Real life behaviour of direct oral anticoagulants in patients with nonvalvular atrial fibrillation and morbid obesity

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ABSTRACT

Background: Atrial fibrillation (AF) is the most prevalent arrhythmia worldwide and the main cause of anticoagulation, being direct oral anticoagulants (DOAC) increasingly used in this context. On the other hand, obesity is a known risk thromboembolic factor. In the clinical trials that led to the approval of DOAC for ischemic stroke prevention, patients with morbid obesity were underrepresented. The International Society of Thrombosis and Haemostasis suggests not using these drugs in morbid obese patients. Thus, the primary objectives of this study were to analyse the rates of mortality, thrombotic and haemorrhagic events in patients with morbid obesity. As secondary objectives, factors statistically associated with these events were analysed. **Methods:** multicentre retrospective study that included patients diagnosed with AF on treatment with DOAC from January 2013 to December 2016. The subgroup of patients with morbid obesity (BMI > 40 and / or weight > 120 kg) was analysed. Mean follow-up was 1.7 years. **Results:** Amongst 2,492 patients included in the study, 135 patients had morbid obesity (mean age was 71 ± 11 years). The mean scores of the CHA_2DS_2-VASc and HAS-BLED risk scales were 3.7 ± 1.6 and 2.2 ± 0.9, respectively. Neither differences were found regarding mortality (5.2 vs 6/100 patient-years, p = 0.662), ischemic stroke (0.8 vs 1.9/100 patient-years, p = 0.261) and major bleeding rates (3 vs 3.1/100 patient-years, p = 0.983) between morbidly obese population and general population. Nor was there an association found between the degree of obesity and any of the events studied. **Conclusion:** DOAC are safe and effective in morbidly obese patients.

1. Background

Atrial fibrillation (AF) is the most prevalent arrhythmia worldwide and it is the main cause of anticoagulation. It is estimated to affect more than 43 million people in the world, being more prevalent in developed countries [1–2]. The prevalence of AF has increased in recent years. According to OFRECE study, in 2013, the prevalence of AF in Spain in patients older than 40 years was 4.4 %, with a progressive increase in patients over 60 years [3]. If the projections of the Rotterdam study become real, by 2060 the number of patients with AF in the European Union will have doubled [4]. This increase in the prevalence of AF can be attributed to an improvement in the detection of silent AF, aging population and other entities that favour the development of this arrhythmia, such as hypertension, heart failure and chronic kidney disease, amongst others [5].

On the other hand, obesity is a known risk factor for developing venous thromboembolism and arterial disease. This, added to the risk of ischemic stroke conferred by AF, make these patients especially susceptible to suffer thromboembolic complications [6]. In 2016, the World Health Organization estimated that more than 1.9 billion adults aged 18 years or older were overweight, of which more than 650 million were obese. In the last 40 years, obesity has almost tripled worldwide. The majority of the world's population lives in countries where overweight and obesity cause more deaths than underweight. In Spain, the ENPE [7] study revealed that the prevalence of obesity between 2014 and 2015 was 21.6%, with patients with obesity grade ≥ III representing 1.6%.

In the clinical trials that led to the approval of the four available DOAC [8–11] (apixaban, rivaroxaban, edoxaban and dabigatran), the obese population was underrepresented. Furthermore, there are few pharmacodynamic and pharmacokinetic studies of DOAC in terms of safety and efficacy in this group of patients [12–17]. The available studies reveal a lower concentration of the drug in obese patients, since

Table 1
Baseline characteristics of morbid obesity vs non morbid obesity population.

	Morbid Obesity N = 135	Non Morbid Obesity N = 1994	p
Baseline characteristics			
Age (years)	71 ± 11	76 ± 9	<0.001
Sex (women)	82 (60.7 %)	1046 (52.4 %)	0.065
Type of DOAC			0.003
	54 (40.0 %)	794 (38.8 %)	
• Rivaroxaban	42 (30.4 %)	765 (38.4 %)	
• Apixaban	39 (28.9 %)	366 (18.3 %)	
• Dabigatran	0 (0 %)	69 (3.5 %)	
• Edoxaban			
Smoking	11 (8.1 %)	124 (6.2 %)	0.410
Alcoholism	2 (1.5 %)	41 (2.0 %)	0.644
Weight (Kg)	112.2 ± 17.1	77.8 ± 13.7	<0.001
BMI	43.4 ± 6.5	28.4 ± 7.3	<0.001
Previous VKA	60 (44.4 %)	902 (45.4 %)	0.832
Standard dose	99 (77.3 %)	1179 (59.3 %)	0.001
CrCl	115 ± 51	71 ± 32	<0.001
	6 (4 %)	509 (26 %)	
• ClCr < 50 ml/min			
Hypertension	124 (91.6 %)	1749 (87.7 %)	0.156
Diabetes	51 (37.8 %)	666 (33.5 %)	0.301
Heart failure	29 (21.5 %)	377 (19.0 %)	0.465
Valvular disease	23 (17.0 %)	380 (19.0 %)	0.562
Previous ischemic stroke/ TIA	21 (15.6 %)	426 (21.4 %)	0.108
Previous Major bleeding	8 (6.0 %)	173 (9.0 %)	0.266
Ischemic heart disease	15 (11.1 %)	337 (16.9 %)	0.079
Peripheral arterial disease	2 (1.5 %)	68 (3.4 %)	0.223
COPD	25 (18.5 %)	274 (13.7 %)	0.123
Liver disease	4 (3.0 %)	21 (1.0 %)	0.046
Active or previous neoplasia	18 (13.3 %)	244 (12.2 %)	0.711
Antiplatelets	11 (8.1 %)	207 (10.4 %)	0.408
NSAIDs	1 (0.7 %)	22 (1.1 %)	0.691
Corticosteroids	2 (1.5 %)	39 (2.0%)	0.695
CHA$_2$DS$_2$-VASc	3.7 ± 1.6	4.1 ± 1.6	0.009
HAS-BLED	2.2 ± 0.9	2.5 ± 0.9	0.015

BMI: body max index. CrCl: creatinine clearance. COPD: chronic obstructive pulmonary disease. NSAIDs: non-steroidal anti-inflammatory drugs. TIA: transient ischemic attack. VKA: vitamin K antagonists.
The results are expressed in absolute frequency and percentage for qualitative variables. and mean ± standard deviation for quantitative variables.

they have a greater volume of distribution, in addition to an increased clearance of the drug, which could theoretically translate into a higher rate of stroke and thromboembolic events. Based on this, the International Society of Thrombosis and Haemostasis (ISTH) recommended not using these drugs in patients with a body mass index (BMI) > 40 kg / m^2 or weight > 120 kg [18]. However, despite these recommendations, the truth is that these drugs are frequently used in daily practice regardless of weight, without relevant evidence that support their use.

2. Methods

2.1. Design and study population

Multicentre retrospective study that included consecutively all patients with AF who were prescribed DOAC for the first time from January 1, 2013 to December 31, 2016. The subgroup of patients with morbid obesity was analysed separately. Patients with an indication for concomitant anticoagulation for a reason other than AF, anticoagulation without indication for long-term oral anticoagulation (with the objective of electrical or pharmacological cardioversion), patients referred for ablation, and patients with hypertrophic cardiomyopathy, moderate or severe mitral stenosis of rheumatic origin and mechanical valve prostheses were excluded. The clinical and demographic data were collected through electronic medical records, and were recorded on a form with pre-coded variables. Included hospitals were Virgen de la Arrixaca

University Clinical Hospital, Vega Baja Hospital and Noroeste Comarcal Hospital. The start date to follow-up was the date of the first DOAC prescription and the end date to follow-up was set on the 31sr of January 2018, or the date of death if it preceded the end of the study. The mean follow-up was 20.2 ± 7.3 months (1.7 years). The primary objectives of the study were to analyze the rates of mortality, thrombotic and haemorrhagic events in patients with morbid obesity. As secondary objectives, the factors statistically associated with each of the events were analysed.

2.2. Variables

Although the concept of morbid obesity only takes into account BMI, in this study we refer to it as BMI > 40 kg/m^2 and/or weight > 120 kg. Major and minor bleeding were defined according to the 2005 ISTH criteria [19]. Ischemic stroke was defined as signs or symptoms of neurological dysfunction secondary to a central nervous system infarction and transient ischemic attack (TIA) was defined as signs or symptoms lasting less than 24 h without evidence of injury on neuroimaging techniques [20]. Significant valve disease was defined as moderate - severe grade or related symptoms.

2.3. Statistical analysis

For the descriptive analysis, the quantitative variables were described with measures of central tendency and dispersion: mean and standard deviation for the variables of normal distribution, and median and interquartile range for the variables with a non-normal distribution. Kolmogorov-Smirnov test was used to check the normality of the variables. The qualitative variables were described as absolute (n) and relative (%) frequency. Furthermore, categorical variables were compared using the $\chi 2$ test. In order to compare numerical variables with dichotomous categorical variables, the Student's t test or the Mann-Whitney U test were used if the variable was normal or non-normal, respectively. If the categorical variable was polytomous, the one-way analysis of variance (ANOVA) was used. The rate of death, ischemic and haemorrhagic events were expressed as events per 100 patient-years. To identify factors associated with these events, the Hazard ratios (HR) with their 95% confidence intervals were calculated using a univariate analysis and subsequently a multivariate Cox regression analysis. The variables included in the univariate analysis were those considered by the researcher as a possible causal relationship with the event (see Appendix) and those included in the multivariate were those statistically associated with the event studied in the univariate analysis. Statistical significance was established as a value of p < 0.05. For statistical analysis, the IBM® SPSS® Statistics v25 program (SPSS Inc., Chicago, Illinois, USA) was used. The Bonferroni method of the SPSS program was applied when several statistical tests were being performed simultaneously.

2.4. Ethical aspects

The project was carried out according to the principles of the Declaration of Helsinki and it was authorized by the Ethics Committee of Hospital Virgen de la Arrixaca (code: 2017-11-1-HCUVA).

3. Results

A total of 2492 patients were included in the registry, of which 135 patients (5%) met the criteria for morbid obesity. The specific data of the general population of this cohort were already published in 2019 and can be consulted [21]. The most frequently prescribed drug in this group was rivaroxaban (40%). There were no patients being on treatment with edoxaban in this group. Even more, patients with morbid obesity were younger (mean age 71 years) and with better renal function than those without morbid obesity. Most of them (77.3%) took the standard dose of

Table 2
Events in morbidly obese vs. non morbidly obese populations.

	Morbid Obesity mórbida		Non Morbid Obesity		p
	n (%)	Ev. 100p-years	n (%)	Ev. 100p-years	
Death*	12 (8.9)	5.2	200 (10.1)	6.0	0.662
	2 (16.7)		63 (30.0)		
• Cardiovascular	9 (75.0)		118 (59.0)		
• Non cardiovascular	1 (8.3)		19 (9.5)		
• Indeterminate					
Ischemic stroke/TIA	2 (1.5)	0.8	64 (3.2)	1.9	0.261
Systemic embolism	0	0.0	3 (0.2)	0.0	0.652
ICH	0	0.0	12 (0.6)	0.0	0.366
Major bleeding*	7 (5.2)	3.0	104 (5.3)	3.1	0.983
	0 (0.0)		12 (11.5)		
• Intracranial	4 (57.1)		57 (54.8)		
• Digestive	0 (0.0)		2 (1.9)		
• Retroperitoneal	0 (0.0)		1 (1.0)		
• Otorhinolaryngology	0 (0.0)		7 (6.7)		
• Genitourinary	1 (14.3)		12 (11.5)		
• Skin	2 (28.6)		13 (12.1)		
• Others					
Minor bleeding	10 (7.4)	4.4	289(14.5)	8.6	0.021

TIA: transient ischemic attack. Ev.100p-years: events per 100patient-years. ICH: intracranial hemorrhage.

* The % of cause of death and location of bleeding are expressed within the event of death and major bleeding, respectively.

each drug. For further information, the baseline characteristics of the cohort are shown in Table 1.

Regarding main events - mortality, ischemic stroke and major bleeding -, no differences were observed between both groups. An increase in minor bleeding was observed in the population without morbid obesity (Table 2). Amongst 11 patients who took concomitantly antiplatelet in the morbid obesity group, none of them had major bleeding. Moreover, no deaths due to fatal bleeding were recorded.

When analysing the events by degree of obesity (BMI 30–34.9, 35–39.9 and $\geq$ 40), neither significant differences nor a trend towards an increased risk for any of the events studied were found (Fig. 1).

Comparing a DOAC to the rest, it was observed that apixaban was the drug with the highest mortality rate in a statistically significant way (Table 3).

Regarding the predictive events of death (Table 4), of all the variables studied, diabetes and heart failure were independently associated with a higher risk of death, while taking the standard dose of the drug was a protective factor of death. For the ischemic stroke event, no statistically significant independent factor was found in the univariate analysis. In addition, in terms of major bleeding, only neoplasia and age were related to this event in the univariate. No more variables were found to demonstrate their association by multivariate analysis.

4. Discussion

In our cohort, 5% of patients had BMI > 40 kg/m^2 and/or weight > 120 kg, a similar percentage to that included in the ARISTOTLE trial (5.4% of patients with apixaban weighed > 120 kg) [22] and ENGAGE-AF TIMI 48 trial (5.5% of patients with edoxaban had a BMI $\geq$ 40 kg/m^2) [23]. In the RE-LY trial, 10% of patients receiving dabigatran had a BMI > 36 kg/m^2 [24]. There are no data about patients with morbid obesity included in the ROCKET trial. In our study, none of the morbidly obese patients were being treated with edoxaban, probably because the end date of the study (December 2016) was considerably close to the marketing date of this drug in Spain.

Compared to published registries about morbid obesity population [25–27], within our cohort we observed a similar rate of ischemic stroke, whereas the rate of major bleeding was higher. In previous publications of our registry where we analysed the general population [21,28], we also found a higher rate of bleeding with respect to clinical trials and other published real-life registries, finding the most remarkable difference the rivaroxaban group [29–30]. This increase in major bleeding was seen in both the obese and non-obese populations and it

may be explained by the worse clinical profile of our patients with respect to those studies. In this context, we observed that patients taking apixaban in our cohort were the oldest, with poorer renal function and with higher thromboembolic and haemorrhagic risk, which could explain the higher mortality rate in this group compared to the rest of DOAC.

When comparing the events between the group with morbid obesity and the general population within our cohort, no significant differences for any of the events studied were found. It could be explained because patients with morbid obesity were younger, more often received standard doses of DOAC, had lower thromboembolic and haemorrhagic risk and had better renal function compared to those without morbid obesity, which could diminished differences. Regarding minor bleeding, an increase in the general population was observed, compared to morbidly obese group, maybe because non-morbidly obese patients had higher score in haemorrhagic risk, had history of previous major bleeding and took more often concomitant drugs that could increase the risk of bleeding such as antiplatelet, non-steroidal anti-inflammatory drugs and corticosteroids. Curiously concomitant platelet therapy in our study had no real impact on bleeding, the reason why might be due to people on treatment with antiplatelets had higher CHA$_2$DS$_2$-VASc scores (4.7 vs 3.5, p = 0.03).

Surprisingly, although it was not significant, within the group with morbid obesity there was a lower rate of ischemic stroke than in the non-morbid obesity group (0.8 vs 1.9 / 100 patient-years, p = 0.261). According to this phenomenon, called the "obesity paradox" [23,31–32], patients with a degree of obesity who are free of the typical metabolic derangements associated with adiposity like insulin resistance, diabetes and chronic systemic inflammation would have fewer cardiovascular events than the general population. Some studies have shown that insulin-sensitive morbidly obese subjects had lower levels of thromboxane A2 than the obese subjects and lean subjects, suggesting that reduced platelet activation could play a role in the paradoxical protection of morbidly obese subjects from atherosclerosis, despite the greater levels of leptin [33–34]. In our case, the lower incidence of ischemic events in the morbidly obese group could also be influenced by the fact that they were younger, with better renal function and with lower scores in CHA$_2$DS$_2$-VASc and HAS.BLED scales.

Diabetes and heart failure were predictors of mortality. This information could be useful when referring patients early to the corresponding specialist (endocrinology, cardiology…) and thus carry out a closer follow-up in this kind of patients. On the other hand, it was observed that taking the standard dose of the drug was a protective
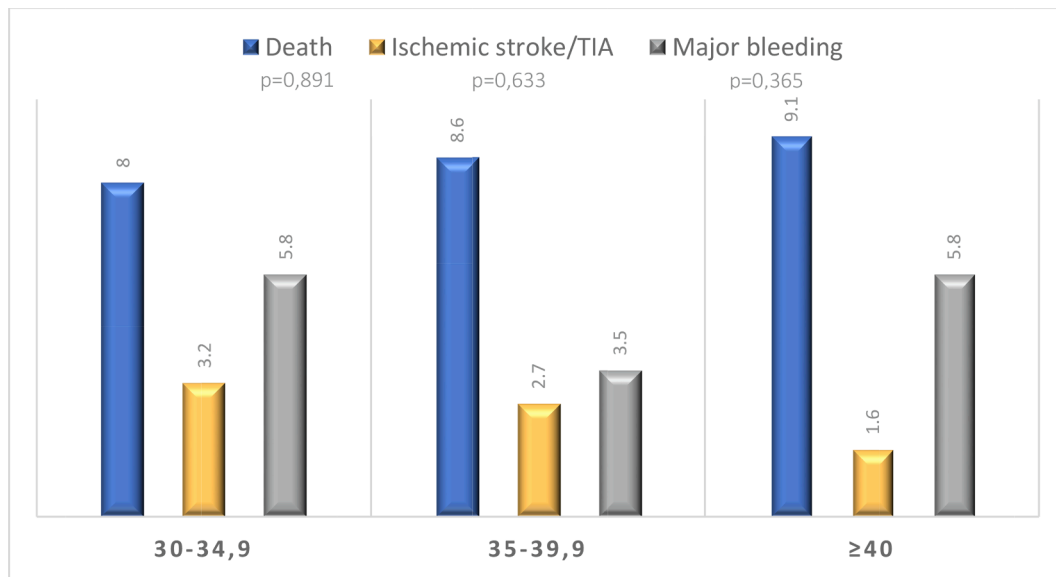
Fig. 1. Events (%) according BMI range.

Table 3
Events according DOAC in morbidly obese population.

	Rivaroxaban N = 54	Apixaban N = 39	Dabigatran N = 42	p[a]	p[b]	p[c]
Death	3 (5.6 %)	7 (16.7 %)	2 (5.1 %)	0.266	0.033	0.328
Ischemic stroke/TIA	0	1 (2.4 %)	1 (2.6 %)	0.245	0.561	0.507
Systemic embolism	0	0	0	–	–	–
ICH	0	0	0	–	–	–
Major bleeding	4 (7.4 %)	2 (4.8 %)	1 (2.6 %)	0.342	0.882	0.381
Minor bleeding	3 (5.6 %)	3 (7.1 %)	4 (10.3 %)	0.502	0.937	0.420

TIA: transient ischemic attack. ICH: intracranial hemorrhage.
p[a]: Rivaroxaban vs. resto. p[b]: Apixaban vs. resto. p[c]: Dabigatran vs. resto.

Table 4
Hazard ratios (HR) by Cox regression analysis for death.

	Univariate			Multivariate		
	HR	CI	p	HR	CI	p
Diabetes	4.850	1.312–17.927	0.018	4.543	1.334–15.756	0.035
Heart failure	6.114	1.935–19.135	0.002	4.056	1.093–11.622	0.031
Peripheral arterial disease	45.272	8.119–252.427	<0.001	4.997	0.356–44.999	0.182
COPD	3.729	1.180–11.782	0.025	2.144	0.443–8.657	0.285
Standard dose	0.155	0.046–0.514	0.002	0.177	0.065–0.641	0.009

COPD: chronic obstructive pulmonary disease.

factor for mortality, so we must follow the recommendations of the technical sheets and not prescribe a suboptimal dose, as occurs in a considerable percentage of the population, with the increased mortality that it causes [35].

Published pharmacodynamic studies demonstrate a lower drug concentration in obese patients. In the case of apixaban, in patients weighing > 120 kg, the drug concentration decreased by 30% compared to the control population [13]; in the case of dabigatran, the concentration was 20% lower in patients weighing > 100 kg [36] compared to the control; for rivaroxaban, the pharmacokinetic profile was comparable in patients weighing > 120 kg and the control population [17]. With edoxaban there are no pharmacokinetic studies to date. This difference in plasma concentrations could be due to the two-compartment model followed by dabigatran and apixaban [37–38], compared with rivaroxaban, which follows a single-compartment model [39]. Rivaroxaban has the lowest lipid solubility of the DOAC. Maybe because of this, the volume of distribution is larger. Hence, bleeding tendency

might be increased in the non-obese cohort largely due to a more pathological state. In patients with low weight (<50 kg) an increased risk of bleeding has been shown, as they have a higher concentration of the drug [37]. Notwithstanding, it has not been possible to demonstrate that morbidly obese patients have an increased risk of ischemic stroke despite having lower drug concentrations.

In sub-analysis of the ENGAGE-AF TIMI 48, ARISTOTLE, and RE-LY clinical trials in morbidly obese patients, edoxaban, apixaban, and dabigatran, respectively, showed comparable effectiveness and safety to VKA [24]. For rivaroxaban, higher rates of ischemic events have not been found compared to VKA in published studies [40]. Recent studies about the use of DOAC in morbid obesity population have shown that these drugs are safe and effective [41–42]. Our results are in consonance with these articles.

The main limitation of our study is the small sample size (only 135 patients with morbid obesity), however, it is a similar number to that included in clinical trials, taken to the real world, and we consider that it

can provide relevant information in practice daily clinic and it can help to resolve the uncertainty about this drugs in morbidly obese population.

Thus, given the results of recent publications and those of our study, which support the efficacy and safety of DOAC in the morbidly obese population, the recommendations of the ISTH guide should be re-evaluated.

5. Conclusion

We have not found significative differences regarding ischemic stroke, mortality or bleeding in our study, nor have we observed statistical association between the degree of obesity and these events. According to these results, we can suggest that DOAC can be used safely and effectively in morbidly obese patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2021.100913.

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