Impact of different dose reduction criteria on dose assignment of current DOACs and related outcomes: an analysis from 4-year data of the ETNA-AF Europe programme

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Background

- Clinical guidelines and the Summary of Product Characteristics (SmPC) recommend different dose reduction criteria (e.g., weight, creatinine clearance) for each of the four direct oral anticoagulants (DOACs), resulting in various dose reduction criteria for each DOAC (apixaban, dabigatran, rivaroxaban and edoxaban)[1]
- In clinical practice, however, several studies report frequent use of non-recommended doses of DOACs, which may influence efficacy and safety outcomes[2]
- Edoxaban Treatment in routiNe clinical prActice (ETNA-AF) is a prospective, observational study evaluating the safety and effectiveness of edoxaban in patients with AF from Europe
- Data from real-world studies such as ETNA-AF EU, can be helpful in determining the extent of this phenomena and its impact on clinical outcomes

Purpose

To assess the percentage of patients qualifying for dose reduction and explore associated outcomes in a large, unselected, real-world population using 4-year data from the ETNA-AF EU study (NCT02944019)

Methods

- Only patients with available data on all SmPC dose reduction criteria of the four currently available DOACs were included
- Patients with a creatinine clearance <30 mL/min were excluded
- Patients were classified by dose reduction criteria for each DOAC
  - Full dose for all [FULL]
  - Reduced dose for all [REDUCED]
  - Full dose of one DOAC and reduced dose of another DOAC [INTERMEDIATE]

Results

Patient characteristics and dose reduction criteria

- Overall, 12,866 patients from the ETNA-AF EU study were included in this analysis
- According to the SmPC dose reduction criteria, the percentage of patients eligible for dose reduction in the ETNA population differed between the four DOACs (apixaban: 5.7%, dabigatran: 52.9%, rivaroxaban: 16.8%, edoxaban: 23.8%)
- Among the 11,003 assignable patients, differences in the dose reduction criteria in each SmpC was reflected by the distribution of patients in the three pre-specified groups, with the majority included in the INTERMEDIATE group (**Figure 1**)

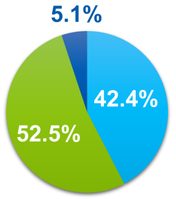
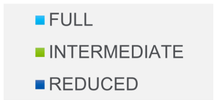


Figure 1. Distribution of patients classified by dose reduction criteria



- Theoretically, patients assigned to the INTERMEDIATE group could receive either a FULL or REDUCED dose of any DOAC, depending on the selected agent (**Table 1**):
  - 65.2% actually received a FULL dose of edoxaban
  - 31.0% actually received a REDUCED dose of edoxaban
- The INTERMEDIATE group included most patients who were known to be at risk of adverse events: i.e., very elderly (≥85 years: 76.5%), frail as per the investigator (73.3%), history of previous stroke (60.4%) or history of bleeding (61.3%)

Table 1. Baseline patient characteristics

Baseline Characteristics	FULL dosage (N=4669)	REDUCED dosage (N=562)	INTERMEDIATE dosage (N=5772)	Not assignable (N=1863)
Male	3087 (66.1)	208 (37.0)	2940 (50.9)	1130 (60.7)
Age, yrs, mean ± SD	65.8 ± 7.2	84.6 ± 4.1	78.7 ± 6.2	72.5 ± 9.2
Age subgroups, years				
<65	1531 (32.8)	1 (0.2)	151 (2.6)	312 (16.7)
65–74	3138 (67.2)	2 (0.4)	593 (10.3)	709 (38.1)
75–84	0 (0.0)	298 (53.0)	4177 (72.4)	721 (38.7)
≥85	0 (0.0)	261 (46.4)	851 (14.7)	121 (6.5)
Weight, kg, mean ± SD	88.3 ± 17.1	64.8 ± 15.4	76.8 ± 14.5	83.5 ± 16.9
BMI, kg/m^2, mean ± SD	29.6 ± 5.4	24.3 ± 4.3	27.3 ± 4.5	28.4 ± 4.8
CrCl*, mL/min, mean ± SD	90.2 ± 22.4	38.7 ± 5.5	62.9 ± 18.9	76.0 ± 21.5
AF type				
Paroxysmal	2618 (56.1)	251 (44.7)	2949 (51.1)	1120 (60.1)
Persistent	1264 (27.1)	131 (23.3)	1351 (23.4)	369 (19.8)
Long-standing persistent	116 (2.5)	13 (2.3)	136 (2.4)	45 (2.4)
Permanent	663 (14.2)	167 (29.7)	1328 (23.0)	320 (17.2)
Congestive heart failure	665 (14.2)	126 (22.4)	994 (17.2)	168 (9.0)
Hypertension	3437 (73.6)	453 (80.6)	4595 (79.6)	1426 (76.5)
Dyslipidaemia	1974 (42.3)	234 (41.6)	2643 (45.8)	667 (35.8)
Diabetes mellitus	968 (20.7)	128 (22.8)	1351 (23.4)	348 (18.7)
COPD	380 (8.1)	50 (8.9)	625 (10.8)	117 (6.3)
Valvular heart disease	548 (11.7)	151 (26.9)	1122 (19.4)	348 (18.7)
HAS-BLED, mean ± SD	2.0 ± 1.0	3.1 ± 0.6	2.9 ± 0.8	2.4 ± 1.0
CHA_2DS_2-VASc, mean ± SD	2.3 ± 1.2	4.2 ± 1.1	3.8 ± 1.2	2.9 ± 1.3
Antiplatelet agents	925 (19.8)	158 (28.1)	1392 (24.1)	354 (19.0)
Edoxaban dose				
30 mg	281 (6.0)	445 (79.2)	1790 (31.0)	276 (14.8)
60 mg	4227 (90.5)	95 (16.9)	3765 (65.2)	1496 (80.3)

Data presented as n (%) unless otherwise specified. *Cockcroft–Gault formula. **AF**, atrial fibrillation; **BMI**, body mass index; **CHA_2DS_2-VASc**, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischaemic attack, vascular disease, age 65 to 74 years, sex category; **COPD**, chronic obstructive pulmonary disease; **CrCl**, creatinine clearance; **HAS-BLED**, hypertension, abnormal liver/renal function, stroke history, bleeding history or predisposition, labile INR, elderly, drug/alcohol usage; **INR**, International Normalised Ratio; **SD**, standard deviation.

Clinical outcomes

- When adjusted for edoxaban, adverse clinical outcomes at four years were significantly higher in the INTERMEDIATE (**Figure 2**) and REDUCED (**Figure 3**) groups when compared with the FULL group, with the only exception of haemorrhagic stroke

Figure 2. Clinical outcomes at four years of patients included in the INTERMEDIATE dose group (n=5772) compared with the FULL dose group (n=4669)

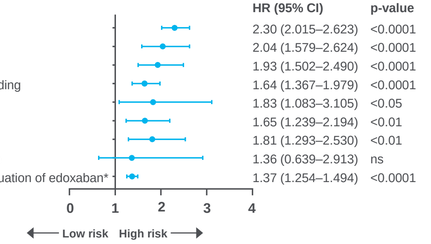
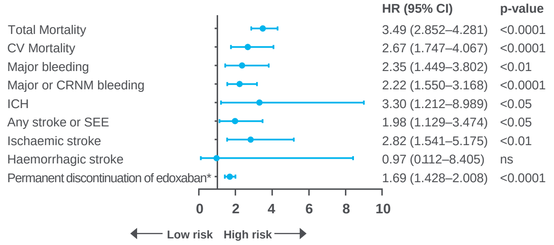


Figure 3. Clinical outcomes at four years of patients included in REDUCED dose group (n=562) compared with the FULL dose group (n=4669)



HRs are adjusted for actually prescribed dose of edoxaban.
*29 patients with documented permanent discontinuation of edoxaban had a missing stop date. Furthermore, two patients had permanent discontinuation of edoxaban at baseline. These 31 patients were excluded when analysing permanent discontinuation.**CI**, confidence interval; **CRNM**, clinically relevant non-major bleeding; **CV**, cardiovascular; **HR**, hazard ratio; **ICH**, intracranial haemorrhage; **ns**, not significant; **SEE**, systemic embolic event.

Conclusions

Due to the different dose reduction criteria, only 42.4% of patients with atrial fibrillation and an indication for anticoagulation were eligible for a FULL dose for each DOAC, and a further 5.1% were eligible for a REDUCED dose. The dose depended on the DOAC chosen in 52.5% of patients, providing a choice and uncertainty for clinical practice

Further research is needed to explore how the selection of DOACs impacts clinical outcomes

Presented at European Heart Rhythm Association (EHRA) 2024
Berlin, Germany, 07–09 April 2024

Acknowledgements

Medical writing support was provided by Luke Jones, MSc, of inScience Communications, and funded by Daiichi Sankyo, Inc.

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