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ORIGINAL ARTICLE
Stroke

Prescribing Patterns and Outcomes of Edoxaban in Atrial Fibrillation Patients From Asia

— One-Year Data From the Global ETNA-AF Program —

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Background: This study reports prescribing patterns and the 1-year effectiveness and safety of edoxaban in an Asian cohort of Edoxaban Treatment in routiNe clinical prActice (ETNA)-Atrial Fibrillation (AF) patients.

Methods and Results: The Global ETNA-AF program integrates prospective, observational, noninterventional regional studies, collecting data on characteristics and clinical outcomes of patients with AF receiving edoxaban for stroke prevention. Baseline characteristics, medical history, and 1-year clinical event rates were assessed in patients from South Korea, Taiwan, Hong Kong, and Thailand. Clinically relevant events assessed at 12 months included all-cause death, cardiovascular death, ischemic and hemorrhagic stroke, systemic embolic events (SEEs), bleeding, and net clinical outcome (NCO). Overall, 3,359 patients treated with edoxaban 60 or 30 mg once daily completed 1-year follow-up; 70.9% of patients received recommended dosing according to local labels. Baseline mean±standard deviation age was 71.7±9.6 years, CHA_2DS_2-VASc score was 3.1±1.5, and modified HAS-BLED score was 2.3±1.1. Mean age and sex were similar across countries/regions. The 1-year event rate for all-cause death was 1.8%; major bleeding, 1.3%; ischemic stroke, 1.1%; cardiovascular mortality, 0.7%; hemorrhagic stroke, 0.3%; SEEs, 0%; and NCO, 4.1%; with differences observed between countries/regions and dosing groups.

Conclusions: Most Asian patients with AF were prescribed recommended edoxaban dosing in routine care settings. At 1-year follow-up, this analysis supports the effectiveness and safety of edoxaban in these patients.

Key Words: Asia; Atrial fibrillation; Dosing; Edoxaban; Oral anticoagulation

Nonvitamin K antagonist oral anticoagulants (NOACs) are the standard of care for stroke prevention in patients with atrial fibrillation (AF).[1–6] In contrast to physicians in non-Asian countries, physicians in Asian countries more frequently prescribe a reduced dose of NOACs,[7,8] which may be partly attributed to the lower mean body weight and higher risk of bleeding observed in Asian patients with AF.[9–12] Globally, the recommended dose of the NOAC edoxaban is reduced to 30 mg once daily (QD) in patients with creatinine clearance (CrCl) 15–50 mL/min, body weight ≤60 kg, or concomitant use of potent P-glycoprotein inhibitors. For Asian patients, the latest Asia Pacific Heart Rhythm Society guidelines recommend the use of standard-dose edoxaban (60 mg

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Table 1. Demographics and Baseline Characteristics by Country/Region

	Total (N=3,359)	South Korea (n=1,887)	Taiwan (n=983)	Hong Kong (n=190)	Thailand (n=299)
Sex, male, n (%)	1,996 (59.4)	1,145 (60.7)	583 (59.3)	112 (58.9)	156 (52.2)
Age, years, mean±SD*	71.7±9.6	70.9±9.0	73.0±10.1	72.9±10.9	71.5±10.3
Weight, kg, mean±SD	65.9±12.4	65.8±11.7	66.3±12.6	64.3±13.3	66.5±15.3
Body mass index, kg/m^2, mean±SD**	25.0±3.8	24.8±3.5	25.3±3.9	24.8±4.1	25.4±4.6
eGFR, mL/min/1.73 m^2, mean±SD*	62.6±23.8	65.8±23.0	59.1±24.3	55.3±23.3	60.1±24.2
CHA_2DS_2-VASc, mean±SD*	3.1±1.5	3.0±1.4	3.1±1.4	3.4±1.7	3.5±1.6
Modified HAS-BLED, mean±SD	2.3±1.1	2.2±1.0	2.3±1.1	2.3±1.1	2.5±1.1
Type of AF, n (%)					
Paroxysmal*	1,509 (45.0)	658 (34.9)	607 (62.0)	85 (44.7)	159 (53.2)
Persistent*	792 (23.6)	542 (28.7)	132 (13.5)	73 (38.4)	45 (15.1)
Long-standing persistent*	423 (12.6)	319 (16.9)	93 (9.5)	6 (3.2)	5 (1.7)
Permanent*	631 (18.8)	368 (19.5)	147 (15.0)	26 (13.7)	90 (30.1)
Diabetes mellitus, n (%)	999 (29.7)	534 (28.3)	305 (31.0)	67 (35.3)	93 (31.1)
Hypertension, n (%)*	2,427 (72.3)	1,335 (70.7)	706 (71.8)	135 (71.1)	251 (83.9)
Heart failure, n (%)*,†	418 (12.4)	182 (9.6)	154 (15.7)	21 (11.1)	61 (20.4)
COPD, n (%)**	161 (4.8)	74 (3.9)	64 (6.5)	6 (3.2)	17 (5.7)
Peripheral artery disease, n (%)**	25 (0.7)	6 (0.3)	15 (1.5)	2 (1.1)	2 (0.7)
History of ischemic stroke, n (%)*	507 (15.1)	326 (17.3)	84 (8.5)	42 (22.1)	55 (18.4)
History of major or CRNM bleeding, n (%)*	106 (3.2)	43 (2.3)	32 (3.3)	13 (6.8)	18 (6.0)
History of major bleeding, n (%)	76 (2.3)	37 (2.0)	20 (2.0)	6 (3.2)	13 (4.3)

*P value for difference <0.0001, **P value for difference <0.05. †A medical history of heart failure was determined if the patient met one of the following criteria: documented congestive heart failure (CHF) or, if CHF was not reported, documentation of ischemic cardiomyopathy; ejection fraction <40%; frequent dyspnea (≥1/day) without chronic obstructive pulmonary disease and with documented severe valvular heart disease, coronary artery disease post-myocardial infarction, valve replacement, or hypertension treated with ≥3 antihypertensive drugs. AF, atrial fibrillation; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age, Diabetes, Prior Stroke/Transient Ischemic Attack, Vascular disease, and Sex category; COPD, chronic obstructive pulmonary disease; CRNM, clinically relevant nonmajor; eGFR, estimated glomerular filtration rate; HAS-BLED, Hypertension, Abnormal renal and liver function, Stroke, Bleeding history or disposition, Labile international normalized ratio, Elderly, Drugs or alcohol; SD, standard deviation.

QD) for stroke prevention unless the local label recommends the reduced-dose regimen.[13–15] Despite these recommendations, studies report that up to 70% of patients receive a nonrecommended NOAC dose in routine care, with a larger proportion of those patients being under- rather than overdosed.[8,16,17] Although nonrecommended dosing of NOACs is common in routine clinical practice, its effect on treatment effects and clinical event risk is unclear.

The prospective, observational Global Edoxaban Treatment in routiNe clinical prActice (ETNA)-AF program assesses the effectiveness and safety of edoxaban usage in patients with AF in routine clinical practice.[18] Globally, 1-year event rates of hemorrhagic stroke, intracranial hemorrhage (ICH), and other major bleeding events in these patients are low.[19] However, as Asian patients on oral anticoagulation drugs may be at higher bleeding risk than patients from non-Asian countries,[7,8] data from Asian populations are needed. In this analysis of the ETNA-AF program, we report the 1-year results on the effectiveness and safety of edoxaban and the frequency of nonrecommended dosing in patients from South Korea, Taiwan, Hong Kong, and Thailand.

Methods

Design

The study design of the Global ETNA-AF program has been described in detail previously.[18] Briefly, the Global ETNA-AF program integrates prospective, observational, noninterventional, and regional studies from Europe, Japan, and other Asian countries/regions (South Korea/Taiwan [NCT02951039], Hong Kong [NCT03247582], and Thailand [NCT03247569]).[18,20,21] The ETNA-AF study protocols received the appropriate review board approvals.[19,20] The program complied with the latest version of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practices standards.[22] All study participants provided written informed consent before enrollment.

The current analyses include 1-year data from patients who were separated post hoc into 2 cohorts — those meeting and those not meeting dose-reduction criteria for edoxaban. Comparisons were made between those meeting the dose-reduction criteria who received the nonrecommended 60-mg dose vs. the recommended 30-mg dose and between patients not meeting dose-reduction criteria who received the recommended edoxaban 60-mg dose vs. the nonrecommended 30-mg dose.

Inclusion and Exclusion Criteria

Full inclusion and exclusion criteria for the Global ETNA-AF program have been described previously.[18] Adult patients treated with edoxaban for stroke prevention in AF according to the local labels were eligible to participate. Patients were excluded if they were unable to provide informed consent or if they were simultaneously participating in any interventional study.

Table 2. Demographics and Baseline Characteristics by Edoxaban Dose

	Patients with no dose-reduction criteria met		Patients who met ≥1 dose-reduction criterion	
	Recommended 60 mg (n=1,293)	Nonrecommended 30 mg (n=601)	Recommended 30 mg (n=1,088)	Nonrecommended 60 mg (n=377)
Sex, male, n (%)	1,000 (77.3)	388 (64.6)	437 (40.2)	171 (45.4)
Age, years, mean±SD	67.0±8.9	71.4±8.9	77.3±8.0	71.8±8.9
Weight, kg, mean±SD	73.9±9.8	72.4±9.1	57.1±9.8	58.3±7.8
Body mass index, kg/m^2, mean±SD	26.6±3.4	26.8±3.4	23.1±3.5	23.1±2.9
eGFR, mL/min/1.73 m^2, mean±SD	78.1±19.9	72.9±20.6	44.4±16.0	54.5±16.9
CHA_2DS_2-VASc, mean±SD	2.6±1.4	3.0±1.4	3.8±1.4	3.3±1.4
HAS-BLED, mean±SD	2.1±1.0	2.3±1.0	2.5±1.1	2.2±1.1
Type of AF, n (%)				
Paroxysmal	559 (43.3)	272 (45.3)	505 (46.5)	173 (46.0)
Persistent	337 (26.1)	143 (23.8)	235 (21.6)	77 (20.5)
Long-standing persistent	150 (11.6)	109 (18.2)	120 (11.0)	44 (11.7)
Permanent	246 (19.0)	76 (12.7)	227 (20.9)	82 (21.8)
Diabetes mellitus, n (%)	399 (30.9)	182 (30.3)	319 (29.3)	99 (26.3)
Hypertension, n (%)	916 (70.8)	435 (72.4)	821 (75.5)	255 (67.6)
Heart failure, n (%)*	111 (8.6)	70 (11.6)	195 (17.9)	42 (11.1)
COPD, n (%)	52 (4.0)	23 (3.8)	64 (5.9)	22 (5.8)
Peripheral artery disease, n (%)	8 (0.6)	3 (0.5)	14 (1.3)	0
History of ischemic stroke, n (%)	198 (15.3)	76 (12.6)	151 (13.9)	82 (21.8)
History of major or CRNM bleeding, n (%)	26 (2.0)	18 (3.0)	51 (4.7)	11 (2.9)
History of major bleeding, n (%)	18 (1.4)	15 (2.5)	34 (3.1)	9 (2.4)

*A medical history of heart failure was determined if the patient met one of the following criteria: documented CHF or, if CHF was not reported, documentation of ischemic cardiomyopathy; ejection fraction <40%; frequent dyspnea (≥1/day) without chronic obstructive pulmonary disease and with documented severe valvular heart disease, coronary artery disease post-myocardial infarction, valve replacement, or hypertension treated with ≥3 antihypertensive drugs. Abbreviations as in Table 1.

Assessments and Outcomes

Patient characteristics and medical history were collected at baseline. Medical history, clinical events, and adverse drug reactions were coded using the Medical Dictionary for Regulatory Activities. Clinically relevant events, including all-cause death, cardiovascular (CV)-related death, ischemic stroke, hemorrhagic stroke, systemic embolic events (SEEs), and bleeding, were systematically evaluated over a 12-month period after enrollment. Bleeding was classified as major, clinically relevant nonmajor (CRNM), or minor in accordance with the International Society on Thrombosis and Haemostasis (ISTH).[23] The NCO, which assessed composite rates of all strokes, SEEs, myocardial infarction, major bleeding (ISTH defined), and all-cause death, was also determined at 12 months.

Statistical Analysis

Baseline characteristics are presented as frequencies and/or as summary statistics. Differences in baseline characteristics between countries/regions were evaluated with Chi-square or Kruskal-Wallis tests. Clinical outcomes are presented as summary statistics (n, mean, standard deviation [SD]) for numerical parameters and as absolute and relative frequencies for categorical variables. Wald Type 3 tests compared 1-year clinical outcomes between countries/regions. Statistical comparisons between dosing groups were not performed. Strokes and SEEs were combined in this analysis, as there was only 1 SEE reported.

Results

Patient Population and Baseline Characteristics by Country/Region

Of the 3,462 patients from whom case reports were collected, 3,359 (97%) were included in this analysis (**Supplementary Figure 1**). The baseline characteristics and medical history for all patients are shown in **Table 1**. Of the 3,359 patients included, comprising from South Korea (n=1,887), Taiwan (n=983), Hong Kong (n=190), and Thailand (n=299), 59.4% were male with a mean±SD age of 71.7±9.6 years. The proportion of male patients and mean patient age were similar across the 4 countries/regions. The mean±SD CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke/transient ischemic attack, Vascular disease, and Sex category) score was 3.1±1.5, and the modified HAS-BLED (Hypertension, Abnormal renal and liver function, Stroke, Bleeding history or disposition, Labile international normalized ratio, Elderly, Drugs or alcohol) score was 2.3±1.1; for both parameters, Thailand had the highest mean±SD scores (CHA_2DS_2-VASc: 3.5±1.6; modified HAS-BLED: 2.5±1.1) and South Korea had the lowest mean±SD scores (CHA_2DS_2-VASc: 3.0±1.4; modified HAS-BLED: 2.2±1.0). Other differences in demographic and baseline characteristics across the countries/regions include CrCl and history of heart failure, previous ischemic stroke, and prior major or CRNM bleeding (P<0.0001 for all).

Nonrecommended and Recommended Edoxaban Dosing

At baseline, 49.7% of patients (1,670/3,359) received edox-

Table 3. Clinical Outcomes at 1 Year by Country/Region

Outcomes at 1 year, n (annual incidence, %) [95% CI]	Total (N=3,359)	South Korea (n=1,887)	Taiwan (n=983)	Hong Kong (n=190)	Thailand (n=299)	P value*
All-cause death	58 (1.78) [1.38; 2.31]	16 (0.87) [0.54; 1.43]	21 (2.19) [1.43; 3.36]	10 (5.45) [2.93; 10.12]	11 (3.90) [2.16; 7.03]	<0.0001*
CV death	22 (0.68) [0.45; 1.03]	9 (0.49) [0.26; 0.94]	6 (0.63) [0.28; 1.39]	3 (1.63) [0.53; 5.07]	4 (1.42) [0.53; 3.77]	0.2
Hemorrhagic stroke	9 (0.28) [0.14; 0.53]	5 (0.27) [0.11; 0.66]	2 (0.21) [0.05; 0.84]	2 (1.09) [0.27; 4.38]	0 [0.00; NE]	0.3
Ischemic stroke	37 (1.14) [0.83; 1.58]	17 (0.93) [0.58; 1.50]	11 (1.16) [0.64; 2.09]	1 (0.55) [0.08; 3.88]	8 (2.85) [1.43; 5.70]	0.06
SEEs	1 (0.03) [0.00; 0.22]	0 [0.00; NE]	0 [0.00; NE]	0 [0.00; NE]	1 (0.36) [0.05; 2.52]	1.0
Major bleeding (ISTH)	43 (1.33) [0.99; 1.79]	18 (0.99) [0.62; 1.57]	13 (1.37) [0.79; 2.35]	7 (3.88) [1.85; 8.14]	5 (1.78) [0.74; 4.29]	0.02*
Major GI bleeding	18 (0.55) [0.35; 0.88]	5 (0.27) [0.11; 0.66]	5 (0.52) [0.22; 1.26]	3 (1.64) [0.53; 5.10]	5 (1.78) [0.74; 4.29]	0.01*
Intracranial hemorrhage	12 (0.37) [0.21; 0.65]	5 (0.27) [0.11; 0.66]	4 (0.42) [0.16; 1.11]	3 (1.65) [0.53; 5.12]	0 [0.00; NE]	0.1
Major or CRNM bleeding	70 (2.18) [1.72; 2.75]	26 (1.43) [0.97; 2.10]	23 (2.44) [1.62; 3.66]	11 (6.23) [3.45; 11.24]	10 (3.60) [1.94; 6.69]	0.0004*
Net clinical outcome†	132 (4.11) [3.47; 4.88]	50 (2.77) [2.10; 3.65]	44 (4.66) [3.46; 6.26]	15 (8.34) [5.03; 13.84]	23 (8.29) [5.51; 12.47]	<0.0001*

*Significant P values indicate a significant effect of the region (based on Wald test). †All strokes, SEEs, myocardial infarctions, major bleeding (ISTH), and all-cause death. CI, confidence interval; CRNM, clinically relevant nonmajor; CV, cardiovascular; GI, gastrointestinal; ISTH, International Society on Thrombosis and Haemostasis; NE, not estimable; SEE, systemic embolic event.

aban 60 mg, which was the nonrecommended dose for 22.6% (**Supplementary Figure 2**). Of all patients, 50.3% (1,689/3,359) received edoxaban 30 mg and this was the nonrecommended dose for 35.6% (**Supplementary Figure 2**). During the 1-year follow-up period, 348 (10.4%) patients discontinued edoxaban therapy. Overall, the majority of patients (70.9%) received the recommended dose. Of the countries/regions included in this analysis, the recommended 60-mg dose was most common in South Korea, whereas the recommended 30-mg dose was most often received by patients in Hong Kong. South Korea had the highest proportion of patients receiving nonrecommended edoxaban 30 mg, whereas Hong Kong had the lowest. The highest proportion of patients receiving nonrecommended edoxaban 60 mg occurred in Thailand, while South Korea had the lowest.

Patient Population and Baseline Clinical Characteristics by Dose

The baseline characteristics and medical history for patients grouped by edoxaban dosing are shown in **Table 2**. Of the patients who did not meet dose-reduction criteria, among those receiving the recommended 60-mg dose, 77.3% were male and had a mean±SD age of 67.0±8.9 years. Of the patients receiving the nonrecommended 30-mg dose, 64.6% were male and had a mean±SD age of 71.4±8.9 years. Compared with patients receiving the recommended edoxaban 60-mg dose, patients receiving nonrecommended edoxaban 30 mg had lower CrCl, higher CHA_2DS_2-VASc and modified HAS-BLED scores, and more frequently had a history of major or CRNM bleeding.

For patients meeting ≥1 dose-reduction criteria, among those receiving the recommended 30-mg dose, 40.2% were male with a mean±SD age of 77.3±8.0 years. Among patients receiving the nonrecommended 60-mg dose, 45.4% were male with a mean±SD age of 71.8±8.9 years (**Table 2**). Patients receiving the recommended edoxaban 30-mg dose had lower CrCl, higher CHA_2DS_2-VASc and modified HAS-BLED scores, and were less likely to have a history of ischemic stroke compared with patients receiving nonrecommended edoxaban 60 mg. Patients meeting ≥1 dose-reduction criteria had lower body weight compared with those who did not meet dose-reduction criteria.

1-Year Outcomes

Outcome event rates by country/region at the 1-year follow-up are displayed in **Table 3**. The 1-year event rates were as follows: 1.8% for all-cause death, 2.2% for major or CRNM bleeding, 1.3% for major bleeding, 1.1% for ischemic stroke, 0.7% for CV death, 0.6% for major gastrointestinal (GI) bleeding, 0.4% for ICH, 0.3% for hemorrhagic stroke, and 0% for SEEs; the NCO event rate was 4.1%. There was a significant difference in outcome event rates across countries/regions. Differences in event rates between countries/regions included all-cause death (P<0.0001), major bleeding (P=0.02), and the NCO (P<0.0001). Of the 4 countries/regions, patients in Hong Kong had the numerically highest rates of all-cause death, CV death, hemorrhagic stroke, major bleeding, ICH, and major or CRNM bleeding and had the highest NCO, while patients in Thailand had the numerically highest rates of ischemic stroke, SEEs, and major GI bleeding.

Overall, there were significant differences in all-cause death (P=0.001) and the NCO (P=0.003) across dosing groups (**Table 4**). The 1-year rates of all-cause death, CV death, hemorrhagic stroke, major bleeding, major or CRNM bleeding, ICH, and major GI bleeding were numerically higher in patients receiving the recommended edoxaban 30-mg dose than in all other dosing groups. In patients not meeting dose-reduction criteria, patients receiving nonrecommended edoxaban 30 mg had numerically higher rates of all-cause death and the NCO, and numerically lower rates of major or CRNM bleeding, than patients receiving recommended edoxaban 60 mg. For

Table 4. Clinical Outcomes at 1 Year Stratified by Edoxaban Dose

Outcomes at 1 year, n (annual incidence, %) [95% CI]	Total (N=3,359)	Patients without dose-reduction criteria		Patients with ≥1 dose-reduction criterion		P value*
		Recommended 60 mg (n=1,293)	Nonrecommended 30 mg (n=601)	Recommended 30 mg (n=1,088)	Nonrecommended 60 mg (n=377)	
All-cause death	58 (1.78) [1.38; 2.31]	9 (0.71) [0.37; 1.37]	11 (1.88) [1.04; 3.40]	32 (3.07) [2.17; 4.34]	6 (1.64) [0.74; 3.64]	0.001*
CV death	22 (0.68) [0.45; 1.03]	7 (0.55) [0.26; 1.16]	3 (0.51) [0.17; 1.59]	12 (1.15) [0.65; 2.03]	0 [0.00; NE]	0.4
Hemorrhagic stroke	9 (0.28) [0.14; 0.53]	3 (0.24) [0.08; 0.74]	2 (0.34) [0.09; 1.37]	4 (0.38) [0.14; 1.02]	0 [0.00; NE]	0.9
Ischemic stroke	37 (1.14) [0.83; 1.58]	13 (1.04) [0.60; 1.79]	8 (1.38) [0.69; 2.76]	13 (1.25) [0.73; 2.16]	3 (0.82) [0.26; 2.54]	0.8
SEEs	1 (0.03) [0.00; 0.22]	0 [0.00; NE]	0 [0.00; NE]	1 (0.10) [0.01; 0.68]	0 [0.00; NE]	1.0
Major bleeding (ISTH)	43 (1.33) [0.99; 1.79]	16 (1.28) [0.78; 2.08]	6 (1.03) [0.46; 2.30]	18 (1.74) [1.10; 2.76]	3 (0.82) [0.26; 2.55]	0.5
Major GI bleeding	18 (0.55) [0.35; 0.88]	5 (0.40) [0.17; 0.95]	1 (0.17) [0.02; 1.22]	9 (0.87) [0.45; 1.67]	3 (0.82) [0.26; 2.55]	0.3
Intracranial hemorrhage	12 (0.37) [0.21; 0.65]	4 (0.32) [0.12; 0.85]	2 (0.34) [0.09; 1.37]	6 (0.58) [0.26; 1.29]	0 [0.00; NE]	0.8
Major or CRNM bleeding	70 (2.18) [1.72; 2.75]	25 (2.00) [1.35; 2.96]	8 (1.38) [0.69; 2.76]	30 (2.93) [2.05; 4.19]	7 (1.93) [0.92; 4.05]	0.2
Net clinical outcome†	132 (4.11) [3.47; 4.88]	33 (2.65) [1.88; 3.72]	27 (4.71) [3.23; 6.86]	60 (5.85) [4.54; 7.53]	12 (3.30) [1.87; 5.80]	0.003*

*Significant P values indicate a significant effect of dose recommendation (recommended 60 mg, nonrecommended 30 mg, recommended 30 mg, nonrecommended 60 mg) based on Wald test. †All strokes, SEEs, myocardial infarctions, major bleeding (ISTH), and all-cause death. Abbreviations as in Table 3.

patients meeting dose-reduction criteria, those receiving nonrecommended edoxaban 60 mg had numerically lower rates of all-cause death, major bleeding, major or CRNM bleeding, and the NCO when compared with patients receiving the recommended edoxaban 30 mg. The 1-year bleeding event rates were <2% for all edoxaban doses assessed.[19]

Discussion

In this 1-year follow-up analysis of data from the Global ETNA-AF program, we assessed the effectiveness and safety of recommended and nonrecommended dosing of edoxaban for the treatment of AF in 3,359 patients in routine care settings from 4 Asian countries/regions. Differences were observed in patient baseline characteristics and edoxaban dosing across countries/regions. Furthermore, overall clinical outcomes, including rates of all-cause death, CV death, hemorrhagic stroke, major bleeding, major or CRNM bleeding, and the NCO, were numerically higher in patients receiving recommended edoxaban 30 vs. 60 mg (either recommended or nonrecommended dosing). Regardless of the dosing received, these data provide additional evidence for the effectiveness and safety of edoxaban in the Asian patient population with AF. This is an important confirmation of the results from the ENGAGE-AF TIMI 48 trial (NCT00781391) in routine clinical practice with a patient population that had a higher bleeding risk and lower body size and body weight than in other populations in the world.[2,7,8]

Overall, 50.3% of patients received edoxaban 30 mg and 49.7% received edoxaban 60 mg, with most patients (70.9%) receiving a recommended dose. Even though most patients received a recommended dose, this finding was comparatively lower than in the Global ETNA-AF (82.6%) and ETNA-AF-Japan (86.3%) studies.[19,24] The prospective, multicenter, observational Global ETNA-AF program included 26,823 patients from Europe, Japan, South Korea, Taiwan, Hong Kong, and Thailand; the ETNA-AF-Japan study included 11,107 Japanese patients; and the current analysis included patients from South Korea, Taiwan, Hong Kong, and Thailand (N=3,359).[18,19,24] The discrepancy between the analyses regarding the recommended dose may be due to country/regional differences in baseline demographics and clinical characteristics or in the prescribing practices of physicians. A previous analysis of patients from South Korea and Taiwan in the Global ETNA-AF study found that physicians take patient clinical characteristics (e.g., bleeding risks) into consideration when deviating from the dosing recommendation per local label.[25]

In the current analysis of patients from South Korea, Taiwan, Hong Kong, and Thailand, baseline characteristics varied between dosing groups; patients receiving the recommended edoxaban 30-mg dose had a higher mean age and a higher risk of stroke and bleeding (CHA_2DS_2-VASc and modified HAS-BLED scores) than the other dosing groups. This finding is similar to that from the CODE-AF registry, in which Asian patients with AF receiving an on-label, reduced dose of apixaban, dabigatran, edoxaban, or rivaroxaban had a higher mean age and mean HAS-BLED score than the other dosing groups.[16] Of the countries/regions analyzed, South Korea had the highest proportion of patients receiving nonrecommended edoxaban 30 mg, and Thailand had the highest proportion of patients receiving nonrecommended edoxaban 60 mg. These country/regional differences in dosing could be at least partly attributed to variations in baseline characteristics, as mean baseline CHA_2DS_2-VASc and modified HAS-BLED scores and history of hypertension, heart failure,

and major bleeding were lowest/least frequent for patients from South Korea and highest/most frequent for patients from Thailand. Alternatively, these differences could be due to chance, because of the small sample size of the study population. Further investigation into country/regional differences with regards to dosing is needed.

The proportion of patients receiving the nonrecommended 30-mg dose reported here is consistent with previous observations from other similar studies in routine care conducted in Taiwan and South Korea, but slightly higher than the nonrecommended dosing observed in Europe and Japan.[16,21,24,25] In the retrospective, observational study of 11,275 patients from Taiwan receiving NOACs, approximately 32% of patients received a nonrecommended dose (27% under- vs. 5% overdosed); the proportion of patients receiving the recommended dose varied for rivaroxaban (81%), edoxaban (67%), apixaban (65%), and dabigatran (44%).[16,26,27] The CODE-AF registry evaluated NOAC label adherence in 3,080 South Korean patients with AF in routine clinical practice; 61.9% received the recommended NOAC dose, and 38.1% received the nonrecommended NOAC dose (36.4% under- vs. 1.6% overdosed).[16] In patients receiving edoxaban, 68% were prescribed the recommended dose and 32.1% the nonrecommended dose (23.5% under- vs. 8.6% overdosed).[16] Conversely, in our analysis, the proportion of patients who received a higher-than-recommended dose was larger than that reported in previous studies. Although more patients in the ETNA-AF-Japan study vs. the current study were prescribed the recommended dose of edoxaban (86.3% vs. 70.9%), in both studies, more patients who received the nonrecommended dose were under- vs. overdosed.[24] In ETNA-AF-Japan, 1,486 (13.7%) patients were prescribed the nonrecommended dose, of which 1,235 (11.4%) were underdosed and 251 (2.3%) were overdosed.[24] However, it is important to note that most previous studies assessed only the proportion of patients receiving the nonrecommended vs. recommended doses relative to the overall population, whereas our analysis further stratified patients according to the specific dosage received (30 mg or 60 mg). The breakdown by dose adopted here provides useful information on edoxaban prescribing patterns in Asia.

Rates of all-cause death, CV death, hemorrhagic stroke, major bleeding, major or CRNM bleeding, and the NCO were highest in patients receiving recommended edoxaban 30 mg and lowest in patients receiving edoxaban 60 mg (either recommended or nonrecommended dosing), although this difference was not statistically significant. In comparison with our study, patients from the ETNA-AF-Japan study who received the 30-mg vs. 60-mg edoxaban dose had numerically higher incidences of major bleeding alone (1.22%/year vs. 0.72%/year), major bleeding and CRNM bleeding (4.03%/year vs. 3.29%/year), and death (1.46% vs. 0.59%/year).[24] Those receiving the nonrecommended edoxaban 30-mg dose had numerically higher rates of all-cause death and the NCO, but numerically lower rates of major or CRNM bleeding. Those receiving nonrecommended edoxaban 60 mg had numerically lower rates of all-cause death, major bleeding, major or CRNM bleeding, and the NCO. As noted, all comparisons between dosing groups were numerical; no statistical tests were performed between individual dosing groups.

In a large administrative database of NOAC dosing assessing data from 14,865 apixaban-, dabigatran-, or rivaroxaban-treated patients in the USA, 43.0% of patients with a renal indication for dose reduction received a higher dose than recommended, and this higher dose was associated with a higher risk of major bleeding.[26] Of patients with no renal indication for dose reduction, 13.3% received a lower-than-recommended dose, which was associated with a higher risk of ischemic stroke.[26] Patients receiving a lower-than-recommended dose of apixaban had a higher risk of ischemic stroke and a similar risk of major bleeding compared with patients who received recommended apixaban dosing; there was no significant association between dose reduction and the risk of stroke or bleeding for dabigatran- or rivaroxaban-treated patients.[26] It should be noted that this previous study encompassed data from different regions and multiple NOACs. In a retrospective, observational analysis of data from NOAC-treated patients with AF from Taiwan, patients who received the nonrecommended lower dose had an increased risk of ischemic stroke and SEEs, whereas those who received the nonrecommended higher dose had an increased risk of major bleeding.[27] Therefore, consistent with the data presented here, underdosed patients appear to have numerically higher rates of ischemic stroke. On the other hand, although previous studies of real-world NOAC use suggest that overdosed patients have higher rates of major bleeding, this was not confirmed by our study. Compared with patients in US-based studies, patients in the Taiwan- and South Korea-based studies received lower-than-recommended NOAC dosing more frequently (36.4% and 27.0% vs. 13.0%, respectively) and received higher-than-recommended dosing less frequently (1.6% and 5% vs. 40.3%, respectively).[16,26–28] This may reflect the reluctance of physicians to prescribe high-dose NOACs in an Asian population, which typically has a higher baseline risk of bleeding and a lower weight than European cohorts.[12]

In our analysis, South Korea had the largest proportion of patients who received nonrecommended edoxaban 30 mg. Additionally, patients from South Korea also had the lowest modified HAS-BLED and CHA_2DS_2-VASc scores and significantly lower rates of all-cause death, major bleeding, major GI bleeding, major or CRNM bleeding, and the NCO compared with the other countries/regions. In contrast, patients from Thailand, who more likely received nonrecommended edoxaban 60 mg than patients in the other countries/regions, had the highest baseline CHA_2DS_2-VASc and modified HAS-BLED risk scores and had significantly higher rates of major GI bleeding and numerically higher rates of ischemic stroke and SEEs. A significantly higher proportion of patients from Hong Kong had a history of major or CRNM bleeding and ischemic stroke with significantly higher rates of all-cause death, major bleeding, major or CRNM bleeding, and the NCO; these patients also had the numerically highest rates of CV death, hemorrhagic stroke, and ICH. Taken together, these data suggest that variations in baseline characteristics between dosing groups and countries/regions may have contributed to group differences in 1-year outcomes.

Study Limitations

As the Global ETNA-AF program does not include a direct comparator arm, no direct conclusions can be drawn from this study about the effectiveness or safety of edoxaban relative to vitamin K antagonists or any of the other NOACs. When interpreting the data subcategorized by country/region or edoxaban dosing group, the relatively

small number of patients in this study and potential subgroup differences in baseline characteristics should be taken into consideration. Additionally, no statistical comparisons were drawn between individual dosing subgroups due to lack of power. Future studies with a larger number of patients and longer duration may be able to further assess statistical differences in clinical outcomes between dosing subgroups.

The purpose of this analysis across multiple countries/regions was to describe real-world edoxaban prescribing patterns and clinical outcomes in a Southeast Asian population, which would not have been achieved by utilizing statistical methods intended to balance subgroups by adjusting for baseline covariates. The real-world nature of the study provided the unique opportunity to assess clinical outcomes in patients receiving recommended and non-recommended edoxaban dosing for which data were still insufficient. Lastly, this study presented 1-year follow-up data; a longer follow-up period to evaluate effectiveness and safety is ongoing.

Conclusions

This analysis of edoxaban treatment patterns in routine care in Southeast Asia demonstrated that the majority of patients were prescribed the recommended dose of edoxaban. In addition to the high adherence to the recommended dose of edoxaban, the event rates for ischemic stroke and major bleeding remained low (<1.5%) over the 1-year follow-up period. Overall, this analysis supports the favorable effectiveness and safety of edoxaban in the Asian patient population with AF.

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Conflicts of Interest

J.-I.C. reports consulting, speaker, and teaching fees or honoraria from Abbott, Boehringer Ingelheim, Daiichi Sankyo, Chong Kun Dang, Daewoong, Hanmi Pharmaceutical, Menarini, Novartis, Roche, Samjin Pharmaceutical Co., Ltd., Sanofi, and Yuhan; research grants from Chong Kun Dang, Medtronic, Samjin Pharmaceutical, and Sanofi; and a scholarship from the European Society of Cardiology. S.K., P.J., H.F.T., Y.O.Y.S., and C.H.L. declare no competing interests. C.-C.W. declares honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Novartis, and Pfizer. L.P. has received fees and honoraria from Beckman Coulter, Daiichi Sankyo, and SOTIO. M.U. is an employee of Daiichi Sankyo. R.D.C. reports grants, personal fees, and nonfinancial support from Daiichi Sankyo during the conduct of the study; and personal fees from Boehringer Ingelheim, Bayer, BMS/Pfizer, Novartis, Sanofi, Menarini, Guidotti, Milestone, and Roche outside the submitted work. P.K. reports nonfinancial and other support from Daiichi Sankyo Europe during the conduct of the study; consulting fees and honoraria from 3M Medica, MEDA Pharma, AstraZeneca, Bayer Healthcare, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Medtronic, Merck, Merck Sharp & Dohme, Otsuka Pharmaceutical, Pfizer, Sanofi, Servier, Siemens, and Takeda; research grants from 3M Medica, Cardiovascular Therapeutics, MEDA Pharmaceutical, Medtronic, OMRON, Sanofi, St. Jude Medical, German Federal Ministry for Education and Research, Foundation Leducq, German Research Foundation, and the European Union; and travel support from the European Heart Rhythm Association, the European Society of Cardiology, and the German Atrial Fibrillation Competence NETwork. In addition, P.K. is listed as an inventor on 2 patents held by the University of Birmingham (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783).

IRB Information

The Global ETNA protocols were approved in all participating countries by the responsible ethics committees and institutional review boards (IRB) prior to initiation. Japan did not require IRB approval because it was postmarketing surveillance. The program complied with the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice standards. All Global ETNA-AF participants provided written consent before enrollment (**Supplementary Table**).

Data Availability Statement

The data underlying this article cannot be shared publicly, as the Global ETNA-AF program is currently ongoing.

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Supplementary Files

Please find supplementary file(s);
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