Zagazig University Medical Journal
www.zumj.journals.ekb.eg

https://doi.org/10.21608/zumj.2024.234154.2873 Volume 30, Issue 1.6, September 2024, Supplement Issue

Manuscript ID:ZUMJ-2312-3034(R1) DOI:10.21608/ZUMJ.2024.253538.3034.

ORIGINAL ARTICLE

# Obesity and Non-Valvular Atrial Fibrillation: An Unexpected Paradox

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Submit Date 17-12-2023
Revise Date 17-01-2024
Accept Date 18-01-2024

**ABSTRACT**

**Background:** Obesity is believed to be one of the major cardiovascular morbidity and mortality risk factors. Furthermore, a strong link has been observed between obesity and atrial fibrillation, the most common cardiac arrhythmia. We aimedto assess how obesity affects anticoagulation outcomes for bleeding and thrombotic incidents in patients with non-valvular atrial fibrillation and investigate the paradox of obesity in thesepatients. **Results:**Of the 300 cases, 105 were obese according to BMI. Besides obesity, hypertension, diabetes mellitus, smoking, dyslipidemia, CHA2DS2-VASc score, and the number of episodes were independent predictors for MACEs. Warfarin-treated non-obese patients had more complications than their obese counterparts. In contrast, the difference in complication rates among patients on DOACs was insignificant between the two groups. **Conclusions:** Non-valvular atrial fibrillation patients with obesity have a paradoxically lower risk of bleeding, stroke, and cardiovascular mortality on vitamin K antagonist treatment than non-obese patients.

**Keywords:** Non-valvular Atrial Fibrillation, Obesity, MACEs.

## INTRODUCTION

Obesity is a major risk factor in the general population for cardiovascular disease (CVD) and mortality [1]. A notable positive link has been observed between body mass index (BMI) and the likelihood of developing cardiovascular disease (CVD) [2]. Long-term follow-up studies have revealed an "obesity paradox," which suggests that overweight or obese individuals may have a better cardiovascular prognosis [3,4]. Studies show that patients with cardiovascular diseases like heart failure, hypertension, and ischemic heart disease exhibit the obesity paradox [6].

Atrial fibrillation (AF) is a persistent cardiac arrhythmia strongly associated with obesity. Several studies have shown a significant link between obesity and the occurrence of AF, supported by evidence regarding epidemiology, mechanism, and clinical data [6]. In patients with established AF, there is also a discernible obesity paradox in the incidence of major adverse cardiovascular events (MACEs) [7]. The ARIC (Atherosclerosis Risk in Communities) study discovered that a higher body mass index was responsible for 17.9% of incident AF cases, second only to hypertension in frequency [8]. In longitudinal cohort studies, the probability of developing persistent AF increased linearly with increasing obesity [9,10]. Research shows that obesity leads to an increased incidence of AF due to a complex process that involves atrial electrical remodeling, fatty tissue infiltration from epicardial fat, and interstitial fibrosis [11,12,13].

Our study aimed to evaluate the effect of obesity on the thromboembolic and hemorrhagic outcomes of anticoagulation in individuals suffering from non-valvular atrial fibrillation, as well as to assess the link between body mass index (BMI) and the responsiveness of patients to medical therapy, the rate of recurrence of clinical episodes of AF, and progression to persistent or long-standing AF.

## METHODS

This observational prospective follow-up study was carried out at a tertiary center. The study screened 389 patients with non-valvular AF who were treated at Assiut University Heart Hospital between October 1, 2019, and September 30, 2020, from the hospital database.

***Inclusion criteria:***Individuals who were diagnosed with non-valvular atrial fibrillation (AF), which is defined as atrial fibrillation that is not caused by valvular heart disease, and were receiving oral anticoagulant therapy, specifically direct oral anticoagulants (DOACS) or vitamin K antagonists (VKA).

***Exclusion criteria:*** Patients whohave a history of bleeding tendency, mechanical prosthetic heart valves, valvular AF (including moderate/severe mitral stenosis), a history of cerebrovascular stroke, mental retardation, or chronic renal impairment (defined as abnormalities of kidney structure or function for three months with health implications) [14]. Chronic kidney disease (CKD) is defined as a drop in glomerular filtration rate (GFR) of less than 60 ml/min/1.73 $m^2$, as estimated by the Cockcroft-Gault method [14, 15]. Also, patients who had absolute or relative contraindications to the oral anticoagulation therapy and had high risk of bleeding, according to the CHAD2S2-VASc score.

***Sample Size:***The study screened 389 patients withnon-valvular AF. Out of this group, 361 patients were enrolled in this study, one patient refused to participate, and 27 patients were out of reach. From the enrolled group, 320 patients had sufficient data for analysis and 41 had critical missing data and were excluded from the analysis. Out of these patients with complete data, 300 patients (93.75%) were followed up, and 20 patients (6.25%) were lost to follow-up(Figure 1).

***Data Collection and Procedures:***

The observational approach was chosen for this study so that patients could be assessed in their regular lifestyle without restrictions to their dietary or lifestyle habits.

The data collected included information about the patient's age, sex, and medical history, including any previous diagnoses of diabetes mellitus (DM), hypertension (HTN), smoking habits, and dyslipidemia. Vital signs were measured based on the European Society of Cardiology (ESC) guidelines for arterial hypertension, using a mercury sphygmomanometer to assess arterial pulse and blood pressure [4]. The patient's height and weight were measured at the presentation to determine their BMI, calculated by dividing their weight in kilograms by their height in meters squared ($kg/m^2$) [16].

All patients underwent a 12-lead resting ECG evaluation by a cardiologist within 10 minutes of hospital arrival. All patients underwent transthoracic two-dimensional echocardiography using a GE VIVID S5 ultrasound system to assess left atrium (LA) diameter and exclude LA thrombus [17].

For six months, all research participants were monitored for any significant adverse cardiovascular events, such as cardiac deaths, all-cause deaths, strokes, and thromboembolic complications. Follow-up information was gathered via hospital records, patient interviews (in-person or over the phone), family interviews, and primary care physician consultations.

***Ethical and administrative considerations:*** All participants received thorough and accurate information about the study's methods and their rights before the experiment. Each subject provided informed consent after receiving comprehensive information regarding each study phase. Participants received information that all information gathered will be kept private and used exclusively for legitimate scientific research.Additionally, the ethics committee of the Assiut University Faculty of Medicine authorized the study (approval number:

17100752).The research was conducted in adherence to the World Medical Association's Code of Ethics (Declaration of Helsinki) regarding human experimentation.

## STATISTICAL ANALYSIS

The researcher verified and coded the data, then analyzed it using IBM-SPSS 24.0 (Statistical Package for the Social Sciences, version 24, IBM, and Armonk, New York). The following descriptive statistics were computed: means, medians, standard deviations, frequencies, ranges, and percentages. The Chi-square/Monte Carlo Exact test (MCE) was implemented to assess the disparity between the frequency distributions of several groups. For continuous variables with more than two categories, such as BMI categories, the one-way ANOVA test was used to assess mean differences of the data, with a post-hoc test calculated using Bonferroni corrections. Factors with proven statistical significance from bivariate analyses were used in multivariable logistic regression models for the independent effect of obesity on disease complications. A significant P-value was considered when it was less than 0.05.

## RESULTS

Three hundred patients identified as non-valvular AF were screened for eligibility at Assiut University Heart Hospital during the study period. According to BMI, patients were categorized into two groups: group I: non-obese (< 30 kg/m2) and group II: obese (≥ 30 kg/m2) [18].

Table (1) shows the baseline characteristics of the study patients, with no statistically significant differences in the distributions of age and sex between the two groups. We found that obese patients had a higher incidence of dyslipidemia compared to non-obese patients (P=0.001), as illustrated in figure (2). In contrast, figure (3) shows that a majority of non-obese patients were smokers compared to obese patients (P=0.035). There were no significant differences in the incidence of hypertension (HTN) and diabetes mellitus (DM) between both groups.

Regarding cardiac findings, we found that the mean heart rate (HR) had astatistically significantly higher value in the obese group than the non-obese group (P=0.024). The distribution of AF pattern (paroxysmal or persistent) and CHA2DS2-VASc score were statistically insignificant between both groups, as shown in table (2).

It was found that there were statistically insignificant differences among both BMI groups regarding left atrium (LA) diameter and LA thrombus by echocardiography assessment(Table 3).There wasa statistically insignificant difference in the rate of occurrence of thromboembolic, bleeding, and cerebrovascular stroke (CVS) complications or even death rates among both BMI categories. Likewise, nostatistically significant difference was detected for the international normalized ratio (INR) target among two groups (P=0.087)(Table 4).

Table (5) shows the multivariable logistic regression analysis outcomes that examined the independent factors associated with complications in the studied group. After matching for age and sex, the study found that obesity was statistically significantly associated with complications (P=0.006). The final model identified six independent predictors of complications, including diabetes, hypertension, dyslipidemia, smoking, CHA2DS2-VASc score, and the rate of tachy-palpitation attacks. We found that patients with diabetes mellitus had a 3.2 times higher risk of having complications (P=0.001), while hypertensive patients had twice the risk (P=0.037). Similarly, patients with dyslipidemia had 2.4 times the risk of complications (P=0.007), and smokers were 2.2 times more likely to have complications (P=0.003). Furthermore, the study found that with each one-point increase in the

CHA2DS2-VASc score, the risk of complications increased by 2.2 times (P<0.001). Additionally, for each one-point increase in the number of tachy-palpitation attacks, the risk of complications increased by 38% (P=0.049).

Tables (6) and (7) depict the occurrence of complications in each BMI category according to the type of treatment and AF pattern. The non-obese group treated with warfarin had more incidence of complications than the obese group (P=0.037). However, the difference in the rate of complications among patients with different AF patterns, paroxysmal or persistent, and those treated with DOACs was not significant.

**Table (1):** Baseline data of studied patients.

| Variables | Non-obese (n = 195) | Obese (n = 105) | P-value* |
|---|---|---|---|
| **Age/year** | 64.36 ± 11.9 | 63.93 ± 10.9 | = 0.755* |
| **Sex:** | | | |
| **Male** | 129 (66.2%) | 58 (55.2%) | = 0.083** |
| **Female** | 66 (33.8%) | 47 (44.8%) | |
| **DM** | | | |
| Yes | 68 (34.9%) | 43 (41%) | = 0.298** |
| No | 127 (65.1%) | 62 (59%) | |
| **Dyslipidemia** | | | |
| Yes | 119 (61%) | 84 (80%) | **= 0.001**** |
| No | 76 (39%) | 21 (20%) | |
| **Smoking** | | | |
| Yes | 101 (51.8%) | 41 (39%) | **= 0.035**** |
| No | 94 (48.2%) | 64 (61%) | |
| **HTN** | | | |
| Yes | 92 (47.2%) | 59 (56.2%) | = 0.137** |
| No | 103 (52.8%) | 46 (43.8%) | |
| **SBP (mmHg)** | 117.03 ± 14.3 | 118.10 ± 15.9 | = 0.558* |
| **DBP (mmHg)** | 75.54 ± 11.2 | 75.02 ± 11.1 | = 0.718* |

*Independent sample t-test was used to compare the mean difference among both groups. **Chi-square test was used to compare the proportion difference among both groups.DM: Diabetes mellitus. HTN: Hypertension. SBP: Systolic blood pressure. DBP: Diastolic blood pressure.

**Table (2):**Clinical data of studied patients.

| Variables | Non-obese (n = 195) | Obese (n = 105) | P-value* |
|---|---|---|---|
| **HR (beat/min)** | 91.51 ± 14.6 | 99.10 ± 16.8 | **= 0.024*** |
| **AF Pattern**<br>**•Paroxysmal**<br>**•Persistent** | <br>124 (63.6%)<br>71 (36.4%) | <br>68 (64.8%)<br>37 (35.2%) | = 0.840** |
| **$CHA_2DS_2VASc$ score**<br>**Low Risk**<br>**High Risk** | <br>35 (17.9%)<br>160 (82.1%) | <br>21 (20%)<br>84 (80%) | 0.664** |

*Independent sample t-test was used to compare the mean difference among both groups.**Chi-square test was used to compare the proportion difference among both groups. HR: Heart rate. AF: Atrial fibrillation.

**Table (3):** Echocardiographic data of studied patients.

| Variables | Non-obese (n = 195) | Obese (n = 105) | P-value* |
|---|---|---|---|
| **LA diameter** | 4.48 ± 0.8 | 4.52 ± 0.7 | = 0.696* |
| **LA thrombus**<br>**Yes**<br>**No** | <br>1 (0.5%)<br>194 (99.5%) | <br>0 (0%)<br>105 (100%) | = 0.650** |

*Independent sample t-test was used to compare the mean difference among both groups. **Chi-square test was used to compare the proportion difference among both groups. LA: Left atrium.

**Table (4):** Complications data of studied patients.

| Variables | Non-obese (n = 195) | Obese (n = 105) | P-value* |
|---|---|---|---|
| **Ischemic Manifestation**<br>• **No**<br>• **Yes** | <br>98 (50.3%)<br>97 (49.7%) | <br>50 (47.6%)<br>55 (52.4%) | = 0.663** |
| **No. of tachy-palpitation attacks** | 2.32 ± 0.1 | 2.18 ± 0.1 | = 0.280* |
| **Complications**<br>• **Bleeding**<br>• **CVS**<br>• **Death** | <br>13 (6.7%)<br>24 (12.3%)<br>61 (31.3%) | <br>3 (2.9%)<br>9 (8.6%)<br>26 (24.8%) | <br>= 0.127***<br>= 0.324**<br>= 0.235*** |
| **Target INR**<br>• **Yes**<br>• **No**<br>• **Non** | <br>97 (49.7%)<br>51 (26.2%)<br>47 (24.1%) | <br>62 (57.1%)<br>17 (16.2%)<br>26 (24.8%) | = 0.087** |

*Independent sample t-test was used to compare the mean difference among both groups.**Chi-square test was used to compare the proportion difference among both groups. ***MCE test was used to compare the proportion difference among both groups. CVS: Cerebrovascular stroke. INR: international normalized ratio.

**Table 5:** Independent effect of obesity on complications among studied patients: Multivariate logistic regression model.

| Variables | OR (95% CI) * | P-value |
|---|---|---|
| **Age/years** | 0.997 (0.966 – 1.029) | = 0.835 |
| **Sex (Female)** | 0.445 (0.172 – 1.156) | = 0.097 |
| **BMI Category** | | |
| **Non-obese** | 1 (Reference) | **= 0.006** |
| **Obese** | 0.585 (0.358 – 0.953) | **= 0.031** |
| **DM** | 3.226 (1.613 – 6.453) | **= 0.001** |
| **HTN** | 2.123 (1.045 – 4.352) | **= 0.037** |
| **Dyslipidemia** | 2.410 (1.279 – 4.559) | **= 0.007** |
| **Smoker** | 2.254 (1.102 – 4.633) | **= 0.003** |
| **$CHA_2DS_2$-VASc score** | 2.246 (1.638 – 3.081) | **< 0.001** |
| **Number of attacks** | 1.376 (1.001 – 1.890) | **= 0.049** |

**Table 6**:Relationship of complications rate to AF pattern among BMI categories.

| Variables | Non-obese (n = 195) | Obese (n = 105) | P-value* |
|---|---|---|---|
| **AF Pattern** | | | |
| **Paroxysmal** | 124 (63.6%) | 68 (64.8%) | = 0.127 |
| **• Complications** | 56 (45.2%) | 23 (33.8%) | |
| **Persistent** | 71 (36.4%) | 37 (35.2%) | = 0.122 |
| **• Complications** | 38 (53.5%) | 14 (37.8%) | |

**Table (7):** Rate of complications concerning treatment among BMI categories.

| | Non-obese (n = 195) | Obese (n = 105) | P-value |
|---|---|---|---|
| **Treatment** | | | |
| **Warfarin** | 148 (75.9%) | 79 (75.2%) | **= 0.037*** |
| • **Complications$** | 76 (51.4%) | 30 (38%) | |
| ○**Bleeding** | 12 (8.1%) | 3 (3.8%) | = 0.082** |
| ○**CVS** | 20 (13.5%) | 6 (7.6%) | = 0.075** |
| ○**Death** | 47 (31.8%) | 22 (27.8%) | = 0.542* |
| **DOACs** | 47 (24.1%) | 26 (24.8%) | = 0.236 |
| • **Complications** | 18 (38.3%) | 7 (26.9%) | |
| ○**Bleeding** | 1 (2.1%) | 0 (0%) | = 0.644** |
| ○**CVS** | 4 (8.5%) | 3 (11.5%) | = 0.694** |
| ○**Death** | 14 (29.8%) | 4 (15.4%) | = 0.093* |

*Chi-square test was used to compare the proportion difference between groups.

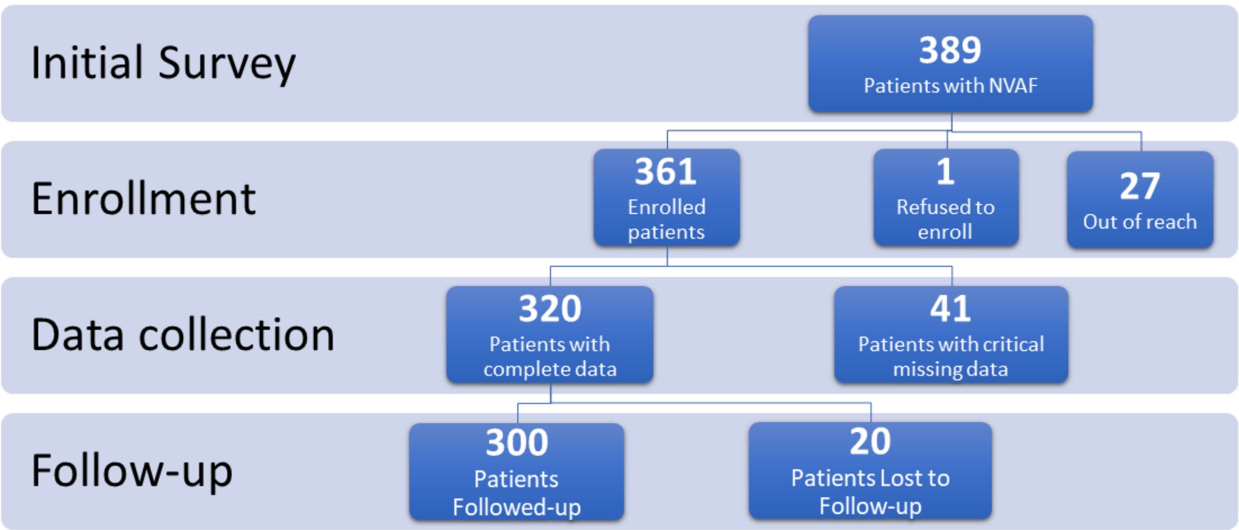


*Figure 1:* ***Patient study flow diagram.***

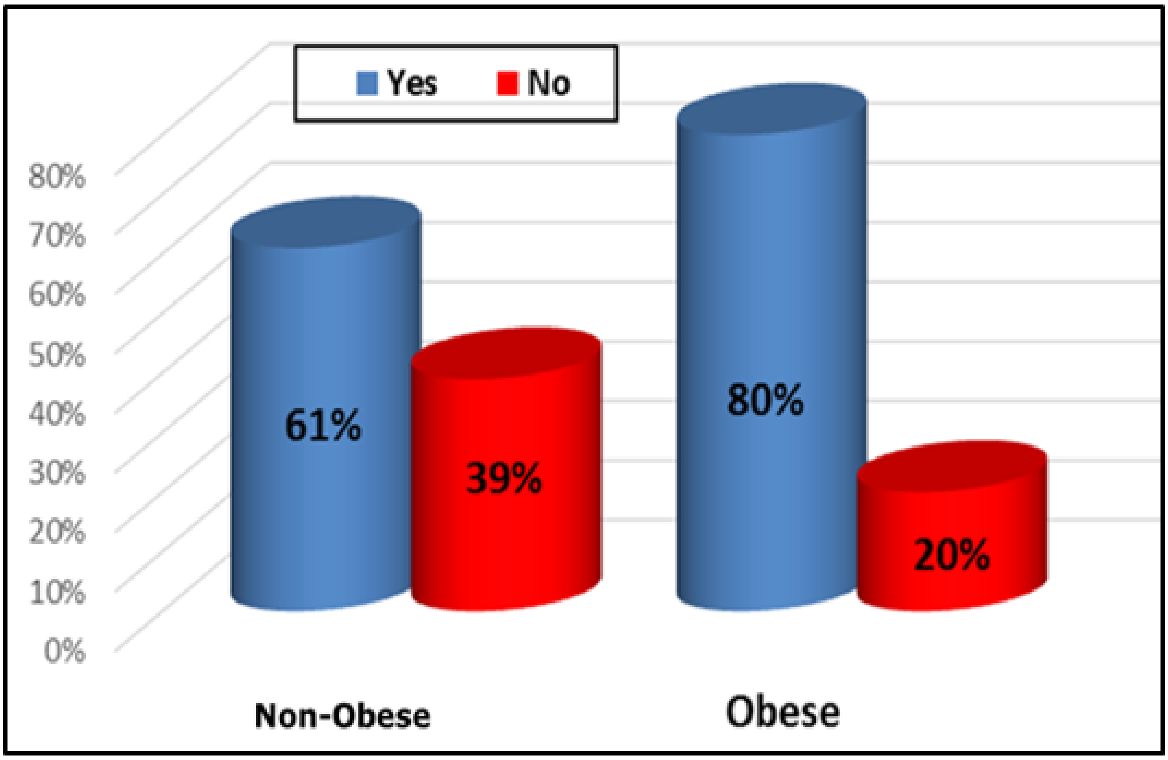


*Figure 2:* ***Relationship between dyslipidemia and BMI categories.***

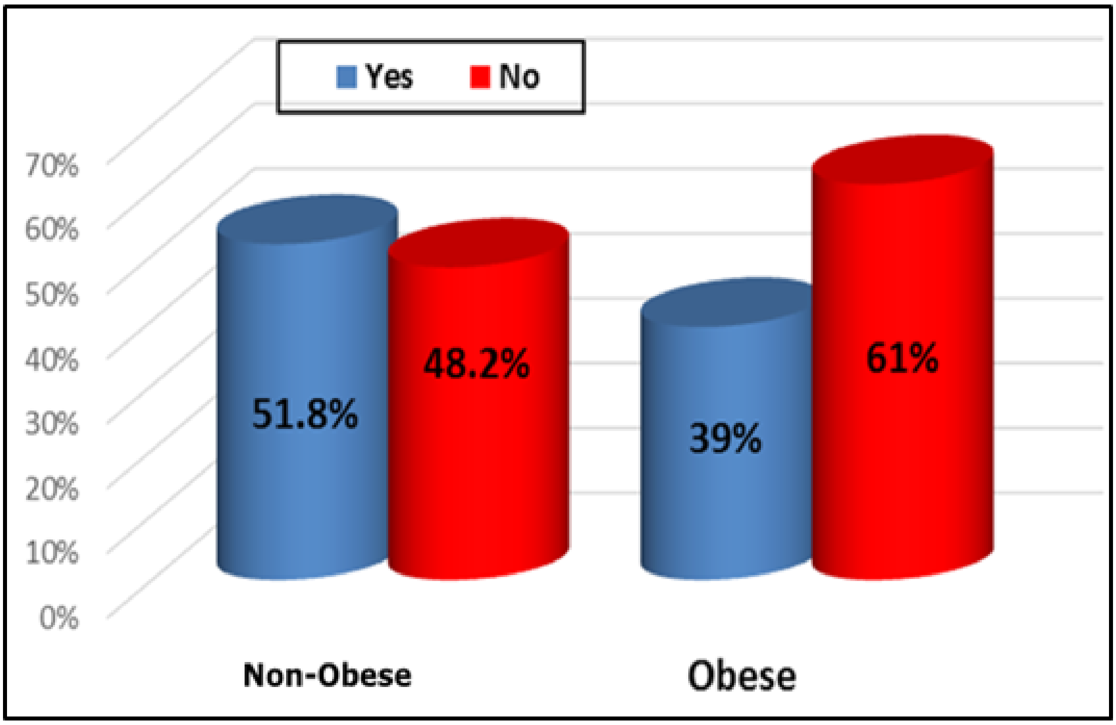


*Figure 3:* ***Relationship between Smoking and BMI categories.***

## DISCUSSION

Recent clinical studies in the field of obesity have uncovered a phenomenon defined as the "obesity paradox", which is a term that describes the counterintuitive situation where patients who are obese and have cardiovascular disease exhibit a lower risk of both short-term and long-term adverse outcomes[19].In patients with non-valvular atrial fibrillation (NVAF) treated with oral anticoagulants, we aimed to assess the influence of obesity, as evaluated by Body Mass Index (BMI), on the outcomes of anticoagulation therapy concerning bleeding and thromboembolic events. Based on their BMI, patients were divided into two categories: non-obese and obese.

We found that, with most patients using warfarin, there were no notable differences between the two groups' clinical presentations or usage of oral anticoagulants. Most of the patients had an AF paroxysmal pattern. The difference between CHA2DS2-VASc scores in both groups was not statistically significant, corroborating those of earlier research[21, 7]. Inoue and colleagues' results, in contrast to ours, indicated that individuals who were obese had a higher frequency of permanent AF. The researchers found that underweight patients had significantly higher CHA2DS2-VASc and CHA2DS2 scores [21]. Our study sought to assess the incidence of four outcomes, namely bleeding, cerebrovascular stroke, deep venous thrombosis, and cardiovascular death, among patients with NV-AF. We observed that non-obese patients had an increased frequency of complications compared to obese patients. Numerous researches have examined the correlation between obesity and the incidence of MACEs among individuals diagnosed with AF [7,21,22,23,24]. The research on the obesity paradox among AF patients has been conflicting. While some studies have shown that overweight and obese individuals have a reduced risk of stroke, cardiovascular death, and death from all causes, other studies have produced different results. Therefore, there is no agreement on the link between weight and mortality risk among AF patients [19].

There has been much debate surrounding the results of many studies investigating the obesity paradox theory [19].We used a multivariate regression analysis model to identify five predictors of complications among NV-AF patients. These predictors are diabetes, hypertension, dyslipidemia, smoking, and CHA2DS2-VASc Score > 2. However, obesity was not a significant predictor in this regression model.Badheka *et al*. conducted the first study to indicate an obesity paradox among AF patients. According to their findings, being overweight or obese was linked to a reduced risk of cardiovascular mortality, all-cause mortality, or a composite endpoint of all MACEs. Moreover, their regression model using BMI revealed that the risk of all-cause mortality progressively diminished with each BMI 1 $kg/m^2$ increase [7]. A recent subgroup analysis suggests that obesity and being overweight may lower the risk of stroke and systemic embolism, as well as all-cause death. Furthermore, a combined outcome analysis shows an independent correlation between a higher BMI (increasing by 5 kg/m2) and a reduced likelihood of these events occurring [22].

Two meta-analyses, one by Proietti *et al*. and another by Zhou *et al*., contradicted the conclusions of Liu *et al*. The former two studies primarily pooled data from randomized clinical trials (RCTs) and consistently showed that individuals with a higher BMI had a lower risk of stroke [25, 26]. These findings align with Liu *et al*.'s study, which also found that overweight and obesity were correlated with decreased adverse events among patients with atrial fibrillation (AF) [24]. Our study validated all prior findings and indicated that obese individuals were less likely than non-obese people to experience complications such as bleeding, cerebrovascular stroke, and cardiovascular death.Unlike our research, the European Society of Cardiology, Overvad *et al*., and a thorough systematic review and meta-analysis examining the obesity paradox in patients with atrial fibrillation (AF) discovered that overweight and obese AF patients faced comparable adverse outcomes to those of normal-weight AF patients [20,22,27].

The "obesity paradox" has been widely discussed and analyzed. Most research indicates that patients' average age decreases as their BMI increases. Additionally, individuals who are overweight or obese have a higher likelihood of experiencing comorbidities compared to those with a healthy weight [28].It has been observed that patients who are overweight or obese are often administered pharmaceutical treatments at an earlier stage and with greater intensity than those with average weight.Additionally, they are more frequently prescribed medications to manage cardiac and cardiovascular conditions and mitigate related hazards. Based on the results obtained, one can deduce that patients who are overweight or obese are provided with more frequent and comprehensive follow-up treatment over an extended period, as opposed to those who have a healthy body weight [5]. It is worth mentioning that accounting for every possible factor influencing the outcome, particularly in multivariate analysis, is a challenging task. These factors and others are believed to be possible reasons for the obesity paradox, observed generally and among patients with atrial fibrillation [5].

There has been a suggestion regarding a likely explanation for the obesity paradox, known as the "Metabolically Healthy Obese" (MHO) group. This group comprises individuals who are obese but maintain a healthy metabolic profile and physical activity levels [5]. Multiple studies have stated that MHO individuals have a significantly lower chance of encountering adverse outcomes. Additionally, a distinct form of adipose tissue biology has been associated with a comparable clinical profile, which seems to lower the risk of unfavorable consequences [5, 29].Despite the overwhelming evidence, the European Society of Cardiology recommended patient empowerment and appropriate education as part of their management guidelines for atrial fibrillation (AF). For obese individuals, reducing weight in conjunction with managing other risk factors was crucial to mitigating the negative impact and symptoms of AF and improving outcomes [30].

Furthermore, we assessed the connection between BMI and associated consequences and oral anticoagulants. We found that, in terms of related problems, the adoption of DOACS was more advantageous for obese individuals. Zhou *et al*. discovered that overweight patients experienced a marginally positive benefit from DOAC treatment, which aligns with our findings [26]. However, Proietti *et al*. found that among patients of average weight, DOACs outperformed VKAs regarding stroke and severe bleeding events [25]. Generally, by examining published research, contradictory information regarding the varying effects of the various OAC kinds according to BMI class could be found [19]. The arguments around the obesity paradox should not deter campaigns to support sensible weight loss strategies and encourage more exercise and physical activity. These continue to be fully backed by the generally negative impacts of being overweight or obese, according to international experts on health, weight, and obesity, and they ought to be encouraged for both AF sufferers and the general public. However, there is still a need for more investigation and clarification about the obesity paradox in cardiovascular care.

***Limitations:***

For instance, this study aimed at evaluation of short-term outcomes within six months follow-up, which may not give the full impression about the impact of obesity on long-term outcomes. Moreover, there are various potential confounding factors, including age, sex, smoking, cardiorespiratory fitness, and the severity of results, that could initially impact the relationship between BMI and AF outcomes. These confounders could interact in many ways with obesity and AF and may further complicate the patient outcomes. Therefore, we recommend that future studies focus on how each factor contributes to "the obesity conundrum" in AF. Additionally, BMI may not always accurately indicate body fat content, but it was the best available method during the study period mainly due to logistic limitations. However, other measurements, such as waist circumference and waist-hip ratio, have validated "the obesity conundrum" in patients with other cardiovascular conditions, such as coronary artery disease and heart failure [24].

***Impact on Practice:***

The study indicated that obesity may have an unexpected paradoxical impact on the outcomes of patients with non-valvular AF. However, there are other confounders that may impact these outcomes and those confounders should be addressed and managed accordingly, especially those modifiable risk factors such as hypertension, diabetes, smoking and dyslipidemia that can be treated with prompt results, unlike obesity that usually requires a significant effort and multiple lines of intervention to achieve proper weight control. Such efforts could be even more difficult to pursue in some patient populations, such as patients in low socio-economic conditions or the elderly group with significant skeletal disability and lack of fitness for routine surgery. Therefore, efforts should be directed towards lifestyle or medical treatment of controllable risk factors, and the guidelines should thoroughly consider such options while managing these patients.

***Declaration of interest:***

The authors report no conflicts of interest. The authors along are responsible for the content and writing of the paper.

***Funding information:***

The authors declare that this work has not taken any funding.

## CONCLUSION

Our research showed that obese patients with non-valvular AF may demonstrate a reduced risk of bleeding, cerebrovascular stroke, and cardiovascular death if they take an oral vitamin K antagonist anticoagulant compared to non-obese patients.

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**Citation:**

**Abdelsabour, M., Bakhet, C., Atta, S. Obesity and Non-Valvular Atrial Fibrillation: An Unexpected Paradox. *Zagazig University Medical Journal*, 2024; (3008-3019): -. doi: 10.21608/zumj.2024.253538.3034**