Low rates of haemorrhagic stroke, not increased by age, renal/hepatic impairment, concomitant anti-platelet use and high CHA_2DS_2-VASc scores, in the 4-year follow-up of ETNA-AF-Europe

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BACKGROUND

- In patients with atrial fibrillation (AF), direct oral anticoagulants (DOACs) are preferred over vitamin K antagonists for stroke prevention; however, concerns remain over the perceived risk of bleeding associated with DOAC use.[1,2]
- Long-term reporting of routine safety data are necessary to understand the risk–benefit balance and to ensure optimal use of oral anticoagulants in this patient population.[3]

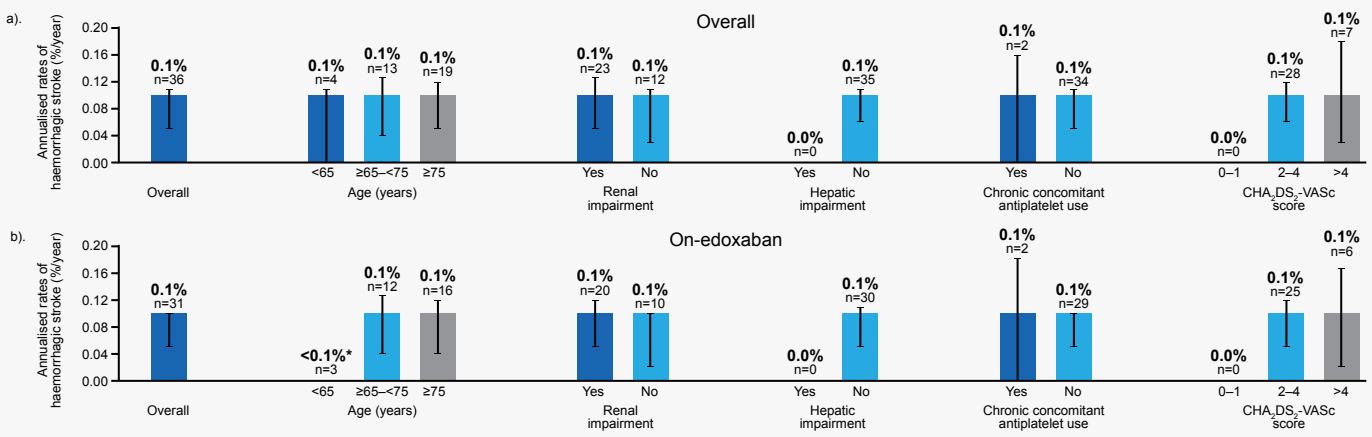
PURPOSE

- To report annualised rates of haemorrhagic stroke in various sub-populations of patients with AF treated with edoxaban during the 4-year follow-up of ETNA-AF-Europe.

METHODS

- ETNA-AF-Europe was a post-authorisation, observational study conducted across 776 sites from 10 European countries, which assessed the risks and benefits of edoxaban use in patients with AF.
- Here, we present the annualised event rates of adjudicated haemorrhagic stroke during the 4-year follow-up that occurred in the overall population (on-/off-edoxaban), the on-edoxaban population in the full analysis set, and sub-populations stratified by age, renal impairment, hepatic impairment, chronic concomitant antiplatelet use and CHA_2DS_2-VASc score.

Figure 1. Annualised a) overall and b) on-edoxaban rates of haemorrhagic stroke



Errors bars represent 95% confidence intervals. Adjudicated haemorrhagic stroke events were analysed. *Incidence rate for <65 years for the 'on-edoxaban' events was <0.1 (0.00, 0.10). Renal impairment was defined as: Cockcroft-Gault formula ≤80 mL/min or CrCl ≤80 mL/min or investigator-reported renal disease (excluding Stage 1 chronic kidney disease) if these data or measurement of serum creatinine were not available. Hepatic impairment was considered present if the bilirubin value exceeded 2× ULN and the AST/ALT exceeded 3× ULN. It was also considered present if the investigator indicated its presence when laboratory values were not available
AST/ALT, aspartate aminotransferase/alanine aminotransferase; **CrCl**, creatinine clearance; **ULN**, upper limit of normal

RESULTS

Baseline characteristics

- A total of 13,164 patients were included in the full analysis set, including 7461 (56.7%) men and 5703 (43.3%) women (**Table 1**).
- Patients aged ≥75 years, those with renal/hepatic impairment, chronic concomitant antiplatelet use and high CHA_2DS_2-VASc score were more likely to be frail in comparison with their counterparts (**Table 1**).
- CHA_2DS_2-VASc scores were higher for patients with renal impairment and chronic antiplatelet use in comparison with their counterparts (**Table 1**).

Rates of haemorrhagic stroke

- The overall and on-edoxaban annualised haemorrhagic stroke rates were low (number of events, % [95% confidence interval]): 36, 0.1 (0.05, 0.11) and 31, 0.1 (0.05, 0.10), respectively (**Figure 1**).

Overall and on-edoxaban annualised rates of haemorrhagic stroke in different subgroups

- The overall and on-edoxaban rates remained low in subgroups stratified by **age, renal/hepatic impairment, chronic concomitant antiplatelet use** and **CHA_2DS_2-VASc scores** (**Figure 1**).

Table 1. Baseline demographics and clinical characteristics

n (%) or median (IQR)	Total (n=13,164)	Age			Renal impairment		Hepatic impairment		Chronic concomitant antiplatelet use		CHA_2DS_2-VASc score (points)		
		<65 years (n=2000)	≥65 and <75 years (n=4458)	≥75 years (n=6706)	Yes (n=7576)	No (n=4933)	Yes (n=102)	No (n=11,857)	Yes (n=895)	No (n=12,269)	Low (0–1) (n=1473)	Moderate (2–4) (n=9205)	High (>4) (n=2164)
Age, years	75.0 (68.0, 80.0)	59.0 (55.0, 62.0)	70.0 (68.0, 73.0)	80.0 (77.0, 84.0)	78.0 (73.0, 83.0)	68.0 (62.0, 74.0)	73.0 (67.0, 80.0)	75.0 (68.0, 80.0)	75.0 (69.0, 81.0)	75.0 (68.0, 80.0)	62.0 (56.0, 67.0)	75.0 (69.0, 80.0)	80.0 (76.0, 84.0)
Male	7461 (56.7)	1385 (69.3)	2642 (59.3)	3434 (51.2)	3751 (49.5)	3304 (67.0)	55 (53.9)	6661 (56.2)	607 (67.8)	6854 (55.9)	1357 (92.1)	5188 (56.4)	717 (33.1)
Weight, kg	80.0 (70.0, 90.0)	90.0 (78.0, 103.0)	82.0 (72.0, 94.0)	75.0 (66.0, 85.0)	74.0 (65.0, 83.0)	90.0 (80.0, 100.0)	80.5 (70.0, 97.0)	80.0 (69.0, 90.0)	80.0 (70.0, 90.0)	80.0 (70.0, 90.0)	87.0 (78.0, 100.0)	80.0 (69.0, 90.0)	75.0 (65.0, 85.0)
Frailty	1410 (11.5)	29 (1.5)	170 (4.1)	1211 (19.5)	1208 (17.0)	180 (3.9)	19 (19.2)	1349 (12.1)	143 (17.0)	1267 (11.1)	16 (1.2)	851 (9.9)	504 (24.9)
CHA_2DS_2-VASc*	3.0 (2.0, 4.0)	1.0 (1.0, 2.0)	3.0 (2.0, 3.0)	4.0 (3.0, 5.0)	4.0 (3.0, 4.0)	2.0 (2.0, 3.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	4.0 (3.0, 5.0)	3.0 (2.0, 4.0)	1.0 (1.0, 1.0)	3.0 (2.0, 4.0)	5.0 (5.0, 6.0)
HAS-BLED†	2.0 (1.0, 2.0)	0.0 (0.0, 1.0)	2.0 (1.0, 2.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	1.0 (1.0, 2.0)	3.0 (2.0, 3.0)	2.0 (1.0, 2.0)	3.0 (2.0, 3.0)	2.0 (1.0, 2.0)	1.0 (0.0, 1.0)	2.0 (1.0, 2.0)	2.0 (2.0, 3.0)
Serum creatinine, mg/dL	0.96 (0.80, 1.14)	0.90 (0.80, 1.06)	0.94 (0.80, 1.10)	1.00 (0.83, 1.20)	1.04 (0.89, 1.24)	0.86 (0.74, 0.97)	0.93 (0.80, 1.12)	0.96 (0.80, 1.14)	1.03 (0.87, 1.23)	0.96 (0.80, 1.13)	0.96 (0.85, 1.09)	0.95 (0.80, 1.13)	1.00 (0.81, 1.23)
CrCl‡, mL/min	68.88 (52.73, 87.92)	100.33 (84.26, 118.55)	78.90 (65.00, 94.11)	57.14 (44.63, 70.56)	58.25 (46.20, 68.40)	96.43 (87.23, 110.31)	69.49 (55.08, 89.47)	68.70 (52.50, 87.80)	63.75 (49.28, 83.11)	69.31 (53.00, 88.29)	93.45 (78.49, 111.64)	68.78 (53.65, 86.71)	56.17 (42.93, 72.31)
Renal impairment	7576 (60.6)	313 (16.5)	2018 (47.7)	5245 (82.2)	–	–	–	–	–	–	326 (23.3)	5352 (61.4)	1709 (81.1)
Renal disease	3582 (29.4)	254 (13.7)	916 (22.3)	2412 (38.8)	3069 (41.7)	513 (10.6)	35 (36.5)	3404 (29.5)	293 (34.6)	3289 (29.0)	178 (13.1)	2406 (28.4)	910 (44.0)
Hepatic impairment	102 (0.9)	16 (0.9)	41 (1.0)	45 (0.7)	–	–	–	–	–	–	12 (0.9)	72 (0.9)	13 (0.6)
Chronic hepatic disease	175 (1.5)	32 (1.8)	62 (1.5)	81 (1.3)	103 (1.4)	71 (1.5)	39 (38.2)	135 (1.2)	12 (1.4)	163 (1.5)	18 (1.4)	118 (1.4)	33 (1.6)
History of antiplatelet use	2913 (22.1)	345 (17.3)	933 (20.9)	1635 (24.4)	1850 (24.4)	935 (19.0)	17 (16.7)	2645 (22.3)	895 (100.0)	2018 (16.4)	200 (13.6)	1895 (20.6)	745 (34.4)

*Modified CHA_2DS_2-VASc score (heart failure [1 point], hypertension [1 point], ≥75 years old [2 points], diabetes mellitus [1 point], stroke/TIA/SEE [2 points], vascular disease [1 point], aged 65 to 74 years [1 point], female sex [1 point]). †Modified HAS-BLED (hypertension [1 point], CrCl ≤80 mL/min or liver disease [1 or 2 points], stroke history [1 point], prior major bleeding or predisposition to bleeding [1 point], aged >65 years [1 point], medication usage predisposing to bleeding or alcohol usage [1 or 2 points]). ‡Values outside of the 5–150 range were considered missing for CrCl
CrCl, creatinine clearance; **IQR**, interquartile range; **SEE**, systemic embolic event; **TIA**, transient ischaemic attack

CONCLUSIONS

The overall and on-edoxaban annualised rates of adjudicated haemorrhagic stroke were low and were not increased by non-modifiable risk factors, such as age, renal or hepatic impairment, concomitant antiplatelet use or CHA_2DS_2-VASc score during the 4-year follow-up

The overall and on-edoxaban annualised adjudicated haemorrhagic stroke rates reported in ETNA-AF-Europe were comparable with the incidence rates reported in age-stratified populations in the literature (incidence/100 person-years), 55–64 years: 0.06 (0.04, 0.07); 65–74 years: 0.10 (0.09, 0.10); 75–84 years: 0.20 (0.10, 0.20)

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