Underweight Is A Major Risk Factor of Atrial Fibrillation In Asian People With Type 2 Diabetes Mellitus

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Abstract

Background: Atrial fibrillation (AF) is prevalent in patients with type 2 diabetes mellitus (T2DM). Obesity commonly accompanies with T2DM and increases AF incidence. However, the dose-relationship of body mass index (BMI) and the risk of AF has seldom been studied in diabetes patients.

Methods: This cohort study was conducted utilizing a database from National Taiwan University Hospital, a tertiary medical center in Taiwan. Between 2014 and 2019, a total of 64339 adult patients with T2DM were enrolled for analysis. The BMI was measured and categorized into several groups including underweight (BMI <18.5), normal range (18.5 ≤ BMI <24), overweight (24 ≤ BMI <27), obesity class 1 (27 ≤ BMI <30), obesity class 2 (30 ≤ BMI <35), and obesity class 3 (BMI ≥35). Multivariate Cox regression models and spline regression model were employed to estimate the relationship between BMI and the risk of AF in patients with T2DM.

Results: The incidence rate of AF was 1.97 per 1000 person-year during a median follow-up period of 70.7 months. In multivariate Cox regression model, by using normal BMI as reference group, individuals with underweight (HR 1.47, 95%CI 1.19-1.81, p<0.001) was significantly associated with increased risk of AF while overweight was significantly associated with reduced risk of AF (HR 0.83, 95%CI 0.76-0.91, p<0.001). The Kaplan-Meier analysis showed that the risk of AF was highest in the underweight group, followed by obesity class 3, while the overweight group had the least incidence of AF (log-rank test, p<0.001). Cubic restrictive spline model showed a “J-shaped” or “L-shape” relationship between BMI and the risk AF.

Conclusions: We found that underweight carries the highest risk of AF in Asian patients with T2DM.

Introduction

Type 2 diabetes mellitus (T2DM) and atrial fibrillation (AF) are worldwide public health challenges and important causes of death and cardiovascular events. [1] A multitude of studies have indicated DM as an independent risk for AF, in conjunction with coexisting precipitating environment for AF. [2, 3] Serving as one of the notorious risk factors, obesity has been closely mirrored trends in prevalence of T2DM. In United States, 61% to 85% of people with T2DM are overweight or obese. [4, 5] Moreover, obesity is also an established risk factor for AF. Compared to nonobese individual, obesity increased the risk of developing AF by 49% in the general population, and the risk parallelly escalated with increased body mass index (BMI). [6, 7] In the Framingham Heart Study, every unit increase in BMI correlated with a 4–5% increase in AF risk. [8] Besides, a population-based study showed that each BMI reduction of 1 and 5 kg/m2 were associated with a 7% and 12% reduction in the risk of new-onset AF. [9]

BMI is the most commonly used parameter to determine the degree of obesity. However, the data for BMI and AF in T2DM population was relatively scarce. A synergistic effect on the risk of new-onset AF was ever observed between body weight and DM. [10] Although DM is usually associated with overweight and obesity, its prevalence among normal-weight individuals has been noticed. Of concern, Asians are more likely to be overweight but less likely to be obese, and 30%–50% more likely to develop DM than their white counterparts despite having a lower BMI. [11] Significant racial and ethnic disparities in the definition of obese with BMI cutoffs continued to persist. In a recent study, the prevalence of T2DM was 5.4% and 23.5% in underweight and normal weight Asian men and 0.0% and 6.1% in the BMI counterparts of White men. The prevalence of T2DM was 5.6% and 13.6% in underweight and normal weight Asian women and 2.3% and 2.8% in underweight and normal weight White women. [12]

In addition, the intriguing observation that J- and U-shaped distributions of BMI aligns with cardiovascular complications and mortality implies that the impact of being underweight may be overlooked. The risk is rather difficult to address possibly because underweight comprises a relatively small proportion in Caucasians than Asians. There is lack of...
compelling evidence about the obesity paradox for AF in diabetes patients. Thus, we plan to explore the dose-relationship between BMI and AF in patients with T2DM.

**Methods**

**Study Population**

We evaluated the longitudinal data of Taiwanese who were diagnosed with T2DM and aged 50 years or older in a tertiary medical center between January 1, 2014 and December 31, 2019. The detailed medical records were from the National Taiwan University Hospital Integrated Medical Database (NTUH-iMD) which were well-established based on the International Classification of Diseases, tenth revision codes and ATC (Anatomical Therapeutic Chemical Classification) drug codes, and regulated examination codes in Taiwan. The study was approved by the Institutional Review Board (IRB) of National Taiwan University Hospital.

Patients with previous AF since the inception of the T2DM or lost to follow-up (defined as an absence of follow-up at the outpatient clinics more than three months) were excluded. Baseline characteristics including hypertension (HTN), hyperlipidemia, gout, heart failure, coronary artery disease (CAD), valvular heart disease (VHD), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), peripheral arterial occlusive disease (PAOD) were obtained from the electronic health records (EHRs). Estimated glomerular filtration rate (eGFR) was calculated by modification of diet in renal disease (MDRD) equation. History of transient ischemic accident (TIA) or ischemic stroke was defined as the occurrence of TIA or ischemic stroke before the diagnosis of DM, and history of heart failure was constrained to those patients who had been hospitalized because of acute decompensated heart failure. Prescription information were categorized into antiarrhythmic agents, calcium channel blocker (CCB), beta-blocker, angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), mineralocorticoid-receptor antagonist (MRA), anticoagulants including direct oral anticoagulant (DOAC) and warfarin, and anti-diabetic medications including insulin, metformin, sodium-glucose co-transporter−2 (SGLT2) inhibitor, dipeptidyl peptidase 4 (DPP4) inhibitor, sulphphonylurea, repaglinide, acarbose, thiazolidinedione (TZD), glucagon like peptide−1 (GLP−1) agonist. Echocardiographic studies were performed with Phillips iE33 (Phillips, Bothell, WA, USA) and two-dimensional-guided M-mode measurements with a 3.0- or 3.5-MHz transducer. Left atrium (LA) size, left ventricular internal dimension in end-diastole (LVIDd) and systole (LVIDs), and left ventricular ejection function (LVEF) were collected in the parasternal long-axis view with M-mode cursor. LA size was anterior-posterior diameter measured at the end-ventricular systolic phase. Left ventricular mass (LVM) was calculated by using the Devereux formula. All the echocardiographic data were assessed from the EHRs.

**Data Measurement**

Body height was measured using a stadiometer against the wall. Subjects stood in an upright position on the flat surface of the stadiometer without shoes, with the back of the heels and the occiput on the stadiometer. The body height was recorded with a unit of centimeter (cm) round off to the first decimal place. Body weight was measured using an electronic digital scale and recorded with a unit of kilogram (kg) nearest 0.1 kg. BMI was calculated by dividing weight in kilograms by height in meters squared (kg/m2). Subjects were categorized into 5 groups according to BMI following the recommendations from Health Promotion Administration, Ministry of Health and Welfare, Taiwan: underweight, BMI <18.5; normal range, 18.5≤BMI <24; overweight, 24≤BMI <27; obese class 1 (mild), 27≤BMI <30; obese class 2 (moderate), 30≤BMI <35; obese class 3 (severe), BMI≥35.

New-onset AF and its occurrence time were identified by the diagnosis code from either the EHRs or the standard 12-lead electrocardiogram. The end point of study was AF occurrence, last clinical visit or death.

**Statistical Analysis**
Continuous variables were described as mean (SD) and categorical variables were presented as frequency (percentage). Differences among groups were tested by using chi square test for categorical variables and analysis of variance (one-way ANOVA) test for continuous variables. The relationship between BMI and the AF was assessed by Multivariate Cox’s regression models from which hazard ratios (HRs) and 95% confidence intervals (CIs) were derived. We adjusted the confounders step by step to make sure the association was consistent through increasingly complex models. In the basic model, we adjusted for baseline characteristics including age, gender (male as reference group), hyperlipidemia, gout, history of heart failure, VHD, CAD, COPD, PAOD, prior TIA/ischemic stroke, baseline HbA1C, baseline FG, and baseline eGFR. Subsequently, we further adjusted model 2 with three echocardiogram parameters including baseline LA size, LVEF, and LVM. The estimated cumulative incidences for AF were derived by using Kaplan–Meier approach and the significance of difference between curves were examined by a log-rank test.

Since non-linear dose-response associations were expected, restricted cubic splines with five knots located at the 5th, 27.5th, 50th, 72.5th and 95th percentiles of the BMI distribution were used to determine the relationship of BMI and AF. [13] We also conducted the subgroup analyses stratified by gender and age. Missing values were handled by discard. The forest plot was displayed for subgroup analyses with adjusted hazard ratios (aHR) along with confidence intervals and p-values are plotted for each variable.

A two-tailed p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using R version 3.6.2 (University of Auckland, Auckland, New Zealand) and SPSS statistical software 25.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline Characteristics

The flowchart of patient selection was demonstrated in Figure 1. A total of 74835 with T2DM diagnosis code between 2014 and 2019 were enrolled. Among them, 121 patients without firm evidence of T2DM (only one blood test or without DM medications) and 1607 patients aged below 50 years were excluded. We excluded 1745 patients with pre-existing AF, and 7023 patients with missing BMI values. Finally, a total of 64339 subjects were enrolled for the DM-BMI cohort analysis.

Among the study subjects, 2.9% (n = 1862) were classified as underweight, 35.6% (n = 22933) as normal range, 30.6% (n = 19713) as overweight, 18.5% (n = 11875) as obesity class 1, 10.0% (n = 6456) as obesity class 2, 2.33% (n = 1500) as obesity class 3. The baseline characteristics were shown in Table 1. The underweight patients were older and had a worse baseline eGFR while the severely obese patients were more likely to have cardiovascular risk factors such as hypertension, hyperlipidemia, gout, and CKD. After a median follow-up period of 70.7 months, 5692 individuals (8.8% of total population, 1.97 per 1000 person-year) developed AF. The incidence rates of AF were 3.60, 2.03, 1.86, 1.95, 1.88, and 2.25 per 1000 person-year for groups of underweight, normal range, overweight, obesity class 1, obesity class 2, and obesity class 3, respectively.

The risk of AF according to the BMI classification in univariable and multivariable Cox regression models was demonstrated in Table 2. In univariate analysis, by using normal BMI group as reference, underweight group was associated with significantly increased risk of AF (HR 1.60, 95%CI 1.39–1.83, p<0.001) while overweight group was significantly associated with reduced risk of AF (HR 0.91, 95%CI 0.85–0.97, p = 0.003). The risk of AF for underweight group remained significantly increased after multivariable adjustment for baseline risk factors and echocardiographic parameters (HR 1.47, 95%CI 1.19–1.81, p<0.001). Also, the risk of AF for overweight group remained significantly decreased after full adjustment (HR 0.83, 95%CI 0.76–0.91, p<0.001). For obesity groups (class 1–3), the risks of AF were not significantly different to that of normal BMI group.
The cumulative incidence of AF curves of different groups were illustrated in Figure 2. As shown in Figure 2, the cumulative incidence of AF was highest in the underweight group, followed by obesity class 3, and normal group. The overweight group had the least cumulative incidence of AF. The log-rank test was significant (Log-rank test, p <0.001).

The relationship between AF risk and BMI was demonstrated in Figure 3 by using cubic spline models and by using normal BMI group as reference. As depicted in Figure 3, the relationship between AF risk and BMI was “L-shape” (Figure 3a) initially and became “J-shape” (Figure 3b and Figure 3c) after the adjustment of age and gender and comorbidities (model 1). The relationship was back to “L-shape” with the underweight group carrying the highest risk of AF after further adjustment of echocardiographic parameters (Figure 3D).

A forest plot of HRs for subgroup analyses were demonstrated in Figure 4. Covariates including age above 65, hypertension, gout, VHD, COPD, CAD, PAOD, CKD, history of TIA/old ischemic stroke, LA size >4.0cm, LVEF <50%, LVM more than 200 mg were associated with higher incidence of new-onset AF.

Discussion

Our study demonstrated a “L-shape” relationship between BMI and the risk of AF in patients with T2DM. To our knowledge, this is the first dose-response analysis to survey the non-linear trend of BMI with the development of AF in T2DM in Asian people.

There is mounting epidemiological evidence for the link of obesity and AF. The proposed mechanisms of facilitating AF by obesity are multifactorial including structural remodeling caused by increased atrial stretch, atrial fibrosis affected by endothelial dysfunction, increased systemic inflammation, impaired diastolic function, enlarged LA volume and increased pericardial fat. [14, 15] Increased LA pressure and volume, and shortened effective refractory period (ERP) in the left atrium and pulmonary vein are potential factors predisposing and perpetuating AF in obese patients. [16] In this study, the relationship between BMI and the risk of AF in obesity groups became insignificant after adjusting the echocardiography parameters (LA, LVEF, LVM) suggesting that the effects of obesity on AF were mainly mediated through obesity-mediated cardiac structural changes. By contrast, sustained weight loss is associated with reverse remodeling of the AF substrate and reduction in AF burden in conjunction with favorable changes in the coexisting cardiometabolic risk factors. [17, 18] In an ovine model, weight loss is actually associated with structural and electrophysiological reverse remodeling and a reduced propensity for AF. [19]

However, without direct conflict, several studies have noticed that being underweight is also a risk factor for new-onset AF and worse cardiovascular outcomes. [20, 21] In general population, underweight is an independent risk factor for AF, just secondary to obesity class 2. One study demonstrated that 1-unit increase of BMI is associated with a 6%–7% increased risk of AF while 1-unit decrease of BMI is associated with a 13% increase in AF risk. [22] Besides, not only being obese but also underweight was reported to have higher AF recurrence after catheter ablation. [23]

Data from the ORIGIN trial revealed that obesity and weight loss were inversely related to mortality and cardiovascular outcomes in T2DM. [24] A recent meta-analysis also showed that obesity paradox existed with respect to all-cause and cardiovascular mortality. [25] The obesity paradox for heart failure and cardiovascular mortality has been explained by several aspects. Obesity-related paradoxically increased mobilization of endothelial progenitor cells, increased ghrelin sensitivity, decreased thromboxane production and decreased TNF levels all have potential contributions to the enhancement of myocardial function. Besides, several adipokines produced by adipose tissue have shown to be cardiovascular protective. [26] Sympathetic nervous system activation has been supposed to be less toxic in obesity-related hypertension. [27] Although the mechanisms of “L-shape” phenomenon in our study is unknown, it is likely that both the inflammatory cytokines and autonomic nervous system may play a role. It is well-known that those who have
normal BMI but higher waist circumference and worse metabolic profiles are more prevalent in nonwhites and is characterized as “metabolically unhealthy normal-weight”. [28, 29]

There were debates on the existence of obesity paradox. The major doubt was whether the utility of BMI could reflect the true nutrition status such as body composition and body fat distribution. [30] Evidence has shown that abdominal obesity might be more accurate in predicting AF in nonobese Asian. [31] Nevertheless, BMI is still considered as important as or even more important than the total adiposity measures assessed by using complex and expensive methods, and is consistently proved to be a stronger predictor of cardiovascular outcomes. [32]

The WHO has proposed lower BMI cutoff values for defining overweight BMI $\geq 23$ kg/m$^2$ and obesity BMI $\geq 25$ kg/m$^2$ in Asian populations but most of the evidence were from cross-sectional studies. In line with previous studies which do not support the use of lower BMI cutoff values for overweight and obesity in Asian populations, [33] our study adopted the BMI criteria from the suggestion of Taiwan government. Furthermore, in our study, underweight (BMI $< 18.5$) is associated with the highest risk for AF which surpassed the obesity class 3 (BMI $\geq 35$) in full adjustment model. Because obesity is one of the potential targets for lifestyle modification to reduce AF occurrence, the interpretation of our study should be cautious and further studies are needed.

**Limitations**

This study has some limitations. First, since we did not measure body weight in every outpatient clinic visits, the influence of temporal changes of BMI was not addressed. Second, other obesity-related parameters such as waist circumference or physical activity were not assessed in this study. Third, some potential confounders such as smoking status, alcohol intake, and obstructive sleep apnea were not also not evaluated in this study.

**Conclusion**

We found that in patients with T2DM, underweight is a major risk factor for AF development.

**Abbreviations**

ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; HTN, hypertension; CAD, coronary artery disease; CCB, calcium channel blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DOAC, direct oral anticoagulant; DPP4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; EHRs, electronic health records; GLP–1, glucagon like peptide–1; LA, left atrium; LVEF, left ventricular ejection function; LVIDd, left ventricular internal dimension in end-diastole; LVIDs, left ventricular internal dimension in systole; LVM, left ventricular mass; MDRD, modification of diet in renal disease; MRA, mineralocorticoid-receptor antagonist; PAOD, peripheral arterial occlusive disease; SGLT2, sodium-glucose co-transporter–2; T2DM, type 2 diabetes mellitus; TIA, transient ischemic accident; TZD, thiazolidinedione; VHD, valvular heart disease

**Declarations**

**Ethics approval and consent to participate**

The study protocol complies with the Declaration of Helsinki and was approved by the Institutional Review Board of National Taiwan University Hospital.

**Consent for publication**

Not applicable.
Availability of data and materials

The datasets used in this study were only available in the National Taiwan University Hospital. The R programs (codes) involved for this study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

LY-L contributed to the conception or design of the work. YY-Y, SL-C, and YW-C contributed to the acquisition of data for the work. JC-H analyzed data and drafted the manuscript. LY-L critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Tables

Table 1: Baseline Characteristics According to BMI Categories
|                                | Total N=64339 | Underweight BMI <18.5 N=1862 | Normal range 18.5≤BMI <24 N=22933 | Overweight 24≤BMI <27 N=19713 | Obesity class 1 27≤BMI <30 N=11875 | Obesity class 2 30≤BMI <35 N=6456 | Obesity class 3 BMI≥35 N=1500 | P-value |
|--------------------------------|--------------|-------------------------------|-----------------------------------|-------------------------------|-----------------------------------|-----------------------------------|---------------------------------|---------|
| Age (yr)                       | 67.7 ± 9.9   | 71.6 ± 11.6                  | 68.9 ± 10.1                      | 67.6 ± 9.7                    | 66.7 ± 9.6                        | 65.1 ± 9.3                        | 63.0 ± 8.6                      | <0.001  |
| <65                            | 26723 (41.6) | 559 (30.0)                   | 8443 (36.8)                      | 8112 (41.2)                   | 5352 (45.1)                       | 3360 (52.0)                       | 897 (59.8)                      |         |
| 65-74                          | 20989 (32.6) | 564 (30.3)                   | 7596 (33.1)                      | 6632 (33.6)                   | 3826 (32.2)                       | 1933 (29.9)                       | 438 (29.2)                      |         |
| ≥75                            | 16627 (25.8) | 739 (39.7)                   | 6894 (30.1)                      | 4969 (25.2)                   | 2697 (22.7)                       | 1163 (18.1)                       | 165 (11.0)                      |         |
| Male                           | 33930 (52.7) | 813 (43.7)                   | 11486 (50.1)                     | 11241 (57.0)                  | 6565 (55.2)                       | 3199 (49.6)                       | 626 (41.7)                      | <0.001  |
| Body height (cm)               | 160.8 ± 8.5  | 159.8 ± 8.3                  | 160.6 ± 8.2                      | 161.4 ± 8.4                   | 161.0 ± 8.7                       | 160.2 ± 8.9                       | 158.8 ± 9.7                      | <0.001  |
| Body weight (kg)               | 65.9 ± 12.8  | 44.1 ± 5.4                   | 56.8 ± 7.1                       | 66.4 ± 7.3                    | 73.6 ± 8.2                        | 81.9 ± 9.6                        | 96.6 ± 14.8                      | <0.001  |
| BMI (kg/m2)                    | 25.4 ± 4.2   | 17.2 ± 1.1                   | 21.9 ± 1.4                       | 25.4 ± 0.9                    | 28.3 ± 0.8                        | 31.8 ± 1.3                        | 38.3 ± 6.1                       | <0.001  |
| Hypertension                   | 42088 (65.4) | 946 (50.8)                   | 13244 (57.8)                     | 13079 (66.3)                  | 8634 (72.7)                       | 4939 (76.5)                       | 1246 (83.1)                      | <0.001  |
| Hyperlipidemia                 | 30339 (47.2) | 541 (29.1)                   | 9795 (42.7)                      | 9640 (48.9)                   | 6075 (51.2)                       | 3389 (52.5)                       | 789 (66.7)                      | <0.001  |
| Gout                           | 5831 (9.1)   | 93 (5.0)                     | 1539 (6.7)                       | 1861 (9.4)                    | 1312 (11.0)                       | 833 (12.9)                        | 193 (12.9)                      | <0.001  |
| History of heart failure       | 61 (0.1)     | 5 (0.3)                      | 19 (0.1)                         | 16 (0.1)                      | 9 (0.1)                           | 11 (0.2)                          | 1 (0.1)                         | 0.049   |
| VHD                            | 569 (0.9)    | 22 (1.2)                     | 212 (0.9)                        | 182 (0.9)                     | 100 (0.8)                         | 45 (0.7)                          | 8 (0.5)                         | 0.182   |
| COPD                           | 4076 (6.3)   | 210 (11.3)                   | 1406 (6.1)                       | 1157 (5.9)                    | 746 (6.3)                         | 443 (6.9)                         | 114 (7.6)                       | <0.001  |
| CAD                            | 4163 (6.4)   | 64 (3.4)                     | 1080 (4.7)                       | 1360 (6.9)                    | 977 (8.2)                         | 555 (8.6)                         | 127 (8.5)                       | <0.001  |
| CKD                            | 8460 (13.1%) | 212 (11.4)                   | 2950 (12.8)                      | 2598 (13.2)                   | 1599 (13.5)                       | 887 (13.7)                        | 214 (14.3)                      | 0.044   |
| PAOD                           | 695 (1.1)    | 18 (1.0)                     | 263 (1.1)                        | 204 (1.0)                     | 138 (1.2)                         | 63 (1.0)                          | 9 (0.6)                         | 0.288   |
| History of TIA/old stroke      | 692 (1.1)    | 31 (1.6)                     | 240 (1.0)                        | 201 (1.0)                     | 144 (1.2)                         | 65 (1.0)                          | 11 (0.7)                        | 0.054   |
| Baseline FG (mg/dL)            | 136.8 ± 53.4 | 136.0 ± 62.9                 | 136.8 ± 59.4                     | 136.1 ± 49.1                  | 136.7 ± 46.6                      | 138.7 ± 50.8                      | 141.2 ± 62.7                     | 0.006   |
| Baseline HbA1C (%)             | 7.2 ± 1.5    | 7.2 ± 1.7                    | 7.2 ± 1.5                        | 7.2 ± 1.4                     | 7.3 ± 1.4                         | 7.3 ± 1.5                         | 7.3 ± 1.4                       | <0.001  |
| Baseline eGFR (mL / min / L)   | 72.1 ± 32.9  | 64.9 ± 45.2                  | 66.6 ± 32.2                      | 72.0 ± 29.7                   | 75.7 ± 31.0                       | 82.3 ± 35.1                       | 95.5 ± 43.0                     | <0.001  |
| CHA2DS2-VASc score | 2.5 ± 1.1 | 2.8 ± 1.1 | 2.6 ± 1.1 | 2.5 ± 1.1 | 2.5 ± 1.2 | 2.4 ± 1.2 | 2.4 ± 1.1 | <0.001 |
|---------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|---------|
| UCG                |           |           |           |           |           |           |           |         |
| LA size (cm)       | 3.9 ± 0.7 | 3.4 ± 0.8 | 3.7 ± 0.7 | 3.9 ± 0.6 | 4.0 ± 0.6 | 4.1 ± 0.6 | 4.2 ± 0.7 | <0.001 |
| DT (sec)           | 0.22 ± 0.07 | 0.21 ± 0.07 | 0.22 ± 0.07 | 0.23 ± 0.07 | 0.22 ± 0.06 | 0.23 ± 0.06 | <0.001   |
| E (mm/sec)         | 80.7 ± 27.4 | 81.7 ± 29.7 | 81.6 ± 28.5 | 79.5 ± 26.8 | 80.2 ± 26.4 | 81.8 ± 27.1 | 82.9 ± 26.7 | <0.001 |
| A (mm/sec)         | 97.3 ± 24.9 | 94.5 ± 26.8 | 96.9 ± 26.1 | 97.5 ± 24.4 | 97.7 ± 23.7 | 97.6 ± 23.5 | 98.6 ± 25.2 | 0.110 |
| E/A                | 0.9 ± 7.6 | 1.5 ± 12.2 | 1.1 ± 12.6 | 0.9 ± 2.3 | 0.8 ± 0.5 | 0.8 ± 0.4 | 0.8 ± 0.4 | 0.387 |
| E/E'               | 21.5 ± 123.1 | 12.6 ± 6.5 | 20.0 ± 107.9 | 24.9 ± 147.7 | 25.6 ± 152.7 | 15.0 ± 54.4 | 11.9 ± 6.0 | 0.466 |
| LVEF (%)           | 64.8 ± 12.4 | 63.3 ± 14.9 | 64.4 ± 13.3 | 65.2 ± 12.1 | 64.9 ± 11.8 | 65.3 ± 11.0 | 65.3 ± 10.3 | <0.001 |
| LVIDs (cm)         | 3.0 ± 0.7 | 2.8 ± 0.8 | 3.0 ± 0.7 | 3.0 ± 0.7 | 3.1 ± 0.7 | 3.1 ± 0.6 | 3.2 ± 0.6 | <0.001 |
| LVIDd (cm)         | 4.7 ± 0.6 | 4.3 ± 0.7 | 4.6 ± 0.7 | 4.8 ± 0.6 | 4.8 ± 0.6 | 4.9 ± 0.6 | 5.0 ± 0.6 | <0.001 |
| LV mass (gm)       | 201.4 ± 61.7 | 158.1 ± 56.8 | 186.1 ± 58.8 | 201.4 ± 57.4 | 213.9 ± 60.9 | 225.8 ± 63.9 | 238.5 ± 61.1 | <0.001 |
| Medication         |           |           |           |           |           |           |           |         |
| Antiplatelet       | 20584 (32.0) | 439 (23.6) | 6524 (28.4) | 6445 (32.7) | 4289 (36.1) | 2338 (36.2) | 549 (36.6) | <0.001 |
| Anticoagulant      | 2774 (4.3) | 73 (3.9) | 906 (4.0) | 807 (4.1) | 559 (4.7) | 325 (5.0) | 104 (6.9) | <0.001 |
| CCB                | 27767 (43.2) | 719 (38.6) | 8892 (38.8) | 8531 (43.3) | 5592 (47.1) | 3254 (50.4) | 779 (51.9) | <0.001 |
| Beta-blocker       | 19073 (29.6) | 424 (22.8) | 6082 (26.5) | 5873 (29.8) | 3922 (33.0) | 2249 (34.8) | 534 (35.6) | <0.001 |
| ACEI/ARB           | 27703 (43.1) | 578 (31.0) | 8570 (37.4) | 8675 (44.0) | 5768 (48.6) | 3313 (51.3) | 799 (53.3) | <0.001 |
| Diuretics          | 16060 (25.0) | 509 (27.3) | 5241 (22.9) | 4525 (23.0) | 3202 (27.0) | 2028 (31.4) | 555 (37.0) | <0.001 |
| Statin             | 23732 (36.9) | 372 (20.0) | 7572 (33.0) | 7509 (38.1) | 4937 (41.6) | 2723 (42.2) | 618 (41.2) | <0.001 |
| Metformin          | 32407 (50.4) | 799 (42.9) | 11174 (48.7) | 10173 (51.6) | 6163 (51.9) | 3344 (51.8) | 754 (50.3) | <0.001 |
| SGLT2i             | 5385 (8.4) | 62 (3.3) | 1324 (5.8) | 1641 (8.3) | 1269 (10.7) | 851 (13.2) | 238 (15.9) | <0.001 |
| DDP4i              | 22464 (34.9) | 631 (33.9) | 7793 (34.0) | 6844 (34.7) | 4283 (36.1) | 2380 (36.9) | 533 (35.5) | <0.001 |
| Abbreviations: BMI: body mass index; VHD, valvular heart disease; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; PAOD, peripheral arterial occlusive disease; FPG, fasting glucose; eGFR, estimated glomerular filtration rate; LA, left atrium; DT, deceleration time; E/A, early diastolic transmitral flow velocity/late diastolic transmitral flow velocity; E', early diastolic mitral annular velocity; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal diameter in diastole; LVIDs, left ventricular internal diameter in systole; LV mass, left ventricle mass; CCB, calcium channel blocker; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; SGLT-2 inhibitor, sodium-glucose co-transporter-2 inhibitor; DPP4 inhibitor, dipeptidyl peptidase 4 inhibitor; TZD, thiazolidinediones; GLP-1 agonist, glucagon like peptide-1 agonist. 

Table 2: Adjusted hazard ratio for AF incidence across category of BMI

| Continuous per unit increase | 0.99 (0.98-0.99) | <0.001 | 1.03 (1.02-1.03) | <0.001 | 0.99 (0.99-1.00) | 0.435 |
| Underweight | 1.60 (1.39-1.83) | <0.001 | 1.33 (1.12-1.58) | 0.001 | 1.47 (1.19-1.81) | <0.001 |
| Normal range | 1 | 1 |
| Overweight | 0.91 (0.85-0.97) | 0.003 | 0.92 (0.85-0.99) | 0.034 | 0.83 (0.76-0.91) | <0.001 |
| Obesity class 1 | 0.98 (0.91-1.06) | 0.663 | 1.05 (0.96-1.14) | 0.299 | 0.88 (0.80-0.98) | 0.016 |
| Obesity class 2 | 0.95(0.87-1.05) | 0.325 | 1.15 (1.03-1.28) | 0.014 | 0.89 (0.79-1.02) | 0.088 |
| Obesity class 3 | 1.15 (0.98-1.36) | 0.084 | 1.50 (1.25-1.82) | <0.001 | 0.97 (0.78-1.21) | 0.783 |

Model 1 (**): adjusting age (<65, 65-74, ≥75), gender, hypertension, hyperlipidemia, gout, history of heart failure, VHD, CAD, COPD, PAOD, prior TIA/ischemic stroke, baseline HbA1C, baseline FG, CKD.

Model 2 (**): adjusting model 1, plus baseline LA size, baseline LVEF, baseline LVM.

(**): p-value <0.001

Figures
Figure 1

Study flowchart
Figure 2

Cumulative incidence for AF by BMI categories
Figure 3

The association between BMI and AF among overall and adjustment: Crude (3a), adjust age and gender (3b), Model 1 (3c) or Model 2 (3d)
Figure 4

Subgroup analyses for AF