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ORIGINAL ARTICLE

Two-year clinical outcomes of Taiwanese and other Asian ethnicities with atrial fibrillation treated with edoxaban in the ETNA-AF Asia registry

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Abstract

Background: The non-vitamin K oral anticoagulant (NOAC), edoxaban, is approved for stroke prevention in patients with atrial fibrillation (AF) in many Asian countries. Nonetheless, data on its long-term effectiveness and safety in routine clinical practice are limited in Taiwan.

Methods: The Global ETNA-AF (Edoxaban Treatment in routiNe clinical prActice) registry is an observational study that integrates data of AF patients receiving edoxaban from multiple regional registries. Here, we report the subgroup analysis of two-year outcomes in Taiwan ($N = 973$) and three Asian countries (South Korea, Hong Kong, Thailand; $N = 2326$).

Results: Compared with other Asian ethnicities, edoxaban users in Taiwan were older and had lower creatinine clearance levels. The incidence of clinical events was low and comparable in four Asian countries. Upon 2 years of observation, the annualized rates of cardiovascular death and ischemic stroke/systemic embolic event were 0.50% and 0.90% in Taiwan and 0.33% and 0.91% in other Asian ethnicities, respectively. The

annualized rates of major/clinically relevant non-major bleeding and major gastrointestinal bleeding were 2.06% and 0.39% in Taiwan and 2.06% and 0.49% in other Asian ethnicities, respectively. Intracranial hemorrhage was rarely reported in four Asian countries (annualized rate: 0.35%).

Conclusions: Although some differences in patient characteristics were observed among Asian ethnicities, the low clinical event rates in two-year ETNA-AF data reassure the effectiveness and safety of edoxaban in routine care for AF patients in Taiwan, South Korea, Hong Kong, and Thailand.

KEYWORDS
atrial fibrillation, edoxaban, long-term outcome, real-world evidence, Taiwan

1 | INTRODUCTION

Atrial fibrillation (AF), one of the leading causes of ischemic stroke, is the most common cardiac arrhythmia worldwide, affecting 1% of the Asian population and 2% of the Caucasian population approximately.[1] Non-vitamin K oral anticoagulants (NOACs) such as dabigatran, rivaroxaban, apixaban, and edoxaban, representing a safe and effective alternative to warfarin, have been the cornerstone for the prevention of thromboembolic events in patients with AF.

Despite the incidence rate of AF in Asians being lower than the Caucasian population, the prevalence of AF increases remarkably in Asia due to the growing elderly population.[2] It is estimated that the AF patients in Asia will be more than double the AF patients from Europe and the United States in 2050.[3,4] The real-world effectiveness and safety in patients with AF under edoxaban treatment is the key information for understanding the management of AF, especially in Asian countries where the real-world evidence regarding NOAC in AF is limited.

Edoxaban, an oral, once-daily NOAC, has been approved in numerous countries, including Taiwan, South Korea, Hong Kong, and Thailand in Asia, for the prevention of stroke and systemic embolic event (SEE) in patients with nonvalvular AF based on the randomized ENGAGE AF-TIMI 48 trial.[5] The Global ETNA-AF (Edoxaban Treatment in routiNe clinical prActice for patients with nonvalvular AF) registry is a noninterventional study integrating real-world data from AF patients receiving edoxaban from multiple countries. Previously, we have reported one-year clinical outcomes of 2677 AF patients from Taiwan and Korea and reassured the safety and effectiveness of edoxaban in routine clinical practice in these two countries.[6]

As of now, the ETNA-AF registry has accumulated two-year real-world evidence on edoxaban use in the Asian population. Considering that Taiwan has the highest prevalence rate of chronic kidney disease (CKD) in the world[7] and renal function is one of the key considerations in edoxaban dosing strategy. In this article, we report the two-year outcomes following edoxaban treatment in Asian patients from Taiwan, South Korea, Hong Kong, and Thailand, with a particular focus on understanding the outcomes in Taiwanese patients compared with other Asian ethnicities.

2 | METHODS

2.1 | Study design

The study design of the Global ETNA-AF registry has been published previously.[8] In brief, the Global ETNA-AF registry is a prospective, observational, and noninterventional study integrating real-world data from several countries, including Europe (Germany, Austria, Switzerland, Belgium, Italy, Spain, United Kingdom, Ireland, the Netherlands, and Portugal), Japan, and other Asian countries (trial registration number: Europe [NCT02944019], Japan [UMIN000017011], and Korea/Taiwan [NCT02951039]). Unselected routine patients with AF receiving edoxaban were prospectively enrolled and followed up for 2 years in Asian countries and 4 years in European countries in a real-world setting.

The ETNA-AF registry was conducted in accordance with the Declaration of Helsinki and the standards for Good Pharmacoepidemiology Practice. The study was approved by the ethics committees and institutional review boards of all participating hospitals. All patients or their legal representatives provided written informed consent.

2.2 | Patient selection

Patients with AF receiving edoxaban for stroke prevention according to the locally approved label were eligible. To ensure that the study protocol did not influence the physician's prescribing behavior, patients were only included after the physician had made the clinical decision to prescribe edoxaban. Patients were excluded if they had simultaneously participated in other interventional studies.

2.3 | Outcomes and assessments

Baseline information, including demographics, vital signs, medical history (e.g., hypertension, diabetes, heart failure, ischemic stroke,

etc.), AF-related history and diagnosis, renal and hepatic parameters, and bleeding history, was captured. Clinical characteristics regarding CHA_2DS_2-VASc score (congestive heart failure/left ventricular dysfunction, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack (TIA)/thromboembolism, vascular disease, age of 65–74 years, and sex category)[9] and HAS-BLED score (hypertension, abnormal liver/renal function, stroke, bleeding history, bleeding predisposition, elderly, and drug use)[10] were determined based on the medical records. Administration status of edoxaban and concomitant treatments were also collected throughout the follow-up period.

Clinical events were systematically captured at 12 and 24 months after enrolment. Events of interest include stroke, SEE, bleeding, myocardial infarction (MI), all-cause death, and cardiovascular (CV)-related death. Bleeding was characterized as major, clinically relevant non-major (CRNM), or minor bleeding based on the International Society on Thrombosis and Hemostasis.[11]

2.4 | Statistical analysis

Data analyses were conducted descriptively. Results were presented separately for Taiwanese patients and other Asian ethnicities pooled from South Korea, Hong Kong, and Thailand. Baseline characteristics are summarized descriptively as frequencies (*n*%) or mean value ± standard deviation (SD). The number of patients with at least one clinical event is presented separately for each type of clinical event as annualized rates. Continuous variables were analyzed with a *t*-test, while categorical variables were assessed using the chi-square test. A *p*-value less than .05 was deemed to be statistically significant. Statistical analyses were performed using SAS® version 9.3 or higher (SAS Institute, Cary, NC, USA).

3 | RESULTS

3.1 | Baseline characteristics

A total of 973 patients from Taiwan and 2326 patients from South Korea ($N = 1812$), Hong Kong ($N = 225$), and Thailand ($N = 289$) who enrolled in the ENTA-AF registry were included in the analysis. Overall, patient characteristics regarding body weight, CHA_2DS_2-VASc score, and HAS-BLED score were similar among Taiwanese patients and other Asian ethnicities (Table 1). The mean age was around 71.2–73.1 years, with more patients aged ≥85 years in Taiwan (Taiwan vs. other Asian ethnicities: 13.7% vs. 5.8%; $p < .0001$). The median CHA_2DS_2-VASc and HAS-BLED scores were both 3.0. Of note, the mean creatinine clearance (CrCl) of Taiwanese patients was significantly lower than other Asian ethnicities (58.7 ± 24.1 mL/min vs. 64.0 ± 23.6 mL/min; $p < .0001$), and there were significantly more patients with paroxysmal AF from Taiwan than other Asian ethnicities (61.6% vs. 38.3%; $p < .0001$). Other Asian ethnicities had a significantly higher number of patients with a history of ischemic stroke and who were taking anti-platelet therapy in comparison to Taiwan. Conversely, Taiwan exhibited a higher prevalence of patients with conditions such as heart failure, chronic obstructive pulmonary disease, peripheral artery disease, and valvular heart disease (VHD) when compared to other Asian ethnicities. A higher proportion of Taiwanese patients discontinued the study (15.6% in Taiwan vs. 12.6% in other Asian ethnicities), primarily due to withdrawal of consent.

3.2 | Exposure to edoxaban

The utilization rate of edoxaban 30 mg was found to be greater among Taiwanese patients compared to patients of other Asian ethnicities (56.9% vs. 47.7%), potentially attributed to the lower CrCl levels in Taiwanese patients. The proportion of patients who were administered a non-recommended dose (i.e., 60 mg for patients meeting dose-reduction criteria or 30 mg for those not meeting such criteria) was comparable among Taiwanese patients (overall 29.9%) and other Asian ethnic groups (overall 26.8%), which was also similar to the global population (overall 27.8%).

3.3 | Clinical events at two-year follow-up

Across 2 years, the incidence rates of thromboembolic and bleeding events were very low, with a declining trend observed for all four Asian countries (Table 2). There were no significant differences in the occurrence of thromboembolic and bleeding events between Taiwan and other Asian ethnic groups.

In terms of thromboembolic events, the annualized rates of CV death, any stroke, and ischemic stroke or SEE were 0.5%, 0.96%, and 0.9% among Taiwanese patients; and 0.33%, 1.2%, and 0.91% among other Asian ethnic groups, respectively, over a 2-year observation period.

For bleeding events, Taiwanese patients experienced annualized rates of 2.06% for major or CRNM bleeding, 0.39% for major GI bleeding, and 0.34% for ICH; similarly, other Asian ethnic groups showed rates of 2.06%, 0.49%, and 0.35% for the respective events during a 2-year observation period.

3.4 | Analysis of clinical outcomes in relation to renal function

Due to the higher prevalence of CKD in Taiwan,[12] a subgroup analysis based on CrCl levels was conducted to examine the influence of renal function on the clinical outcomes under edoxaban treatment (Table 3).

In a two-year observational period, it was found that patients with CrCl <30 mL/min exhibited significantly higher annualized rates of mortality, stroke, and ischemic stroke compared to those with CrCl >50 mL/min in Taiwan. This trend was similarly observed among other Asian ethnic groups, where all-cause mortality was

TABLE 1 Demographics and baseline characteristics of the overall population.

	Overall $N=3299$	Taiwan $N=973$	KR/HK/TH $N=2326$	p-value[†]
Male, *n* (%)	1944 (58.9)	571 (58.7)	1373 (59.0)	.8547
Age [year], mean ± SD	71.7 ± 9.7	73.1 ± 10.1	71.2 ± 9.4	<.0001*
Age [year], *n* (%)				<.0001*
<65	657 (19.9)	155 (15.9)	502 (21.6)	
65– <75	1285 (39.0)	374 (38.4)	911 (39.2)	
75– <85	1089 (33.0)	311 (32.0)	778 (33.4)	
≥85	268 (8.1)	133 (13.7)	135 (5.8)	
Weight [kg], mean ± SD	65.9 ± 12.5	66.2 ± 12.6	65.8 ± 12.5	.4336
BMI [kg/m^2], mean ± SD	25.1 ± 3.8	25.3 ± 3.9	25.0 ± 3.8	.0236*
CrCl (CG formula) [ml/min], mean ± SD	62.3 ± 23.9	58.7 ± 24.1	64.0 ± 23.6	<.0001*
>50, *n* (%)	2007 (67.9)	587 (63.1)	1420 (70.1)	
30–50, *n* (%)	756 (25.6)	243 (26.1)	513 (25.3)	
30, *n* (%)	194 (6.6)	100 (10.8)	94 (4.6)	
Missing	342	43	299	
CHA_2DS_2-VASc, mean ± SD	3.2 ± 1.5	3.2 ± 1.4	3.1 ± 1.5	.3134
CHA_2DS_2-VASc, median	3.0	3.0	3.0	
HAS-BLED[a], mean ± SD	2.6 ± 1.0	2.5 ± 0.9	2.6 ± 1.0	.0037*
HAS-BLED[a], median	3.0	3.0	3.0	
Type of AF, *n* (%)				<.0001*
Paroxysmal	1489 (45.2)	597 (61.6)	892 (38.3)	
Persistent	768 (23.3)	129 (13.3)	639 (27.5)	
Long-standing persistent or permanent	1038 (31.5)	243 (25.1)	795 (34.2)	
Missing	4	4	0	
Diabetes mellitus, *n* (%)	987 (29.9)	303 (31.1)	684 (29.4)	.3212
Hypertension, *n* (%)	2391 (72.5)	701 (72.0)	1690 (72.7)	.7198
Heart failure, *n* (%)	438 (13.3)	158 (16.2)	280 (12.0)	.0012*
COPD, *n* (%)	157 (4.8)	60 (6.2)	97 (4.2)	.0141*
Peripheral artery disease, *n* (%)	24 (0.7)	15 (1.5)	9 (0.4)	.0004*
History of ischemic stroke, *n* (%)	443 (13.4)	71 (7.3)	372 (16.0)	<.0001*
History of major bleeding, *n* (%)	75 (2.3)	22 (2.3)	53 (2.3)	.9754
Vascular disease[b], *n* (%)	83 (2.5)	37 (3.8)	46 (2.0)	.0023*
Valvular heart disease[c], *n* (%)	486 (14.7)	321 (33.0)	165 (7.1)	<.0001*
Anti-platelet therapy at baseline, *n* (%)	227 (6.9)	43 (4.4)	184 (7.9)	.0003*
Edoxaban dose at baseline, *n* (%)				<.0001*
60 mg	1608 (49.6)	412 (43.1)	1196 (52.3)	
Recommended	1063 (35.9)	279 (30.0)	784 (38.5)	
Non-recommended[d]	363 (12.3)	115 (12.4)	248 (12.2)	
Not judgable[f]	182	18	164	
30 mg	1637 (50.4)	545 (56.9)	1092 (47.7)	
Recommended	1077 (36.3)	372 (40.0)	705 (34.7)	
Non-recommended[e]	460 (15.5)	163 (17.5)	297 (14.6)	
Not judgable[f]	100	10	90	
Missing[g]	54	16	38	

TABLE 1 (Continued)

	Overall $N = 3299$	Taiwan $N = 973$	KR/HK/TH $N = 2326$	p-value[†]
Study discontinuation, *n* (%)	445 (13.5)	152 (15.6)	293 (12.6)	.0206[*]
Lost to follow-up	137 (4.2)	40 (4.1)	97 (4.2)	
Death	110 (3.3)	40 (4.1)	70 (3.0)	
Withdrawal of consent	88 (2.7)	57 (5.9)	31 (1.3)	
Transferred to other hospitals	55 (1.7)	14 (1.4)	41 (1.8)	
Unknown reasons	55 (1.7)	1 (0.1)	54 (2.3)	

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CG, Cockcroft and Gault; 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; CrCl, creatinine clearance; 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; HK, Hong Kong; KR, South Korea; SD, standard deviation; TH, Thailand.

[†]The *p*-value assesses the difference between the Taiwan group and the combined KR/HK/TH group.

[*]Statistical significance.

[a]Modified HAS-BLED: without "labile INR".

[b]Vascular disease included coronary heart disease, peripheral artery disease, and myocardial infarction.

[c]Valvular heart disease was defined as history or baseline echocardiography evidence of moderate/severe aortic regurgitation, mitral regurgitation, aortic stenosis, or prior valve surgery (bioprosthesis replacement, valve repair, or valvuloplasty).

[d]Patients who met dose-reduction criteria but still received the standard 60-mg dose.

[e]Patients who did not meet dose-reduction criteria but still received the reduced 30-mg dose.

[f]Patients who were not judgable were excluded from the percentage calculation of recommended and non-recommended groups due to missing data for eGFR or body weight.

[g]Patients with missing data for dose were excluded from the percentage calculation.

TABLE 2 Clinical events at two-year follow-up.

Number (annual incidence, %) (95% CI)	Taiwan $N = 973$	KR/HK/TH $N = 2326$	p-value[a]
All-cause mortality	40 (2.24) (1.64; 3.05)	70 (1.63) (1.29; 2.05)	.1058
CV mortality	9 (0.50) (0.26; 0.97)	14 (0.33) (0.19; 0.55)	.3090
Ischemic stroke or SEE	16 (0.90) (0.55; 1.47)	39 (0.91) (0.67; 1.25)	.9611
Any stroke	17 (0.96) (0.60; 1.55)	51 (1.20) (0.91; 1.57)	.4236
Ischemic stroke	15 (0.85) (0.51; 1.40)	38 (0.89) (0.65; 1.22)	.8637
Hemorrhagic stroke	2 (0.11) (0.03; 0.45)	11 (0.26) (0.14; 0.46)	.2798
MI	3 (0.17) (0.05; 0.52)	3 (0.07) (0.02; 0.22)	.2666
Major or CRNM bleeding	36 (2.06) (1.48; 2.85)	87 (2.06) (1.67; 2.54)	.6673
Major bleeding	18 (1.02) (0.64; 1.62)	48 (1.13) (0.85; 1.49)	.7067
Major GI bleeding	7 (0.39) (0.19; 0.83)	21 (0.49) (0.32; 0.75)	.6095
ICH	6 (0.34) (0.15; 0.75)	15 (0.35) (0.21; 0.58)	.9382

[a]Value was conducted by Cox regression.

Abbreviations: CrCl, creatinine clearance; CRNM, clinically relevant non-major; CV, cardiovascular; GI, gastrointestinal; HK, Hong Kong; ICH, intracranial hemorrhage; KR, South Korea; MI, myocardial infarction; SEE, systemic embolic event; TH, Thailand.

notably elevated in patients with compromised renal function. Furthermore, regarding safety outcomes, the annualized rates of major bleeding and/or major GI bleeding were significantly higher in patients with CrCl <30 mL/min across all four Asian countries. Notably, the incidence rate of ICH was low across all Asian countries and exhibited similarity among patients with varying levels of CrCl.

TABLE 3 Clinical events at two-year follow-up based on renal function.

Number (annual incidence, %) (95% CI)	Taiwan $N = 973$				KR/HK/TH $N = 2326$			
	CrCl <30 $N = 100$	CrCl 30–50 $N = 243$	CrCl >50 $N = 587$	*p*-value[a]	CrCl <30 $N = 94$	CrCl 30–50 $N = 513$	CrCl > 50 $N = 1420$	*p*-value[a]
All-cause mortality	11 (6.33) (3.50; 11.42)	16 (3.60) (2.21; 5.88)	12 (1.10) (0.62; 1.94)	<.0001*	16 (9.67) (5.92; 15.78)	17 (1.79) (1.11; 2.87)	24 (0.91) (0.61; 1.35)	<.0001*
CV mortality	4 (2.30) (0.86; 6.13)	4 (0.90) (0.34; 2.40)	1 (0.09) (0.01; 0.65)	.0150*	1 (0.60) (0.09; 4.29)	3 (0.32) (0.10; 0.98)	9 (0.34) (0.18; 0.65)	.8439
Any stroke	5 (2.93) (1.22; 7.03)	2 (0.45) (0.11; 1.81)	8 (0.74) (0.37; 1.48)	.0241*	3 (1.83) (0.59; 5.69)	13 (1.38) (0.80; 2.38)	28 (1.07) (0.74; 1.55)	.5680
Ischemic stroke or SEE	5 (2.93) (1.22; 7.03)	2 (0.45) (0.11; 1.81)	8 (0.74) (0.37; 1.48)	.0227*	2 (1.22) (0.31; 4.89)	13 (1.38) (0.80; 2.38)	20 (0.76) (0.49; 1.18)	.2387
Major bleeding	5 (2.95) (1.23; 7.09)	8 (1.84) (0.92; 3.67)	4 (0.37) (0.14; 0.98)	.0057*	5 (3.08) (1.28; 7.39)	11 (1.17) (0.65; 2.11)	24 (0.92) (0.61; 1.37)	.0514
Major GI bleeding	3 (1.76) (0.57; 5.45)	3 (0.68) (0.22; 2.11)	1 (0.09) (0.01; 0.65)	.0386*	5 (3.08) (1.28; 7.39)	6 (0.63) (0.28; 1.41)	6 (0.23) (0.10; 0.51)	.0001*
ICH	1 (0.58) (0.08; 4.08)	3 (0.68) (0.22; 2.12)	1 (0.09) (0.01; 0.65)	.2116	1 (0.60) (0.09; 4.29)	2 (0.21) (0.05; 0.84)	9 (0.34) (0.18; 0.66)	.6753

Note: CrCl was based on the Cockcroft Gault formula (unit: ml/min). CrCl data of 43 patients from Taiwan and 299 patients from KR, HK, TH were missing and excluded from the percentage calculation.

Abbreviations: CrCl, creatinine clearance; CV, cardiovascular; GI, gastrointestinal; HK, Hong Kong; ICH, intracranial hemorrhage; KR, South Korea; MI, myocardial infarction; SEE, systemic embolic event; TH, Thailand.

*Statistical significance.

[a]*P*-value was conducted by Cox regression.

In the subgroup analysis of patients with CrCl <30 mL/min, the incidence rates of clinical events were not significantly different between Taiwanese patients and other Asian ethnic groups (Table S2). However, these findings should be interpreted cautiously due to uneven distribution across CrCl subgroups, and no adjustments were made for multiple tests.

4 | DISCUSSION

In this analysis, we present the real-world clinical outcomes of patients from Taiwan, South Korea, Hong Kong, and Thailand over 2 years as documented in the Global ETNA-AF registry. Previously, the one-year data from ETNA-AF Taiwan and Korea demonstrated the effectiveness and safety of edoxaban in routine practice.[6] A decreasing trend in the incidence rates of CV and bleeding events was noticeable in this two-year outcome of the Taiwanese population, affirming the enduring effectiveness and safety of edoxaban over 2 years in a real-world setting.

In all, the incidence rates of thromboembolic and bleeding events were very low across four Asian countries in a real-world setting, even compared to controlled trials and other real-world registries conducted nationwide in Taiwan. The Asian subgroup analysis of the randomized ENGAGE AF-TIMI 48 study[13] reported an annualized rate of 1.34%–2.52% for ischemic stroke or SEE, 0.81–1.08% for CV death, 1.59%–2.86% for major bleeding, and 0.46–0.60% for ICH. In a study using the Taiwan National Health Insurance research database, the incidence rate of stroke was 4.17%–5.80% for Taiwanese AF patients with a CHA_2DS_2-VASc score of 3–4.[14] A study of nationwide Taiwanese AF cohort receiving oral anticoagulants reported a major bleeding rate of 4.06% in patients with a HAS-BLED score of 2.[15] In this study, the low rates of clinical events over 2 years compared to studies mentioned above provide evidence supporting the effectiveness and safety of edoxaban in AF patients from Taiwan, South Korea, Hong Kong, and Thailand in a real-world setting.

The occurrence rates of most clinical events were comparable among Taiwanese patients and other Asian ethnic groups. Despite being no statistically significant difference, there appeared to be a higher numerical incidence of all-cause and CV mortality in Taiwanese patients in comparison to other Asian ethnicities. This variance could potentially be linked to variations in patient characteristics across regions. Taiwanese patients exhibited a slightly older age profile, with a greater proportion of patients aged 85 years and older, as well as lower CrCl levels, in contrast to other Asian ethnicities. Consequently, the utilization rate of edoxaban 30 mg was slightly higher among Taiwanese patients.

The Global ETNA-AF registry enrolled >27,000 patients, with 48.8% from Europe, 41.2% from Japan, and 10.0% from other Asian countries.[16,17] Compared with the global population, the population from four Asian countries showed lower rates of all-cause and CV death at 1 year ([global] all-cause death: 3.03%, CV death: 1.22%; [4 Asian countries] all-cause death: 1.92%, CV death: 0.46%). However, rates of stroke and major bleeding at 1 year were comparable among populations of global and four Asian countries ([global] stroke: 1.12%, major bleeding: 1.12%; [4 Asian countries] stroke: 1.40%, major bleeding: 1.24%). When comparing with other regions in the ETNA-AF registry, Taiwanese patients showed lower ischemic stroke rates than Japanese patients (0.85% vs. 1.02%, respectively), with similar safety profiles in terms of major bleeding and ICH.[18] To compare with the European population, rates of mortality and myocardial infarction in East Asian countries were much lower than in European countries (mortality of East Asia vs. Europe = 2.24%–2.41% vs. 3.87%); however, rates of stroke or SEE seemed to be higher in East Asian than in European countries (1.02%–1.22% vs. 0.7%).[19] For safety, East Asian countries demonstrated higher incidence rates of major or CRNM bleeding and ICH than those observed in European countries (major/CRNM bleeding: 2.06% vs. 1.89%; ICH: 0.34%–0.35% vs. 0.2%).[19] Consistent with our findings, the randomized ENGAGE AF-TIMI 48 sub-study also revealed numerically higher rates of mortality and MI in the non-East Asian population and higher rates of stroke, SEE, and major/CRNM bleeding in the East Asian population.[13] Patient characteristics may be the plausible cause leading to the difference in bleeding rates.

In this analysis of the Asian population, 27.8% of patients received a non-recommended dose of edoxaban (overdosing 60 mg: 12.3%; underdosing 30 mg: around 15.5%). The proportion of patients receiving non-recommended dosages was greater among Asian patients (27.8%) than among European patients (16.9%)[19] in the ETNA-AF registry. Additionally, when compared to European patients in the ENTA-AF registry, Asian patients had lower body weight and CrCl levels, and a higher incidence of major bleeding history (2.3% in Asian patients vs. 1.0% in European patients[19]), highlighting the need for dosage adjustments. A real-world meta-analysis investigating the prevalence of off-label use of NOAC in AF patients reported a relatively high prevalence rate of NOAC off-label doses (overall: 24%; edoxaban: 26%), with underdose being predominant; moreover, the percentage of off-label dosing was found to be greater among physicians in Asia (32%) compared to those in North America (14%) or Europe (22%).[20] Findings from a study on dosing stratification in the ETNA-AF registry indicated that physicians consider patient factors such as age, bleeding risks, and history of bleeding and stroke when adjusting dosing regimens beyond dosing recommendations per label.[21] Together, these findings may indicate suboptimal prescribing practices influenced by conservative decision-making in Asian countries.

Concerning the influence of renal function on patient outcomes, our research noted a marked rise in ischemic and bleeding incidents in patients with a CrCl level<30 mL/min when compared to those with a CrCl level>50 mL/min. Determining the appropriate dosage of edoxaban to achieve a balance between the risks of thromboembolic events and bleeding is a crucial consideration for patients with renal impairment. Clinical guidelines recommend careful evaluation of renal function before initiating NOACs and at regular intervals during treatment, particularly for patients with renal impairment.[22] The frequency of renal function monitoring during NOAC treatment for patients with renal impairment is based on several factors, including the severity of renal impairment and clinical stability, which ensures that patients receive the appropriate dosage to minimize

risks while maintaining therapeutic efficacy. Per the dosing criteria of edoxaban, in patients with mild renal impairment (CrCl >50–80 mL/min), the recommended dose is 60 mg once daily; in patients with moderate or severe renal impairment (CrCl 15–50 mL/min), the recommended dose is 30 mg once daily. In addition, a very-low-dose edoxaban (15 mg) was approved in Taiwan in June 2022 for very old AF patients (≥80 years) who were not eligible for a standard dose due to low CrCl (15–30 mL/min) or having high risks of bleeding based on the results of randomized ELDERCARE-AF trial.[23] Edoxaban 15 mg may offer a solution for elderly patients with severe renal impairment at high risk of bleeding to optimize safety and therapeutic outcomes.

In comparison to other Asian ethnicities, Taiwanese patients showed elevated incidences of ischemic events among those with a CrCl level <30 mL/min. Nevertheless, the occurrence of bleeding events did not increase in Taiwanese patients with a CrCl level <30 mL/min when compared with other Asian ethnic groups. Incidences of ICH were infrequently documented in Taiwanese patients, regardless of renal function status. To investigate the potential determinants influencing the results, we conducted a detailed examination of patient characteristics within the cohort with a CrCl level <30 mL/min (Table S1). Age, body weight, CHA_2DS_2-VASc score, HAS-BLED score, and edoxaban dosing were comparable between Taiwanese patients and other Asian ethnicities. However, the percentages of patients with diabetes, vascular diseases, and VHD were higher in Taiwanese patients than in other Asian ethnicities. Diabetes and vascular disease are important modifiable risk factors for stroke, especially ischemic strokes.[24,25] In addition, several studies have shown increased risks of stroke or SEE in AF patients with VHD.[26–28] In the ENGAGE AF-TIMI 48 Trial, the presence of VHD increased the risk of death and major adverse CV events compared to non-VHD AF patients.[29] Finally, it is important to acknowledge that the sample size of patients was restricted, and there was an imbalance in baseline characteristics among different CrCl groups in this study. Therefore, the findings from subgroup analyses based on CrCl should be approached with caution. Presently, real-world data on edoxaban in patients with a CrCl level <30 mL/min is lacking. Further real-world evidence is required to gain insights into edoxaban treatment in individuals with moderate to severe CKD.

The study exhibited some limitations. One limitation was the absence of real-world data for comparison with other NOACs or vitamin K antagonists. Additionally, the study had a relatively small number of participants from Taiwan compared to Japan ($N = 11,569$) and Korea ($N = 1,769$), potentially limiting the generalizability of the findings to the broader Taiwanese population.[6,18] Furthermore, there was an imbalance in the distribution of participants between Taiwanese patients and individuals from other Asian ethnicities, and the data were not adjusted for potential confounding variables. Consequently, it is advisable to interpret the study results with caution.

5 | CONCLUSIONS

Although some differences in patient characteristics were observed among different Asian ethnicities, the low clinical event rates observed in two-year ETNA-AF data reassure the effectiveness and safety of edoxaban in routine care for AF patients in Taiwan, South Korea, Hong Kong, and Thailand.

AUTHOR CONTRIBUTIONS

Conception and design of the study: CC Wang, M Unverdorben, and C Chen. Conducted the study and acquired the data: CC Wang, CI Cheng, KC Ueng, WS Lin, TF Chao, LY Lin, CL Huang, KC Chang, GY Mar, and YC Hsieh. Analysis and interpretation of data: CC Wang, CI Cheng, KC Ueng, WS Lin, TF Chao, LY Lin, CL Huang, KC Chang, GY Mar, and YC Hsieh. Drafting the article: CC Wang. Revise the article critically for important intellectual content: CC Wang, CI Cheng, KC Ueng, WS Lin, TF Chao, LY Lin, CL Huang, KC Chang, GY Mar, YC Hsieh, M Unverdorben, and C Chen. All authors reviewed and approved the final version to be submitted.

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CONFLICT OF INTEREST STATEMENT

Mark Unverdorben and Cathy Chen are employees of Daiichi Sankyo Inc. Other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data are not publicly available due to privacy or ethical restrictions. Research data are not shared.

ETHICS STATEMENT

The study has obtained approval from appropriate institutional review board and ethics committee of participating hospitals.

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