**Risks of atrial fibrillation in young adults with isolated diastolic hypertension, isolated systolic hypertension and systolic-diastolic hypertension: A nationwide cohort study**

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**Abstract**

**Background:** There is limited evidence regarding the comparative risks of incident atrial fibrillation (AF) associated with stage 1 isolated systolic hypertension (ISH), isolated diastolic hypertension (IDH), and systolic diastolic hypertension (SDH), especially amongst young adults aged 20 to 39 years.

**Methods:** From the Korean nationwide health screening database, 2,958,544 subjects aged 20 to 39 years who were not prescribed antihypertensive medication at the index examination in 2009 were included. Subjects were categorized into 8 groups according to the 2017 American College of Cardiology/American Heart Association blood pressure (BP) guideline; normal BP , elevated BP, stage 1 IDH, stage 1 ISH, stage 1 SDH, stage 2 IDH, stage 2 ISH, and stage 2 SDH. The primary outcome was new-onset AF during follow-up.

**Results:** During a median follow-up of 8.3 years, 7,347 subjects had incident AF (incidence rate of 0.3 per 1,000 person-years). Compared to the normal BP group, stage 1 IDH (adjusted hazard ratio [HR] 1.160, 95% confidence interval [CI] 1.086-1.240) and stage 1 SDH (1.250, 1.165-1.341) were associated with higher risks of incident AF, but not stage 1 ISH. Stage 2 IDH, ISH, and SDH were associated with higher risks of incident AF by 24%, 37%, and 61%, respectively. As continuous variables, SBP ≥140 mmHg and DBP ≥70 mmHg were associated with a statistically significant higher risk of incident AF.

**Conclusions:** Among young adults, stage 1 IDH and SDH were associated with a higher risk of incident AF compared to those with normal BP. The risk of incident AF with stage 2 IDH was similar to that of stage 1 SDH. Optimal control of diastolic BP is crucial for preventing new-onset AF, even amongst young adults.

**Keywords:** atrial fibrillation, hypertension, blood pressure, young adult

**Introduction**

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and increases the risk of cardiovascular events, including stroke, heart failure, and all-cause death [1-3]. Since the prevalence of AF is high in the elderly population, this population easily meets the criteria for initiation of oral anticoagulation therapy for stroke prevention when stroke risk factors such as hypertension are present [3-5]. In contrast, the risks associated with incident AF in the younger population are under-studied.

Although AF is relatively rare in the young population, the relative risk of death for patients with AF compared to the general population remains more prominent at a younger age [6]. Also, AF is closely associated with a higher risk of major adverse cardiovascular events, including stroke, heart failure, cardiovascular death and all-cause death as well as impaired quality of life and higher risk of cognitive dysfunction or incident dementia [3,5,7,8]. If AF starts from a young age, this could lead to lifetime-long exposure, markedly increasing the overall health-care burden. Thus, accurately identifying modifiable risk factors and directing more attention to primary prevention of AF would be the best approach to reduce AF-related complications in the young population.

Hypertension is one of the most prevalent risk factors for AF [9,10]. Among the young population aged 20 to 39 years, 50% of the total population had stage 1 (systolic, 130-139 mmHg; diastolic, 80-89 mmHg) or 2 (systolic ≥140 mmHg; diastolic ≥90 mmHg) hypertension in South Korea [11]. However, disease awareness, rate of treatment utilisation, and achievement of optimal blood pressure (BP) were less common especially in the young population with hypertension when compared to an older population with hypertension [12,13].

In a previous study, a high diastolic BP (80 to 89 mmHg) had a higher risk of incident AF compared with those with a normal diastolic BP (<80 mmHg), but a higher systolic BP (120 to 139 mmHg) and the BP ranged systolic 120-139 or diastolic 80-89 mmHg (previously defined as prehypertension) did not show significant association with the risk of incident AF in the healthy general population [14]. Recently, the young population with stage 1 hypertension, whether stage 1 isolated systolic or diastolic hypertension (ISH and IDH), was associated with an increased risk of future cardiovascular disease compared to those with normal BP [15]. However, there was limited data on the association between early stages of hypertension, such as stage 1 ISH or IDH, and the risk of AF, especially in the young population.

In this study using nationwide health screening data from the Korean National Health Insurance database, we evaluated the risk of incident AF associated with hypertension stratifying from early stages to stage 2 hypertension among young adults aged 20 to 39 years.

**Methods**

**Data sources and study population**

This study was based on the Korean national general health screening database linked with the Korean National Health Insurance Service (NHIS) database [16,17]. Briefly, all Korean are mandatorily included as the beneficiaries of NHIS and the NHIS provides comprehensive and universal coverage to its beneficiaries. The NHIS database includes the beneficiaries’ sociodemographic information, medical claims, including information on the diagnoses identified by the 10th revision of the International Classification of Disease (ICD-10) codes, prescription, treatment, and admission. Among all beneficiaries, for the adult population, the National Health Insurance Corporation recommends and provides the national general health screening examination biennially. The examination includes a physical exam, including anthropometric measurement and BP measurement, regular blood tests, chest X-ray, and questionnaires on subjects’ medical history.

Based on this dataset, we firstly identified the subjected aged 20 to 39 years who received a national health screening examination in 2009 (n=3,307,229). Those with any medication for prevalent hypertension, diabetes mellitus, or dyslipidemia within 1-year before index health examination were excluded (n=123,497). Also, subjects with prevalent AF (n=3,747) and those with missing values among health examination parameters (n=194,441) were excluded from the analysis.

This study was exempted from review by the Seoul National University Hospital Institutional Review Board (E-2012-109-1183). All data and materials have been available after the approval for the request to access the dataset from qualified researchers (National Health Insurance Sharing Service assessed at http://nhiss.nhis.or/kr/bd/ab/bada000eng.do.)

**Classification of BP groups and other covariates**

BP was measured during the general health screening examination by a trained clinician. After at least 5 minutes of rest with a seated position, two repeated BP measurements were performed in a 5-minute interval using auscultatory or oscillometric methods [18]. Study population were categorized into eight groups according to BP ranges as follow: (1) systolic BP (SBP) <120 mmHg and diastolic BP (DBP) <80mmHg as a normal BP group; (2) SBP 120-129 mmHg and DBP <80 mmHg as elevated BP group; (3) SBP <130 mmHg and DBP 80-90 mmHg as a stage 1 IDH group; (4) SBP 130-139 mmHg and DBP <80 mmHg as a stage 1 ISH group; (5) SBP 130-139 mmHg and DBP 80-89 mmHg as a stage 1 SDH group; (6) SBP <140 mmHg and DBP ≥90 mmHg as a stage 2 IDH group; (7) SBP ≥140 mmHg and DBP <90 mmHg as a stage 2 ISH group; and (8) SBP ≥140 mmHg and DBP ≥90 mmHg as a stage 2 SDH group [19].

Subjects’ demographic information, including age and sex and comorbidities such as hypertension, diabetes mellitus, dyslipidemia, heart failure, previous myocardial infarction, previous stroke, and chronic kidney disease, were collected. Detailed definitions of comorbidities are presented in **Supplementary Table 1** [4,17]. Charlson Comorbidity Index (CCI) was calculated to estimate the burden of comorbidities (**Supplementary Table 2**) [20]. Body mass index (BMI) calculated by body weight in kilograms divided by the square of height in meters, fasting glucose, total cholesterol, and estimated glomerular filtration rate (eGFR) were collected from the health screening examinations. From the self-reported questionnaires in the examinations, smoking status (non, ex-smoker, and current smoker), alcohol consumption (non, mild to moderate [<30 g/day], and heavy [≥30 g/day]), and exercise status. Regular exercise was defined as performing moderate physical activity (defined as ≥30 min per day of brisk walking, dancing, or gardening) at least 5 times per week or strenuous physical activity (defined as ≥20 min per day of running fast, cycling, or aerobic) at least 3 times per week [21,22]. Low income was defined as a household income level at the lower 25%.

**Study outcome and follow-up**

The primary outcome was incident AF. New-onset AF was identified when subjects had the relevant diagnostic codes (ICD-10 codes, I480-I484, and I489) among their claims either one diagnosis during hospitalization or at least two diagnoses in the outpatient clinic during follow-up [3,4,14,17]. Subjects were followed up until the end of the study period (December 31, 2017) or death.

**Statistical analysis**

Baseline characteristics of study subjects are presented using mean ± standard deviation for continuous variables and number (percentage) for categorical variables. A linear trend test using a generalized linear model for continuous variables and the Cochran-Armitage trend test for categorical variables were used to compare the baseline characteristics across different BP groups. The incidence rate of new-onset AF was calculated by dividing the number of AF events by the total follow-up duration (per 1,000 person-years) for each BP group. The cumulative incidence of AF, according to the BP groups, was analyzed using the Kaplan-Meier method. The association between the BP groups and the incidence of AF was assessed using the Cox proportional hazards regression using hazard ratio (HR) and 95% confidence interval (CI), with subjects with normal BP as the reference group. Unadjusted HRs were analyzed in model 1, and HRs were adjusted for age and sex in model 2. In model 3, HRs were adjusted for age, sex, diabetes mellitus, dyslipidemia, heart failure, previous myocardial infarction, previous stroke, chronic kidney disease, BMI, smoking status, alcohol consumption, regular exercise, and low income. Covariates included in the multivariable Cox model were selected a priori based on their known associations with AF risk [5,10,23]. Cubic spline curves for adjusted HRs and 95% CIs by model 3 were constructed to visualize the association between SBP or DBP as a continuous variable and AF risk. The proportional hazards assumption was tested by graphical inspection of log-minus-log plot and Schoenfeld residuals. The results showed parallel log-log survival curves and random patterns in Schoenfeld residuals, indicating no significant departure from the proportionality assumption.

All statistical analyses in this study were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA), and a P-value <0.05 indicated statistical significance.

**Subgroup analyses**

Subgroup analyses were performed, stratifying the study population by age subgroups (20 to 29 years and 30 to 39 years) and sex.

**Sensitivity analysis**

Although we excluded subjects treated with antihypertensive medication before the study period, considering the effect of hypertension treatment initiated during follow-up, we performed a sensitivity analysis whereby subjects who initiated antihypertensive medication during follow-up were censored.

**Results**

A total of 2,958,544 subjects (mean age 31.3±4.8 years, 64.5% of men) were finally included in this analysis (**Figure 1**). Baseline characteristics of the total study population are described in **Supplementary Table 3**. Among total study population, 46.8% (n=1,384,262) were classified as the normal BP group, 11.5% (n=341,321) had elevated BP, 17.4% (n=516,009) had stage 1 IDH, 4.2% (n=124,947) had stage 1 ISH, 13.5% (n=399,032) had stage 1 SDH, 1.9% (n=56,738) had stage 2 IDH, 1.3% (n=39,033) had stage 2 ISH, and 3.2% (n=97,202) had stage 2 SDH. Baseline characteristics of each group are presented in **Table 1**.

Subjects with a more advanced stage of hypertension tended to be older, more likely to be men, showed a higher prevalence of comorbidities such as diabetes mellitus, dyslipidemia, and prior myocardial infarction. Subjects with a more advanced stage of hypertension also had higher mean BMI, fasting glucose, and TC and showed a higher prevalence of current smokers and heavy drinkers.

**Primary analysis: association between BP groups and AF risk**

During a median follow-up of 8.3 years (interquartile ranges 8.1-8.5), 7,347 (0.25% of the total study population, incidence rate of 0.3 per 1,000 person-years) had new-onset AF. Comparison of baseline characteristics according to incident AF and the results of univariable Cox regression analysis are presented in **Supplementary Table 3**. AF incidence rates per 1,000 person-years were 0.23 for normal BP, 0.29 for elevated BP, 0.33 for stage 1 IDH, 0.32 for stage 1 ISH, 0.39 for stage 1 SDH, 0.42 for stage 2 IDH, 0.46 for stage 2 ISH, and 0.58 for stage 2 SDH (**Table 2 and Figure 2**)**. Figure 3** shows the cumulative incidence curves.

In unadjusted Cox analysis (model 1), subjects with stage 1 IDH, stage 1 ISH, and stage 1 SDH were associated with a higher risk for incident AF compared to the normal BP group (**Table 2**). Although the associations were attenuated in multivariable Cox analysis (model 3), stage 1 IDH and stage 1 SDH were respectively associated with 16% and 25% higher risk of incident AF than the normal BP group (**Table 2** and **Figure 2**). Stage 1 ISH did not show a significant association with the risk of AF after multivariable adjustment. Stage 2 IDH, ISH, and SDH were all significantly associated with a higher risk of AF compared to normal BP in the unadjusted (model 1) and multivariable (model 3) Cox analyses (**Table 2** and **Figure 2**). After multivariable adjustment, all stage 2 groups were significantly associated with a higher risk of incident AF by 24%, 37%, and 61%, respectively, than normal BP.

As continuous variables, SBP 140 mmHg or higher and DBP 70 mmHg or higher showed statistically significant association with a higher risk of AF in cubic-spline curves of adjusted HR (95% CI) (**Figure 4**). This finding was consistent with the main results that stage 1 IDH, stage 1 SDH, and all stage 2 groups were associated with higher risks of AF.

**Subgroup analyses**

Subgroup analyses stratifying the total study population by age (20 to 29 years and 30 to 39 years) and sex were performed.

The incidence rates of subjects aged 20 to 29 years were lower than those aged 30 to 39 years in the same BP groups (**Supplementary Table 4**). In subjects aged 30 to 39, the association between BP groups and AF risk were consistent with the results of the primary analysis, while only stage 1 IDH, stage 1 SDH, and stage 2 ISH groups remained significantly associated with a higher risk of AF in those with aged 20 to 29 years (p-for-interaction = 0.034).

Likewise, in age subgroups, men showed higher incidence rates than women in the same BP group (**Supplementary Table 5**). In men, the association between BP groups and AF risk was consistent with the results of primary analysis. Elevated BP, stage 1 IDH, and stage 2 ISH groups were significantly associated with a higher risk of AF than normal BP in the women subgroup. There was a significant interaction between men and women subgroups on the association between BP groups and AF risk (p-for-interaction = 0.008).

Although there were interactions between certain subgroups and the association between BP groups and AF risk, the consistent finding was that stage 1 IDH was significantly associated with a higher risk of AF (**Supplementary Tables 4 and 5**).

**Sensitivity analysis**

Of the stage 1 IDH group in this study, only less than 0.1% of subjects with stage 1 IDH initiated antihypertensive medication during follow-up (**Supplementary Table 7**). In follow-up BP measurement during the study period, a substantial proportion of stage 1 IDH at the index health examination stayed in stage 1 IDH (25.5%), while 3.9% were classified as stage 1 ISH, 16.3% were classified as stage 1 SDH, and 7.6% were classified as stage 2 hypertension (**Supplementary Figure**).

After censoring subjects who initiated antihypertensive medication during follow-up, stage 1 IDH, stage 1 SDH, stage 2 IDH, stage 2 ISH, and stage 2 SDH remained significantly associated with a higher risk of incident AF, while the HRs were attenuated compared to the primary analysis (**Supplementary Table 6** and **Figure 5**).

**Discussion**

In this nationwide population-based study, including a large number of Korean young adults aged 20 to 39 years (n=2,958,544), we demonstrated the associations between BPs categorized by the 2017 ACC/AHA classification and the risk of incident AF. This study has the following principal findings: (i) according to the 2017 ACC/AHA BP classification, a substantial proportion of young adults aged 20 to 39 years (42%) had hypertension; (ii) not only stage 2 hypertension, but stage 1 IDH and stage 1 SDH were significantly associated with higher risks of incident AF by 16% and by 25%, respectively; (iii) in subjects aged 20 to 29 years, stage 1 IDH and stage 1 SDH were consistently associated with higher risks of incident AF by 22% and 33%, respectively; and (iv) SBP lower than 140 mmHg and DBP lower than 70 mmHg might be an optimal target to reduce the future risk of incident AF in young adults.

AF occurs symptoms, impairs quality of life, and is associated with increased risk of major cardiovascular and cerebral events [1-3, 5-7]. Development of an abnormal atrial substrate and disease progression is a chronic process in patients with AF, and several risk factors such as age, hypertension, diabetes mellitus, obesity, and lifestyle factors are involved [10]. To prevent AF, early recognition and treatment of modifiable risk factors for AF is crucial.

The abnormal atrial substrate, including left atrial enlargement, atrial fibrosis, increased conduction heterogeneity, and variable changes in atrial refractoriness attributable to hypertension, have been well-demonstrated in several experimental models [10]. In human electrophysiological studies, hypertension was associated with increasing atrial low voltage zone, slowing atrial conduction velocity, and increasing electrogram fractionation [24]. Epidemiologically, hypertension is one of the most common risk factors for AF [9,14,25,26]. However, the definition of hypertension varied in different studies.

In one historical observational study, hypertension was defined as an SBP of at least 160 mmHg or a DBP of at least 95 mmHg, and hypertension was a significant predictor of AF (odds ratio [OR] 1.5, 95% CI 1.2-2.0 in men, OR 1.4, 95% CI 1.1-1.8 in women) [9]. In the subgroup enrolled in the Framingham Heart Study between 1998 and 2007, hypertension treatment was associated with an increased risk of incident AF (HR 1.32, 95% CI 1.08-1.60), but the various SBP ranges from 120-129 mmHg, 130-139 mmHg, 140-159 mmHg, and ≥160 mmHg did not show significant association with the risk of AF [24]. In a previous study included middle-aged women, SBP 130-139 mmHg (HR 1.28, 95% CI 1.00-1.63) and DBP from 85-89 mmHg (HR 1.53, 1.05-2.23) were associated with a significantly higher risk of AF [25]. Considering the impact of “previously defined” prehypertension on the risk of AF in a healthy Asian population, SBP 120-139 mmHg did not show significant association with increased risk of AF compared to SBP <120 mmHg, but DBP 80-89 mmHg was associated with increased risk of AF (HR 1.11, p=0.045) when compared to DBP <80 mmHg [14,27]. However, this study defined those with hypertension by 2017 ACC/AHA classification as prehypertension. Still, the association between the early stage of hypertension and the risk of incident AF is unclear, especially amongst the younger population.

In 2017, the ACC/AHA BP management guideline suggested a new definition of hypertension starting from BP of 130/80 mmHg based on several studies reporting that the stage 1 hypertension BP range was associated with a higher risk of cardiovascular disease [19]. After the update of this guideline, large-scale observational studies demonstrated that stage 1 hypertension, even IDH or ISH, was associated with a higher risk of cardiovascular disease [11,15]. Although a substantial proportion of the adult population are being classified as hypertensive patients [28], limited data are available regarding the clinical impact of stage 1 hypertension on the risk of AF.

In a recent study, prehypertension (either SBP 120-139 mmHg or DBP 80-89 mmHg) and hypertension (SBP ≥140 mmHg or DBP ≥90 mmHg) had a more prominent contributory role to the development of incident AF in the younger age group than in older age group [29]. Prehypertension did not show a significant association with incident AF (HR 1.000, 95% CI 0.964-1.037) when compared to non-hypertension among subjects older than 70 years, but prehypertension was significantly associated with a higher risk of AF (HR 1.256, 95% CI 1.154-1.366) among young adults aged 20-29 years. In the present study, based on the new BP classification, we demonstrated that stage 1 IDH and stage 1 SDH were significantly associated with higher risks of incident AF, which was consistently observed in subgroup analyses and sensitivity analysis. Early-onset hypertension can be easily under-recognized, its risks under-estimated, and the condition under-treated, even though it had a great clinical impact on the risks of cardiovascular disease, including incident AF and all-cause death compared to late-onset hypertension [13,29-31].

In our study, subjects with stage 1 IDH were significantly associated with a higher risk of AF and the risk of AF increased from DBP ≥70 mmHg. ~~Of the stage 1 IDH group in this study, only less than 0.1% of subjects with stage 1 IDH initiated antihypertensive medication during follow-up (~~**~~Supplementary Table 7~~**~~). In follow-up BP measurement during the study period, a substantial proportion of stage 1 IDH at the index health examination stayed in stage 1 IDH (25.5%), while 3.9% were classified as stage 1 ISH, 16.3% were classified as stage 1 SDH, and 7.6% were classified as stage 2 hypertension (~~**~~Supplementary Figure~~**~~).~~ Although the HRs were attenuated in a multivariable analysis, stage 1 IDH to stage 1 ISH or stage 1 SDH, or stage 2 hypertension showed an increased risk of AF by 22%, 38%, and 92%, respectively, compared to the group “stage 1 IDH to normal BP”. Our results therefore suggest that young adults with hypertension might benefit from early detection, and intensive control of BP, including lifestyle intervention and antihypertensive therapy, given their considerably longer lifetime exposure to high BP.

**Limitations**

Although the gold-standard method for AF diagnosis is an electrocardiogram, the nationwide claims database and health screening examination database did not include actual data on the 12-lead electrocardiogram. During follow-up, incident AF was identified using relevant diagnostic codes; therefore, the diagnosis of AF could be under-or over-estimated. Second, we did not include family history of AF and could not consider genetic factors related to AF risk. Third, we excluded the patients who were taking antihypertensive medications and in this observational study, we could not assess the optimal target BP for patients who were prescribed antihypertensive drugs. Further studies are needed to define the optimal BP goals to reduce the future risk of AF. Lastly, although we partially addressed the initiation of antihypertensive medication and BP changes during follow-up, more comprehensive analyses are warranted to consider trajectories of BP during long-term follow-up [32]

**Conclusions**

Among young adults, stage 1 IDH and SDH were associated with a higher risk of incident AF compared to those with normal BP. The risk of incident AF with stage 2 IDH was similar to that of stage 1 SDH. Optimal control of diastolic BP is crucial for preventing new-onset AF, even amongst young adults.

**Disclosures**

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**Figure legends**

**Figure 1. Study enrollment flow**

**Figure 2. Incidence rates and multivariable adjusted (model 3) hazard ratios for incident AF in different BP groups**

Abbreviation: AF, atrial fibrillation; BP, blood pressure; CI, confidence interval; HR, hazard ratio; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; SDH, systolic diastolic hypertension.

**Figure 3. Cumulative AF incidence by Kaplan-Meier methods according to BP groups**

Abbreviation: AF, atrial fibrillation; BP, blood pressure; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; SDH, systolic diastolic hypertension.

**Figure 4. Adjusted cubic-spline curves for the association between BP and the risk of AF**

**(A) SBP**

**(B) DBP**

Red arrows indicated the points that 95% CI ranges met the baseline.

Abbreviation: AF, atrial fibrillation, BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; SBP, systolic blood pressure.

**Figure 5.** **Sensitivity analysis: censoring subjects who initiated antihypertensive medication during follow-up period, incidence rates and multivariable adjusted (model 3) hazard ratios for incident AF in different BP groups**

Abbreviation: AF, atrial fibrillation; BP, blood pressure; CI, confidence interval; HR, hazard ratio; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; SDH, systolic diastolic hypertension.

**Table 1. Baseline characteristics of the study population**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Normal BP**  **(n=1,384,262)** | **Elevated BP**  **(n=341,321)** | **Stage 1 hypertension** | | |  | **Stage 2 hypertension** | | | **p-value** |
| **Stage 1 IDH**  **(n=516,009)** | **Stage 1 ISH**  **(n=124,947)** | **Stage 1 SDH**  **(n=399,032)** |  | **Stage 2 IDH**  **(n=56,738)** | **Stage 2 ISH**  **(n=39,033)** | **Stage 2 SDH**  **(n=97,202)** |
| **Age** |  |  |  |  |  |  |  |  |  |  |
| **Mean (years)** | 30.5±4.9 | 31.2±4.5 | 31.5±4.8 | 31.3±4.7 | 31.9±4.6 |  | 32.8±4.4 | 32.2±4.5 | 33.0±4.3 | <0.001 |
| **30-39 years** | 754,793  (54.5) | 207,768  (60.9) | 325,310 (63.0) | 77,328  (61.9) | 268,069  (67.2) |  | 42,355  (74.7) | 27,119  (69.5) | 74,365  (76.5) | <0.001 |
| **Men** | 657,588  (47.5) | 244,551  (71.7) | 375,358  (72.7) | 106,364  (85.1) | 350,722  (87.9) |  | 48,830  (86.1) | 35,561  (91.1) | 89,529  (92.1) | <0.001 |
| **Comorbidities** |  |  |  |  |  |  |  |  |  |  |
| **Hypertension** | 589  (0.04) | 222  (0.1) | 494  (0.1) | 134  (0.1) | 1,033  (0.3) |  | 56,738  (100) | 39,033  (100) | 97,202  (100) | <0.001 |
| **Diabetes mellitus** | 10,911  (0.8) | 4,669  (1.4) | 8,149  (1.6) | 2,612  (2.1) | 10,394  (2.6) |  | 1,821  (3.2) | 1,603  (4.1) | 5,268  (5.4) | <0.001 |
| **Dyslipidemia** | 60,645  (4.4) | 21,010  (6.2) | 37,804  (7.3) | 9,692  (7.8) | 40,084  (10.1) |  | 7,009  (12.4) | 4,981  (12.8) | 15,450  (15.9) | <0.001 |
| **Heart failure** | 348  (0.03) | 110  (0.03) | 106  (0.02) | 38  (0.03) | 110  (0.03) |  | 21  (0.04) | 10  (0.03) | 32  (0.03) | 0.017 |
| **MI** | 803  (0.06) | 227  (0.07) | 318  (0.06) | 91  (0.07) | 289  (0.07) |  | 51  (0.09) | 24  (0.06) | 76  (0.08) | 0.001 |
| **Previous stroke** | 569  (0.04) | 163  (0.05) | 224  (0.04) | 46  (0.04) | 167  (0.04) |  | 41  (0.07) | 16  (0.04) | 59  (0.06) | 0.002 |
| **CKD** | 37,865  (2.7) | 8,692  (2.6) | 10,071  (2.0) | 4,335  (3.5) | 9,129  (2.3) |  | 754  (1.3) | 650  (1.7) | 1,616  (1.7) | <0.001 |
| **CCI** |  |  |  |  |  |  |  |  |  |  |
| **0** | 1,055,904  (76.3) | 265,097  (77.7) | 400,910  (77.7) | 99,251  (79.4) | 317,593  (79.6) |  | 44,361  (78.2) | 31,244  (80.1) | 78,259  (80.5) | <0.001 |
| **1** | 260,267  (18.8) | 60,870  (17.9) | 91,426  (17.7) | 20,450  (16.4) | 65,066  (16.3) |  | 9,752  (17.2) | 6,204  (15.9) | 14,884  (15.3) |  |
| **2** | 52,552  (3.8) | 11,794  (3.5) | 17,092  (3.5) | 3,974  (3.2) | 12,350  (3.1) |  | 1,904  (3.4) | 1,195  (3.1) | 2,912  (3.0) |  |
| **≥3** | 15,539  (1.1) | 3,560  (1.0) | 5,771  (1.1) | 1,272  (1.0) | 4,023  (1.0) |  | 721  (1.3) | 390  (1.0) | 1,147  (1.2) |  |
| **Health exam** |  |  |  |  |  |  |  |  |  |  |
| **BMI (kg/m2)** | 21.9±3.0 | 23.3±3.2 | 23.4±3.3 | 24.2±3.3 | 24.7±3.5 |  | 25.2±3.7 | 25.8±3.7 | 26.4±3.9 | <0.001 |
| **Fasting glucose**  **(mg/dL)** | 88.5±12.3 | 90.9±13.9 | 90.8±14.9 | 92.8±15.3 | 93.4±17.2 |  | 94.4±19.2 | 96.5±20.3 | 97.9±22.9 | <0.001 |
| **SBP (mmHg)** | 107.9±7.2 | 122.6±3.0 | 119.6±4.9 | 132.6±2.9 | 132.2±3.1 |  | 129.3±5.8 | 144.7±5.9 | 148.6±9.4 | <0.001 |
| **DBP (mmHg)** | 67.6±5.9 | 71.5±4.3 | 80.9±2.1 | 73.1±4.1 | 82.4±3.1 |  | 91.8±3.5 | 81.6±5.0 | 96.4±6.9 | <0.001 |
| **TC (mg/dL)** | 180.3±31.8 | 185.2±33.1 | 188.0±33.7 | 188.7±34.1 | 193.9±34.8 |  | 197.3±35.8 | 197.6±36.3 | 202.8±36.9 | <0.001 |
| **GFR (ml/min)** | 95.9±61.1 | 97.1±69.1 | 93.5±47.5 | 94.3±56.0 | 91.8±40.8 |  | 95.0±55.5 | 96.8±63.9 | 93.2±47.1 | <0.001 |
| **Smoking** |  |  |  |  |  |  |  |  |  | <0.001 |
| **Non** | 865,329  (62.5) | 160,896  (47.1) | 235,589  (45.7) | 47,300  (37.9) | 137,065  (34.4) |  | 20,091  (35.4) | 12,796  (32.8) | 29,015  (29.9) |  |
| **Ex-smoker** | 125,994  (9.1) | 42,125  (12.3) | 63,537  (12.3) | 17,495  (14.0) | 58,262  (14.6) |  | 8,504  (15.0) | 5,714  (14.6) | 14,892  (15.3) |  |
| **Current smoker** | 392,939  (28.4) | 138,300  (40.5) | 216,883  (42.0) | 60,152  (48.1) | 203,705  (51.1) |  | 28,143  (49.6) | 20,523  (52.6) | 53,295  (54.8) |  |
| **Alcohol** |  |  |  |  |  |  |  |  |  | <0.001 |
| **Non** | 591,468  (42.7) | 117,161  (34.3) | 169,281  (32.8) | 36,557  (29.3) | 103,672  (26.0) |  | 14,622  (25.8) | 10,078  (25.8) | 20,688  (21.3) |  |
| **Mild to moderate** | 710,971  (51.4) | 192,603  (56.4) | 292,680  (56.7) | 73,128  (58.5) | 237,740  (59.6) |  | 33,154  (58.4) | 22,470  (57.6) | 57,398  (59.1) |  |
| **Heavy** | 81,823  (5.9) | 31,557  (9.3) | 54,048  (10.5) | 15,262  (12.2) | 57,620  (14.4) |  | 8,962  (15.8) | 6,485  (16.6) | 19,116  (19.7) |  |
| **Regular exercise** | 172,598  (12.5) | 49,409  (14.5) | 74,873  (14.5) | 19,714  (15.8) | 61,510  (15.4) |  | 8,475  (14.9) | 6,003  (15.4) | 14,207  (14.6) | <0.001 |
| **Low income** | 371,378  (26.8) | 91,450  (26.8) | 129,898  (25.2) | 31,618  (25.3) | 86,417  (21.7) |  | 12,459  (22.0) | 9,353  (24.0) | 18,812  (19.4) | <0.001 |
| **Follow-up,**  **Median [IQR]**  **(years)** | 8.3  [8.1-8.5] | 8.2  [8.1-8.5] | 8.3  [8.1-8.6] | 8.2  [8.1-8.5] | 8.3  [8.1-8.6] |  | 8.2  [8.1-8.5] | 8.2  [8.1-8.5] | 8.2  [8.1-8.5] | <0.001 |

Abbreviation: BMI, body mass index; BP, blood pressure; CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; DBP, diastolic blood pressure; GFR, glomerular filtration rate; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; IQR, interquartile range; MI, myocardial infarction; SBP, systolic blood pressure; SDH, systolic diastolic hypertension; TC, total cholesterol.

**Table 2. The risk of incident atrial fibrillation by blood pressure groups**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Group** | **Number** | **AF** | **IR** | **Model 1**  **HR (95% CI)** | **Model 2**  **HR (95% CI)** | **Model 3**  **HR (95% CI)** |
| **Normal BP** | 1,384,262 | 2,678 | 0.23 | 1 (reference) | 1 (reference) | 1 (reference) |
| **Elevated BP** | 341,321 | 819 | 0.29 | 1.245 (1.151-1.347) | 1.090 (1.007-1.179) | 1.058 (0.977-1.145) |
| **Stage 1 IDH** | 516,009 | 1,403 | 0.33 | 1.406 (1.318-1.500) | 1.205 (1.129-1.287) | 1.160 (1.086-1.240) |
| **Stage 1 ISH** | 124,947 | 331 | 0.32 | 1.378 (1.229-1.544) | 1.146 (1.021-1.286) | 1.083 (0.965-1.216) |
| **Stage 1 SDH** | 399,032 | 1,305 | 0.39 | 1.693 (1.584-1.809) | 1.344 (1.255-1.440) | 1.250 (1.165-1.341) |
| **Stage 2 IDH** | 56,738 | 197 | 0.42 | 1.808 (1.564-2.089) | 1.372 (1.186-1.588) | 1.241 (1.071-1.438) |
| **Stage 2 ISH** | 39,033 | 147 | 0.46 | 1.970 (1.669-2.326) | 1.526 (1.291-1.804) | 1.372 (1.159-1.624) |
| **Stage 2 SDH** | 97,202 | 467 | 0.58 | 2.509 (2.274-2.768) | 1.849 (1.672-2.044) | 1.612 (1.453-1.789) |
| p-for-trend | | | | <0.001 | <0.001 | <0.001 |

Model 1: unadjusted

Model 2: age and sex-adjusted

Model 3: age, sex, diabetes mellitus, dyslipidemia, heart failure, myocardial infarction, previous stroke, chronic kidney disease, body mass index, smoking status, alcohol consumption, regular exercise, and low income.

Abbreviation: AF, atrial fibrillation; BP, blood pressure; CI, confidence interval; HR, hazard ratio; IDH, isolated diastolic hypertension; IR, incidence rate; ISH, isolated systolic hypertension; SDH, systolic diastolic hypertension.