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 > 30 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 CHA₂DS₂-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 6.0/100 patient-years, p = 0.261) and major bleeding rates (3.7 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 (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
severe mitral stenosis of rheumatic origin and mechanical valve pros-
ablation, and patients with hypertrophic cardiomyopathy, moderate or
2. Methods
theses were excluded. The clinical and demographic data were collected
tients with AF who were prescribed DOAC for the first time from
- or weight
using these drugs in patients with a body mass index (BMI)
- BMI: body max index. CrCl: creatinine clearance. COPD: chronic obstructive
- NSAIDs: non-steroidal anti-inflammatory drugs. TIA: transient ischemic attack. VKA: vitamin K antagonists.
- BMI < 50 ml/min
- Hypertension
- Diabetes
- Heart failure
- Valvular disease
- Previous ischemic stroke/ TIA
- Previous Major bleeding
- Ischemic heart disease
- Peripheral arterial disease
- COPD
- Liver disease
- Active or previous neoplasia
- Antiplatelets
- NSAIDs
- Corticosteroids
- CHA2DS2-VASc
- HAS-BLED
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.

| Baseline characteristics   | Morbid Obesity N = 135 | Non Morbid Obesity N = 1994 | p       |
|----------------------------|------------------------|-----------------------------|---------|
| Age (years)                | 71 ± 11                | 76 ± 9                      | <0.001  |
| Sex (women)                | 82 (60.7 %)            | 1046 (52.4 %)               | 0.065   |
| Type of DOAC               | 54 (40.0 %)            | 794 (38.8 %)                | 0.003   |
| • 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  |
| • CCr < 50 ml/min          | 6 (4 %)                | 509 (26 %)                  |         |

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

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 Interna-
tional Society of Thrombosis and Haemostasis (ISTH) recommended not
using these drugs in patients with a body mass index (BMI) > 40 kg / m²
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 pa-
tients 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 objec-
tive 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 pros-
theses 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 hae-
morrhagic events in patients with morbid obesity. As secondary objec-
tives, 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/m² 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 infarc-
tion and transient ischemic attack (TIA) was defined as signs or symp-
toms 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 vari-
ables. The qualitative variables were described as absolute (n) and
relative (%) frequency. Furthermore, categorical variables were
compared using the χ² 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 ra-
tios (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 sta-
tistical 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
an increased risk for any of the events studied were found (Fig. 1). No differences were observed between both groups. An interesting independent factor was found in the univariate analysis, which could diminished differences. Regarding minor bleeding, an increase in the general population was observed, compared 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 CHA2DS2-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 thrombomodulin 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 CHA2DS2-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

| Event                      | Morbid Obesity morbida | Non Morbid Obesity | p   |
|----------------------------|------------------------|--------------------|-----|
| **Death**                  | 12 (8.9)               | 200 (10.1)         | 0.662|
| Cardiovascular             | 2 (16.7)               | 63 (30.0)          |     |
| Non cardiovascular         | 9 (75.0)               | 118 (59.0)         |     |
| Indeterminate              | 1 (8.3)                | 19 (9.5)           |     |
| **Systemic embolism**      |                        |                    |     |
| Ischemic stroke/TIA        | 2 (1.5)                | 64 (3.2)           | 0.261|
| * Intracranial*            | 0 (0.0)                | 3 (0.2)            |     |
| * Digestive                | 4 (57.1)               | 12 (11.5)          |     |
| * Retropertitoneal         | 0 (0.0)                | 57 (54.8)          |     |
| * Otorhinolaryngology      | 0 (0.0)                | 1 (1.0)            |     |
| * Genitourinary            | 1 (14.3)               | 7 (6.7)            |     |
| * Skin                     | 2 (28.6)               | 12 (11.5)          |     |
| Others                     |                        | 13 (12.1)          |     |
| **Minor bleeding**         | 10 (7.4)               | 289 (14.5)         | 0.021|
| * Intracranial             | 3 (28.6)               | 1 (1.0)            |     |
| * Digestive                | 57 (4.7)               | 12 (11.5)          |     |
| * Retropertitoneal         | 0 (0.0)                | 6.0                | 0.662|
| * Otorhinolaryngology      | 0 (0.0)                | 6.0                | 0.662|
| * Genitourinary            | 1 (14.3)               | 3.0                |     |
| * Skin                     | 2 (28.6)               | 104 (5.3)          | 0.983|
| **Others**                 |                        | 12 (11.5)          |     |

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

[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.

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. No more variables 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/m² 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 ≥ 40 kg/m²) [23]. In the RE-LY trial, 10% of patients receiving dabigatran had a BMI > 36 kg/m² [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.
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

### Table 3

Events according DOAC in morbidly obese population.

|               | Rivaroxaban | Apixaban | Dabigatran | p<sup>a</sup> | p<sup>b</sup> | p<sup>c</sup> |
|---------------|-------------|----------|------------|---------------|---------------|---------------|
| 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         |
| 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<sup>a</sup>: Rivaroxaban vs. resto. p<sup>b</sup>: Apixaban vs. resto. p<sup>c</sup>: 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.
cording to these results, we can suggest that DOAC can be used safely 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 sta-
tistical association between the degree of obesity and these events. Ac-
cording 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 influenced the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.

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