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CLINICAL RESEARCH

Outcomes of patients with atrial fibrillation on oral anticoagulation with and without heart failure: the ETNA-AF-Europe registry

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Aims Heart failure (HF) is a risk factor for major adverse events in atrial fibrillation (AF). Whether this risk persists on non-vitamin K antagonist oral anticoagulants (NOACs) and varies according to left ventricular ejection fraction (LVEF) is debated.

Methods and results We investigated the relation of HF in the ETNA-AF-Europe registry, a prospective, multicentre, observational study with an overall 4-year follow-up of edoxaban-treated AF patients. We report 2-year follow-up for ischaemic stroke/transient ischaemic attack (TIA)/systemic embolic events (SEE), major bleeding, and mortality. Of the 13 133 patients, 1854 (14.1%) had HF. Left ventricular ejection fraction was available for 82.4% of HF patients and was <40% in 671 (43.9%) and ≥40% in 857 (56.1%). Patients with HF were older, more often men, and had more comorbidities. Annualized event rates (AnERs) of any stroke/SEE were 0.86%/year and 0.67%/year in patients with and without HF. Compared with patients without HF, those with HF also had higher AnERs for major bleeding (1.73%/year vs. 0.86%/year) and all-cause death (8.30%/year vs. 3.17%/year). Multivariate Cox proportional models confirmed HF as a significant predictor of major bleeding [hazard ratio (HR) 1.65, 95% confidence interval (CI): 1.20–2.26] and all-cause death [HF with LVEF <40% (HR 2.42, 95% CI: 1.95–3.00) and HF with LVEF ≥40% (HR 1.80, 95% CI: 1.45–2.23)] but not of ischaemic stroke/TIA/SEE.

Conclusion Anticoagulated patients with HF at baseline featured higher rates of major bleeding and all-cause death, requiring optimized management and novel preventive strategies. NOAC treatment was similarly effective in reducing risk of ischaemic events in patients with or without concomitant HF.

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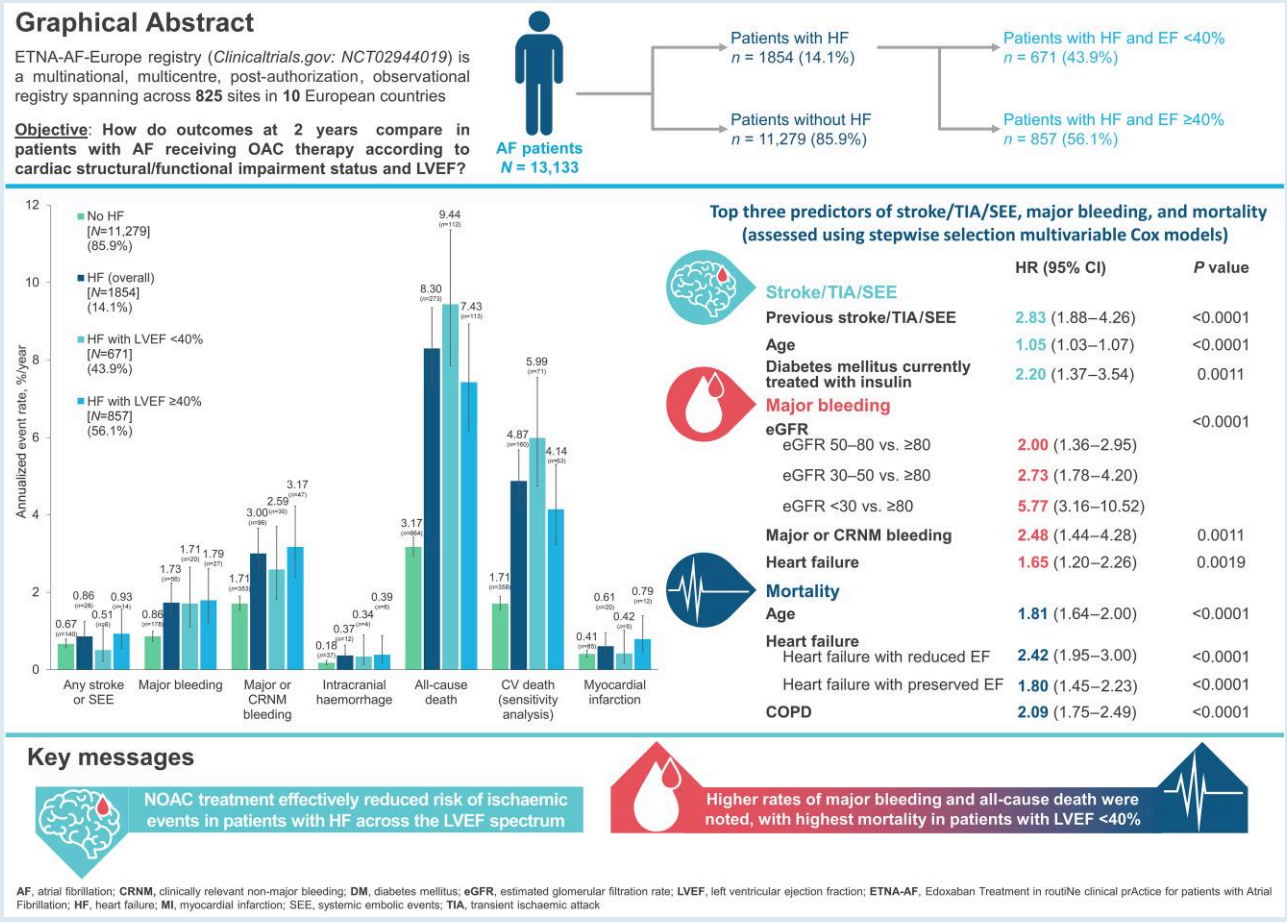
Graphical Abstract



Keywords Non-vitamin K antagonist oral anticoagulant • Edoxaban • Heart failure • Left ventricular ejection fraction • Registry • Atrial fibrillation

What's new?

- The ETNA-AF-Europe subanalysis compared 2-year outcomes in edoxaban-treated patients with atrial fibrillation (AF) categorized by cardiac structural/functional impairment status and left ventricular ejection fraction (LVEF).
- Ischaemic event rates were similar in patients with and without heart failure (HF). Patients with HF had higher annualized event rates of major bleeding and cardiovascular and overall mortality.
- No relevant differences were observed for ischaemic or bleeding events by HF subtype (LVEF ≥40% or <40%); mortality tended to be highest in patients with HF and LVEF <40%.
- The benefit of edoxaban treatment was demonstrated by the decrease in the differences in thromboembolic event rates between patients with HF (across HF subtypes) and those without HF.
- The broad array of predictors of overall and cardiovascular deaths observed in this analysis highlights the importance of taking comorbidities into consideration and the requisite for comprehensive management of patients with AF and HF beyond consequent oral anticoagulant.

Introduction

More than 70% of patients with atrial fibrillation (AF) are estimated to have a cardiovascular (CV) comorbidity.[1] Most comorbidities such as hypertension, coronary artery disease (CAD) and structural heart disease alongside obesity, diabetes, chronic kidney disease (CKD) and chronic obstructive pulmonary disease (COPD) are related to cardiac structural and functional abnormalities. These manifestations result in a reduction in cardiac output and/or elevated intracardiac pressure and predispose patients to the development of heart failure (HF). Many risk factors are shared between AF and HF, and there are multiple physiological mechanisms by which HF can develop in patients with AF.[1] Indeed, patients with AF have up to a five-fold higher risk of HF.[2] In permanent AF, HF is prevalent in more than half of the patients.[3] Heart failure is accounted for in the CHA_2DS_2-VASc score [HF (1 point), hypertension (1 point), ≥75 years (2 points), diabetes mellitus (1 point), stroke/transient ischaemic attack (TIA)/systemic embolic events (SEE; 2 points), vascular disease (1 point), age 65–74 years (1 point), and female sex (1 point)] used to assess stroke risk.[4] Further, mortality is significantly increased if HF occurs in patients with AF.[5–7]

Currently, non-vitamin K antagonist oral anticoagulants (NOACs) are the preferred treatment for the prevention of stroke and SEE in patients with AF.[4] In randomized controlled trials (RCTs), NOACs have demonstrated efficacy in stroke reduction in subsets of patients with HF and are now commonly used in patients with concomitant HF and AF.[8–10] In order to optimize the management of patients with AF and HF, patients' risks of stroke and bleeding need to be understood and considered in the implementation of an individualized care pathway.[4] However, it remains largely unknown whether HF is related to the risk of adverse events despite NOAC treatment, and, if so, whether the effect is different according to left ventricular ejection fraction (LVEF).

Data from routine clinical practice on NOAC treatment in patients with AF who have coexisting chronic structural and/or functional heart disease can enhance our understanding of the use of NOACs in this patient population and may impact treatment. The Edoxaban Treatment in routiNe clinical prActice for patients with nonvalvular AF in Europe (ETNA-AF-Europe) registry is a post-authorization observational study designed to collect safety data during routine clinical care by assessing the risks and benefits of edoxaban in unselected European patients with AF. The objective of the current analysis of the data from ETNA-AF-Europe was to compare 2-year outcomes in AF patients receiving oral anticoagulant (OAC) therapy according to cardiac structural/functional impairment status and LVEF.

Methods

Study design

Overview

The ETNA-AF-Europe registry (Clinicaltrials.gov: NCT02944019) is part of the global ETNA programme conducted in Europe, Japan, and Korea/Taiwan.[11] It is a multinational, multicentre, post-authorization, observational registry spanning across 825 sites in 10 European countries (Austria, Belgium, Germany, Ireland, Italy, The Netherlands, Portugal, Spain, Switzerland, and the UK). Enrollment commenced in May 2015 in Switzerland and in August 2015 in Germany; however, this was stalled in agreement with the newly formed Pharmacovigilance Risk Assessment Committee (PRAC). Following revision of the study protocol according to the PRAC guidance, patient enrollment resumed in Germany, Ireland, The Netherlands, Switzerland, and the UK in November 2016 and in Austria, Belgium, Italy, Portugal, and Spain in the first quarter of 2017, with an overall follow-up of 4 years.[12] A detailed account of the design has been reported previously.[11,12] Unselected routine patients with AF treated with edoxaban were enrolled. No exclusion criteria were applied, in order to fully capture routine clinical practice.

For the current analysis, patients with and without HF were analysed over a 2-year follow-up period, including data obtained up to the data cut-off point on 26 October 2020. Patients with documented structural/functional cardiac abnormality were grouped as HF patients including patients with documented congestive HF, documented ischaemic cardiomyopathy, LVEF <40%, or frequent dyspnoea (≥1/day) without COPD and at least one of the following: documented severe valvular heart disease, documented CAD post-myocardial infarction, valve replacement, or documented hypertension treated with at least three drugs. Patients with HF were further categorized into two groups: those with HF and LVEF <40% and those with HF and LVEF ≥40% (combining patients with mildly reduced and preserved EF; Supplementary material online, *Figure S1*). Echocardiography was available in 7226 (64.1%) of the 11 279 patients without HF (see Supplementary material online, *Figure S1*). We did not perform imputation analyses to harmonize the results with the report of this study and other publications. We calculated the CHA_2DS_2-VASc and HAS-BLED [uncontrolled hypertension (1 point), renal disease or liver disease (1 or 2 points), stroke history (1 point), prior major bleeding or predisposition to bleeding (1 point), labile international normalised ratio (INR) (1 point), age > 65 years (1 point), medication predisposing to bleeding or alcohol usage (1 or 2 points)] scores. Alcohol consumption was categorized as ≤2 glasses/day, >2–4 glasses/day, >4 glasses/day, or unknown. Smoking status was captured using the categories current smoker, former smoker, never smoked, or unknown. Estimated creatinine clearance was calculated using the Cockcroft–Gault formula[13] and categorized as ≥80, ≥50–<80, ≥30–<50, or <30 mL/min.

Outcomes

At 12 and 24 months, follow-up was performed, and clinical events were collected based on physicians' diagnosis. Outcomes relevant to this analysis were stroke, SEE, major bleeding, clinically relevant non-major bleeding (CRNM), TIA, and all-cause death during the 2-year follow-up. We used all bleeding, including major and CRNM bleeding, in accordance with the International Society on Thrombosis and Haemostasis definition.[14]

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. It is registered under clinicaltrials.gov NCT02944019. All participants provided written informed consent.

Statistical analysis

Descriptive summaries are provided as frequencies, *n* (%) and mean [standard deviation (SD)] for patient demographics and other baseline characteristics. Annualized event rates (AnERs), *n* (% per year) with 95% confidence intervals (CIs), are presented for clinical outcomes, including several composite outcomes. Cumulative event rates over 2 years were reported for any stroke or SEE, major bleeding, and all-cause mortality and are presented as Kaplan–Meier (KM) curves. *P* values were adjusted for age and CHA_2DS_2-VASc score. Multivariate Cox proportional hazards models were used for stepwise selection of predictors of ischaemic stroke/TIA/SEE, major bleeding, and all-cause death. Competing risk models for major bleeding and for ischaemic stroke/TIA/SEE confounded by all-cause death (Fine and Gray model) were calculated and are reported in Supplementary material online.[15] Potential interactions of HF status and outcomes by antiplatelet therapy were also tested.

Results

Demographics

The baseline characteristics are provided in *Table 1*. Among the 13 133 patients with AF included in this registry, 1854 (14.1%) had HF. Heart failure with LVEF ≥40% was more frequent (56.1%). Baseline characteristics for patients with HF and missing LVEF values ($n = 326$) are available in Supplementary material online, *Table S1*. More men were reported to have HF (64.6%) vs. a more balanced sex mix in those without HF (55.4% men). Antiplatelet therapy was more commonly prescribed in patients with HF.

A total of 2286 (17.4%) patients were lost to follow-up/discontinued from the study while living and on edoxaban. No or minor differences were observed between the baseline characteristics of these patients vs. those patients who remained in the study (see Supplementary material online, *Table S2*). Overall, 7.13% (937/13 133) patients died during the 2-years of follow-up.

Clinical characteristics

Patients without HF had a lower mean (SD) CHA_2DS_2-VASc score than those with HF (*Table 1*). Among patients with HF, those with LVEF <40% had relatively lower scores vs. those with LVEF ≥40%. The dominant form of AF reported in patients with and without HF was paroxysmal. Shortness of breath, perceived frailty (surrogate measure used to inform clinical decision-making[16]), and other comorbidities were more frequent in patients with HF vs. those without.

Outcomes

Stroke/systemic embolic events

The AnERs of any stroke or SEE were 0.86%/year and 0.67%/year in patients with and without HF, respectively (*Figure 1A*). The AnERs of

Table 1 Demographic and clinical characteristics of participants in the ETNA-AF-EU 2-year follow-up analysis set, stratified by HF and EF status

Variables	No heart failure *n* = 11 279	Heart failure *n* = 1854	HF with EF <40% *n* = 671 (43.9%)	HF with EF ≥40% *n* = 857 (56.1%)
Men, *n* (%)	6254 (55.4)	1197 (64.6)	500 (74.5)	489 (57.1)
Age (years), mean (SD)	73.5 (9.4)	74.6 (9.8)	72.3 (10.8)	75.9 (8.7)
Weight (kg), mean (SD)	80.9 (17.2)	81.3 (17.5)	81.6 (17.5)	80.5 (16.8)
Systolic blood pressure (mmHg), mean (SD)	134.2 (17.7)	129.1 (18.4)	125.4 (18.3)	131.3 (17.3)
Heart rate (b.p.m.), mean (SD)	75.7 (19.1)	76.4 (18.0)	78.9 (20.2)	75.0 (16.8)
Dyslipidaemia, *n* (%)	4634 (41.1)	1010 (54.5)	309 (46.1)	517 (60.3)
Antiplatelets, *n* (%)	1640 (14.5)	360 (19.4)	113 (16.8)	172 (20.1)
Smoking, *n* (%)				
Current smoker	695 (6.2)	128 (6.9)	56 (8.3)	46 (5.4)
Former smoker	2333 (20.7)	525 (28.3)	209 (31.1)	231 (27.0)
Never smoker	6278 (55.7)	972 (52.4)	302 (45.0)	491 (57.3)
Unknown	1973 (17.5)	229 (12.4)	104 (15.5)	89 (10.4)
Estimated glomerular filtration rate (mL/min/1.73 m^2), mean (SD)	75.4 (30.2)	68.2 (30.9)	68.9 (31.1)	67.5 (29.7)
CHA_2DS_2-VASc, mean (SD)	3.0 (1.3)	4.3 (1.4)	3.8 (1.5)	4.5 (1.3)
HAS-BLED, mean (SD)	2.5 (1.1)	2.8 (1.1)	2.6 (1.2)	3.0 (1.1)
Type of atrial fibrillation, *n* (%)				
Paroxysmal	6298 (56.0)	758 (40.9)	268 (40.1)	343 (40.0)
Persistent	2665 (23.7)	510 (27.5)	202 (30.2)	246 (28.7)
Long-standing persistent and permanent	2293 (20.3)	584 (31.5)	199 (29.7)	268 (31.3)
Sinus rhythm, *n* (%)	1204 (10.7)	136 (7.4)	39 (5.9)	64 (7.5)
Current atrial fibrillation symptoms at baseline, *n* (%)	2655 (23.5)	567 (30.6)	200 (29.8)	290 (33.8)
EHRA score, mean (SD)	2.90 (0.84)	3.36 (0.82)	3.24 (0.85)	3.47 (0.77)
Perceived frailty[a], *n* (%)	1058 (10.1)	347 (19.9)	122 (19.6)	160 (19.8)
Diabetes mellitus, *n* (%)	2299 (20.4)	586 (31.6)	183 (27.3)	280 (32.7)
Currently treated without insulin, *n* (%)	2190 (19.4)	565 (30.5)	174 (25.9)	273 (31.9)
Currently treated with insulin, *n* (%)	455 (4.0)	150 (8.1)	49 (7.3)	69 (8.1)
Chronic obstructive pulmonary disease, *n* (%)	938 (8.3)	269 (14.5)	108 (16.1)	110 (12.8)
Coronary heart disease, *n* (%)	1858 (16.5)	894 (48.2)	277 (41.3)	429 (50.1)
Valvular disease, *n* (%)	1772 (15.7)	514 (27.7)	170 (25.3)	295 (34.4)
Prior stroke/TIA/SEE, *n* (%)	1056 (9.4)	173 (9.3)	50 (7.5)	87 (10.2)
Prior MI, *n* (%)	313 (2.8)	254 (13.7)	72 (10.7)	126 (14.7)
Prior major or non-major clinically relevant bleeding, *n* (%)	213 (1.9)	60 (3.2)	16 (2.4)	34 (4.0)
Hypertension, *n* (%)	8660 (76.8)	1469 (79.2)	473 (70.5)	733 (85.5)
Previous and/or current use of any antihypertensive treatment, *n* (%)	8328 (73.8)	1434 (77.3)	463 (69.0)	709 (82.7)
Cardiac interventions, *n* (%)				
Ablation, *n* (%)	678 (6.0)	97 (5.2)	24 (3.6)	58 (6.8)
Electric cardioversion, *n* (%)	1916 (17.0)	354 (19.1)	144 (21.5)	162 (18.9)
Pharmacological cardioversion, *n* (%)	820 (7.3)	147 (7.9)	54 (8.0)	82 (9.6)
Defibrillator implantation, *n* (%)	61 (0.5)	103 (5.6)	71 (10.6)	16 (1.9)
Pacemaker implantation, *n* (%)	539 (4.8)	116 (6.3)	34 (5.1)	66 (7.7)

Numbers are mean (standard deviation) or number (%). Estimated glomerular filtration rate was calculated using the Cockcroft–Gault formula.
CHA_2DS_2-VASc score, heart failure (1 point), hypertension (1 point), ≥75 years (2 points), diabetes mellitus (1 point), stroke/TIA/SEE (2 points), vascular disease (1 point), age 65–74 years (1 point), and female sex (1 point); eGFR, estimated glomerular filtration rate; HAS-BLED, uncontrolled hypertension (1 point), renal disease or liver disease (1 or 2 points), stroke history (1 point), prior major bleeding or predisposition to bleeding (1 point), labile INR (1 point), age >65 years (1 point), and medication usage predisposing to bleeding or alcohol usage (1 or 2 points); INR, international normalised ratio; LA, left atrial diameter; SEE, systemic embolic event; TIA, transient ischaemic attack.
[a]Surrogate measure used to inform clinical decision-making.[16]

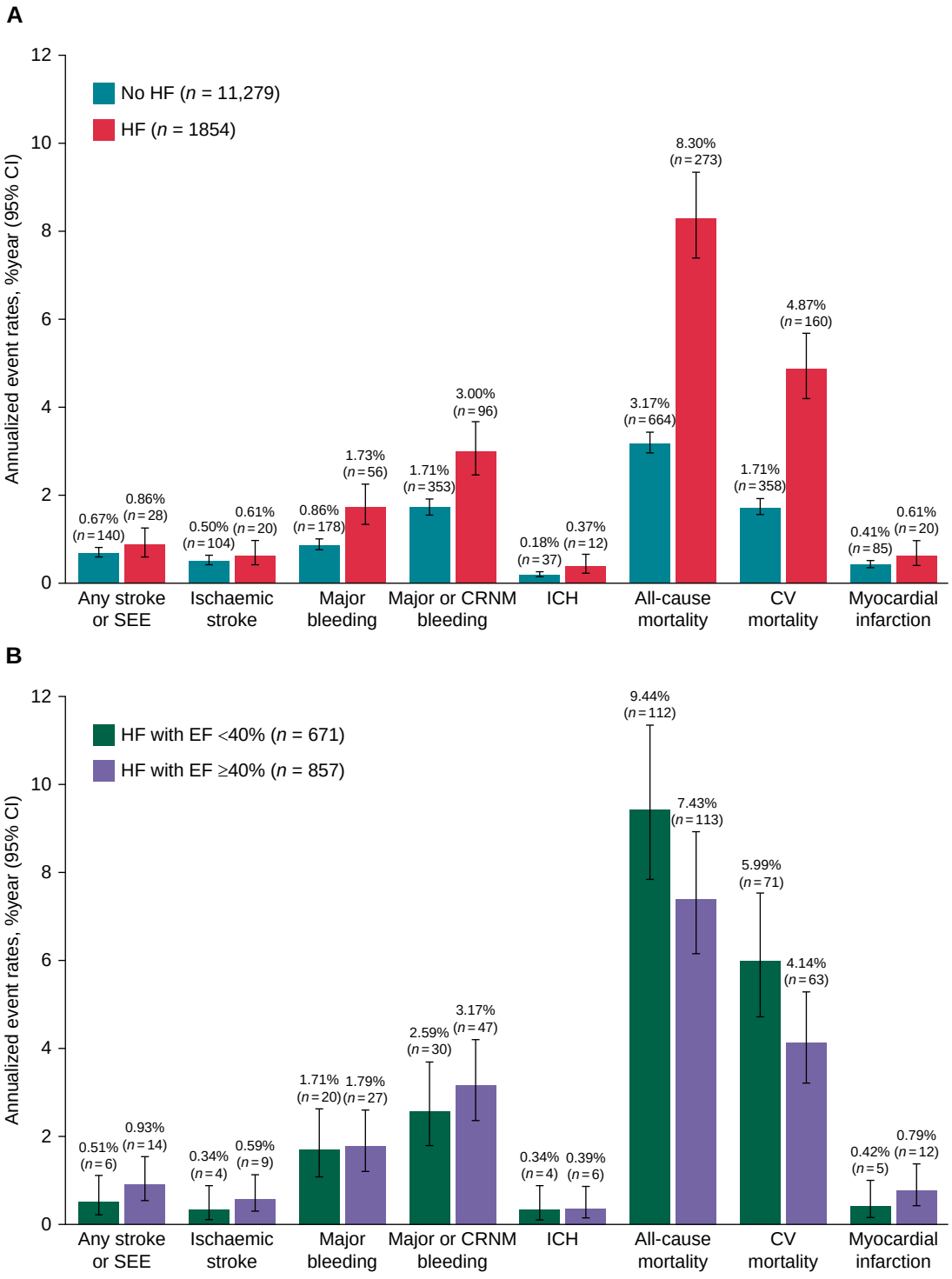


Figure 1 Clinical outcomes for participants in the ETNA-AF-EU 2-year follow-up analysis set, stratified by HF and EF status. (*A*) Patients with or without heart failure. (*B*) Patients with HF and EF <40% or ≥40%. For 326 patients with HF, the EF was not documented. CI, confidence interval; CRNM, clinically relevant non-major; CV, cardiovascular; EF, ejection fraction; HF, heart failure; ICH, intracranial haemorrhage; MI, myocardial infarction; SEE, systemic embolic events.

ischaemic stroke were similar in patients with and without HF. The KM curves began to separate in the second year of the analysis (*Figure 2A*). Among those with HF and LVEF ≥40% and <40%, AnERs of any stroke or SEE were 0.93%/year and 0.51%/year, respectively (*Figure 1B*). The KM curves by EF crossed each other (*Figure 2B*). Besides age, stepwise selection models for stroke/TIA/SEE selected previous embolic events with an almost three-fold increased hazard ratio (HR) 2.83 (95% CI: 1.88–4.26), and a two-fold increased risk for insulin-treated diabetes

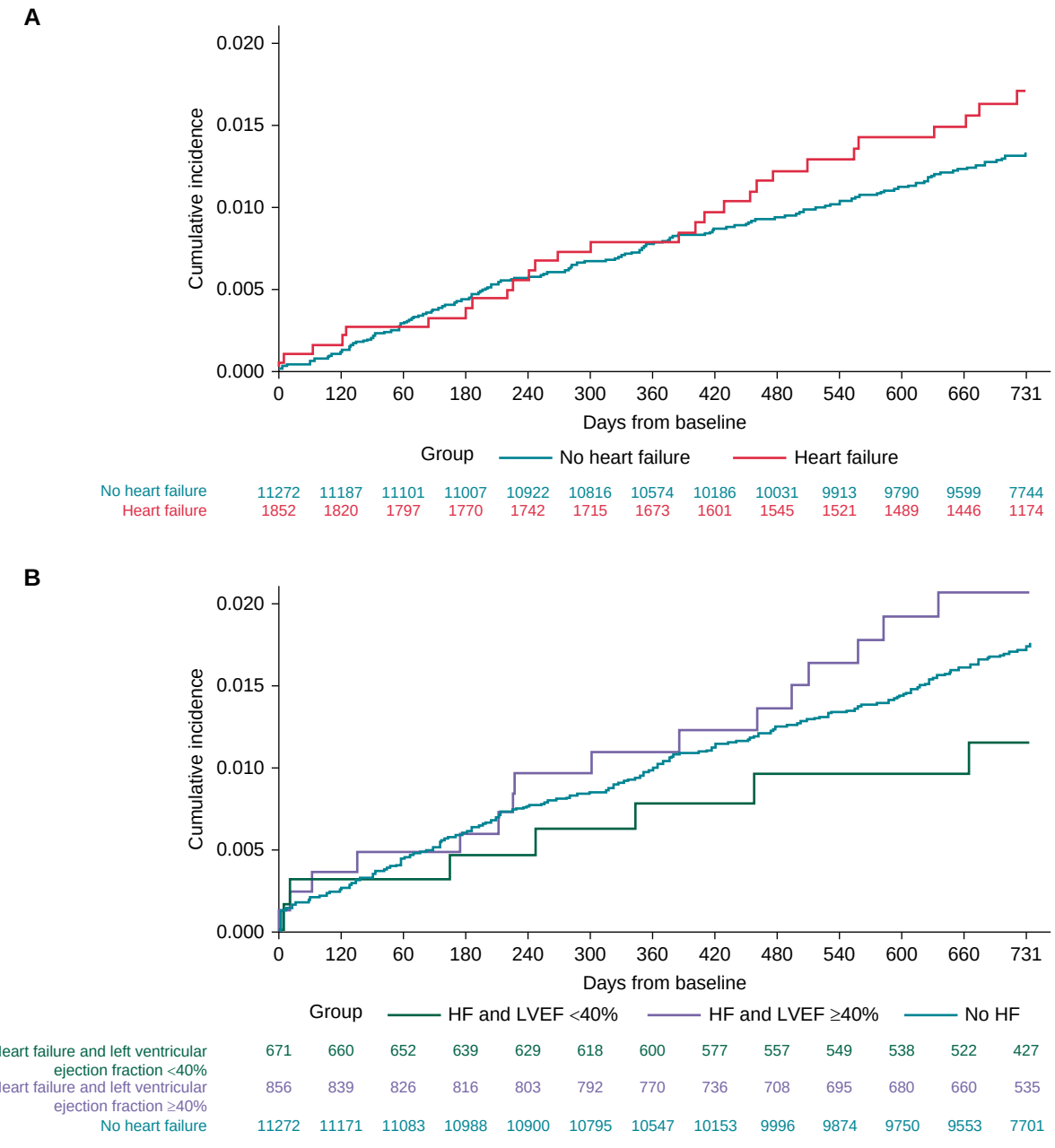


Figure 2 Cumulative incidence of stroke or systemic embolic event at 2-year follow-up, stratified by HF status and adjusted for age and CHA_2DS_2-VASc score. (*A*) Stratified by HF status. (*B*) Stratified by EF. For 326 patients with HF, LVEF was not documented. HF, heart failure; LVEF, left ventricular ejection fraction.

mellitus, and TIA as the strongest predictors (*Table 2*). Heart failure was not selected by the model. No interaction by antiplatelet therapy was observed (*P* value of interaction: 0.65).

Major bleeding

Patients with HF reported higher AnERs of major bleeding compared with those without HF (1.73%/year vs. 0.86%/year, respectively) (*Figure 1A*). Annualized event rates of intracranial haemorrhage were 0.37%/year and 0.18%/year in patients with and without HF, respectively. Among those with HF, major bleeding occurred in 1.79%/year and 1.71%/year of patients with HF and EF ≥40% and <40%, respectively (*Figure 1B*). Separation of the KM curves for major bleeding events between the groups began at Day 30 (*Figure 3A* and *B*). In stepwise selection, HF was selected by the model as a predictor, as well as renal impairment represented by estimated glomerular filtration rate (eGFR), prior major or CRNM bleeding, COPD, smoking variables, and HAS-BLED score (*Table 2*). Accounting for competing risk of death did not change the results for stroke/SEE or major bleeding markedly (see Supplementary material online, *Figure S2*). No interaction by antiplatelet therapy was observed (*P* value of interaction: 0.40).

Mortality

All-cause deaths and CV deaths (sensitivity analysis) were higher in patients with HF vs. those without HF (8.30%/year vs. 3.17%/year

Table 2 Stepwise selection multivariable Cox models for predictors of stroke/TIA/SEE, major bleeding, and mortality

Variable	Hazard ratio	95% confidence interval	*P* value
Stroke/TIA/SEE			
Previous stroke/TIA/SEE	2.83	1.88–4.26	<0.0001
Age, years	1.05	1.03–1.07	<0.0001
Diabetes mellitus currently treated with insulin	2.20	1.37–3.54	0.0011
Previous TIA	1.97	1.18–3.31	0.0099
Major bleeding			
eGFR, mL/min/1.73 m^2			<0.0001
50–80 vs. ≥80	2.00	1.36–2.95	0.0004
30–50 vs. ≥80	2.73	1.78–4.20	<0.0001
<30 vs. ≥80	5.77	3.16–10.52	<0.0001
History of major or CRNM bleeding	2.48	1.44–4.28	0.0011
Heart failure	1.65	1.20–2.26	0.0019
Chronic obstructive pulmonary disease	1.51	1.03–2.20	0.033
HAS-BLED score cont.	1.17	1.03–1.33	0.018
Smoking			0.039
Current smoker	2.40	1.26–4.57	0.0078
Former smoker	1.58	0.93–2.67	0.090
Never smoker	1.31	0.80–2.13	0.28
Mortality			
Age, years	1.81	1.64–2.00	<0.0001
Heart failure with reduced ejection fraction	2.42	1.95–3.00	<0.0001
Heart failure with preserved ejection fraction	1.80	1.45–2.23	<0.0001
Chronic obstructive pulmonary disease	2.09	1.75–2.49	<0.0001
eGFR, mL/min/1.73 m^2 vs. ≥80			<0.0001
50–80	1.18	0.95–1.46	0.14
30–50	1.56	1.21–2.01	0.0005
<30	2.66	1.88–3.76	<0.0001
Diabetes mellitus			<0.0001
Currently not treated with insulin	1.27	1.06–1.52	0.0082
Currently treated with insulin	2.31	1.82–2.93	<0.0001
Body mass index, reference 18.5–35 kg/m^2			<0.0001
<18.5 kg/m^2	2.31	1.53–3.51	<0.0001
≥35 kg/m^2	1.40	1.07–1.84	0.015
Dyslipidaemia[a]	0.72	0.62–0.84	0.0001
Peripheral arterial disease	1.58	1.20–2.08	0.0010
Smoking			0.0005
Current smoker	1.58	1.14–2.17	0.0056
Former smoker	0.99	0.78–1.26	0.93
Never smoker	0.86	0.70–1.06	0.16
Major or CRNM bleeding	1.64	1.16–2.30	0.0046
History of ischaemic stroke, TIA, and SEE	1.38	1.08–1.77	0.0096
Hepatic disease	1.60	1.05–2.43	0.028
Alcohol use ≥1 glass/day	0.80	0.68–0.94	0.0080
Female sex	0.82	0.70–0.96	0.015

Provided are hazard ratios and 95% confidence intervals. If not indicated differently, hazard ratios are for the conditions present vs. not present. Smoking and alcohol is vs. unknown smoking/alcohol drinking status. *P* values are for multivariable Cox models.
CRNM, clinically relevant non-major; eGFR, estimated glomerular filtration rate; SEE, systemic embolic event; TIA, transient ischaemic attack.
[a]84.3% of patients with dyslipidaemia were on lipid lowering treatment.

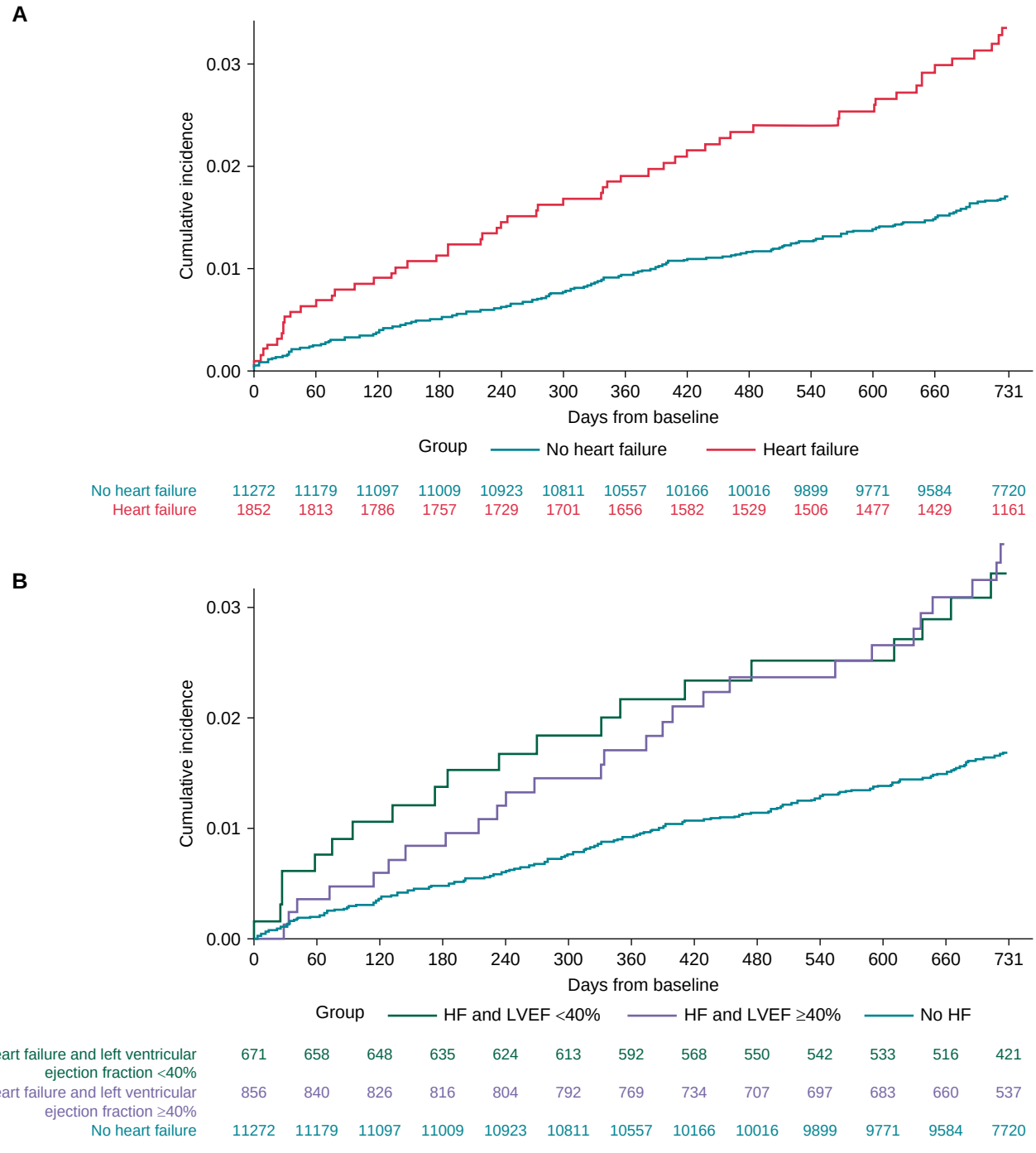


Figure 3 Cumulative major bleeding at 2-year follow-up, stratified by HF status and adjusted for age and CHA_2DS_2-VASc score. (*A*) Stratified by HF status. (*B*) Stratified by LVEF. For 326 patients with HF, LVEF was not documented. HF, heart failure; LVEF, left ventricular ejection fraction.

[$P < 0.0001$] and 4.87%/year vs. 1.71%/year, respectively; *Figure 1A*). More patients with HF and LVEF <40% died due to any as well as CV causes vs. those with HF and LVEF ≥40% (9.44%/year vs. 7.43%/year and 5.99%/year vs. 4.14%/year, respectively; *Figure 1B*). Distinct separation of the all-cause mortality curve between no HF and HF groups was apparent by Day 30 (*Figure 4*). No interaction by antiplatelet therapy was observed (*P* value of interaction: 0.11).

Besides age and sex, stepwise selection models indicated HF with LVEF < 40% [HR (95% CI): 2.42 (1.95 to 3.00)] and HF with LVEF ≥ 40% [1.80 (1.45–2.23)] as two of the strongest predictors of death, with an additional 11 predictors identified. Annualized event rates of composite endpoints including efficacy, safety, and death parameters were higher in patients with HF vs. those without HF (see Supplementary material online, *Table S3* and *Figure S3A* and *B*).

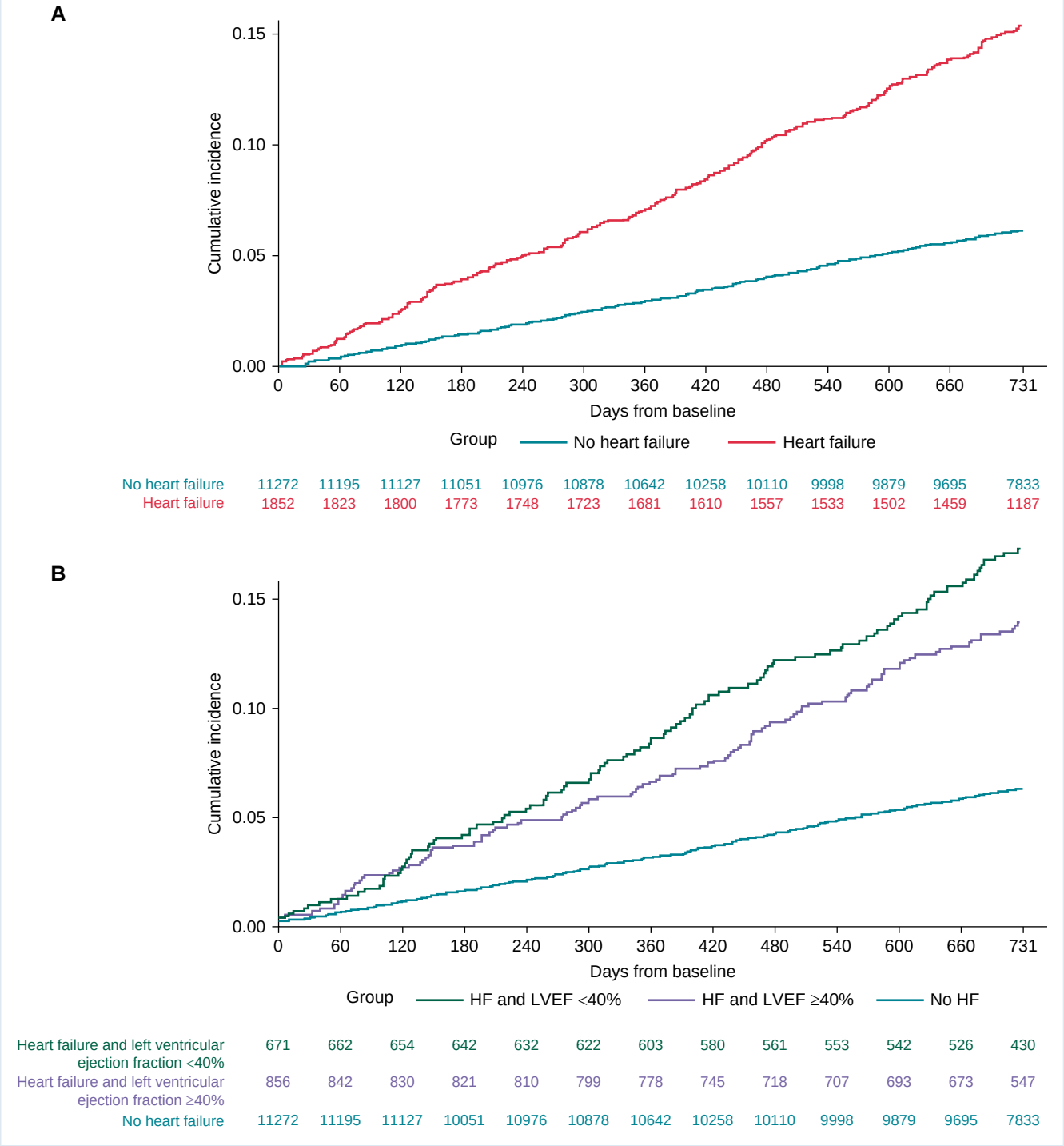


Figure 4 Cumulative all-cause mortality at 2-year follow-up, stratified by HF status and adjusted for age and CHA_2DS_2-VASc score. (*A*) Stratified by HF status. (*B*) Stratified by LVEF. For 326 patients with HF, LVEF was not documented. HF, heart failure; LVEF, left ventricular ejection fraction.

Annualized event rates of composite endpoints were mostly similar in patients with HF and LVEF ≥ or <40%.

Discussion

In our contemporary cohort of patients with AF receiving OAC, overall event rates were low, with <1% attributable to ischaemic events or intracranial haemorrhage. Over 2 years of follow-up, ischaemic event rates were similar in patients with and without HF. Patients with HF had higher AnERs of major bleeding and CV and overall mortality. No relevant differences were observed for ischaemic or bleeding events by HF subtype (with LVEF ≥40% or <40%) whereas mortality tended to be highest in patients with HF and LVEF <40%. Importantly, these findings provide information across the spectrum of HF while also showing consistency with other NOAC studies.[17,18]

Atrial fibrillation in the presence of HF is associated with poor outcomes, warranting the use of anticoagulants.[19,20] Initial NOAC trials and their secondary analyses demonstrated that event rates can be effectively and safely reduced in patients with HF compared with warfarin and support the use of NOACs as an alternative to warfarin in patients with AF and HF.[21–26] In a subanalysis of the ENGAGE AF-TIMI 48 trial, edoxaban compared with warfarin was similarly effective in preventing stroke/SEE in patients with and without HF.[25] Our analysis of clinical practice data outside the RCT setting can extend the knowledge from prior trials on NOACs and demonstrate that thromboembolic event rates in patients with HF can be reduced to levels observed in patients without HF independent of LVEF and baseline differences according to HF status and HF subgroups. Despite higher stroke and bleeding risk scores and, overall, more comorbidities in patients with HF and LVEF ≥40% vs. LVEF <40%, our real-world findings now show the benefit of NOAC treatment by diminishing the difference in event rates between patients with HF, across the spectrum of HF subtypes, and those without HF during the 2 years of follow-up. Although it should be mentioned, the viewpoint has been expressed as to whether the CHA_2DS_2-VASc criteria should be extrapolated to patients with HF and preserved EF and AF.[27] The definition of HF used in the CHA_2DS_2-VASc criteria (recent congestive HF exacerbation without a LVEF criterion) differs from that used in this study and was based mainly on patients with HF and reduced EF, leading to questioning of the appropriateness of its use in patients with HF and preserved EF. Despite this, in the absence of RCT data in patients with HF and preserved EF and with no pathophysiological reason for why data should differ among HF patients with reduced or preserved EF, anticoagulation should be considered for both HF populations.

Compared to 6170 patients with AF treated mainly with vitamin K antagonists in Prevention of thromboembolic events - European Registry in Atrial Fibrillation (PREFER in AF),[28] the stroke rates, on average, were lower in the ETNA-AF-Europe study with patients on edoxaban. In PREFER in AF, stroke incidence was also higher in patients with HF vs. those without HF (1.3% vs. 0.6%) with annual incidence linearly and inversely related to LVEF.

On OAC therapy, AF patients with HF may be prone to increased bleeding events.[29] Hence, bleeding risks of different antithrombotic agents in patients with HF are a key consideration in treatment decision-making. Various secondary analyses from the NOAC RCTs evaluating the subsets of patients with HF have provided insights into the efficacy and safety of NOACs in this higher risk population and support the use of NOACs as an alternative to warfarin.[24–26] A recent meta-analysis focusing on RCTs comparing the effect of NOACs with warfarin in patients with AF and HF showed that NOACs have become the preferred choice for preventing stroke/SEE and major bleeding in AF patients with HF.[30] Annualized event rates in our analyses, though low, were almost twice as high for major bleeding in patients with vs. without HF and comparable across HF subgroups. We confirmed the moderate predictive ability of the variables comprised in the HAS-BLED score for bleeding.[31] The score does not comprise HF as a risk indicator. Our data therefore suggest that the higher bleeding risk observed in patients with HF receiving OAC needs to be considered beyond the HAS-BLED components, and the bleeding risk assessment requires refinement.

As expected, mortality was higher in patients with AF and HF.[5] This observation is explained not only by the prognostic impact of cardiac disease in itself but also by the overall higher burden of comorbidities and the fact that almost twice as many patients were perceived as frail (20% vs. 10%). In AF and HF patients, frailty is known to increase adverse outcomes,[32,33] though evidence on the treatment is limited.[34] It appears to be associated with slower uptake of OAC and non-recommended anticoagulant dosages but possibly also carries a higher risk of bleeding on NOACs.[35–39]

Whereas the number of comorbidities on average was higher among patients with LVEF ≥40%, mortality in the male-dominated HF with LVEF <40% subgroup was nominally highest. The large number of predictors of death selected in the regression analyses besides HF subtypes indicates that no single factor explains the higher mortality; however, the spectrum of comorbidities with HF is one of the strongest among them.

These data from routine clinical practice further highlight the importance of the comprehensive management of concomitant CV risk factors in patients with AF and HF beyond consequent oral anticoagulation.[40–42] This approach is supported by the ESC guidelines, which recommend that risk factors and comorbidities should be well managed to reduce AF burden.[4] A comprehensive care approach to AF, as defined by the Atrial Fibrillation Better Care pathway, was associated with clinical benefit across all adjudicated clinical endpoints in the ENGAGE AF-TIMI 48 trial and real-world data.[42] Furthermore, the 8th AFNET/EHRA consensus conference of the Atrial Fibrillation NETwork (AFNET) and the European Heart Rhythm Association (EHRA) concluded that implementation of new evidence-based approaches to AF screening pathway and rhythm management could lead to improvement in outcomes in patients with AF.[40] For example, cardiac interventions such as ablation therapy were less frequently performed in patients with reduced vs. preserved EF.[43]

Limitations

ETNA-AF-Europe analyses are derived from registry data with known potential of bias in treatment selection and outcomes ascertainment, as well as residual confounding. Another potential source of bias included the enrollment criterion that patients had to be continued on edoxaban.

Approximately 17% of patients were lost to follow-up or discontinued from the study while living and receiving edoxaban. The adherence to the drug was reasonable considering it was an observational study; however, it was lower than the adherence to dosing observed in a RCT setting.

The data presented are also limited by the pre-determined fields included in the Case Report Form and relied upon the accurate and complete input of data by treating physicians. Thus, patients could not be classified according to stage of HF because of limitations of the data. Since multiple comparisons were performed, no adjustment for the level of significance was implemented.

Currently, a lack of head-to-head data prevent the direct comparison between NOAC agents. Whether novel OACs such as factor XIa inhibitors can further reduce the bleeding risk in AF patients with HF needs to be demonstrated.[44] However, the strength of the registry is that it comprises a large number of individuals with almost complete follow-up that help to understand the natural history, effectiveness, and safety of edoxaban by providing insights into the use of treatments during routine clinical practice. The efficacy and safety results from this registry study are consistent with those from the ENGAGE AF-TIMI 48 trial across the spectrum of HF severity and other NOACs.[17,25]

Conclusions

Our data suggest that in patients with AF, edoxaban treatment is effective in reducing the higher risk of ischaemic events observed with concomitant HF across the LVEF spectrum to a similar risk to patients without HF during a 2-year period. Patients with HF remain at a higher risk of major bleeding events. Therefore, HF status should be considered in addition to the HAS-BLED score to assess bleeding risk when treating patients with AF. Mortality risk also remains higher in patients with AF and HF, with highest event rates in HF with LVEF <40%. A broad spectrum of clinical mortality predictors for overall and CV deaths indicates the relevance of comorbidities and highlights the

importance of comprehensive management of patients with AF and HF beyond consequent OAC.

Supplementary material

Supplementary material is available at *Europace* online.

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Data availability

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

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