitivity analysis was restricted to 105,794 (66.9%) patients with 10-year CVD risk <18.2% and did not alter the main findings (Online Table 5).

SUPPLEMENTAL ANALYSIS. Among subjects with or without treated hypertension, the assessed risk of adverse outcomes without censoring at the date of oral anticoagulant initiation was consistent with our primary findings (Online Tables 6 and 7).

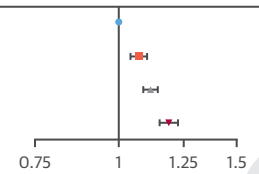
DISCUSSION

The present study includes 5 principal findings, as follows: 1) after applying the 2017 ACC/AHA guideline, 79.4% of patients with AF were estimated to have hypertension, including the addition of 17.2% with newly redefined hypertension; 2) after applying the new definition of hypertension to the CHA_2DS_2-VASc score instead of the previous definition, 9.4% of patients with AF initially categorized as having low stroke risk would be reclassified as having higher stroke risk, and the proportion of patients with high stroke risk would increase by 5.4%; 3) patients with AF and newly redefined hypertension were at significantly higher risks of major cardiovascular events, ischemic stroke, intracranial hemorrhage, and heart failure admission versus nonhypertensive patients; 4) among patients with AF and treated hypertension, patients with SBP/DBP ≥130/80 mm Hg or SBP/DBP <120/80 mm Hg were at significantly higher risks

FIGURE 3 Risk of Adverse Outcomes According to Hypertension Diagnosis Based on the JNC7 Guideline and the 2017 ACC/AHA Guideline (Model 1)

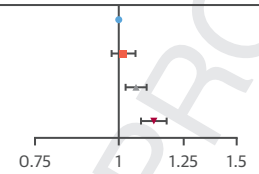
Major Cardiovascular Event

HTN Diagnosis According to Different Guidelines	Number of Patients	Number of Events	Rate (95% CI)	Adjusted HR (95% CI)	P value
Nonhypertensive	61,461	9,698	4.21 (4.13-4.29)	1	-
Newly redefined HTN	51,214	9,378	4.41 (4.32-4.49)	1.07 (1.04-1.10)	<0.001
HTN by 2017 ACC/AHA	78,768	16,025	4.49 (4.42-4.56)	1.12 (1.09-1.14)	<0.001
HTN by JNC7	27,554	6,647	4.67 (4.58-4.78)	1.19 (1.15-1.23)	<0.001



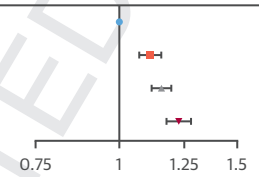
Death from All Causes

HTN Diagnosis According to Different Guidelines	Number of Patients	Number of Events	Rate (95% CI)	Adjusted HR (95% CI)	P value
Nonhypertensive	61,461	4,969	2.02 (1.97-2.08)	1	-
Newly redefined HTN	51,214	4,555	1.92 (1.87-1.98)	1.02 (0.98-1.06)	0.435
HTN by 2017 ACC/AHA	78,768	8,144	1.98 (1.94-2.03)	1.06 (1.02-1.10)	0.001
HTN by JNC7	27,554	3,589	2.08 (2.01-2.15)	1.13 (1.08-1.18)	<0.001



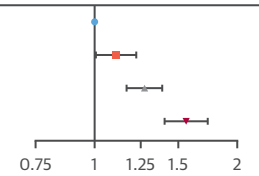
Ischemic Stroke

HTN Diagnosis According to Different Guidelines	Number of Patients	Number of Events	Rate (95% CI)	Adjusted HR (95% CI)	P value
Nonhypertensive	61,461	5,434	2.24 (2.18-2.30)	1	-
Newly redefined HTN	51,214	5,485	2.45 (2.39-2.51)	1.11 (1.07-1.16)	<0.001
HTN by 2017 ACC/AHA	78,768	9,438	2.49 (2.44-2.54)	1.16 (1.12-1.20)	<0.001
HTN by JNC7	27,554	3,953	2.57 (2.49-2.65)	1.23 (1.18-1.28)	<0.001



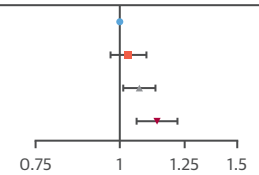
Intracranial Hemorrhage

HTN Diagnosis According to Different Guidelines	Number of Patients	Number of Events	Rate (95% CI)	Adjusted HR (95% CI)	P value
Nonhypertensive	61,461	833	0.32 (0.30-0.34)	1	-
Newly redefined HTN	51,214	805	0.34 (0.32-0.37)	1.11 (1.01-1.22)	0.041
HTN by 2017 ACC/AHA	78,768	1,507	0.39 (0.37-0.41)	1.27 (1.17-1.39)	<0.001
HTN by JNC7	27,554	702	0.46 (0.42-0.50)	1.56 (1.40-1.73)	<0.001



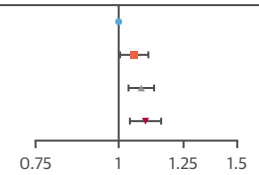
Myocardial Infarction

HTN Diagnosis According to Different Guidelines	Number of Patients	Number of Events	Rate (95% CI)	Adjusted HR (95% CI)	P value
Nonhypertensive	61,461	2,162	0.88 (0.84-0.91)	1	-
Newly redefined HTN	51,214	2,009	0.86 (0.82-0.90)	1.03 (0.97-1.10)	0.340
HTN by 2017 ACC/AHA	78,768	3,390	0.87 (0.84-0.90)	1.07 (1.01-1.13)	0.017
HTN by JNC7	27,554	1,381	0.90 (0.85-0.96)	1.14 (1.07-1.22)	<0.001



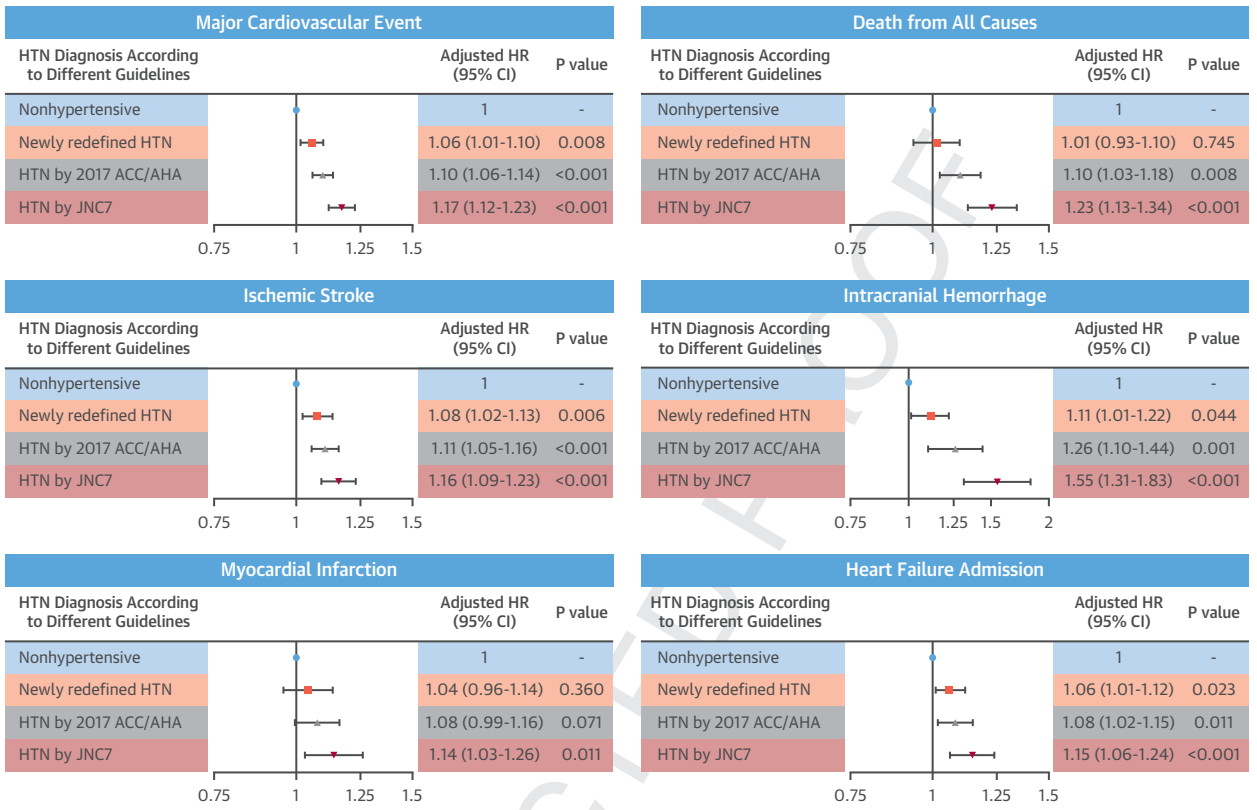
Heart Failure Admission

HTN Diagnosis According to Different Guidelines	Number of Patients	Number of Events	Rate (95% CI)	Adjusted HR (95% CI)	P value
Nonhypertensive	61,461	3,443	1.19 (1.15-1.23)	1	-
Newly redefined HTN	51,214	3,294	1.20 (1.16-1.24)	1.06 (1.01-1.11)	0.031
HTN by 2017 ACC/AHA	78,768	5,659	1.21 (1.18-1.24)	1.08 (1.04-1.13)	<0.001
HTN by JNC7	27,554	2,365	1.25 (1.20-1.30)	1.10 (1.04-1.16)	0.001



The event rates are adjusted for age and sex (per 100 person-years). CI = confidence interval; HR = hazard ratio; other abbreviations as in Figure 2.

FIGURE 4 Risk of Adverse Outcomes According to HTN Diagnosis Based on the JNC7 Guideline and the 2017 ACC/AHA Guideline Based on the Time-Updated Cox Regression Analysis Among AF Patients Who Had at Least 1 Follow-up Blood Pressure Measurement After the Baseline Visit (Model 2)



HRs are adjusted for all variables adjusted in model 1 as well as blood pressure levels (3 groups: <130/80 mm Hg, 130 to 139/80 to 89 mm Hg, and ≥140/90 mm Hg) and use of antihypertensive medications at follow-up examinations. Abbreviations as in Figures 2 and 3.

of major cardiovascular events than patients with SBP of 120 to 129 mm Hg and DBP <80 mm Hg, which was the optimal BP target range for our patients with AF; and 5) patients with AF would receive greater benefit than harm from aiming for a controlled BP target range of 120 to 129/<80 mm Hg, compared with that of 130 to 139/80 to 89 mm Hg, regardless of their estimated CVD risk.

INCREASED HYPERTENSION DIAGNOSIS AMONG PATIENTS WITH AF. Among the U.S. general population, the prevalence of hypertension was estimated to be 45.6% and 31.9% according to the 2017 ACC/AHA and JNC7 guidelines, respectively, with 13.7% representing newly redefined hypertension (16). In this Korean AF cohort, applying the new 2017 ACC/AHA guideline redefined 17.2% of patients with AF as newly hypertensive. The greater increase of hypertension prevalence in patients with AF than the general population might be explained by the higher prevalence of hypertension in AF patients than in the general population (17). This increase of hypertension prevalence also reclassified 9.4% of patients with low stroke risk into higher stroke risk categories. However, the reclassification of risk according to thromboembolic risk scores (e.g., $CHADS_2$ [congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and stroke/transient ischemic attack] score, CHA_2DS_2-VASc score, and ATRIA [Anticoagulation and Risk Factors in Atrial Fibrillation] score) recalculated by using the new definition of hypertension should be interpreted with caution because the scores were developed and validated based on the previous definition of hypertension. Further research is needed to investigate the predictive abilities of recalculated risk scores for stroke and the impacts of anticoagulation recommendations. In the present study, higher CVD risk in the newly redefined hypertension was evident in a "real-world" AF population, suggesting that the new definition of

TABLE 2 Event Rates and Hazard Ratios for Adverse Outcomes According to BP Control Status Among Patients With AF and Treated Hypertension

		BP Control Status			
	Patients With AF and Treated Hypertension (n = 158,145)	Intensive Control <120/80 mm Hg (n = 31,269)	Optimal Control 120-129/<80 mm Hg (n = 16,602)	Suboptimal Control 130-139/80-89 mm Hg (n = 56,843)	Poor Control ≥140/90 mm Hg (n = 53,431)
Major cardiovascular event*					
No. of events	42,685	8,085	4,087	14,727	15,786
Rate (95% CI)†	8.32 (8.25-8.40)	8.82 (8.64-9.00)	7.99 (7.76-8.22)	8.08 (7.96-8.21)	8.43 (8.31-8.55)
Hazard ratio (95% CI)‡		1.05 (1.01-1.09)	Reference	1.05 (1.01-1.08)	1.13 (1.09-1.16)
p value		0.026	Reference	0.011	<0.001
Death from all causes					
No. of events	20,768	4,353	1,969	6,834	7,612
Rate (95% CI)†	3.38 (3.33-3.42)	3.97 (3.85-4.08)	3.26 (3.12-3.40)	3.17 (3.09-3.24)	3.33 (3.26-3.40)
Hazard ratio (95% CI)‡		1.14 (1.08-1.20)	Reference	1.02 (0.98-1.07)	1.06 (1.01-1.12)
p value		<0.001	Reference	0.293	0.017
Ischemic stroke					
No. of events	25,552	4,496	2,418	8,823	9,815
Rate (95% CI)†	4.57 (4.52-4.63)	4.43 (4.31-4.56)	4.33 (4.17-4.50)	4.46 (4.37-4.55)	4.82 (4.73-4.91)
Hazard ratio (95% CI)‡		1.00 (0.96-1.05)	Reference	1.05 (1.01-1.10)	1.16 (1.11-1.21)
p value		0.910	Reference	0.030	<0.001
Intracranial hemorrhage					
No. of events	3,172	525	298	1,017	1,332
Rate (95% CI)†	0.52 (0.50-0.54)	0.48 (0.44-0.52)	0.50 (0.44-0.55)	0.47 (0.44-0.50)	0.60 (0.57-0.63)
Hazard ratio (95% CI)‡		0.93 (0.81-1.08)	Reference	1.00 (0.88-1.14)	1.29 (1.14-1.47)
p value		0.340	Reference	0.980	<0.001
Myocardial infarction					
No. of events	8,904	1,663	857	3,088	3,296
Rate (95% CI)†	1.51 (1.48-1.54)	1.57 (1.50-1.65)	1.49 (1.39-1.59)	1.47 (1.42-1.52)	1.52 (1.46-1.57)
Hazard ratio (95% CI)‡		0.98 (0.91-1.07)	Reference	1.04 (0.97-1.13)	1.13 (1.05-1.22)
p value		0.680	Reference	0.270	0.002
Heart failure admission					
No. of events	18,155	3,891	1,679	6,227	6,358
Rate (95% CI)†	2.51 (2.48-2.55)	3.05 (2.96-3.15)	2.36 (2.25-2.47)	2.44 (2.38-2.50)	2.37 (2.32-2.43)
Hazard ratio (95% CI)‡		1.18 (1.11-1.25)	Reference	1.08 (1.02-1.14)	1.09 (1.03-1.15)
p value		<0.001	Reference	0.006	0.002
All-cause serious adverse event§					
No. of events	20,064	4,038	1,971	6,865	7,190
Rate (95% CI)†	2.74 (2.71-2.78)	3.05 (2.96-3.14)	2.74 (2.62-2.86)	2.65 (2.59-2.71)	2.69 (2.63-2.76)
Hazard ratio (95% CI)‡		1.08 (1.02-1.14)	Reference	1.00 (0.96-1.06)	1.04 (0.99-1.09)
p value		0.008	Reference	0.880	0.150

*Major cardiovascular events included ischemic stroke, intracranial hemorrhage, myocardial infarction, and heart failure requiring hospitalization. †The event rates were adjusted for age and sex. The rates are per 100 person-years. ‡Adjusted for age, sex, income status, smoking history, BMI, heart failure, diabetes mellitus, previous ischemic stroke, previous myocardial infarction, previous intracranial hemorrhage, peripheral artery disease, dyslipidemia, chronic kidney disease, and use of antiplatelet agents, statins, and antihypertensive medications listed in Table 1, with mortality as the competing risk for all outcomes other than death from all-causes. §Included hypotension, syncope, bradycardia, electrolyte abnormality, injurious falls, and acute kidney injury or acute renal failure.

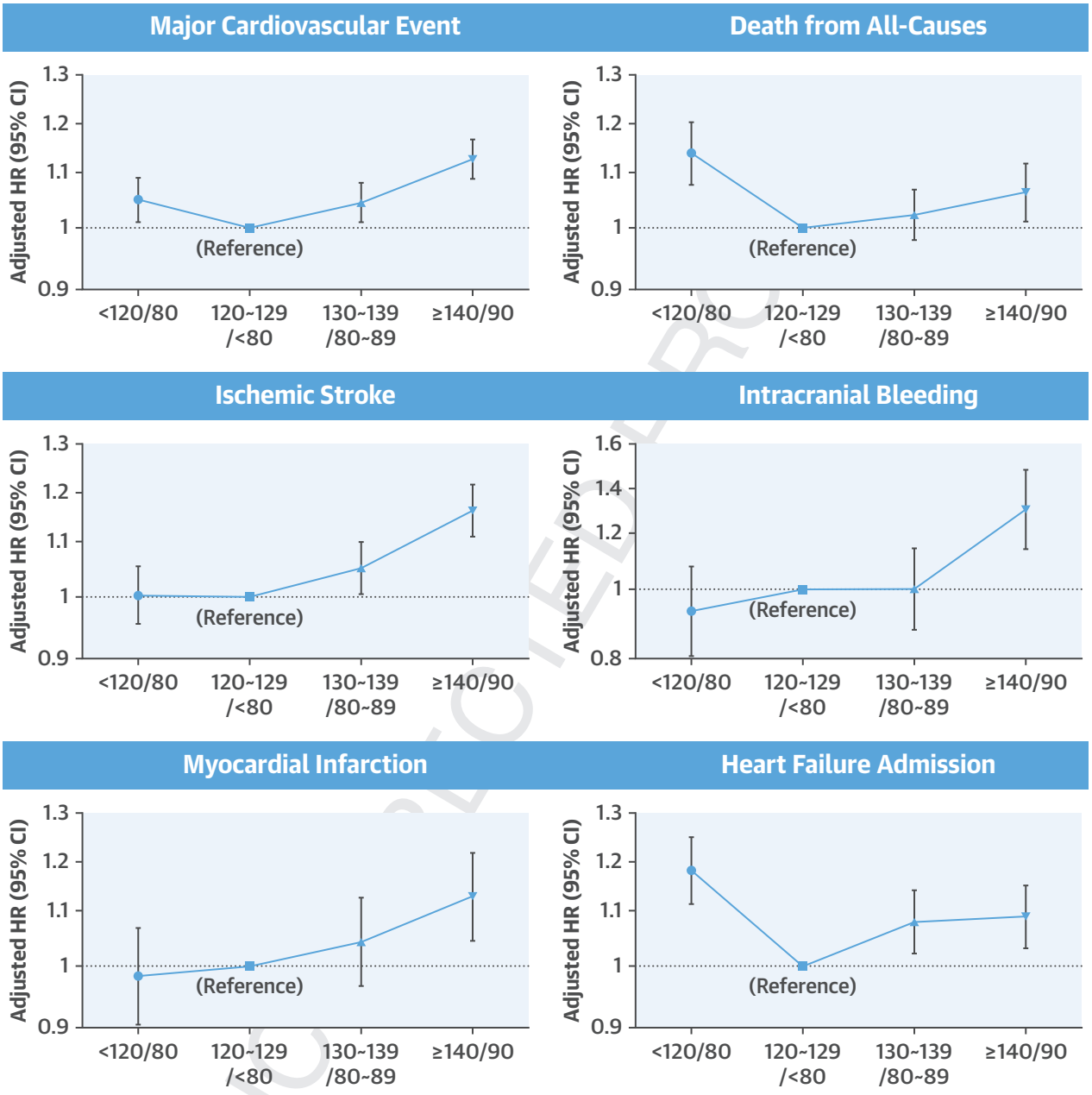
CI = confidence interval; other abbreviations as in Table 1.

hypertension should be adopted for earlier detection and optimal timing to control BP and other comorbid risk factors in patients with AF.

WHAT IS THE IDEAL BP TREATMENT THRESHOLD FOR AF? Hypertension and prehypertension are independently associated with AF (12,18). Indeed, AF can be regarded as a manifestation of target organ damage due to hypertension. Hypertension is also a risk factor for stroke in patients with AF. High, uncontrolled BP enhances the risk of stroke and bleeding events and may lead to recurrent AF (7,8,17). Therefore, good BP control should form an integral part of the management of patients with AF (18,19). However, the optimal BP threshold for treating patients with AF and hypertension has not been determined.

In the present study, patients with AF and newly redefined hypertension based on the 2017 ACC/AHA guideline were at significantly higher risk of major cardiovascular events, suggesting that the stricter BP threshold of the new guideline is more appropriate for use in patients with AF than that of the JNC7 guideline. The 2017 ACC/AHA guideline recommends

CENTRAL ILLUSTRATION **Blood Pressure Control Status Among Patients With AF and Treated Hypertension: Risk of Adverse Outcomes**



Kim, D. et al. J Am Coll Cardiol. 2018;■(■):■-■.

In patients with atrial fibrillation (AF) undergoing hypertension treatment, patients with systolic blood pressure/diastolic blood pressure (SBP/DBP) ≥130/80 mm Hg or SBP/DBP <120/80 mm Hg were at significantly higher risk of major cardiovascular events than those with SBP 120 to 129 mm Hg and DBP <80 mm Hg, which was the optimal BP target range. CI = confidence interval; HR = hazard ratio.

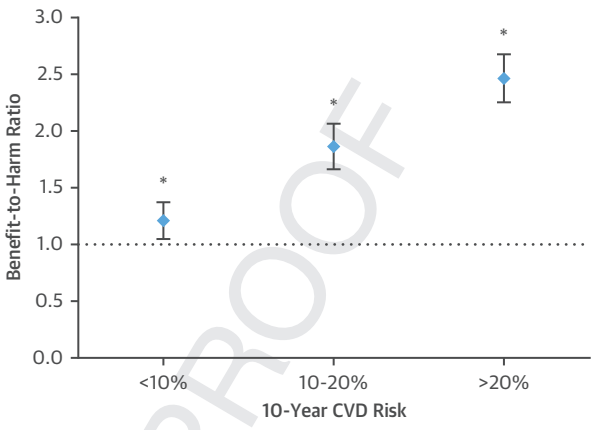
nonpharmacological therapy for the majority of patients with newly redefined hypertension due to a lack of evidence to support antihypertensive drug treatment in addition to nonpharmacological therapy for adults with newly redefined hypertension and low CVD risk (1,16). Among patients with hypertension, having AF on its own is associated with a 2-fold increased risk of cardiovascular events, ~3-fold

higher risk of fatal and nonfatal stroke, and a 5-fold increased rate of hospitalization for heart failure (20). In our sensitivity analysis restricted to patients with AF and low CVD risk, the newly redefined hypertension group reported similarly increased risk adverse outcomes, suggesting that even patients with low CVD risk might benefit from antihypertensive treatment in AF. Further research is required to investigate whether AF should be considered a high CVD risk condition such as diabetes or chronic kidney disease, and to determine the specific BP treatment threshold for patients with AF.

SHOULD WE AIM EVEN LOWER? Recent trials have investigated the effects of aggressive BP control in patients with AF. For example, RACE 3 (Routine Versus Aggressive Risk Factor Driven Upstream Rhythm Control for Prevention of Early Atrial Fibrillation in Heart Failure) showed that targeted therapy of underlying conditions, including a BP goal <120/80 mm Hg, improves sinus rhythm maintenance in patients with persistent AF and heart failure (21). However, in SMAC-AF (Substrate Modification with Aggressive Blood Pressure Control), aggressive BP treatment (with a BP goal <120/80 mm Hg) did not reduce atrial arrhythmia recurrence after catheter ablation for patients with AF but rather resulted in more hypotension (22).

In the general population of patients with AF and hypertension, optimal BP targets to improve cardiovascular outcomes remain unknown. Our study shows that BP control status of SBP 120 to 129 mm Hg and DBP <80 mm Hg was associated with the best clinical outcomes in patients with AF taking antihypertensive medications, whereas SBP/DBP <120/80 or ≥130/80 mm Hg was associated with increased adverse cardiovascular outcomes (**Central Illustration**). The U-shaped relationship has been subject to much debate and controversy, but given that patients with AF are often elderly with multiple comorbidities, this U-shaped relationship may be evident among the AF population. In this study, BP measurements were performed in less well-controlled circumstances (manual measurement with an attending provider in ordinary clinics) rather than in rigid protocol-based trials such as SPRINT (Systolic Blood Pressure Intervention), in which automated measurements include 3 consecutive BP readings while the patient is seated in a quiet place. However, we should take into account that the optimal SBP level of 120 to 129 mm Hg in this study might be equivalent to an SBP level of 130 to 139 mm Hg taken in a typical office practice because research study BP readings are generally 10/7 mm Hg lower than routine office BP readings (23).

FIGURE 5 Benefit-to-Harm Ratios of Optimal BP Control (120-129/<80 mm Hg) Compared With Suboptimal BP Control (130-139/80-89 mm Hg) According to 10-Year Predicted CVD Risk Subgroup



All possible pairwise comparisons of between-subgroup mean values of benefit-to-harm ratios were significantly different (*p < 0.001). BP = blood pressure; CVD = cardiovascular disease.

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Even in a previous trial that reported marked cardiovascular benefits with the implementation of lower BP goals, there were more frequent serious adverse events such as hypotension, syncope, electrolyte abnormalities, and acute kidney injury (24). Although the 2017 ACC/AHA guideline recommends intensive treatment with an SBP target <130 mm Hg for all SPRINT-eligible patients (1), the recent analysis of Phillips et al. (14) suggested that the harm of intensive treatment outweighs the benefits in SPRINT participants with a 10-year CVD risk <18.2%. The predictive model in this study suggests that the benefit of a BP control of 120 to 129/<80 mm Hg would outweigh the harm even for those with a 10-year CVD risk <10%.

STUDY LIMITATIONS. First, such studies using administrative databases could be susceptible to errors arising from coding inaccuracies. To minimize this problem, we applied definitions that we had already validated in previous studies which used the Korean NHIS cohort (4,5,12). Second, although the repeated measurements of initially elevated BP used in this study could reduce the risk of overestimation through an association with a median 8 mm Hg decrease in SBP (compared with initial readings) (25), BP was measured at a single visit. Therefore, the figure of 17.2% with newly redefined hypertension might be an overestimate. Unlike rigid protocol-based trials, such studies using nationally representative databases (e.g., the National Health and Nutrition Examination Survey of the United States) are prone to

this limitation (16). On the contrary, these studies may better reflect the "real-world" clinical practice. Third, the pooled cohort equation used in this study might underestimate the risks of patients with AF because participants with AF were not included in the population used to develop the equation. Fourth, we were unable to differentiate between AF and atrial flutter, and data regarding types of AF (paroxysmal vs. nonparoxysmal) were not available. We could therefore not investigate whether ideal BP thresholds differed between AF and atrial flutter, or according to types of AF. Last, in the present study we enrolled only patients of East Asian ancestry, and whether the results can be extrapolated to other populations thus remains uncertain.

Despite these limitations, this study is the first comprehensive investigation to evaluate optimal BP thresholds in patients with AF using the entire population of one country. It presents the largest population dataset available in the literature to investigate the relationships between BP levels and cardiovascular outcomes in oral anticoagulant-naive patients with AF.

CONCLUSIONS

Patients with AF and newly redefined hypertension according to the 2017 ACC/AHA guideline were at higher risks of major cardiovascular events, ischemic stroke, intracranial hemorrhage, and heart failure admission compared with nonhypertensive patients, suggesting that the new BP threshold may be beneficial for patients with AF. In these patients with AF undergoing hypertension treatment, a U-shaped relationship of major cardiovascular events was evident, with SBP 120 to 129 and DBP <80 mm Hg as the optimal BP treatment target.

ADDRESS FOR CORRESPONDENCE: Dr. Boyoung Joung, 50 Yonseiro, Seodaemun-gu, Seoul, Republic of Korea 03722. E-mail: cby6908@yuhs.ac. OR Dr. Gregory Y.H. Lip, Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, England, United Kingdom. E-mail: g.y.h.lip@bham.ac.uk. Twitter: @cby6908, @yonsei_u, @unibirmingham.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Patients with AF and hypertension as defined under the 2017 ACC/AHA guideline (130-139/80-89 mmHg) are at greater risk of cardiovascular events, stroke, intracranial hemorrhage, and heart failure than normotensive patients. In patients with AF treated for hypertension, there is a U-shaped relationship between blood pressure and cardiovascular events, with optimum outcomes associated with a BP range of 120-129/<80 mmHg.

TRANSLATIONAL OUTLOOK: Further research is needed to determine whether the optimum target blood pressure for patients with AF and hypertension differs for those with other risk factors, such as diabetes and chronic kidney disease.

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KEY WORDS atrial fibrillation, cardiovascular outcome, guideline, hypertension

APPENDIX For an expanded Methods section, as well as supplemental tables and figures, please see the online version of this paper.

Ideal Blood Pressure in Patients With Atrial Fibrillation

Daehoon Kim, Pil-Sung Yang, Tae-Hoon Kim, Eunsun Jang, Hyejung Shin, Ha Yan Kim, Hee Tae Yu, Jae-Sun Uhm, Jong-Youn Kim, Hui-Nam Pak, Moon-Hyoung Lee, Boyoung Joung, Gregory Y.H. Lip

The goal of this study was to investigate the impacts of the 2017 American College of Cardiology/American Heart Association hypertension guideline and identify the ideal blood pressure (BP) threshold for the management of high BP in patients with atrial fibrillation (AF). Patients with newly redefined hypertension based on the 2017 American College of Cardiology/American Heart Association guideline, accounting for 17.2% of total patients with AF, had greater risks of major cardiovascular events, ischemic stroke, intracranial hemorrhage, and heart failure admission compared with nonhypertensive patients, suggesting that the new BP threshold is beneficial. A U-shaped relationship for major cardiovascular events was evident, with 120 to 129/<80 mm Hg identified as the optimal BP target for patients with AF taking antihypertensive medications.

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