Real-world use and clinical outcomes among patients with atrial fibrillation using low-dose edoxaban and apixaban in Italy

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PURPOSE

- Reduced-dose direct oral anticoagulants (DOACs) are often used in some patients with atrial fibrillation (AF) who have a high bleeding risk or other contraindications to standard dosing[1]
- While apixaban is the most commonly prescribed DOAC in Italy,[2] edoxaban, though the least prescribed, has seen steadily increasing use since 2017, reflecting a growing preference for this anticoagulant[3]
- No head-to-head randomised controlled trial comparing clinical outcomes with reduced-dose edoxaban and apixaban is available,[4] nor is one expected, leaving real-world evidence as the primary source of data to inform clinical decision making
- The present retrospective cohort study compares the real-world use and clinical outcomes of reduced-dose edoxaban and apixaban in Italian patients with AF

METHODS

- Adult patients with AF who received their first DOAC prescription as reduced-dose edoxaban (30 mg once daily) or reduced-dose apixaban (2.5 mg twice daily) between January 2016 and December 2021 were identified from the Italian IQVIA® Longitudinal Patient Database, a representative sample of the total population extracted from general practitioner records
- To avoid bias from patients who switched to a reduced dose from the standard dose after an adverse event, patients who received any DOAC within 12 months prior were excluded
- Patient characteristics were summarised for those receiving reduced-dose edoxaban and reduced-dose apixaban
- The clinical outcome measures included the event rates for effectiveness (ischaemic stroke [IS] or systemic embolism [SE]) and safety (any major bleeding [MB])
- Propensity score–matching (PSM) was performed to adjust for confounding factors by matching the edoxaban cohort to the apixaban cohort in a 1:1 ratio. Matching was based on demographic and baseline clinical characteristics, using a caliper width of <20% of the standard deviation
- A multivariate Cox regression analysis was conducted post-PSM to adjust for any residual confounding factors. Adjusted hazard ratios (HRs) and 95% confidence intervals (CI) for the reported outcomes were computed

RESULTS

- In total, 2661 patients were identified, with 46.1% (n = 1226) prescribed edoxaban 30 mg and 53.9% (n = 1435) prescribed apixaban 2.5 mg (**Figure 1**)
- Baseline demographics and clinical characteristics are shown in **Table 1**
  - The mean age of the patient cohorts was 84.3 years for edoxaban and 85.5 years for apixaban; most patients were female (edoxaban, 65.9%; apixaban, 63.4%)

Pre-matching

- Before PSM, the annualised rate of IS or SE events were numerically lower for the edoxaban cohort (4.9/100 person-years) compared with the apixaban cohort (6.2/100 person-years), as were the rates of IS events (edoxaban, 4.7/100 person-years; apixaban, 6.1/100 person-years); however, the rates of SE events were the same (edoxaban, 0.2/100 person-years; apixaban, 0.2/100 person-years; **Table 2**)
- Before PSM, the annualised rate of any MB (edoxaban, 1.1/100 person-years; apixaban, 1.4/100 person-years), intracranial haemorrhage ([ICH]; edoxaban, 0.3/100 person-years; apixaban, 0.9/100 person-years), and other MB (edoxaban, 0.2/100 person-years; apixaban, 0.4/100 person-years) were numerically lower for the edoxaban cohort compared with the apixaban cohort; however, the rate of major gastrointestinal (GI) bleeding was numerically higher for edoxaban (0.6/100 person-years) compared with apixaban (0.2/100 person-years; **Table 2**)

Post-matching

- After adjusting for baseline and clinical characteristics, each cohort comprised 1144 patients
- After PSM and adjusting for residual confounding factors, the risk of IS or SE was significantly lower for edoxaban vs apixaban (hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.47–0.98; *P* = 0.04), as was the risk of IS (HR, 0.66; 95% CI, 0.45–0.96; *P* = 0.03; **Figure 2**)
- There was no significant difference in the risk (HR, 95% CI) of any MB (0.83, 0.36–1.92; *P* = 0.7), major GI bleeding (3.00, 0.61–14.86; *P* = 0.2), ICH (0.22, 0.05–1.02; *P* = 0.05) or other MB (1.99, 0.18–21.93; *P* = 0.6) for edoxaban vs apixaban after adjusting for residual confounding factors (**Figure 2**)

Patients with AF from Italy prescribed reduced-dose edoxaban exhibited a lower risk of ischaemic stroke or systemic embolism compared with those receiving reduced-dose apixaban without an increased risk for any major bleeding

CONCLUSIONS

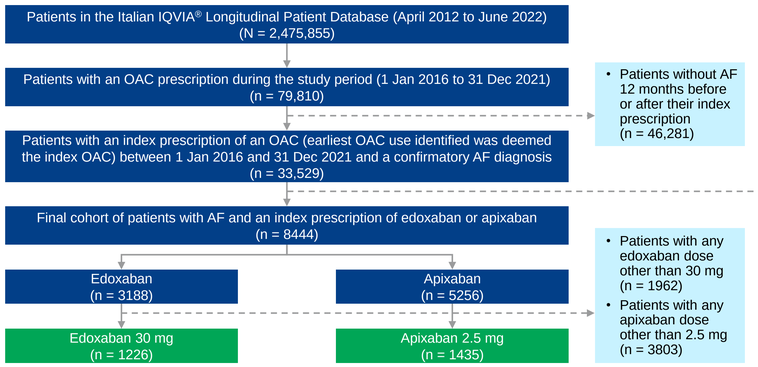
In this analysis of real-world data from routine clinical practice in Italy, the adjusted risk for IS or SE and IS were significantly lower among patients with AF treated with reduced-dose edoxaban vs reduced-dose apixaban; no significant differences were observed for the risk of SE

The adjusted risk for any MB, major GI bleeding, ICH, and other MB was similar between the two reduced-dose DOACs

Our results suggest that reduced-dose edoxaban may offer some advantages over reduced-dose apixaban in preventing thromboembolism among Italian patients with AF. Both treatments have similar safety profiles, but further research is needed to confirm these findings

TABLES AND FIGURES

Figure 1. Patient selection



AF, atrial fibrillation; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; OAC, oral anticoagulant; PE, pulmonary embolism; VKA, vitamin K antagonist.

Table 1. Patient baseline characteristics (n = 2661) before PSM

	Edoxaban 30 mg (n = 1226)	Apixaban 2.5 mg (n = 1435)
Age, years		
Mean ± SD	84.3 ± 7.2	85.8 ± 6.2
Median (Q1, Q3)	85.0 (81.0, 89.0)	86.0 (82.0, 90.0)
≤64 years	19 (1.6)	12 (0.84)
65–74 years	100 (8.2)	45 (3.1)
≥75 years	1107 (90.3)	1378 (96.0)
Sex		
Female	808 (65.9)	910 (63.4)
Male	418 (34.1)	525 (36.4)
$CHADS_2$ score, mean ± SD	2.3 ± 0.8	2.4 ± 0.8
CHA_2DS_2-VASc score, mean ± SD	4.0 ± 1.0	4.1 ± 1.0
Charlson Comorbidity Index		
0	619 (50.5)	632 (44.0)
1	332 (27.1)	417 (29.1)
2	152 (12.4)	193 (13.5)
>2	123 (10.0)	193 (13.5)
Medical history		
Vascular disease	92 (7.5)	165 (11.5)
Stroke/transient ischaemic attack	59 (4.8)	97 (6.8)
Bleeding history or predisposition	9 (0.7)	20 (1.4)
Hypertension	1149 (93.7)	1329 (92.6)
Congestive heart failure	126 (10.3)	190 (13.2)
Diabetes mellitus	257 (21.0)	308 (21.5)
Renal disease	75 (6.1)	120 (8.4)
Cancer	77 (6.3)	103 (7.2)
Medications		
Antiplatelets	152 (12.4)	238 (16.6)
NSAIDs	86 (7.0)	96 (6.7)
H_2-receptor antagonists	20 (1.6)	26 (1.8)
Proton pump inhibitors	617 (50.3)	763 (53.2)
ACEI-ARB	554 (45.2)	655 (45.6)
Amiodarone	120 (9.8)	160 (11.2)
Statins	415 (33.9)	472 (32.9)

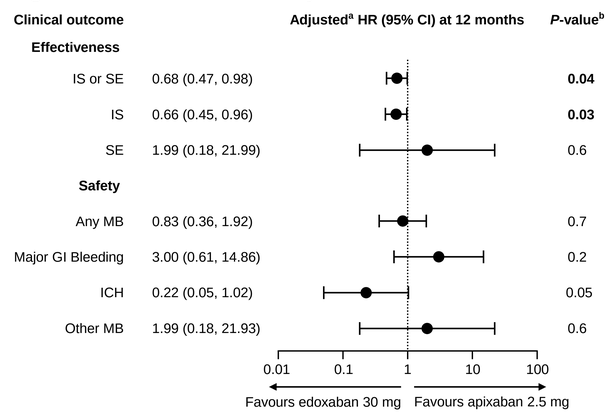
Data are shown as n (%) unless otherwise noted.
ACEI-ARB, angiotensin-converting enzyme inhibitor-angiotensin receptor blocker; $CHADS_2$, Congestive heart failure, Hypertension, Age ≥75, Diabetes, Stroke (doubled); CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65 to 74, and Sex category (female); H_2, histamine 2; NSAID, nonsteroidal anti-inflammatory drug; PSM, propensity score–matching; Q1, first quartile; Q3, third quartile; SD, standard deviation.

Table 2. Clinical outcomes: event rate before and after PSM

Event rate	Event rate before PSM (n = 2661)		Event rate after PSM (n = 2288)	
	Edoxaban 30 mg (n = 1226)	Apixaban 2.5 mg (n = 1435)	Edoxaban 30 mg (n = 1144)	Apixaban 2.5 mg (n = 1144)
Effectiveness				
IS or SE	4.9	6.2	4.6	6.8
IS	4.7	6.1	4.4	6.7
SE	0.2	0.2	0.2	0.1
Safety				
Any MB	1.1	1.4	1.0	1.2
Major GI bleeding	0.6	0.2	0.6	0.2
ICH	0.3	0.9	0.2	0.9
Other MB	0.2	0.4	0.2	0.1

Data shown as event rate per 100 person-years.
GI, gastrointestinal; ICH, intracranial haemorrhage; IS, ischaemic stroke; MB, major bleeding; PSM, propensity score–matching; SE, systemic embolism.

Figure 2. Clinical outcome: adjusted HRs after PSM



[a]Hazard ratios were adjusted for age and sex.
[b]Bolded values indicate a *P* <0.05.
CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; ICH, intracranial haemorrhage; IS, ischaemic stroke; MB, major bleeding; PSM, propensity score–matching; SE, systemic embolism.

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DECLARATION OF INTEREST

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