Impact of the Duration and Degree of Hypertension and Body Weight on New-Onset Atrial Fibrillation

A Nationwide Population-Based Study

Yun Gi Kim,* Kyung-Do Han,* Jong-Il Choi, Ki Yung Boo, Do Young Kim, Suk-Kyu Oh, Kwang-No Lee, Jaemin Shim, Jin Seok Kim, Young-Hoon Kim

Abstract—Hypertension and obesity are known risk factors for atrial fibrillation (AF). However, it is unclear whether uncontrolled, long-standing hypertension has a particularly profound effect on AF. Because they have a similar underlying pathophysiology, hypertension and obesity could act synergistically in the context of AF. We evaluated how various stages of hypertension and body weight status affect new-onset AF. We analyzed a total of 9 797 418 participants who underwent a national health checkup. Hypertension was classified into 5 stages: nonhypertension, prehypertension, hypertension without medication, hypertension with medication <5 years, and hypertension with medication ≥5 years. The participants were also stratified based on body mass index and waist circumference. During the 80 130 161 person×years follow-up, a total of 196 136 new-onset AF cases occurred. The incidence of new-onset AF gradually increased among the 5 stages of hypertension: the adjusted hazard ratio for each group was 1 (reference), 1.145, 1.390, 1.853, and 2.344 for each stage of hypertension. A graded escalation in the risk of new-onset AF was also observed in response to increased systolic and diastolic blood pressure. The incidence of new-onset AF correlated with body mass index and waist circumference, with obese people having a higher risk than others. Hypertension and obesity acted synergistically: obese people with hypertension on medication ≥5 years had the highest risk of AF. In conclusion, the degree and duration of hypertension, as well as the presence of hypertension, were important factors for new-onset AF. Body weight status was significantly associated with new-onset AF and acted synergistically with hypertension. (***Hypertension*****. 2019;74:e45-e51. DOI: 10.1161/HYPERTENSIONAHA.119.13672.)** • **Online Data Supplement**

Key Words: atrial fibrillation ■ body weight ■ obesity ■ risk factor ■ waist circumference

Atrial fibrillation (AF) is a significant public health burden worldwide, and its incidence is expected to rise rapidly in the near future, largely because of the aging of the general population. In addition to a substantially impaired quality of life, the risk of ischemic stroke, systemic embolism, heart failure, and mortality all increase significantly in patients with AF.[1–4] Despite the enormous health care burden of AF, the mainstream of medical attention is focused on the treatment of AF and its complications, not on its prevention.[5,6]

The underlying pathophysiology of AF is not fully understood. Although genetic predisposition contributes to its development, it is largely an acquired disease with multiple risk factors that are mostly correctable or manageable.[7,8] Those risk factors include advanced age, hypertension, diabetes mellitus, obesity, underweight, sleep apnea, heart failure, ischemic heart disease, and various inflammatory diseases.[7,9–12]

Hypertension is a global health burden affecting 20% to 50% of the adult population.[13–15] Although patients with hypertension have an increased risk of AF, the underlying cause of the association is unclear. One proposed mechanism is left ventricular hypertrophy (LVH) caused by hypertension.[16,17] In the presence of LVH, the diastolic function of the left ventricle (LV) is impaired, and the diastolic filling pressure is increased. The volume of the left atrium (LA) increases in response to the elevated diastolic filling pressure of the LV, which in turn predisposes individuals to the occurrence of new-onset AF.[18–20] The activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system in patients with hypertension is another possible mechanism for the increased risk of new-onset AF.[21,22] The abovementioned mechanisms are possibly cumulative over time and blood pressure degree–dependent. Therefore, patients with a longer duration of hypertension, multiple medications, or uncontrolled blood pressure might show a higher incidence of new-onset AF compared with patients whose hypertension is well controlled or people without hypertension. Obesity and

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From the Division of Cardiology, Korea University College of Medicine and Korea University Anam Hospital, Seoul, Republic of Korea (Y.G.K., J.-I.C., K.Y.B., D.Y.K., S.-K.O., K.-N.L., J.S., J.S.K., Y.-H.K.); and Department of Biostatistics, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea (K.-D.H.).

*These authors contributed equally to this work.

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Correspondence to Jong-Il Choi, MD, PhD, MHSc, [1]Division of Cardiology, Korea University College of Medicine and Korea University Anam Hospital, 73 Inchon-ro, Seongbuk-gu, Seoul 02841, Republic of Korea. Email jongilchoi@korea.ac.kr

hypertension are both significant risk factors for new-onset AF, and they are both associated with LA enlargement and LVH, which are potential underlying mechanisms linking obesity and hypertension to an increased risk of new-onset AF.[20,23] We performed this nationwide population-based study to evaluate the association between the degree of hypertension and the incidence of new-onset AF. The effect of obesity on new-onset AF and its interaction with hypertension were also examined.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Cohort

The majority of Koreans (97.1%) are mandatory subscribers to the Korean National Health Insurance Service (K-NHIS), which is the single medical insurer in the Republic of Korea and managed by the government. The remaining 3% of the population are medical aid subjects. The K-NHIS database contains baseline demographics, diagnosis codes for various diseases, use of inpatient and outpatient services, pharmacy dispensing claims, and mortality data. To ensure correct diagnosis and proper prescriptions, the Health Insurance Review & Assessment Service, an independent organization, randomly reviews the adequacy of diagnoses and prescriptions.

The K-NHIS offers a regular national health checkup for all subscribers that includes the following: a health questionnaire; laboratory tests, such as lipid profile, serum creatinine, and fasting blood sugar; chest X-ray; and measurement of blood pressure, body weight, height, and waist circumference (WC). The K-NHIS database is open to medical researchers whose study protocols are approved by the official review committee (https://nhiss.nhis.or.kr/). The current study included participants who underwent the national health checkup in 2009. We obtained systolic blood pressure (SBP) and diastolic blood pressure (DBP) for all participants and were able to retrieve diagnosis codes related to AF and hypertension. The authors have no conflict of interest with K-NHIS. This study was approved by the Institutional Review Board of Korea University Medical Centre Anam Hospital, and informed consent was waived.

Definitions

The diagnosis of AF required 2 outpatient records or 1 inpatient record of *International Classification of Diseases, Tenth Revision* codes for AF in the K-NHIS database. The identification of people with hypertension required 1 outpatient or inpatient record of *International Classification of Diseases, Tenth Revision* codes for hypertension. Participants with SBP ≥120 or DBP ≥90 were also included in the hypertension group. The exact diagnosis codes for AF, hypertension, and other diseases are described in Table S1 in the online-only Data Supplement.

Participants were classified into 5 hypertension groups as follows: (1) nonhypertension (people with no prior diagnosis of hypertension, SBP <120, and DBP <80); (2) prehypertension (people with no prior diagnosis of hypertension but SBP 120–140 or DBP 80–90); (3) hypertension without medication (people with a prior diagnosis of hypertension but not taking medication for it); (4) hypertension with medication for <5 years (people diagnosed with and taking medication for hypertension for <5 years); (5) hypertension with medication for ≥5 years (people diagnosed with and taking medication for hypertension for ≥5 years). Participants were also divided into 4 groups based on their measured SBP and DBP: (1) <120 (mm Hg); (2) 120–140; (3) 140–160; (4) >160 for SBP and (1) <80; (2) 80–90; (3) 90–100; (4) >100 for DBP.

Body weight status was classified into 5 stages according to body mass index (BMI): underweight (BMI<18.5 [kg/m^2]), reference (18.5≤BMI<23.0), upper normal (23.0≤ BMI<25.0), overweight (25.0≤BMI<30.0), and obese (BMI≥30.0). We used the WC to complement the BMI, and we classified it into 6 stages: WC <80.0 (cm), 80.0≤WC<85.0, 85.0≤WC<90.0, 90.0≤WC<95.0, 95.0≤WC<100.0, and WC≥100.0 for males and WC<75.0, 75.0≤WC <80.0, 80.0≤WC<85.0, 85.0≤WC< 90.0, 90.0≤WC<95.0, and WC≥95.0 for females.

Study End Points

The occurrence of new-onset AF was the end point of this study. The incidence of new-onset AF was defined as the number of new-onset AF cases calculated per 1000 person×years. The influence of hypertension on new-onset AF was evaluated through various subgroup analyses. The effect of body weight on new-onset AF and its interaction with hypertension were also evaluated.

Statistical Analysis

Continuous variables are described as the mean±SD and were compared using a Student *t* test. Categorical variables are presented as percentile values and were compared with a χ^2 test or Fisher exact test, as appropriate. Cox regression analyses were performed to calculate hazard ratios (HRs) with 95% CIs. Both univariate and multivariate analyses were performed using Cox regression analyses. Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, smoking status, alcohol consumption status, physical activity, income level, diabetes mellitus, hypertension, and dyslipidemia. A receiver operating characteristic curve analysis was performed to predict the future risk of new-onset AF. All significance tests were 2-tailed, and P≤0.05 were considered statistically significant. All statistical analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC).

Results

Study Cohort

A total of 9797418 participants were included in the analysis. A flowchart of the study population enrollment is summarized in Figure 1. The baseline characteristics of the study

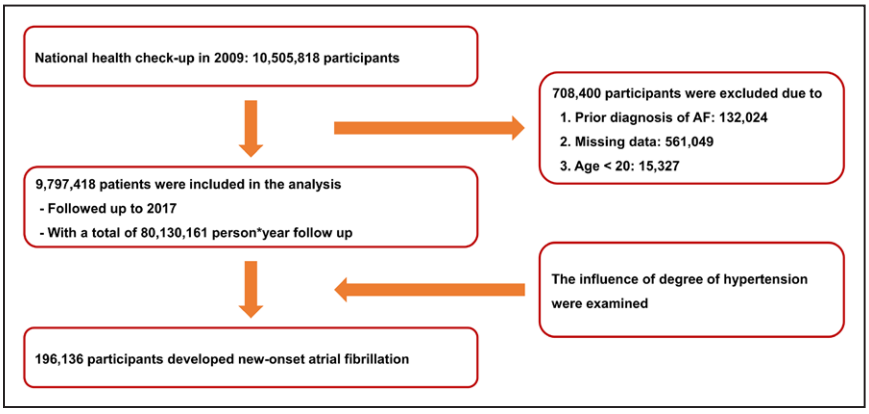

Figure 1. Flowchart of the study. AF indicates atrial fibrillation.

Table 1. Baseline Demographics of People With and Without Hypertension

Variable	Total (N=9 797 418)	Hypertension (–) (n=7 310 713)	Hypertension (+) (n=2 486 705)	*P* Value
Male	5 356 943 (54.68%)	3 946 021 (53.98%)	1 410 922 (56.74%)	<0.0001
Smoking				<0.0001
Nonsmoker	5 832 072 (59.53%)	4 333 269 (59.27%)	1 498 803 (60.27%)	
Ex-smoker	1 394 168 (14.23%)	959 895 (13.13%)	434 273 (17.46%)	
Current-smoker	2 571 178 (26.24%)	2 017 549 (27.60%)	553 629 (22.26%)	
Alcohol consumption				<0.0001
Nondrinker (0 g per wk)	5 037 180 (51.41%)	3 652 558 (49.96%)	1 384 622 (55.68%)	
Mild-drinker (0≤g <105 per wk)	4 087 517 (41.72%)	3 188 223 (43.61%)	899 294 (36.16%)	
Heavy-drinker (≥210 g per wk)	672 721 (6.87%)	469 932 (6.43%)	202 789 (8.15%)	
Regular exercise (yes)	5 022 112 (51.26%)	3 812 910 (52.16%)	1 209 202 (48.63%)	<0.0001
Income (lower quartile)	2 590 673 (26.44%)	1 925 819 (26.34%)	664 854 (26.74%)	<0.0001
Diabetes mellitus	842 848 (8.60%)	363 270 (4.97%)	479 578 (19.29%)	<0.0001
Dyslipidemia	1 773 560 (18.10%)	957 564 (13.10%)	815 996 (32.81%)	<0.0001
Hypertension 5 levels				<0.0001
Nonhypertension	6 739 088 (68.78%)	3 398 817 (46.49%)		
Prehypertension	2 215 482 (22.61%)	3 911 896 (53.51%)		
Hypertension without medication	287 417 (2.93%)		863 727 (34.73%)	
Hypertension with medication <5 y	289 883 (2.96%)		750 354 (30.17%)	
Hypertension with medication ≥5 y	265 548 (2.71%)		872 624 (35.09%)	
Age, y	47.02±14.06	43.74±12.93	56.65±12.78	<0.0001
Height, cm	163.89±9.22	164.56±9.02	161.92±9.50	<0.0001
Weight, kg	63.90±11.59	63.23±11.42	65.87±11.84	<0.0001
Body mass index, kg/m^2	23.70±3.21	23.25±3.07	25.02±3.23	<0.0001
Waist circumference, cm	80.19±9.07	78.71±8.79	84.51±8.45	<0.0001
Systolic blood pressure, mm Hg	122.38±14.94	117.61±11.27	136.42±15.56	<0.0001
Diastolic blood pressure, mm Hg	76.28±9.97	73.47±7.92	84.56±10.75	<0.0001
Fasting glucose, mg/dL	97.07±22.85	94.40±19.66	104.93±28.95	<0.0001
Total cholesterol, mg/dL	195.07±36.59	193.42±35.77	199.92±38.48	<0.0001
High density lipoprotein, mg/dL	55.43±18.86	56.02±18.27	53.67±20.41	<0.0001

population are summarized in Table 1. A total of 2 486 705 (25.38%) people were diagnosed with hypertension: 863 727 (34.73%), 750 354 (30.17%), and 872 624 (35.09%) people were not taking medication, took medication <5 years, and took medication ≥5 years, respectively. Among those without hypertension, 3 911 896 (53.51%) people were prehypertensive. The baseline demographics of people with and without hypertension are presented in Table 1. In brief, people with hypertension were more likely than those without hypertension to be male, older, and have a higher BMI and a higher prevalence of diabetes mellitus and dyslipidemia.

Hypertension and New-Onset AF

A total of 196 136 cases of new-onset AF were diagnosed during the 80 130 161 person×years follow-up (mean follow-up duration=8.2±1.0 years). The risk of new-onset AF differed significantly among the different stages of hypertension. The raw incidence of new-onset AF was 1.320, 1.825, 2.859, 4.881, and 7.415 for nonhypertension, prehypertension, hypertension without medication, hypertension with medication <5 years, and hypertension with medication ≥ 5 years, respectively (Figure 2A); the adjusted HRs for each group were 1 (reference), 1.145, 1.390, 1.853, and 2.344, respectively (Figure 2B). When stratified by both hypertension stage and WC, the risk of new-onset AF increased gradually as the stages of hypertension advanced regardless of WC (Figure 2C and 2D and Table 2). A general trend for a higher risk of new-onset AF was observed as WC increased (Figure 2C and 2D and Table 2). Hypertensive people taking medication ≥5 years with the highest WC had the highest risk for new-onset AF (Figure 2C and 2D and Table 2). The risk of new-onset AF stratified by both hypertension stage and BMI is summarized

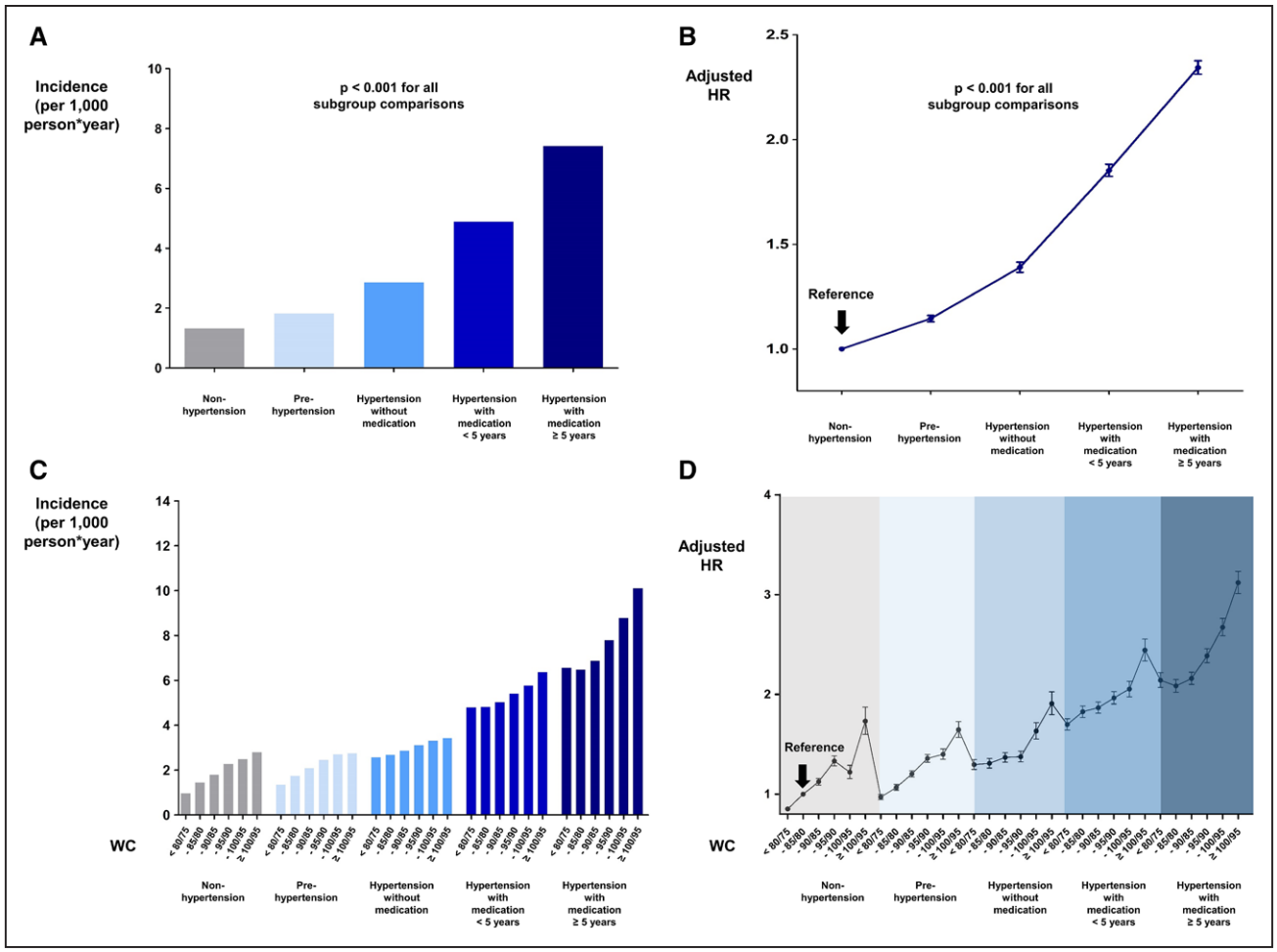

Figure 2. The risk of new-onset atrial fibrillation (AF) stratified by hypertension stage and waist circumference (WC). **A**, The incidence of new-onset AF stratified by the stages of hypertension. **B**, Adjusted hazard ratios (HRs) of new-onset AF stratified by the stages of hypertension. **C**, The incidence of new-onset AF stratified by the stages of hypertension and WC. **D**, Adjusted HRs for new-onset AF stratified by the stages of hypertension and WC. HRs are adjusted for age, sex, smoking status, alcohol consumption, regular physical activity, income, diabetes mellitus, and dyslipidemia.

in Table S2 and also shows a synergistic effect between hypertension and obesity.

Participants were also classified based on their SBP and DBP levels. The incidence of new-onset AF gradually increased with an increase in SBP (adjusted HR: 1 [reference], 1.174, 1.419, and 1.640 for each stage) and DBP (adjusted HR: 1 [reference], 1.143, 1.262, and 1.359 for each stage; Figure 3A and 3B). A multivariate Cox regression analysis also revealed a gradual increase in the HR with increasing SBP and DBP (Figure 3C and Table S3). The incidence of new-onset AF increased by 4.3% per 5 mm Hg increase in SBP and 4.6% per 5 mm Hg increase in DBP (Figure 3C and Table S3). The influence of hypertension on new-onset AF was observed throughout all age groups (Table S4), although the relative influence diminished in old participants, and prehypertension did not increase the risk of new-onset AF in participants ≥60 years. The estimated number of new-onset AF cases attributable to hypertension was 43 826 per year nationwide (Table S5).

BMI and New-Onset AF

In people without hypertension, those who were underweight (adjusted HR, 1.165; 95% CI, 1.127–1.206), upper normal weight (adjusted HR=1.079; 95% CI=1.062–1.096), overweight (adjusted HR, 1.186; 95% CI, 1.167–1.204), or obese (adjusted HR, 1.228; 95% CI, 1.179–1.279) had a significantly higher risk of new-onset AF than the reference group (Table S6). In hypertensive people, those who were overweight (adjusted HR, 1.053; 95% CI, 1.037–1.070) or obese (adjusted HR, 1.314; 95% CI, 1.279–1.350) had an increased risk of new-onset AF. Obesity was associated with an increased risk of new-onset AF throughout the different stages of hypertension (Table S7).

WC was also closely associated with the risk of new-onset AF. Irrespective of the presence of hypertension, a gradual increase in the risk of new-onset AF was observed as the WC increased (Table S6). This gradual increase in the risk of new-onset AF, according to WC, was maintained throughout the different stages of hypertension (Table S7).

Prediction of New-Onset AF

We established an AF risk prediction model by including multiple variables, including hypertension and BMI. The area under the curve was 0.740 (95% CI, 0.738–0.740; $P<0.001$; Table S8).

Table 2. Degree of Hypertension and New-Onset AF

Hypertension Stage	WC (M/F)	n	Event	Person×Years	Incidence (Per 1000 Person×Years)	Incidence (Subgroup)	HR (95% CI)
Nonhypertension	<80/75	1 827 739	14 513	15 115 749	1.320	0.960	0.852 (0.830–0.875)
	–85/80	767 456	9143	6 338 198		1.443	1 (reference)
	–90/85	485 414	7195	4 002 026		1.798	1.124 (1.089–1.159)
	–95/90	215 094	4013	1 768 859		2.269	1.332 (1.283–1.382)
	–100/95	73 930	1508	607 168		2.484	1.221 (1.155–1.289)
	≥100/95	29 184	669	238 844		2.801	1.731 (1.600–1.872)
Prehypertension	<80/75	1 351 127	14 885	11 113 920	1.825	1.339	0.971 (0.946–0.997)
	–85/80	1 011 123	14 471	8 317 055		1.740	1.068 (1.040–1.096)
	–90/85	820 584	14 086	6 741 084		2.090	1.203 (1.172–1.235)
	–95/90	453 686	9105	3 719 268		2.448	1.357 (1.318–1.397)
	–100/95	185 550	4104	1 519 255		2.701	1.400 (1.349–1.453)
	≥100/95	89 826	2018	734 297		2.748	1.646 (1.568–1.727)
Hypertension without medication	<80/75	190 867	3954	1 540 992	2.859	2.566	1.295 (1.248–1.345)
	– 85/80	206 151	4491	1 673 964		2.683	1.309 (1.263–1.356)
	–90/85	210 077	4890	1 708 860		2.862	1.368 (1.321–1.417)
	–95/90	142 769	3604	1 160 585		3.105	1.375 (1.323–1.430)
	–100/95	69 908	1882	567 839		3.314	1.633 (1.554–1.716)
	≥100/95	43 955	1218	356 417		3.417	1.908 (1.797–2.025)
Hypertension with medication <5 y	<80/75	148 800	5667	1 181 105	4.881	4.798	1.698 (1.642–1.756)
	–85/80	189 548	7326	1 523 195		4.810	1.826 (1.770–1.883)
	–90/85	219 679	8907	1 770 952		5.029	1.866 (1.812–1.922)
	–95/90	160 561	6980	1 293 049		5.398	1.964 (1.904–2.027)
	–100/95	82 155	3817	661 520		5.770	2.053 (1.976–2.133)
	≥100/95	49 581	2527	396 832		6.368	2.442 (2.336–2.552)
Hypertension with medication ≥5 y	<80/75	102 899	5244	799 646	7.429	6.558	2.142 (2.070–2.217)
	–85/80	152 936	7814	1 206 433		6.477	2.085 (2.022–2.149)
	–90/85	200 914	10 931	1 589 810		6.876	2.160 (2.100–2.222)
	–95/90	161 918	9959	1 277 686		7.795	2.386 (2.318–2.456)
	–100/95	92 889	6402	729 485		8.776	2.672 (2.587–2.760)
	≥100/95	61 098	4813	476 067		10.110	3.119 (3.010–3.232)

HRs are adjusted for age, sex, smoking, alcohol consumption, regular physical activity, social income, diabetes mellitus, and dyslipidemia. AF indicates atrial fibrillation;

F, female; HR, hazard ratio; M, male; and WC, waist circumference.

Discussion

In this study, we have revealed that (1) both the presence of hypertension and the degree of hypertension are important risk factors for new-onset AF; (2) the risk of new-onset AF increases gradually with the SBP and DBP; (3) both BMI and WC are significantly associated with new-onset AF; and (4) synergistic effect was observed between hypertension and body weight status. The major strength of this study is the sample size: 9 797 418 AF-naive people from a single medical insurance system with blood pressure, BMI, and WC measurements available. Because of our large sample size, we could perform various subgroup analyses, such as those based on different stages of hypertension and body weight status.

Hypertension and New-Onset AF

Hypertension is an established risk factor for new-onset AF. Based on the Framingham Heart study, hypertension increases the risk of AF by ≈1.5-fold.[24] Hypertension, if uncontrolled and long-standing, can lead to LVH, decreased diastolic function, and elevated LA pressure that will eventually lead to LA dilation and fibrosis.[25] Those adverse changes in the LV and LA contribute to the development of new-onset AF.[26–28] We have demonstrated that hypertensive people who have required medication

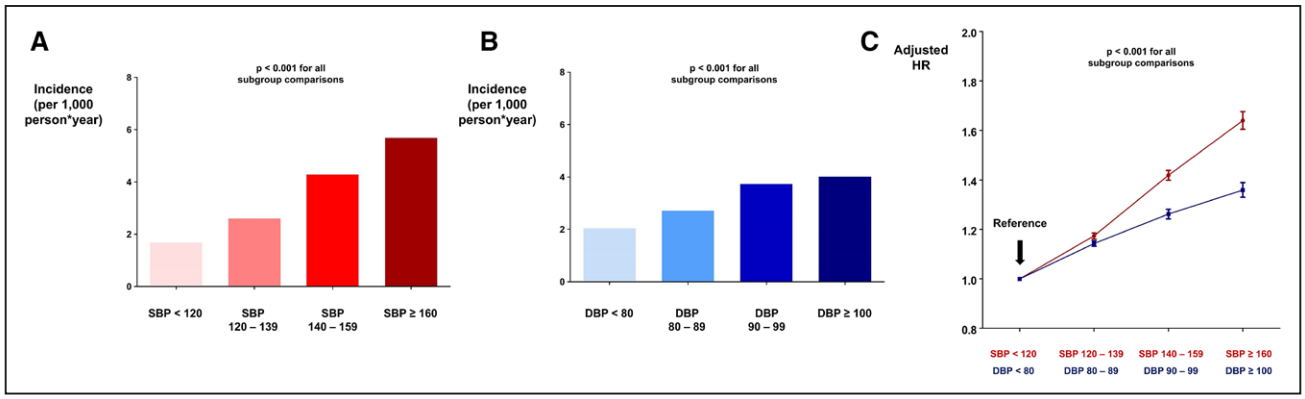

Figure 3. Risk of new-onset atrial fibrillation stratified by degree of systolic blood pressure (SBP) and diastolic blood pressure (DBP). The incidence (**A** and **B**) and adjusted hazard ratio (HR; **C**) of new-onset AF increased gradually with increasing SBP and DBP.

for >5 years had the highest risk of new-onset AF. Furthermore, the risk of new-onset AF showed a linear relationship with SBP and DBP. Thus, uncontrolled and long-standing hypertension is especially dangerous in terms of the occurrence of new-onset AF. As suggested in previous studies,[26–28] LVH and LA dilation are a gradual process, and the time-dependent damage of hypertension appears to be critical to the development of AF.

Whether lowering SBP and DBP can reverse the adverse remodeling of LV and LA is an important issue for future research. In our data, the risk of new-onset AF showed a linear relationship with SBP and DBP. Considering the results of this and previous studies[26–28] describing the underlying mechanism of the increased AF risk in hypertensive people, it might be possible to reverse the adverse effects of hypertension on the LV and LA by maintaining optimal blood pressure, at least in part. This hypothesis should be tested in future clinical trials and studies of nationwide population data.

Body Weight and New-Onset AF

Overweight and obesity are known risk factors for new-onset AF.[29,30] Hypertension, diabetes mellitus, obstructive sleep apnea, inflammation, increased LA size, and oxidative stress are mechanisms that have been proposed to explain the association between obesity and the increased risk of new-onset AF.[29] A previous study by Wang et al[30] reported that the excess risk of new-onset AF in obese people seems to be mediated by LA enlargement, a pathophysiology shared with hypertension. Therefore, obesity and hypertension might act synergistically; our analysis confirmed such synergistic action, with hypertensive people with a high WC or BMI having the highest risk of new-onset AF (Figure 2C and 2D). WC showed a linear relationship with new-onset AF, with a higher WC correlating with an increased risk of new-onset AF. In our data, WC showed a more linear relationship with new-onset AF than BMI (Table S6), suggesting that abdominal obesity is also an important factor for new-onset AF. Irrespective of the presence of hypertension, both BMI and WC are important, potentially modifiable determinants of new-onset AF. Therefore, the effect of achieving an optimal BMI and WC should be tested in future studies.

Limitations

This study has several limitations. First, because we analyzed an administrative database, our study is vulnerable to errors originating from coding inaccuracies. Second, we could not classify the AF type (paroxysmal or nonparoxysmal). Third, our data are based on East Asian people, so caution is required when applying our results to other ethnic groups. Fourth, no echocardiographic data were available. Because the underlying link between hypertension and AF is thought to be LV and LA remodeling, echocardiographic data would have significantly enhanced the findings of our research. Fifth, some of our findings were previously reported. However, we have here confirmed what many authors have previously found in studies with smaller sample sizes.

Conclusions

The degree and duration of hypertension are important factors associated with new-onset AF. Body weight status is also a significant determinant of new-onset AF. Furthermore, hypertension and obesity acted synergistically, with obese and hypertensive people having the highest risk for new-onset AF. A subsequent large-scale study is needed to confirm whether medical interventions to lower blood pressure and achieve optimal body weight could reduce the population burden of AF.

Perspectives

Our results suggest degree and duration of hypertension are important risk factors for new-onset AF. Obesity was also associated with new-onset AF and synergism was observed between hypertension and obesity, indicating that maintaining adequate blood pressure and body weight might prevent new-onset AF.

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Disclosures

None.

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Novelty and Significance

What Is New?

- Significantly large sample size (80 130 161 person×years follow-up) enabled us to perform various subgroup analyses to evaluate relationship among hypertension, body weight status, and new-onset atrial fibrillation (AF).

What Is Relevant?

- Not only the presence of hypertension but also its severity and duration are important factors for new-onset AF. New-onset AF was also related to body mass index and waist circumference, with obese patients having a higher risk. Synergism was observed between hypertension and obesity.

Summary

Upstream therapy to prevent AF is important. Our study suggests that obtaining an optimal blood pressure and body weight may have the potential to reduce the AF burden of a given population.