ESC European Society of Cardiology

European Heart Journal Open (2025) **5**, oeaf004
https://doi.org/10.1093/ehjopen/oeaf004

ORIGINAL ARTICLE
Miscellaneous

Edoxaban treatment in routine clinical practice is highly concordant with the 2020 European Society of Cardiology atrial fibrillation guidelines: results from the noninterventional Global ETNA-AF programme

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Received 28 March 2024; revised 24 July 2024; accepted 12 December 2024; online publish-ahead-of-print 28 March 2025

Handling Editor: Magnus Bäck

Aims

The 2020 European Society of Cardiology (ESC)–atrial fibrillation (AF) guidelines recommend a risk-based approach to oral anticoagulation (OAC) therapy in patients with AF; however, it is unknown if current practice aligns with these recommendations. This study assessed the associated effectiveness and safety of edoxaban in patients with AF according to the 2020 ESC-AF guidelines and the approved label in routine clinical care.

Methods and results

The Global ETNA-AF programme is a large prospective, noninterventional programme evaluating safety and effectiveness of edoxaban. Baseline characteristics and 2-year clinical event data were analysed in subgroups, defined by ESC-AF guidelines indication of OAC therapy according to CHA_2DS_2-VASc score [no OAC to be considered, OAC should be considered (2 for females/1 for males), and OAC recommended (≥3 for females/≥2 for males)] and modified HAS-BLED score [(≥3 (bleeding risk high) vs. <3 (bleeding risk low)]. Of 19 960 patients included, 16 912 (84.7%) were categorized as OAC recommended and 2501 (12.5%) as OAC should be considered; 547 (2.7%) were in the no OAC to be considered group. In the OAC recommended group, 12 006 (71.0%) had high bleeding risk. Clinical event rates were <5%/year across all risk groups, even in the OAC recommended and high bleeding risk groups. In the OAC recommended and high bleeding risk groups, patients had low ischaemic stroke and bleeding event rates, regardless of receiving the 30 or 60 mg dose.

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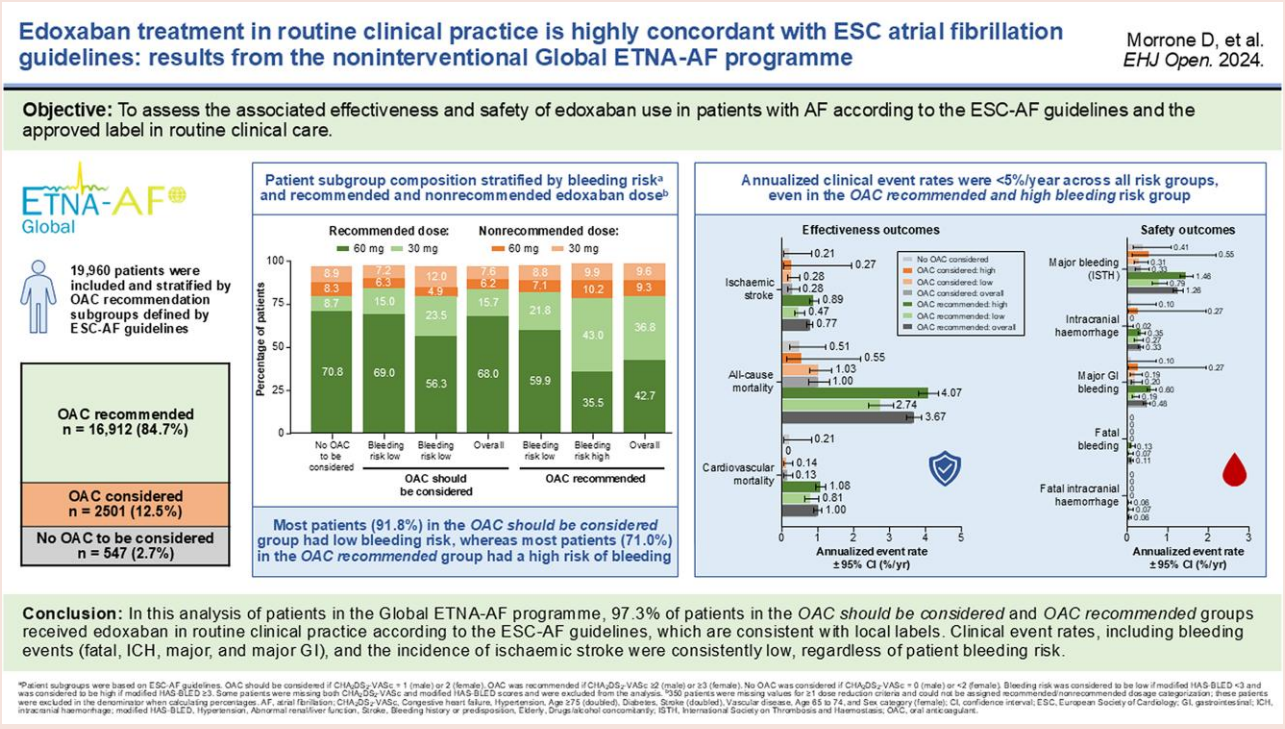
Conclusion This study demonstrated that edoxaban use in patients with AF largely aligns with 2020 ESC-AF guidelines, while maintaining low clinical event rates.

Registration Europe (NCT02944019), Japan (UMIN000017011), and Korea/Taiwan (NCT02951039).

Graphical abstract



Keywords Atrial fibrillation • Edoxaban • Oral anticoagulation

Introduction

Atrial fibrillation (AF) is the most common arrhythmia, with an estimated prevalence in adults between 2% and 4%, affecting 46.3 million people worldwide.[1,2] Studies have shown that AF is associated with an increased risk of stroke, heart failure, and increased mortality.[2–4] Oral anticoagulant (OAC) treatment is pivotal in reducing the risk of ischaemic stroke in patients with AF.[1,4] For years, vitamin K antagonists (VKAs) were the preferred treatment for the prevention of thrombo-embolic events in patients with AF; however, direct oral anticoagulants (DOACs; i.e. apixaban, dabigatran, edoxaban, and rivaroxaban) have become the first-line therapy in clinical practice and recommended in preference to VKA for thrombo-embolic stroke prevention in patients with AF.[1,5–10] Four key randomized controlled trials (RCTs) demonstrated that DOACs were noninferior to VKA (warfarin) in the prevention of stroke or systemic embolic events (SEEs).[5–8] Additionally, a meta-analysis of these RCTs showed that compared with VKAs, DOACs were associated with a significant reduction in the risk of the composite of stroke or systemic embolism, as well as a significant reduction in all-cause mortality risk and intracranial haemorrhage (ICH) risk, and a nonsignificant reduction in major bleeding risk in patients with AF.[11] Furthermore, real-world evidence studies confirmed the effectiveness of DOACs as the risk of stroke was low in patients with AF who received DOACs in routine clinical practice.[9,12] Notably, the Global Edoxaban Treatment in routiNe clinical prActice (ETNA)-AF programme, the largest prospective observational study of a single DOAC (edoxaban), showed that any stroke, ICH, and other major bleeding events were low after one year in patients with AF treated with the DOAC edoxaban in routine care.[9]

The 2016 European Society of Cardiology (ESC) guidelines for AF (ESC-AF) management, developed in collaboration with the European Association for Cardio-Thoracic Surgery, recommend (Class 1A) DOACs over VKAs, and a switch to DOACs may be considered if the time in therapeutic range (TTR) is suboptimal despite good adherence to treatment regimen (Class IIb).[13] The 2020 ESC-AF guidelines on diagnosis and management upgraded treatment recommendations, indicating a switch from VKA to DOAC as a Class I recommendation (recommended or indicated) for patients with TTR < 70%.[1] It is important to note that treatment with OAC should be considered in all patients with AF and stroke risk factors, as reflected by the CHA_2DS_2-VASc [(Congestive heart failure, Hypertension, Age ≥ 75 (doubled), Diabetes, Stroke (doubled), Vascular disease,

Age 65–74, and Sex category (female)] score.[1] The 2020 ESC-AF guidelines state OACs should be considered if CHA_2DS_2-VASc score is 2 for female or 1 for male and OACs are recommended if CHA_2DS_2-VASc score is 3 for female or 1 for male.[1] Additionally, OAC treatment should be considered independently of the risk of bleeding, as reflected by the HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly) score, and high bleeding risk scores should not be used as a reason to withhold OACs.[1] Good adherence to OAC treatment is crucial for effective ischaemic stroke prevention, and poor adherence is associated with increased stroke risk; however, physicians may be hesitant to administer DOACs to patients with high bleeding risk (HAS-BLED score ≥ 3).[14,15] The SAFE II study found that the presence of potential contraindications, such as high bleeding risk, lack of an indication, low compliance, and fear of bleeding, were barriers to physician guideline adherence and use of OAC.[16] The 2020 ESC-AF management guidelines recommended a risk-based approach to OAC therapy in patients with AF. However, it is unknown if current practice aligns with these recommendations. The present study aimed to assess edoxaban use in patients with AF according to the OAC recommendation subgroups defined by the 2020 ESC-AF management guidelines in routine clinical care and the associated effectiveness and safety profiles. Additionally, the use of edoxaban dose recommendations according to the label (recommended or nonrecommended) was evaluated.

Methods

The study design of the Global ETNA-AF programme was previously published.[17] Briefly, the Global ETNA-AF programme integrates data from several prospective, observational, and noninterventional regional studies from Europe (NCT02944019; Germany, Austria, Switzerland, Belgium, Italy, Spain, the UK, Ireland, the Netherlands, and Portugal), Japan (UMIN000017011), and other Asian countries/regions [South Korea/Taiwan (NCT02951039), Hong Kong (NCT03247582), and Thailand (NCT03247569)].[17–19] Participating sites included hospitals and outpatient clinics. The programme complied with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice standards. The ETNA-AF study protocols received approvals from the responsible ethics committees and institutional review boards, except for Japan, where such approval is not required for post-marketing surveillance studies in compliance with the Japanese Pharmaceuticals and Medical Devices Act.[9]

Inclusion and exclusion criteria

Patients with AF treated with edoxaban for stroke prevention according to the local label were eligible. In Japan, patients were included only if they were receiving edoxaban for the first time to prevent ischaemic stroke and SEEs. Patients were excluded for failure to provide written informed consent and simultaneous participation in an interventional study.

Study drug

According to the label, edoxaban 60 mg once daily is approved for the prevention of stroke and SEEs in patients with AF; dose reduction criteria for edoxaban 30 mg once daily is recommended for patients with creatinine clearance (CrCl) 15 to 50 mL/min, low body weight (≤ 60 kg), and/or concomitant use of P-glycoprotein inhibitors.[20] Due to the real-world nature of the study, dosing decisions were made at the clinician's discretion.

Outcomes

Baseline information, medical history, and clinical events were collected. The following clinical events were systematically captured during the 2-year observational period after enrolment: ischaemic stroke, major bleeding, fatal bleeding, ICH, fatal ICH, major gastrointestinal (GI) bleeding, all-cause death, and cardiovascular-related death. Bleeding was characterized as major, clinically relevant nonmajor, or minor, in accordance with the International Society on Thrombosis and Haemostasis (ISTH).[21] Clinical events were reported based on physician diagnosis and assessment per available guideline definitions, with adjudication for major bleeding, clinically relevant nonmajor bleeding, stroke, SEEs, and deaths. The net clinical outcome, used in the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial and defined as the composite of stroke (ischaemic or haemorrhagic), SEE, major bleeding (ISTH), or death, was included.[8]

Statistical analysis

Baseline characteristics and clinical event rates were presented in OAC recommendation subgroups defined by the 2020 ESC-AF guidelines. Patients with a CHA_2DS_2-VASc score ≥ 3 for females or ≥ 2 for males were in the OAC recommended group; those with a CHA_2DS_2-VASc score of 2 for females or 1 for males were in the OAC should be considered group; and the no OAC to be considered group consisted of patients with a CHA_2DS_2-VASc score of 1 for female or 0 for male. Patients in the OAC recommended and OAC should be considered groups were further stratified by bleeding risk as defined by the modified HAS-BLED score [bleeding risk high (≥ 3) vs. bleeding risk low (< 3)]. Patients with missing modified HAS-BLED scores were excluded from the analysis. The details for how each variable was scored are presented in Supplementary material online, *Table S1*.

Data were presented as frequencies and percentages for categorical variables and as means and standard deviations (SDs) for continuous variables for the overall OAC subgroups and for each OAC subgroup stratified by bleeding risk. For percentage calculations pertaining to dosage groups, patients with a 'missing' or 'other' dose at baseline were excluded (i.e. the denominator was not equal to the *n*'s provided in the column header). Clinical events and bleeding risk in the OAC should be considered and OAC recommended groups overall and stratified by bleeding risk score (low vs. high) and the no OAC to be considered group were presented as annualized rates [percentage of patients with at least one event per year and displayed as %/year with 95% confidence intervals (CIs)]. No adjustments for baseline characteristics were made between the three OAC recommendation subgroups when presenting the annualized rates of clinical events in order to describe real-world differences in clinical outcomes in routine clinical care.

A subgroup analysis was performed in patients in the OAC recommended and high bleeding risk groups; this population was analysed in accordance with edoxaban label recommendations (60 mg recommended vs. 30 mg nonrecommended and 30 mg recommended vs. 60 mg nonrecommended) to better understand the impact of adherence to or deviation from dose recommendation within this subgroup. For comparing baseline characteristics between the recommended and nonrecommended dosing groups, the Wilcoxon two-sample test and χ^2 test were applied. Baseline variables considered in the adjusted hazard ratios (HRs) were dose reduction criteria (i.e. CrCl, weight, and use of P-glycoprotein inhibitors), age, prior ischaemic stroke, and prior major bleeding. The main goal for the OAC recommended and high bleeding risk subgroup analysis was to report real-world data related to edoxaban dosing in routine clinical care. As a result, baseline characteristics and unadjusted outcomes were first compared to report a real-world picture of clinical risks (indicated by the baseline characteristics) under different observed prescribing patterns. Secondly, in the OAC recommended and high bleeding risk subgroups, an adjusted analysis comparing outcomes between dosing groups was conducted to account for differences in baseline characteristics that were statistically significant and clinically different ($P < 0.05$), including dose reduction criteria (i.e. CrCl, weight, and use of P-glycoprotein inhibitors), age, prior ischaemic stroke, and prior major bleeding. The same variables were included for adjustment when comparing 60 mg recommended vs. 30 mg nonrecommended or 60 mg nonrecommended vs. 30 mg recommended doses. Adjusted and unadjusted HRs for clinical events were calculated by using a Cox regression model and were reported along with 95% CIs and *P* values. Patients who had missing information for dose reduction criteria could not be assigned a recommended or nonrecommended dosage.

Results

Baseline characteristics

Overall, 26 805 edoxaban-treated patients were included in the Global ETNA-AF programme. In this analysis, 6845 patients were excluded

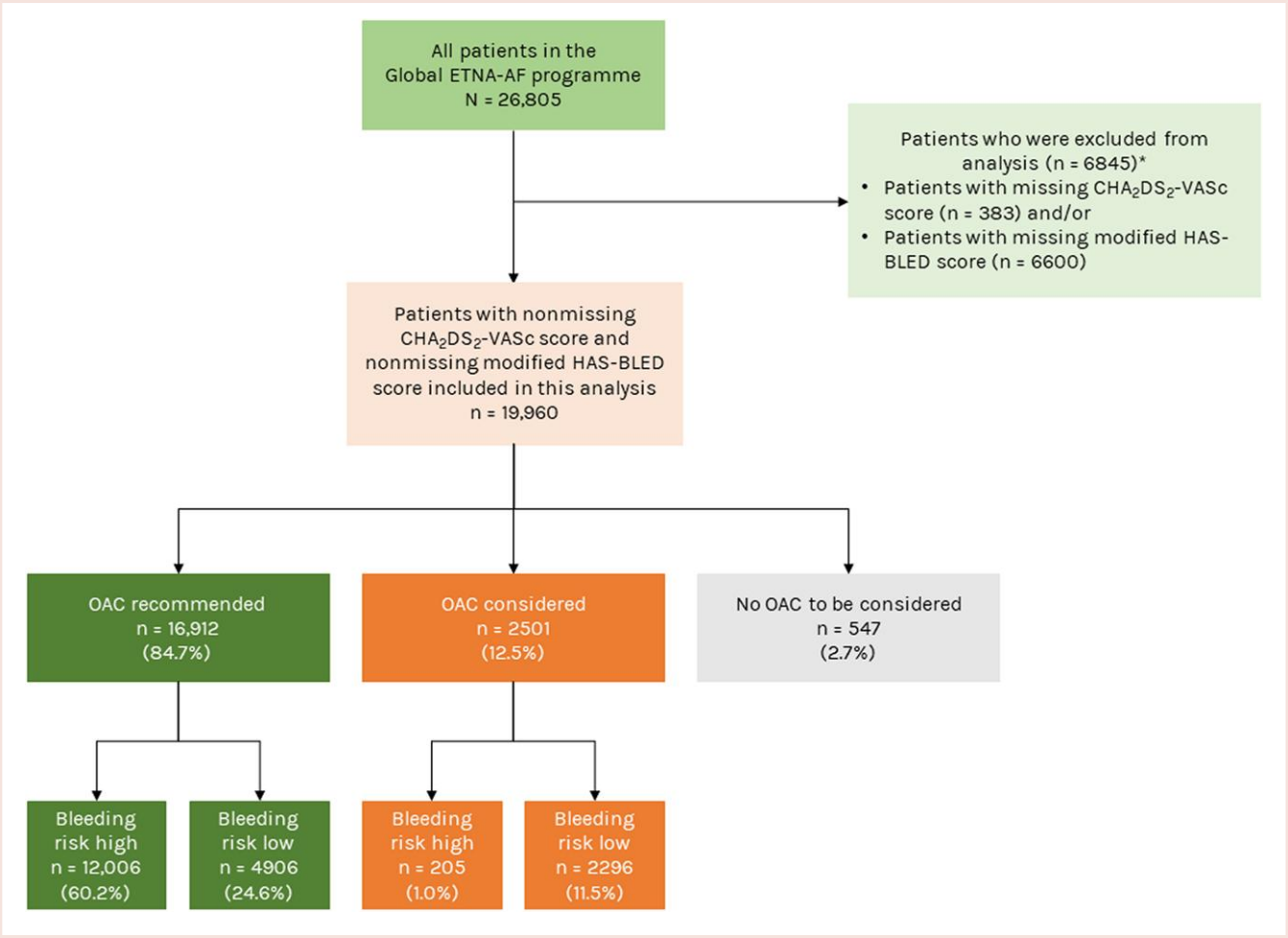


Figure 1 Patient disposition. *Some patients were missing both CHA_2DS_2-VASc and modified HAS-BLED scores and were excluded from the analysis. CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥ 75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex category (female); modified HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Elderly, Drugs/alcohol concomitantly; OAC, oral anticoagulant.

due to missing modified HAS-BLED scores ($n = 6600$) and/or missing CHA_2DS_2-VASc scores ($n = 383$), resulting in the inclusion of 19 960 patients (*Figure 1*). Of those included, 547 (2.7%) were in the no OAC to be considered group, 2501 (12.5%) were in the OAC should be considered group, and 16 912 (84.7%) were in the OAC recommended group. Baseline demographics and clinical characteristics stratified by OAC and bleeding risk subgroups are shown in *Table 1*.

No oral anticoagulant to be considered

Patients in the no OAC to be considered group were younger (mean ± SD age, 55.4 ± 8.0 years) compared with those in the OAC should be considered (63.4 ± 7.5 years) and OAC recommended (75.8 ± 8.2 years) groups (*Table 1*). Patients in the no OAC to be considered group also had higher baseline CrCl (102.7 ± 33.8 mL/min) compared with those in the OAC should be considered (90.3 ± 30.3 mL/min) and OAC recommended (64.9 ± 25.8mL/min) groups (*Table 1*). Patients in the no OAC to be considered group had similar body weight as those in the OAC should be considered group (77.7 ± 18.6 kg and 77.3 ± 19.0 kg, respectively). Conversely, body weight was lower in the OAC recommended group (71.1 ± 17.7 kg). Body mass index was similar in all three groups.

Oral anticoagulant should be considered

Of those in the OAC should be considered group ($n = 2501$), 205 (8.2%) had high bleeding risk (modified HAS-BLED ≥ 3) and 2296 (91.8%) had low bleeding risk (modified HAS-BLED < 3; *Figure 1*). Patients with a low bleeding risk were younger (mean ± SD, 63.1 ± 7.6 years vs. 66.0 ± 6.2 years) and had a higher weight (78.0 ± 19.2 kg vs. 69.4 ± 14.9 kg) and higher baseline CrCl clearance (92.1 ± 30.4 mL/min vs. 70.5 ± 20.3 mL/min) than those with a higher bleeding risk (*Table 1*). Additionally, a greater proportion of the low bleeding risk group received the 60 mg recommended dose compared with the high bleeding risk group (69.0% vs. 56.3%; *Figure 2*).

Oral anticoagulant recommended

In the OAC recommended group ($n = 16\,912$), 4906 (29.0%) patients had low bleeding risk (modified HAS-BLED < 3) and 12 006 (71.0%) had high bleeding risk (modified HAS-BLED ≥ 3; *Figure 1*); 2910 (59.3%) and 6562 (54.7%) patients being males, respectively (*Table 1*). Patients with high bleeding risk had a mean age of 77.5 ± 6.9 years, whereas those with a low bleeding risk had a mean age of 71.5 ± 9.4 years. Patients with a high vs. low bleeding risk had higher incidences

Table 1 Baseline demographics and clinical characteristics stratified by OAC and bleeding risk subgroups

	No OAC to be considered[a]	OAC should be considered[a]			OAC recommended[a]		
	Overall (*n* = 547)	Bleeding risk low (*n* = 2296)	Bleeding risk high (*n* = 205)	Overall (*n* = 2501)	Bleeding risk low (*n* = 4906)	Bleeding risk high (*n* = 12 006)	Overall (*n* = 16 912)
Region, % (*n*)[b]							
Europe (*n* = 13 164)	54.3 (297)	60.9 (1399)	44.9 (92)	11.3 (1491)	61.2 (3001)	51.0 (6114)	69.2 (9115)
Korea, Taiwan, Thailand, and Hong Kong (*n* = 3299)	17.9 (98)	16.0 (368)	12.2 (25)	11.9 (393)	15.0 (734)	14.5 (1742)	75.1 (2476)
Japan (*n* = 10 342)	27.8 (152)	23.0 (529)	42.9 (88)	6.0 (617)	23.9 (1171)	34.6 (4150)	51.5 (5321)
Male, % (*n*)	70.0 (383)	61.1 (1402)	79.5 (163)	62.6 (1565)	59.3 (2910)	54.7 (6562)	56.0 (9472)
Age, years, mean ± SD	55.4 ± 8.0	63.1 ± 7.6	66.0 ± 6.2	63.4 ± 7.5	71.5 ± 9.4	77.5 ± 6.9	75.8 ± 8.2
Body weight, kg, mean ± SD	77.7 ± 18.6	78.0 ± 19.2	69.4 ± 14.9	77.3 ± 19.0	77.8 ± 20.6	68.3 ± 15.5	71.1 ± 17.7
BMI, kg/m^2, mean ± SD	26.3 ± 5.2	27.1 ± 5.4	24.5 ± 3.9	26.9 ± 5.3	27.7 ± 5.8	25.6 ± 4.4	26.2 ± 5.0
CrCl, mL/min, mean ± SD	102.7 ± 33.8	92.1 ± 30.4	70.5 ± 20.3	90.3 ± 30.3	83.4 ± 30.5	57.5 ± 19.1	64.9 ± 25.8
Serum creatinine, mg/dL, mean ± SD	0.89 ± 0.35	0.92 ± 1.05	1.01 ± 0.24	0.92 ± 1.0	0.89 ± 0.26	1.03 ± 0.34	0.99 ± 0.32
Clinical characteristics, % (*n*)							
Hypertension	0.0 (0)	44.9 (1030)	39.5 (81)	44.4 (1111)	56.5 (2772)	93.6 (11 242)	82.9 (14 014)
Diabetes	0.0 (0)	3.7 (84)	0.0 (0)	3.4 (84)	29.6 (1452)	27.4 (3288)	28.0 (4740)
Dys-/hyperlipidaemia	19.0 (104)	30.2 (693)	34.6 (71)	30.5 (764)	38.6 (1892)	47.3 (5676)	44.7 (7568)
Heart failure[c]	0.0 (0)	7.0 (160)	1.0 (2)	6.5 (162)	22.2 (1090)	22.6 (2716)	22.5 (3806)
Prior ischaemic stroke	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	4.1 (201)	16.4 (1963)	12.8 (2164)
Prior major bleeding	0.0 (0)	0.1 (2)	2.0 (4)	0.2 (6)	0.5 (26)	2.4 (293)	1.9 (319)

AF, atrial fibrillation; BMI, body mass index; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥ 75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex category (female); CrCl, creatinine clearance; ESC, European Society of Cardiology; FAS, full analysis set; modified HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Elderly, Drugs/alcohol concomitantly; MI, myocardial infarction; OAC, oral anticoagulant; SD, standard deviation.

[a]Subgroups were stratified based on the 2020 ESC-AF guidelines. OAC should be considered if CHA_2DS_2-VASc = 1 (male) or 2 (female). OAC was recommended if CHA_2DS_2-VASc ≥ 2 (male) or ≥ 3 (female). No OAC was considered if CHA_2DS_2-VASc = 0 (male) or < 2 (female). Bleeding risk was considered to be low if modified HAS-BLED < 3 and was considered to be high if modified HAS-BLED ≥ 3.

[b]The *N* values for regions were calculated for all patients in the FAS. Percentages were based on column header *N* values (i.e. missing and unknown patients were not excluded from the denominator when calculating the percentages).

[c]A medical history of heart failure required the fulfilment of one of the following criteria: documented congestive heart failure, or if congestive heart failure 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-MI, valve replacement, or hypertension treated with ≥ 3 drugs.

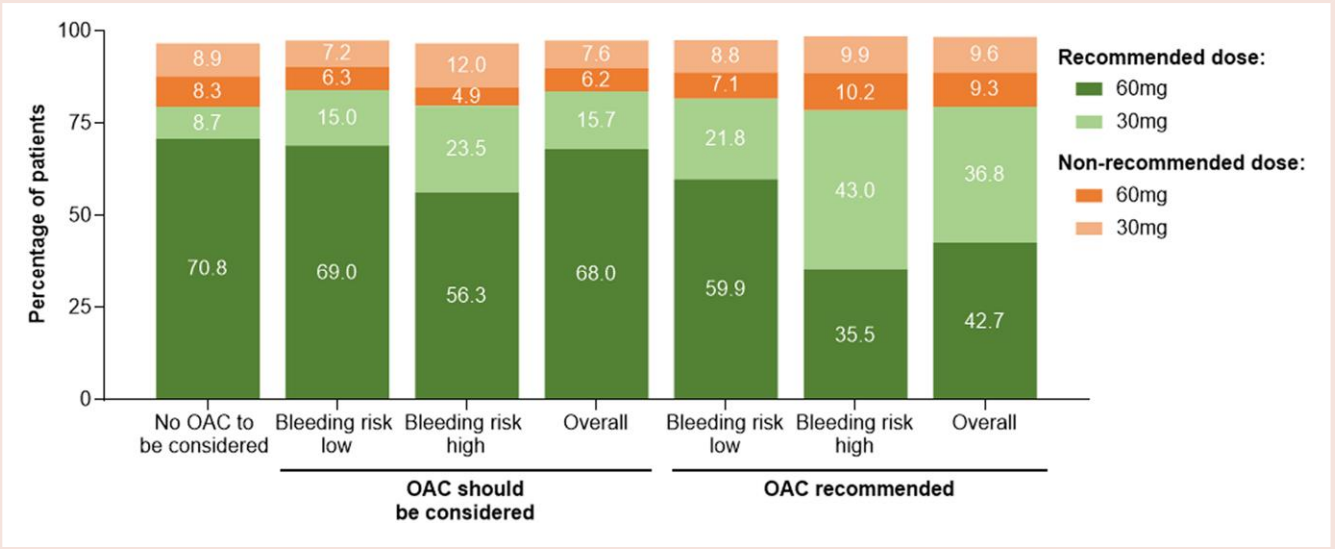


Figure 2 Patient subgroup composition overall and stratified by recommended and nonrecommended edoxaban dose. Three hundred and fifty patients were missing values for ≥ 1 dose reduction criteria and could not be assigned recommended/nonrecommended dosage categorization; these patients were excluded in the denominator when calculating percentages. OAC, oral anticoagulant.

of hypertension (93.6% vs. 56.5%), hyperlipidaemia (47.3% vs. 38.6%), prior ischaemic stroke (16.4% vs. 4.1%), and prior major bleeding (2.4% vs. 0.5%), but similar incidence of history of heart failure (22.6% vs. 22.2%). Notably, patients in the OAC recommended group had more comorbidities compared with patients in the OAC should be considered and no OAC to be considered subgroups.

Among patients with high bleeding risk for whom OAC is recommended ($n = 12\,006$), 4069 (35.5%) received the 60 mg recommended edoxaban dose, while 4918 (43.0%) patients received the 30 mg recommended dose (*Figure 2*). The proportion of patients within edoxaban dose recommendation subgroups (60 mg recommended vs. 30 mg nonrecommended and 60 mg nonrecommended vs. 30 mg recommended doses) was significantly different across regions ($P < 0.0001$ for both; *Table 2*). Additionally, patients who received the 60 mg recommended vs. 30 mg nonrecommended dose were significantly younger (mean ± SD, 75.0 ± 6.1 years vs. 76.7 ± 6.2 years), had higher body weight (78.3 ± 12.3 kg vs. 76.8 ± 13.0 kg), and higher CrCl (71.2 ± 16.1 mL/min vs. 64.7 ± 13.4 mL/min; $P < 0.0001$ for all). Compared with patients who received the 60 mg nonrecommended dose, those who received the 30 mg recommended dose were significantly older (79.9 ± 6.9 years vs. 77.4 ± 6.8 years), had a lower body weight (58.7 ± 12.6 kg vs. 65.9 ± 11.4 kg), and lower CrCl (45.4 ± 13.9 mL/min vs. 52.6 ± 16.0 mL/min; $P < 0.0001$ for all). Lastly, a number of clinical characteristics were significantly different between patients who received the 60 mg recommended vs. 30 mg nonrecommended dose, with the exception of hypertension (*Table 2*). Similarly, there were significant differences in clinical characteristics between patients who received the 60 mg nonrecommended vs. the 30 mg recommended dose, with the exception of hypertension and diabetes.

Clinical outcomes

No oral anticoagulant to be considered

Overall, the rate of ischaemic stroke (0.21%/year), major bleeding (0.41%/year), major GI bleeding (0.1%/year), all-cause mortality (0.51%/year), and cardiovascular (CV) mortality (0.21%/year) were generally low with edoxaban treatment in patients in the no OAC to be considered group, and there were no events of fatal bleeding and fatal ICH in these patients (*Figure 3*). The annualized rate of the net clinical outcome [composite of stroke, SEE, major bleeding (ISTH), or death] was low at 1.14% (95% CI, 0.63–2.05).

Oral anticoagulant should be considered

In the patients for whom OAC should be considered, clinical event rates with edoxaban treatment were similar in patients with high vs. low bleeding risk, with the exception of major bleeding and all-cause mortality. Patients who had high bleeding risk had a numerically higher rate of major bleeding (0.55%/year), but numerically lower rate of all-cause mortality (0.55%/year) compared with those who had low bleeding risk (major bleeding, 0.31%/year; all-cause mortality, 1.03%/year; *Figure 3*). Overall, the annualized rate of the net clinical outcome was 1.61% (1.28–2.02); those with high bleeding risk had a rate of 1.37% (95% CI, 0.57–3.30), whereas those with low bleeding risk had a rate of 1.63% (95% CI, 1.29–2.07).

Oral anticoagulant recommended

In the OAC recommended category, those with high vs. low bleeding risk had numerically higher event rates of ischaemic stroke (0.89%/year vs. 0.47%/year), major bleeding (1.46%/year vs. 0.79%/year), ICH (0.35%/year vs. 0.27%/year), major GI bleeding (0.60%/year vs. 0.19%/year), all-cause mortality (4.07%/year vs. 2.74%/year), and CV mortality (1.08%/year vs. 0.81%/year; *Figure 3*). Overall, the annualized rate of the net clinical outcome was 5.3% (95% CI, 5.04–5.56). In patients with low bleeding risk, the annualized rate of the net clinical outcomes was 3.75% (95% CI, 3.36–4.17), compared with 5.95% (95% CI, 5.63–6.30) in those with high bleeding risk.

For patients in whom OAC was recommended with high bleeding risk, clinical event rates were compared between those without dose reduction criteria who received 60 mg recommended vs. 30 mg nonrecommended edoxaban dosing and those with ≥ 1 dose reduction criteria who received 60 mg nonrecommended vs. 30 mg recommended dosing (*Figure 4*). Those who received the 60 mg recommended vs. 30 mg nonrecommended dose had significantly lower event rates of all-cause mortality (2.67%/year vs. 3.53%/year; unadjusted HR, 0.75; 95% CI, 0.58–0.99; $P = 0.04$) and significantly higher event

Table 2 Baseline demographics and clinical characteristics for patients with oral anticoagulation recommended and high bleeding risk by dose recommendation

	OAC recommended and high bleeding risk[a] (*N* = 12 006)					
	60 mg recommended (*n* = 4069)	30 mg nonrecommended (*n* = 1135)	*P* value	60 mg nonrecommended (*n* = 1164)	30 mg recommended (*n* = 4918)	*P* value[b]
Region, % (*n*)[c]			**<0.0001**			**<0.0001**
Europe (*n* = 13 164)	72.7 (2958)	45.9 (521)		64.1 (746)	31.3 (1539)	
Korea, Taiwan, Thailand, and Hong Kong (*n* = 3299)	10.9 (442)	22.0 (250)		19.5 (227)	15.3 (751)	
Japan (*n* = 10 342)	16.4 (669)	32.1 (364)		16.4 (191)	53.4 (2628)	
Age, years, mean ± SD[d]	75.0 ± 6.1	76.7 ± 6.2	**<0.0001**	77.4 ± 6.8	79.9 ± 6.9	**<0.0001**
Male, % (*n*)	68.3 (2780)	67.8 (770)	0.8	45.2 (526)	41.8 (2054)	**0.03**
Body weight, kg, mean ± SD[d]	78.3 ± 12.3	76.8 ± 13.0	**<0.0001**	65.9 ± 11.4	58.7 ± 12.6	**<0.0001**
BMI, kg/m^2, mean ± SD	27.6 ± 3.9	27.9 ± 4.3	0.1	24.8 ± 3.6	23.5 ± 3.9	**<0.0001**
CrCl, mL/min, mean ± SD[d]	71.2 ± 16.1	64.7 ± 13.4	**<0.0001**	52.6 ± 16.0	45.4 ± 13.9	**<0.0001**
Serum creatinine, mg/dL, mean ± SD	0.97 ± 0.19	1.02 ± 0.25	**<0.0001**	1.06 ± 0.32	1.07 ± 0.42	**0.02**
Clinical characteristics, % (*n*)						
Hypertension	94.8 (3857)	95.4 (1083)	0.4	93.3 (1086)	92.6 (4553)	0.4
Diabetes	26.6 (1083)	30.3 (344)	**0.01**	25.5 (297)	28.0 (1376)	0.09
Dys-/hyperlipidaemia	50.5 (2053)	47.0 (533)	**0.04**	53.1 (618)	43.5 (2139)	**<0.0001**
Heart failure[e]	16.4 (668)	22.3 (253)	**<0.0001**	16.8 (195)	29.1 (1430)	**<0.0001**
Prior ischaemic stroke[d]	14.2 (577)	11.9 (135)	**0.05**	14.4 (168)	19.0 (932).	**0.0003**
Prior major bleeding[d]	1.5 (62)	2.5 (28)	**0.03**	1.6 (19)	3.2 (156)	**0.005**

BMI, body mass index; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥ 75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65-74, and Sex category (female); CrCl, creatinine clearance; ESC, European Society of Cardiology; MI, myocardial infarction; modified HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Elderly, Drugs/alcohol concomitantly; OAC, oral anticoagulant; SD, standard deviation.

[a]These subgroups were based on ESC guidelines. OAC was recommended if CHA_2DS_2-VASc ≥ 2 (male) or ≥ 3 (female). Bleeding risk was considered to be high if modified HAS-BLED ≥ 3.

[b]Bolded *P* values are significant.

[c]Percentages were based on column header *N* values (i.e. missing and unknown patients were not excluded from the denominator when calculating the percentages).

[d]Baseline differences including age, dose adjustment criteria (i.e. weight, CrCl, and use of P-glycoprotein inhibitors), prior ischaemic stroke, and prior major bleeding were included in an adjusted analysis of outcomes comparing recommended and nonrecommended dosing groups.

[e]A medical history of heart failure required the fulfilment of one of the following criteria: documented congestive heart failure, or if congestive heart failure 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-MI, valve replacement, or hypertension treated with ≥ 3 drugs.

rates of ICH (0.48%/year vs. 0.10%/year; unadjusted HR, 4.87; 95% CI, 1.17–20.21; *P* = 0.03). Patients who received the 60 mg recommended vs. 30 mg nonrecommended dose had numerically lower event rates of CV mortality and numerically higher event rates of major bleeding and fatal bleeding; however, these data were not significantly different between cohorts (*Figure 4A*). After adjusting for age, dose reduction criteria (weight, CrCl, use of P-glycoprotein inhibitors), prior ischaemic stroke, and prior major bleeding, ICH was the only clinical event that was significantly higher in patients who received the 60 mg recommended vs. the 30 mg nonrecommended dose (HR, 5.44; 95% CI, 1.30–22.75; *P* = 0.02). The net clinical outcome did not differ significantly between patients who received the 60 mg recommended vs. the 30 mg nonrecommended dose, with or without adjustment.

Patients who received the 60 mg nonrecommended vs. 30 mg recommended edoxaban dose had significantly lower rates of all-cause mortality (3.75%/year vs. 5.53%/year; unadjusted HR, 0.68; 95% CI, 0.53–0.86; *P* = 0.002; *Figure 4B*). The incidence of the net clinical outcome was also significantly lower in patients who received the 60 mg nonrecommended vs. 30 mg recommended dose (5.62%/year vs. 7.69%/year; unadjusted HR, 0.73; 95% CI, 0.60–0.90; *P* = 0.002). Additionally, those who received the 60 mg nonrecommended vs. 30 mg recommended dose had numerically lower rates of ischaemic stroke and major bleeding. These data were not significantly different between cohorts. Additionally, there were no significant differences in adjusted clinical outcomes for patients receiving the 60 mg nonrecommended vs. 30 mg recommended dose.

Discussion

In this analysis of the Global ETNA-AF programme, 97.3% (i.e. those in the OAC should be considered and OAC recommended subgroups) of patients treated with edoxaban in routine clinical practice were treated according to the 2020 ESC-AF guidelines, which are consistent with the approved edoxaban product labels. Most patients (91.8%) in the OAC should be considered group had low bleeding risk, whereas most patients (71.0%) in the OAC recommended group had a high risk of bleeding. For patients in whom OAC should be considered, the rates of bleeding events were low across both the high bleeding risk group and the low bleeding risk group. In patients in the OAC recommended and high bleeding risk groups, clinical events were generally low and similar across dosing groups, indicating the recommended dose was beneficial even in patients with a high bleeding risk.

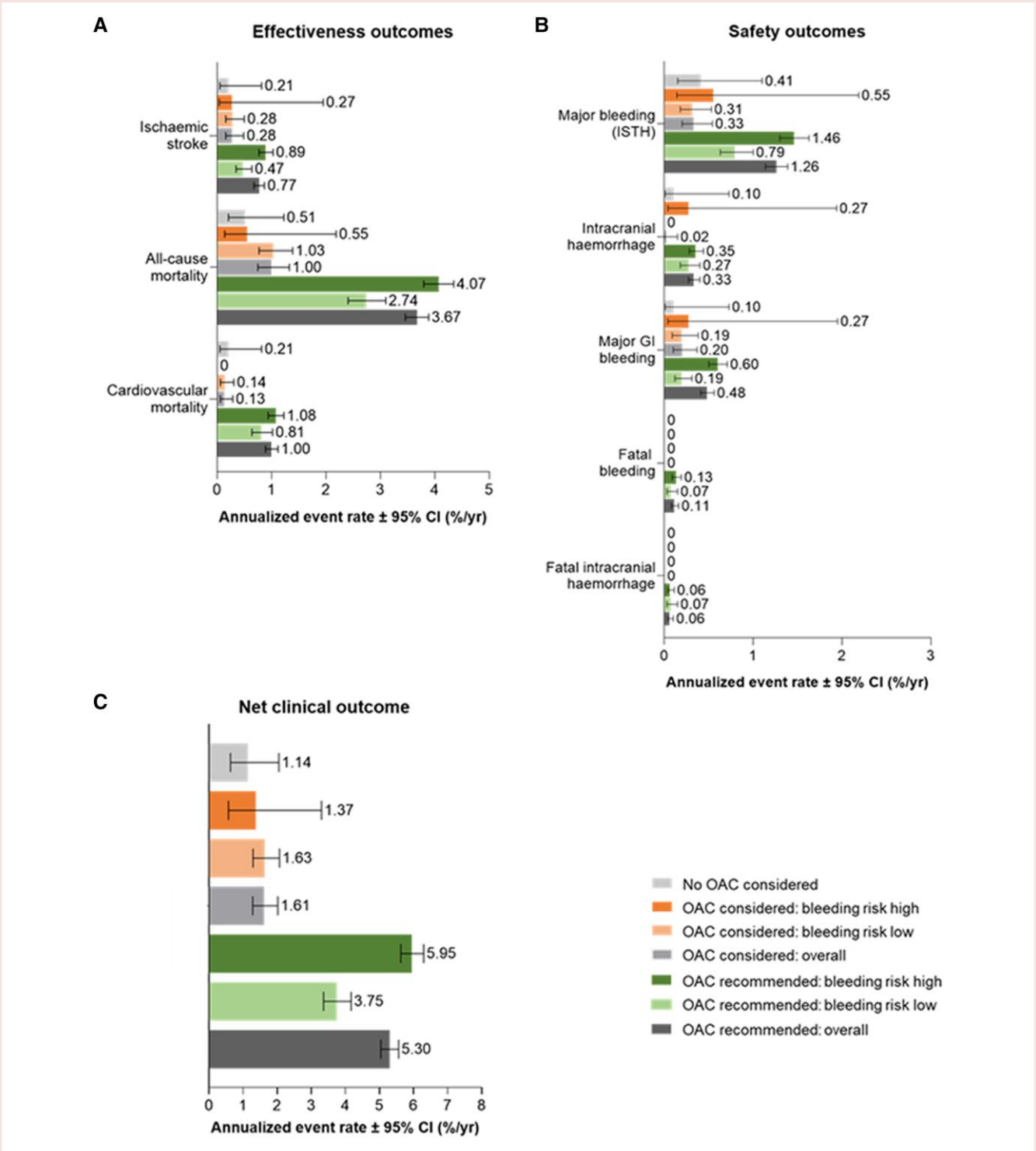


Figure 3 Annualized event rates for effectiveness (*A*), safety (*B*), and net clinical (*C*) outcomes in patients with AF on edoxaban overall and stratified by bleeding risk and OAC recommendation subgroups. Patient subgroups were based on the 2020 ESC-AF guidelines. OAC should be considered if CHA_2DS_2-VASc = 1 (male) or 2 (female). OAC was recommended if CHA_2DS_2-VASc ≥ 2 (male) or ≥ 3 (female). No OAC was considered if CHA_2DS_2-VASc = 0 (male) or < 2 (female). Bleeding risk was considered to be low if modified HAS-BLED < 3 and was considered to be high if moderated HAS-BLED ≥ 3. Net clinical outcome is defined as a composite of stoke (ischaemic or haemorrhagic), SEE, major bleeding (ISTH), or death. AF, atrial fibrillation; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥ 75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex category (female); CI, confidence interval; ESC, European Society of Cardiology; GI, gastrointestinal; ISTH, International Society on Thrombosis and Haemostasis; modified HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Elderly, Drugs/alcohol concomitantly; OAC, oral anticoagulant; SEE, systemic embolism event.

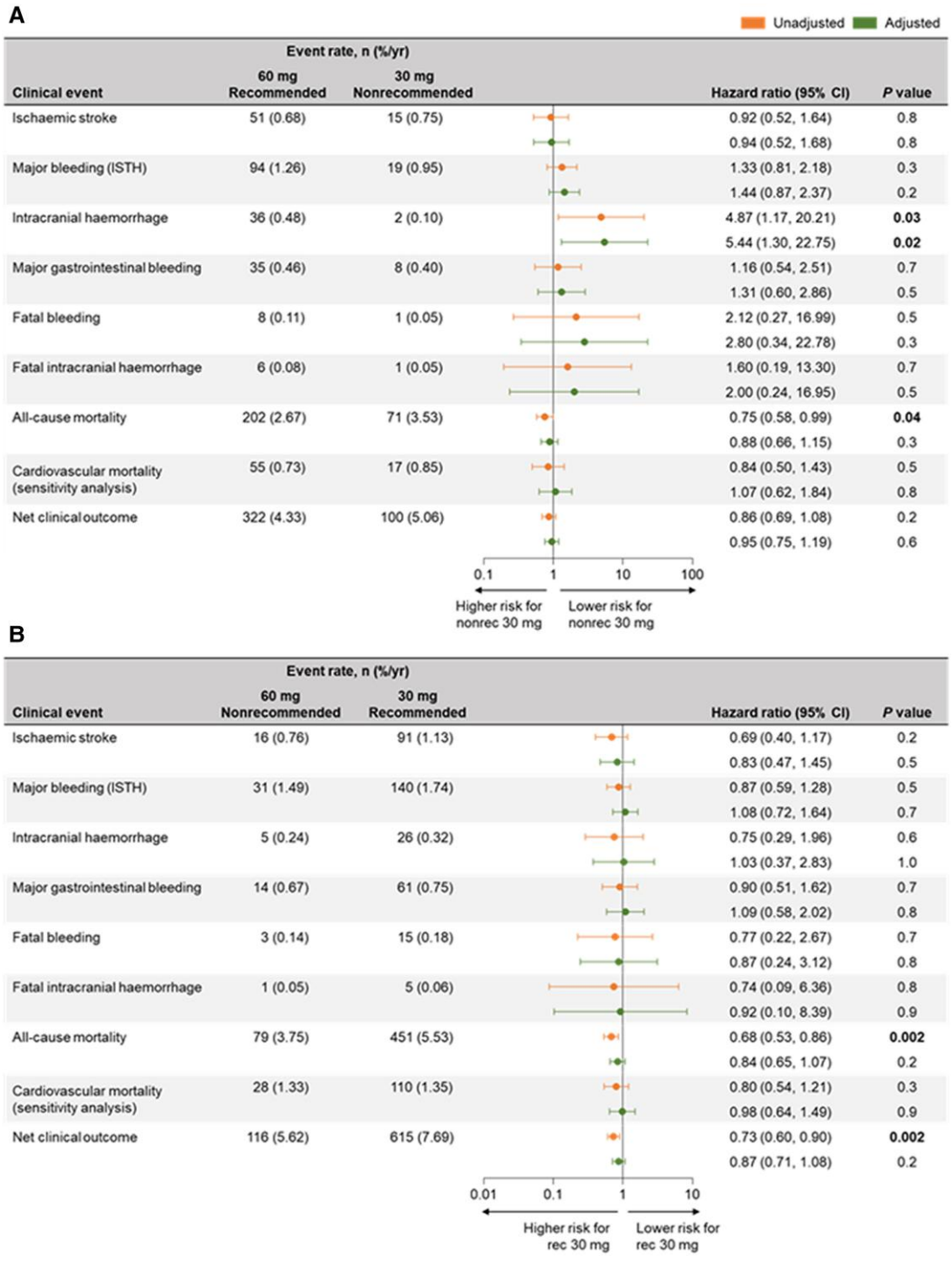


Figure 4 Unadjusted and adjusted hazard ratios (95% CIs) for clinical events in patients who were in the OAC recommended and high bleeding risk groups stratified by (*A*) 60 mg recommended vs. 30 mg nonrecommended and (*B*) 60 mg nonrecommended vs. 30 mg recommended dose subgroups. These subgroups were based on the 2020 ESC-AF guidelines. OAC was recommended if CHA_2DS_2-VASc ≥ 2 (male) or ≥ 3 (female). Bleeding risk was considered high if modified HAS-BLED ≥ 3. Net clinical outcome is defined as a composite of stoke (ischaemic or haemorrhagic), SEE, major bleeding (ISTH), or death. Baseline variables included in the adjusted HRs were dose reduction criteria (i.e., CrCl, weight, and use of P-glycoprotein inhibitors), age, prior ischaemic stroke, and prior major bleeding. Net clinical outcome is defined as a composite of stoke (ischaemic or haemorrhagic), SEE, major bleeding (ISTH), or death. AF, atrial fibrillation; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥ 75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex category (female); CI, confidence interval; CrCl, creatinine clearance; ESC, European Society of Cardiology; ISTH, International Society on Thrombosis and Haemostasis; modified HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Elderly, Drugs/alcohol concomitantly; nonrec, nonrecommended; OAC, oral anticoagulant; rec, recommended; SEE, systemic embolism event.

The goal of management guidelines in patients with AF is to enhance patient outcomes and minimize healthcare expenses, yet adherence to guidelines remains moderate on a global scale.[1,22] Evidence suggests that physicians adopting DOACs as first-line therapy have contributed to an upsurge in guideline-aligned stroke prevention measures.[23,24] This aspect has been previously investigated within both European and Asian populations. In an analysis of 2535 elderly (≥ 65 years) patients with AF from the REgistro POliterapie SIMI (REPOSI) study, 40.9% of patients were treated according to the 2012 ESC-AF guidelines, whereas 6.8% of patients were overdosed and 52.3% were underdosed after a 1-year observational period.[23] Moreover, results from the All Nippon AF In the Elderly (ANAFIE) registry demonstrate that compared with warfarin, DOACs were used less often in the high bleeding risk group than the low bleeding risk group.[24] Further research may be needed to close the gap among healthcare providers that may prevent them from following guideline recommendations when it comes to prescribing DOACs in patients with high stroke or bleeding risk.

Assessment of bleeding risk is clinically important in patients with AF and is needed to determine anticoagulation strategies. In defining high bleeding risk, the modified HAS-BLED score was utilized, which included hypertension, abnormal renal/liver function, history of stroke, history of bleeding or predisposition, elderly age, and concomitant use of drugs/alcohol. Bleeding risk was high if the modified HAS-BLED score was ≥ 3. The distribution of high bleeding risk characteristics varied across the three groups according to OAC recommendation. Specifically, patients in the OAC recommended group had a higher prevalence of hypertension, abnormal renal function, and prior stroke compared with those in the OAC should be considered and no OAC to be considered groups. This distribution underscores the importance of individualized assessment in guiding OAC therapy decisions.

Patients for whom no oral anticoagulant was considered

Patients in the no OAC to be considered group were younger, had higher mean CrCl, and had fewer comorbidities compared with those in the OAC should be considered and OAC recommended groups. These patients had no prior history of ischaemic stroke or major bleeding and had low incidences of ischaemic events and fatal bleeding. Previously, an observational study that investigated the prescription rate of OACs and described incident bleeding events in patients with a low risk of stroke (CHA_2DS_2-VASc score of 0 for males and 1 for females) found that the incidence of bleeding was slightly higher in OAC users vs. those who didn't use OAC (2.6% vs. 1.8%).[25] These results highlight the need for continued research in this low-risk patient population to bolster the literature in an effort to mitigate overuse of prescription OAC currently seen in this patient population.

Patients for whom oral anticoagulant should be considered

In this study of patients with AF, 12.5% of patients were at low risk for stroke, as assessed by a CHA_2DS_2-VASc score of 1 for males and 2 for females. According to the 2020 ESC-AF guidelines, individualized treatment with OAC should be based on evaluating the net clinical benefit and weighing the potential stroke risk reduction against the risk of bleeding associated with OAC therapy compared with no treatment.[1] The literature on OAC therapy for low-risk patients is controversial. A study that analysed 456 960 patients with AF in Sweden demonstrated that OAC did not lower the risk of ischaemic stroke (sub hazard ratio, 0.92; 95% CI, 0.78–1.09); however, a net benefit was observed in patients with a CHA_2DS_2-VASc score of < 1.[26] In the small group that received a DOAC, there were no ICHs and the composite endpoint of all forms of brain injury (stroke, brain haemorrhage, and dementia) was lower (HR, 0.42; 95% CI, 0.19–0.93) compared with VKA (HR, 0.74; 95% CI, 0.55–1.0).[26] In the ENGAGE AF-TIMI 48 clinical trial, the primary edoxaban publication ($n = 21\,105$), the annualized rate for the net clinical outcome [composite of stroke, SEE, major bleeding (ISTH), or death] in patients who received high-dose edoxaban (60 mg) was 7.26%, 6.79% in those who received low-dose edoxaban (30 mg), and 8.11% in those who received VKA.[8] In this analysis of real-world findings, the annualized rate for the net clinical outcome was low in the overall OAC should be considered subgroup (1.61%). The results from the current study demonstrate that the safety and effectiveness of edoxaban shown in the clinical trial population are generalizable to a lower risk real-world population of patients.

More recently, a multicentre, European observational study of 59 076 patients with AF showed a positive net clinical benefit compared with no treatment or VKA treatment in patients who were at low risk of stroke.[15] Comparing DOAC use with no treatment, the rate of ischaemic stroke was lower (HR, 0.72; 95% CI, 0.55–0.94), and the rate for ICH was not higher (HR, 0.84; 95% CI, 0.54–1.30).[15] These observational data suggest that DOAC treatment may be associated with a positive clinical benefit compared with no treatment or VKA in patients for whom OAC should be considered. In this study, the rate of ischaemic stroke was low in those that were in the OAC should be considered category receiving edoxaban: 0.28%/year for those with low bleeding risk and 0.27%/year in those with high bleeding risk. Furthermore, the rates of net clinical outcomes with edoxaban were numerically higher in patients with low bleeding risk group compared with those in the high bleeding risk (1.63% vs. 1.37%, respectively). In comparison to this analysis, a systematic review and meta-analysis assessing the rate of ischaemic stroke in patients with AF receiving OAC with CHA_2DS_2-VASc scores of 0 and 2 found that the annual risk of ischaemic stroke was 0.50%, 0.87%, and 1.93% for patients with CHA_2DS_2-VASc scores of 0, 1, and 2, respectively.[27] Therefore, consistent with previous findings, edoxaban had a favourable net clinical outcome and was beneficial in patients in this study with a CHA_2DS_2-VASc score of 1.

Regardless of bleeding risk, rates of major bleeding, fatal bleeding, major GI bleeding, and ICH were low in patients receiving edoxaban. The annualized rate of major bleeding events was similarly low in both bleeding risk groups (low risk, 0.31%; high risk, 0.55%). These results suggest that patient bleeding risk did not significantly correlate with adverse clinical outcomes in this cohort of patients with AF on edoxaban; however, this finding must be interpreted with caution due to the small number of events and patients, as well as the variability in dosing and individual risk factors. Notably, within this low-risk stroke population, the majority belonged to the low bleeding risk group, likely because the risk of stroke and bleeding are generally associated with each other, and CHA_2DS_2-VASc and HAS-BLED have common risk factors like hypertension, history of stroke, and age.[28,29]

Patients for whom oral anticoagulant was recommended

The majority of patients in the OAC recommended group had a high bleeding risk (71.0%). Within the OAC recommended and high bleeding risk groups, 35.5% of patients received the recommended 60 mg dose and 43.0% received the recommended 30 mg edoxaban dose. Of note, some patients in this analysis had missing information for dose reduction criteria and could not be assigned to a recommended or nonrecommended dose. The randomized, controlled phase 3 ENGAGE AF-TIMI 48 trial comparing edoxaban 60 and 30 mg dosing regimens with warfarin showed that edoxaban reduced the risk of major bleeding regardless of baseline CHA_2DS_2-VASc score (HR, 0.76–0.85, P-interaction = 0.96).[30] While the HR for ICH in patients treated with warfarin increased with increasing CHA_2DS_2-VASc score (HR, 1.25; 95% CI, 1.13–1.38 per point increment, $P < 0.001$), no such increase was seen in those treated with edoxaban (HR, 1.03; 95% CI,

0.87–1.22, $P = 0.7$).[30] This is consistent with the current analysis where the risk of major bleeding events was low across dosing groups, regardless of bleeding risk and CHA_2DS_2-VASc score.

Literature shows that OAC under- or overdosing, or deviating from OAC management guideline recommendations, was found to be associated with increased risk of adverse outcomes, especially ischaemic stroke and death.[31] Several studies have consistently demonstrated that patients receiving treatment aligned with guideline recommendations exhibit improved outcomes compared with those whose treatment deviates from these standards.[32,33] In the current analysis, of the patients without edoxaban dose reduction criteria in the OAC recommended and high bleeding risk groups, those who were 'underdosed' (received the 30 mg nonrecommended dose) showed similar rates of ischaemic stroke with those receiving the 60 mg recommended dose (0.75%/year vs. 0.68%/year). In these 'underdosed' patients in the OAC recommended and high bleeding risk groups, no significant differences in bleeding rates were observed, but a significantly lower risk of ICH was observed. Among patients with ≥ 1 dose reduction criteria, those who were 'overdosed' (received a 60 mg nonrecommended dose) did not have a higher rate of major bleeding events compared with those receiving the 30 mg recommended dose (1.49%/year vs. 1.74%/year). These findings align with a previous analysis of the Global ETNA-AF programme in which edoxaban underdosing was not associated with better effectiveness outcomes and overdosed patients did not have a higher rate of major bleeding.[8] Deviations from recommended dosing could be attributed to several factors, including clinicians' concerns about bleeding risk in high-risk populations (i.e. in older patients or those with multiple comorbidities), even when the standard dose is indicated.[34] Additionally, variations in clinician experience, regional differences in clinical practice, and patient preferences may also play a role. The findings of the current analysis highlight the ongoing challenges in adhering strictly to recommended dosing and underscore the need for further education and strategies to support guideline-concordant prescribing to optimize patient outcomes. More detailed exploration of these factors in future analyses could provide valuable insights into improving guideline adherence in routine clinical practice.

Limitations

There are several limitations to this study. Due to the nature of the study design of ETNA-AF, only patients receiving edoxaban at baseline were included. As the study did not have a comparator arm, no conclusions can be drawn about the effectiveness or safety of edoxaban relative to VKAs or other DOACs. Additionally, the Global ETNA-AF programme only included patients who were prescribed edoxaban at baseline and did not include data from patients who were prescribed other OACs. Therefore, this study does not fully describe concordance with the 2020 ESC-AF guideline recommendations for anticoagulant use across all patients with AF. Lastly, this is a 2-year analysis of data; therefore, a longer follow-up period may be needed on the long-term safety and effectiveness of edoxaban.

Conclusion

In this analysis of patients with AF in the Global ETNA-AF programme, 97.3% of patients (i.e. those in the OAC should be considered and OAC recommended subgroups) received edoxaban in routine clinical practice according to the 2020 ESC-AF guidelines, which are consistent with the approved edoxaban labels. Overall, clinical event rates, including bleeding events (fatal, ICH, major, and major GI), and the incidence of ischaemic stroke were consistently low, regardless of patient bleeding risk. For patients in whom OAC should be considered, the low rates of ischaemic stroke and bleeding events could help clinicians make individualized decisions regarding anticoagulation in this population.

Lead author biography

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Data availability

Data will not be made available from this analysis because the study is still ongoing.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

Acknowledgements

The authors thank Young-Hoon Kim, MD, for their contributions to the study. Medical writing and editorial support were provided by Kimberly Dent-Ferguson, MBS, MPH, of Red Nucleus, and funded by Daiichi Sankyo.

Funding

This study was funded by Daiichi Sankyo.

Conflict of interest: D.M. was sponsored for the ESC Congress 2023 Meeting for abstract presentation from Daiichi Sankyo. L.D. declares a research grant from Farapulse and was supported by the Research Promotion Fund of the Faculty of Medicine (Hamburg, 'Clinician Scientist Program'). J.A.G.d.S. is an employee of Daiichi Sankyo Europe GmbH. C.C. and M.U. are employees of Daiichi Sankyo. P.K. declares research support for basic, translational, and clinical research projects from the British Heart Foundation, the European Union, the German Center for Cardiovascular Research, and the Medical Research Council (UK); and funding and honoraria from several drug and device companies active in atrial fibrillation in the past, but not in the last 3 years. Y.K. declares honoraria from Boehringer Ingelheim, Bristol Myers Squibb/Pfizer, and Daiichi Sankyo. L.P. declares to have received funding for the statistics of this report from Daiichi Sankyo. C.-C.W. declares honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Novartis, and Pfizer. T.Y. declares fees, honoraria, and research funding from Bayer, Bristol Myers Squibb, Daiichi Sankyo, Ono Pharmaceutical, and Toa Eiyo. R.D.C. declares fees, honoraria, and research funding from Amgen, Bayer, Boehringer Ingelheim, Bristol Myers Squibb/Pfizer, Daiichi Sankyo, Menarini, Merck, Novartis, Portola, Roche, and Sanofi-Aventis.

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