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ORIGINAL ARTICLE

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Postmarketing surveillance on clinical use of edoxaban in patients with nonvalvular atrial fibrillation (ETNA-AF-Japan): Three-month interim analysis results

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Abstract

Background: Direct oral anticoagulants are the first-line drugs for anticoagulation therapy in nonvalvular atrial fibrillation (NVAF). However, a real-world, large-scale, clinical study on edoxaban has not been performed. Our ongoing postmarketing surveillance, ETNA-AF-Japan (*E*doxaban *T*reatment in routi*N*e clinical pr*A*ctice in patients with non-valvular *A*trial *F*ibrillation; UMIN000017011), was designed to collect such data.

Methods: Enrollment started on 13 April 2015 and ended on 30 September 2017. Eligible patients were those diagnosed with NVAF who were to receive edoxaban for the first time and provided written consent for study participation. Baseline patient characteristics and adverse events (AEs) were collected.

Results: A total of 11 569 patients were enrolled. Data for 8157 patients in the first 3 months were analyzed. Mean age, body weight, creatinine clearance (CLcr), and $CHADS_2$ score were 74.2 ± 10.0 years, 60.0 ± 12.6 kg, 64.0 ± 25.6 mL/min, and 2.2 ± 1.3, respectively. Female patients, and patients with age ≥75 years, body weight ≤60 kg, and CLcr <30 mL/min constituted 40.7%, 52.4%, 54.6%, and 4.7%, respectively. Patients with paroxysmal, persistent, and permanent AF constituted 46.1%, 38.7%, and 15.1%, respectively. Most patients (85.3%) received dosages according to the prescribing information, and 90.8% continued the medication for 3 months. Bleeding AEs occurred in 3.29%, including major bleeding in 0.29%.

Conclusions: The majority (90.8%) of patients continued medication and no significant safety concerns related to edoxaban were reported during the first 3 months of treatment. Clearer safety and efficacy profiles of edoxaban await data analyses after the 2-year follow-up period.

KEYWORDS

anticoagulant, edoxaban, elderly patient, nonvalvular atrial fibrillation, observational study

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with a 5-fold increased risk of stroke.[1] The introduction of non-vitamin K antagonist oral anticoagulants, direct oral anticoagulants (DOACs), has been a major advance in stroke prevention in patients with AF. Compared with warfarin, DOACs are more convenient to use and demonstrated at least equivalent effectiveness, with less intracranial bleeding, in pivotal clinical trials.[2–5]

Edoxaban is an oral, reversible, and direct factor Xa inhibitor[6–8] that originated in Japan and has a linear and predictable pharmacokinetic profile: 62% oral bioavailability, maximum concentration achieved within 1-2 hours,[9] and 50% excreted by the kidney.[10] It was approved for prevention of ischemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF) in Japan in 2014. It is also used for two further indications: treatment and prevention of recurrence of venous thromboembolism, and prevention of postoperative venous thromboembolism after lower extremity orthopedic surgery.[11] Edoxaban is the only DOAC approved for these three indications in Japan.

The number of patients with AF in Japan is predicted to surpass 1 million by 2050,[12,13] and thus the requirement for DOAC therapy to prevent stroke is expected to increase. Because edoxaban is also available as an orally degradable formulation (OD tablet), it can be prescribed for elderly patients with dysphagia and will become a drug of choice, once its safety and effectiveness profiles are fully established. However, no large-scale clinical study of edoxaban in a real-world setting is currently available. Our ongoing study, ETNA-AF-Japan (UMIN000017011), was initiated in the hope of collecting such data for a 2-year follow-up period.

In this article, we describe an interim analysis on data from the 3-month case reports in ETNA-AF-Japan. This interim analysis was conducted to provide healthcare professionals with outcomes of practical use promptly even though the case report collection was not completed, because no other data for large-scale postmarketing surveillance on real-world use of edoxaban are available. A periodic safety report based on the identical interim data set (8377 patients) has been submitted to Pharmaceuticals and Medical Devices Agency.

2 | METHODS

This post-authorization safety and effectiveness study of edoxaban in Japanese patients with NVAF was conducted in accordance with the standards for Good Post-marketing Study Practice provided by the Ministry of Health, Labour, and Welfare in Japan.

2.1 | Study design

ETNA-AF-Japan is a real-world, prospective, observational study that aims to collect the baseline characteristics of Japanese patients with NVAF and survey the effectiveness and safety of edoxaban in these patients.

The standard observation period was 2 years and the target patient number was 10 000. The enrollment started on 13 April 2015, and 11 569 patients were enrolled by 30 September 2017. The observational study was carried out using a central registration system.

2.2 | Patient population

Eligible patients were those who fulfilled the following criteria: patients diagnosed with NVAF and intending to receive edoxaban for the first time to prevent ischemic stroke and systemic embolism; patients who started to take edoxaban within the contract period (determined for each participating institution) and within the registration period; patients who could participate for the observation period; and patients who provided written consent to participate at the time of registration.

2.3 | Survey variables

The survey variables for the patients included patient background characteristics, clinical characteristics, administration status of edoxaban and concomitant drugs, nonpharmacological therapy for AF, invasive treatments including minor surgery other than therapy for AF, clinical course, clinical laboratory tests, clinical events (death, stroke other than transient ischemic attack (TIA), systemic embolism, myocardial infarction)/adverse events (AEs) including bleeding AEs, $CHADS_2$ (congestive heart failure/left ventricular (LV) dysfunction, hypertension, age ≥75 years, diabetes mellitus, and stroke/TIA), CHA_2DS_2-VASc (congestive heart failure/LV dysfunction, hypertension, age ≥75 years, diabetes mellitus, stroke/TIA/thromboembolism, vascular disease, age of 65-74 years, and sex category (female)), and HAS-BLED (hypertension, abnormal liver/renal function, stroke, bleeding history, bleeding predisposition, elderly, and drug use).

The data for these survey variables were collected on case report forms after 3, 12, and 24 months of study participation, and stored in an electronic data capture system. In the present analysis, we evaluated the data from the case report forms collected after 3 months of study participation.

2.4 | Study outcomes

The data for the survey variables were expected to provide an assessment and estimation of the safety of edoxaban in clinical practice. The outcomes were recorded as AEs including bleeding events, as well as clinical events such as death, ischemic stroke, systemic embolism, and cardiac infarction, which may provide information to estimate the effectiveness of edoxaban. The classification of bleeding was categorized by the attending physicians based on the definitions in the *E*ffective a*N*ticoa*G*ulation with factor x*A* next *GE*neration in *A*trial *F*brillation—*T*rombolysis *I*n *M*yocardial *I*nfarction study 48 (ENGAGE AF-TIMI 48)[14] with slight modifications (Appendix S1).

2.5 | Data analysis

For categorical variables, incidence rates were calculated and cross-frequency tables were compiled. For continuous variables, summary statistics (mean, standard deviation) were obtained. The software used for the statistical analyses was SAS® System Release 9.2 (SAS Institute Japan Ltd., Tokyo, Japan).

3 | RESULTS

3.1 | Disposition of participating institutions and patients

A total of 11 569 patients from 1367 institutions were registered. Based on the 3-month case report forms, the data for 8377 patients were finalized. Of those patients, data for 220 patients were excluded from the safety evaluation of edoxaban for the following reasons: 30 patients for serious protocol violation; 156 patients for unimplemented safety evaluation; and 34 patients for consent withdrawal. Consequently, data for 8157 patients were used for the safety evaluation of edoxaban.

3.2 | Baseline characteristics

The baseline characteristics of the patients are summarized in Table 1, and the distribution of important factors including age, CLcr, $CHADS_2$ score, CHA_2DS_2-VASc score, and HAS-BLED score are shown in Figure 1. The mean age was 74.2 ± 10.0 years, and 52.4% of patients were aged ≥75 years (Figure 1A). Female patients constituted 40.7%. The mean body weight was 60.0 ± 12.6 kg, and 54.6% of patients had body weight ≤60 kg. Regarding types of AF, 46.1% of patients had paroxysmal AF, 38.7% had persistent AF, and 15.1% had permanent AF. The mean CLcr was 64.0 ± 25.6 mL/min, and patients with CLcr >50 to <80 mL/min were most common at 45.4% (Figure 1B). Meanwhile, 4.7% of patients had CLcr <30 mL/min, which was an exclusion criterion for the phase 3 study (ENGAGE AF-TIMI 48[14]). The mean $CHADS_2$ score was 2.2 ± 1.3, and the most common score was 2 in 29.8% of patients (Figure 1C). Overall, 34.2% of patients had $CHADS_2$ scores ≤1 (Figure 1C), which were outside the inclusion criteria for the ENGAGE AF-TIMI 48. The mean CHA_2DS_2-VASc score was 3.5 ± 1.6 and the most common score was 3 (Figure 1D). The mean HAS-BLED score was 2.0 ± 1.0 and the most common score was 2 (Figure 1E). Among 24.2% patients treated with other anticoagulants prior to administration of edoxaban, 12.2%, 4.0%, 3.3%, and 3.2%, were treated with warfarin, rivaroxaban, apixaban, and dabigatran, respectively. At the start of edoxaban, antiplatelet agents were used in 12.0% of patients, including aspirin (7.1%) and dual antiplatelet therapy (1.2%). Among the P-glycoprotein (P-gp) inhibitors, quinidine, verapamil, erythromycin, and cyclosporine were used in 5.3% of patients, and other P-gp inhibitors were used in 9.2% of patients.

3.3 | Medical history and comorbidities

Table 2 summarizes the medical histories and comorbidities. Medical history of bleeding was found in 5.7% of patients, including intracranial bleeding (2.5%) and gastrointestinal bleeding (1.7%). Medical history other than bleeding included hypertension (72.4%), dyslipidemia (36.4%), and diabetes mellitus (23.3%).

3.4 | Dosage levels and their adjustment factors

Table 1 summarizes the numbers of patients at each dosage level. As a starting daily dose, 27.0%, 72.3%, and 0.7% of patients were given 60, 30, and 15 mg edoxaban, respectively, as also illustrated in Figure 2A. Following the prescribing information, the dosage for individual patients was determined as follows (Figure 2B). Patients with body weight >60 kg were generally given 60 mg edoxaban. The dosage level was reduced to 30 mg if patients had body weight ≤60 kg, CLcr ≤50 mL/min, or concomitant medication with P-gp inhibitor, quinidine, verapamil, erythromycin, and/or cyclosporine. Of the total 8157 patients, information on dose-adjusting factors was available for 8027 patients, and the initial dose for these patients was analyzed as shown in Figure 2B. Overall, 6848 (85.3%) of the 8027 patients received a recommended dosage of edoxaban, and the remaining 1179 (14.7%) patients received a nonrecommended dosage: 1002 (12.5%) patients had a reduced dose (30 mg in 945 (11.8%) patients and 15 mg in 57 (0.7%) patients) and 177 (2.2%) patients had an increased dose (60 mg). At least one factor was found in 63.4% of patients, of whom 95.5% were given 30 mg edoxaban in accordance with the prescribing information. The details of patients with one of the three factors or a combination of two or three factors are shown in Figure 2C. The remaining 36.6% of patients had none of the three factors. Of these patients, 67.7% were administered 60 mg edoxaban and 32.1% were administered 30 mg. The dose reduction in patients with no dose-adjusting factors was determined by each attending physician based on the clinical status of the individual patient and factors including age (43.6%), CLcr (23.3%), body weight (12.9%), combination use of P-gp inhibitors (7.6%), and others (26.4%).

3.5 | Continuation and discontinuation of medication

Table 3 summarizes the numbers of patients who continued and discontinued edoxaban administration, and the reasons for discontinuation. Of the 8157 patients, 7406 (90.8%) continued the medication. The main reason for discontinuation was clinical events or AEs (3.7%), followed by failure to visit or hospital transfer (2.6%), switching to other medicines (1.7%), and treatment completed as planned (0.6%). The mean administration period including the stop-dosing period was 113.8 ± 70.6 days.

3.6 | Bleeding AEs and adverse drug reactions during edoxaban treatment

Bleeding AEs were reported in 3.29% of patients, including major bleeding in 0.29%, clinically relevant bleeding in 1.66%, and minor bleeding in 1.37%. The major bleeding events included gastrointestinal bleeding (11 events including gastric, gastric ulcer, upper gastrointestinal, and lower gastrointestinal bleeding) and intracranial bleeding (six events including cerebellar, cerebral, putamen, and

TABLE 1 Patient characteristics

	60 mg (N = 2201)	30 mg (N = 5897)	15 mg (N = 59)	All (N = 8157)
Female	309 (14.0)	2975 (50.4)	32 (54.2)	3316 (40.7)
Age, y				
Mean ± SD	67.6 ± 9.5	76.5 ± 9.0	82.5 ± 9.6	74.2 ± 10.0
Body weight, kg				
<40	1 (0.0)	247 (4.2)	6 (10.2)	254 (3.1)
≥40 to ≤60	125 (5.7)	4038 (68.5)	35 (59.3)	4198 (51.5)
>60	2061 (93.6)	1526 (25.9)	17 (28.8)	3604 (44.2)
Unknown	14 (0.6)	86 (1.5)	1 (1.7)	101 (1.2)
Mean ± SD	71.4 ± 10.4	55.7 ± 10.5	53.7 ± 11.6	60.0 ± 12.6
Body mass index, kg/m^2				
Mean ± SD	25.7 ± 3.6	22.7 ± 3.5	23.2 ± 4.0	23.5 ± 3.8
Creatinine clearance[a], mL/min				
Mean ± SD	84.7 ± 25.8	56.4 ± 20.8	38.6 ± 21.1	64.0 ± 25.6
Smoking habit				
Yes	303 (13.8)	337 (5.7)	2 (3.4)	642 (7.9)
Previous smoker	726 (33.0)	1338 (22.7)	6 (10.2)	2070 (25.4)
Never	798 (36.3)	3178 (53.9)	32 (54.2)	4008 (49.1)
Unknown	374 (17.0)	1044 (17.7)	19 (32.2)	1437 (17.6)
Drinking habit				
No	810 (36.8)	3461 (58.7)	31 (52.5)	4302 (52.7)
Yes	1022 (46.4)	1396 (23.7)	8 (13.6)	2426 (29.7)
Unknown	369 (16.8)	1040 (17.6)	20 (33.9)	1429 (17.5)
Types of atrial fibrillation				
Paroxysmal	1020 (46.3)	2715 (46.0)	27 (45.8)	3762 (46.1)
Persistent (duration >7 days)	891 (40.5)	2240 (38.0)	24 (40.7)	3155 (38.7)
Permanent	287 (13.0)	937 (15.9)	8 (13.6)	1232 (15.1)
Unknown	3 (0.1)	5 (0.1)	0 (0.0)	8 (0.1)
$CHADS_2$ score				
Mean ± SD	1.8 ± 1.2	2.3 ± 1.4	2.6 ± 1.4	2.2 ± 1.3
CHA_2DS_2-VASc score				
Mean ± SD	2.7 ± 1.5	3.8 ± 1.6	4.2 ± 1.6	3.5 ± 1.6
HAS-BLED score[b]				
Mean ± SD	1.8 ± 1.0	2.1 ± 0.9	2.4 ± 1.2	2.0 ± 1.0
Switch from other anticoagulants				
No	1693 (76.9)	4446 (75.4)	45 (76.3)	6184 (75.8)
Yes	508 (23.1)	1451 (24.6)	14 (23.7)	1973 (24.2)
Warfarin	248 (11.3)	745 (12.6)	6 (10.2)	999 (12.2)
Rivaroxaban	92 (4.2)	237 (4.0)	1 (1.7)	330 (4.0)
Apixaban	59 (2.7)	209 (3.5)	4 (6.8)	272 (3.3)
Dabigatran	79 (3.6)	176 (3.0)	2 (3.4)	257 (3.2)
Others	31 (1.4)	84 (1.4)	1 (1.7)	116 (1.4)

SD, standard deviation.

Data are presented as number (%) unless otherwise indicated.

[a]Creatinine clearance was estimated using the Cockcroft & Gault equation.

[b]Labile international normalized ratio and alcohol use were not counted; thus, the highest total score was 7.

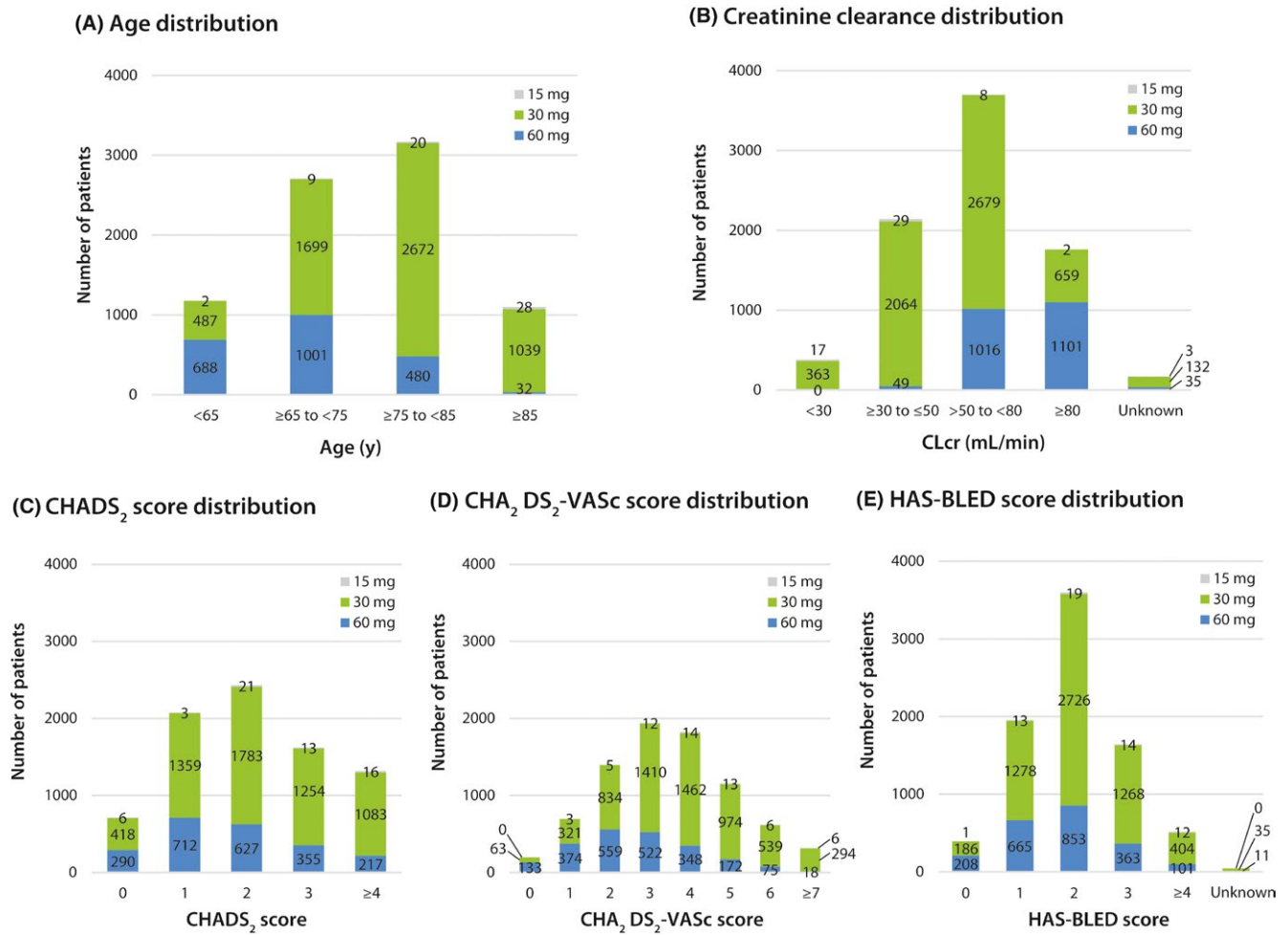

FIGURE 1 Distributions of patient baseline characteristics stratified by different doses. A, Age; B, Creatinine clearance; C, $CHADS_2$; D, CHA_2DS_2-VASc; and E, HAS-BLED. The figures in the bars represent the number of patients. Creatinine clearance was estimated using the Cockcroft & Gault equation

subarachnoid bleeding). Adverse drug reactions (ADRs) were detected in 5.22% of patients, with serious ADRs in 0.99%.

4 | DISCUSSION

This is a 3-month interim report on 8157 patients among the 11 569 patients enrolled in ETNA-AF-Japan, an ongoing, large-scale, prospective, observational study to evaluate the safety and effectiveness of edoxaban in Japanese patients with NVAF. In the present study, we focused on the baseline characteristics of patients and bleeding AEs, which we believe to be of clinical importance in the early stages of anticoagulant therapy. A more detailed profile of the safety and effectiveness of edoxaban treatment including thromboembolic AEs will be reported after completion of the 1-year follow-up as an interim report and then after completion of the ongoing 2-year observation study as a report of the final results.

The baseline characteristics of these 8157 patients revealed that 52.4% were aged ≥75 years, and 31.4% were aged ≥80 years. Because AF is estimated to occur in 7%-15% and 2%-3% of people aged ≥80 years in Western countries[15] and in Japan,[12,13] respectively, and because epidemiological studies demonstrated a high risk of cerebral infarction development in elderly patients with AF,[1,16] the present report together with the ongoing 2-year study may provide real-world information on the safety and effectiveness of edoxaban for the prevention of ischemic stroke and systemic embolism in these elderly patients as well as real-world information on the risk factors for developing these clinical events.

ENGAGE AF-TIMI 48,[5] a phase 3 study, clearly established the safety and effectiveness of edoxaban in patients with AF. The baseline characteristics of the patients in the present study differ somewhat from those in ENGAGE AF-TIMI 48. The patients in ENGAGE AF-TIMI 48 had $CHADS_2$ scores >1, while 34.2% of patients in the present study in a real-world clinical setting had $CHADS_2$ scores ≤1. While ENGAGE AF-TIMI 48 excluded patients with CLcr <30 mL/min, the present study included such patients at 4.7%. Furthermore, ENGAGE AF-TIMI 48 excluded patients with high risk of bleeding, while the present study included 2.5% of patients with intracranial bleeding history. Finally, patients receiving dual antiplatelet therapy

TABLE 2 Medical history and comorbidities

Items	Patients, number (%) (N = 8157)
Bleeding history	
Yes	465 (5.7)
Intracranial bleeding	206 (2.5)
Gastrointestinal bleeding	139 (1.7)
Others	135 (1.7)
Nonbleeding medical history/comorbidities	
Hypertension	5902 (72.4)
Diabetes mellitus	1899 (23.3)
Dyslipidemia	2972 (36.4)
Myocardial infarction	301 (3.7)
Angina pectoris	907 (11.1)
Cardiac insufficiency/left ventricular systolic dysfunction	2204 (27.0)
Cerebral infarction/transient ischemic attack	1683 (20.6)
Malignant tumor	615 (7.5)
Ulcer	303 (3.7)
Anemia	345 (4.2)

were excluded from ENGAGE AF-TIMI 48, while the present study included such patients at 1.2%. Among 8157 patients in the present study, 4407 (54.0%) patients fulfilled the enrollment criteria for the ENGAGE AF-TIMI 48. The mean age and $CHADS_2$ score were 72 years and 2.8, respectively, in patients in the ENGAGE AF-TIMI 48 in Japan,[17] and 76 years and 2.8, respectively, in 4407 patients in the present study. The medical history and comorbidities of patients in both studies were similar indicating the patient populations in both groups were similar except for age. Whether the outcome of the 4407 patients receiving edoxaban therapy matches with that of the ENGAGE AF-TIMI 48 awaits the final analysis in the ongoing 2-year observational study.

The mean age and age distribution of the patients in the present study were quite similar to those in the Fushimi registry.[18] The mean CLcr was identical in both studies. The $CHADS_2$ score and its distribution were also similar in both studies.

Two recent reports, XAPASS (Xarelto Post-Authorization Safety & Effectiveness Study in Japanese Patients with Atrial Fibrillation)[19] and J-dabigatran surveillance,[20] are of interest because both described independent surveillance data targeting Japanese patients with NVAF. The mean age, mean CLcr, and mean $CHADS_2$ score were 73.1 years, 67.7 mL/min, and 2.2 in the XAPASS, and 70.8 years, 72.8 mL/min, and 1.8, in the J-dabigatran surveillance, respectively. The mean age of patients in the present study was 74.2 years, the mean CLcr was lower with 64.0 mL/min, and the mean $CHADS_2$ score was 2.2. The mean $CHADS_2$ score in the present study was identical to that in the XAPASS with a similar distribution. Thus, the patients in the present study were older with lower renal function and higher risk for stroke than those in the two previous studies.

Based on the above comparisons, the patient population in the present study appears to overlap the populations in the Fushimi registry, XAPASS, and J-dabigatran surveillance, and thus seems to reflect the current general elderly patient population with NVAF.

In the present study, the initial dose of edoxaban was 60 mg in 27.0% of patients and 30 mg in 72.3%. The prescribing information for edoxaban recommends 60 mg in patients with body weight >60 kg and reduction to 30 mg in patients with one of the following conditions: body weight ≤60 kg, CLcr ≤50 mL/min, or combination therapy with P-gp inhibitors, quinidine, verapamil, erythromycin, and/or cyclosporine. Thus, 85.3% of patients received edoxaban at the recommended dosage level. The remaining 14.7% of patients received a nonrecommended dose, the majority of whom (11.8%; 945 of 8027 patients) had a reduced dose of 30 mg. Since the time when warfarin was the only available anticoagulant to the present era with availability of warfarin and DOACs, insufficient doses of anticoagulants have often been prescribed in fear of the bleeding risk, resulting in otherwise avoidable incidences of stroke and systemic embolism.[21,22] In ORBIT-AF II (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation), 96% of patients receiving standard DOAC doses were prescribed a dose consistent with the package insert, and only 43% of patients receiving reduced DOAC doses fulfilled the FDA-recommended criteria for these doses. Compared with those appropriately receiving standard doses, patients receiving inappropriately reduced DOAC doses had higher unadjusted rates of thromboembolic events and death. However, after adjustment for baseline characteristics of the patients, the outcomes did not differ significantly, but showed a tendency to favor patients with appropriate doses.[23] In the Fushimi AF registry, 36%-59% of patients receiving reduced doses of DOAC were prescribed a dose inconsistent with the recommended dose (off-label underdose).[24] Using a large US administration database, Yao et al[25] identified and examined 14 865 patients with AF who initiated treatment with apixaban, dabigatran, or rivaroxaban. They demonstrated that, among the 1473 patients with renal indications for dose reduction, 43.0% received the standard dose, which was associated with a higher risk of major bleeding, but no significant difference for risk of stroke. Among the 13 392 patients with no renal indications for dose reduction, 13.3% received the reduced dose, which was associated with a higher risk of stroke, but no significant difference in risk of major bleeding in apixaban-treated patients. As described above, 11.8% of patients without dose-adjusting factors received a reduced dose in the present study. Of note, a significant proportion of patients were given a reduced edoxaban dose of 30 mg despite having none of the three dose-adjusting factors. According to the attending physicians' reports, the main reasons for the reduction included age, CLcr, and body weight in relation to the clinical status of each patient. The clinical status of these patients might be better interpreted by using terms such as sarcopenia, frailty, fragility of the congealing fibrinogenolysis system, and/or a combination of these. These clinical statuses may account for the undertreatment of elderly patients in anticoagulation therapy or prescribing underdoses of DOACs as discussed above. It is

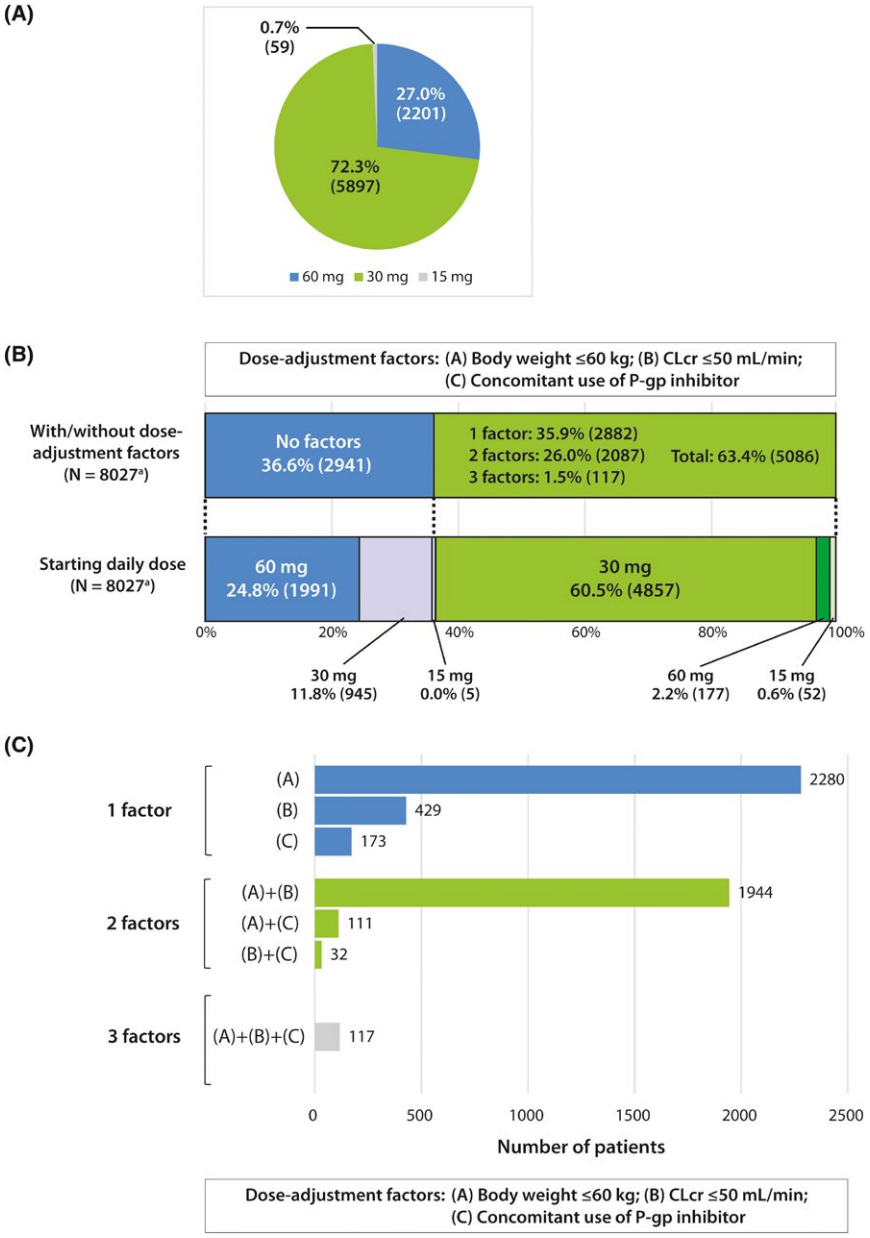

FIGURE 2 Starting daily doses and dose adjustments. A, Distribution of starting daily doses. B, Dose adjustment factors and actual doses given to patients. Figures in parentheses following the percentages represent the numbers of patients. [a]From the total of 8157 patients, 130 patients without records for the three factors were excluded. P-gp inhibitors: quinidine, verapamil, erythromycin, and/or cyclosporine. C, Number of patients having each dose-adjusting factor or a combination of factors.

difficult, however, to determine whether the reduced dose was clinically appropriate at this early stage of edoxaban treatment. We are aware of the importance of this issue, and will continue to carefully observe the clinical outcome of these patients. Upon completion of the ongoing 2-year observation study, we expect to provide more information to help establish a better strategy for the treatment of elderly patients with NVAF.

To date, 90.8% of patients have continued administration of edoxaban for >3 months, a higher rate compared with other studies of longer duration,[21,26] except for a study by Inoue et al[20] in which the adherence rate for the first 3 months was >90% and comparable to the present study. It will be interesting to see whether this adherence continues for a longer period.

This article describes the results for the 3-month follow-up data and no significant safety concerns were found. The final 2-year follow-up results are awaited.

4.1 | Limitations

The present study was an open-label observational study with no positive control. The duration of the study was also very limited. However, the ongoing 2-year research may add more convincing data and may provide a clearer view regarding the safety and effectiveness profiles of edoxaban in real-world clinical practice as well as hints for better adherence to DOAC therapy.

5 | CONCLUSIONS

The present study, an interim analysis at 3 months on 8157 patients analyzed in ETNA-AF-Japan, has demonstrated that treatment with edoxaban for 3 months was well tolerated in Japanese patients with NVAF, including those with limited renal function who were excluded

TABLE 3 Continuations/discontinuations of edoxaban treatment

Medication status	Patients, number (%) (N = 8157)
Medication status in the ongoing study	
Administration ongoing	7406 (90.8)
Administration stopped/discontinued	751 (9.2)
Reasons for administration stopped/discontinued[a]	
Due to clinical events or AEs	298 (3.7)
Failed to visit hospital/transferred to a different hospital	214 (2.6)
Switched to other medicines	139 (1.7)
Treatment completed as planned	50 (0.6)
Planned to receive nonpharmacological therapy for atrial fibrillation	12 (0.1)
Planned to receive an invasive procedure	9 (0.1)

[a]Some overlap is present.

from ENGAGE AF-TIMI 48. A clearer picture regarding real-world clinical practice and the safety and efficacy profiles of edoxaban will materialize after the 2-year observation period.

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CONFLICT OF INTEREST

TY received consulting and lecture fees from Daiichi Sankyo Co. Ltd., Bayer Yakuhin Ltd., Bristol Myers Squibb, Ono Pharmaceutical Co. Ltd., Toa Eiyo Ltd., and Boehringer Ingelheim Japan Co. Ltd, and research funding from Daiichi Sankyo Co. Ltd., Bayer Yakuhin Ltd., and Bristol Myers Squibb. YK received consulting and lecture fees from Daiichi Sankyo Co. Ltd., Bayer Yakuhin Ltd., Bristol Myers Squibb, and Boehringer Ingelheim Japan Co. Ltd. MI, KS, and SK are employees of Daiichi Sankyo Co. Ltd.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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