Edoxaban dose, frailty, and outcomes in patients with atrial fibrillation: the ETNA-AF-Europe 4-year follow-up

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Background: Frailty is a common reason to choose non-recommended (non-rec) doses of non-vitamin-K-antagonist oral anticoagulants in patients with atrial fibrillation (AF); however, it is not known how this practice affects stroke and bleeding outcomes.

Purpose: To assess clinical outcomes in frail patients with AF receiving non-rec vs recommended (rec) doses of edoxaban using 4-yr follow-up data from ETNA-AF-Europe.

Methods: The prospective, observational ETNA-AF-Europe study followed patients with AF receiving edoxaban for up to 4 yrs. In ETNA-AF-Europe, perceived frailty was based on investigators' own clinical binary judgement in each patient. Objective frailty was determined using a simplified adaptation of the Rockwood's Frailty Index. For objective frailty, patients with missing index were categorised as non-frail. Patients with perceived or objective frailty were combined for this analysis. Baseline characteristics and hazard ratios (HRs) with 95% confidence intervals (CIs) assessing risk of outcomes in frail patients prescribed non-rec vs rec edoxaban doses (i.e., non-rec 60mg vs rec 30mg and non-rec 30mg vs rec 60mg) are presented. Data were adjusted for age, sex, and derived versions of the CHA2DS2-VASc and HAS-BLED scores. Net clinical benefit was defined as any stroke/systemic embolic event (SEE), transient ischaemic attack, venous thromboembolic event, major bleeding, or cardiovascular death, whichever came first.

Results: Of 13164 patients, 1786 were frail (13.6%; perceived frailty [n=1410], age [IQR]: 82.0 [78.0-86.0] yrs, women: 57.9%; objective frailty [n=540], age [IQR]: 77.0 [71.0-82.0] yrs, women: 31.9%; both, n=164). Baseline characteristics are reported in Table 1.

Risk of all-cause death was higher in frail patients treated with non-rec 30mg vs rec 60mg (HR [95% CI]: 1.44 [1.06,1.96]). The annualised rate [CI] of any stroke/SEE was non-significantly higher (HR [95% CI]:1.60 [0.80,3.20]) with non-rec 30mg (n=169; 2.25 [1.25,4.06]) vs rec 60mg (n=622; 1.54 [1.08,2.20]). There was, however, no association between treatment received and risk (HR [95% CI]) of major bleeding (1.19 [0.58,2.43]) or net clinical benefit (1.26 [0.84,1.87]) (Figure 1).

In frail patients who received non-rec 60mg (n=183) vs rec 30mg (n=695), risk of any stroke/SEE (HR [95% CI]) was higher (2.15 [1.03,4.49]), but there were no significant differences in the risk (HR [95% CI]) of major bleeding (1.03 [0.52,2.01]), net clinical benefit (1.15 [0.78,1.71]), or all-cause death (0.79 [0.59,1.05]) (Figure 1).

Conclusions: In this large European AF registry, the presence of frailty should not drive dosing recommendations for edoxaban. In particular, when compared with the rec 60mg dose, the non-rec 30mg (reduced) dose, was associated with more all-cause death and no benefits on major bleeding.

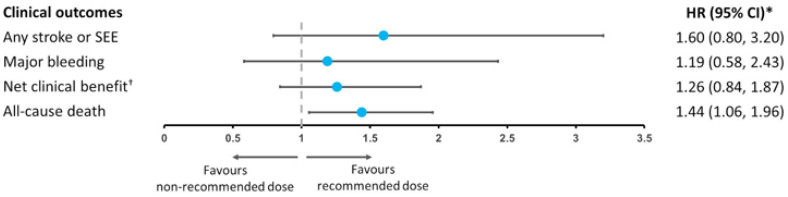
Baseline Characteristics	Frail patients (objective or perceived frailty)*			
	Recommended edoxaban 60 mg (n=622)	Non-recommended edoxaban 60 mg (n=183)	Recommended edoxaban 30 mg (n=695)	Non-recommended edoxaban 30 mg (n=169)
Male	404 (65.0)	68 (37.2)	236 (34.0)	92 (54.4)
Age [years], median (IQR)	78.0 (72.0–82.0)	81.0 (76.0–86.0)	84.0 (80.0–88.0)	80.0 (75.0–83.0)
Age [years]				
<65	50 (8.0)	9 (4.9)	5 (0.7)	9 (5.3)
≥65–74	170 (27.3)	27 (14.8)	52 (7.5)	32 (18.9)
≥75–80	189 (30.4)	54 (29.5)	148 (21.3)	46 (27.2)
>80	213 (34.2)	93 (50.8)	490 (70.5)	82 (48.5)
Weight [kg], median (IQR)	81.0 (74.0–93.0)	65.0 (59.0–75.0)	64.0 (55.0–75.0)	80.0 (73.0–87.0)
Derived CrCl[†] (CG formula) [ml/min], median (IQR)	72.5 (61.0–87.5)	45.4 (39.4–52.9)	40.2 (33.6–45.6)	59.7 (54.5–71.6)
CHA_2DS_2-VASc score[‡,§], median (IQR)	4.0 (3.0–5.0)	4.0 (4.0–5.0)	4.0 (4.0–6.0)	4.0 (3.0–5.0)
HAS-BLED score[‡,‖], median (IQR)	3.0 (2.0–3.0)	3.0 (3.0–4.0)	3.0 (3.0–4.0)	3.0 (3.0–3.0)
Diabetes mellitus	231 (37.1)	60 (32.8)	200 (28.8)	47 (27.8)
Hypertension	543 (87.3)	156 (85.2)	582 (83.7)	142 (84.0)
Congestive heart failure	216 (34.7)	57 (31.1)	240 (34.5)	59 (34.9)
Chronic obstructive pulmonary disease	130 (20.9)	36 (19.7)	107 (15.4)	30 (17.8)
History of stroke/TIA/SEE	185 (29.7)	45 (24.6)	142 (20.4)	22 (13.0)
History of major bleeding	8 (1.3)	4 (2.2)	23 (3.3)	6 (3.6)

Data are n (%) unless otherwise specified. *Objective frailty was determined using a Modified Frailty Index, a simplified adaptation of the Rockwood's Frailty Index. Perceived frailty was based on investigators' own clinical binary judgement in each patient. †Values out of 5–150 range are considered as missing for CrCl. ‡Derived version, assuming that - when adding up the single components of the score - missing components are contributing with 0. §Modified CHA_2DS_2-VASc score (heart failure [1 point], hypertension [1 point], ≥75 years [2 points], diabetes mellitus [1 point], stroke/TIA/SEE [2 points], vascular disease [1 point], age 65 to 74 years [1 point], female sex 1 point]). ‖Modified HAS-BLED (hypertension [1 point], CrCl ≤80mL/min or liver disease [1 or 2 points], stroke history [1 point], prior major bleeding or predisposition to bleeding [1 point], age of >65 years [1 point], medication usage predisposing to bleeding or alcohol usage [1 or 2 points]. **CG**, Cockcroft-Gault; **CrCl**, creatinine clearance; **SD**, standard deviation; **SEE**, systemic embolic event; **TIA**, transient ischaemic attack.

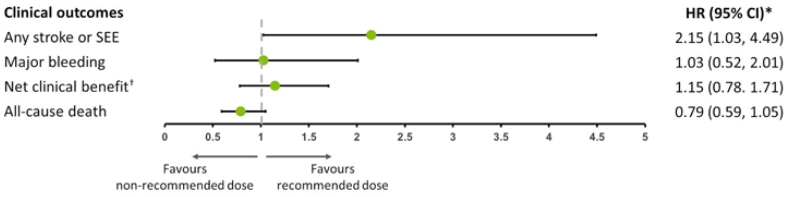
Baseline Characteristics

Figure 1: Clinical outcomes in frail patients receiving a) non-recommended edoxaban 30mg vs recommended 60mg or b) non-recommended edoxaban 60 mg vs recommended 30mg

a) Non-recommended edoxaban 30mg vs recommended 60mg



b) Non-recommended edoxaban 60mg vs recommended 30mg



*HRs (95% CIs) calculated from an adjusted Cox-regression model. The model includes dose recommendation, frailty and the corresponding interaction term as well as age, sex and derived versions of CHA_2DS_2-VASc score and HAS-BLED score (as displayed in Table 1) as additional covariates. †Net clinical benefit is defined as any stroke or SEE or major bleeding or VTE or TIA or CV death (whichever comes first). **CI**, confidence interval; **CV**, cardiovascular; **HR**, hazard ratio; **SEE**, systemic embolic event; **TIA**, transient ischaemic attack; **VTE**, venous thromboembolism