

Effect of perceived and objectively-assessed frailty on outcomes in edoxaban-treated patients with atrial fibrillation: data from the ETNA-AF-Europe 4-year follow-up

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Funding Acknowledgements: Type of funding sources: Private company. Main funding source(s): This study was funded by Daiichi Sankyo Europe GmbH

Background: Frailty is common in patients with atrial fibrillation (AF). However, different definitions of frailty are used, and these may variably overlap with frailty perception among physicians. Long-term data on outcomes based on perceived versus objective frailty in patients with AF treated with a non-vitamin K antagonist oral anticoagulant are lacking.

Purpose: To assess the effect of perceived versus objective frailty on outcome events in patients with AF treated with edoxaban during the 4-year follow-up of the ETNA-AF-Europe registry (NCT02944019).

Methods: ETNA-AF-Europe is a multinational, multicentre, post-authorisation, observational study conducted in patients with AF receiving edoxaban. In this sub-analysis, patients were evaluated in terms of perceived or objective frailty status (yes or no categories). Perceived frailty was based on investigators' own clinical binary judgement in each patient. Objective frailty was determined using a Modified Frailty Index, a simplified adaptation of the Rockwood's Frailty Index. Patient demographics and characteristics were collected at baseline. The efficacy and safety outcomes are reported here comparing frailty status (yes versus no) among perceived or objectively classified patients.

Results: Among the 13,164 patients with 4 years of follow-up, the prevalence of perceived and objective frailty was 10.7% and 4.1%, respectively. Compared with the objectively frail group, those perceived as frail were older, with a lower proportion of males, had lower body weight and creatinine clearance values, yet lower CHA₂DS₂-VASC and modified HAS-BLED scores (Table 1). Further, patients with objective frailty tended to have more comorbidities (e.g., diabetes, heart failure, hypertension; Table 1). Those deemed frail were more likely to receive the reduced 30 mg edoxaban dose versus non-frail patients ($p < 0.001$ for both groups), and non-recommended dosing regimens (60 or 30 mg) were more often prescribed in frail versus non-frail patients ($p < 0.0001$ for all comparisons; Table 1). Patients perceived as frail had a significantly higher risk of all evaluated outcomes compared with non-frail patients (p -value range: < 0.0001 – 0.0459 ; Figure 1). Similar data were seen for objectively frail patients, with the exception of no significant differences in the risk of intracranial haemorrhage (ICH, $p = 0.0918$) or haemorrhagic stroke ($p = 0.1619$; Figure 1).

Conclusions: Frailty was associated with an inappropriate dosing of edoxaban and an increased incidence of outcome events, quantitatively similar in the perceived and objective frailty groups. After 4 years of therapy, even if ICH risk was increased in frail subjects, its cumulative incidence was low.

Table 1: Baseline patient demographics and clinical characteristics

	Perceived frailty			Objective frailty			Total (n=13,164)
	No (n=11,876)	Yes (n=1,288)	P value	No (n=12,834)	Yes (n=540)	P value	
Male, n (%)	6,080 (50.7)	583 (45.3)	<0.0001	7,003 (54.2)	368 (68.2)	<0.0001	7,663 (58.3)
Age (years), mean (SD)	73.4 (9.2)	81.4 (7.2)	<0.0001	73.4 (9.2)	75.4 (8.7)	<0.0001	73.4 (9.2)
Age (years)							
<65	1,875 (15.7)	29 (2.3)		1,944 (15.4)	16 (3.0)		2,060 (15.7)
65-74	4,264 (35.9)	170 (13.2)	<0.0001	4,399 (34.3)	157 (29.2)	<0.0001	4,498 (34.3)
75-84	4,233 (35.7)	328 (25.5)		4,093 (31.9)	243 (45.0)		4,336 (33.0)
≥85	795 (6.7)	469 (36.5)		1,298 (10.1)	84 (15.6)		1,382 (10.5)
Weight (kg), mean (SD)	61.9 (13.4)	71.4 (14.2)	<0.0001	60.9 (13.3)	60.4 (15.4)	<0.0001	60.9 (13.3)
Recalculated CrCl (GFR formula) (ml/min), mean (SD)	71.2 (30.3)	54.3 (23.8)	<0.0001	74.4 (30.4)	66.0 (27.8)	<0.0001	74.4 (30.4)
Recalculated CrCl _{BSC} (mL/min, mean (SD)	8.1 (3.4)	6.1 (3.0)	<0.0001	8.1 (3.4)	7.4 (3.2)	<0.0001	8.1 (3.4)
Recalculated modified HAS-BLED, mean (SD)	2.5 (1.0)	3.0 (1.0)	<0.0001	2.5 (1.0)	2.6 (1.0)	<0.0001	2.5 (1.0)
Diabetes mellitus	2,276 (19.1)	303 (23.6)	<0.0001	2,634 (20.5)	247 (45.7)	<0.0001	2,881 (22.0)
Hypertension	8,339 (70.4)	1,157 (90.1)	<0.0001	9,493 (73.9)	536 (99.3)	<0.0001	10,029 (76.9)
Heart failure (diagnosed)	1,345 (11.3)	373 (29.0)	<0.0001	1,713 (13.3)	126 (23.3)	<0.0001	1,839 (14.0)
Chronic obstructive pulmonary disease	920 (7.7)	217 (16.9)	<0.0001	1,084 (8.4)	132 (24.5)	<0.0001	1,216 (9.2)
History of ischaemic stroke	538 (4.5)	149 (11.6)	<0.0001	685 (5.3)	111 (20.6)	<0.0001	697 (5.3)
History of major bleeding	75 (0.6)	38 (3.0)	<0.0001	107 (0.8)	34 (6.3)	<0.0001	139 (1.0)
Edoxaban dose at baseline, n (%)							
30mg	8,400 (70.8)	589 (45.8)	<0.0001 for	9,298 (73.2)	517 (95.7)	<0.0001 for	9,815 (74.6)
Recommended	6,175 (52.0)	483 (37.6)	30mg vs 60mg	6,852 (53.4)	399 (73.9)	30mg vs 60mg	7,251 (55.5)
Non-recommended	2,225 (18.8)	1,066 (83.1)	no 30mg vs	1,446 (11.4)	118 (21.9)	no 30mg vs	1,564 (11.9)
60mg	2,282 (19.2)	582 (45.4)	non-rec 30mg	2,446 (19.1)	280 (51.9)	non-rec 30mg	2,726 (20.8)
Recommended	1,275 (10.7)	629 (49.0)	no 30mg vs	1,895 (14.8)	138 (25.6)	no 30mg vs	2,033 (15.5)
Non-recommended	677 (5.7)	339 (26.4)	non-rec 30mg	771 (6.0)	48 (9.1)	non-rec 30mg	819 (6.3)

Data are n (%). unless otherwise specified. SD, standard deviation; HAS-BLED, haemorrhage, stroke, bleeding, edoxaban, dose; CrCl, creatinine clearance; BSC, body surface area.

Figure 1: Outcome events according to frailty status after 4 years of follow-up in ETNA-AF-Europe

