Long-term effectiveness and safety of edoxaban in patients with atrial fibrillation: 4-year follow-up of more than 13,000 patients from the ETNA-AF-Europe study

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BACKGROUND

- Non-vitamin K antagonist oral anticoagulants (NOACs) have replaced vitamin K antagonists as the first-choice therapy for stroke prevention in patients with atrial fibrillation (AF)[1]
- There are limited non-interventional studies with a long-term follow-up to assess effectiveness and safety of NOACs in patients with AF
- ETNA-AF-Europe (Edoxaban Treatment in routiNe clinical prActice in patients with nonvalvular Atrial Fibrillation) is a prospective, observational, multi-centre, post-authorisation safety study in unselected patients with AF with long-term follow-up data on edoxaban
- Here, we present 4-year outcome data in 13,164 European patients treated with edoxaban in ETNA-AF-Europe

OBJECTIVES

- The primary objective of ETNA-AF-Europe (NCT02944019) was to evaluate the real-world safety of edoxaban in patients with non-valvular atrial fibrillation (NVAF) treated for up to 4 years
- Effectiveness outcomes were explored as a secondary objective

METHODS

- Patients were enrolled from 776 sites across 10 European countries; Austria, Belgium, Germany, Ireland, Italy, the Netherlands, Portugal, Spain, Switzerland, and the United Kingdom[2]
- The study ran from 2016 to 2022 and patients were followed-up every 12 ± 2 months for 4 years enabling long-term monitoring of real-world outcomes on the use of edoxaban
- Overall, 13,164 patients were included in the full analysis set, including patients with missing doses. Patients who discontinued edoxaban were still followed-up
- Key outcomes presented in this poster include:
  - Safety outcomes: bleeding events including intracranial haemorrhage (ICH), major bleeding, major gastrointestinal (GI) bleeding; all-cause and cardiovascular (CV) death
  - Effectiveness outcomes: any stroke, transient ischaemic attack (TIA), and systemic embolic events (SEE)
- All the aforementioned key outcomes were adjudicated apart from TIA and minor bleeding events

RESULTS

Baseline demographics (BL) and clinical characteristics split by edoxaban dose

- 13,164 patients with AF treated with edoxaban (60 mg once daily [OD] n=9617; 30 mg OD n=3042; missing dose n=505) at BL (**Table 1**)
- Compared with patients receiving edoxaban 60 mg at BL, those prescribed 30 mg were older, had greater frail proportion, had a lower CrCl and had a higher CHA_2DS_2-VASc score (**Table 1**)

Clinical outcomes

- The annualised rates of all-cause and CV deaths in the overall population were 4.1%/year and 1.0%/year, respectively; higher in patients treated with edoxaban 30 mg vs 60 mg at BL (**Figure 1**)
- The annualised rates of stroke, TIA and SEE were <1%; the proportions were mostly similar between patients treated with 60 and 30 mg at BL except slightly higher rates of stroke in patients treated with edoxaban 30 mg versus 60 mg (**Figure 1**)
- The annualised rates of major bleeding, ICH and major GI bleeding were low, with higher major bleeding and major GI bleeding reported in patients treated with edoxaban 30 mg (**Figure 1**)
- Annualised rates of ICH were similar in patients treated with 60 and 30 mg at BL
- The time-to-first event curves for cumulative events of all-cause death, stroke and major bleeding were almost linear throughout the 4-year follow-up (**Figure 2**), irrespective of the dose received at BL

Table 1. Demographics and clinical characteristics of the overall population and split by edoxaban dose* at baseline

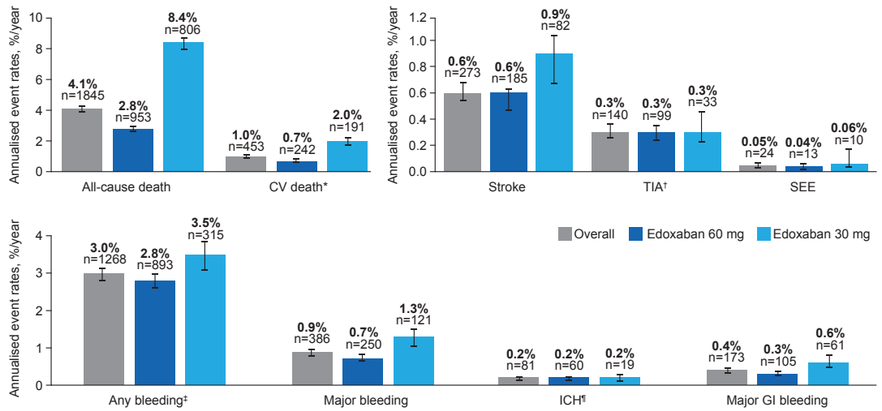
Characteristic, n (%) or median (IQR)	Overall (N=13,164)	Edoxaban 60 mg (N=9617)	Edoxaban 30 mg (N=3042)
Age (years)	75.0 (68.0–80.0)	73.0 (66.0–78.0)	80.0 (75.0–85.0)
Male	7461 (56.7)	5834 (60.7)	1328 (43.7)
Weight (kg)	80.0 (70.0–90.0)	81.0 (72.0–92.0)	71.0 (60.0–83.0)
Uncontrolled hypertension episode	1907 (17.3)	1390 (17.1)	439 (17.5)
Frailty	1410 (11.5)	589 (6.6)	762 (27.0)
CHA_2DS_2-VASc[1]	3.0 (2.0–4.0)	3.0 (2.0–4.0)	4.0 (3.0–5.0)
Modified HAS-BLED[1]	2.0 (1.0–2.0)	2.0 (1.0–2.0)	2.0 (2.0–3.0)
Serum creatinine (mg/dL)	0.96 (0.80–1.14)	0.92 (0.80–1.07)	1.15 (0.90–1.44)
CrCl (mL/min)	68.9 (52.7–87.9)	75.9 (61.9–93.8)	46.1 (37.4–59.0)
Renal impairment[2]	7576 (60.6)	4670 (51.2)	2623 (89.2)
Renal disease[2]	3582 (29.4)	1875 (21.1)	1593 (55.6)

*BL data for 'missing dose at baseline' category are not shown in the table.
[1]Derived variable: Modified HAS-BLED and CHA_2DS_2-VASc: The HAS-BLED score has been calculated without the term "labile INR" and used renal impairment (derived) instead of abnormal renal function as a criterion. The two scores were calculated using uncontrolled episodes of hypertension (instead of hypertension) as a criterion
[2]Renal disease is displayed as reported by the investigator, while renal impairment was derived **CHA_2DS_2-VASc**, CHF, hypertension, age (≥65 = 1 point, ≥75 = 2 points), diabetes, prior stroke/transient ischaemic attack (2 points), vascular disease, and sex category; **CrCl**, creatinine clearance; **IQR**, interquartile range; **HAS-BLED**, hypertension, abnormal liver/renal function, stroke history, bleeding history or predisposition, labile INR, elderly, drug/alcohol usage

CONCLUSIONS

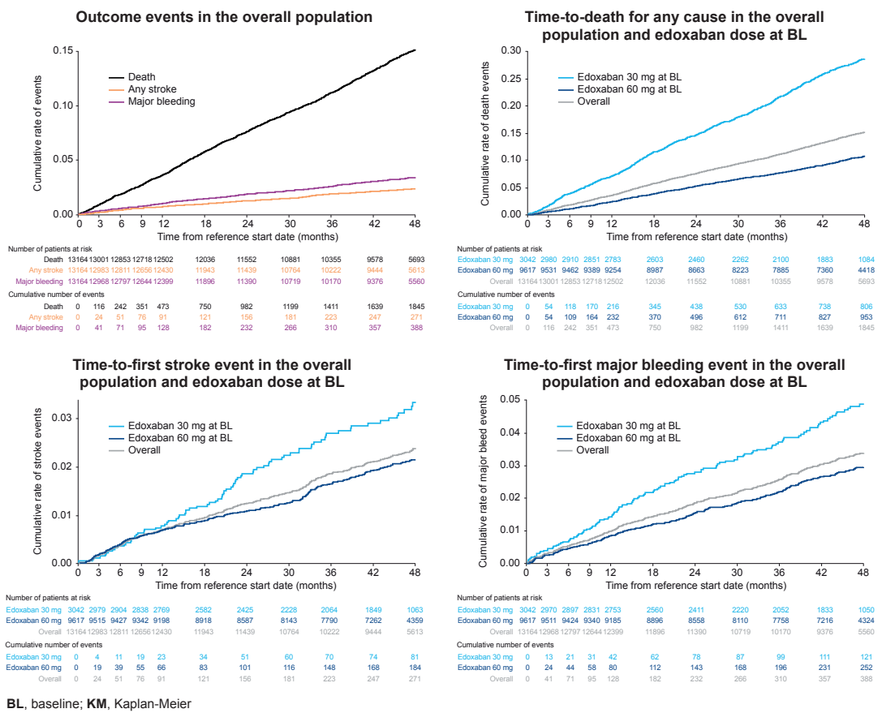
- Low annualised rates of death, stroke and major bleeding in the 4-year follow-up data from ETNA-AF-Europe provides robust evidence for the clinical effectiveness and safety of edoxaban in patients receiving 60 and 30 mg doses. Higher event rates in patients receiving edoxaban 30 mg were potentially due to the older population with greater perceived frailty receiving this dose
- Treatment with edoxaban over 4 years in patients with AF is associated with a low, linearly increasing rate of all-cause death and ischaemic stroke
- Rates of bleeding, especially ICH and major GI bleeding, were low

Figure 1. Annualised event rates (%/year) in the overall population and split by edoxaban dose at baseline



*CV-related death includes VTE-related death; †TIA events were not adjudicated; ‡Minor events were not adjudicated; ¶Haemorrhagic stroke or epidural / subdural haematoma. **CV**, cardiovascular; **GI**, gastrointestinal; **ICH**, intracranial haemorrhage; **SEE**, systemic embolic event; **TIA**, transient ischaemic attack

Figure 2. KM evaluation of 4-year outcomes in the overall population and split by edoxaban dose at baseline



BL, baseline; **KM**, Kaplan-Meier

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REFERENCES

1. Steffel J, et al. *Europace* 2021;23(10):1612–76
2. De Caterina R, et al. *J Cardiovasc* Med *(Hagerstown)* 2019;20(2):97–104

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