Safety and Effectiveness of Edoxaban in Japanese Patients With Venous Thromboembolism

— An Interim Analysis of Data From a Japanese Postmarketing Observational Study (ETNA-VTE-Japan) —

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Background: ETNA-VTE-Japan is an ongoing prospective observational study conducted as part of a postmarketing observational study to investigate the safety and effectiveness of edoxaban in Japanese patients for whom the drug has been newly prescribed to treat venous thromboembolism (VTE) and prevent VTE recurrence. The results of an interim analysis of data collected at 3 months are presented.

Methods and Results: A total of 1,732 patients were enrolled. The safety and effectiveness analyses included data from 1,703 and 1,699 patients, respectively. In the safety analysis set, 39.4% of patients were aged ≥ 75 years, 58.2% had body weight ≤ 60 kg, and 22.2% had creatinine clearance < 50 mL/min. Approximately 90% of patients received a dose in accordance with the package insert. Approximately 80% of patients continued treatment; the mean treatment period was 74.5 days. The incidence of bleeding adverse events and major bleeding was 6.3% and 1.4%, respectively. The incidence of VTE recurrence and symptomatic VTE recurrence in the on-treatment population was 0.8% and 0.4%, respectively. Safety and effectiveness profiles of edoxaban in patients receiving the low dose (30 mg/day), generally administered to patients with high bleeding risk, were similar to those of the standard dose (60 mg/day).

Conclusions: The results confirm no major concerns about the safety and effectiveness of edoxaban in Japanese patients with VTE in the first 3 months of treatment. (Trial registration No.: UMIN000016387.)

Key Words: Bleeding adverse events; Edoxaban; Japan; Postmarketing observational study; Venous thromboembolism

Venous thromboembolism (VTE), which comprises deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major global health problem and a common vascular disease.¹ In Japan, the incidence of VTE is generally lower than in Western countries, but it seems to be following an upward trend. Based on data from a 2006 questionnaire survey of medical institutions in Japan, the estimated numbers of new cases of DVT and PE were 14,674 and 7,864, respectively, with the latter representing a doubling over the course of a decade.² Corresponding figures based on data from a similar survey carried out in 2011 were 24,538 and 16,096, respectively, again showing a marked increase.³

The mainstay of treatment for VTE and prevention of its recurrence is anticoagulation. The vitamin K antagonist warfarin, which acts by suppressing the synthesis of vitamin K-dependent coagulation factors, has been widely

used for this purpose for over 60 years. However, warfarin therapy has several disadvantages, including the inconvenience of dietary restrictions and the requirement for dosage adjustment with frequent blood sampling to monitor the international normalized ratio (INR), as determined by prothrombin time (PT).

The therapeutic options for VTE have been expanded in recent years by the introduction of non-vitamin K antagonist oral anticoagulants known as direct oral anticoagulants (DOACs). Unlike warfarin, DOACs are novel direct-acting medications that are selective for a specific coagulation factor, namely thrombin (factor IIa) or factor X. They are more convenient to use than warfarin, with no requirement for dietary restriction and generally no requirement for PT-INR monitoring, and have shown at least equivalent efficacy and safety in pivotal clinical trials.^{4–7}

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Edoxaban is a DOAC used in many countries, including Japan, and is available in tablet form. It is a reversible direct factor Xa inhibitor^{8–10} with a linear and predictable pharmacokinetic profile: its oral bioavailability is 62%, maximum plasma concentration is achieved within 1–2 h,¹¹ and 50% is cleared by renal excretion.¹² In 2014, edoxaban was approved in Japan for the treatment of VTE and prevention of its recurrence. It is also used for 2 other indications: prevention of ischemic stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF), and prevention of postoperative VTE after lower extremity orthopedic surgery.¹³ Edoxaban is currently the only DOAC approved for these 3 indications in Japan. For the treatment of AF and VTE, the daily dose of edoxaban for individual patients is determined in accordance with the package insert (PI), as follows. The standard dose (60 mg) is administered to patients with body weight >60 kg. The dose is reduced to 30 mg if the following dosage adjustment factors are present: body weight ≤60 kg, creatinine clearance (Cl_{Cr}) ≤50 mL/min, or concomitant use of a P-glycoprotein inhibitor (cyclosporine, erythromycin, quinidine, or verapamil).

Given the increasing incidence of VTE in Japan, the use of DOAC for VTE treatment and prevention of its recurrence is expected to increase. Once its safety and effectiveness profiles have been fully established, edoxaban is likely to become the DOAC of choice, especially considering that its availability as an orally degradable formulation (the OD tablet) allows it to be prescribed for elderly patients with dysphagia. However, to date, no large-scale clinical study of the safety and effectiveness of edoxaban in a real-world setting has been conducted.

The aim of the ongoing study ETNA-VTE-Japan (Edoxaban Treatment in routine clinical practice in patients with Venous ThromboEmbolism – Japan) is to investigate the safety and effectiveness of edoxaban by analyzing data collected from Japanese patients for whom the drug had been newly prescribed to treat VTE or prevent its recurrence. The study population includes patients with high bleeding risk; the safety of this group is of particular interest because such patients were excluded from earlier pre-approval clinical trials of edoxaban. The final analysis will use data collected at 12 months. The Japanese guidelines (JCS 2017)¹⁴ recommend that anticoagulant treatment be continued for at least 3 months for the treatment of VTE. Here, we report the results of an interim analysis of data collected at the end of the first 3 months.

Methods

Study Design

ETNA-VTE-Japan is a real-world prospective observational study carried out as part of the postmarketing observational study of edoxaban in Japan. The observation period was 12 months, and the target number of patients was 1,500. We present the results of an interim analysis of data collected at 3 months.

Setting

Patients were recruited from medical institutions throughout Japan. Enrollment, using a central registration system, began on February 1, 2015. At completion of the registration period (July 31, 2017), 1,732 patients had been enrolled.

Patients

Eligible patients were those diagnosed with VTE (DVT or PE) and for whom edoxaban had been newly prescribed to treat VTE or prevent its recurrence, and who had started to take edoxaban within the period of the contract with each participating institution and within the registration period and additionally were considered able to participate for the whole observation period.

Ethics Statement

The study was conducted by Daiichi Sankyo Co., Ltd. (Tokyo, Japan) in accordance with the Good Postmarketing Study Practice standards specified by the Ministry of Health, Labour and Welfare in Japan. All patients provided written informed consent before registration.

Variables

The survey variables were as follows: data on patients' background characteristics, including risk factors for VTE and clinical characteristics; medication status for edoxaban, drug treatment for VTE before starting edoxaban treatment, and drugs used concomitantly; non-pharmacological therapy for VTE; invasive treatment, including minor surgery other than therapy for VTE; clinical course; clinical laboratory test results; adverse events (AEs), including bleeding; and clinical events, including recurrence of VTE (symptomatic and asymptomatic). Bleeding AEs were classified by the attending physicians based on the definitions used in the Hokusai-VTE (which investigated edoxaban vs. warfarin for the treatment of symptomatic VTE),⁴ with slight modifications (**Supplementary Table 1**). Data were collected from each patient's case report form after 3 and 12 months of participation in the study. Here we present the results of an interim analysis at 3 months.

The data on the survey variables were used in the assessment and evaluation of the safety and effectiveness of edoxaban in clinical practice. The safety outcomes were assessed by AEs or adverse drug reactions (ADRs), including bleeding AEs. ADRs were defined as AEs for which a causal relationship with edoxaban could not be ruled out. Bleeding AEs were categorized by individual treating physicians based on International Society on Thrombosis and Haemostasis criteria.¹⁵ The effectiveness outcome was the incidence of VTE recurrence.

Statistical Analysis

For categorical variables, proportion was calculated and contingency tables were created. For continuous variables, summary statistics (mean, standard deviation) were calculated. For each risk factor for bleeding AEs and VTE recurrence, the incidence (with 95% confidence interval [CI]) was calculated and the hazard ratio was determined by Cox proportional hazards model. To identify risk factors for all bleeding AEs, a multivariate Cox proportional hazards model with a step-wise variable selection method was used. Variables used in the multivariate analyses were sex, age, body weight, smoking status, alcohol drinking habit, history of intracranial bleeding, history of gastrointestinal bleeding, complications (hypertension, diabetes mellitus, heart disease, peptic ulcer, cancer, anemia, congenital or acquired disease related to bleeding), pretreatment Cl_{Cr}, pretreatment aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT), starting daily dose of edoxaban, concomitant use of other medications during

the edoxaban treatment period (antiplatelet agents [including aspirin], non-steroidal anti-inflammatory drugs [NSAIDs] other than low-dose aspirin, P-glycoprotein inhibitors [cyclosporine, erythromycin, quinidine, and verapamil], P-glycoprotein inhibitors [other than cyclosporine, erythromycin, quinidine, and verapamil], dual antiplatelet therapy [DAPT]), drug treatment for VTE before starting edoxaban treatment, and starting daily dose of edoxaban according to the PI (recommended dose, non-recommended under-dose or non-recommended over-dose).

A significance level of 0.05 was set to allow the addition or removal of a variable from the model. However, 1 variable, namely the daily dose at the start of edoxaban treatment, was included in every model.

The software used for the statistical analyses was SAS System Release 9.2 (SAS Institute Japan Ltd., Tokyo, Japan). AEs were encoded using the Medical Dictionary for Regulatory Activities Terminology (MedDRA)/J 21.0.

Trial Registration

ETNA-VTE-Japan is registered with the UMIN Clinical Trials Registry under the number UMIN000016387.

Results

Patient Disposition

Patient disposition is shown in **Figure 1**. A total of 1,732 patients attending 281 institutions were enrolled. At 3 months, data from 1,724 patients had been collected and the data set was finalized. Data from 21 of these patients were excluded from the safety analysis set for the following reasons: serious protocol violation (14 patients), safety evaluation not performed (5 patients), and withdrawal of consent (2 patients). Therefore, the safety analysis set comprised data from 1,703 patients.

Data from 4 of these 1,703 patients were excluded from the effectiveness analysis set for the following reasons: effectiveness evaluation not performed (2 patients) and off-label use (2 patients). Therefore, the effectiveness analysis set comprised data from 1,699 patients.

Baseline Patients' Characteristics

The baseline characteristics of the patients in the safety analysis set (n=1,703) are summarized in **Table 1**. In the safety analysis set, 39.4% of patients were aged ≥ 75 years, 58.2% had body weight ≤ 60 kg, and 22.2% had $\text{Cl}_{\text{Cr}} < 50$ mL/min. The proportion of inpatients was 60.0%. The proportion of patients with a diagnosis of PE, proximal DVT, and isolated distal DVT only was 42.3%, 26.1% and 31.2%, respectively. VTE risk factors were present in 74.6% of patients, the most common factor being active cancer (26.8%). The proportion of patients who had received drug treatment for VTE before starting edoxaban treatment was 56.1%. For these patients, the most commonly used drug was unfractionated heparin. Regarding medical history and comorbidities, 7.7% of patients had a history of bleeding, including intracranial bleeding (3.0%) and gastrointestinal bleeding (1.9%). Medical history other than bleeding included hypertension (43.8%) and cancer (28.0%).

Regarding the concomitant use of other medications, antiplatelet agents (including aspirin) were used by 9.3% of patients, and DAPT was used by 0.9%. NSAIDs other than low-dose aspirin were used by 10.3% of patients. The P-glycoprotein inhibitors cyclosporine, erythromycin, quinidine, and verapamil were used by 1.3% of patients.

In the analysis of effectiveness, we also analyzed data from patients with acute VTE that was diagnosed within 14 days before starting edoxaban treatment. The baseline characteristics of this group of patients in the safety analysis set (n=1,024) are summarized in **Supplementary Table 2** (by VTE diagnosis). Although most of the baseline characteristics were similar to those of all the patients in the safety analysis set (n=1,703), the proportions of inpatients and those treated with unfractionated heparin before starting edoxaban treatment were higher (71.7% and 43.8%, respectively) in patients with acute VTE. When patients were stratified according to VTE diagnosis (PE, proximal DVT, and isolated distal DVT only), an imbalance in the proportions of patients was found in terms of inpatients (PE 85.0%; proximal DVT 71.1%; isolated distal DVT only 54.8%), symptomatic VTE (PE 75.3%; proximal DVT

	Total n (%) (N=1,703)	Edoxaban 60mg n (%) (N=582)	Edoxaban 30mg n (%) (N=1,099)	Edoxaban 15mg n (%) (N=22)
Sex				
Female	1,027 (60.3)	216 (37.1)	794 (72.2)	17 (77.3)
Age (years)				
Mean±SD	68.0±14.3	62.1±14.2	70.9±13.4	76.8±13.4
≥75	671 (39.4)	135 (23.2)	523 (47.6)	13 (59.1)
Body weight (kg)				
Mean±SD	59.3±13.9	71.6±12.5	53.0±9.6	50.8±11.3
≤60	991 (58.2)	47 (8.1)	926 (84.3)	18 (81.8)
Pretreatment Cl_{cr}* (mL/min)				
<15	2 (0.1)	0 (0.0)	1 (0.1)	1 (4.5)
≥15 to <30	48 (2.8)	1 (0.2)	44 (4.0)	3 (13.6)
≥30 to ≤50	328 (19.3)	18 (3.1)	300 (27.3)	10 (45.5)
>50 to <80	642 (37.7)	175 (30.1)	464 (42.2)	3 (13.6)
≥80	667 (39.2)	383 (65.8)	279 (25.4)	5 (22.7)
Not calculable	16 (0.9)	5 (0.9)	11 (1.0)	0 (0.0)
Mean±SD	77.1±34.7	98.3±36.2	66.2±28.1	53.6±31.2
Inpatient or outpatient status				
Inpatient	1,021 (60.0)	363 (62.4)	653 (59.4)	5 (22.7)
VTE diagnosis				
PE with or without DVT	721 (42.3)	295 (50.7)	419 (38.1)	7 (31.8)
Symptomatic	556 (32.6)	249 (42.8)	301 (27.4)	6 (27.3)
Proximal DVT	445 (26.1)	147 (25.3)	291 (26.5)	7 (31.8)
Symptomatic	316 (18.6)	111 (19.1)	200 (18.2)	5 (22.7)
Isolated distal DVT only	532 (31.2)	139 (23.9)	385 (35.0)	8 (36.4)
Symptomatic	304 (17.9)	93 (16.0)	206 (18.7)	5 (22.7)
Other (e.g., DVT at unknown site)	5 (0.3)	1 (0.2)	4 (0.4)	0 (0.0)
Risk factors at VTE onset				
No	395 (23.2)	155 (26.6)	233 (21.2)	7 (31.8)
Yes	1,270 (74.6)	414 (71.1)	841 (76.5)	15 (68.2)
Cancer (active)	457 (26.8)	139 (23.9)	313 (28.5)	5 (22.7)
History of VTE	161 (9.5)	63 (10.8)	97 (8.8)	1 (4.5)
Drug treatment for VTE before starting edoxaban treatment				
Yes	956 (56.1)	328 (56.4)	620 (56.4)	8 (36.4)
Unfractionated heparin	649 (38.1)	242 (41.6)	403 (36.7)	4 (18.2)
Warfarin	262 (15.4)	72 (12.4)	185 (16.8)	5 (22.7)
History of bleeding				
Present	131 (7.7)	37 (6.4)	92 (8.4)	2 (9.1)
Intracranial bleeding	51 (3.0)	16 (2.7)	35 (3.2)	0 (0.0)
Gastrointestinal bleeding	33 (1.9)	6 (1.0)	27 (2.5)	0 (0.0)
Past medical history except for bleeding, and complications				
Hypertension	746 (43.8)	255 (43.8)	480 (43.7)	11 (50.0)
Diabetes mellitus	245 (14.4)	92 (15.8)	147 (13.4)	6 (27.3)
Dyslipidemia	482 (28.3)	161 (27.7)	316 (28.8)	5 (22.7)
Heart disease	237 (13.9)	51 (8.8)	180 (16.4)	6 (27.3)
Cerebrovascular disorder	145 (8.5)	36 (6.2)	105 (9.6)	4 (18.2)
Peptic ulcer	104 (6.1)	41 (7.0)	62 (5.6)	1 (4.5)
Cancer	476 (28.0)	139 (23.9)	332 (30.2)	5 (22.7)
Anemia	155 (9.1)	35 (6.0)	117 (10.6)	3 (13.6)
Congenital or acquired disease related to bleeding	21 (1.2)	6 (1.0)	15 (1.4)	0 (0.0)

Data are expressed as n (%) unless otherwise specified. *Calculated with the Cockcroft-Gault formula. Cl_{cr}, creatinine clearance; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Table 2. Incidence of Bleeding Adverse Events During the Edoxaban Treatment Period in the Safety Analysis Set (n=1,703)				
	Total n (%) (N=1,703)	Edoxaban 60 mg n (%) (N=582)	Edoxaban 30 mg n (%) (N=1,099)	Edoxaban 15 mg n (%) (N=22)
All bleeding	107 (6.3)	34 (5.8)	72 (6.6)	1 (4.5)
Major bleeding	23 (1.4)	4 (0.7)	19 (1.7)	0 (0.0)
Intracranial bleeding*	3 (0.2)	0 (0.0)	3 (0.3)	0 (0.0)
Gastrointestinal bleeding**	10 (0.6)	1 (0.2)	9 (0.8)	0 (0.0)
Hematuria***	6 (0.4)	2 (0.3)	4 (0.4)	0 (0.0)
Clinically relevant non-major bleeding	36 (2.1)	8 (1.4)	27 (2.5)	1 (4.5)
Nuisance bleeding	50 (2.9)	22 (3.8)	28 (2.5)	0 (0.0)

*Intracranial tumor hemorrhage, cerebral hemorrhage, and subdural hematoma. **Ischemic colitis, hemorrhagic intestinal diverticulum, gastric hemorrhage, gastrointestinal hemorrhage, esophageal hemorrhage, upper gastrointestinal hemorrhage, large intestinal hemorrhage, and acute hemorrhagic ulcerative colitis. ***Hematuria and hemorrhage from urinary tract.

72.9%; isolated distal DVT only 51.4%) and those with initial VTE treatment before edoxaban (PE 68.2%; proximal DVT 51.4%; isolated distal DVT only 31.3%).

Dosage Levels and Dosage Adjustment Factors

Regarding the daily dose at the start of edoxaban treatment, 34.2%, 64.5%, and 1.3% of patients received 60, 30, and 15 mg, respectively.

Of the total 1,703 patients whose data were included in the safety analysis set, information on dosage adjustment factors was available for 1,688 (Figure 2). Of the 63.2% patients with dosage adjustment factors, 92.5% received edoxaban 30 mg. Of the 36.8% without dosage adjustment factors, 83.0% received edoxaban 60 mg, in accordance with the PI. Overall, 1,502 (89.0%) of the 1,688 patients received edoxaban at the recommended dosage. The remainder (186/1,688, 11.0%) received a non-recommended dosage: 125 (7.4%) received a reduced dose (under-dose; 30 mg for 103 [6.1%] and 15 mg for 22 [1.3%]) and 61 (3.6%) received an over-dose (60 mg).

Continuation or Discontinuation of Treatment and Treatment Duration

Of the 1,703 patients whose data were included in the safety analysis set, 1,358 (79.7%) continued and 345 (20.3%) discontinued treatment. The main reason for discontinuation was clinical events or AEs (7.5%), and patients who completed treatment as planned constituted 4.3%. Mean duration of edoxaban treatment during the

3-month (90-day) observation period was 74.5±25.9 days. When patients were stratified by VTE diagnosis, no difference was found in this respect. The mean duration of edoxaban treatment was 74.4±25.9 days, 74.8±25.2, and 74.2±26.5 days in patients with PE, proximal DVT and isolated distal DVT only, respectively. The continuation rate was slightly lower in patients with isolated distal DVT only (77.6%), compared with those with PE (81.8%) and proximal DVT (78.9%).

Safety

The incidence of bleeding AEs during the edoxaban treatment period in the safety analysis set (n=1,703) is shown in Table 2 (details are shown in Supplementary Table 3). Bleeding AEs were reported in 6.3% (n=107) of all patients, with a similar incidence between patients who received low-dose edoxaban (30 mg/day) and patients who received the standard dose (60 mg/day) (6.6% and 5.8%, respectively). The bleeding AEs included major bleeding (1.4%, n=23); the most common type of major bleeding was gastrointestinal bleeding (0.6%, n=10). The cumulative incidence of bleeding AEs is shown in Figure 3A. Approximately two-thirds of bleeding AEs occurred within the first 30 days of edoxaban treatment.

Multivariate analyses identified the following factors associated with significantly increased bleeding risk: pre-treatment Cl_{Cr} ≥30 to ≤50 mL/min and >50 to <80 mL/min (reference: ≥80 mL/min), AST and/or ALT ≥50 to <100 IU (reference: AST and ALT <50 IU), cancer, anemia, con-

Figure 3. Cumulative incidences, as determined by the Kaplan-Meier method. **(A)** Bleeding adverse events during the edoxaban treatment period in the safety analysis set ($n=1,703$). **(B)** Cumulative incidence of venous thromboembolism (VTE) recurrence in the effectiveness analysis set ($n=1,699$). **(C)** Cumulative incidence of VTE recurrence in the effectiveness analysis set for patients with acute VTE ($n=1,023$). ITT, intention to treat.

genital or acquired disease related to bleeding, and concomitant use of NSAIDs other than low-dose aspirin (all $P<0.05$; **Table 3**). The incidence of bleeding AEs was 6.2% (93/1,502) in patients receiving the recommended dose, whereas it was 9.8% (6/61) in patients receiving a non-recommended over-dose, and 6.4% (8/125) in patients

receiving a non-recommended under-dose. The incidence was slightly higher in patients receiving a non-recommended over-dose, but the difference was not significant.

ADRs were reported in 8.7% of patients. Serious ADRs were reported in 2.4% (**Supplementary Table 4**).

Table 3. Significant Factors Associated With Bleeding Adverse Events (All Bleeding) During the Edoxaban Treatment Period, Identified by Multivariate Analysis

	Hazard ratio	95% CI	P value
Pretreatment Cl_{cr}* (reference: ≥80 mL/min)			
<15 mL/min	0.000	0.000, –	0.0269
≥15 to <30 mL/min	1.823	0.530, 6.268	
≥30 to ≤50 mL/min	2.555	1.400, 4.664	
>50 to <80 mL/min	2.071	1.257, 3.410	
Pretreatment AST or ALT (reference: AST and ALT <50 IU)			
AST and/or ALT ≥50 to <100 IU	2.237	1.297, 3.857	0.0167
AST and/or ALT ≥100 to <500 IU	0.382	0.086, 1.687	
AST and/or ALT ≥500 IU	0.000	0.000, –	
Complications			
Cancer	2.384	1.611, 3.529	<0.0001
Anemia	1.938	1.168, 3.217	0.0105
Congenital or acquired disease related to bleeding	4.676	1.792, 12.199	0.0016
Concomitant use of NSAIDs other than low-dose aspirin (during the edoxaban treatment period)	2.122	1.302, 3.459	0.0025
Daily dose at the start of edoxaban treatment (reference: 60 mg)			
30 mg	0.819	0.511, 1.313	0.6879
15 mg	0.655	0.086, 4.967	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; Cl_{cr}, creatinine clearance; NSAID, non-steroidal anti-inflammatory drug.

Effectiveness

The incidence of VTE recurrence in the effectiveness analysis set (n=1,699) was 0.8% (n=14) in the on-treatment population (the on-treatment period being the time during which patients were receiving edoxaban, as opposed to the treatment period, which may have included periods during which edoxaban treatment was interrupted) and 1.2% (n=20) in the intention to treat (ITT) population (during the whole 3-month observation period) (Table 4). The incidence of recurrence of symptomatic VTE in the on-treatment population and the ITT population was 0.4% (n=6) and 0.5% (n=9), respectively. The incidence of VTE recurrence in the on-treatment population was not higher in patients who received low-dose edoxaban (30 mg/day) than in patients who received the standard dose (60 mg/day) (0.4% and 1.5%, respectively).

The incidence of VTE recurrence in the effectiveness analysis set for patients with acute VTE (n=1,023) is shown in Table 5. The incidence of VTE recurrence in the on-treatment population was 0.8% (8/1,023) (Table 5A). When patients were stratified by acute VTE diagnosis, the incidence of VTE recurrence (on-treatment population) was 1.4% (6/420), 0% (0/280) and 0.6% (2/323) in patients with PE, proximal DVT and isolated distal DVT only, respectively (Table 5B). When patients were stratified by with or without initial VTE treatment before edoxaban, the incidence of VTE recurrence (on-treatment population) was 1.3% (7/531) in patients with initial treatment (6 PE patients, 0 proximal DVT patient; 1 isolated distal DVT only patient) and 0.2% (1/492) in patients without initial treatment (0 PE patient; 0 proximal DVT patient; 1 isolated distal DVT only patient) (Table 5C).

The cumulative incidence of VTE recurrence in the effectiveness analysis set (n=1,699) is shown in Figure 3B, and the cumulative incidence of VTE recurrence in the effectiveness analysis set for patients with acute VTE (n=1,023) is shown in Figure 3C. There was no specific trend in the

time of onset of VTE recurrence.

The incidence of VTE recurrence in the on-treatment population in patients who received a non-recommended reduced dose of edoxaban was 0.8% (1/124), which was similar to the incidence in patients who received the recommended dose (0.9%, 13/1,499).

Discussion

In the present interim analysis of data from the postmarketing observational study on edoxaban, we evaluated the safety and effectiveness of edoxaban at 3 months in Japanese patients with VTE in the clinical setting. A relatively large number of patients (n=1,732) were enrolled, representing the real-world VTE patient population. In addition, the study enrolled patients with very high bleeding risk (i.e., those with Cl_{cr} <30 mL/min and concomitant use of DAPT), a group that was excluded from the phase III study, Hokusai-VTE.⁴ The results of the present analysis of data from the early period of treatment revealed that edoxaban did not increase the risk of AEs, including the incidence of bleeding events, and it showed similar effectiveness in terms of prevention of VTE recurrence compared with previous reports; no increase in risks or new safety concerns was noted.

Proportions of VTE patients with high bleeding risk (e.g., the elderly and those with low body weight or renal dysfunction) are greater in Japanese compared with Western populations, as shown by phase III studies of DOACs.^{4,7,16–18} Among the currently available DOACs for VTE patients, edoxaban is the only agent for which the dosage reduction criteria have been established to reduce bleeding risk. In accordance with the PI, patients with high bleeding risk are likely to receive a low dose (30 mg) of edoxaban, therefore obtaining data on the safety and effectiveness of edoxaban in such patients in the real-world setting is particularly important. We found that the safety and effectiveness of

Table 4. VTE Recurrence in the Effectiveness Analysis Set (n=1,699)

	On-treatment population			
	Total n (%) (N=1,699)	Edoxaban 60 mg n (%) (N=582)	Edoxaban 30 mg n (%) (N=1,095)	Edoxaban 15 mg n (%) (N=22)
All	14 (0.8)	9 (1.5)	4 (0.4)	1 (4.5)
Symptomatic	6 (0.4)	2 (0.3)	3 (0.3)	1 (4.5)
PE	2 (0.1)	1 (0.2)	1 (0.1)	0 (0.0)
Symptomatic	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
DVT alone	12 (0.7)	8 (1.4)	3 (0.3)	1 (4.5)
Symptomatic	5 (0.3)	2 (0.3)	2 (0.2)	1 (4.5)
	ITT population (during the whole 3-month observation period)			
	Total n (%) (N=1,699)	Edoxaban 60 mg n (%) (N=582)	Edoxaban 30 mg n (%) (N=1,095)	Edoxaban 15 mg n (%) (N=22)
All	20 (1.2)	11 (1.9)	8 (0.7)	1 (4.5)
Symptomatic	9 (0.5)	2 (0.3)	6 (0.5)	1 (4.5)
PE	3 (0.2)	2 (0.3)	1 (0.1)	0 (0.0)
Symptomatic	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
DVT alone	17 (1.0)	9 (1.5)	7 (0.6)	1 (4.5)
Symptomatic	8 (0.5)	2 (0.3)	5 (0.5)	1 (4.5)

ITT, intention to treat. Other abbreviations as in Table 1.

edoxaban in patients who received the low dose (30 mg/day) were similar to those in patients who received the standard dose (60 mg/day) during the early (3-month) period of treatment.

The present study enrolled a greater proportion of patients with high bleeding risk compared with the Hokusai-VTE⁴ (for comparison: patients aged ≥ 75 years, 13.6%; those with body weight ≤ 60 kg, 12.7%; those with renal function ≤ 50 mL/min, 6.5%; and those with cancer, 9.2%). The patient characteristics in the present study were similar to those reported in the COMMAND VTE Registry¹⁹ and in a study using data from a Japanese healthcare database,²⁰ both of which contain information on patients considered representative of the general population of VTE patients in Japan.

It was found that the dose of edoxaban at the start of treatment was 60 mg, 30 mg, and 15 mg in 34.2%, 64.5%, and 1.3%, respectively, and approximately 90% of patients received a dose in accordance with the PI. The remaining 11.0% did not receive the recommended dose, and the majority of these (7.4%) were under-dosed. The incidence of under-dosing of DOACs was investigated in the RIETE registry, which enrolled patients with VTE receiving DOACs.²¹ In that study, 17% of patients receiving rivaroxaban and 50% of patients receiving apixaban were under-dosed. However, in the present study, the proportion of patients who received an under-dose of edoxaban was low (7.4%). This is considered to be related to appropriate dosage reduction criteria, which have been established only for edoxaban among the currently available DOACs for the treatment of VTE. In the present study, the treatment continuation rate for edoxaban was $\approx 80\%$ at the first 3 months, showing the high tolerability of edoxaban in a real-world setting.

Although a direct comparison is not possible because of differences in patients' characteristics and follow-up periods, the incidence of bleeding AEs was lower in the present study than in the Hokusai-VTE (21.7%).⁴ Although the

incidence of major bleeding in the present study was similar to that in the Hokusai-VTE (1.4%),⁴ it was not higher than in the COMMAND VTE Registry ($\approx 4.0\%$ during the first 3 months).¹⁹ The most common major bleeding AE was gastrointestinal bleeding, which was similar to the findings from the Hokusai-VTE.⁴ The results suggested that edoxaban is not likely to increase bleeding risk and that it is tolerable in the real-world settings of Japanese VTE patients during their first 3 months of treatment.

As mentioned, unlike other DOACs, edoxaban is the only agent for which dosage reduction criteria have been defined, and its usefulness was demonstrated in the Hokusai-VTE.⁴ Based on these criteria, in clinical practice patients with a high bleeding risk are likely to receive low-dose edoxaban (30 mg/day). In fact, in the present study, which enrolled Japanese VTE patients in a real-world setting, approximately two-thirds of patients received low-dose edoxaban (30 mg/day), and the safety profile was similar to that in patients who received the standard dose (60 mg/day), thereby showing the high tolerability of edoxaban 30 mg/day in clinical practice.

Although the incidence of bleeding AEs was not high, several factors were identified as being associated with bleeding AEs: the complications of renal dysfunction, hepatic dysfunction, cancer, anemia, and bleeding-related congenital or acquired diseases, and the concomitant use of NSAIDs other than low-dose aspirin. The bleeding risk factors identified in the present analysis are similar to those reported in previous studies.^{22–26} In the subanalysis of the Hokusai-VTE, female sex was a risk factor for bleeding AEs,²⁷ and low body weight was also identified as a risk factor for bleeding AEs during treatment with DOACs.²⁸ However, in the present interim analysis at 3 months, female sex and low body weight were not identified as significant risk factors associated with bleeding AEs. Nevertheless, we found that the incidence of bleeding AEs tended to be slightly higher in female and low body weight patients: 5.8% (39/676) and 6.6% (68/1,027) in male and

Table 5. VTE Recurrence in the Effectiveness Analysis Set for Patients With Acute VTE (n=1,023), by Dose (A), by VTE Diagnosis (On-Treatment Population) (B) and by VTE Diagnosis as Well as With/Without Drug Treatment for VTE Before Starting Edoxaban Treatment (On-Treatment Population) (C)

On-treatment population								
(A)	Total n (%) (N=1,023)	Edoxaban 60 mg n (%) (N=361)	Edoxaban 30 mg n (%) (N=655)	Edoxaban 15 mg n (%) (N=7)				
All	8 (0.8)	6 (1.7)	2 (0.3)	0 (0.0)				
Symptomatic	2 (0.2)	1 (0.3)	1 (0.2)	0 (0.0)				
PE	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)				
Symptomatic	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)				
DVT alone	7 (0.7)	6 (1.7)	1 (0.2)	0 (0.0)				
Symptomatic	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)				
ITT population (during the whole 3-month observation period)								
	Total n (%) (N=1,023)	Edoxaban 60 mg n (%) (N=361)	Edoxaban 30 mg n (%) (N=655)	Edoxaban 15 mg n (%) (N=7)				
All	14 (1.4)	8 (2.2)	6 (0.9)	0 (0.0)				
Symptomatic	5 (0.5)	1 (0.3)	4 (0.6)	0 (0.0)				
PE	2 (0.2)	1 (0.3)	1 (0.2)	0 (0.0)				
Symptomatic	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)				
DVT alone	12 (1.2)	7 (1.9)	5 (0.8)	0 (0.0)				
Symptomatic	4 (0.4)	1 (0.3)	3 (0.5)	0 (0.0)				
On-treatment population								
(B)	PE n (%) (N=420)	Proximal DVT n (%) (N=280)	Isolated distal DVT only n (%) (N=323)					
All	6 (1.4)	0 (0.0)	2 (0.6)					
Symptomatic	2 (0.5)	0 (0.0)	0 (0.0)					
PE	1 (0.2)	0 (0.0)	0 (0.0)					
Symptomatic	1 (0.2)	0 (0.0)	0 (0.0)					
DVT alone	5 (1.2)	0 (0.0)	2 (0.6)					
Symptomatic	1 (0.2)	0 (0.0)	0 (0.0)					
On-treatment population								
Drug treatment for VTE before starting edoxaban treatment								
(C)	Yes				No			
	Total n (%) (N=531)	PE n (%) (N=286)	Proximal DVT n (%) (N=144)	Isolated distal DVT only n (%) (N=101)	Total n (%) (N=492)	PE n (%) (N=134)	Proximal DVT n (%) (N=136)	Isolated distal DVT only n (%) (N=222)
All	7 (1.3)	6 (2.1)	0 (0.0)	1 (1.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.5)
Symptomatic	2 (0.4)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PE	1 (0.2)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Symptomatic	1 (0.2)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
DVT alone	6 (1.1)	5 (1.7)	0 (0.0)	1 (1.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.5)
Symptomatic	1 (0.2)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations as in Tables 1,4.

female patients, respectively, and 9.0% (7/78), 6.5% (59/913), and 5.9% (41/699) in patients with body weight <40 kg, 40–60 kg, and >60 kg, respectively. The results reported for the Hokusai-VTE were for a 1-year observation, whereas those for the present study were interim results for 3 months, so we plan to conduct the same multivariate analyses at the completion of the study at 1 year.

Regarding the effectiveness of edoxaban in terms of prevention of VTE recurrence, although a direct comparison is again not possible because of differences in patients' characteristics and follow-up periods, the incidence of VTE recurrence was lower in the present analysis than in

the Hokusai-VTE (1.6% in the on-treatment population and 3.2% in the ITT population).⁴ Moreover, the incidence of recurrence of symptomatic VTE was low in the present analysis, providing evidence to support the effectiveness of edoxaban.

Although the use of edoxaban 30 mg would be expected to be beneficial in terms of safety, lack of effectiveness at this lower dose is a potential concern. However, the present analysis showed that the incidence of VTE recurrence in patients receiving 30 mg/day was not higher than in patients receiving 60 mg/day. Therefore, there were no major concerns about the effectiveness of edoxaban at a

low dose.

With regard to anticoagulation therapy for VTE and prevention of its recurrence, treatment of patients with acute VTE (i.e., PE or proximal DVT) is particularly important. The present analysis showed that the incidence of VTE recurrence in these patients was also low. In addition, although (according to the PI) an initial drug treatment for VTE (i.e., a heparin lead-in) is recommended before the start of edoxaban treatment for acute VTE, in the present study, almost 50% of patients did not receive initial VTE treatment (**Supplementary Table 2**). However, the incidence of VTE recurrence was not higher, as compared with those with initial VTE treatment. Nevertheless, a higher proportion of patients without initial VTE treatment were outpatients, and had isolated distal DVT only or asymptomatic VTE, which are relatively mild and were not included in the pre-approval clinical trials for edoxaban (**Supplementary Table 5**). These background factors may have affected the results. Generally, patients with PE and proximal DVT have a higher risk of recurrence than those with isolated distal DVT, and once VTE has recurred, the prognosis is likely to be fatal. Of the 8 patients who had VTE recurrence, 6 had PE. Therefore, despite the findings from the present study, we consider that initial treatment with heparin lead-in is necessary, particularly for PE and proximal DVT patients. Of note, the incidence of bleeding AEs was 4.9% (26/532) and 8.5% (42/492) in patients with and without initial VTE treatment before edoxaban, respectively, and the difference was not significant.

A lack of effectiveness in under-dosed patients was also a matter of concern. In the RIETE registry, patients receiving under-doses of DOACs experienced a higher rate of VTE recurrence, and similar results were shown in some studies of patients with AF.^{21,29,30} In the present study, the incidence of VTE recurrence was not increased in under-dosed patients. However, it is not possible to draw a firm conclusion from the results at 3 months, so further monitoring of the outcomes in these patients will be necessary.

Study Limitations

First, it was an observational study, without control groups. Second, the observation period was short; this was an interim analysis of data collected at 3 months. Third, comparison of the safety and effectiveness of edoxaban in this study with the results of analyses of safety and efficacy from clinical trials of edoxaban are difficult because of the short duration of the observation period and the different background characteristics (e.g., patients with very high bleeding risk were included in ETNA-VTE-Japan but excluded from the Hokusai-VTE⁴). However, ETNA-VTE-Japan is an ongoing study, and analysis of data collected at the end of the whole 12-month observation period will clarify the safety profile and effectiveness of edoxaban in real-world clinical practice, and will highlight ways to improve adherence to DOAC therapy.

Conclusions

Our interim results confirmed no major concerns about the safety and effectiveness of edoxaban in Japanese patients with VTE in the first 3 months of treatment in a real-world setting. Furthermore, the results show no major concerns about the safety and effectiveness of low-dose edoxaban (30mg/day), which is likely to be prescribed for patients

with high bleeding risk.

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Supplementary Files

Please find supplementary file(s);
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