**Body mass index and clinical outcomes in Asian patients with atrial fibrillation receiving oral anticoagulation therapy: a nationwide population-based study**

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**Abstract**

**Background and Purpose:** The influence of body mass index (BMI) on clinical outcomes in patients with atrial fibrillation (AF) remains controversial, especially amongst Asians. We aimed to evaluate the association between BMI and clinical outcomes in Asian patients with AF receiving oral anticoagulants (OACs).

**Methods:** Using the Korean National Health Insurance database between January 2015 and December 2017, we identified OAC naïve non-valvular AF patients with BMI information. We analyzed ischemic stroke, intracranial hemorrhage (ICH), hospitalization for gastrointestinal (GI) bleeding, major bleeding, all-cause death, and the composite clinical outcome according to BMI categories.

**Results:** A total of 43,173 patients were included across BMI categories (kg/m2): underweight (<18.5) in 3%, normal (18.5 to <23) in 28%, overweight (23 to <25) in 24%, obese I (25 to <30) in 39%, and obese II (≥30) in 6%. Higher BMI (per 5 kg/m2 increase) was significantly associated with lower risks of ischemic stroke (hazard ratio [HR] 0.891, 95% confidence interval [CI] 0.801-0.992), hospitalization for GI bleeding (HR 0.785, 95% CI 0.658-0.937), major bleeding (HR 0.794, 95% CI 0.686-0.919), all-cause death, (HR 0.658, 95% CI 0.605-0.716) and the composite clinical outcome (HR 0.751, 95% CI 0.706-0.799), except for ICH (HR 0.815, 95% CI 0.627-1.061). The underweight group was associated with an increased risk of composite clinical outcome (HR 1.398, 95% CI 1.170-1.671), mainly driven by an increased risk of all-cause death. The effects of NOAC vs. warfarin on clinical outcomes were similar across BMI groups.

**Conclusion:** Higher BMI was independently associated with a lower risk of ischemic stroke, major bleeding, and better survival. Underweight patients also had a higher risk of all-cause death and the composite clinical outcome. The optimal BMI for patients with AF should be defined, and managed according to an intergrated care pathway.

**Keywords:** body mass index, oral anticoagulant, atrial fibrillation, clinical outcomes

**Introduction**

Atrial fibrillation (AF) is the most common cardiac arrhythmia and the prevalence of AF has increased globally [1,2]. AF was significantly associated with increased risks of stroke, heart failure, and death. A comprehensive, identifying risk factors for incident AF is important [3].

Body mass index (BMI) has been demonstrated as a factor closely associated with incident AF, as in other cardiovascular diseases [4,5]. Overweight and obesity are well-known risk factors for incident AF, and underweight is also a risk factor for new-onset AF [6]. Not only on the risk of incident AF, but BMI also affects the risk of adverse outcomes in patients with AF. Although a higher BMI is associated with an increased risk of all-cause death in the general population, an ‘obesity paradox’ that higher BMI was associated with favorable outcomes has been observed in patients with cardiovascular diseases, such as hypertension, coronary heart disease, and heart failure [7-11]. However, the influence of BMI for clinical outcomes in patients with AF is still controversial [12-14]. Based on previous studies, the obesity paradox might exist for patients with AF with regard to the risks for stroke, cardiovascular, and all-cause death; however, results are conflicting on the risk for major bleeding [12,13,15].

Oral anticoagulant (OAC) treatment is essential for stroke prevention in patients with AF [16]. Asians are known to have higher risks of stroke and intracranial hemorrhage (ICH) compared to non-Asians on warfarin therapy [17]. The introduction of non-vitamin K antagonist oral anticoagulants (NOACs), which are effective and safer alternatives to warfarin, has led to the more widespread use of anticoagulation therapy [18]. Even when using NOACs, being underweight has been suggested as a risk factor for major bleeding [19]. In contrast, overweight status and obesity also increases the risk of major bleeding in anticoagulated patients with AF [15]. Furthermore, most previous studies conducted in the non-Asian population have shown different BMI distributions compared to the Asian population. Indeed, data evaluating the relationship between BMI and outcomes in Asian patients with AF are sparse.

In this study, we aimed to evaluate the association between BMI and clinical outcomes in Asian patients with AF who were prescribed OAC, using a nationwide population-based cohort.

**Methods**

*Data sources*

This retrospective observational nationwide cohort study was conducted using administrative claims data of the Korean National Health Insurance Service (NHIS) and the linked health checkup database of the National Health Insurance Corporation (NHIC) between 2013 to 2017. The Korean NHIS provides comprehensive medical care coverage for the entire Korean population (approximately 50 million people). The Korean NHIS database includes individual demographic information and all data related medical expenses including diagnoses based on the 10th revision of the International Classification of Disease (ICD-10) codes, prescription and procedure records [20]. A national health checkup provided by the Korean NHIC is conducted biennially and includes physical examinations of the patients, regular blood tests, chest X-ray examinations, and questionnaires on their medical history [20]. The Korean NHIS provides randomly selected 50% sample cohort by customized conditions for the analysis including detailed information about the prescription. This study was exempted from review by the Seoul National University Hospital Institutional Review Board (E-1811-010-982).

*Study design*

A detailed study enrollment flow is presented in Figure 1. We included OAC new users diagnosed with AF between January 2015 and December 2017. Patients with aged <20 years, those who were regarded as valvular AF patients (patients with mitral stenosis or prosthetic heart valve), those with possible alternative indications for OAC (pulmonary embolism, deep vein thrombosis, or recent joint replacement surgery) and those with end-stage renal disease were excluded from the analysis. Finally, included those patients with BMI information recorded.

*Covariates and comorbidities*

Patients’ demographic data, comorbidities, and concomitant medications were ascertained from the Korean NHIS database. Supplementary Table 1 summarized the definitions of comorbidities. Hypertension, diabetes, dyslipidemia, heart failure, prior ischemic stroke and myocardial infarction, peripheral artery disease, chronic obstructive pulmonary disease, and cancer were defined using diagnosis codes in the *International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM),* combining prescription records and inpatient/outpatient hospital visits within 1 year prior to the index date (Supplementary Table 1). The CHA2DS2-VASc score was calculated based on patients’ demographic findings, comorbidities, and medical history [21]. Concomitant use of antiplatelet agents (aspirin or clopidogrel) was identified.

From the health checkup data, body weight, height, BMI, and estimated glomerular filtration rate (eGFR) were collected. BMI was defined as weight in kilograms (kg) divided by the square of height in meters (m), and eGFR was calculated by a creatinine-based equation used from Modification of Diet in Renal Disease [22]. According to BMI following the World Health Organization recommendation for Asian population, study patients were categorized into 5 groups: underweight, <18.5 kg/m2; normal range, 18.5 to <23 kg/m2; overweight, 23 to <25 kg/m2; obese I, 25 to <30 kg/m2; and obese II, ≥30 kg/m2 [23].

*Study outcomes and follow-up*

We assessed 6 clinical outcomes including ischemic stroke, ICH, hospitalization for gastrointestinal (GI) bleeding, major bleeding, all-cause death, and a composite clinical outcome of ‘XXX’ [24,25]. Detailed definitions of clinical outcomes are presented in Supplementary Table 1. Patients were censored at the clinical outcomes, end of the study period (December 2018), or the discontinuation of index treatment, whichever came first.

*Statistical analysis*

Continuous variables are presented as mean ± standard deviation or median (interquartile ranges). Categorical variables are presented as numbers and percentages. Baseline characteristics were compared across 5 BMI categories with a linear trend test using a generalized linear model for continuous variables and the Cochran-Armitage trend test for categorical variables. The incidence rates of clinical outcomes were calculated based on the number of events during the follow-up period divided by 100 person-years at risk.

In the primary analyses, the association between BMI as a continuous variable (per 5 kg/m2 increase) and clinical outcomes were evaluated using a Cox proportional hazard model to derived unadjusted and adjusted hazard ratios (HRs) [26]. Adjusted cubic spline curves were used to visualize the relationship between BMI and the risk of clinical outcomes. In the secondary analyses, the association between different BMI categories and clinical outcomes were explored using adjusted Cox proportional hazard models. Patients with a normal range of BMI defined as 23 to <25 kg/m2 were used as the reference group. We performed this analysis in the total study population and also in the warfarin and NOAC groups. Covariates in the multivariable analysis included age, sex, CHA2DS2-VASc score, hypertension, diabetes, dyslipidemia, chronic obstructive pulmonary disease, prior myocardial infarction, prior ischemic stroke, peripheral artery disease, heart failure, cancer, use of antiplatelet agents, and OAC treatment (warfarin or NOAC). For the analysis in the NOAC group, NOAC dose regimens (standard or low doses) were also adjusted.

We evaluated the HRs of 6 clinical outcomes in the NOAC group compared to the warfarin group (as the reference group) in different BMI categories. The statistical significance (p <0.1) of the interaction between treatment (warfarin or NOAC) in the subgroup with different BMI categories was evaluated.

All analyses were two-tailed, and P-value <0.05 was considered significant. Statistical analyses were conducted with SAS 9.3 (ASA Institute Inc., Cary, NC, USA).

**Results**

A total of 43,173 patients were finally induced in this study (Figure 1). Mean BMI of the total study population was 24.7±3.4 kg/m2. Mean age was 71.3±10.0 years and mean CHA2DS2-VASc score was 3.9±1.7. Patient distribution according to BMI groups is presented in Figure 2. Among the total study population, 2.7% were categorized as ‘underweight’, 27.6% were ‘normal weight’, 24.5% were ‘overweight’, 38.9% were ‘obese I’, and 6.3% were classified as ‘obese II’, respectively.

*Baseline characteristics*

Baseline characteristics according to BMI categories are presented in Table 1. Patients with lower BMI were older, more likely to have a previous history of ischemic stroke, and had a higher CHA2DS2-VASc score. Chronic obstructive pulmonary disease and any cancer were more prevalent in patients with lower BMI. Patients with higher BMI were more likely to have more comorbidities such as hypertension, diabetes mellitus, dyslipidemia and peripheral artery disease. For heart failure and myocardial infarction, the underweight group showed the highest prevalence among the study population. Mean body weight was 44 kg in underweight, 55 kg in normal, 62 kg in overweight, 71 kg in obese I, and 83 kg in obese II group, respectively. Of the patients in underweight group, 79.5% were extremely low body weight (<50 kg), 20.3% of were 50-60kg, and only 0.3% of patients (n=3) were over 60 kg. Patients in the obese II group, 99.6% were over 60 kg and only 0.4% (n=11) were under 60 kg.

Of the total study population, 22% received warfarin and 78% received NOACs. Among patients with NOACs, 36.4% were prescribed rivaroxaban, 20.8% dabigatran, 25.2% apixaban, and 17.5% edoxaban. There were no significant differences in the proportion of warfarin vs. NOACs use according to BMI categories. In patients taking NOACs, patients with lower BMI had a higher likelihood of receiving lower dose NOACs.

*Association between clinical outcomes and body mass index*

During a mean follow-up of 0.8±0.7 years, there were 816 (1.9%) ischemic strokes, 142 (0.3%) ICH, 314 (0.7%) hospitalizations for GI bleeding, 456 (1.1%) major bleeding, 1,409 (3.3%) all-cause death, and 2,555 (5.9%) of the composite clinical outcome. The crude event numbers and incidence rates of each clinical outcome are presented in Table 2.

Supplementary Table 2 shows unadjusted HRs for BMI (as a continuous variable per 5 kg/m2 increase) and clinical outcomes in the total study population. Higher BMI was associated with a lower risk of ischemic stroke, ICH, hospitalization for GI bleeding, major bleeding, all-cause death, and composite clinical outcome. After adjustment for age, sex, CHA2DS2-VASc score, comorbidities, treatment (warfarin or NOACs), antiplatelet use, and renal function, higher BMI (per 5 kg/m2 increase) was significantly and independently associated with lower risks of ischemic stroke (HR 0.891, 95% confidence interval [CI] 0.801-0.992, p=0.034), hospitalization for GI bleeding (HR 0.785, 95% CI 0.658-0.937, p=0.007), major bleeding (HR 0.794, 95% CI 0.686-0.919, p=0.002), all-cause death (HR 0.658, 95% CI 0.605-0.716), and the composite clinical outcome (HR 0.751, 95% CI 0.706-0.799, p<0.001, except for ICH (HR 0.815, 95% CI 0.627-1.061, p=0.128) (Figure 3). Figure 4 shows the adjusted cubic splines curves with the relationship between BMI and clinical outcomes.

*Clinical outcomes according to body mass index categories*

In a multivariable analysis considering the BMI categories, the risk of ischemic stroke was significantly lower in patients with BMI ≥30 kg/m2 (Figure 5). Also, the risk of death was lower as BMI increased but obviously higher in the underweight group. Major bleeding events were lower as higher BMI categories, especially at BMIs 23-25 kg/m2 and 25-30 kg/m2. Therefore, patients at higher BMI categories showed a lower risk of composite clinical outcome and patients with underweight were associated with an increased risk of composite clinical outcome, mainly driven by all-cause death. Although statistical significance was attenuated due to smaller sample size, these trends were consistently observed both in warfarin and NOAC groups (Supplementary Tables 3 and 4).

*Effectiveness and safety of NOACs vs. warfarin according to body mass index*

Baseline characteristics between warfarin and NOAC groups in different BMI categories are presented in Supplementary Table 5, and crude event numbers and incidence rates of the two treatment groups according to BMI categories are presented in Supplementary Table 6. As in the total study population (Supplementary Table 7), there was no significant interaction between BMI and the effectiveness and safety of NOACs compared to warfarin (Supplementary Table 7). Because of the small sample size in each BMI subgroup, statistical significance for the benefit of NOACs over warfarin was generally attenuated. These results should be cautiously interpreted givenf the small number of events in particular subgroups.

**Discussion**

To the best of our knowledge, this is the first large-scale Asian nationwide population-based study to investigate the association between BMI and clinical outcomes in patients with AF receiving OAC. Our study has the following principal findings: (1) among Asian patients with AF receiving OAC, 3% were underweight, 24% were overweight, and 45% were obese; (2) higher BMI (as a continuous variable, per 5 kg/m2 increase) was associated with lower risks of ischemic stroke, major bleeding, all-cause death, and composite clinical outcome; (3) the obese II groups was associated with a lower risk of ischemic stroke compared to the normal BMI group, without an increased risk of major bleeding; (4) the overweight and obese I groups were associated with lower risks of major bleeding compared to normal BMI group; (5) the underweight group was associated with an increased risk of all-cause death, whereas patients with overweight, obese I, and obese II had a lower risk of all-cause death compared with the normal BMI group; and (6) overall, the overweight, obese I and II groups were associated with a lower risk of the composite clinical outcome and underweight group was associated with a higher risk of composite clinical outcome, among patients with AF receiving OACs.

Obesity has become increasingly more common in the Asian population [27]. In the general population, obesity is a well-known risk factor for cardiovascular disease and a strong predictor of cardiovascular and overall mortality [7,8,28]. The ‘obesity paradox’ is a phenomenon whereby being overweight or obesity is associated with a better prognosis in subjects with cardiovascular disease [9-11]. Although several previous studies reported the relationship between BMI and clinical outcomes in patients with AF, such an obesity paradox remains controversial, and there was no data from a large-scale Asian cohort.

For stroke and death, previous AF studies reported consistent results that higher BMI was associated with a lower risk [12,13,15,29-31]. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study showed lower risks of all-cause and cardiovascular mortality compared to normal BMI AF patients [12]. A post hoc analyses of the more recent NOAC trials showed consistent results [13,15,29]. About 77% of patients were classified into either overweight or obese in these 3 NOAC trials. For example, in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial, the overweight and obese groups were associated with a decreased risk of stroke compared to normal BMI group (HR 0.81 and 0.69, respectively) [29]. In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, overweight and obese population showed significantly lower risks of all-cause death (HR 0.67 for overweight and 0.63 for obese) and the composite outcome of stroke/systemic embolism/myocardial infarction/all-cause death (HR 0.74 for overweight and 0.68 for obese) [13]. In the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial, an increased BMI was associated with lower risks of stroke (HR 0.88) and all-cause death (HR 0.91) [29]. Obese patients were significantly associated with a lower risk of stroke (HR 0.82 for moderately obese, 0.68 for severely obese, and 0.54 for very severely obese), and overweight/obese patients showed a better survival (HR for all-cause death, 0.75 to 0.79) [29]. In a meta-analysis of NOAC trials, an obesity paradox was evident, with overweight and obese patients reporting a lower risk for stroke/systemic embolism [30].

Although our study applied a different BMI classification for Asian population [23], almost 70% of the study population was classified into either overweight (BMI 23-25 kg/m2) or obese (≥ 25 kg/m2) and patients with ≥ 25 kg/m2 were 45% of the total study population. Our study showed consistent findings with previous studies reporting an obesity paradox in AF patients for stroke and death. Indeed, the obese II group (BMI ≥30 kg/m2)showed a significantly lower risk of ischemic stroke. Compared to normal BMI (BMI 18.5-23 kg/m2), overweight (BMI 23-25 kg/m2), obese I (BMI 25-30 kg/m2) and obese II (BMI ≥30 kg/m2) groups reported a lower risk of all-cause death. In a single-center Chinese retrospective cohort, both overweight and obesity were reported as an independent risk factor of thromboembolic events, however, only a small number of patients were included [32].

Hence, this study was a first to describe an obesity paradox in Asian patients with AF for stroke and all-cause death. Differed from the previous studies, our analyses included a large number of patients with underweight (BMI <18.5 kg/m2, n=1,154) and underweight patients had a higher risk of all-cause death compared to normal BMI patients. This finding is partly consistent with a previous meta-analysis for Asian patients with AF [31]. Obese patients may have several protective effects against systemic inflammation and atrial remodeling [33-35]. However, the precise mechanism(s) for the obesity paradox is still unclear. Another possible reason is that the obese population may have more comorbidities such as hypertension and coronary heart disease, and they may receive more aggressive treatment. Indeed, obese patients were more likely to receive renin-angiotensin system inhibitors, beta-blockers, and statins than subjects with normal BMI in prior studies [12,13,15,29].

Previous reports of the association between BMI and major bleeding in patients with AF have been controversial. In the ARISTOTLE trial, overweight patients showed a marginally lower risk of major bleeding than normal BMI group, whereas no statistically significant difference was evident between normal and obese patients [13]. In the ENGAGE AF-TIMI 48 trial, only BMI ≥35 kg/m2 was associated with a higher risk of major or clinically relevant non-major bleeding and there was no association between BMI categories and any bleeding [15]. In contrast, underweight was associated with an increased risk of major bleeding in a small retrospective Asian cohort with AF receiving NOACs [19]. In patients with AF receiving either warfarin or NOACs, being more underweight (<50 kg) was associated with a higher incidence of major bleeding [24]. Our study patients did not include extremely obese patients; thus, it was not conclusive whether extremely obese increased the risk of major bleeding in anticoagulated patients with AF in our study.

Our study has shown no significant association between BMI and the incidence of ICH. For the hospitalization for GI bleeding and major bleeding, we found that being overweight or obese might have a protective effect, consistent with a previous meta-analysis [30]. From the results of previous studies and our study, there was no consistent or strong relationship between BMI and the incidence of major bleeding. In anticoagulated patients with AF, the type and dosing of anticoagulants might also play a more important role in determining bleeding events.

Although the comparison between warfarin and NOAC was not the primary purpose of this study, there were consistent trends of the benefit of NOAC over warfarin across different BMI categories. For the composite clinical outcomes, a significant treatment benefit of NOACs was observed in patients with normal BMI and overweight, consistently with a previous study [30].

*Strengths and limitations*

The strengths of our study included the largest population with underweight (BMI <18.5 kg/m2, 3% of the total study population, n=1,154). Although obesity is less prevalent in Asians compared to non-Asians, this cohort contains 19,512 obese patients, up to 45% of the total study population. However, this study had several limitations. First, the study population was collected retrospectively from an administrative database. Although the use of a nationwide administrative database has increased for clinical research, these studies are potentially susceptible to errors from coding inaccuracies. To minimize this limitation, we validated the definitions of covariates and clinical outcomes [2,24,25,36]. Second, treatment quality of warfarin and actual drug adherence of both warfarin and NOACs could not be accurately evaluated due to an inherent limitation of the claims database. Third, although this study generated the hypothesis about the existence of obesity paradox in Asian patients with AF receiving OAC, pharmacokinetic and pharmacodynamic data are not available to explain the clinical observation. Fourth, the cause of death could not be identified due to an inherent limitation of claims database from the Korean NHIS. Lastly, we only included patients with BMI information among OAC new users with non-valvular AF. Although up to 70% of the entire Korean adult patients aged 40 years or older were included in the national health checkup examination, there might be a possibility of selection bias. A previous study showed that subjects receiving the national health checkup examinations were younger, more likely to be male, had less prevalent comorbidities and had lower CHA2DS2-VASc score than those without the information of the health checkup examination [37]. Thus, these data should be interpreted and applied cautiously to the general population.

**Conclusions**

Higher BMI was independently associated with a lower risk of ischemic stroke, major bleeding, and better survival. Underweight patients also had a higher risk of all-cause death and the composite clinical outcome. The optimal BMI for patients with AF should be defined, and managed according to an intergrated care pathway.

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**Figure legends**

**Figure 1. Study enrollment flow**

Abbreviation: AF, atrial fibrillation; BMI, body mass index; NHIS, national health insurance service; OAC, oral anticoagulant.

**Figure 2. Distribution of body mass index**

Abbreviation: BMI, body mass index

**Figure 3. Adjusted hazard ratios (95% confidence interval) of body mass index as a continuous variable (per 5 kg/m2 increase) for clinical outcomes**

Abbreviation: BMI, body mass index; GI, gastrointestinal; ICH, intracranial hemorrhage.

**Figure 4. Adjusted cubic spline curves for the relationship between body mass index and clinical outcomes**

Abbreviation: CI, confidence interval; GI, gastrointestinal; HR, hazard ratio.

**Figure 5. Clinical outcome according to different body mass index categories**

IR, per 100 person-years

Abbreviation: CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; IR, incidence rate.