Baseline Characteristics and 3-Year Outcome of Nonvalvular Atrial Fibrillation Patients Treated with the Four Direct Oral Anticoagulants (DOACs)

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Direct oral anticoagulants (DOACs) represent the cornerstone therapy for cardioembolic events prevention in patients with nonvalvular atrial fibrillation (NVAF). In practice, the choice of one DOAC over another is guided by the decision-making process of the physician, which considers specific patient and drug characteristics. This study aimed to evaluate the clinical features and long-term outcomes of a real-world population treated with DOACs, where the use of the 4 different DOACs is quite equal. We conducted a retrospective observational, single-center, multidisciplinary study enrolling consecutive NVAF patients treated with one of the 4 DOACs. From an initial number of 753 patients, we excluded 72 patients because of loss to follow-up, at the end we enrolled 681:174 (23%) treated with dabigatran, 175 (23%) with apixaban, 190 (25%) with rivaroxaban, and 214 (29%) with edoxaban. Patients treated with apixaban were significantly older, more women represented ($p < 0.001$), and with a higher cardioembolic and bleeding risk ($p < 0.001$). Dabigatran was preferred in patients with liver failure ($p = 0.008$), whereas Apixaban and Edoxaban were chosen in chronic kidney disease ($p = 0.002$). At 3-year follow-up, 20 patients (2.7%) experienced a systemic thromboembolic event without significant differences in the 4 DOACs. In the same period, an International Society of Thrombosis and Hemostasis classification major bleeding event occurred in 26 patients (3.6%), more statistically correlated to edoxaban (6.1%) ($p = 0.038$). Thromboembolic events or major bleeding were higher in the edoxaban group (10%) compared with the others ($p = 0.014$). In our single-center real-world experience, the choice of the DOAC for a patient with NVAF was tailored to specific clinical features and drug pharmacokinetics of the patient. As a result, a small number of adverse events were observed. **(Am J Cardiol 2023;206:125−131)**

Keywords: atrial fibrillation, bleeding risk, direct oral anticoagulant, thromboembolism

Atrial fibrillation (AF) is the most common sustained arrhythmia, currently affecting over 33 million subjects worldwide, and its prevalence is expected to more than double over the next 40 years.[1] Patients with AF have a fivefold increase in ischemic stroke risk and direct oral anticoagulants (DOACs) represent the primary therapy for preventing cardioembolic events in patients with nonvalvular atrial fibrillation (NVAF). The availability of DOACs has changed the cornerstones of treatment of NVAF. Indeed, DOACs have shown at least equal efficacy and safety to vitamin K antagonists (VKAs) in large phase III clinical trials.[2−5] Moreover, all DOACs resulted in a lower risk of hemorrhagic stroke or cerebral hemorrhage when compared with VKA. Each of the 4 drugs presents both standard and reduced doses, which are administered based on patient-specific factors. However, the choice of one DOAC over another is often guided by the decision-making process of the physician, which takes into consideration specific clinical features of patients and the pharmacokinetic and

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pharmacodynamic properties of the drugs. Whether there is any difference in efficacy or safety between different DOACs is unknown and limited data are available regarding direct matching in the real world. Therefore, this observational registry aimed to evaluate the clinical features and long-term outcomes of a real-world population treated with DOACs.

Methods

We conducted a retrospective, observational, single-center, multidisciplinary study from the INSigHT registry,[6–8] we analyzed the data from 753 patients with NVAF who started one of the 4 DOACs (i.e., dabigatran, apixaban, rivaroxaban, and edoxaban), receiving either anticoagulation naïve or switching from a VKA, between August 2016 and December 2020. All patients were followed up to 3 years by in-person visits, inpatient and outpatient medical records, or phone interviews. In the present analysis, we enrolled patients who began anticoagulant therapy with DOACs after the release of edoxaban, which was the last DOAC approved in Italy in September 2016.

All patients presenting moderate to severe rheumatic mitral stenosis and/or mechanical heart valve were considered to have valvular AF and were thus excluded. Moreover, patients with indications for DOACs other than NVAF (pulmonary embolism, deep vein thrombosis, or recent hip/knee surgery) were excluded, and patients with end-stage renal disease required hemodialysis. Finally, patients lost to follow-up were also excluded (Figure 1).

The present study aimed to investigate the clinical outcome in patients prescribed the 4 different DOACs. Therefore, 4 different cohorts were evaluated, and 2 primary end points of efficacy and safety were identified. The primary efficacy end point was thromboembolic events, including ischemic stroke, transient ischemic attack, and systemic embolism (SE). The primary safety end point was major bleeding, defined according to the International Society of Thrombosis and Hemostasis classification (ISTH; decrease in the hemoglobin level of at least 2 g/100 ml, transfusion of at least 2 U of packed red cells, occurring at a critical site or resulting in death). Moreover, overall bleeding, including minor bleeding, gastrointestinal, intracranial, symptomatic, and fatal bleeding were recorded in the registry. Secondary end points included overall death, cardiovascular death, and treatment discontinuation because of either shift to other anticoagulant therapy or permanent drug withdrawal. Net clinical benefit end points included thromboembolic events *or* major bleeding events. Clinical follow-up was censored at the date of the last follow-up or at the 3-year time, whichever came first, to balance the different follow-up times between treatment groups.

In all the patients in hospital database, only those discharged from cardiology, internal medicine, or neurology departments and treated with DOACs during the study period were considered. Two data cleaning operators, Fuzzy Lookup and Fuzzy Grouping (Microsoft SQL Server 2005 Integration Services, SSIS), were utilized by a DBA (M.P.) for data cleaning and match search data into the overall hospital database of more than 30,000 patients (Galileo/SAP ISH), considering all patients on DOACs discharged from different departments between August 2016 and December 2020. The observation period of the patients started from the beginning of DOAC treatment and lasted until the latest follow-up. A dedicated noninsurance database for prespecified data entry and clinical-event end point adjudication has been used to avoid selection bias or incomplete data reports. For data entry control, completing at least 95% of clinical forms for each patient was required to be included in the final analysis. In case of treatment change, such as shift to another DOAC, shift to another anticoagulant regimen, or drug interruption, all subsequent events were analyzed and adjudicated based on the treatment patients took at the time of the event.

Continuous variables were reported as mean ± SD or median and compared with Student's *t* test or Mann-Whitney or Wilcoxon tests, based on the normality of the data (which was verified by Kolmogorov-Smirnov goodness-of-fit test). Categorical variables (such as frequencies or percentages) were compared with the chi-square test without

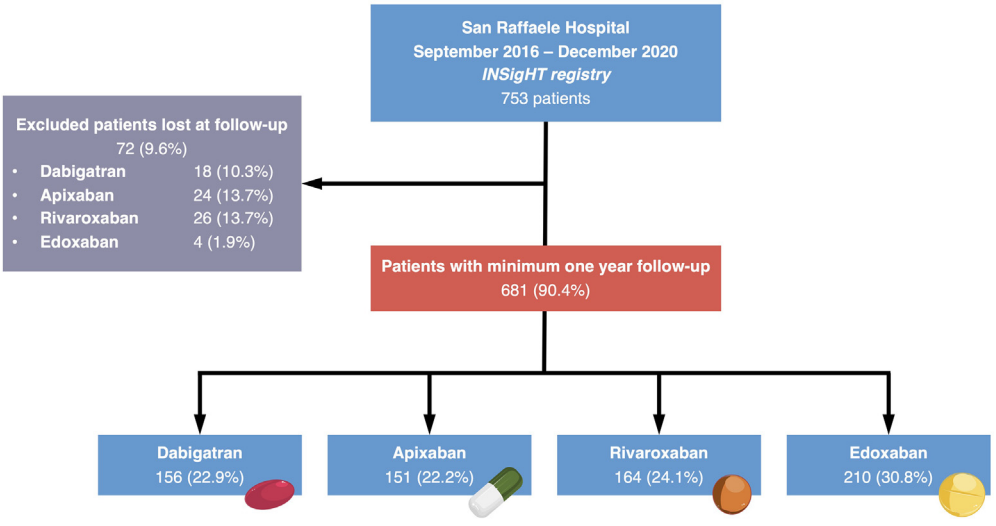

Figure 1. Study flow chart of patients on DOACs from *INSigHT* database

Yates correction for continuity[9] or Fisher's exact test as appropriate.[10] Clinical outcomes and adverse events of the *INSIghT* registry were prospectively monitored at 1-year, 2-year, and 3-year by outpatient visits, phone interviews, or contact with the referring physician of each department, and specific hospital files were requested when needed. Event-free survival was assessed according to the unadjusted Kaplan-Meier method, and survival in groups was compared using the log-rank test (Cox-Mantel test). Clinical follow-up was censored at the date of the last follow-up or 36 months (3 years), whichever came first, to balance the follow-up time between treatment groups having DOACs approved at different times. Data for patients lost to follow-up were censored at the time of the last contact. Two-sided p values <0.05 were considered statistically significant. The statistical analysis was performed using SPSS 23 (SPSS Inc., Chicago, Illinois). Kaplan-Meier survival curves were generated with GraphPad Prism software (version 6; GraphPad, Inc, San Diego, California).

Results

During the index period, from an initial number of 753 patients, we excluded 72 patients because of loss at follow-up, so a total of 681 consecutive patients were enrolled from the Italian DOACs HospiTal (*INSigHT*) registry in the present analysis according to the inclusion/exclusion criteria: 156 patients (23%) received an indication for dabigatran, 151 (22%) for apixaban, 164 (24%) for rivaroxaban, and 210 (31%) for edoxaban. In the overall cohort, all patients presented at least 1 year of follow-up (100%), 662 more than 2 years (97.2%), and 561 3 years (86.6%). Baseline patients and treatment characteristics of the DOAC cohorts are listed in Table 1.

Compared with the other groups, patients treated with apixaban were significantly older (p <0.001), more women represented (p <0.001), with greater CHA2DS2-VASc and HAS-BLED scores (p <0.001), and higher rates of previous stroke/transient ischemic attack/SE (p = 0.003). Edoxaban was the most utilized in patients who switched from a VKA. Dabigatran was preferred in patients with liver failure (patients with liver cirrhosis or total bilirubin 2 times above the upper limits, or aspartate aminotransferase and alanine aminotransferase 3 times above the limits) (p = 0.006). Finally, Apixaban and Edoxaban were used more in patients with chronic kidney disease (CKD) (p <0.001).

Low doses of DOACs were prescribed to 269 patients (40%). In detail, low-dose dabigatran in 60 patients (38%), apixaban in 74 patients (50%), rivaroxaban in 52 patients (32%), and edoxaban in 83 patients (39%) (p = 0.014). In all appropriate prescriptions, appropriate high doses were prescribed in 390 patients (57.7%): in particular, 93 patients on dabigatran (56.9%), 75 patients on apixaban (50%), 108 patients on rivaroxaban (66%), and 114 patients on edoxaban (54%) (p = 0.022). Appropriate low doses were used in 208 patients (30%): 42 patients on dabigatran (27%), 52 on apixaban (34%), 41 on rivaroxaban (25%), 73 on edoxaban (35%) (p = 0.103). Inappropriate low doses were prescribed in 60 patients (8.8%): 17 patients on dabigatran (11%), 23 on apixaban (15%), 11 on rivaroxaban (7%) and 9 on edoxaban (4%) (p = 0.002). Inappropriate high doses were prescribed in 23 patients (3.4%): 4 on dabigatran (2.6%), 1 on apixaban (0.7%), 4 on rivaroxaban (2.4%) and 14 on edoxaban (7%) (p = 0.011).

Table 1
Baseline clinical characteristics of patients treated with DOACs

	Dabigatran N = 156	Apixaban N = 151	Rivaroxaban N = 164	Edoxaban N = 210	p value
Age (years), mean ± SD	70 ± 11	**79 ± 10**	72 ± 12	72 ± 12	**<0.001**
median	72 ± 11	**80 ± 10**	73 ± 12	75 ± 12	
Weight (Kg), mean ± SD	81 ± 20	80 ± 21	79 ± 18	76 ± 15	0.201
Female gender, n (%)	47 (30)	**70 (46)**	57 (35)	78 (37)	**0.027**
CrCl (mL/min), mean ± SD	72 ± 28	67 ± 39	72 ± 30	67 ± 30	0.569
Co-morbidities, n (%)					
Hypertension	106 (68)	120 (80)	127 (77)	152 (72)	0.085
Diabetes mellitus	24 (16)	32 (21)	22 (13)	38 (18)	0.280
COPD	10 (6)	23 (15)	15 (9)	23 (11)	0.079
Peripheral vascular disease	43 (28)	40 (26)	49 (30)	59 (28)	<0.925
Liver failure	**13 (8)**	5 (3)	5 (3)	3 (1)	**0.006**
CKD	7 (4)	**28 (19)**	15 (9)	37 (18)	**<0.001**
Previous stroke/TIA/SE	21 (13)	**35 (23)**	14 (8)	29 (14)	**0.003**
Heart failure	19 (12)	16 (11)	23 (14)	32 (15)	0.595
Previous bleeding	2 (1)	4 (3)	4 (2)	**13 (6)**	**0.049**
Prior AMI	19 (12)	21 (14)	26 (16)	21 (10)	0.381
Bioprosthetic heart valve, n (%)	6 (4)	6 (4)	8 (5)	4 (2)	0.450
CHA2DS2-VASc score, mean ± SD	2.9 ± 2	**3.9 ± 1**	3.1 ± 2	3.2 ± 2	**<0.001**
HAS-BLED score, mean ± SD	1.9 ± 1	**2.6 ± 1**	2.14 ± 1	2.2 ± 1	**<0.001**
Prior use of VKA, n (%)	23 (15)	12 (8)	20 (12)	**52 (25)**	**<0.001**
Drugs, n (%)					
SAPT	15 (10)	21 (14)	25 (15)	25 (12)	0.453
DAPT	9 (6)	8 (5)	10 (6)	8 (4)	0.752

AMI = acute myocardial infarct; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease.; DAPT = double antiplatelet therapy TIA = transient ischemic attack; SAPT = single antiplatelet therapy; SE = systemic embolism; VKA = vitamin K antagonist.

Table 2
The comparison of clinical outcomes at 3 y between DOACS groups

	Dabigatran N = 156	Apixaban N = 151	Rivaroxaban N = 164	Edoxaban N = 210	p value
Days follow-up	1049 ± 10	1019 ± 15	1053 ± 10	1026 ± 11	0.105
Thromboembolic events (stroke, TIA, SE, and IM), n (%)	1 (0.6)	4 (2.6)	6 (3.7)	9 (4.3)	0.147
Ischemic stroke	0 (0)	3 (2)	3 (1.8)	5 (2.4)	0.319
TIA	0 (0)	1 (0.7)	1 (0.6)	2 (1)	0.702
MI	1 (0.6)	0 (0)	1 (0.6)	2 (1)	0.710
SE	0 (0)	0 (0)	1 (0.6)	0 (0)	0.368
Bleeding, n (%)	7 (4.5)	7 (4.6)	12 (7.3)	34 (16.2)	**<0.001**
Major bleeding (ISTH)	4 (2.6)	2 (1.3)	7 (4.3)	13 (6.2)	**0.038**
Fatal bleeding	0 (0)	1 (0.7)	0 (0)	0 (0)	0.319
Intracranial bleeding	0 (0)	0 (0)	1 (0.6)	2 (1)	0.437
Gastrointestinal bleeding	3 (1.9)	1 (0.7)	6 (3.7)	5 (2.4)	0.339
Minor bleeding	3 (1.9)	5 (3.3)	5 (3)	21 (10)	**<0.001**
bleeding in critical organ	1 (0.6)	0 (0)	1 (0.6)	4 (1.9)	0.251
Thromboembolic events *or* major bleedings*	5 (3)	6 (4)	12 (7)	21 (10)	**0.014**
All-cause death, n (%)	10 (6.4)	12 (7.9)	12 (7.3)	31 (14.8)	**0.007**
Cardiac death	4 (2.6)	8 (5.3)	7 (4.3)	7 (3.3)	0.722
Bleeding	0 (0)	0 (0)	0 (0)	1 (0.5)	0.523
Cancer	2 (1.3)	3 (2)	2 (1.2)	8 (3.8)	0.273
Other	4 (2.6)	1 (0.7)	4 (2.4)	15 (7)	**0.005**
Drug discontinuation, n (%)					
Shift to other DOACs	12 (7.7)	7 (5)	7 (4.5)	16 (7.7)	0.487
DOACs Interruption	25 (16)	15 (10)	37 (23)	43 (20)	**0.016**

MI = myocardial infarct; SE = systemic embolism; TIA = transient ischemic attack.
* Two patients (1 in edoxaban group, 1 in rivaroxaban group) had both a major bleeding event and thromboembolism event.

Outcomes are listed in Table 2. The median follow-up time was similar between DOACs.

During the follow-up time, 20 patients (2.7%) experienced a systemic thromboembolic event, with no significant differences between groups: 1 event in dabigatran group (0.6%), 4 events in apixaban (2.3%), 6 events in rivaroxaban (3.2%) and 9 events in edoxaban (4.2%) (p = 0.147).

In terms of safety end points, the overall ISTH major bleeding rate occurred in 26 patients (3.5%), 4 in Dabigatran (2.3%), 2 in Apixaban (1.1%), 7 in Rivaroxaban (3.7%), 13 in Edoxaban (6.1%) (p = 0.038). In particular, 3 intracranial bleeding were reported (2 in edoxaban and 1 in rivaroxaban) (p = 0.437), and only 1 fatal bleeding in the apixaban group (0.6%), (p = 0.319). A total of 6 bleeding in critical organs (intraspinal, intraocular, intraarticular, intramuscular, pericardial, or retroperitoneal hemorrhage) occurred during the follow-up, of these, 4 in edoxaban (2%), 1 in rivaroxaban (0.6%) and 1 in dabigatran (0.6%). A total of 15 gastrointestinal bleeding were reported (2%), 3 in dabigatran (1.7%), 1 in apixaban (0.6%), 6 in edoxaban (3.2%), and 5 in rivaroxaban (2.3%) Similarly, no differences were evident in terms of intracranial and gastrointestinal bleeding. Minor bleeding occurred in 34 patients (4.5%), 3 in dabigatran (1.7%), 5 in apixaban (2.9%), 5 in rivaroxaban (2.6%) and 21 in edoxaban (9.8%) (p = 0.001).

A total of 44 patients (6.5%) had a thromboembolic event or major bleeding (Net clinical benefit end points): 5 in dabigatran (3%), 6 (4%) in apixaban, 12 (7%) in rivaroxaban and 21 (10%) in edoxaban (p = 0.014).

All-cause death was significantly higher in edoxaban group versus the other groups (p = 0.007), instead no significant differences were found in terms of cardiac death between groups (p = 0.722).

We divided the patients into 2 groups: people treated with an appropriate dose (88%) and people with misdosage (12%). We made statistical analysis to evaluate the basic characteristics of patients treated with misdosage, to definite possible clinical factors associated with it. All the baseline characteristics of the 2 groups are listed in Table 3. As a result, patients with liver failure have a higher risk of inappropriate dosing (misdosage).

We also compared outcomes in specific subgroups of the population: specifically, in patients with overdose, we compared the risk of major bleeding events (p value: 0.487), whereas in patients with underdose, we assessed the risk of thromboembolic events across different groups (p value: 0.591). In both cases, no statistically significant differences were observed. Outcomes of subgroups are listed in Table 4.

Discussion

In the present single-center real-world experience, we evaluated the clinical characteristics and the 3-year outcome of NVAF patients treated with 1 of the 4 DOACs. The main results can be summarized as follows: (1) several differences are evident concerning DOAC indications for specific subset of patients; for instance, Apixaban was the most utilized in older patients, whereas Apixaban and Edoxaban were in those with CKD; (2) inappropriate DOAC dosing is a nonnegligible concern: inappropriate low- and high-doses were prescribed in 8.8% and 3.4% of the patients, respectively. Apixaban was the most commonly underdosed drug, whereas edoxaban was the most frequently overdosed one; (3) no significant difference was observed in cardioembolic events in DOACs; however, a significant trend against Edoxaban was noticed concerning

Table 3
Baseline clinical characteristics of patients treated with misdosage and appropriate dose

	Misdosage N = 83 (12.2%)	Appropiate Dose N = 598 (88%)	p value
Age (years), mean ± SD	74 ± 11	73 ± 12	0.201
Weight (Kg), mean ± SD	77 ± 17	78 ± 18	0.848
Female gender, n (%)	29 (35)	223 (37)	0.678
CrCl (mL/min), mean ± SD	70 ± 31	69 ± 32	0.589
Co-morbidities, n (%)			
Hypertension	69 (83)	**436 (73)**	**0.046**
Diabetes mellitus	19 (23)	97 (16)	0.130
COPD	7 (8)	64 (11)	0.526
Peripheral vascular disease	28 (34)	163 (27)	0.218
Liver failure	7 (8)	16 (3)	**0.007**
CKD	11 (13)	76 (13)	0.889
Previous stroke/TIA/SE	12 (14)	87 (14)	0.982
Heart failure	14 (17)	76 (13)	0.295
Previous bleeding	3 (4)	20 (3)	0.898
Prior AMI	15 (18)	72 (12)	0.123
CHA2DS2-VASc score, mean ± SD	3.49 ± 2	3.22 ± 2	0.130
HAS-BLED score, mean ± SD	2.46 ± 1	2.17 ± 1	<0.416

*Misdosage = underdose + overdose.

Table 4
The comparison of clinical outcome at 3 y in underdose group and overdose group

	Dabigatran	Apixaban	Rivaroxaban	Edoxaban	P value
Overdose	4 (3)	1 (1)	4 (2)	14 (7)	**0.011**
-Major bleeding (ISTH), n (%) in overdose group	0 (0)	0 (0)	0 (0)	3 (21.4)	0.487
Underdose	17 (11)	**23 (15)**	11 (7)	9 (4)	**0.002**
- Thromboembolic events (stroke, TIA, SE, and IM), n (%) in underdose group	0 (0)	1 (4)	1 (9)	0 (0)	0.591

major and minor bleeding events. Net clinical benefits were significantly lower in the edoxaban group compared with the others.

DOACs used according to clinical features of patients and pharmacological properties of the drugs: In the present experience, dabigatran was the DOAC most used in patients with liver failure. This finding can be explained by considering that this molecule excretion is mainly renal. Consequently, dabigatran is safer in patients with hepatic insufficiency than other DOACs because its metabolism depends poorly on the function of the liver. A previous study confirmed that dabigatran and apixaban led to greater safety in bleeding outcomes in this subset of patients.[11] DOACs are differently removed through the kidneys: 80% for Dabigatran (50%) for Edoxaban (33%) for Rivaroxaban, and 27% for Apixaban. As a result, drug plasma concentrations depend on creatinine clearance. Apixaban and Edoxaban are less influenced by kidney function, which is why in our cohort these drugs were the most prescribed in patients with CKD.

A meta−analysis confirmed that by comparing factor Xa inhibitors and dabigatran with warfarin separately, factor Xa inhibitors significantly reduced the risk of stroke and major bleeding in NVAF patients. Comparing each DOAC with warfarin separately, apixaban was associated with a significantly better risk reduction of stroke/SE/venous thromboembolism (25% risk reduction) and major bleeding (35% risk reduction) than warfarin.[12] Another study proved that in patients with CKD (estimated glomerular filtration rate <60 ml/min/1.73 m^2) Edoxaban and Apixaban were associated with reduced major bleeding events compared with warfarin. However, Rivaroxaban and Dabigatran showed no significant difference in major bleeding versus warfarin.[13]

In our study, edoxaban was the drug more frequently prescribed in patients who switched from a VKA. This may be because most patients in our study on VKA therapy switched to DOACs between 2016 and 2017, the period in which edoxaban had just entered the market and therefore the physician prescribed it to patients who had to start a DOACs instead of VKA.

Inappropriate dosage of DOACs: As previously shown by our group,[8] inappropriate DOAC dose prescription is not infrequent in the real-world population. In the present analysis, it exceeded 10% of all prescriptions. An inappropriate low dose was prescribed in 8.8% and overdosing had a prevalence of 3.4%. Nevertheless, other studies revealed an even higher rate of incorrect dosage prescription.[14−16]

Apixaban was the drug most frequently prescribed in inappropriate low doses, in line with larger previous real-world studies.[17] This observation could be explained because patients treated with Apixaban were older and with more co-morbidities. Probably, physicians tended to underdose apixaban in these patients because of the bleeding risk. Moreover, apixaban was also the preferred drug in older patients, those with CKD, and those with a higher CHA2DS2-VASc and HAS-BLED score in line with expert consensus who suggest apixaban use in patients older than

75 years.[18] Edoxaban was the most frequently prescribed DOAC with an inappropriately high dose. Edoxaban underdosing is required if it fulfilled any of the following: creatine clearance 15 to 50 ml/min, body weight <60 kg, or concomitant use of dronedarone, cyclosporine, erythromycin, or ketoconazole.[19] To explain why Edoxaban is the most overdosed drug, we can speculate that body weight is a very fluctuating variable over time, it can decrease quickly for several reasons. In addition, we must consider that in our study population edoxaban, and even more apixaban, was prescribed to a higher number of female patients, who have a weight closer to the reduction criteria threshold. Although there are no specific dosage recommendations for dabigatran based on renal filtration, our trial adhered to the European Society of Cardiology guidelines, which suggest reducing dabigatran dosage in the following situations: when the patient age is over 80 years, when there is concomitant use of verapamil, or when there is an increased risk of bleeding.

Interestingly, patients with liver failure have a higher risk of inappropriate dosing (misdosage). This increased risk may be because liver failure is a known predisposing factor for bleeding, resulting from insufficient production of coagulation factors. Consequently, patients with liver failure tend to be treated with underdose medication because of the fear of experiencing bleeding complications. Because of this reason, our analysis revealed a significant association between liver failure and underdose ($p = 0.003$). However, no significant association was found between liver failure and overdose ($p = 0.794$).

DOACs and clinical outcome: In the present analysis, we did not find significant differences in thromboembolic events at 3 years of follow-up between patients treated with different DOACs. A trend toward a lower rate of thromboembolic events in the dabigatran group was evident; however, the absolute number of events was low, and this study was underpowered to claim robust statistical results. Dabigatran had the better profile in terms of net clinical events (ischemic events or major bleeding). In contrast, in this study edoxaban had the worst net clinical benefit.

In our trial, edoxaban is the drug most associated with overdose, which could be considered a bias explaining why the drug appears to be more associated with bleeding events compared with others. Other studies have hypothesized that there are no correlations between events and inappropriate dosage.[8] Despite the limited number of major bleeding events, we performed a statistical analysis using Kaplan-Meier curves to exclude any correlation between major bleeding events in the edoxaban group and drug overdose. Performing a sub-analysis including only patients who experienced overdosing (3.4%), we found no statistically significant difference in the occurrence of bleeding events across the 4 DOACs groups ($p = 0.487$). This indicates that, in our study, the occurrence of major bleeding events cannot be related to overdose in the edoxaban group.

Furthermore, performing a correlation between events in patients would require a much larger sample size and, most importantly, a greater number of events to make it statistically relevant. The objective is not to compare events between the 2 groups of misdosage and appropriate dose but to emphasize how a clinical choice of the drug based on pharmacokinetics and individual patient characteristics could reduce the total number of adverse events.

Of course, the present analysis does not claim to demonstrate which of these drugs has the best outcome, as it could only be derived from large-size randomized controlled trials. However, there are few direct comparison studies of DOACs in real-world populations, especially considering those including patients on edoxaban. Moreover, data are contrasting regarding reported differences in bleeding and ischemic end points.

A recent Danish propensity-matched study showed that in patients with NVAF in routine clinical practice, there were no statistically significant differences in risk of stroke or SE or major bleeding between Apixaban, Dabigatran, and Rivaroxaban used in standard doses.[20] Another retrospective cohort study, using a representative database of 3.5 million statutory health-insured lives in Germany, compared clinical outcomes of all 4 DOACs in 21,038 patients with NVAF. Edoxaban was associated with a lower risk of either ischemic stroke or SE than any other DOAC or VKA; ISTH major bleeding was similar between Edoxaban and Apixaban or Dabigatran, but higher with Rivaroxaban or VKA.[21] In a nationwide retrospective cohort study, based on data from the Taiwan National Health Insurance Research Database, comparing patients with NVAF taking 4 DOACs and warfarin, Edoxaban, Apixaban, and Rivaroxaban were associated with a lower risk of ischemic stroke/systemic embolism than warfarin. All DOACs had a lower risk of major bleeding than warfarin. The risk of major bleeding was lower with apixaban compared with Rivaroxaban and Dabigatran, and comparable between Edoxaban and Apixaban.[22]

Finally, in our study, all-cause death was significantly higher in the edoxaban group ($p = 0.007$) but there were no differences in cardiac death between groups. Therefore, we may speculate that the overall death has been altered by unpredictable causes not related to cardiological diseases.

In conclusion, all 4 DOACs showed comparable effectiveness with some differences in safety profile that need further investigation. Given the insufficient evidence regarding the choice of one drug over another, a patient-tailored approach should be advised, integrating data on pharmacokinetic and pharmacodynamic characteristics of DOACs with patient characteristics including age, renal and liver function, weight, and concomitant medications.

Our study has several limitations. First, the principal limit is represented by its observational nature. Second, the low number of patients in this study could lead to an underestimation of the events during follow-up. Future trials should include a larger number of patients to adequately reflect the diversity of the real-world population, and stratify efficacy and safety for different types of DOACs in a real-world population.

In conclusion, in this single-center real-world experience on DOAC in patients with NVAF, apixaban was the most chosen in elderly patients and those with higher cardioembolic and bleeding risk. Because of its pharmacokinetics, dabigatran was the most used drug in patients with liver failure, whereas Apixaban and Edoxaban were more prescribed in patients with CKD. In total, 2.7% of patients experienced a systemic thromboembolic event without

significant rate differences in the 4 DOACs. In contrast, a significant trend emerged regarding higher bleeding rates in patients treated with edoxaban. The net clinical benefit was significantly lower in the edoxaban group compared with the others. However, because of the small sample size, statistical correlations could not be reliably established. Therefore, further trials with larger sample sizes are necessary.

A tailored choice of DOACs based on individual characteristics should be a global good practice for all medical hospitals.

Author Contributions

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Declaration of Competing Interest

The authors have no competing interests to declare.

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