Risultati real-world sull'uso di edoxaban nei pazienti con fibrillazione atriale: il registro ETNA-AF-Europe

Background

- Anticoagulation is key in the management of stroke prevention in atrial fibrillation (AF).
- Findings from landmark randomised clinical trials 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).
- Edoxaban is indicated in the prevention of stroke and SEE in adult patients with 'non-valvular' AF 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.
- 1–4% of anticoagulated AF patients still suffer from stroke or SEE and ~2% experience a major bleed annually. Recent research has therefore focussed on identifying risk factors that could be helpful in identifying patients at high-risk of cardiovascular events on anticoagulation.

EHJ- Cardiovascular Pharmacotherapy (2023) **9**, 47

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

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EHJ- Cardiovascular Pharmacotherapy (2023) **9**, 47

ETNA-AF Europe

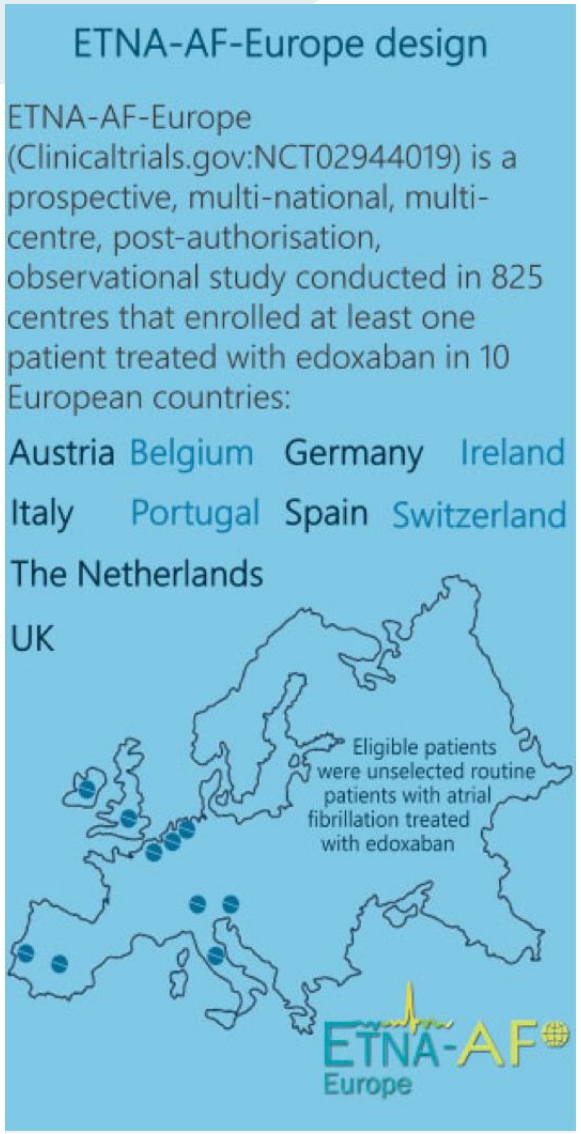


Table 1 Inclusion and exclusion criteria in ETNA-AF-Europe, PREFER in AF, and ENGAGE AF-TIMI 48 studies

	ETNA-AF-Europe	PREFER in AF[8]	ENGAGE AF-TIMI 48[6]
Inclusion criteria	Adult patients will be eligible for inclusion if: They provide written informed consent to participate, Are treated with edoxaban for AF according to the edoxaban summary of product characteristics, and Are not simultaneously participating in any interventional study	Adult patients were eligible for inclusion if: They gave written informed consent for participation in the registry They had a confirmed diagnosis of AF according to the 2010 ESC guidelines,[19] as documented by electrocardiography or an implanted pacemaker or defibrillator within the preceding 12 months Suspected, but unconfirmed, AF cases were not eligible	Adult patients were eligible for inclusion if They were aged ≥21 years and were able to provide written informed consent Had a history of AF documented by any electrical tracing within the prior 12 months and for which ACT is indicated and planned for the duration of the study Had a $CHADS_2$ index score ≥2
Exclusion criteria	No other explicit exclusion criteria will be set to avoid selection bias and to allow documentation of routine clinical practice	No explicit exclusion criteria were defined in order to avoid selection bias and to achieve a cohort close to 'real life'	A long list of exclusion criteria were applied

Methods

- Eligible patients were unselected routine patients with AF treated with edoxaban.
- The overall ETNA-AF-Europe study will follow patients for four years.
- The study outcomes were:
  - bleeding events [major, clinically relevant non- major (CRNM), and ICH as defined by the International Society on Thrombosis and Haemostasis] to evaluate safety;
  - clinical events, including death [all-cause and cardiovascular (CV) death], any stroke or SEE, ischaemic stroke, and myocardial infarction, to evaluate effectiveness.
  - Age-adjusted risk predictors of major bleeding, ischaemic stroke/SEE [including transient ischaemic attack (TIA)], all-cause death and CV death were also assessed.

Baseline characteristics

- ~85% of the patients aged > 65 years.
- 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.

	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)

EHJ- Cardiovascular Pharmacotherapy (2023) **9**, 47

Baseline characteristics

	Total [N = 13 133] (100.0%)	60 mg [N = 10 036] (76.4%)	30 mg [N = 3097] (23.6%)
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)

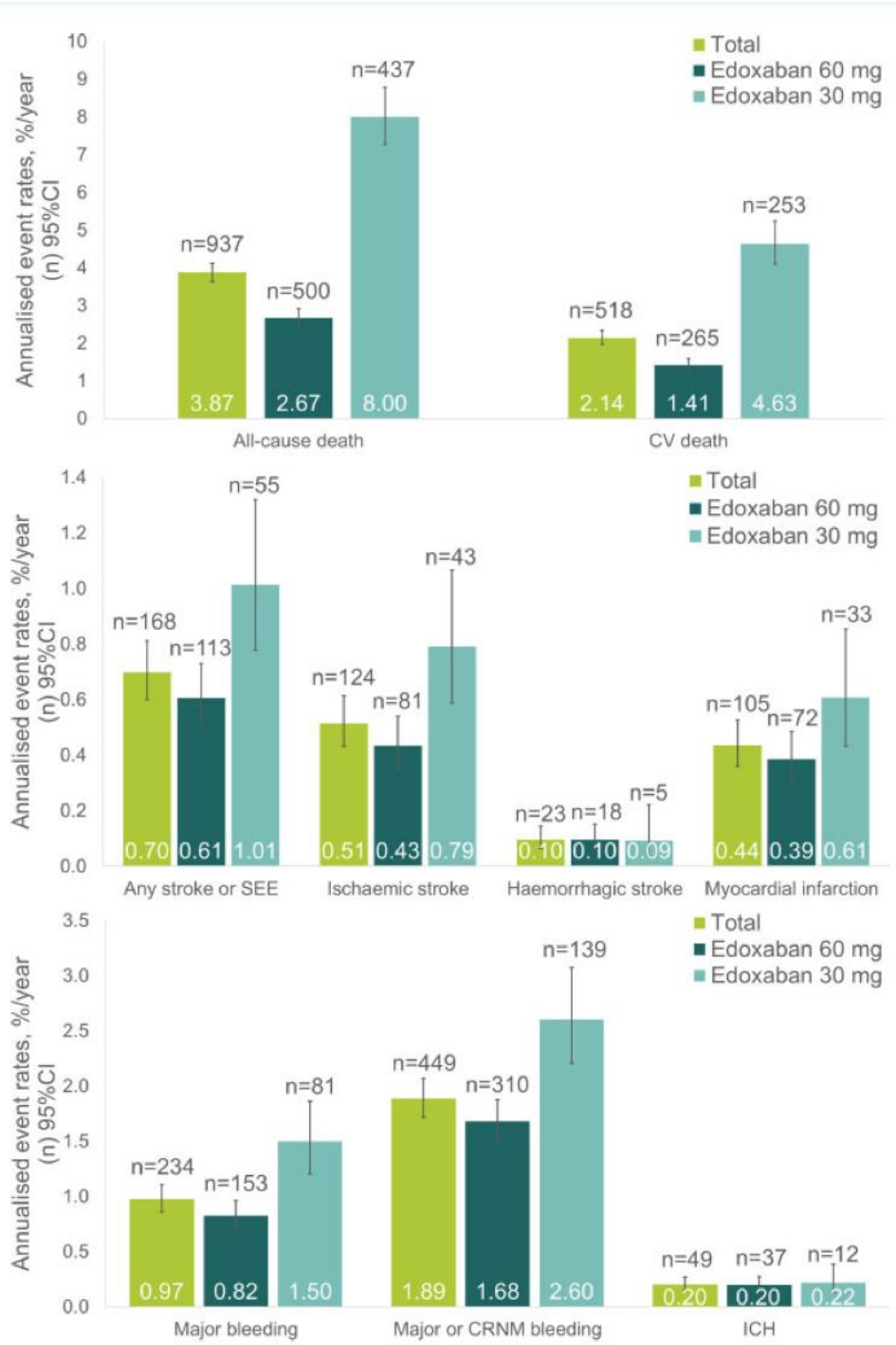
EHJ- Cardiovascular Pharmacotherapy (2023) **9**, 47

Results

- By the end of the 2-year period:
  - 68.7% (9017/13 133) of patients were still on edoxaban and alive,
  - 532/13 133 (4.1%) died on edoxaban or within 3 days of the last edoxaban dose
  - 1298/13 133 (9.9%) died and had permanently discontinued edoxaban >3 days before death
  - 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

Annualised event rates of clinical outcomes in the overall population during the 2-year follow-up

- After adjustment for predictors of stroke and calculation of competing risk of all-cause-death, no significant differences between two doses in:
  - risk of any stroke or SEE and ischaemic stroke,
  - risk of haemorrhagic stroke
- After adjustment for predictors of major bleeding and calculation of competing risk of all-cause-death, no significant differences between two doses in:
  - risk of major bleeding and major or CRNM bleeding
  - risk of ICH

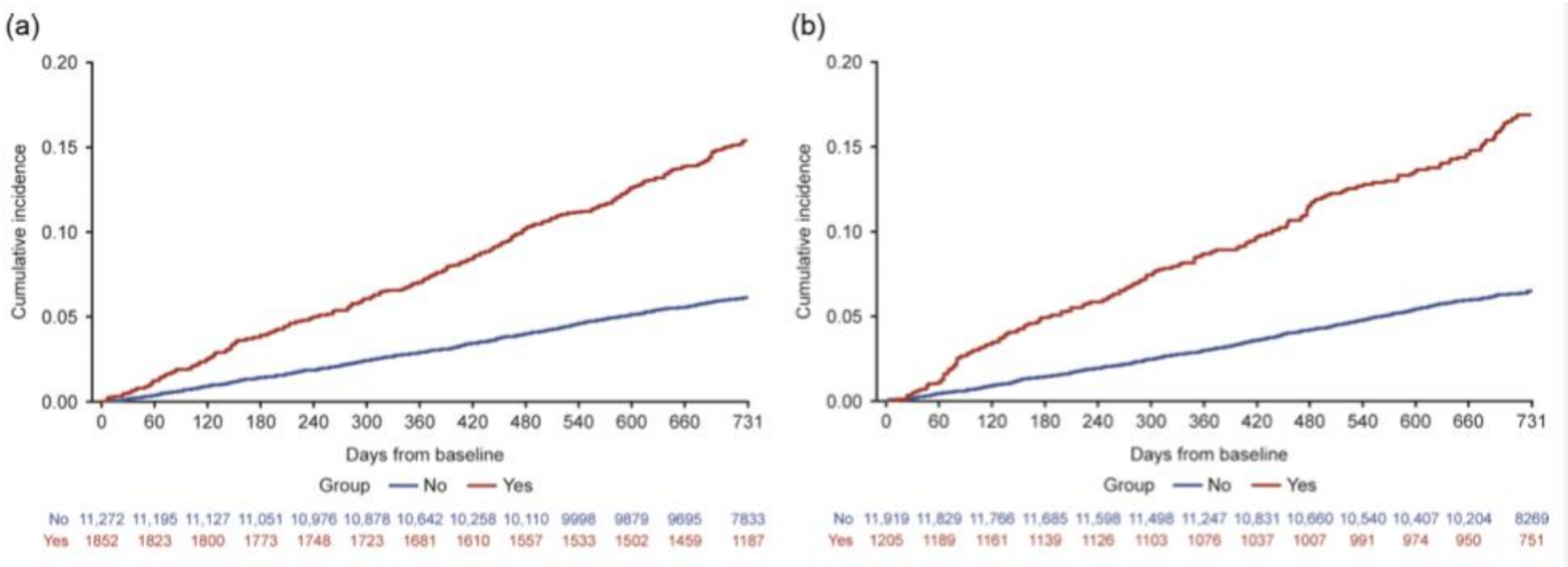


EHJ- Cardiovascular Pharmacotherapy (2023) **9**, 47–57

Age-adjusted predictors of all-cause death during the 2-year follow-up

Heart failure (derived)
Age-adjusted HR 2.40 (2.08–2.76)

COPD
Age-adjusted HR 2.56 (2.18–2.99)



EHJ- Cardiovascular Pharmacotherapy (2023) **9**, 47

Forest plot showing age-adjusted predictors of all-cause death during the 2-year follow-up

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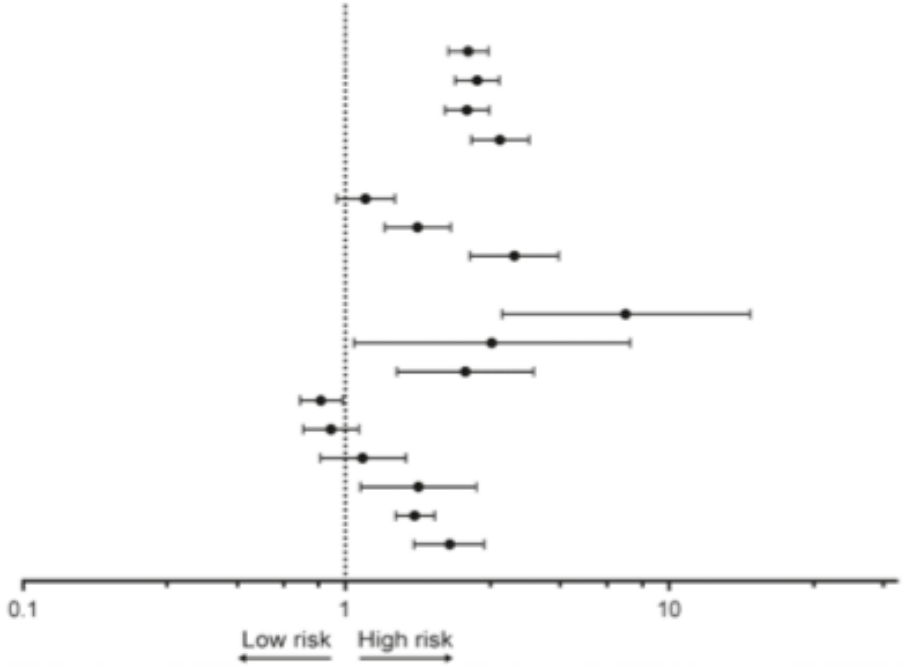


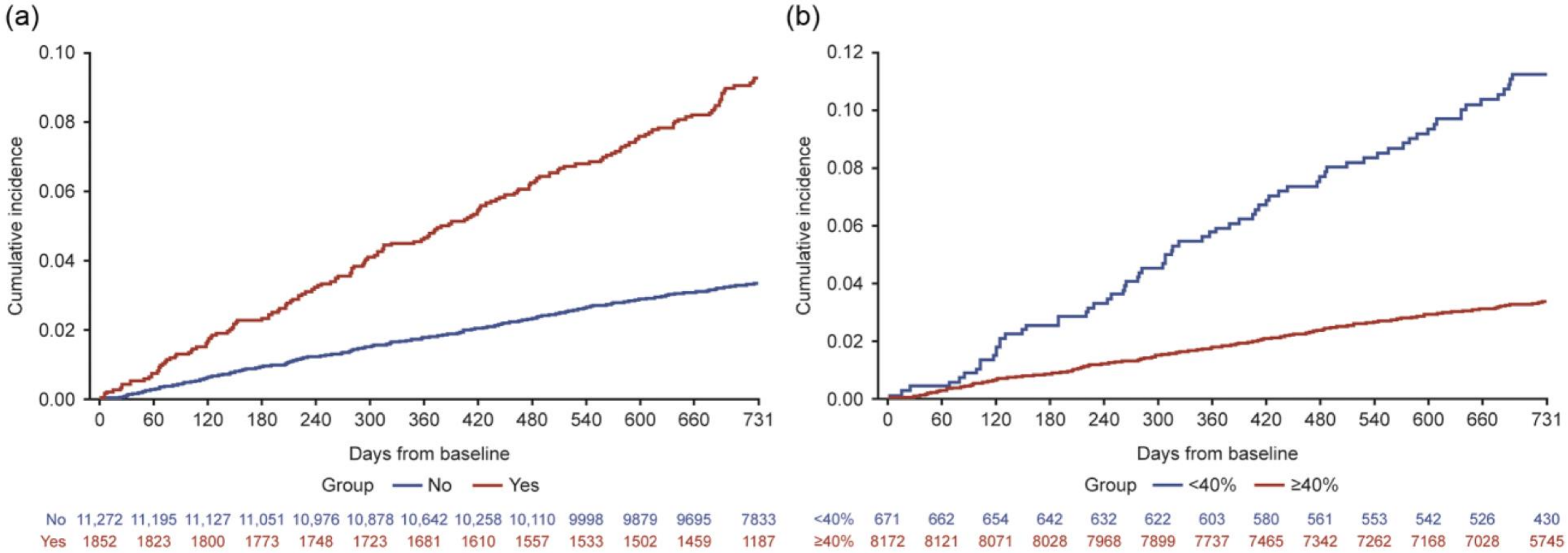
	HR (95% CI)	p-value	Wald Chi-square
History of HF (derived)	2.40 (2.08–2.76)	<0.0001	146.9857
COPD	2.56 (2.18–2.99)	<0.0001	136.5794
Frailty	2.38 (2.03–2.79)	<0.0001	116.3253
LVEF categorised by 40%	3.01 (2.45–3.70)	<0.0001	110.9341
CrCl-CG		<0.0001	71.3574
Stage 2 vs stage 1	1.15 (0.94–1.42)	0.1695	1.8870
Stage 3 vs stage 1	1.67 (1.32–2.12)	<0.0001	18.0365
Stage 4 + ESRD vs stage 1	3.33 (2.43–4.57)	<0.0001	55.2400
BMI categorised		<0.0001	55.4061
Severely underweight vs normal weight	7.38 (3.05–17.87)	<0.0001	19.6365
Moderately underweight vs normal	2.83 (1.06–7.60)	0.0387	4.2720
Mildly underweight vs normal weight	2.34 (1.44–3.82)	0.0007	11.6211
Overweight vs normal weight	0.84 (0.72–0.98)	0.0303	4.9623
Class 1 obesity vs normal weight	0.90 (0.74–1.10)	0.2904	1.1179
Class 2 obesity vs normal weight	1.13 (0.83–1.54)	0.4285	0.6270
Class 3 obesity vs normal weight	1.68 (1.11–2.54)	0.0144	5.9909
Diabetes mellitus	1.64 (1.43–1.88)	<0.0001	50.0308
Peripheral artery disease	2.10 (1.63–2.69)	<0.0001	33.9999

EHJ- Cardiovascular Pharmacotherapy (2023) **9**, 47

Age-adjusted predictors of cardiovascular death during the 2-year follow-up

Heart failure (derived)
Age-adjusted HR: 2.60 (2.16–3.13)

LVEF< 40%
Age-adjusted HR: 3.57 (2.75–4.64)



EHJ- Cardiovascular Pharmacotherapy (2023) **9**, 47

Forest plot showing age-adjusted predictors of CV death during the 2-year follow-up

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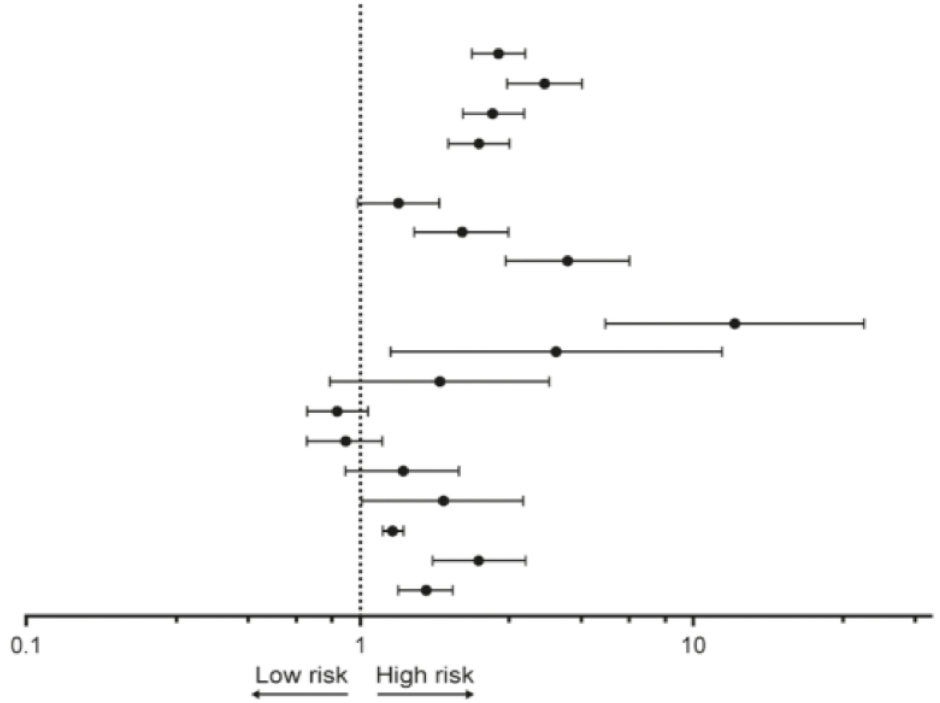


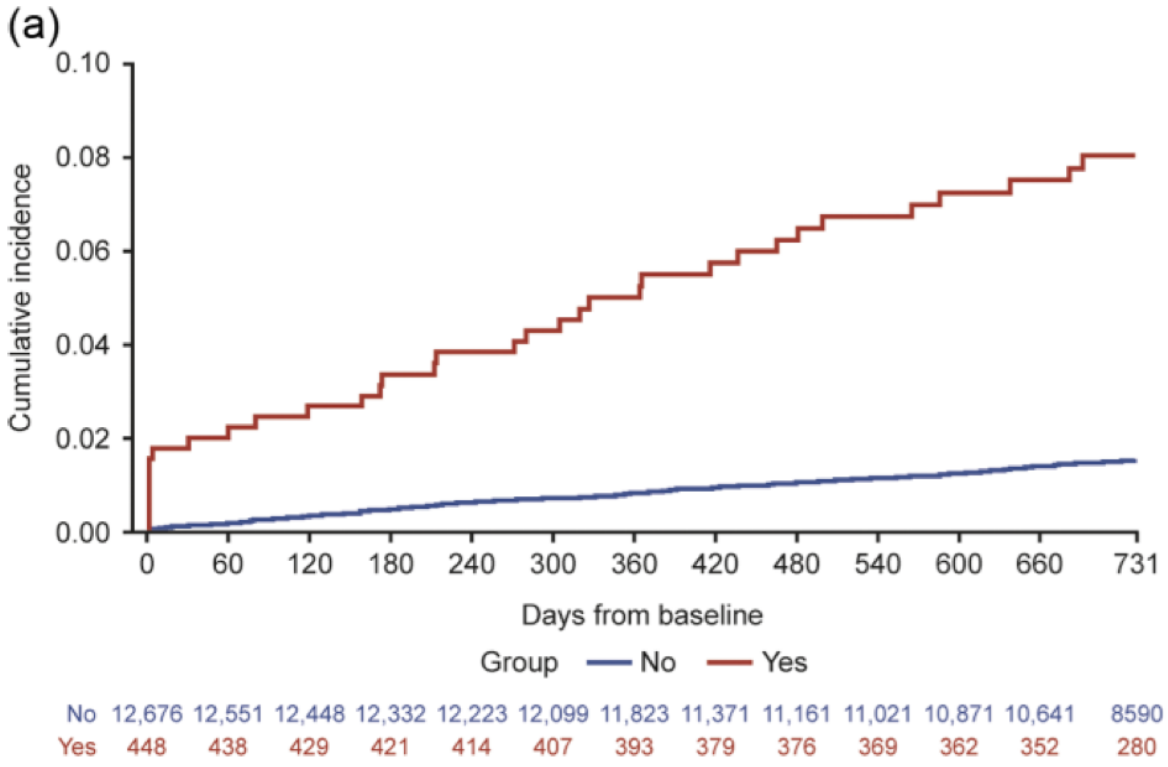
	HR (95% CI)	p-value	Wald Chi-square
History of HF (derived)	2.60 (2.16–3.13)	<0.0001	100.3774
LVEF categorised by 40%	3.57 (2.75–4.64)	<0.0001	90.5100
COPD	2.50 (2.02–3.10)	<0.0001	71.3819
Frailty	2.27 (1.84–2.80)	<0.0001	57.9926
CrCl-CG		<0.0001	54.4196
Stage 2 vs stage 1	1.30 (0.98–1.72)	0.0739	3.1936
Stage 3 vs stage 1	2.01 (1.45–2.78)	<0.0001	17.6033
Stage 4 + ESRD vs stage 1	4.18 (2.74–6.39)	<0.0001	43.8267
BMI categorised		<0.0001	53.9805
Severely underweight vs normal weight	13.26 (5.44–32.31)	<0.0001	32.3570
Moderately underweight vs normal	3.87 (1.23–12.12)	0.0203	5.3843
Mildly underweight vs normal weight	1.73 (0.81–3.69)	0.1156	2.0167
Overweight vs normal weight	0.85 (0.69–1.05)	0.1391	2.1884
Class 1 obesity vs normal weight	0.90 (0.69–1.17)	0.4267	0.6318
Class 2 obesity vs normal weight	1.34 (0.90–1.97)	0.1469	2.1038
Class 3 obesity vs normal weight	1.77 (1.01–3.08)	0.0446	4.0322
CHA_2DS_2-VASc score	1.25 (1.17–1.34)	<0.0001	41.1310
Peripheral artery disease	2.26 (1.64–3.12)	<0.0001	24.4417
Diabetes mellitus	1.57 (1.30–1.89)	<0.0001	22.3478

EHJ- Cardiovascular Pharmacotherapy (2023) **9**, 47

Age-adjusted predictors of stroke during the 2-year follow-up

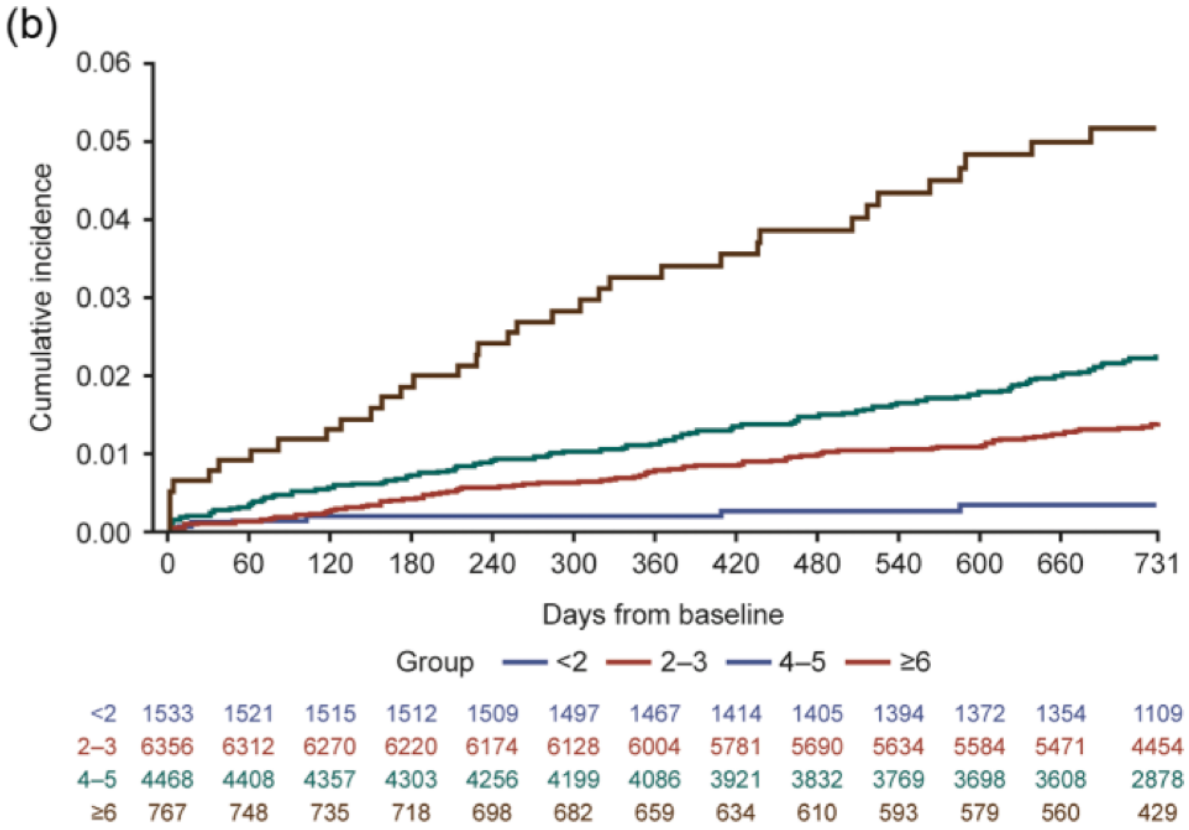
History of TIA

age-adjusted HR: 5.01 (3.47–7.24)



CHA2DS2-VASc score

Age-adjusted HR: 1.39 (1.26–1.54)



EHJ- Cardiovascular Pharmacotherapy (2023) **9**, 47

Forest plot showing age-adjusted predictors of ischaemic stroke/TIA/systemic embolic events during the 2-year follow-up

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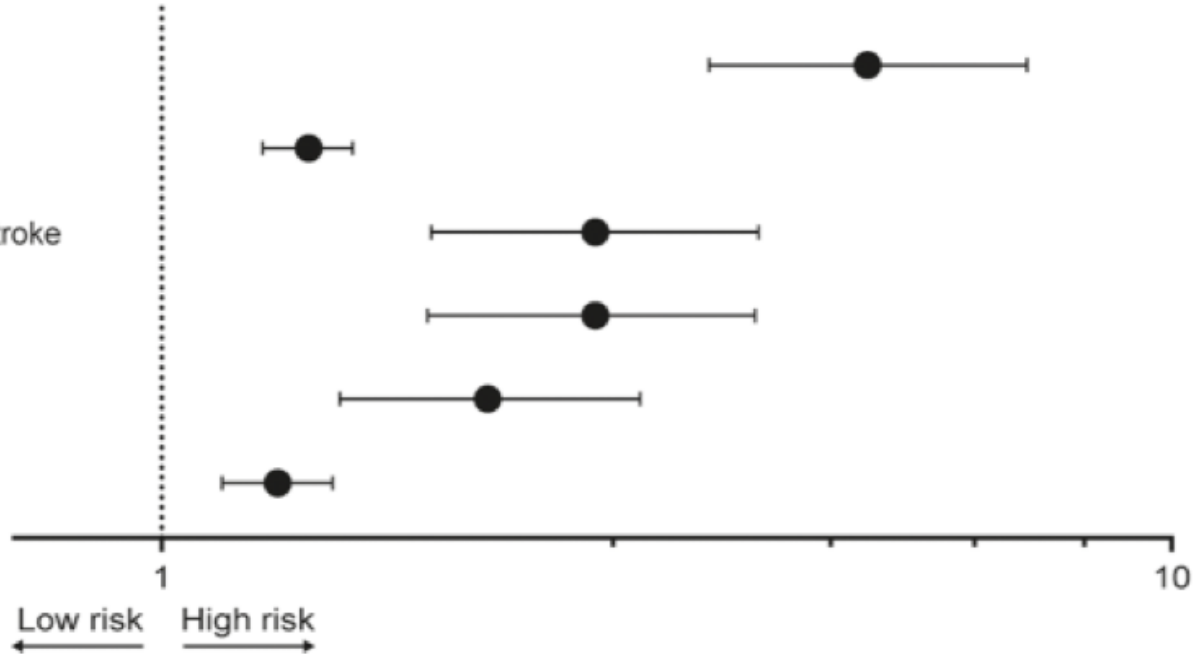


	HR (95% CI)	p-value	Wald Chi-square
History of TIA	5.01 (3.47–7.24)	<0.0001	73.6301
CHA_2DS_2-VASc score	1.39 (1.26–1.54)	<0.0001	40.3894
History of ischaemic stroke	2.69 (1.85–3.89)	<0.0001	27.1083
History of stroke	2.67 (1.84–3.87)	<0.0001	26.8274
Frailty	2.11 (1.50–2.98)	<0.0001	18.1796
HAS-BLED	1.30 (1.15–1.47)	<0.0001	16.5332

EHJ- Cardiovascular Pharmacotherapy (2023) **9**, 47

Age-adjusted predictors of major bleeding during the 2-year follow-up

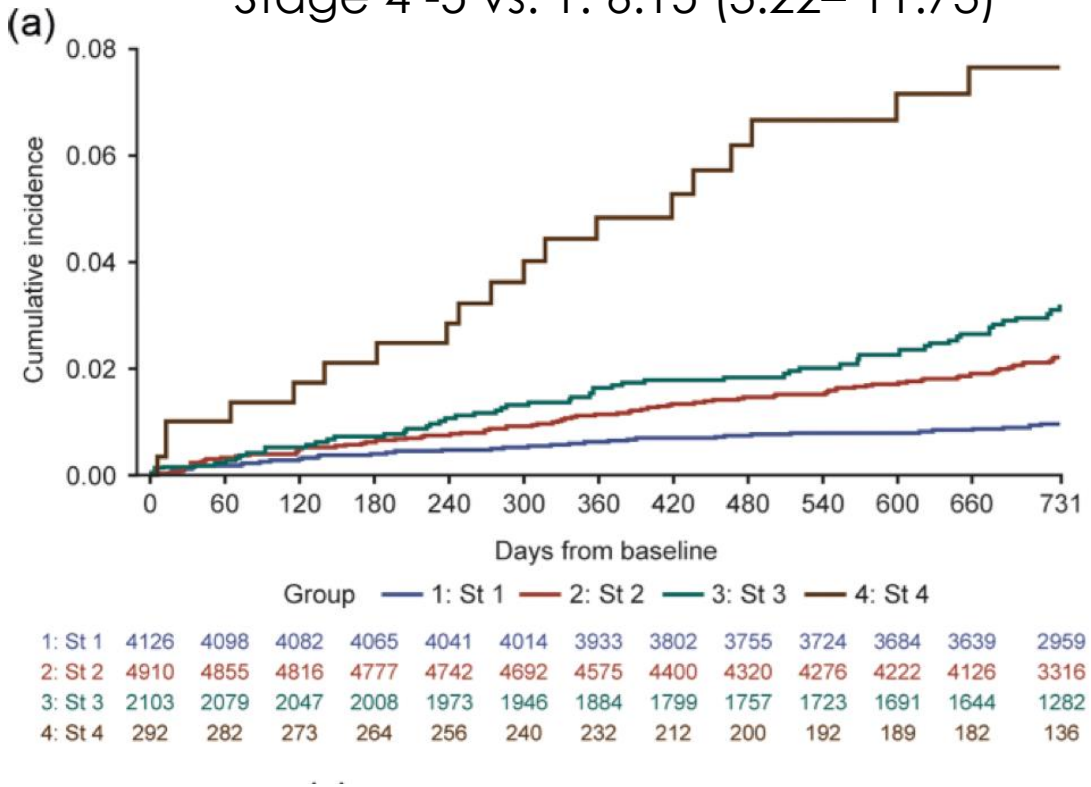
Chronic kidney disease

Age-adjusted HR

Stage 2 vs. 1: 1.94 (1.29–2.92)

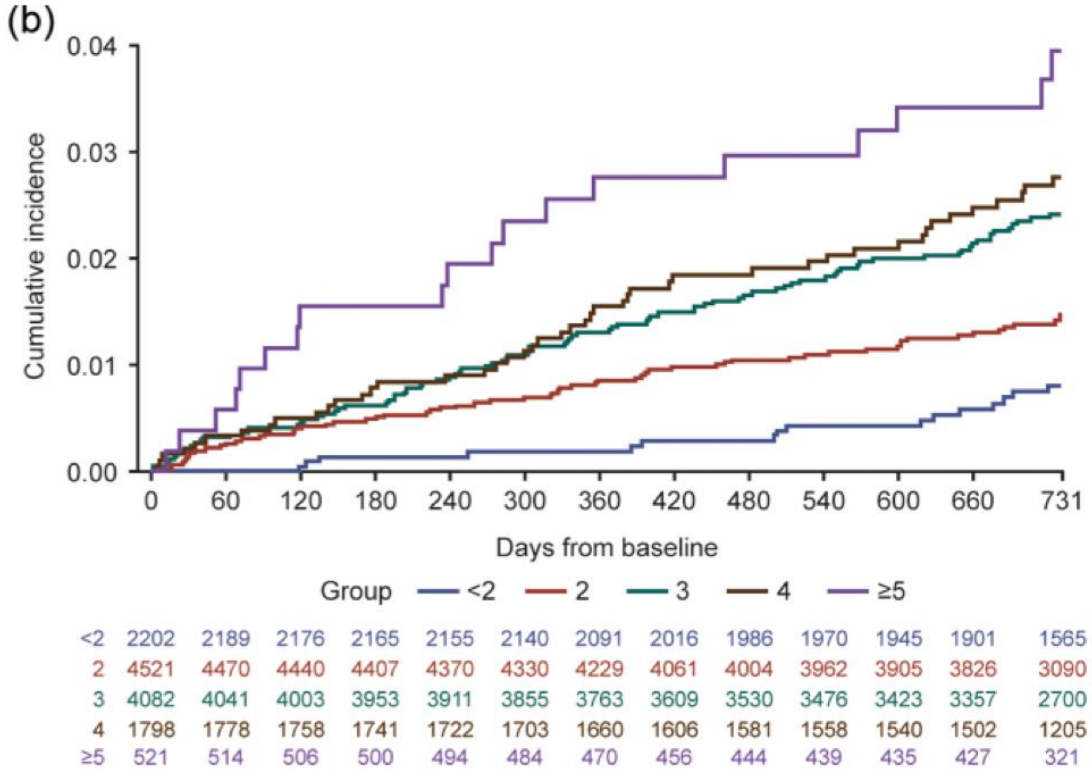
Stage 3 vs. 1: 2.51 (1.53–4.09)

Stage 4 -5 vs. 1: 6.15 (3.22– 11.73)



HAS-BLED score

Age-adjusted HR: 1.31 (1.16–1.48)



EHJ- Cardiovascular Pharmacotherapy (2023) **9**, 47

Forest plot showing age-adjusted predictors of major bleeding during the 2-year follow-up

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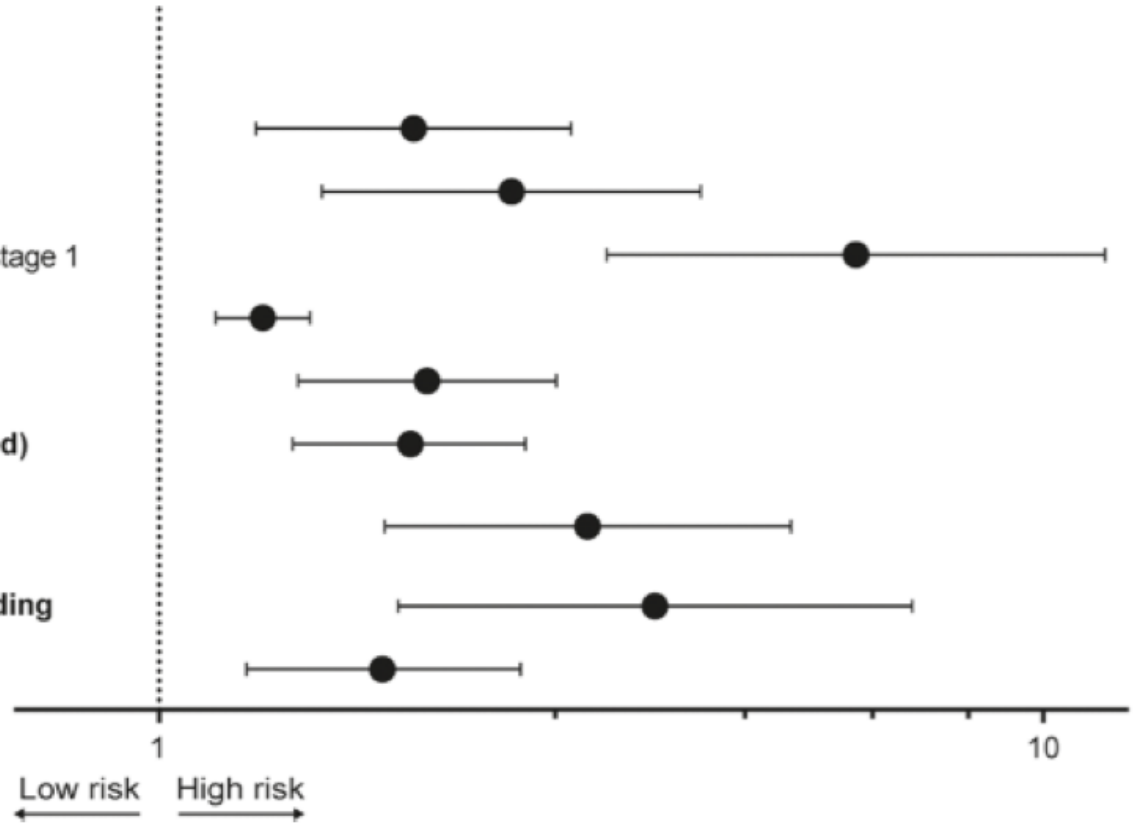

	HR (95% CI)	p-value	Wald Chi-square
CrCl-CG		<0.0001	30.6807
Stage 2 vs stage 1	1.94 (1.29–2.92)	0.001	10.0932
Stage 3 vs stage 1	2.51 (1.53–4.09)	0.0002	13.4728
Stage 4 + ESRD vs stage 1	6.15 (3.22–11.73)	<0.0001	30.3469
HAS-BLED	1.31 (1.16–1.48)	<0.0001	19.6089
Frailty	2.01 (1.44–2.81)	<0.0001	18.1716
History of HF (derived)	1.92 (1.42–2.59)	<0.0001	17.9321
Previous major or CRNM bleeding	3.06 (1.81–5.17)	<0.0001	17.5231
Previous major bleeding	3.64 (1.87–7.08)	0.0001	14.3984
COPD	1.79 (1.26–2.56)	0.0013	10.3861

EHJ- Cardiovascular Pharmacotherapy (2023) **9**, 47

Limitations

- 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 one observed in a RCT 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.
- The open-label nature of the study may have introduced ascertainment bias due to awareness about treatment.
- Under- reporting 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 the 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
- 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.

EHJ- Cardiovascular Pharmacotherapy (2023) **9**, 47