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PERSPECTIVE

Obesity Paradox in Atrial Fibrillation and its Relation with the New Oral Anticoagulants

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Abstract: Obesity, a chronic disease established as a global epidemic by the World Health Organization, is considered a risk factor for atrial fibrillation (AF), the most common sustained cardiac arrhythmia, which has high morbidity and mortality. Although both obesity and AF are diseases associated with negative outcomes, studies have shown the presence of an obesity paradox, in which patients with a high body mass index (BMI) and AF have a better prognosis than patients with a normal BMI. Despite the fact that the mechanisms that lead to this paradox are still uncertain, adequate anticoagulation in obese patients seems to play an important role in reducing adverse events in this group. In this perspective article, the authors discuss the relationship between new oral anticoagulants (NOACs), namely, apixaban, edoxaban and rivaroxaban (factor Xa inhibitors) and dabigatran (direct inhibitor of thrombin), and the obesity paradox, seeking to deepen the understanding of the mechanism that leads to this paradox.

Keywords: Obesity, new oral anticoagulants, atrial fibrillation, obesity paradox, apixaban, edoxaban, rivaroxaban, dabigatran.

1. INTRODUCTION

The obesity paradox is a finding widely described in the literature, but there is still some uncertainty about its causes and mechanisms. More recently, the New Oral Anticoagulants (NOACs) have been introduced as a first-line treatment for Atrial Fibrillation (FA), despite conflicting opinions in the literature on the effectiveness of its use in patients with obesity and morbid obesity. Furthermore, a number of studies have shown that the use of NOACs could have an influence on the obesity paradox. This perspective article seeks to discuss the relation between NOACs and the obesity paradox, as well as the safety of these drugs in obese and morbidly obese patients.

2. ATRIAL FIBRILLATION AND THE OBESITY PARADOX

Obesity corresponds, in a simplified way, to the excessive deposition of body fat, which can be harmful to the health of the individual. The most frequently used criterion for the classification of overweight and obesity is the Body Mass Index (BMI). Waist circumference and body adiposity index can also be evaluated [1]. Being considered as part of the group of chronic non-communicable diseases, obesity has been increasing in prevalence in several countries, which has led the World Health Organization to consider it a global epidemic [2].

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AF is the most common sustained cardiac arrhythmia and is associated with significant morbidity and mortality [3,4]. It is well established that a high BMI is a risk factor for the development of AF, which is more severe and persistent in such patients [5]. The Framingham Heart Study, with almost 14 years of follow-up, has shown that obese patients have a 1.5 times higher risk of developing AF, and that a 1-point increase in BMI is associated with a 4% increase in the likelihood of developing AF [6]. In addition, the ARIC study established that approximately 1 in 5 cases of AF could be attributed to overweight or obesity [7], which reinforces the relevance of studies relating these two diseases.

The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study, which included 18,201 randomized patients, indicated the presence of a contradictory relationship between obesity and AF, in which overweight patients (BMI 25-30) and obese patients (BMI > 30) with AF exhibited a better prognosis than patients with normal BMI (BMI < 25); this finding is called the obesity paradox [8-10]. The ARISTOTLE study showed a reduced risk of overall mortality and cardiac death and a lower composite risk of stroke, systemic embolism, acute myocardial infarction, and all-cause mortality in obese patients with AF [8]. In addition, the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) cohort study found a 35% reduction in all-cause mortality in patients with class I obesity compared to patients with normal BMI. These results are similar to those of the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study [10, 11].

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The mechanisms involved in the obesity paradox are not yet fully understood, and it remains unclear whether this is a true biological phenomenon or whether it occurs as a result of residual confounding factors [12].

There are a few possible explanations for this paradox. It has been observed in several studies that the patients with normal BMI have advanced age, an important predictor of mortality in AF, while obese patients are often younger [13-15]. Furthermore, it is believed that an increased BMI, compared to a normal one, may help in the response to increased catabolic stress in AF due to a greater metabolic reserve [12, 13].

Other possible confounding factors are sex, with females having a better prognosis [15, 16], and obese patients' greater use of drugs that act on the cardiovascular system, such as angiotensin-converting enzyme inhibitors, diuretics, statins, beta-blockers and anticoagulants, which deserve special attention due to their specificities and their role in AF [8, 12, 13].

3. NEW ORAL ANTICOAGULANTS AND THE OBESITY PARADOX

The NOACs have been introduced more recently as a first-line therapy option for pulmonary embolism, deep vein thrombosis and atrial fibrillation, to prevent systemic embolism and stroke [17].

Currently, four NOACs are available on the market, namely apixaban, edoxaban and rivaroxaban (factor Xa inhibitors), and dabigatran (direct inhibitor of thrombin) [18]. These drugs represent an improvement in the quality of life of patients as compared to the vitamin K antagonist warfarin, an anticoagulant established decades ago for the treatment of AF. Unlike warfarin, NOACs do not require laboratory monitoring of their concentration in the body, have a fixed-dose regimen that does not require dose adjustments based on weight, and it has been demonstrated that the NOACs are more efficacious and generally more, although not always, safer than warfarin in various bodyweight categories [19].

Regarding the use of these drugs in obese patients, due to the concern that the fixed doses regime could lead to sub-anticoagulation, the *International Society of Thrombosis and Hemostasis* (ISTH) recommends that the use of NOACs in patients with a BMI greater than 40 kg/m^2 or with a weight greater than 120 kg be avoided [20]. In fact, at the present time, studies evaluating the safety and efficacy of NOAC use in obese patients, especially in morbidly obese ones, are limited. However, there is a growing amount of data favorable to the effectiveness of these drugs regardless of BMI or patient weight [14, 18, 21].

It is not yet clear whether there is a relationship between the use of NOACs and the obesity paradox. However, some recent publications have shown the possible participation of appropriate anticoagulation in the mitigation of this paradox [9]. The main finding of the post-hoc analysis of the Stroke Prevention Using an Oral Direct Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) trial was a reduction in the difference between the risks of the BMI categories when good anticoagulation control was achieved [22]. In this study, patients who remained within the ideal range of the international normalized ratio (INR) control, *i.e.*, those with a *time in therapeutic range* (TTR) greater than 70%, showed no significant association between the BMI categories and outcomes of stroke and death. The results of the trial Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation (AMADEUS) showed obese patients to have good anticoagulation control, highlighting the difference in optimal treatment between the BMI groups [23]. Such difference in AF treatment strategies between obese and normal-weight patients was also observed in the initial observations of the ARISTOTLE trial [8], as well as in the data from the trial 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) [24]. Thus, NOACs, which have been established as the most effective and safe therapeutic options for all BMI categories, can contribute to the understanding of the obesity paradox, which is still a source of confusion.

Despite this confusing scenario, the paradox should not be a distraction in the fight against obesity, which is one of the main primary modifiable risk factors for various cardiovascular conditions, especially AF [25].

CONCLUSION

The obesity paradox involves mechanisms that are still of uncertain origin, and many studies point to possible biases, given the differences in baseline characteristics between the BMI groups, in addition to other undetected confounding factors [12]. As shown in this review, several studies have been reported on the safety of NOACs in overweight and obese populations. However, further research is needed, ideally randomized clinical trials, which evaluate the participation of new anticoagulants in BMI categories with the standardization of baseline and clinical characteristics, such as age and drugs used. Therefore, it will be possible to better understand the mechanism which causes this paradox, especially with regards to the use of new anticoagulants.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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