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ORIGINAL ARTICLE

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Effect of the number of dose adjustment factors on bleeding risk in patients receiving 30 mg/day edoxaban

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Abstract

What is known and objective: Edoxaban has three dose adjustment factors (creatinine clearance, 15-50 mL/min; body weight, 60 kg or less; and concomitant medication with potent P-glycoprotein inhibitors) to prevent bleeding that results from elevated blood concentrations of the drug. A dose reduction (from 60 to 30 mg/day of edoxaban) is recommended for patients with even one of those. However, it is not clear whether 30 mg/day of edoxaban is adequate for patients with multiple dose adjustment factors. We thus investigated the association between the number of the dose adjustment factors and bleeding risk in patients receiving edoxaban.

Methods: We retrospectively analysed 198 patients who received 30 mg/day of edoxaban between April 2015 and March 2017 with follow-up for 1 year.

Results: The incidences of major bleeding were 1.4%, 7.3% and 20.0% in patients with 0-1, 2 and 3 dose adjustment factors, respectively. The Cox proportional hazards regression model revealed that the risk of major bleeding was higher in patients with 2 (hazard ratio [HR]: 5.80, 95% confidence interval [CI]: 0.96-44.05, $P = .055$) or 3 (HR: 17.70, 95% CI: 2.12-147.70, $P = .012$) dose adjustment factors than in those with 0-1 dose adjustment factor.

What is new and conclusion: This is the first study to evaluate the risk of bleeding in patients administered 30 mg/day of edoxaban based on the number of dose adjustment factors in clinical practice. For patients receiving edoxaban, as the number of the dose adjustment factors increases, the risk of major bleeding is elevated. In patients with multiple dose adjustment factors, not only one level of dose reduction, but further dose reductions may be considered. Further studies with a larger sample size are needed to confirm these findings.

KEYWORDS

atrial fibrillation, bleeding, direct oral anticoagulants, dose reduction, edoxaban, venous thromboembolism

1 | WHAT IS KNOWN AND OBJECTIVE

Direct oral anticoagulants (DOACs) are used for the prevention and/or treatment of stroke, systemic embolism (SE), and venous thromboembolism (VTE). Although the influence of food and drug on the anticoagulant effect of DOACs is smaller, compared to that with warfarin, coagulation tests such as PT-INR cannot reflect the effect of DOACs.[1] The dosage of DOACs is usually adjusted according to the criteria of the recommended dose reduction.

Edoxaban has three dose adjustment factors [an estimated creatinine clearance (CrCl) of 15-50 mL/min, a body weight of 60 kg or less, or concomitant treatment with potent P-glycoprotein (P-gp) inhibitors] in Japan, as well as in Europe.[2,3] These dose adjustment factors can increase the blood concentration of edoxaban, which results in an increased risk of bleeding.[4] Therefore, for atrial fibrillation or VTE indications, a dose reduction of edoxaban is recommended for patients with dose adjustment factors (from 60 to 30 mg/day).[2,3] However, it is not clear whether 30 mg/day of edoxaban is adequate for patients with multiple dose adjustment factors.

In this study, we aimed to determine the association between the number of the dose adjustment factors and the bleeding risk in patients receiving edoxaban.

2 | METHODS

This retrospective study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Epidemiological Research by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare of Japan, and the protocol was approved by the institutional review board of the Kobe City Medical Center General Hospital, Japan (Approval No. zn190101).

Patient characteristics including age, sex, body weight, medical history, incidence of bleeding complications, concomitant medications and laboratory data were reviewed using the electronic medical record system. If patients had even one of the three dose adjustment factors (estimated CrCl 15-50 mL/min, body weight ≤60 kg or concomitant treatment with potent P-gp inhibitors), a dose reduction in edoxaban (from 60 to 30 mg/day) was recommended.[2,3]

A total of 640 consecutive patients who received low-dose edoxaban (30 mg/day) in our hospital between 1 April 2015 and 31 March 2017 were included in the present study. The patients were excluded if they received low-dose edoxaban for <3 months (n = 402), started the treatment with edoxaban at another institution (n = 35), or had missing body weight (n = 2) or serum creatinine (n = 3) data. The remaining 198 patients were followed up for 1 year.

The primary outcomes were the incidences of bleeding complications related to the number of dose adjustment factors. Bleeding complications were evaluated by the composite of bleeding events as follows: (a) major bleeding, (b) clinically relevant non-major bleeding (CRNMB) and (c) minor bleeding.[5] Major bleeding was defined as clinically overt bleeding accompanied by a decrease in haemoglobin levels of at least 2 g/dL or the requirement for a transfusion of at least 2 units of packed red blood cells, occurring at a critical site (intracranial, intraocular, intraspinal, intra-articular, intramuscular with compartment syndrome, pericardial or retroperitoneal), or resulting in death.[6] CRNMB was defined as acute or subacute clinically overt bleeding that did not satisfy the criteria of major bleeding, which led to hospitalization for bleeding, physician-guided medical or surgical treatment for bleeding, or a change in antithrombotic therapy (including the study drug) due to bleeding.[5] Minor bleeding was defined as all acute, clinically overt bleeding events not meeting the criteria of either major bleeding or CRNMB. The secondary outcomes were the associations between dose adjustment factors and major bleeding, or CRNMB.

2.1 | Statistical analysis

Statistical analyses were performed using the JMP 13.2.1 (SAS Institute Inc). For continuous data, values were presented as the mean ± standard deviation (SD). Chi-square test and analysis of variance were used to assess differences between the four groups based on the number of dose adjustment factors. Kaplan-Meier curves for the cumulative incidence of major bleeding and CRNMB were estimated for the three groups based on the number of dose adjustment factors with differences assessed statistically by the log-rank test. A Cox proportional hazards regression model was used to obtain the hazard ratio (HR) and the associated 95% confidence interval (CI) and to evaluate risk factors for major bleeding and CRNMB. All *P*-values < .05 were considered statistically significant.

3 | RESULTS

The patient characteristics are shown in Table 1. Vast majority of the patients were less than 60 kg but only 22 were on the P-gp inhibitors. Only 10 patients had 3 dose adjustment factors. The most common edoxaban indication was deep vein thrombosis (DVT). Three patients died during the study period due to cancer progression, interstitial pneumonia and unknown, one of which had no dose adjustment factor and two had one factor. The median follow-up period was 365 days (range, 90 to 365).

Seven, 15 and 24 patients had major bleeding, CRNMB and minor bleeding, respectively. The percentage of patients with CrCl 15-50 mL/min in major bleeding group [5/7 (71.4%)] was higher than those in CRNMB group [3/15 (20.0%)] and others [46/176 (26.1%)]. Similarly, percentage of patients with body weight ≤ 60 kg [7/7 (100%)] and concomitant P-gp inhibitor [2/7 (28.6%)] in major bleeding group was higher than those in CRNMB group and others.

Figure 1 shows the relationships between the number of the dose adjustment factors and the incidences of major bleeding or CRNMB. The incidences of major bleeding at 1 year were 1.4% (2/147), 7.3% (3/41) and 20.0% (2/10) for 0-1, 2 and 3 dose adjustment factors, respectively. Kaplan-Meier curves for cumulative major bleeding or

TABLE 1 Patient characteristics

	Overall (n = 198)	Number of dose adjustment factors				
		0 (n = 27)	1 (n = 120)	2 (n = 41)	3 (n = 10)	*P*-value
Age, years (mean ± SD)	70.1 ± 12.6	70.1 ± 11.7	69.8 ± 12.6	77.6 ± 9.9	72.9 ± 10.2	<.001
Male/female, n	78/120	20/7	40/80	14/27	4/6	.001
Body weight, kg (mean ± SD)	53.7 ± 11.3	69.3 ± 7.9	53.5 ± 11.3	47.9 ± 7.1	48.0 ± 9.3	<.001
Edoxaban indication, n (%)						
DVT	79	10 (37.0%)	54 (45.0%)	12 (29.3%)	3 (30.0%)	N/A
Atrial fibrillation	67	12 (44.4%)	29 (24.2%)	19 (46.3%)	7 (70.0%)	
PE	17	1 (3.7%)	12 (10.0%)	4 (9.8%)	0 (0%)	
DVT + PE	14	2 (7.4%)	10 (8.3%)	2 (4.9%)	0 (0%)	
Atrial flutter	4	0 (0%)	2 (1.7%)	2 (4.9%)	0 (0%)	
Cardiogenic embolism	4	0 (0%)	4 (3.3%)	0 (0%)	0 (0%)	
Other	13	2 (7.4%)	9 (7.5%)	2 (4.9%)	0 (0%)	
Comorbidity, n (%)						
Hypertension	89	16 (59.3%)	46 (38.3%)	20 (48.8%)	7 (70.0%)	N/A
Cancer	79	11 (40.7%)	55 (45.8%)	11 (26.8%)	2 (20.0%)	
Diabetes	37	6 (22.2%)	20 (16.7%)	10 (24.4%)	1 (10.0%)	
Heart failure/low LVEF	28	2 (7.4%)	15 (12.5%)	8 (19.5%)	3 (30.0%)	
Coronary artery disease	24	3 (11.1%)	11 (9.2%)	6 (14.6%)	4 (40.0%)	
Stroke/TIA/systemic embolism	19	2 (7.4%)	10 (8.3%)	5 (12.2%)	2 (20.0%)	
Peripheral artery disease	15	3 (11.1%)	9 (7.5%)	2 (4.9%)	1 (10.0%)	
Cerebral haemorrhage	6	3 (11.1%)	3 (2.5%)	0 (0%)	0 (0%)	
Concomitant medication, n (%)						
PPI or H2RA	94	11 (40.7%)	50 (41.7%)	27 (65.9%)	6 (60.0%)	.040
Antiplatelet	31	4 (14.8%)	16 (13.3%)	8 (19.5%)	3 (30.0%)	N/A
P-gp inhibitor	22	0 (0%)	5 (4.2%)	7 (17.1%)	10 (100%)	N/A
NSAIDs	10	2 (7.4%)	5 (4.2%)	2 (4.9%)	1 (10.0%)	N/A
CrCl (mL/min), n (%)						
>80	43	9 (33.3%)	32 (26.7%)	2 (4.9%)	0 (0%)	.004
>50-80	101	18 (66.7%)	81 (67.5%)	2 (4.9%)	0 (0%)	<.001
>30-50	49	0 (0%)	7 (5.8%)	33 (80.5%)	9 (90.0%)	<.001
>15-30	5	0 (0%)	0 (0%)	4 (9.8%)	1 (10.0%)	N/A

Abbreviations: CrCl, creatinine clearance; DVT, deep vein thrombosis; H2RA, histamine 2 receptor antagonist; LVEF, left ventricular ejection fraction; NSAIDs, non-steroidal anti-inflammatory drugs; PE, pulmonary embolism; P-gp, P-glycoprotein; PPI, proton-pump inhibitor; TIA, transient ischaemic attack.

CRNMB are shown in Figure 2. There were significant differences in the risk of major bleeding among the three groups (P = .001).

When compared to patients with 0-1 dose adjustment factor, the risk of major bleeding for patients with 2 or 3 factors was increased (Table 2). In contrast, the risk of major bleeding or CRNMB tended to be higher in patients with 3 dose adjustment factors than in those with 0-1 dose adjustment factor, but this was not significant (Table 2). Similarly, any bleeding events such as major bleeding, CRNMB and minor bleeding tended to be higher in patients with 3 dose adjustment factors than in those with 0-2 dose adjustment factor [50.0% (5/10) vs 21.8% (41/188), P = .054]. No stroke or SE events for atrial fibrillation and atrial flutter were observed in our patients (0/71). The incidence of the new/recurrent of VTE or other thromboembolism events was 3.1% (4/127).

4 | DISCUSSION

In this retrospective study, we investigated the risk of bleeding associated with the use of low-dose edoxaban based on the number of dose adjustment factors. The results showed that the risk of major bleeding was elevated as the number of the dose adjustment factors

increased (Figure 1). A Cox proportional hazards regression model revealed that the risk of major bleeding was significantly higher in patients with 3 dose adjustment factors, even if they received a half-dose (30 mg/day) of edoxaban, as compared to that in patients with 0-1 dose adjustment factor (Table 2).

To date, each of the dose adjustment factors has been reported to elevate the blood concentration of edoxaban.[7-9] For example, the area under the curve (AUC) of edoxaban was 25, 57 and 97% higher in patients with mild (CrCl = 65 mL/min), moderate (CrCl = 40 mL/min) and severe (CrCl = 20 mL/min) renal impairment than in those with normal renal function.[7] Further, the blood concentration of edoxaban in a ≤60 kg of body weight group was 1.8-fold higher than that in the >60 kg group.[8] Moreover, the AUC of edoxaban increased by 73% concomitant with the use of cyclosporine, which is a P-gp inhibitor.[9] High blood concentrations of edoxaban are also associated with an increased risk of bleeding.[4] Therefore, if patients had at least one dose adjustment factor, the dose of edoxaban was halved (from 60 to 30 mg/day) in phase 3 clinical trials.[10,11] A sub-analysis of this trial showed that 30 mg/day of edoxaban, with the dose adjustment factor, avoided excess drug exposure and preserved the efficacy and safety, as compared to those with 60 mg/day in the non-dose adjustment factor group.[12] According to these clinical trials, only one level of dose reduction is indicated in the package insert of edoxaban.[2,3] Therefore, the same reduced dose of edoxaban is administered in clinical practice, regardless of whether patients have one or multiple dose adjustment factors. However, bleeding risk can increase depending on the number of dose adjustment factors. This is the first study to evaluate the risk of bleeding in patients administered low-dose edoxaban based on the number of dose adjustment factors in clinical practice.

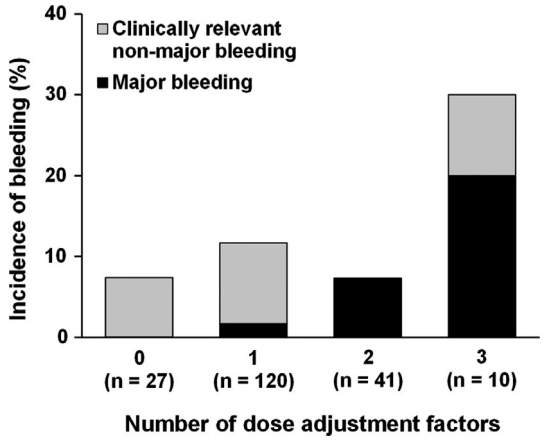

FIGURE 1 Incidences of major bleeding and clinically relevant non-major bleeding based on the number of dose adjustment factors. The numbers of patients in each group are shown

Our results showed that the incidence of major bleeding in all patients (3.54% per year) was similar to that reported in a previous study (3.05% per year) in which 30 mg/day of edoxaban was administered as a reduced dose.[4] However, the incidences of major bleeding were elevated as the number of dose adjustment factors increased (Figure 1). Especially, a Cox proportional hazards model revealed that the risk of major bleeding was significantly higher in patients with all three dose adjustment factors (Table 2). It seems that the elevated risk of bleeding resulted from an additive increase in the blood concentration due to the multiple dose adjustment factors. Thus, the currently recommended dose reduction of only one level is likely insufficient to prevent bleeding complications.

Currently available doses of edoxaban for atrial fibrillation and VTE are 60 and 30 mg/day. Recently, it was reported that the AUC and bleeding risk of 15 mg/day edoxaban for atrial fibrillation patients with severe renal impairment were similar to that of

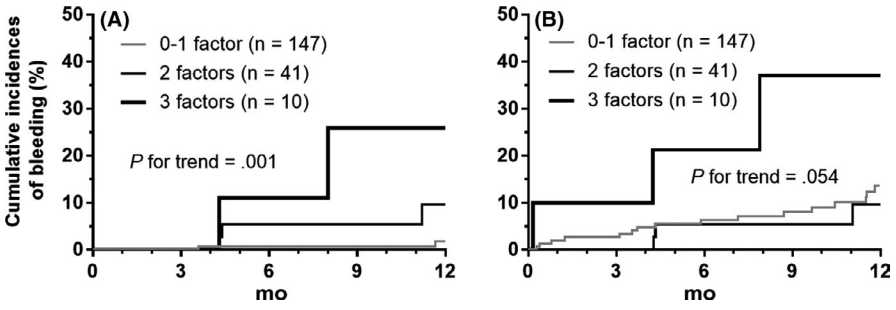

FIGURE 2 Kaplan-Meier curves of major bleeding (A) and clinically relevant non-major bleeding (B) based on the number of dose adjustment factors. Thick line: patients with 3 dose adjustment factors. Thin line: patients with 2 dose adjustment factors. Grey line: patients with 0-1 dose adjustment factor

TABLE 2 Hazard ratios of major bleeding and clinically relevant non-major bleeding events

Number of dose adjustment factors	Major bleeding			Major bleeding or clinically relevant non-major bleeding		
	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
0-1	1.00 (reference)	–	–	1.00 (reference)	–	–
2	5.80	0.96-44.05	.055	0.70	0.16-2.10	.554
3	17.70	2.12-147.70	.012	3.65	0.85-11.00	.077

Abbreviation: CI: confidence interval.

30 mg/day for patients with normal renal function or mild renal impairment.[13,14] Similar to the assessment of 15 mg/day edoxaban for patients with severe renal impairment, evaluating the efficacy and safety of lower-dose edoxaban for patients with atrial fibrillation or VTE who have multiple dose adjustment factors might be needed.

This study has some limitations. First, the study retrospectively evaluated bleeding events. Therefore, the primary endpoint of this study was major bleeding events because sometimes minor bleeding events were not written in the medical record. Second, although we investigated the incidences of thromboembolism events, the sample size was too small to evaluate the efficacy of edoxaban. Therefore, this study could not confirm the efficacy of 30 mg/day edoxaban for patients with 0-3 dose adjustment factors. The appropriateness of dose adjustment of edoxaban should be evaluated by not only the risk of bleeding, balancing the clinical benefit for thromboembolism with bleeding. Finally, the blood concentration of edoxaban or anti-factor Xa activity was not measured.

5 | WHAT IS NEW AND CONCLUSION

This is the first study to evaluate the risk of bleeding in patients administered 30 mg/day of edoxaban based on the number of dose adjustment factors in clinical practice. The results of this study suggested that for patients receiving edoxaban, as the number of dose adjustment factors increases, the risk of major bleeding is also elevated, based on a 1-year follow-up study. Thus, for patients with multiple dose adjustment factors, not only one level of dose reduction but further dose reductions may be considered. Further studies with a larger sample size are needed to confirm these findings.

CONFLICT OF INTEREST

YF received speaker's bureaus from Daiichi Sankyo Co., Ltd.

AUTHOR CONTRIBUTIONS

TT, HI and HN conceived and designed this study. TT, HI, HN and MK collected and analysed data. NM, TK, YF and TH supervised the conduct of this study. TT and IH drafted the manuscript, and all authors contributed substantially to its revision. All authors read and approved the final manuscript.

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