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ORIGINAL RESEARCH ARTICLE

Plasma Concentrations of Direct Oral Anticoagulants in Patients with Nonvalvular Atrial Fibrillation and Different Degrees of Obesity

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Abstract

Background Atrial fibrillation (AF) has multiple cardio-metabolic comorbidities, including obesity. The use of direct oral anticoagulants (DOACs) in patients with AF and obesity is still uncertain owing to the concern of possible ineffective DOAC plasma concentration. We evaluated the peak and trough plasma concentrations of DOACs in AF patients with different degrees of obesity.

Methods Observational single-center study including patients with obesity and AF, between April 2022 and April 2024. Obesity was defined as body mass index (BMI) ≥ 30.0 kg/m^2. The 2-hour peak and trough DOAC plasma concentrations were assessed. Intake of DOAC was verified on site. Multivariable logistic regression analysis was used to assess the odds ratio (OR) and 95% confidence interval (95% CI) of factors associated with below-range trough concentration (BRTC) and below-range peak concentration (BRPC).

Results In total, 160 patients (33.8% women) with a mean age of 73.2 ± 9.1 years were included. The median BMI was 32.3 kg/m^2. DOACs prescribed were apixaban (46.8%), rivaroxaban (21.8%), dabigatran (16.4%), and edoxaban (15.0%); 18.1% and 14.4% had BRTC and BRPC concentrations, respectively. Patients with BRTC were more frequently treated with edoxaban and dabigatran and had a higher BMI. On multivariable logistic regression analysis, dabigatran [hazard ratio (HR) 3.039, 95% CI 1.155–7.999, $p = 0.024$) and BMI ≥ II class (OR 2.625, 95% CI 1.087–6.335, $p = 0.032$] were associated with BRTC. Dabigatran (OR 4.296, 95% CI 1.523–12.120, $p = 0.006$) and apixaban (OR 0.277, 95% CI 0.096–0.802, $p = 0.018$) were directly and inversely associated with BRPC, respectively.

Conclusions A nonnegligible proportion of patients with obesity and AF have below-range plasma concentrations of DOACs. Assessment of DOAC plasma concentration in obesity class ≥ II may be useful in these patients.

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Key Points

A significant proportion of patients with obesity and atrial fibrillation (AF) had below-range trough and peak plasma concentrations of direct oral anticoagulants (DOACs).

Degree of obesity was associated with below-range trough DOAC plasma concentrations in patients with AF and obesity.

Dabigatran, but not factor Xa inhibitors, was associated with below-range peak and trough DOAC plasma concentrations in patients with AF and obesity.

1 Introduction

Obesity has become a major health issue in developed countries, currently ranked as the fifth most common cause of death. Concerns also arise from developing countries where obesity rates have been increasing in the last two decades [1].

The first association between atrial fibrillation (AF) and obesity was observed in patients undergoing cardiac surgery, with high body mass index (BMI) reported as a major risk factor for postoperative AF [2, 3]. The association of obesity and AF was also observed in the Framingham Heart Study, in which a 4.0% increased risk of AF per 1-unit increase in BMI during 13.7 years of follow-up was observed [4]. This association was also confirmed by a meta-analysis performed on 626,603 individuals showing 29.0% higher risk of incident AF for every 5-unit increase in BMI [5].

Once established, patients with AF require long-term therapy with anticoagulants for thromboembolic stroke prophylaxis, either with vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs) [6]. DOACs seem to be safe and effective also in patients with obesity [7], as shown in a recent individual patient data meta-analysis of four randomized clinical trials enrolling 58,464 patients with AF showing a reduction in ischemic stroke and systemic embolic events of 20.0%. The 2024 European Society of Cardiology (ESC) guidelines indicate that DOAC may be a reasonable choice in these patients [8]. However, the 2021 European Heart Rhythm Association (EHRA) guidelines suggest the possibility of considering measuring plasma concentrations of DOACs for patients weighing > 120 kg or with a BMI > 40.0 kg/m^2 [9]. In addition, the current International Society of Thrombosis and Haemostasis (ISTH) guidelines recommend avoiding DOAC in patients with a BMI exceeding 40.0 kg/m^2 or a body weight above 120 kg [10].

It is also uncertain whether the adjustment of DOAC dosing according to this laboratory measurement may provide a clear clinical advantage. For all of these reasons, the management of anticoagulation in these patients may be somewhat challenging, also considering that few real-world data on patients with AF that are obese and very obese exist.

However, recent large cohort studies showed that DOACs may be a possible choice of treatment. Firstly, a study conducted using the Italian START registry, enrolling 10,080 patients with AF and venous thromboembolism (VTE), showed no difference on rate of thrombotic and bleeding events between VKA and DOAC treatment, even in patients with a body weight ≥ 120 kg during a mean follow-up of 1.5 years [11]. In addition, a study performed on 36,094 patients with AF [12] showed that DOACs, compared with warfarin, were associated with lower risk of ischemic stroke, bleeding, and mortality across all BMI groups. Patients enrolled in this cohort were treated with apixaban and rivaroxaban (43.6%) and VKA (48.9%), while only 7.6% of patients were on dabigatran and edoxaban. Furthermore, no data on the time in therapeutic range for the VKA cohort was reported, and this may not allow a true comparison between DOAC and VKA.

An additional helpful tool is represented by the possibility of DOAC plasma concentration assessment in some high-risk subgroups of patients that may be exposed to reduced or increased plasma concentrations, such as patients with cirrhosis or advanced kidney disease or patients taking potentially interacting drugs and in patients with obesity [13–15]. In particular, in these latter patients, few data are available, as they were under-represented in phase 3 randomized clinical trials of DOAC approval.

On the basis of this, we aimed to evaluate the trough and peak plasma concentrations of DOACs using guideline-recommended on-therapy ranges in patients with AF with different classes of obesity and to assess clinical factors associated with below-range concentration of DOACs.

2 Methods

This was a nonprofit, observational, monocentric study promoted by the Department of Clinical Internal, Anesthesiologic and Cardiovascular Sciences of Sapienza University of Rome. Consecutive patients with nonvalvular AF and obesity treated with DOACs to prevent thromboembolic stroke were enrolled in the Atherothrombosis Center of Policlinico Umberto I in Rome between April 2022 and April 2024.

Inclusion criteria were age > 18 years, documented nonvalvular AF [6], starting DOACs between 7 and 15 days before the enrollment (median 11 days; interquartile days 9–13) and obesity, defined as a BMI ≥ 30.0 kg/m^2 [6, 16]. DOACs were prescribed according to European guidelines [6] and DOAC intake was verified on site.

During the first clinical examination, a complete personal medical history was collected, which included: comorbidities, cardiovascular risk factors (arterial hypertension, diabetes mellitus, heart failure, and metabolic syndrome), measurement of anthropometric factors (body weight, height, waist, and hip circumferences) with staging of obesity according to BMI, and collection of routine blood tests with complete blood count, creatinine, transaminases, and lipid profile). Information onwere smoking habits, type of oral anticoagulation, dose of DOAC, and other concomitant therapies was also collected. Previous cardiovascular disease was defined as history of coronary artery disease (either ischemic heart disease or coronary revascularization with

stent or coronary artery bypass graft), while cerebrovascular disease was defined as previous ischemic stroke or transient ischemic attack (TIA).

All patients signed informed written consent at study entry. The study was approved by the local ethics committee of Sapienza University (no. 0234/2022) and was conducted according to the 1975 Declaration of Helsinki.

2.1 Definition of Obesity

The World Health Organization (WHO) defines obesity as an "accumulation of abnormal or excessive fat that may compromise health with the fundamental cause being an energy imbalance between calories consumed and calories burned"[1]. The WHO [17] classifies adult obesity using the BMI with specific cut-offs. BMI is measured by calculating [(weight in kg)/(height in m^2)] and is a simple index intended to classify adults into one of these categories: underweight if BMI is < 18.5 kg/m^2, normal weight if BMI is between 18.5–24.9 kg/m^2, overweight if BMI is 25.0–29.9 kg/m^2, or obese if BMI ≥ 30.0 kg/m^2. Patients with obesity were stratified into class I if they had a BMI of 30.0–34.9 kg/m^2, class II for a BMI of 35.0–39.9 kg/m^2, and class III for a BMI of ≥ 40.0 kg/m^2.

2.2 Blood Sample Collection

Blood samples from patients with AF were collected in tubes with anticoagulant (3.8% sodium citrate) immediately before the administration of the last dose of DOAC to assess the trough plasma concentration and 2 h after DOAC intake to assess the peak plasma concentration. The tubes were centrifuged at 300 *g* for 10 min at room temperature to obtain plasma samples, which were then immediately stored at −80 °C.

2.3 Dabigatran Plasma Concentration

The plasma concentration of dabigatran was measured using the diluted thrombin time (dTT) assay, which is the test of choice for measuring the plasma concentration of dabigatran. To reduce the over-sensitivity of the test to thrombin inhibitors, patient plasma was diluted with a pool of normal plasma. The values were expressed as ng/mL and the results were obtained by interpolating the patient's chromogenic activity on a dose-response curve obtained using calibrator plasmas at known drug concentration. The assay was performed using Siemens reagents, certified calibrators, and specific controls for dabigatran on the BCS Xp automated coagulometer (Siemens).

2.4 Rivaroxaban, Apixaban, and Edoxaban Plasma Concentration

Plasma concentrations of anti-FXa drugs (apixaban, edoxaban, and rivaroxaban) were measured by anti-FXa chromogenic assay. The test reflects the ability of plasma to inhibit FXa. It is performed by mixing the patient's plasma with an excess amount of FXa. A specific chromogenic substrate is used to measure residual FXa. The lower the residual FXa, the higher the drug concentration. The values were expressed as ng/mL and the results are obtained by interpolating the patient's chromogenic activity on a dose-response curve obtained using calibrator plasmas at known drug concentration. The assay was performed using Siemens reagents, certified calibrators, and specific controls for dabigatran on the BCS Xp automated coagulometer (Siemens).

See Supplementary Table 1 for the reference value of trough and peak plasma concentrations.

2.5 Endpoints of the Study

Our study aims to (1) investigate the plasma trough and peak concentration of DOAC and to evaluate the prevalence of patients with below-on therapy range concentrations, and (2) to evaluate the clinical factors associated with below-on therapy range of DOAC plasma concentrations with a focus on obesity class and type of DOAC administered.

2.6 Statistical Analysis

Categorical variables were reported as numbers and percentages and were compared with Pearson's χ^2 test. Mean and standard deviation (SD) or median and interquartile range (IQR) were used for continuous variables, which were compared using Student's *t*-test or Mann–Whitney U test, respectively. Normal distribution of variables was checked by the Kolmogorov–Smirnov test. We divided the cohort into three groups according to the trough plasma concentration: (1) in range, (2) below-range, or (3) above-range, according to each DOAC specific on-therapy range. We also performed a descriptive analysis according to the type of DOAC prescribed and according to obesity class. Then, we performed a descriptive analysis according to peak plasma concentrations, below and in range.

Univariable and multivariable logistic regression analysis was used to calculate the relative odds ratio (OR) and 95% confidence interval (95% CI) for each factor associated with below-range trough and peak concentration, respectively. Given the relatively low number of patients, the multivariable models were adjusted for CHA_2DS_2-VASc score and BMI class.

All tests were two-tailed and only *p*-values < 0.05 were considered statistically significant. The analyses were

performed using SPSS 25.0 software (IBM, Armonk, NY, USA).

3 Results

3.1 Clinical Characteristics

Out of 160 patients, 54 (33.8%) were women and the mean age was 73.2 ± 9.1 years. The median BMI was 32.3 kg/m^2 and the mean waist circumference was 119 cm (Table 1). The most common DOAC prescribed was apixaban in 75 (46.8%) patients, followed by rivaroxaban in 35 (21.8%), dabigatran in 26 (16.4%), and edoxaban in 24 (15.0%). Supplementary Table 2 describes clinical characteristics of patients according to each DOAC. Patients treated with apixaban and edoxaban had higher proportion of class > II obesity (Fig. 1) and were more commonly treated with diuretics (91.7%), while patients on dabigatran had a high proportion of previous stroke/TIA and were treated with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACE-i/ARBs).

Overall, 118 patients had class I and 42 patients had class ≥ II obesity (Table 2). Patients with a higher degree of obesity were younger, with higher waist and hip circumference, and were more likely to be treated with apixaban and dabigatran (Table 2).

3.2 Below-Range Trough DOAC Concentrations

In-range DOAC plasma concentrations were found in 125 (78.1%) patients, while 29 (18.1%) had below-range and 6 (3.8%) had above-range concentrations.

Proportions of patients with plasma below-range concentrations according to DOAC are reported in Fig. 2. Patients with below-range concentrations had a higher history of stroke/TIA and had a higher BMI and were more frequently treated with edoxaban and dabigatran compared with those with in-range concentrations (Table 1). In particular, obesity class ≥ II had a high proportion of patients with below-range trough plasma concentrations (Table 2). No difference was found regarding the proportion of patients with a reduced dose (Table 1).

No difference was observed among groups with regards to hypertension, diabetes, chronic obstructive pulmonary disease (COPD), peripheral artery disease (PAD), liver disease, cancer mean CHA_2DS_2-VASc score, and concomitant treatment. Main characteristics of the population according to the trough plasma concentration are reported in Table 1.

On univariable logistic regression analysis, dabigatran (OR 3.783, 95% CI 1.497–9.562, $p = 0.005$), previous stroke/TIA (OR 4.098, 95% CI 1.655–10.148, $p = 0.002$), BMI ≥ II class (OR 2.858, 95% CI 1.234–6.620, $p = 0.014$), and creatinine clearance (OR 1.013, 95% CI 1.001–1.028, $p = 0.033$), but not serum creatinine, were associated with below-range DOAC plasma trough concentrations (Table 3).

We performed multivariable logistic regression analysis of factors associated with below-range plasma trough concentrations considering each DOAC separately (Table 4, panel A–D). We found an association between dabigatran and below-range plasma trough concentrations (OR 3.039, 95% CI 1.155–7.999, $p = 0.024$) (Table 4, panel A) but no such association was found between rivaroxaban, apixaban, and edoxaban with below-range plasma trough concentrations (Table 4, Panel B, C, and D, respectively). In all multivariable models, BMI ≥ II class was associated with an increased risk of below-range plasma trough concentrations (Table 4 panel A–D).

3.3 DOACs and Below-Range Peak Plasma Concentrations

In total, 23 (14.4%) out of 160 patients had DOAC peak plasma concentration below the therapeutic range. Clinical characteristics according to peak concentrations are reported in Supplementary Table 3. Patients with below-range peak concentrations were treated more frequently with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACE-i/ARBs) and with dabigatran and edoxaban and had a higher creatinine clearance (Supplementary Table 3). Patients with below-range peak concentrations had a higher proportion of below-range trough concentrations (Supplementary Table 3). No further differences were observed in comorbidities, therapy, and clinical characteristics. Obesity class ≥ II had a high proportion of patients with below-range peak DOAC concentrations (Table 2).

Then we performed multiple models of multivariable logistic regression analysis of factors associated with below-range plasma peak concentrations (Supplementary Table 4, panel A–D). We found that dabigatran (OR 4.296, 95% CI 1.523–12.120, $p = 0.006$) and apixaban (OR 0.277, 95% CI 0.096–0.802, $p = 0.018$) were associated with higher and lower risk of below-range plasma peak concentrations, respectively (Supplementary Table 4, panel A and C, respectively).

4 Discussion

Results from this observational study performed on patients with AF and obesity show that 18.1% and 14.4% of patients have below-range trough and peak concentration of DOACs, respectively. We found that obesity class ≥ II was associated with below-range trough levels. Among DOACs, dabigatran was associated with higher risk of both below-range trough and peak plasma concentrations. Conversely, apixaban was

Table 1 Characteristics of patients according to trough concentration: in-range, below-range, and above-range

	Overall ($n = 160$)	In-range ($n = 125$)	Below-range ($n = 29$)	Above-range ($n = 6$)
Age (mean)	73.2 ± 9.1	73.8 ± 8.8	69.8 ± 10.1	75.8 ± 6.6
Female (%)	54 (33.8)	44 (35.2)	10 (34.5)	0 (0.0)
DOAC (%)				
Dabigatran	26 (16.3)	12 (9.6)	10 (34.5)	4 (66.7)
Rivaroxaban	35 (21.9)	32 (25.6)	3 (10.3)	0 (0.0)
Apixaban	75 (46.9)	64 (51.2)	9 (31.0)	2 (33.3)
Edoxaban	24 (15.0)	17 (13.6)	7 (24.2)	0 (0.0)
Reduced dose (%)	15 (9.4)	12 (9.6)	2 (6.9)	1 (16.7)
Hypertension (%)	152 (95.0)	117 (93.6)	29 (100.0)	6 (100.0)
Diabetes (%)	63 (39.4)	47 (37.6)	13 (44.8)	3 (50.0)
Previous MI (%)	34 (21.3)	26 (20.8)	6 (20.7)	2 (33.3)
Previous stroke/TIA (%)	28 (17.5)	17 (13.6)	11 (37.9)	0 (0.0)
Smoker (%)	19 (11.9)	17 (13.6)	2 (6.9)	0 (0.0)
Ex-smoker (%)	70 (43.8)	55 (44.0)	11 (37.9)	4 (66.7)
COPD (%)	33 (20.6)	24 (19.2)	8 (27.6)	1 (16.7)
PAD (%)	11 (6.9)	7 (5.6)	4 (13.8)	0 (0.0)
HF (%)	38 (23.8)	32 (25.6)	4 (13.8)	2 (33.3)
Liver disease (%)	19 (11.9)	14 (11.2)	4 (13.8)	1 (16.7)
Cancer (%)	26 (16.3)	21 (16.8)	3 (10.3)	2 (33.3)
CHA_2DS_2-VASc score	3.9 ± 1.6	3.9 ± 1.6	4.2 ± 1.6	3.5 ± 0.8
HAS-BLED score	1.2 ± 0.7	1.2 ± 0.7	1.2 ± 0.8	1.2 ± 0.4
Therapy				
Antiplatelet (%)	6 (3.8)	5 (4.0)	1 (3.4)	0 (0.0)
ACE-i (%)	43 (26.9)	34 (27.2)	6 (20.79	3 (50.0)
ARBs (%)	76 (48.1)	55 (44.7)	28 (62.1)	3 (50.0)
ACE inhibitors/ARBs (%)	117 (73.1)	90 (72.0)	21 (72.4)	6 (100.0)
Nitrates (%)	4 (2.5)	3 (2.4)	1 (3.4)	0 (0.0)
Beta-blockers (%)	119 (74.4)	91 (72.8)	23 (79.3)	5 (83.3)
Digoxin (%)	15 (9.4)	11 (8.8)	4 (13.8)	0 (0.0)
Antiarrhythmics (%)	35 (21.9)	28 (22.4)	6 (20.7)	1 (16.7)
Amiodarone (%)	9 (5.6)	8 (6.4)	0 (0.0)	1 (16.7)
Statins (%)	120 (75.0)	92 (73.6)	24 (82.8)	4 (66.7)
Ezetimibe (%)	39 (24.4)	29 (23.2)	9 (31.0)	1 (16.7)
Antiepileptic drugs (%)	12 (7.5)	11 (8.8)	1 (3.4)	0 (0.0)
SSRI (%)	12 (7.5)	10 (8.0)	2 (6.9)	0 (0.0)
Diuretics (%)	102 (63.7)	79 (63.2)	20 (69.0)	3 (50.0)
PPI (%)	97 (60.6)	78 (62.4)	15 (51.7)	4 (66.7)
Levotiroxin (%)	38 (23.8)	35 (28.0)	3 (10.3)	0 (0.0)
Allopurinol (%)	28 (17.5)	21 (16.8)	5 (17.2)	2 (33.3)
Clinical and laboratory characteristics				
BMI (continuous)	32.3 [31.0–35.2]	32.0 [31.1–34.5]	34.6 [32.7–38.6]	30.8 [30.1–33.0]
Obesity class				
I (%)	118 (73.8)	97 (77.6)	16 (55.2)	5 (83.3)
II (%)	31 (19.4)	21 (16.8)	9 (31.0)	1 (16.7)
≥ III (%)	11 (6.9)	7 (5.6)	4 (13.8)	0 (0.0)
Waist circumference (cm)	119.0 ± 12.0	118.0 ± 11.6	123.2 ± 12.0	116.0 ± 10.0
Hip circumference (cm)	119.0 ± 10.0	119.0 ± 10.0	123.0 ± 12.0	111.0 ± 7.0
SBP (mmHg)	129.0 ± 15.0	130.0 ± 15.0	129.0 ± 15.0	124.0 ± 15.0
DBP (mmHg)	77.0 ± 9.0	77.0 ± 9.0	77.0 ± 10.0	75.0 ± 5.0
Creatinine (mg/dL)	1.1 ± 0.4	1.1 ± 0.4	1.0 ± 0.2	1.3 ± 0.4

Table 1 (continued)

	Overall ($n = 160$)	In-range ($n = 125$)	Below-range ($n = 29$)	Above-range ($n = 6$)
Creatinine clearance*	87.2 ± 32.1	85.5 ± 31.8	99.1 ± 32.9	65.1 ± 9.3
GOT	21.0 ± 10.0	22.0 ± 10.0	22.0 ± 10.0	19.0 ± 7.0
GPT	21.0 ± 12.0	21.0 ± 12.0	22.0 ± 13.0	14.0 ± 7.0
Time to blood sampling [IQR]	11.0 [9.0–13.0]	11.0 [8.5–13.0]	10.0 [8.5–12.0]	12.0 [10.8–14.3]

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; COPD, chronic obstructive pulmonary disease, DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate, HF, heart failure; IQR, inter quartile range; MI, myocardial infarction; PAD, peripheral artery disease; PPI, proton pump inhibitors; SBP, systolic blood pressure; SSRI, selective serotonin reuptake inhibitor; TIA, transient ischemic attack

*According to Cockroft and Gault formula

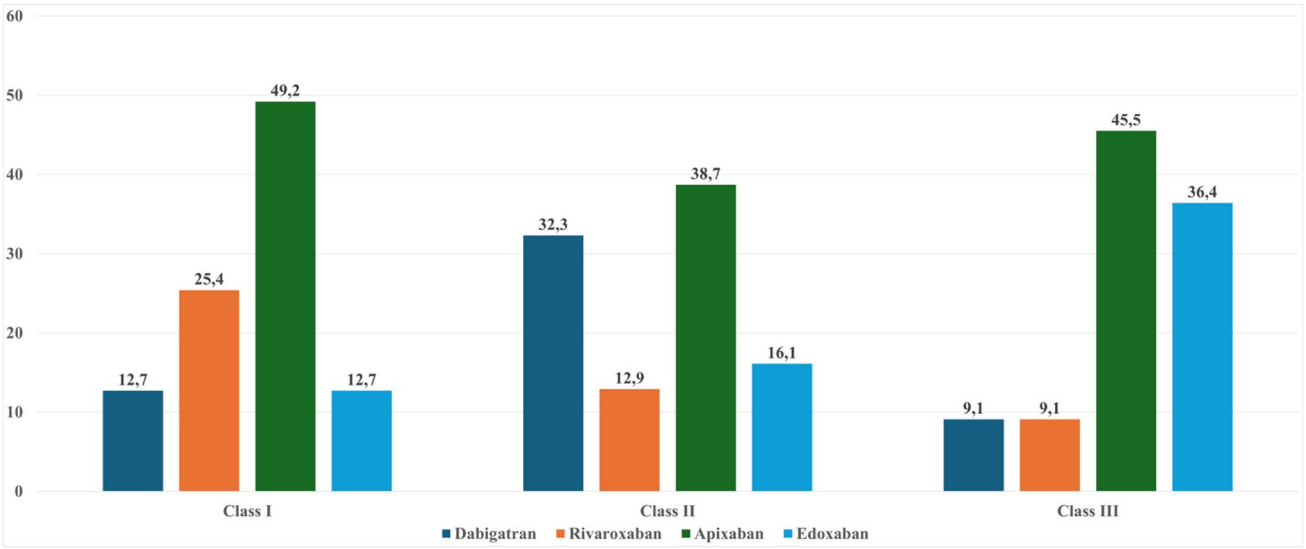

Fig. 1 Distribution (%) of DOACs according to obesity classes

associated with lower risk of below-range peak plasma concentration.

This topic was investigated in few previous studies with small samples. In a study [18] that included 58 patients with a mean BMI of 44.4 kg/m^2, the prevalence of patients with plasma concentration outside of the expected range (defined as below or above the trough and peak levels, respectively) was 15.5%. The authors found that one major driver for plasma concentration outside of the expected range was the inappropriate prescription of reduced DOAC [18].

Regarding peak concentrations, a previous study by Martin et al. [19] including 100 patients with obesity who were treated with apixaban or rivaroxaban for AF or VTE, found that 45.0% of patients on rivaroxaban had a plasma concentration below range at peak, mainly in those for whom VTE was the indication to treatment. In addition, in an observational study [20], which included 38 patients with obesity with a median weight of 135.5 kg affected by AF or VTE, 21.0% of patients had a peak plasma concentration that was below the usual on-therapy range of peak concentration for the corresponding DOAC [20]. We found a lower prevalence of below-range peak plasma concentration (14.4% versus 21.0%), partially explained by different clinical characteristics. Indeed, Piran et al. [20] enrolled patients with either VTE or AF, who were younger, had higher creatinine clearance, and a higher proportion of patients on dabigatran. In addition, patients on a reduced dose of DOACs or those treated with edoxaban were excluded.

Our data indicate that dabigatran is associated with a higher risk of sub-on therapy ranges in both trough and peak plasma concentrations. This may be responsible for the lower efficacy of dabigatran observed in these patients [21]. One possible explanation may be represented by the higher proportion of patients with an obesity class ≥ II in the dabigatran group. Indeed, patients with obesity have a higher distribution volume that, in the case of dabigatran, which is different from other factor Xa inhibitors, has low bio-availability (3.0–7.0% for dabigatran, 50.0% for apixaban, 62.0% for edoxaban, and 66.0–100.0% for rivaroxaban) [6] and may result in sub-on therapy plasma concentrations.

Table 2 Characteristics of patients according to obesity class

	I class ($n = 118$)	≥ II class ($n = 42$)
Age (mean)	74.3 ± 8.3	70.2 ± 10.7
Female (%)	40 (33.9)	14 (33.3)
DOAC (%)		
Dabigatran	15 (12.7)	11 (26.2)
Rivaroxaban	30 (25.4)	5 (11.9)
Apixaban	58 (49.2)	17 (40.5)
Edoxaban	15 (12.7)	9 (21.4)
Reduced dose (%)	10 (8.5)	5 (11.9)
Hypertension (%)	110 (93.2)	42 (100.0)
Diabetes (%)	41 (34.7)	22 (52.4)
Previous MI (%)	32 (27.1)	2 (4.8)
Previous stroke/TIA (%)	19 (16.1)	9 (21.4)
Smoker (%)	15 (12.7)	4 (9.5)
Ex-smoker (%)	48 (40.7)	22 (52.4)
COPD (%)	22 (18.6)	11 (26.2)
PAD (%)	9 (7.6)	2 (4.8)
HF (%)	29 (24.6)	9 (21.4)
Liver disease (%)	13 (11.0)	6 (14.3)
Cancer (%)	22 (18.6)	4 (9.5)
CHA_2DS_2-VASc score	4.0 ± 1.6	3.7 ± 1.4
HAS-BLED score	1.3 ± 0.7	0.9 ± 0.6
Therapy		
Antiplatelets (%)	6 (5.1)	0 (0.0)
ACE-i/ARBs (%)	86 (72.9)	31 (73.8)
Nitrates (%)	2 (1.7)	2 (4.8)
Beta-blockers (%)	85 (72.0)	34 (81.0)
Digoxin (%)	10 (8.5)	5 (11.9)
Antiarrhythmic drugs (%)	28 (23.7)	7 (16.7)
Amiodarone (%)	9 (7.6)	0 (0.0)
Statins	93 (78.8)	27 (64.3)
Ezetimibe	29 (24.6)	10 (23.8)
Antiepileptics (%)	10 (8.5)	2 (4.8)
SSRI (%)	8 (6.8)	4 (9.5)
Diuretics (%)	70 (59.3)	32 (76.2)
PPI (%)	69 (58.5)	28 (66.7)
Levotiroxin (%)	26 (22.0)	12 (28.6)
Allopurinol (%)	17 (14.4)	11 (26.2)
Clinical and laboratory characteristics		
DOAC peak concentration (ng/ml)		
Dabigatran	181.2 ± 131.5	130.5 ± 61.5
Rivaroxaban	224.2 ± 127.5	152.2 ± 108.4
Apixaban	179.9 ± 77.5	170.6 ± 77.9
Edoxaban	233.8 ± 111.6	166.5 ± 12.0
Below-range peak concentrations (%)	13 (11.0)	10 (24.4)
DOAC trough levels (ng/ml)		
Dabigatran	117.4 ± 111.9	61.2 ± 32.6
Rivaroxaban	51.8 ± 38.6	36.1 ± 29.6
Apixaban	98.9 ± 47.8	84.7 ± 63.1
Edoxaban	27.9 ± 15.6	33.2 ± 16.5
Below-range peak concentration (%)	17 (14.2)	13 (31.7)
Waist circumference (IQR)	115.0 [110.0–122.0]	128.0 [122.0–137.0]

Table 2 (continued)

	I class ($n = 118$)	≥ II class ($n = 42$)
Hip circumference (IQR)	115.0 [110.0–122.0]	125.0 [122.0–137.0]
SBP (mmHg)	129.0 ± 15.0	130.0 ± 15.0
DBP (mmHg)	77.0 ± 9.0	78.0 ± 9.0
Creatinine (mg/dL)	1.1 ± 0.4	1.1 ± 0.4
Creatinine clearance*	81.2 ± 25.7	102.5 ± 42.4
GOT	20.0 ± 8.0	25.0 ± 12.0
GPT	20.0 ± 11.0	23.0 ± 13.0
Time to blood sampling [IQR]	11.0 [9.0–13.3]	10.5 [8.0–12.3]

ACE-i, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; COPD, chronic obstructive pulmonary disease, DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate, HF, heart failure; IQR, inter quartile range; MI, myocardial infarction; PAD, peripheral artery disease; PPI, proton pump inhibitors; SBP, systolic blood pressure; SSRI, selective serotonin reuptake inhibitor; TIA, transient ischemic attack

*According to Cockroft and Gault formula

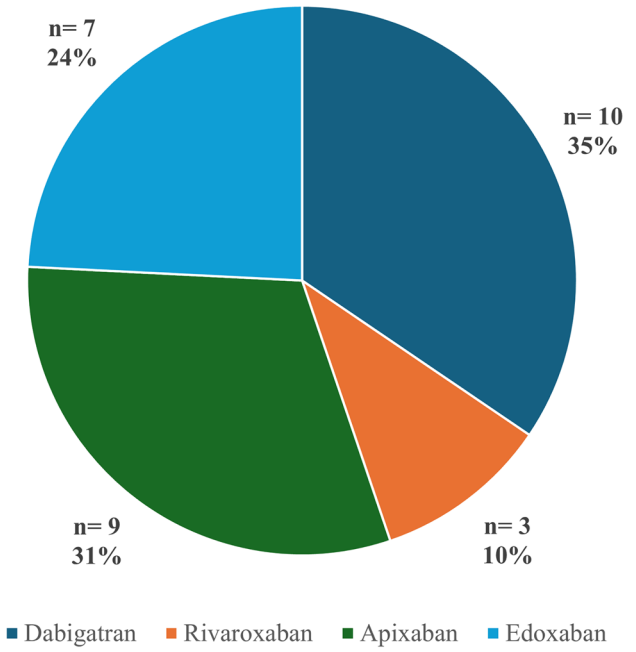

Fig. 2 Proportion of patients with plasma concentration below-range according to DOAC prescribed

Additionally, dabigatran is the only drug administered as a pro-drug that needs to be activated by an esterase-mediated hydrolysis in the stomach [6]. In patients with obesity, some alterations have been described in the function of the stomach, such as a lower gastric retention [22] and a higher gastric pH (2.6 ± 1.6 versus 1.2 ± 1.1, $p < 0.001$) [22] that may alter the absorption of dabigatran.

Finally, patients with obesity have a higher prevalence of gastrointestinal reflux [23] for which antiacid and prokinetic drugs are usually taken. These factors may affect the ability of the pro-drug to be properly activated and adsorbed.

Table 3 Univariable logistic regression models of clinical factors associated with below-range trough concentration of direct oral anticoagulants

	Odds ratio	95% confidence interval	*p*-value
Dabigatran*	3.783	1.497–9.562	0.005
Rivaroxaban*	0.357	0.101–1.258	0.109
Apixaban*	0.443	0.188–1.045	0.063
Edoxaban*	2.134	0.792–5.751	0.134
Previous stroke/TIA	4.098	1.655–10.148	0.002
BMI	1.133	1.034–1.241	0.007
BMI ≥ II class	2.858	1.234–6.620	0.014
Creatinine clearance	1.013	1.001–1.028	0.033
Creatinine	0.335	0.072–1.553	0.162

BMI, body mass index; DOAC, direct oral anticoagulants; TIA, transient ischemic attack

*Versus other DOACs

Nevertheless, only apixaban is associated with lower risk of sub-on therapy peak plasma concentration. It could be hypothesized that apixaban is not influenced by food absorption [6] and proton pump inhibitor (PPI) use [6].

4.1 Clinical Implications

Our study had clinical implications. Our study supports the assessment of DOAC plasma concentration in routinary practice in patients with obesity and AF to reduce the proportion of patients potentially undertreated. This is mainly owing to the evidence that below and above range DOAC plasma concentrations have been associated with an increased risk of thrombotic and bleeding events, respectively [24]. A recent expert consensus proposed the DOAC dipstick to rapidly evaluate the concentration of DOAC in emergency situations, such as surgery, trauma, and bleeding

Table 4 Multivariable logistic regression models of clinical factors associated with below-range trough concentration of direct oral anticoagulants

	Odds ratio	95% confidence interval	*p*-value
A			
Dabigatran*	3.039	1.155–7.999	0.024
CHA_2DS_2-VASc score	1.119	0.858–1.461	0.407
BMI ≥ II class	2.625	1.087–6.335	0.032
B			
Rivaroxaban*	0.435	0.120–1.569	0.203
CHA_2DS_2-VASc score	1.162	0.895–1.510	0.260
BMI ≥ II class	2.806	1.183–6.655	0.019
C			
Apixaban*	0.486	0.202–1.170	0.107
CHA_2DS_2-VASc score	1.152	0.899–1.494	0.285
BMI ≥ II class	2.892	1.221–6.850	0.016
D			
Edoxaban*	1.825	0.656–5.071	0.249
CHA_2DS_2-VASc score	1.167	0.899–1.515	0.245
BMI ≥ II class	2.892	1.223–6.842	0.016

BMI, body mass index; DOAC, direct oral anticoagulants; TIA, transient ischemic attack

*Versus other DOACs

[25]. The usefulness of the DOAC dipstick in patients with obesity needs to be established.

Randomized controlled trials investigating if a strategy of dose adjustment based on measurement of drug levels may result in an improvement of the overall risk-benefit of DOACs in patients with obesity are needed. In addition, there is uncertainty regarding how to manage patients with DOAC plasma concentrations below range, especially in the absence of clinical complications, whether they may benefit from switching to another DOAC or if they should receive VKA therapy.

4.2 Limitations

Our study had some limitations. Firstly, our study was a single-center study that enrolled only Caucasian patients. In addition, given the observational design of the study, we can only deduce association but not causality among clinical and laboratory factors and below-range plasma concentrations of DOACs.

Furthermore, a potential limitation of the study was the lack of a group control of patients without obesity; however, we evaluated the prevalence of below-on therapy range DOAC plasma concentration in our cohort compared with previous literature with nonselected patients. In particular, a study [26] performed on 597 patients on DOAC showed that only 44 patients had a below-on therapy range trough plasma concentration (versus 18.1% in our cohort). However, different clinical characteristics compared with our study make it difficult to make a direct comparison of the two studies in terms of proportion with below-range concentrations.

Finally, although to the best of our knowledge this was the largest study that analyzed trough and peak concentrations with guidelines on-therapy ranges in patients with obesity and AF, further studies on larger patient samples are needed to confirm our data.

4.3 Conclusions

Using guideline-recommended on-therapy ranges of DOACs, we found that patients with obesity and AF had a high risk of having below-range trough and peak plasma concentrations of DOACs. Clinicians should be aware of the possibility of under-therapeutic plasma concentrations of DOAC in patients with obesity class equal to or above II.

Declarations

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Author contributions D.M. and A.P. carried out conceptualization, analysis, writing original draft, and methodology; E.B., V. Cammisotto, V. Castellani, R.M., and I.M.P. carried out data curation, methodology, and investigation; A.C., F.V., J.H., D.P., and P.P. carried out supervision, validation, and reviewing of original draft and editing.

Data availability statement The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval The study was approved by the local ethics committee of Sapienza University (no. 0234/2022) and was conducted according to the 1975 Declaration of Helsinki.

Code availability Not applicable.

Consent to participate All patients signed informed written consent at study entry.

Consent for publication Not applicable.

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