Edoxaban for stroke prevention in atrial fibrillation and age-adjusted predictors of clinical outcomes in routine clinical care

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Aims

Patients with atrial fibrillation (AF) treated with oral anticoagulation still suffer from cardiovascular complications including cardiovascular death, stroke, and major bleeding. To identify risk factors for predicting stroke and bleeding outcomes in anticoagulated patients, we assessed 2-year outcomes in patients with AF treated with edoxaban in routine care. We also report the age-adjusted risk predictors of clinical outcomes.

Methods and results

The Edoxaban Treatment in Routine Clinical Practice for Patients With Non-Valvular Atrial Fibrillation (ETNA-AF) Europe (NCT02944019) is a prospective, multi-centre, post-authorisation, observational study with an overall 4-year follow-up conducted in 825 centres enrolling edoxaban-treated patients in 10 European countries. Of the 13 133 patients with AF (mean age: 73.6 ± 9.5 years), 5682 (43.3%) were female. At the 2-year follow-up, 9017/13133 patients were still on edoxaban; 1830 discontinued treatment including 937 who died (annualised event rate of all-cause death was 3.87%). 518 (2.14%) patients died of cardiovascular causes; 234 (0.97%) experienced major bleeding and 168 (0.70%) experienced stroke or systemic embolic events (SEE). Intracranial haemorrhage was noted in 49 patients (0.20%). History of transient ischaemic attack (TIA) at baseline was the strongest predictor of ischaemic stroke or SEE (Wald $\chi^2$: 73.63; $P < 0.0001$). Low kidney function at baseline was the strongest predictor of major bleeding (Wald $\chi^2$: 30.68; $P < 0.0001$). History of heart failure (HF) was the strongest predictor of all-cause (Wald $\chi^2$: 146.99; $P < 0.0001$) and cardiovascular death (Wald $\chi^2$: 100.38; $P < 0.0001$).

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Conclusion

Patients treated with edoxaban in ETNA-AF-Europe reported low 2-year event rates in unselected AF patients. Prior stroke, reduced kidney function, and HF identify patients at high risk of stroke, bleeding and all-cause/cardiovascular death, respectively.

Graphical Abstract

Keywords

Non-vitamin K oral anticoagulant • Edoxaban • Real-world • Registry • Atrial fibrillation
Most patients received edoxaban 60 and 30 mg doses; however, a few patients received edoxaban 15 mg/other/unspecified edoxaban doses.

**Study outcomes**

The study outcomes were bleeding events [major, clinically relevant non-major (CRNM), and ICH as defined by the International Society on Thrombosis and Haemostasis] for evaluating safety; and clinical events, including death [all-cause and cardiovascular (CV) death], any stroke or SEE, ischaemic stroke, and myocardial infarction, for evaluating effectiveness. Events were adjudicated by a central committee. Age-adjusted risk predictors of major bleeding, ischaemic stroke/SEE [including transient ischaemic stroke (TIA)], all-cause death and CV death were also assessed.

**Statistical analysis**

Baseline characteristics are summarised descriptively as frequencies [n %] or mean value ± standard deviation [SD]. Subjective frailty was categorised using a yes/no option, as perceived by physicians as a personal judgement, without any mandated protocol. Adjudicated annualised event rates (%/year) are presented for the safety and efficacy outcomes. Annualised event rates used sum-of-time accumulated events by all patients using a censoring approach. Therefore, bias due to loss to follow-up is not expected. Unadjusted hazard ratios (HRs) [95% confidence interval (CI)] and adjusted* HRs (95% CI) also taking competing risk of all-cause-death into account, were calculated for stroke and bleeding outcomes.

*For any stroke and SEE, and ischaemic stroke, results were adjusted for age, TIA, CHA2DS2-VASC, history of ischaemic stroke, and HAS-BLED. For haemorrhagic stroke (i.e. not an ischaemic event but a brain bleed) and all bleeding events, data were adjusted for age, estimated creatinine clearance (eCrCl) by Cockcroft–Gault Equation, HAS-BLED, frailty, history of heart failure (HF), history of major or CRNM bleeding, and history of chronic obstructive pulmonary disease (COPD). Optimal categorical split from five proposed categorisations of the adjustment factors (including BMI, CrCl, and body weight) was selected by a stepwise procedure (also considering no categorisation, i.e. including a continuous variable).

Cumulative incidence curves of all outcomes were calculated from start of treatment to date of last dose using the Kaplan–Meier method; if two or more time-to-event data were compared then the log-rank test was used in an exploratory manner. Univariate and multivariate Cox proportional hazards analyses were performed to compare the effects of different factors and to simultaneously evaluate the effect of several risk factors. Analyses were adjusted for age.

**Results**

**Baseline characteristics**

A total of 13 133 patients with AF [edoxaban 60 mg: n = 10 036 (76.4%); edoxaban 30 mg: n = 3097 (23.6%)] were included in the 2-year analysis (Supplementary material online, Figure S1). Patient characteristics at baseline are summarised in Table 1. The mean age of patients was 73.6 ± 9.5 years, with ~85% of the patients aged > 65 years. Mean CHA2DS2-VASC score was 3.2 and mean HAS-BLED score was 2.5; mean scores were higher in patients receiving edoxaban 30 mg vs. edoxaban 60 mg. Mean weight was 81.0 ± 17.3 kg, and eCrCl was 74.3 ± 30.4 ml/min. 14.1% had a history of HF at baseline.

Overall, 11.5% of the patients were perceived to be frail; with the proportion of frail patients being higher in the cohort receiving edoxaban 30 mg vs. 60 mg (Table 1).

By the end of the 2-year period, 68.7% (9017/13 133) of patients were still on edoxaban and alive, 1830 discontinued treatment including 532/13 133 (4.1%) died on edoxaban or within 3 days of the last edoxaban dose, and 1298/13 133 (9.9%) died and had permanently discontinued edoxaban >3 days before death or discontinued edoxaban whilst living. The remaining 2286 patients (17.4%) were lost to follow-up or discontinued from the study whilst living and receiving edoxaban. Overall adherence to label recommended dose was high (83.1%), with higher adherence to edoxaban 60 mg vs. edoxaban 30 mg (Table 1).

**Clinical outcomes during the 2-year follow-up**

Annualised event rates of death due to any cause and CV death in the overall study population were 3.87% and 2.14%, respectively (unadjusted HR: 1.66, 95% CI: 1.21–2.30; P = 0.0020; and unadjusted HR: 1.81, 95% CI: 1.25–2.63; P = 0.0016, respectively); however, no differences in rates of haemorrhagic stroke were observed between the dose groups (unadjusted HR: 0.95; 95% CI: 0.35–2.55; P = 0.9133). After adjustment for predictors of stroke and calculation of competing risk of all-cause-death,
Table 1  Demographics and baseline characteristics of the overall population during the 2-year follow-up period

|                          | Total [N = 13 133] (100.0%) | 60 mg [N = 10 036] (76.4%) | 30 mg [N = 3097] (23.6%) |
|--------------------------|-----------------------------|-----------------------------|---------------------------|
| Male, n (%)              | 7451 (56.7)                 | 6084 (60.6)                 | 1367 (44.1)               |
| Age (years), mean (SD)   | 73.6 (9.5)                  | 71.8 (9.1)                  | 79.5 (7.9)                |
| Age [years], n (%)       |                             |                             |                           |
| < 65                     | 1995 (15.2)                 | 1862 (18.6)                 | 133 (4.3)                 |
| (65, 75)                 | 4449 (33.9)                 | 3891 (38.8)                 | 558 (18.0)                |
| (75, 85)                 | 5313 (40.5)                 | 3756 (37.4)                 | 1557 (50.3)               |
| ≥ 85                     | 1375 (10.5)                 | 527 (5.3)                   | 848 (27.4)                |
| Weight [kg], mean (SD)   | 81.0 (17.3)                 | 83.5 (16.7)                 | 72.9 (16.6)               |
| Recalc. CrCl (CG formula) [ml/min], mean (SD) | 74.3 (30.4)                 | 82.1 (29.1)                 | 50.4 (19.7)               |
| ≥ 80                     | 4127 (36.1)                 | 3907 (45.3)                 | 220 (7.8)                 |
| (50, 80)                 | 4914 (43.0)                 | 4008 (46.5)                 | 906 (32.2)                |
| (30, 50)                 | 2107 (18.4)                 | 675 (7.8)                   | 1432 (50.9)               |
| (15, 30)                 | 289 (2.5)                   | 36 (0.4)                    | 253 (9.0)                 |
| < 15                     | 3 (0.0)                     | 1 (0.0)                     | 2 (0.1)                   |
| Perceived frailty, n (%) | 1405 (11.5)                 | 622 (6.6)                   | 783 (27.2)                |
| Type of AF, n (%)         |                             |                             |                           |
| Paroxysmal               | 7056 (53.8)                 | 5494 (54.9)                 | 1562 (50.5)               |
| Persistent               | 3175 (24.2)                 | 2519 (25.2)                 | 656 (21.2)                |
| Long-standing persistent | 320 (2.4)                   | 232 (2.3)                   | 88 (2.8)                  |
| Permanent                | 2557 (19.5)                 | 1769 (17.7)                 | 788 (25.5)                |
| LVEF categorised by 40%§ |                             |                             |                           |
| <40%                     | 671 (7.6)                   | 431 (6.3)                   | 240 (11.8)                |
| ≥40%                     | 8177 (92.4)                 | 6378 (93.7)                 | 1799 (88.2)               |
| Hypertension, n (%)      | 10 129 (77.1)               | 7634 (76.1)                 | 2495 (80.6)               |
| Heart failure (derived), n (%) | 1854 (14.1)                 | 1191 (11.9)                 | 663 (21.4)                |
| History of ischaemic stroke, n (%) | 787 (6.0)                  | 574 (5.7)                   | 213 (6.9)                 |
| History of TIA, n (%)    | 448 (3.4)                   | 330 (3.3)                   | 118 (3.8)                 |
| History of any bleeding, n (%) | 428 (3.3)                  | 259 (2.6)                   | 169 (5.5)                 |
| History of major or CRNM bleeding, n (%) | 273 (2.1)                 | 162 (1.6)                   | 111 (3.6)                 |
| History of major bleeding, n (%) | 136 (1.0)                  | 82 (0.8)                    | 54 (1.7)                  |
| Valvular disease, n (%)  | 2286 (17.4)                 | 1599 (15.9)                 | 687 (22.2)                |
| Overall adherence to SmPC, n (%) |                             |                             |                           |
| Rec. edoxaban dose at baseline | 10 908/13 133              | 8916/10 036                 | 1992/3097 (64.3)          |
| Non-rec. edoxaban dose at baseline | 2225/13 133                | 1120/10 036                 | 1105/3097 (35.7)         |
| Geographic region, n (%) |                             |                             |                           |
| BeNeLux                  | 2546 (19.4)                 | 2166 (21.6)                 | 380 (12.3)                |
| DACH                     | 5487 (41.8)                 | 4227 (42.1)                 | 1260 (40.7)               |
| Iberia                   | 927 (7.1)                   | 704 (7.0)                   | 223 (7.2)                 |
| Italy                    | 3332 (25.4)                 | 2285 (22.8)                 | 1047 (33.8)               |
| UK & Ireland             | 841 (6.4)                   | 654 (6.5)                   | 187 (6.0)                 |

*CrCl was estimated by Cockcroft-Gault formula. †Not including complex vascular plaque, and the score was based on derived heart failure; ‡Not including labile INR, alcohol use was defined as ≥ 1 unit/day, and defining the presence or absence of renal or hepatic disease was left to the discretion of the physician. §LVEF data were missing for 4285 patients (3227 and 1058 patients in edoxaban 60 mg and 30 mg groups, respectively). †A patient was considered as having a medical history of heart failure if one of the following criteria was fulfilled: documented congestive heart failure (CHF), or, if CHF was not documented, then documentation of ischaemic cardiomyopathy, ejection fraction < 40%, frequent dyspnoea (≥ 1 day) without chronic obstructive pulmonary disease and with documented severe valvular heart disease, coronary heart disease post myocardial infarction, valve replacement, or hypertension treated with ≥ 3 drugs. AF, atrial fibrillation; BeNeLux, Belgium, the Netherlands, and Luxembourg; CrCl, creatinine clearance; CRNM, clinically relevant non-major; CG, Cockcroft-Gault; DACH, Germany, Austria, and Switzerland; Rec., recommended. TIA, transient ischaemic attack; SmPC, summary of product characteristics.
Figure 2 Age-adjusted predictors of all-cause death during the 2-year follow-up. (A) Heart failure (derived) as a predictor of all-cause death. Age-adjusted HR for HF yes vs. no: 2.40 (2.08–2.76). (B) COPD as a predictor of all-cause death. Age-adjusted HR for COPD yes vs. no: 2.56 (2.18–2.99). (C) Forest plot showing age-adjusted predictors of all-cause death during the 2-year follow-up. CrCl stages: Stage 1: CrCl ≥ 80 ml/min; Stage 2: CrCl in [50,80] ml/min; Stage 3: CrCl in [30,50] ml/min; Stage 4 + endstage: CrCl < 30 ml/min. BMI categories: Severely underweight < 16.0 vs. normal weight [18.5; 25.0]; Moderately underweight [16.0; 17.0] vs. normal weight [18.5; 25.0]; Mildly underweight [17.0; 18.5] vs. normal weight [18.5; 25.0]; Overweight [25.0; 30.0] vs. normal weight [18.5; 25.0]; Class 1 obesity [30.0; 35.0] vs. normal weight [18.5; 25.0]; Class 2 obesity [35.0; 40.0] vs. normal weight [18.5; 25.0]; Class 3 obesity ≥ 40.0 vs. normal weight [18.5; 25.0]. CrCl-CG, creatinine clearance—Cockcroft Gault; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction.
Figure 3  Age-adjusted predictors of cardiovascular death during the 2-year follow-up. (A) Heart failure (derived) as a predictor of cardiovascular death. Age-adjusted HR (95% CI) yes: 2.60 (2.16–3.13). (B) Left ventricular ejection fraction < 40% as a predictor of cardiovascular death. Age-adjusted HR (95% CI) < 40% vs. ≥ 40%: 3.57 (2.75–4.64). (C) Forest plot showing age-adjusted predictors of cardiovascular death during the 2-year follow-up. CrCl stages: Stage 1: CrCl ≥ 80 ml/min; Stage 2: CrCl in [50,80] ml/min; Stage 3: CrCl in [30,50] ml/min; Stage 4: ESRD vs. stage 1. BMI categories: Severely underweight (< 16.0) vs. normal weight [18.5; 25.0]; Moderately underweight [16.0; 17.0) vs. normal weight [18.5; 25.0]; Mildly underweight [17.0; 18.5] vs. normal weight [18.5; 25.0]; Overweight [25.0; 30.0] vs. normal weight [18.5; 25.0]; Class 1 obesity [30.0; 35.0] vs. normal weight [18.5; 25.0]; Class 2 obesity [35.0; 40.0] vs. normal weight [18.5; 25.0]; Class 3 obesity ≥ 40.0 vs. normal weight [18.5; 25.0]. CrCl-CG, creatinine clearance—Cockcroft Gault; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction.

The recalculated eCrCl at baseline was the strongest predictor of major bleeding (Wald χ² = 30.68; P < 0.0001) (Figure 5a), followed by the baseline HAS-BLED score (19.61; P < 0.0001), subjective frailty as assessed by physician at baseline (18.17; P < 0.0001), a history of HF (17.93; P < 0.0001), a history of major or CRNM bleeding (17.52; P < 0.0001) (Figure 5b and c), history of major bleeding (14.40; P = 0.0001), and COPD (10.39; P = 0.0013).

Discussion

The 2-year follow-up data from ETNA-AF-Europe provide real-world evidence for the long-term safety and effectiveness of edoxaban in patients with AF. Overall and similar to the one-year outcomes reported previously, rates of stroke and bleeding were low. Thromboembolic rates in ETNA-AF-Europe were indeed much lower than those noted in non-anticoagulated and warfarin-treated patients in datasets outside of ETNA-AF.6,12,13 Outcomes observed in ETNA-AF-Europe seem to confirm effectiveness and safety in routine practice similar to those observed in the edoxaban arms in the randomised
Two-year follow-up of ETNA-AF-Europe

Figure 4 Age-adjusted predictors of stroke during the 2-year follow-up. (A) History of TIA as a predictor of ischaemic stroke/TIA/systemic embolic events. With a history of TIA: age-adjusted HR (95% CI): 5.01 (3.47–7.24). (B) CHA2DS2-VASc score as a predictor of ischaemic stroke/TIA/systemic embolic events. Age-adjusted HR (95% CI) of CHA2DS2-VASc score as numerical variable: 1.39 (1.26–1.54). Categorised CHA2DS2-VASc score, age-adjusted HR (95% CI): 2–3 vs. <2: 3.06 (1.21–7.75); 4–5 vs. <2: 4.28 (1.64–11.17); ≥6 vs. <2: 9.80 (3.59–26.76). (C) Forest plot showing age-adjusted predictors of ischaemic stroke/TIA/systemic embolic events during the 2-year follow-up. HR, hazard ratio, TIA, transient ischaemic attack.

ENGAGE AF-TIMI 48 trial. Of note, in this well-anticoagulated patient population treated with edoxaban, fatal event rates—both CV and all-cause death—were more frequent than stroke or bleeding event rates. There was no relevant impact of edoxaban dosing on these outcomes. After adjusting for baseline characteristics and also taking competing risk of all-cause death into account, differences in the risk of any stroke or SE and ischaemic stroke between the 30 and 60 mg dose groups were not significant. Likewise, the differences in the rates of major bleeding and major or CRNM bleeding between the 30 and 60 mg dose groups were not significant, suggesting that the observed differences in the unadjusted rates were due to expected patient characteristics, rather than due to edoxaban dosing. These findings suggest that both doses were appropriate in their respective patient groups. Patients receiving edoxaban 30 mg were older, had higher CHA2DS2-VASc and HAS-BLED scores, and included more patients perceived as frail compared with those receiving edoxaban 60 mg. In the light of differences in the population characteristics, the dose-reduced patients were at higher risk of ischaemic stroke, major bleeding and death vs. those receiving the 60 mg dose. Adherence to label recommendation at baseline in ETNA-AF-Europe was high (83.1%), with higher percentage of recommended dosing observed in patients receiving edoxaban 60 mg.

Age-adjusted predictors of clinical outcomes in patients treated with non-vitamin K antagonist oral anticoagulants

Slightly contrasting to the relatively low stroke and bleeding rates, the residual rate of CV death was 2.1% and a leading cause of death, illustrating the need to identify anticoagulated patients with AF at risk of CV events. Several independent risk factors for stroke, bleeding, and death have been better identified in anticoagulated patients with AF. Besides, modifiable and non-modifiable risk factors of AF are also risk factors for ischaemic stroke. Advancing age is the most prominent risk factor for AF and AF-related outcomes. Hence, data in our analysis were adjusted for age in order to assess the residual effect of the other risk factors. Of note, HF was a stronger predictor of death and CV death than left ventricular function, highlighting the importance of HF with preserved ejection fraction as an additional marker for risk in patients with AF.
In our analysis, history of TIA at baseline was the strongest predictor of ischaemic stroke, TIA, and SEE. This is similar to the GARFIELD registry analysis of 52,014 patients, reporting a history of prior stroke or TIA as a strong independent risk factor for stroke/SEE and death. There, however, the excess risk was primarily ascribed to a history of stroke (with or without TIA), whereas history of TIA by itself was reported as a weaker predictor.19

In line with our findings, a history of ischaemic stroke (HR: 1.89; \( P = 0.005 \)) was identified as an independent risk factor of stroke/SEE in a prospective study involving 5,717 AF patients (mean age 73.9 years) receiving rivaroxaban.20 To ensure thromboprophylaxis in AF patients, the risk-benefit profile of the drug should be carefully evaluated while taking into account factors associated with the risk of bleeding. The CHA2DS2-VASc and HAS-BLED risk scores are widely used to determine the thromboembolic risk and risk of bleeding even in the era of NOACs.21 The two risk scores at baseline were independent predictors of stroke, TIA and SEE in the ETNA-AF-Europe population. A large administrative database of 39,539 NOAC-treated patients in routine care showed that two stroke scores (CHA2DS2 and CHA2DS2-VASc), and three bleeding scores (HAS-BLED, ORBIT, and ATRIA) had similar performances in predicting major bleeding, suggesting that patients at a high risk of stroke are also at high risk of bleeding.22 In addition to predicting stroke and SEE, the CHA2DS2-VASc risk score has also been found to predict CV deaths in our analysis. However, no statistically significant correlation of stroke scores was observed with serious bleeding. This outcome is coherent with the findings from our analysis, which shows no correlation between the stroke risk score and major bleeding.

Findings from recent registries and administrative databases add to our understanding about predictors of major bleeding. The recalculated eCrCl was the strongest predictor of major bleeding in our analysis, followed by COPD, chronic obstructive pulmonary disease; CRNM, clinically relevant non-major; CrCl-CG, creatinine clearance—Cockcroft Gault; HR, hazard ratio. CrCl stages: Stage 1: CrCl \( \geq \) 80 ml/min; Stage 2: CrCl in [50,80) ml/min; Stage 3: CrCl in [30,50) ml/min; Stage 4 and End Stage: CrCl < 30 ml/min.

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**Figure 5** Age-adjusted predictors of major bleeding during the 2-year follow-up. (A) CrCl-CG as a predictor of major bleeding. Age-adjusted HR (95% CI) of CrCl: HR (95% CI): Stage 2 [CrCl (50, 80 ml/min)] vs. Stage 1 [CrCl (\( \geq \) 80 ml/min)]: 1.94 (1.29–2.92); Stage [CrCl (30,50 ml/min)] vs. Stage 1 [CrCl (\( \geq \) 80 ml/min)]: 2.51 (1.53–4.09); Stage 4 and End Stage [CrCl (< 30 ml/min)] vs. Stage 1 [CrCl (\( \geq \) 80 ml/min)]: 6.15 (3.22–11.73). (B) HAS-BLED score as a predictor of major bleeding. Age-adjusted HR (95% CI) for increasing of HAS-BLED by point: 1.31 (1.16–1.48), categorised. HAS-BLED 2 vs. <2: 1.48 (0.85–2.59); HAS-BLED 3 vs. <2: 2.26 (1.31–3.92); HAS-BLED 4 vs. <2: 2.47 (1.37–4.47); HAS-BLED \( \geq \) 5 vs. <2: 3.46 (1.74–6.89). (C) Forest plot showing age-adjusted predictors of major bleeding during the 2-year follow-up. COPD, chronic obstructive pulmonary disease; CRNM, clinically relevant non-major; CrCl-CG, creatinine clearance—Cockcroft Gault; HR, hazard ratio. CrCl stages: Stage 1: CrCl \( \geq \) 80 ml/min; Stage 2: CrCl in [50,80) ml/min; Stage 3: CrCl in [30,50) ml/min; Stage 4 + end stage: CrCl < 30 ml/min.
Liver disease, history of major bleeding, male sex, antplatelet use, cardiomyopathy, peripheral vascular disease, and COPD have been established as important predictors of major bleeding in some recently published analyses. In keeping with these findings, we observed previous major bleeding and COPD as powerful predictors in our analysis as well.

Impaired renal function or eCrCl worsening is an independent predictor of various clinical outcomes including cardioembolic stroke/SEE, bleeding, and death. Notably, findings from our analysis are coherent with available evidence, showing that recalculated eCrCl at baseline was the strongest predictor of major bleeding and also a significant predictor of all-cause and CV death.

Some interesting observations were made upon exploring frailty and history of falls as predictors of clinical outcomes. The burden of subjective frailty is substantial, with almost 1 out of 5 patients with AF categorised as frail. Frailty index is a well-established predictor of all-cause death, particularly among older patients. Adding to the available evidence, in ETNA-AF-Europe a simple reported subjective frailty perception of clinicians (using a yes/no option) was the strongest predictor of all-cause death, even after adjustment for age. A history of falls is also indicative of the presence of frailty in elderly individuals, and has been independently associated with a higher risk of stroke/SEE and major bleeding, and further associated with all-cause death in the All Nippon AF in the Elderly (ANAFIE) registry enrolling over 30,000 patients aged ≥ 75 years.

Taking all these findings together, the various combinations of predictors of AF-related outcomes warrant further analyses for improving our understanding of the risk factors for outcomes in NOAC-anticoagulated AF patients. This should further aid in the timely and accurate management of high-risk patients.

Strengths and limitations of this analysis
Strengths of ETNA-AF-Europe were the inclusion of 13,133 patients with 2-year follow-up data available for 9017 patients; the prospective, multinational and multicentre study design; the central adjudication of events; and the absence of explicit exclusion criteria, validating the dependability and generalizability of the findings. Notably, we present here interim results of a predefined follow-up duration of four years.

We also acknowledge, however, limitations of our analysis. Just over 9000 patients were still on edoxaban at the end of the 2-year period. Approximately 17% of patients were lost to follow-up or discontinued from the study whilst living and receiving edoxaban. Although adherence to edoxaban dosing was high, it was lower than the dosing observed in a randomised controlled trial setting. Since there was no alternate anticoagulant control group, comparison of different treatments was not possible. Due to the observational design of the study and to avoid interference with routine care, additive systematic information on laboratory and other investigations could not be mandated.

Most relevant, the open-label nature of the study may have introduced ascertainment bias due to awareness about treatment. Finally, underreporting of events is an important inherent limitation of any observational study compared with RCTs. Of note, annualised event rates were estimated using a censoring approach in our analysis, therefore limiting bias due to loss to follow-up.

Conclusions
Oral anticoagulation with edoxaban was associated with low annualised rates of stroke (0.70%) and major bleeding (0.97%) in unselected patients with AF during the 2-year follow-up. Approximately 9000 (68.7%) patients were still on edoxaban at the end of two years of follow-up, with the remaining being lost-to-follow-up or permanently discontinued or died. CV death was the most common cause of death in anticoagulated patients with AF at an annual rate of 2.1%. Prior TIA, reduced kidney function, and prior HF were the strongest predictors for identifying patients at high risk of stroke, bleeding and all-cause/cardiovascular deaths, respectively. These results highlight the need to optimise the management of patients with AF and prior HF especially, to reduce the risk of death.

Supplementary material
Supplementary material is available at European Heart Journal—Cardiovascular Pharmacotherapy online.

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Author contributions
All authors made substantial contributions to drafting the work or substantively revising it; approved the submitted version; agreed to be personally accountable for their own contributions and for ensuring that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and documented in the literature. All authors have read and agreed to the published version of the manuscript.

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active in atrial fibrillation and has received honoraria from several such companies in the past, but not in the last three years. P.K. is listed as inventor on two patents held by University of Birmingham (Atrial Fibrillation Therapy WO 2 015 140 571, Markers for Atrial Fibrillation WO 2 016 012 783). P.K. is employed as Director of the Department of Cardiology, University Heart and Vascular Centre UKE Hamburg and Professor of Cardiovascular Medicine (part-time), University of Birmingham, UK. He is Speaker of the board of AFNET, Germany, and Board member of the ESC. L.P. has received fees and honoraria from Daiichi Sankyo, SOTIO, and Beckman Coulter. A.B. is founder and clinical trial design advisor of Amore Health Ltd, reports support from Daiichi Sankyo for attending meetings and advisory boards; receives honorarium from Daiichi Sankyo, Pfizer, BMS, Bayer, Novartis, Roche, Napp, Boehringer Ingelheim for lecturing and scientific advice outside the submitted work. C.D.A. has received compensation for teaching purposes and procuring from Medtronic, Abbott, Biotronik, Atricure, Cardiotek, Biosense Webster and research grants on behalf of the centre from Biotronik, Medtronic, St Jude Medical Abbott, Livanova, Boston Scientific Biosense Webster. J.R.D.G. reports personal fees from Daiichi Sankyo during the conduct of the study; grants from Abbott, Atricure, Bayer, Boston Scientific, Daiichi Sankyo, Johnson & Johnson and Medtronic; personal fees from Atricure, Bayer, Daiichi Sankyo, Johnson & Johnson, Medtronic, Novartis, and Servier; and other from RhythmCARE outside the submitted work. J.C.D. has received honoraria for lectures from Bayer, Boehringer Ingelheim, and Bristol Myers Squibb. J.C.D. has also received research grants from Boston Scientific, Sorin Group, Biotronik, and Abbott. P.K. has received speaker’s and committee membership from Daiichi Sankyo, and received consulting fee (€ 5000€) from Alexion and Novo Nordisk. He is the Lead Investigator of the HRB Stroke Clinical Trials Network Ireland, which has received grant funding from the Irish government, Irish Heart Foundation, Daiichi Sankyo, Bayer, Boehringer Ingelheim, Pfizer, Bristol Myers Squibb, Amgen, and A Menarini. P.L. acts as a consultant for AstraZeneca, AbbVie, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Eisai, Galapagos, Gamida cell, Gilead, Janssen, Medtronic, MSD, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, and Théa. E.L.-d.-S. reports personal fees from Daiichi Sankyo; grants and personal fees from Servier; ZOLL Medical, and Becton Dickinson; grants from AstraZeneca, Medimmune LLC and Novartis, during the conduct of the study. P.M. is an ETNA-AF investigator and has received lecture and research fees from Daiichi Sankyo, Bayer, Boehringer Ingelheim, and Pfizer/BMS. J.S. has received consultant and/or speaker fees from Abbott, Alexion, Amgen, AstraZeneca, Bayer, Berlin-Chemie, Biosense Webster, Biotronik, Boehringer Ingelheim, Boston Scientific, BMS, Daiichi Sankyo, Medscape, Medtronic, Merck/MSD, Organon, Pfizer, Saja, Servier, and WebMD. He reports ownership of CorXL, J.W. reports personal fees and non-financial support from Biotronik, Boehringer Ingelheim, and Daiichi Sankyo; personal fees from Akkea, Bayer Vital, MSD, Berlin-Chemie and Siemens Healtcareers, outside the submitted work. T.W./W. has received fees, honoraria and research funding from AstraZeneca, Boehringer Ingelheim, Bayer, Bristol Myers Squibb/Pfizer, Daiichi Sankyo, Medtronic, Menarini Pharma, Novartis, and Sanofi Aventis. P.L., M.C.M., and J.S. are employees of Daiichi Sankyo Europe GmbH, Munich, Germany. R.D.C. reports grants, personal fees and non-financial support from Daiichi Sankyo, during the conduct of the study; and reports consulting fees, honoraria and other financial or non-financial interests: Boehringer Ingelheim, Bayer, BMS/Pfizer, Daiichi Sankyo, Janssen, Milestone, Novartis, Sanofi, Menarini, Guidotti, and Roche, outside the submitted work.

Data availability
The data underlying this article are available in the article and in its online Supplementary material.

References
1. Hindricks G, Polpatra T, Dagnes N, Arbelo E, Bax J, Blomstrom-Lundqvist C, Boragni G, Castella M, Dan GA, Diller PE, Faucher L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinta FJ, Thomas GN, Vaginmil G, Van Gelder IC, Van Putte BP, Watkins CL,Group ESCDS. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2021;42:373–498.
2. Khatade VB, Sanders KN, Zou KH. Real world data an opportunity to supplement existing evidence for the use of long-established medicines in health care decision making. J Multidisip Healthc 2018;11:295–304.
3. Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Hauesel KD, Oldingen J, Reinecke H, Roldan-Schilling V, Rowell N, Sinnerve P, Vanassache T, Potpara T, Camm AJ, Heidbuchel H.External r:Lip GYH, Denekne T, Dagnes N, Boraini G, Chao TF, Choi EK, Hils MT, Santos IS, Lane DA, Attar D, Jourg B, Cole OM, Field M. 2021 European heart rhythm association practical guide on the use of non-vitamin k antithrombotic oral anticoagulants in patients with atrial fibrillation. Europace 2021;16:1612–1676.
4. Seiffig DJ, De Marchis GM, Kogi M, Paciaroni M, Wilson D, Cappellari M, Maha Md K, Tiogouil G, Ambler G, Arhiro S, Bonati LH, Bonetti B, Kalminunzer B, Muir KV, Bovi P, Gentzkie H, Inoue M, Schwab S, Yaghish S, Brown MP, Lyer P, Takagi M, Accarresse M, Jager HR, Polymervis AA, Toyoda K, Venti M, Traanka C, Yamagami H, Alberi A, Yoshimura S, Caso V, Engelter ST, Werring DJ, Raf RAPFDC–SNE, Verona registry. C. Ischemic stroke despite oral anticoagulant in patients with atrial fibrillation. Ann Neurol 2020;87:677–687.
5. Camm AJ, Arramendy P, Haas S, Hess S, Kirchhoff P, Kuhls S, van Eckels M, Turpie AG, Investigators X. XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. Eur Heart J 2016;37:1145–1153.
6. Roha M. Weiss TW, Pecen L, Patti G, Siller-Matula JM, Schnabel RB, Schilling R, Kotecha D, Lucerna M, Huber K, De Caterina R, Kirchhof P. Risk factors for thromboembolic and bleeding events in anticoagulated patients with atrial fibrillation: the prospective, multicentre observational PREvention of thromboembolic events - European Registry in Atrial Fibrillation (PREFER in AF). BJM 2019; e022478.
7. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt E, Lukan A, Fetscher T, van Gelder IC, Haase D, Haegel LM, Hamann F, Heidbuchel H, Hindricks G, Kautzner J, Kuck KH, Mont L, Ng GA, Rekzos J, Schoen N, Schotten U, Suling A, Taggess J, Thesmes-toplakis S, Vetters R, Vandas P, Wegscheider K, Willems S, Cirnini H, Breithardt G, Investigators E–AT. Early rhythm-control therapy in patients with atrial fibrillation. N Eng J Med 2020;383:1305–1316.
8. Hughes M, Lip GY. Risk factors for anticoagulation-related bleeding complications in patients with atrial fibrillation: a systematic review. JQM 2007:100:599–607.
9. De Caterina R, Kelly P, Monteiro P, Deharo JC, de Asmundis C, Lopez-de-Sa E, Weiss TW, Waltenberger J, Steffel J, de Groot JR, Levy P, Bakhai A, Zierhut W, Laes P, Reimitz PE, Kirchhof P. Investigators ET-A-E. Design and rationale of the edoxaban treatment in routine clinical care: baseline data from edoxaban treatment in routine clinical care: 1-year follow-up of the prospective observational ETNA-AF Europe study. J Cardiovasc Med (Hagerstown) 2019;20:97–104.
10. De Caterina R, Kelly P, Monteiro P, Deharo JC, de Asmundis C, Lopez-de-Sa E, Weiss TW, Waltenberger J, Steffel J, de Groot JR, Levy P, Bakhai A, Zierhut W, Laes P, Kerwin K, Reimitz PE, Investigators ET-A-E. Edoxaban for stroke prevention in atrial fibrillation in routine clinical care: 1 year follow-up of the prospective observational ETNA-AF Europe study. Eur Heart J Cardiovasc Pharmacother 2021;7:130–139.
11. Gomes T, Mandani MM, Holbrook AM, Paterson JM, Hellingr J, Jaurlien DN. Rates of hemorrhage during warfarin therapy for atrial fibrillation. Can Med Assoc J 2013;185:E121–E127.
12. Oleen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lundharden J, Selmer C, Alehoff O, Olsen AM, Gloason GH, Torg-Pedersen C. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BJM 2011;342:d124.
13. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Wilsal AO, Ezekowitz MD, Weitze JL, Spinar J, Ruzyllo W, Wuda M, Koresuen Y, Betcher J, Shi M, Gip LT, Patel SP, Patel I, Hansky J, Merculni P, Arntzin PE, Investigators ET–A-E. Edoxaban versus warfarin in patients with atrial fibrillation. N Eng J Med 2013;369:2093–2104.
14. Wankowicz P, Nowacki P, Galab-Janowska M. Atrial fibrillation risk factors in patients with ischemic stroke. Arch Med Sci 2021;17:9–24.
15. Pitkouski K, Lip GYH, Apostolakis S. Age as a risk factor for stroke in atrial fibrillation patients: implications in thromboembolism in the era of novel oral anticoagulants. J Arrhythmia 2015;3:6781.
17. Kotecha D, Bunting KV, Gill SK, Mehta S, Stanford M, Jones JC, Haynes S, Calvert MJ, Deeks JJ, Steeds RP, Strauss YH, Rahimi K, Camm AJ, Griffith M, Lip GYH, Townsend JN, Kirchhof P. Rate Control Therapy Evaluation in Permanent Atrial Fibrillation: Effect of digoxin vs bisoprolol for heart rate control in atrial fibrillation on patient-reported quality of life: the RATE-AF randomized clinical trial. JAMA 2020;324:2497–508.

18. Fabritz L, Crijns H, Guasch E, Goette A, Hausler KG, Kotecha D, Lewalter T, Meyer C, Potpara TS, Rienstra M, Schnabel RB, Willems S, Breithardt G, Camm AJ, Chan A, Chuah W, de Melis M, Dimopoulou C, Dobre D, Easter C, Eckardt L, Haase D, Hatem S, Healey JS, Heijman J, Holmroos SH, Huebner T, Ilyas BS, Isaacs A, Kutschka I, Leclercq C, Lip GYH, Marinelli EA, Merino J, Mont L, Nabauer M, Oldgren J, Purerfellner H, Ravens U, Saveleva I, Sinner MF, Stich A, Smolnik R, Steffen J, Stein K, Stoll M, Svensson E, Van Gelder KC, Vardar B, Wakili R, Welboch M, Zeemering S, Ziegler PD, Heidbuchel H, Hindricks G, Schotten U, Kirchhof P. Dynamic risk assessment to improve quality of care in patients with atrial fibrillation: the 7th AFNET/EHRA Consensus Conference. Europace 2021;23:329–344.

19. Hacke W, Bassand JP, Virdone S, Camm AJ, Fitzmaurice DA, Fox KA, Goldhaber SZ, Goto S, Haas S, Kayani G, Mantovani LG, Misselwitz F, Peper KS, Turpie AG, van Eickels M, Verheugt FW, Kakkar AK, Investigators G-A. Prior stroke and transient ischemic attack as risk factors for subsequent stroke in atrial fibrillation patients: a report from the GARFIELD-AF registry. Int J Stroke 2020;15:308–317.

20. Kusano K, Sugishita N, Aka M, Tsuji H, Matsui K, Hiramitsu S, Hatori Y, Odakura H, Kamada H, Miyamoto K, Ogawa H. Effectiveness and safety of rivaroxaban by general practitioners- A Multicenter, prospective study in Japanese patients with non-valvular atrial fibrillation (GENERAL). Circ J 2021;85:1275–1282.

21. Apostolakis S, Lane DA, Guo Y, Buller H, Lip GYH. Performance of the HEMORR(2)HAGES, ATRIA, and HAS-BLED bleeding risk-prediction scores in patients with atrial fibrillation undergoing anticoagulation: the AMADEUS (evaluating and ATRIA risk scores in predicting non-vitamin k antagonist oral anticoagulants-associated bleeding in patients with atrial fibrillation. Am J Cardiol 2017;120:1549–1556.

22. Goodman SG, Wojdyla DM, Piccini JP, White HD, Paolini JF, Nessel CC, Berkowitz SD, Mahaffey KW, Patel MR, Sherwood MW, Becker RC, Halperin JL, Hacke W, Singer DE, Hankey GJ, Breithardt G, Fox KA, Califf RM, Investigators RA. Factors associated with major bleeding events: insights from the ROCKET AF trial (rivaroxaban once-daily oral direct factor Xa inhibition compared with vitamin K antagonist for prevention of stroke and embolism trial in atrial fibrillation). J Am Coll Cardiol 2014;63:891–900.

23. Qazi JZ, Schnitzer ME, Cote R, Martel MJ, Dorais M, Perreault S. Predicting major bleeding among hospitalized patients using oral anticoagulants for atrial fibrillation after discharge. PLoS One 2021;6:e0246691.

24. Kojima G, Iliffe S, Walters K. Frailty index as a predictor of mortality: a systematic review and meta-analysis. Age Ageing 2018;47:193–200.

25. Yasu X, Gersh BJ, Sangaralingham LR, Kent DM, Shah ND, Abraham NS, Noseworthy PA. Comparison of the CHADS2-VASc, CHADS2, HAS-BLED, ORBIT, and ATRIA risk scores in predicting non-vitamin k antagonist oral anticoagulants-associated bleeding in patients with atrial fibrillation. Am J Cardiol 2017;120:1549–1556.