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ORIGINAL ARTICLE
Thrombosis and antithrombotic therapy

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, 9017/13 133 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 χ^2: 73.63; $P < 0.0001$). Low kidney function at baseline was the strongest predictor of major bleeding (Wald χ^2: 30.68; $P < 0.0001$). History of heart failure (HF) was the strongest predictor of all-cause (Wald χ^2: 146.99; $P < 0.0001$) and cardiovascular death (Wald χ^2: 100.38; $P < 0.0001$).

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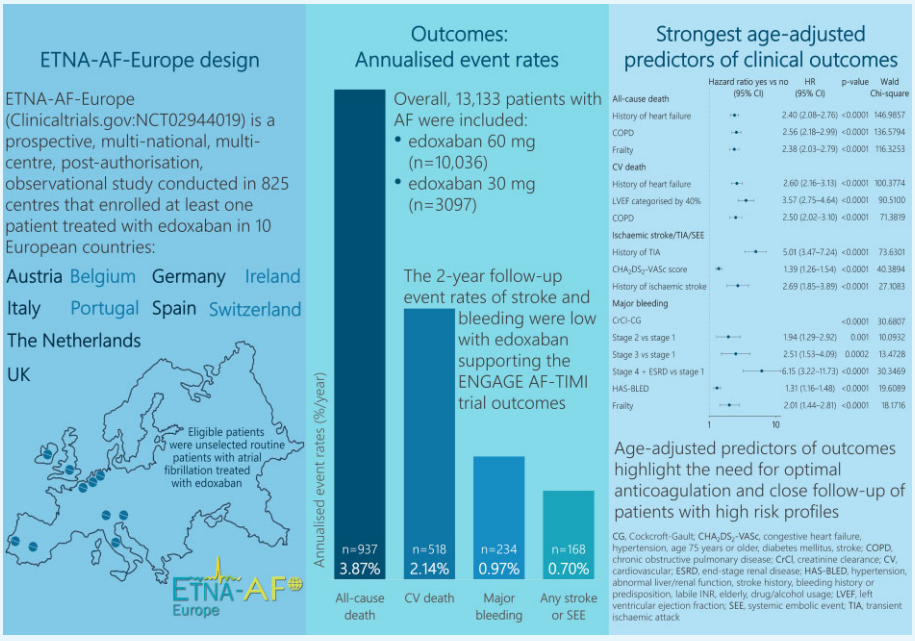
Conclusion Patients treated with edoxaban in ETNA-AF-Europe reported low 2-year event rates in unselected AF patients. Prior stroke, reduced kidney function, and HF identify patients at high risk of stroke, bleeding and all-cause/cardiovascular death, respectively.

Graphical Abstract



Age-adjusted predictors of clinical outcomes in the ETNA-AF-Europe Registry.

Keywords Non-vitamin K oral anticoagulant • Edoxaban • Real-world • Registry • Atrial fibrillation

Introduction

Anticoagulation is key in the management of stroke prevention in atrial fibrillation (AF). Findings from landmark randomised clinical trials (RCTs) of non-vitamin K antagonist oral anticoagulants (NOACs) demonstrated that, compared with vitamin K antagonists (VKAs), NOACs are at least non-inferior in preventing ischaemic stroke and systemic embolic events (SEE) and have a better safety profile, with a distinctly decreased risk of intracranial haemorrhage (ICH).[1]

Edoxaban, a NOAC, is indicated in the prevention of stroke and SEE in adult patients with 'non-valvular' AF (NVAF) with one or more risk factors. Data from ENGAGE AF-TIMI 48, the Phase III RCT of edoxaban vs. warfarin, may not be fully generalisable to the AF population due to exclusion criteria, closer monitoring of patients than in everyday life, and potential selection bias.[2] Besides, the current guidelines for the diagnosis and management of AF[1] and the 2021 EHRA Practical Guide on use of NOACs in AF[3] emphasise shared decision making and patient-centred organization of integrated care of AF patients to help with adherence to long-term anticoagulation therapy. Therefore, it is important to know how patients present in routine care outside the confines of the controlled trials setting.

In addition, despite oral anticoagulation for AF, 1–4% of anticoagulated AF patients still suffer from stroke or SEE and ~2% experience a major bleed annually.[4–6] Early rhythm control[7] and improved detection and therapy of concomitant cardiovascular conditions[1] can reduce this morbidity. Recent research has therefore focussed on identifying risk factors that could be helpful in identifying patients at high-risk of cardiovascular events on anticoagulation.[4] Various patient characteristics have been identified as independent risk factors for bleeding[8] and a substantial number of bleeding events might be prevented if these are identified and modified upstream, where possible.

The Edoxaban Treatment in Routine Clinical Practice for Patients With Non-Valvular Atrial Fibrillation (ETNA-AF-Europe) study, conducted in unselected European patients with AF, gives valuable contemporary data on how patients with AF and an indication for NOAC fare in a real world setting. Here we present outcomes from ETNA-AF-Europe and age-adjusted risk predictors of clinical outcomes during the two-year period.

Methods

The design of ETNA-AF-Europe has previously been published.[9] Briefly, ETNA-AF-Europe (Clinicaltrials.gov: NCT02944019) is a prospective, multi-national, multi-centre, post-authorisation, observational study conducted in 825 centres that enrolled at least one patient treated with edoxaban in 10 European countries (Austria, Belgium, Germany, Ireland, Italy, The Netherlands, Portugal, Spain, Switzerland, and United Kingdom).[9,10]

ETNA-AF-Europe is part of the global ETNA initiative, which comprises separate, non-interventional prospective ETNA-AF registries in Europe, East Asia, and Japan. The study was approved by the institutional review boards and independent Ethics Committees for all participating centres in compliance with Guidelines for Good Pharmacoepidemiological Practice (GPP). All participants provided written informed consent.

Eligible patients were unselected routine patients with AF treated with edoxaban. Explicit exclusion criteria were not defined. Details of the inclusion criteria and secondary objectives can be found in the design paper.[9]

The overall ETNA-AF-Europe study will follow patients for four years. Here we report data of 2 years based on a data snapshot dated 26 October 2020. Overall, 13 167 patients were included in the full analysis set.

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, CHA_2DS_2-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 CHA_2DS_2-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*).

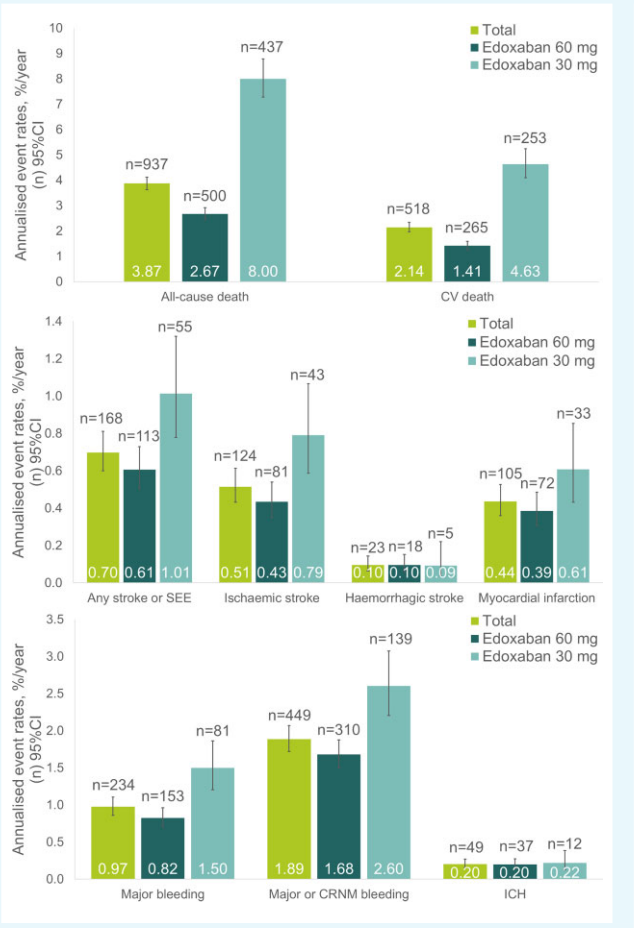


Figure 1 Annualised event rates (%/year) of clinical outcomes in the overall population during the 2-year follow-up.

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 (*Figure 1*). Annualised event rates of any stroke or SEE, ischaemic stroke, and haemorrhagic stroke in the overall study population were 0.70%, 0.51%, and 0.10%, respectively (*Figure 1*).

Proportionately, more deaths were observed in patients receiving edoxaban 30 mg compared with those receiving the full dose of 60 mg (*Figure 1*). The rates of any stroke or SEE and ischaemic stroke were also higher in patients receiving edoxaban 30 mg vs. those receiving edoxaban 60 mg (*Figure 1*) (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)
Recalc. CrCl* (CG formula) [ml/min], *n* (%)			
≥ 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)
Recalc. CHA_2DS_2-VASc,† mean (SD)	3.2 (1.4)	3.0 (1.4)	3.9 (1.3)
Recalc. mod. HAS-BLED,‡ mean (SD)	2.5 (1.1)	2.4 (1.1)	2.9 (1.1)
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)
Perceived frailty, *n* (%)	1405 (11.5)	622 (6.6)	783 (27.2)
COPD	1207 (9.2)	831 (8.3)	376 (12.1)
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 (83.1)	8916/10 036 (88.8)	1992/3097 (64.3)
Non-rec. edoxaban dose at baseline	2225/13 133 (16.9)	1120/10 036 (11.2)	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.

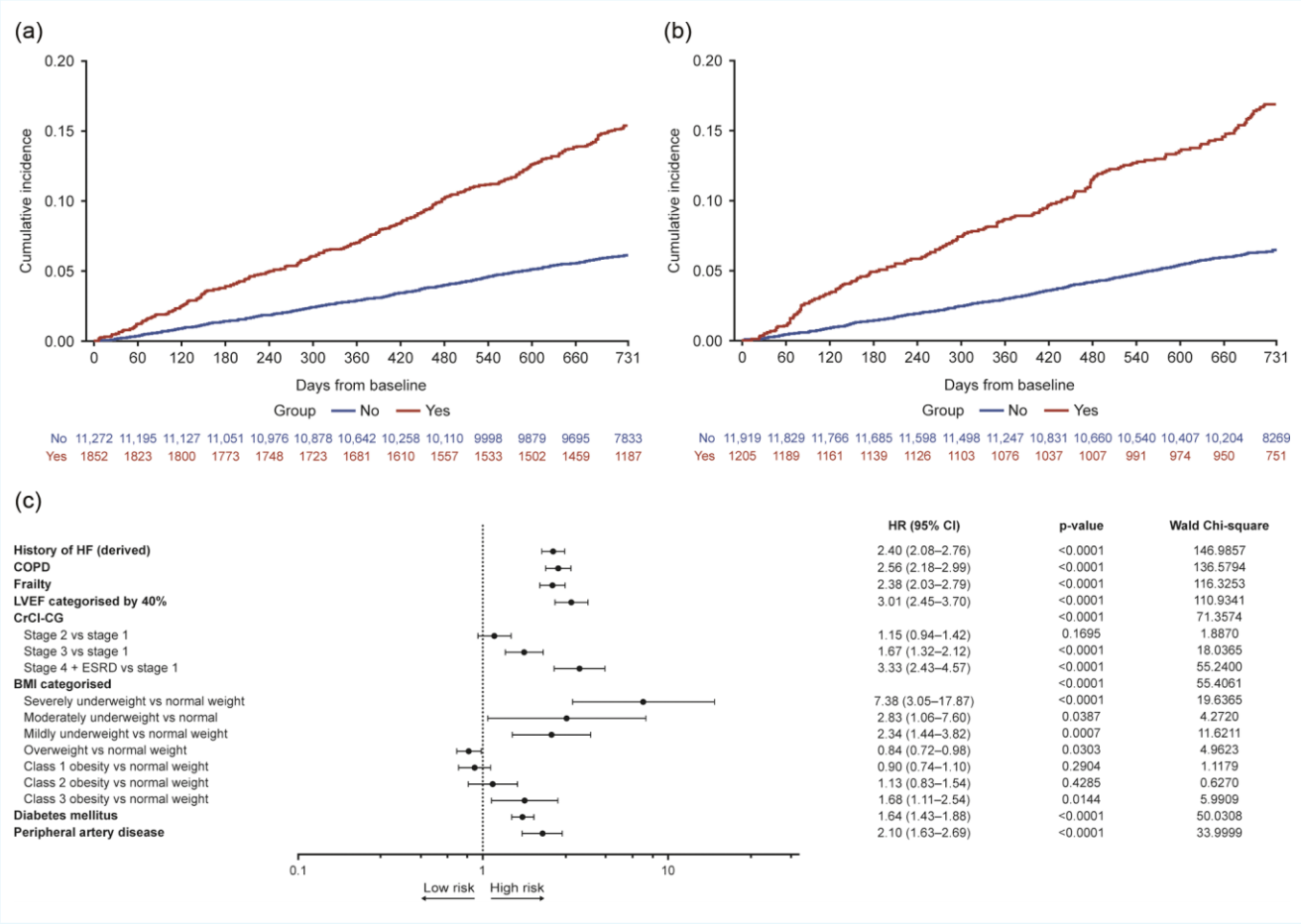


Figure 2 Age-adjusted predictors of all-cause death during the 2-year follow-up. (*A*) Heart failure (derived) as a predictor of all-cause death. Age-adjusted HR for HF yes vs. no: 2.40 (2.08–2.76). (*B*) COPD as a predictor of all-cause death. Age-adjusted HR for COPD yes vs. no: 2.56 (2.18–2.99). (*C*) 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 + end stage: 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.

differences in risk of any stroke or SEE and ischaemic stroke between the dose groups were not significant (adjusted HR: 1.07, 95% CI: 0.74–1.53, $P = 0.7272$; and adjusted HR: 1.12, 95% CI: 0.74–1.70; $P = 0.5862$, respectively). Differences in the risk of haemorrhagic stroke between the dose groups continued to be insignificant after adjustment for predictors of stroke and taking competing risk of all-cause death into account (adjusted HR 0.60, 95% CI: 0.21–1.73; $P = 0.3446$).

Annualised event rates of any major bleeding, major or CRNM bleeding and ICH in the overall study population were 0.97%, 1.89%, and 0.20%, respectively (*Figure 1*). For illustrative purposes, comparisons are made between those on 30 mg and 60 mg although this was not a formal hypothesis. The rates of major bleeding and major or CRNM bleeding were higher in patients receiving edoxaban 30 mg vs. those receiving edoxaban 60 mg (*Figure 1*) [unadjusted hazard ratio (HR): 1.82, 95% CI: 1.39–2.38; $P < 0.0001$; and unadjusted HR: 1.54, 95% CI: 1.26–1.88; $P < 0.0001$, respectively]; however, similar rates of ICH were observed between the two dose groups (unadjusted 1.11, 95% CI: 0.58–2.12; $P = 0.7616$). After adjustment for predictors of major bleeding and calculation of competing risk of all-cause-death, differences in the risk of major bleeding and major or CRNM bleeding between the dose groups were not significant (adjusted HR: 0.89, 95% CI: 0.62–1.28, $P = 0.5347$; and adjusted HR: 0.85, 95% CI: 0.65–1.11; $P = 0.2410$, respectively). Differences in risk of ICH between the dose groups continued to be non-statistically significant after adjustment for predictors of major bleeding and taking competing risk of all-cause death into account (adjusted HR: 0.75, 95% CI: 0.32–1.76; $P = 0.5124$).

Age-adjusted predictors of clinical outcomes during the 2-year follow-up

History of HF was the strongest predictor of all-cause death (Wald χ^2: 146.99; $P < 0.0001$) (*Figure 2a*), followed by history of COPD (136.58; $P < 0.0001$) (*Figure 2b* and *c*), subjective frailty as assessed by physician at baseline (116.33; $P < 0.0001$), left ventricular ejection fraction (LVEF) at baseline categorised by below 40% (110.93; $P < 0.0001$), recalculated eCrCl (71.36; $P < 0.0001$), body mass

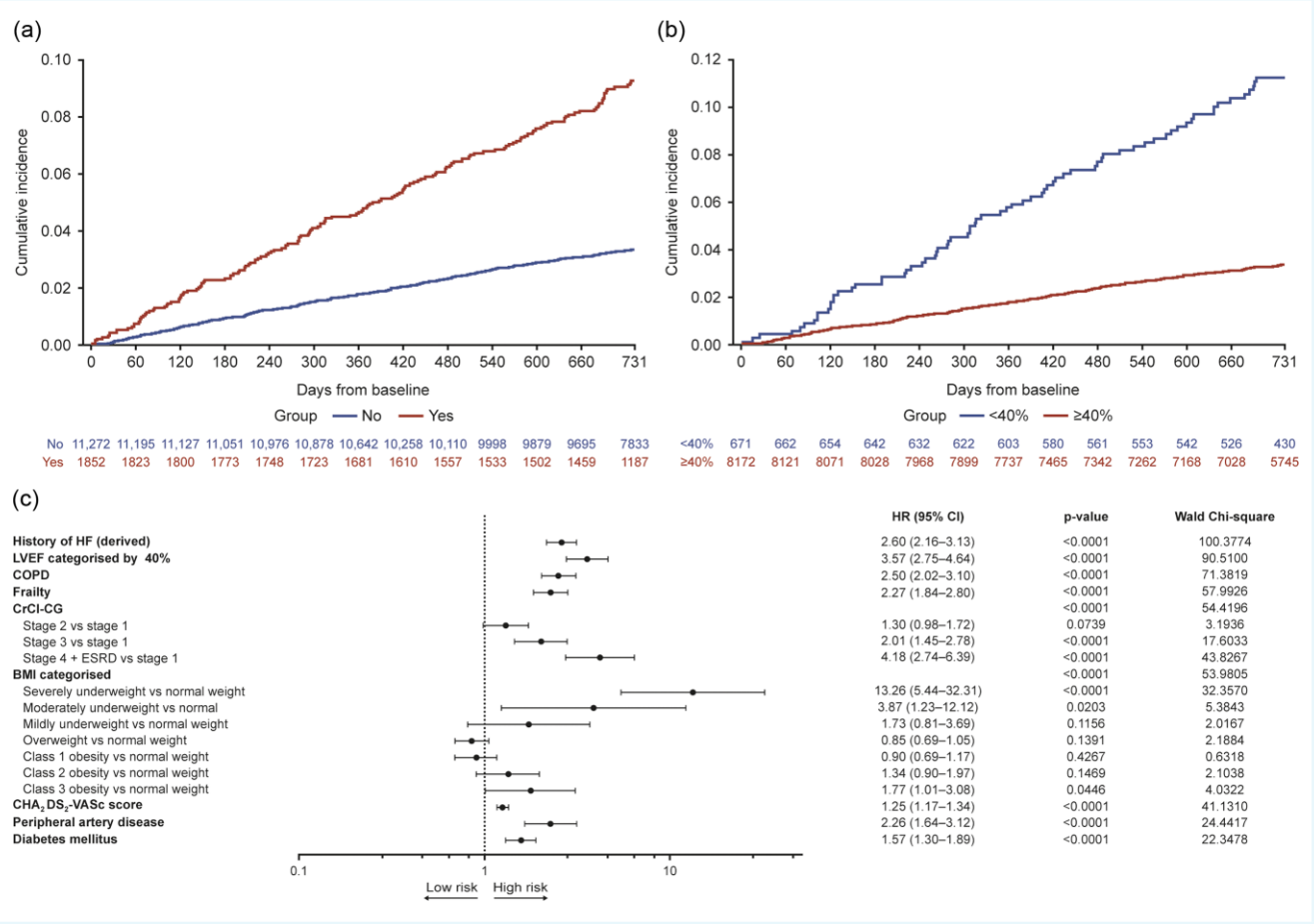


Figure 3 Age-adjusted predictors of cardiovascular death during the 2-year follow-up. (*A*) Heart failure (derived) as a predictor of cardiovascular death. Age-adjusted HR (95% CI) yes: 2.60 (2.16–3.13). (*B*) Left ventricular ejection fraction < 40% as a predictor of cardiovascular death. Age-adjusted 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 + end stage: 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.

index (BMI) (55.41; $P < 0.0001$), diabetes mellitus (50.03; $P < 0.0001$), and peripheral artery disease (34.00; $P < 0.0001$).

History of HF was also the strongest predictor of CV death (Wald χ^2: 100.38; $P < 0.0001$) (*Figure 3a*), followed by baseline levels of LVEF categorised by below 40% (90.51; $P < 0.0001$) (*Figure 3b* and *c*), COPD (71.38; $P < 0.0001$), subjective frailty as assessed by physician at baseline (57.99; $P < 0.0001$), eCrCl (54.42; $P < 0.0001$), BMI (53.98; $P < 0.0001$), CHA_2DS_2-VASc (41.13; $P < 0.0001$), peripheral artery disease (24.44; $P < 0.0001$), and diabetes mellitus (22.35; $P < 0.0001$). HAS-BLED score was a weaker predictor of all-cause death (10.61; $P = 0.001$) and CV death (14.97; $P < 0.0001$).

A history of TIA at baseline was the strongest predictor of ischaemic stroke, TIA, and SEE (Wald χ^2: 73.63; $P < 0.0001$) (*Figure 4a*), followed by the baseline CHA_2DS_2-VASc score (40.39; $P < 0.0001$) (*Figure 4b* and *c*); a history of ischaemic stroke (27.11; $P < 0.0001$); history of any stroke (all strokes combined including stroke of unknown/unspecified type) (26.83; $P < 0.0001$), subjective frailty as assessed by physician (18.18; $P < 0.0001$), and the HAS-BLED score (16.53; $P < 0.0001$).

The recalculated eCrCl at baseline was the strongest predictor of major bleeding (Wald χ^2: 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,[11] 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

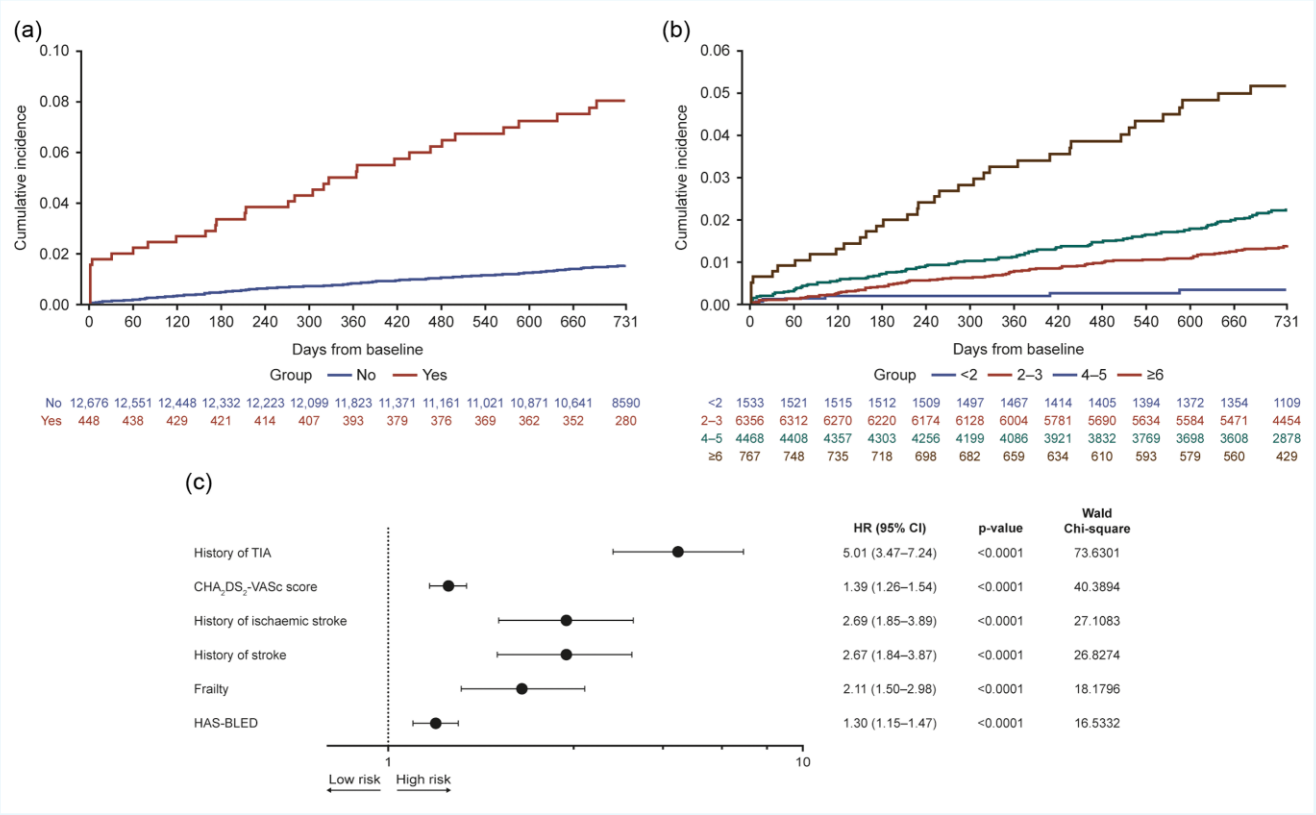


Figure 4 Age-adjusted predictors of stroke during the 2-year follow-up. (*A*) History of TIA as a predictor of ischaemic stroke/TIA/systemic embolic events. With a history of TIA: age-adjusted HR (95% CI): 5.01 (3.47–7.24). (*B*) CHA_2DS_2-VASc as a predictor of ischaemic stroke/TIA/systemic embolic events. Age-adjusted HR (95% CI) of CHA_2DS_2-VASc score as numerical variable: 1.39 (1.26–1.54). Categorised CHA_2DS_2-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[14] 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 SEE 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 CHA_2DS_2-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%),[11] 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 here identified in anticoagulated patients with AF. Besides, modifiable and non-modifiable risk factors of AF are also risk factors for ischaemic stroke.[15] 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.[16]

A history of HF at baseline was a very strong predictor of both all-cause and CV death. This highlights the importance of identifying optimal treatments for patients with AF and HF, including medications to control rate and rhythm.[7,17] 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.[18]

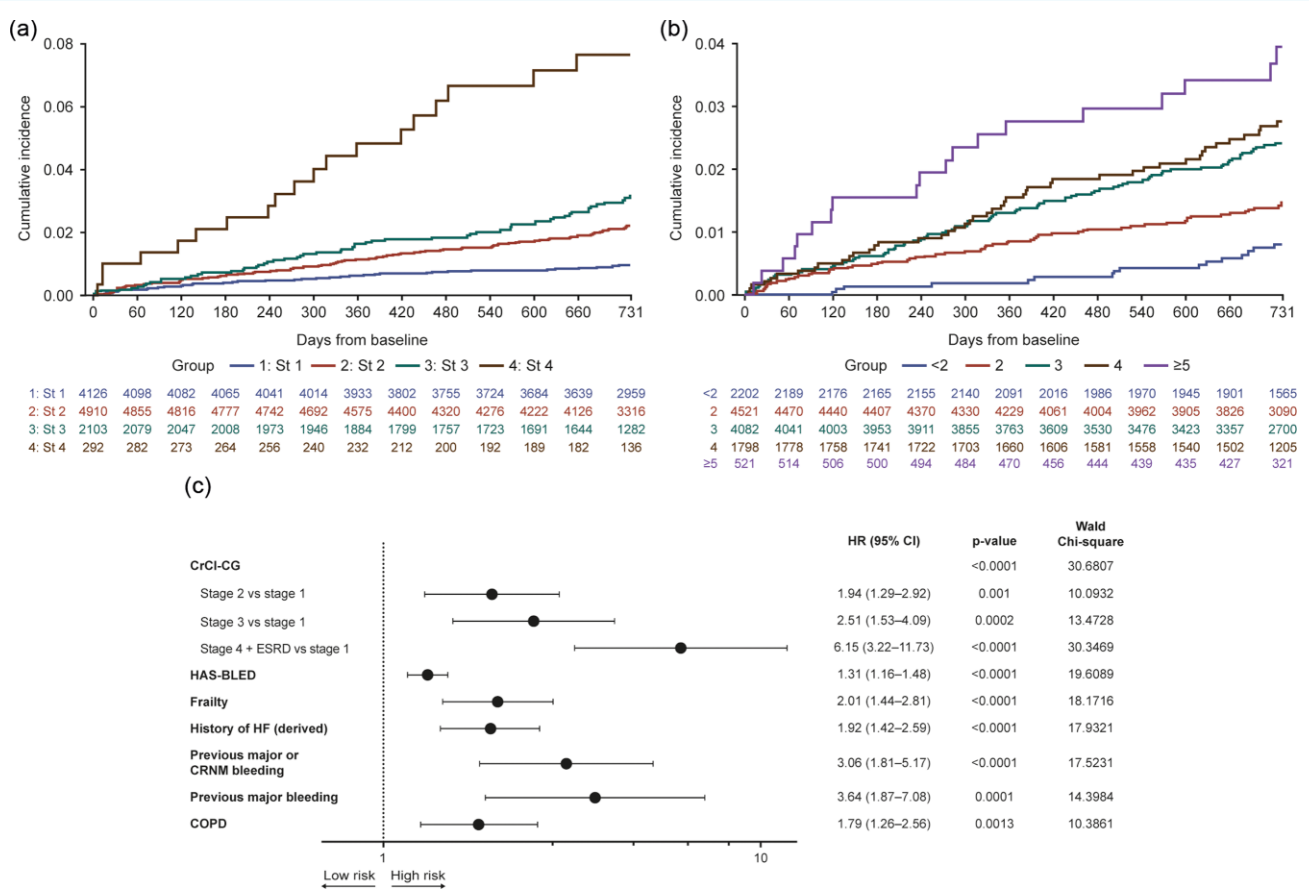


Figure 5 Age-adjusted predictors of major bleeding during the 2-year follow-up. (*A*) CrCl-CG as a predictor of major bleeding. Age-adjusted HR (95% CI) of CrCl: HR (95% CI): Stage 2 [CrCl (50, 80 ml/min)] vs. Stage 1 [CrCl (≥80 ml/min)]: 1.94 (1.29–2.92); Stage [CrCl (30,50 ml/min)] vs. Stage 1 [CrCl (≥80 ml/min)]: 2.51 (1.53–4.09); Stage 4 and End Stage [CrCl (<30 ml/min)] vs. Stage 1 [CrCl (≥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 ≥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 ≥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.

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 5717 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 CHA_2DS_2-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 ($CHADS_2$ and CHA_2DS_2-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 CHA_2DS_2-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 re-calculated eCrCl was the strongest predictor of major bleeding in our analysis, followed by COPD (usually caused by smoking). Similar observations were made in a ROCKET-AF sub-analysis involving 781 patients with AF; patients reporting major bleeds were older and had a lower eCrCl among other risk factors at baseline vs. those without a major bleed.[23] Patients with a major bleed in this analysis were less likely to have a prior stroke or TIA compared with those without a major bleed. Equally, our analysis did not show a correlation between previous history of stroke or TIA and major bleeding outcomes.

Liver disease, history of major bleeding, male sex, antiplatelet use, cardiomyopathy, peripheral vascular disease, and COPD have been established as important predictors of major bleeding in some recently published analyses.[24,25] 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 deaths.[26–28] 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.[29] 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 $\geq$ 75 years.[30]

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.

P.K., R.D.C.: investigation, methodology, writing original draft, writing review and editing; A.B., C.d.A., J.R.d.G., J.C.D., P.K., P.L., E.L.d.S, P.M., J.S., J.W., T.W.W.: investigation, writing review and editing; P.L., M.C.M., J.S.: funding, methodology, project administration, supervision, writing original draft and writing—review and editing; L.P.: software, validation, visualisation, writing review, and editing.

Declaration of Helsinki

The study complies with the Declaration of Helsinki, that the study was approved by the institutional review boards and independent ethics committees for all participating centres. All participants provided written informed consent.

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Institutional Review Board Statement

The study was approved by the institutional review boards and Independent Ethics Committees for all participating centres in compliance with the Declaration of Helsinki and Guidelines for Good Pharmacoepidemiological Practice (GPP).

Informed Consent Statement

All participants provided written informed consent.

Conflict of interest: P.K. receives research support for basic, translational, and clinical research projects from European Union Big-Data@Heart (grant agreement EU IMI 116 074) CATCH ME (grant agreement ID: 633 196) AFFECT-EU (grant agreement ID: 847 770); Leducq foundation, Medical Research Council (UK); German Centre for Cardiovascular Research supported by the German Ministry of Education and Research; from several drug and device companies

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 proctoring from Medtronic, Abbott, Biotronik, Atricure, Cardiotek, Biosense Webster and research grants on behalf of the centre from Biotronik, Medtronic, St Jude Medical Abbot, 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 Akzea, Bayer Vital, MSD, Berlin-Chemie and Siemens Healthineers, 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.

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