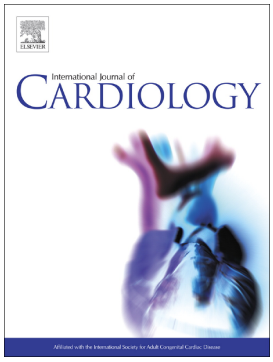


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PII: S0167-5273(20)33388-X

DOI: https://doi.org/10.1016/j.ijcard.2020.06.010

Reference: IJCA 28686

To appear in: *International Journal of Cardiology*

Received date: 16 April 2020

Revised date: 18 May 2020

Accepted date: 9 June 2020

Please cite this article as: G. Patti, L. Pecen, M.C. Manu, et al., Thromboembolic and bleeding risk in obese patients with atrial fibrillation according to different anticoagulation strategies, *International Journal of Cardiology* (2020), https://doi.org/10.1016/j.ijcard.2020.06.010

# Thromboembolic and Bleeding Risk in Obese Patients with Atrial Fibrillation According to Different Anticoagulation Strategies

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## ABSTRACT

**Background**. Data on the relationship between body mass index (BMI), thromboembolic events (TEE) and bleeding in patients with atrial fibrillation (AF) are controversial, and further evidence on the risk of such events in obese patients with AF receiving different anticoagulant therapies (OAC) is needed.

**Methods and Results.** We divided a total of 9,330 participants from the prospective PREFER in AF and PREFER in AF PROLONGATION registries into BMI quartiles at baseline. Outcome measures were TEE and major bleeding complications at the 1-year follow-up. Without OAC, there was a ≥6-fold increase of TEE in the 4$^{th}$ vs other BMI quartiles (P=0.019). OAC equalized the rates of TEE across different BMI strata. The occurrence of major bleeding was highest in patients with BMI in the 1$^{st}$ as well as in the 4$^{th}$ BMI quartile [OR 1.69, 95% CI 1.03-2.78, P=0.039 and OR 1.86, 95% CI 1.13-3.04, P=0.014 vs those in the 3$^{rd}$ quartile, respectively]. At propensity score-adjusted analysis, the incidence of TEE and major bleeding in obese patients receiving non-vitamin K antagonist oral anticoagulants (NOACs) or vitamin K-antagonist anticoagulants (VKAs) was similar (P≥0.34).

**Conclusions**. Our real-world data suggest no obesity paradox for TEE in patients with AF. Obese patients are at higher risk of TEE, and here OAC dramatically reduces the risk of events. We here found a comparable clinical outcome with NOACs and VKAs in obese patients. Low body weight and obesity were also associated with bleeding, and therefore OAC with the best safety profile should be considered in this setting.


**KEYWORDS:** atrial fibrillation; body mass index; obesity; oral anticoagulant therapy; thromboembolic events; bleeding.

## 1. INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with an average prevalence of 3% in adults [1]. Patients with AF have an adverse cardiovascular outcome vs those without [2]. The prevalence of obesity is rapidly increasing in Western countries, reaching epidemic proportions. Obese individuals present a higher risk of AF, as well as of progression from paroxysmal to permanent AF [3-5]. Thus, the association of AF and high body weight is very common. This raises the need for clearly defining the prognostic role of obesity on cardiovascular outcome in AF and for optimizing strategies to prevent AF-related cardiovascular complications in these patients; as a consequence, the issue of whether the newer anticoagulant therapies in obese patients provide a protection from thromboembolic events similar to non-obese patients has a strong clinical relevance.

Previous investigations had shown the so-called "obesity paradox", i.e. an inverse relationship between body mass index (BMI) and poorer outcome in patients with coronary artery disease or congestive heart failure [6,7]. Consistently, various studies have demonstrated the association between high BMI and lower all-cause death, cardiovascular mortality or stroke also in AF [8-12]. However, other investigations contested the abovementioned obesity paradox in AF [13-15]. Furthermore, no study has explored the risk of events across various BMI categories by stratifying patients according to specific and different antithrombotic therapies. Moreover, in randomized phase III trials on patients with AF the use of non-vitamin K antagonist oral anticoagulants (NOACs) was associated with an overall 19% relative reduction of stroke or systemic embolism and a 14% relative reduction of major bleeding vs warfarin [16]. However, among obese patients with AF, sub-analyses of randomized trials raised some concerns on the net benefit of NOACs over warfarin [9,17], real-world data showed controversial results on the efficacy of NOACs [18,19], and recent meta-analyses suggested no higher efficacy and safety with NOACs vs vitamin K anticoagulants (VKAs) [11].

To provide further evidence on these topics, we analyzed individual data of patients included in two real-world, prospective, European registries on AF. We also here compared outcomes with NOACs vs VKAs in obese patients.

## 2. METHODS

### 2.1. Study population and design

Individual patient data were derived from two prospective, European registries: the Prevention of thromboembolic events–European Registry in Atrial Fibrillation (PREFER in AF) [20] and the Prevention of thromboembolic events–European Registry in Atrial Fibrillation PROLONGATION (PREFER in AF PROLONGATION). These registries enrolled AF patients from nine countries (PREFER in AF and PREFER in AF PROLONGATION: Austria, France, Germany, Italy, Spain, Switzerland and the United Kingdom; PREFER in AF PROLONGATION also: Belgium and The Netherlands). PREFER in AF included 7,228 patients from 461 institutions, and PREFER in AF PROLONGATION a total of 4,195 patients from 257 institutions. Approximately 85% of centers in PREFER in AF PROLONGATION participated in the PREFER in AF registry. The registries were consecutively conducted at each site (PREFER in AF: January 2012– January 2014; PREFER in AF PROLONGATION: June 2014 – June 2016). PREFER in AF included patients independently of the antithrombotic therapy aimed to prevent AF-related thromboembolic complications and was conducted before the wide introduction of the NOACs in Europe; thus, in PREFER in AF the large majority of patients receiving oral anticoagulant therapy (OAC) were on VKAs. PREFER in AF PROLONGATION, conversely, only enrolled patients on NOACs. There were no explicit clinical exclusion criteria and other inclusion criteria were similar in both registries: paroxysmal, persistent or permanent AF within the preceding year, as demonstrated by an electrocardiogram or by an implanted pacemaker/defibrillator; age ≥18 years; signed informed consent.

In both registries, patients had a clinical assessment at the time of enrolment and after one year. Demographic features, clinical characteristics and treatments were obtained at baseline. Only those patients having both baseline and 1-year assessment were included in this analysis and only documented outcome measures (with the time of any event being after the baseline visit) were considered as study endpoints. Individual patient data from the two registries were entered into an electronic case report form including various plausibility checks for the considered variables. On-site verification of source data was done at approximately 5% of the sites, randomly selected. Study management was overseen by a scientific Steering Committee. PREFER in AF and PREFER in AF PROLONGATION were sponsored by Daiichi Sankyo Europe GmbH (Munich, Germany) via a contract research organization (SSS International Clinical Research GmbH – Munich, Germany) that coordinated local contract research organizations in each country.

### 2.2. Endpoints and definitions

For the purpose of this study, we divided patients into quartiles of BMI at baseline. We here evaluated the clinical outcome according to various BMI quartiles in patients with vs without OAC, and performed comparisons of outcomes with different antithrombotic approaches (no OAC vs

OAC; OAC + antiplatelet therapy vs OAC alone; NOACs vs VKAs) in obese patients (BMI in the 4$^{th}$ quartile)

We considered the following outcome measures:

- Thromboembolic events, including ischemic stroke, transient ischemic attack (TIA) or systemic embolic event. Stroke was classified according to the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) definition, i.e., abrupt onset of a focal neurologic deficit, generally distributed in the territory of a single brain artery (including the retinal artery) that is not attributable to an identifiable non-vascular cause (i.e., brain tumor or trauma) [21]. The deficit must either be characterized by symptoms lasting >24 hours or cause death within 24 hours of symptom onset. TIA was defined as focal neurologic deficit associated with symptoms lasting <24 hours. Systemic embolic event was classified as abrupt episode of arterial insufficiency with clinical or radiologic documentation of arterial occlusion in the absence of other likely mechanisms (i.e. atherosclerosis, instrumentation); venous thromboembolism and pulmonary embolism were also included in this outcome measure.
- Major bleeding, including fatal bleeding and/or bleeding into a critical organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome) and/or clinically relevant bleeding with a hemoglobin drop ≥2g/dL, consistent with the definition of major bleeding from the International Society on Thrombosis and Haemostasis [22].
- Any cardiovascular event, including ischemic stroke, TIA, systemic embolic event, acute coronary syndrome or coronary revascularization. Acute coronary syndrome was classified as unstable angina, with angiographic documentation of the culprit coronary vessel, or non-ST-segment elevation myocardial infarction or ST-segment elevation myocardial infarction. These were classified according to the definitions available at the time of conduct of the two studies, i.e., the 2011 European Society of Cardiology Guidelines on non-ST-segment elevation Acute Coronary Syndrome for unstable angina/Non ST-segment elevation myocardial infarction [23] and the Third Universal Definition for myocardial infarction, respectively [24]. Coronary revascularization included percutaneous coronary intervention (with or without stenting) or coronary artery bypass surgery for either recurrent stable angina or acute coronary syndrome.

**2.3. Statistics**

We indicated continuous variables as mean ± standard deviation or median and lower and upper quartiles, as appropriate. We reported discrete variables using frequency counts and percentages (n, %). We performed a complete case analysis with the assumption that data were missing at random. We compared baseline features according to BMI quartiles by the Chi-square test for discrete variables and the Wilcoxon rank sum test for continuous variables.

We calculated odds ratios (OR) and 95% confidence interval (CI) by logistic regression analysis between patients with and without events (dependent variables) according to different BMI quartiles in patients with similar antithrombotic strategy and according to different antithrombotic strategies (independent variables) within the same quartile. We included the following adjusting factors into the model: $CHA_2DS_2$-VASc score, HAS-BLED score, chronic renal failure, left atrial dilatation, chronic obstructive pulmonary disease and concomitant antiplatelet therapy. We also adjusted the analyses for demographic/clinical variables appearing statistically different between the two groups, as listed in **Table 1**. For the propensity score adjustment, all available baseline characteristics were initially used as inputs of the stepwise procedure. We selected the following 16 variables from possible 42 baseline parameters via a stepwise procedure into the propensity score: AF type, antiplatelet therapy, vascular disease, left atrial dilatation, previous ablation of AF, concomitant use of any antiarrhythmic drug, previous ischemic stroke, previous TIA, chronic liver disease, arterial hypertension, dyslipidaemia, concomitant coronary artery disease, congestive heart failure, age, BMI, maximum EHRA score. We then applied the propensity score-weighted logistic linear regression model to compare treatment effects in the inverse probability of treatment weighing (IPTW) model. The results of the propensity score are reported as *Supplementary material*. All analyses were purely descriptive/exploratory, and therefore no adjustment for multiple testing was done. All statistical analyses were performed using the SAS version 9.3 software, with a two-tailed significance value set at 0.05.

## 3. RESULTS

### 3.1. Population

This analysis was performed on individual data of 9,330 patients included in the two registries, in whom BMI at baseline and incidence of adverse events during follow-up were available. Of those patients, 360 were given no antithrombotic treatment, 682 received antiplatelet therapy only, and 8,288 were on OAC (4,774 on VKAs and 3,514 on NOACs). Mean follow-up duration was 12±2 months. A flow diagram showing how the final study population was obtained from the two registries is indicated in **Figure 1 of the Appendix.**

Main demographic and clinical characteristics at baseline according to BMI quartiles are reported in **Table 1**. A decreasing age by increase in BMI quartiles was observed; as expected, the proportion of female gender was higher in the lowest BMI quartile, and there was a higher prevalence of systemic hypertension, chronic obstructive pulmonary disease and left atrial dilatation by increasing BMI quartiles. The rate of congestive heart failure was highest in the 4$^{th}$ BMI quartile, whereas the $CHA_2DS_2$-VASc score was highest in the 1$^{st}$ quartile, mainly due to a higher prevalence of prior stroke/TIA.

### 3.2. Clinical outcome according to BMI quartiles with different antithrombotic strategies

Among patients without antithrombotic treatment, an increased incidence of thromboembolic events (stroke, TIA or systemic embolism) by increasing BMI quartiles was apparent (P=0.019) (**Figure 1, panel A**). In particular, the occurrence of thromboembolic complications was 7.23%/year in the 4$^{th}$ vs 0.95%/year in the 1$^{st}$ quartile (P=0.045). The rates of major bleeding were overall non-significantly different among various BMI quartiles (P=0.89), but the incidence of such complication was numerically the lowest in the 3$^{rd}$ quartile (**Figure 2, panel A**). A numerical increase in cardiovascular events was observed across BMI quartiles, with the incidence of this outcome measure being significantly higher in the 4$^{th}$ compared to the 1$^{st}$ quartile (9.64%/year vs 1.91%/year, P=0.024) (**Figure 2 of the Appendix, panel A**). Logistic regression analysis demonstrated a significant 9.5-fold increase in the risk of any cardiovascular complication in the highest vs the lowest quartile (OR 9.49, 95% CI 1.42-63.53, P=0.020), but the confidence interval is large, due to the low number of events.

The rate of patients undergoing cardioversion of AF during follow-up was 30.64% in the 4$^{th}$ quartile vs 31.11% in the lowest quartiles (P=0.65). AF ablation was performed in 4.95% of patients in the highest quartile vs 5.35% in the other quartiles (P=0.43). No data on percentages of success of cardioversion and ablation procedures were collected in the registries.

In patients on OAC, the rates of thromboembolic events were similar across different BMI quartiles (P=0.32) (**Figure 1, panel B**). The occurrence of major bleeding was lowest in the 3$^{rd}$ quartile (1.83%/year) and highest in the 1$^{st}$ and 4$^{th}$ quartiles (2.76%/year and 2.55/year, respectively) (**Figure 2, panel B**). Logistic regression analysis revealed a U-shaped curve: as compared with patients in the 3$^{rd}$ quartile, those in the 1$^{st}$ quartile had a significant 69% relative increase (OR 1.69, 95% CI 1.03-2.78; P=0.039), and those in the 4$^{th}$ quartile had an 86% relative increase in major bleeding (OR 1.86, 95% CI 1.13-3.04; P=0.014). The risk of any cardiovascular event was not significantly different across BMI quartiles (P=0.82) (**Figure 2 of the Appendix, panel B**).

### 3.3. Comparison of different antithrombotic approaches in obese patients

Among patients in the 4th BMI quartile, the occurrence of thromboembolic events in patients on OAC was significantly lower than in those without OAC (i.e., receiving antiplatelet treatment alone or no antithrombotic therapy): 1.70%/year vs 4.37%/year; OR=0.38, 95% CI 0.19, 0.77, P=0.006**.** The risk of major bleeding was similar in patients with and without OAC (2.55%/year and 2.62%/year, respectively, P=0.95)**.** The incidence of any cardiovascular event was 3.68%/year in those on OAC vs 6.11%/year in those without OAC (P=0.07, OR=0.59, 95% CI 0.33, 1.05, P=0.07). Odds ratios for adverse events adjusted also in the propensity score analysis in patients with vs without OAC were: thromboembolic events 0.30, 95% 0.13-0.67, P=0.0009; major bleeding 0.82, 95% CI 0.37-1.84, P=0.82; any cardiovascular event 0.38, 95% CI 0.23-0.64, P=0.001) (**Figure 3 of the Appendix**). The addition of antiplatelet therapy to OAC compared to OAC alone did not further reduce the occurrence of thromboembolic events (0.66%/year vs 1.87%/year, OR 0.35, 95% CI 0.08-1.47, P=0.21) and any cardiovascular event (3.65%/year vs 3.68%/year, OR 0.99, 95% CI 0.52-1.90, P=0.98), but significantly increased major bleeding (4.32%/year vs 2.25%/year, OR 1.96, 95% CI 1.04-3.70, P=0.035).

Similarly to what was observed in the whole cohort of patients on OAC, in the subgroup on NOACs the incidence of both thromboembolic and cardiovascular events was comparable across various BMI strata (**Figure 4 of the Appendix**). At propensity score analysis, the clinical outcome was evaluated in 910 patients on NOACs vs 1,210 patients on VKAs with BMI in the highest quartile. The event rates at one year were: thromboembolic events 1.98%/year vs 1.49%/year, OR 1.16, 95% CI 0.53-2.56, P=0.67; major bleeding 2.09%/year vs 2.89%/year, OR 0.68, 95% CI 0.33-1.38, P=0.34; any cardiovascular event 3.85%/year vs 3.55%/year, OR 1.06%, 95% CI 0.63-1.79, P=0.73) (**Figure 3**).

## 4. DISCUSSION

In this sub-analysis of two large, European prospective registries we found that, among OAC-naïve patients with AF, those in the 4th quartile of BMI feature a higher risk of thromboembolic events compared to those in the lower quartiles. OAC use in obese patients significantly reduces the rates of thromboembolic events to an extent similar to those with lower BMI. Moreover, obese patients are also at increased risk of bleeding complications. NOAC treatment was associated with a comparable occurrence of thromboembolic events across various BMI strata. Safety and efficacy of NOACs and VKAs in obese patients were similar.

Several studies, mainly sub-analyses from randomized trials on anticoagulated patients, had shown the obesity paradox, i.e. an inverse relationship between BMI and overall death, cardiovascular mortality or stroke in AF [8-12]. Various mechanisms have been proposed to explain the lower mortality in obese patients [25]: a different pathophysiologic substrate of the arrhythmia; a lower increases in plasma renin and angiotensin in response to stress; greater metabolic reserve to counteract the increased catabolic stress related to disease progression and exacerbations; younger age and, due to a higher prevalence of risk factors such as diabetes and hypertension, a larger utilization of evidence-based disease-modifying treatments, such as ACE-inhibitors, beta-blockers, lipid lowering drugs; higher prevalence of symptomatic arrhythmic episodes, as well as of prevalent/persistent AF, leading to a larger use of oral anticoagulant therapy and rhythm control strategies, including cardioversion and catheter-based ablation; attenuation in natriuretic peptide levels, adding a protective mechanism alongside the production of tumor necrosis factor-alfa receptors in the adipose tissue, which reduces inflammation. However, other investigations, mainly observational and population-based cohort studies, showed no reduction of overall death, cardiovascular mortality or stroke in obese patients with AF [13-15]. Notably, in the SPORTIF trials [10], including AF patients on VKAs, an obesity paradox was observed only in the subgroup with inadequate INR control. Variable patients risk profiles, concomitant therapies and assessments of the outcome measures, as well as differences in the statistical adjustments for confounding factors, may, at least in part, explain the controversial results on the obesity paradox in AF. To date no study specifically evaluated the relationship between BMI and thromboembolic events according to various and different antithrombotic approaches.

In the present analysis we extracted individual data from >9,300 AF patients enrolled in two multicenter, prospective, real-world registries (PREFER in AF and PREFER in AF PROLONGATION), and assessed the incidence of adverse cardiovascular events and major bleeding at one year across various BMI strata and according to different anticoagulation strategies (no OAC, OAC, type of OAC). In obese patients without antithrombotic treatment we observed a ≥6-fold increased risk of stroke, TIA or systemic embolism compared to those with a lower BMI. The propensity to ischemic complications in obese patients may be explained by a pro-thrombotic status related to immobility, stasis, higher inflammation, enhanced platelet reactivity, increased production of coagulation factors (fibrinogen, von Willebrand factor (VWF), plasminogen activator inhibitor (PAI)-1, factor VII, VIII, IX, XII) and reduced endogenous fibrinolysis [25,26]. Hence, the initiation and maintenance of oral anticoagulation appear mandatory in obese patients with AF, and refraining from such therapy exposes them to an unacceptable risk. Similarly, when all ischemic events (both vascular and coronary) were counted, obese patients showed the highest risk at one

year. Of note, OAC equalized the rates of both thromboembolic and coronary complications across different BMI strata. It may be hypothesized that the pro-thrombotic status associated with a higher body weight protects from bleeding. This analysis seems to disprove such hypothesis, confirming and further expanding the results of the SMART study [26], where the bleeding risk was higher in patients with the lowest BMI and comparable across other BMI strata. In our investigation the rates of major bleeding followed an U-shaped curve, with values in the 4$^{th}$ quartile higher than in the 3$^{rd}$ quartile and similar to those in the lowest quartile; after adjustment for potential confounder this was more evident in the subgroup receiving OAC. Accordingly, both low BMI and obesity are associated with bleeding events, and on OAC the risk of hemorrhagic complications in obese patients is not dissimilar to underweight or normal weight patients. Thus, despite a pro-thrombotic status, obese patients are also prone to bleeding, probably because of a higher prevalence of factors (hypertension, diabetes, liver disease) that increase the hemorrhagic risk, thereby counteracting the effect of the pro-coagulant hemostatic milieu. As a consequence, in obese patients with AF the selection of the type of anticoagulant therapy with the best safety profile appears crucial. Of note, an analysis from the ENGAGE AF-TIMI 48 trial showed an independent increase in the risk of bleeding events for each 5 kg/m$^2$ BMI increase [27].

We then focused on the evaluation of clinical outcomes with different antithrombotic approaches in obese patients (i.e., those in the 4$^{th}$ BMI quartile). Here, after adjustment for potential confounders and for propensity score, OAC use was associated with a 70% relative reduction of thromboembolic events vs no OAC (no antithrombotic treatment or antiplatelet therapy). Importantly, the occurrence of major bleeding was similar in patients with and without OAC; the prescription of OAC in patients with a basically lower bleeding risk, as well as the non-negligible bleeding risk related to antiplatelet therapy in the no-OAC group, may explain this finding. Of note, the addition of antiplatelet therapy to OAC did not further decrease the rates of both thromboembolic and cardiovascular event, but significantly increased major bleeding complications; this confirms the results of our PREFER in AF and PREFER in AF PROLONGATON sub-analysis on patients with myocardial infarction and/or previous coronary stenting [28].

Concerns on the efficacy of NOACs in obese patients exist, due to the high prevalence of comorbid conditions potentially influencing the clinical effects of these agents, as well as to variations in distribution volumes and drug renal clearance [29]. Previous pharmacokinetic data on healthy individuals indicated a 31% reduction in Cmax and a 23% decrease in the area under the curve of apixaban in those with body weight >120 kg [30]. Moreover, a sub-analysis from the ARISTOTLE trial [9] showed smaller relative reductions of both major bleeding and stroke with

apixaban vs warfarin in more obese patients. A recent meta-analysis indicated higher efficacy and safety with NOACs compared to warfarin in underweight, normal weight and overweight patients, but not in obese patients [12]. Our study demonstrated consistent rates of ischemic events across various BMI quartiles with NOACs. In obese patients we observed no significant reduction of thromboembolic and bleeding events with NOACs vs VKAs; however, the advantages of NOACs over VKAs in terms of rapid onset/offset of action, no need for monitoring, low drug interactions and no interaction with foods must be here mentioned.

This analysis has strengths and limitations. PREFER in AF and PREFER in AF PROLONGATION were prospective studies, where, by protocol, a complete baseline evaluation and a nearly complete one-year follow-up, with accurate assessment of treatments and outcome measures, were performed [31-33]. Bias in patient recruitment and selection in treatment decision cannot be excluded, although the enrollment of all consecutive patients at each site was mandatory. There was not an independent, external event adjudication and on-site verification of source data was performed in a minority of centers. Our results were adjusted for possible confounding variables, but residual confounding may exist. Data collected by the two registries derive from Western European countries: thus, caution is needed in extrapolating the results of this analysis to patients from other countries, as well as to patients managed in different clinical settings as compared with PREFER in AF and PREFER in AF PROLONGATION participants. Moreover, no data on specific measures of abdominal adiposity (namely waist circumference) were collected. Both PREFER in AF and PREFER in AF PROLONGATION were conducted before the introduction of edoxaban in clinical practice; thus, no outcome data on patients receiving this type of NOAC are available. However, in the ENSURE trial the difference in the incidence of ischemic events favoring edoxaban vs warfarin was maintained across various BMI strata [13]. We did not take BMI changes during follow-up into account, as well as for other factors, such as nutritional intake or physical activity patterns, that might have influenced our results. Furthermore, the study may be underpowered to selectively evaluate outcome measures at very low incidence, i.e. intracranial bleeding, with NOACs vs VKAs use. Finally, the success of cardioversion and ablation procedures during follow-up in both registries did not represent outcome measures, and therefore such endpoints were not specifically and systematically collected. Thus, we were not able to report the rates of cardioversion and ablation success according to BMI strata.

In conclusion, this analysis indicates no obesity paradox for the incidence of thromboembolic events in AF patients with or without OAC. Notably, a recent analysis from the prospective START-ANTIPLATELET registry also contested the obesity paradox for

cardiovascular events also in the setting of patients with acute coronary syndrome [34]. According to our data, obese patients with AF are at very high risk of thromboembolic events, and OAC use significantly reduces such risk. Obese patients are also prone to bleeding, and should receive the type of OAC with the best safety profile. Logical considerations on NOAC advantages, added to evidence-based data, make these agents the first-choice anticoagulants in this setting of patients. However, as in AF patients with morbid obesity some concerns related to a possible lower efficacy of NOACs due to inadequate drug concentrations may exist, studies comparing clinical outcome with NOACs vs warfarin in this setting would be welcome.

**Funding**

This analysis of the PREFER in AF and PREFER in AF PROLONGATION registries was initiated by the Thrombosis Exchange Meeting in AF, TEAM in AF, funded and sponsored by Daiichi Sankyo Europe.

**Competing interests**

GP: speaker/consultant/advisory board for Amgen, Sanofi, Bayer, Boehringer-Ingelheim, BMS-Pfizer, Daiichi Sankyo, Astra Zeneca, Sigma-Tau, Malesci, PIAM and MSD.
LP: consultant fees from Daiichi-Sankyo, SOTIO, Beckman Coulter, Novartis.

MCM is currently an employee of Daiichi Sankyo Europe.

KH: lecture and consultant fees from Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Daiichi Sankyo and Pfizer.

MR: speaker and advisory fees from Daiichi-Sankyo.

GR: speaker/consultant/advisory board for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi Sankyo.

JSM: lecture or consultant fees from AstraZeneca, Daiichi Sankyo, Eli Lilly, Bayer, Chiesi, Bristol Meyer Squibb.

FR: none

PK: research support from the British Heart Foundation, the European Union, Leducq Foundation, and German Centre for Heart Research, from several drug and device companies active in atrial

fibrillation, and has received honoraria from several such companies. F Syeda, L Fabritz, and P Kirchhof are listed as inventors on a patent (WO2015/140571) held by University of Birmingham on genotype-specific antiarrhythmic drug therapy of atrial fibrillation.

RDC: fees, honoraria and research funding from Sanofi-Aventis, Boehringer Ingelheim, Bayer, BMS/Pfizer, Daiichi Sankyo, Novartis, MSD and Portola.

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**FIGURE LEGENDS**

**Figure 1.** *Panel A:* Incidence of thromboembolic events across different BMI quartiles among patients without antithrombotic therapy. *Panel B:* Incidence of thromboembolic events in BMI quartiles among patients with oral anticoagulant therapy. BMI= Body mass index; OAC= Oral anticoagulant therapy.

**Figure 2.** *Panel A:* Incidence of major bleeding across different BMI quartiles among patients without antithrombotic therapy. *Panel B:* Incidence of major bleeding across different BMI quartiles among patients with oral anticoagulant therapy. BMI= Body mass index; OAC= Oral anticoagulant therapy.

**Figure 3.** Incidence of adverse events and ORs adjusted for the propensity score among patients in the 4$^{th}$ BMI quartile with NOACs vs VKAs. BMI = Body mass index; CV = Cardiovascular; NOACs = Non-vitamin K antagonist oral anticoagulants; TE = Thromboembolic; VKAs = Vitamin K antagonist anticoagulants.

**Figure 1 of the Appendix.** Flow diagram showing how the final study population was obtained from the two registries.

**Figure 2 of the Appendix.** *Panel A:* Incidence of cardiovascular events across different BMI quartiles among patients without antithrombotic therapy. *Panel B:* Incidence of cardiovascular events across different BMI quartiles among patients with oral anticoagulant therapy. BMI= Body mass index; OAC= Oral anticoagulant therapy.

**Figure 3 of the Appendix.** Incidence of adverse events and ORs, adjusted for the propensity score, among patients in the 4$^{th}$ BMI quartile with vs without OAC. BMI = Body mass index; CV = Cardiovascular; OAC = Oral anticoagulant therapy; TE = Thromboembolic

**Figure 4 of the Appendix.** Incidence of thromboembolic (*Panel A*) and cardiovascular (*Panel B*) events across various BMI quartiles in the subgroup of patients receiving NOACs. BMI= Body mass index; NOACs= Non-vitamin K antagonist oral anticoagulants

# Thromboembolic and Bleeding Risk in Obese Patients with Atrial Fibrillation According to Different Anticoagulation Strategies


## ABSTRACT

**Background**. Data on the relationship between body mass index (BMI), thromboembolic events (TEE) and bleeding in patients with atrial fibrillation (AF) are controversial, and further evidence on the risk of such events in obese patients with AF receiving different anticoagulant therapies (OAC) is needed.

**Methods and Results.** We divided a total of 9,330 participants from the prospective PREFER in AF and PREFER in AF PROLONGATION registries into BMI quartiles at baseline. Outcome measures were TEE and major bleeding complications at the 1-year follow-up. Without OAC, there was a ≥6-fold increase of TEE in the 4$^{th}$ vs other BMI quartiles (P=0.019). OAC equalized the rates of TEE across different BMI strata. The occurrence of major bleeding was highest in patients with BMI in the 1$^{st}$ as well as in the 4$^{th}$ BMI quartile [OR 1.69, 95% CI 1.03-2.78, P=0.039 and OR 1.86, 95% CI 1.13-3.04, P=0.014 vs those in the 3$^{rd}$ quartile, respectively]. At propensity score-adjusted analysis, the incidence of TEE and major bleeding in obese patients receiving non-vitamin K antagonist oral anticoagulants (NOACs) or vitamin K-antagonist anticoagulants (VKAs) was similar (P≥0.34).

**Conclusions**. Our real-world data suggest no obesity paradox for TEE in patients with AF. Obese patients are at higher risk of TEE, and here OAC dramatically reduces the risk of events. We here found a comparable clinical outcome with NOACs and VKAs in obese patients. Low body weight and obesity were also associated with bleeding, and therefore OAC with the best safety profile should be considered in this setting.

**Table 1.** Baseline characteristics according to different BMI quartiles*.

| Variable | Q1 (14.0 to 24.6 kg/m$^2$) | Q2 (24.7 to 27.2 kg/m$^2$) | Q3 (27.3 to 30.5 kg/m$^2$) | (3 |
|---|---|---|---|---|
| Age (years) | 74.1 ± 10.5 (76.0) | 72.4 ± 10.2 (74.0) | 71.8 ± 9.5 (73.0) | |
| Female gender | 1177 (50.3) | 785 (34.3) | 803 (33.4) | |
| Systemic hypertension | 1515 (65.1) | 1635 (71.8) | 1851 (77.3) | |
| Congestive heart failure | 609 (26.5) | 636 (28.3) | 616 (26.0) | |
| $CHA_2DS_2$-VASc | 3.50 ± 1.72 (3.0) | 3.34 ± 1.74 (3.0) | 3.36 ± 1.67 (3.0) | |
| HAS-BLED | 1.99 ± 1.10 (2.0) | 2.00 ± 1.12 (2.0) | 2.01 ± 1.12 (2.0) | |
| Left ventricular ejection fraction | 57.3 ± 11.6 (60.0) | 57.1 ± 11.3 (60.0) | 57.3 ± 11.7 (60.0) | 5 |
| Prior TIA/stroke/thromboembolism | 403 (17.4) | 377 (16.6) | 375 (15.7) | |
| Vascular disease | 430 (19.8) | 456 (21.5) | 437 (19.5) | |
| Chronic renal failure | 354 (15.3) | 361 (16.0) | 374 (15.8) | |
| Left atrial dilatation (diameter >40 mm) | 1239 (61.1) | 1314 (66.4) | 1393 (68.7) | |
| Chronic obstructive pulmonary disease | 214 (9.2) | 220 (9.7) | 233 (9.8) | |
| Antithrombotic therapy | | | | |
| No therapy | 105 (5.5) | 87 (3.8) | 85 (3.5) | |
| Antiplatelet only | 190 (8.1) | 175 (7.7) | 171 (7.1) | |
| OAC only | 1795 (76.7) | 1761 (77.0) | 1890 (78.6) | |
| OAC + antiPLT | 250 (10.7) | 265 (11.6) | 242 (10.1) | |
| Type of OAC | | | | |
| VKAs only | 1045 (44.7) | 994 (43.4) | 1078 (44.8) | |
| VKAs + antiplatelet therapy | 144 (6.2) | 143 (6.3) | 144 (6.2) | |
| NOACs only | 750 (32.1) | 767 (33.5) | 812 (33.8) | |
| NOACs + antiplatelet therapy | 106 (4.5) | 122 (5.3) | 98 (4.1) | |
| Type of NOAC | | | | |
| Dabigatran | 243 (10.4) | 260 (11.4) | 249 (10.4) | |
| Rivaroxaban | 415 (17.7) | 446 (19.5) | 436 (18.1) | |
| Apixaban | 198 (8.5) | 183 (8.0) | 225 (9.4) | |

* BMI at baseline was missing in 240 patients, due to missing height. These patients were not included in this analysis

BMI= Body mass index; NOAC= Non-vitamin K antagonist oral anticoagulants; OAC= Oral anticoagulant therapy, TIA= Transient ischemic attack; VKA= vitamin K-antagonist anticoagulant.

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**I declare that: Dr. G. Patti designed the study; Dr. M.C. Manu performed data collection; Dr. L. Pecen performed the analysis; interpretation of the results was done by all authors; the paper was drafted by Dr. G. Patti; critical revision of the paper for important intellectual content was done by all authors.**

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## Highlights

- Patients with atrial fibrillation and BMI in the 4$^{th}$ quartile not receiving oral anticoagulation feature a higher risk of thromboembolic events compared to those in the lower quartiles.
- Oral anticoagulation significantly reduces the rates of thromboembolic events also in obese patients with atrial fibrillation
- Obese patients are also at increased risk of bleeding complications.
- Safety and efficacy of NOACs and VKAs in obese patients were similar.