Renal Replacement Therapy

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Efficacy and safety of edoxaban tosylate hydrate 15 mg in the prevention of venous thromboembolism in patients with impaired renal function after orthopedic surgery of the lower extremities

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Abstract

Background: Although not indicated in the USA, edoxaban tosylate hydrate 15 mg is used for venous thromboembolism (VTE) prophylaxis after orthopedic surgery of the lower extremities in Japan. However, its efficacy and safety in patients with impaired renal function have not been fully evaluated. We aimed to investigate the intervention's effectiveness in these patients.

Methods: From 2018 to 2020, patients who underwent total hip arthroplasty, total knee arthroplasty, hip fracture surgery, or knee arthroplasty single granule replacement and with renal dysfunction were evaluated. Safety was evaluated according to bleeding occurrence during edoxaban treatment and liver function endpoints. Patients were divided into the 15- and 30-mg oral groups, including 23 patients with impaired renal function and 209 with normal renal function, respectively.

Results: VTE incidence in the 15- and 30-mg groups was 8.7% and 8.6%, respectively; the intergroup difference was insignificant (odds ratio [OR] 0.99; 95% confidence interval [CI] 0.22–4.56; $p = 1.00$). Bleeding did not occur in the 15-mg group and was noted in 9 patients in the 30-mg group during treatment with edoxaban; the intergroup difference was insignificant ($p = 1.00$). The increase in aspartate aminotransferase and alanine aminotransferase levels was 30% in the 15-mg group and 19% in the 30-mg group, with no difference between the groups ($p = 0.27$). Multivariate analysis showed that the dose of edoxaban was not a significant factor associated with the incidence of VTE (adjusted OR 2.31; 95% CI 0.39–13.8; $p = 0.36$).

Conclusions: Edoxaban 15 mg in patients with impaired renal function may be as effective as edoxaban 30 mg in patients with normal renal function. However, the number of cases included in this study was small and the power was insufficient; therefore, a study with a larger sample size is desirable.

Keywords: Edoxaban tosylate, Heparin, Deep vein thrombosis, Arthroplasty, Pulmonary thromboembolism

Background

Deep venous thrombosis (DVT) is a major complication that can develop after orthopedic surgery, and in rare cases, it may lead to fatal pulmonary thromboembolism

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(PTE). Therefore, DVT prevention is very important. In orthopedics, the instances of total hip arthroplasty (THA), total knee arthroplasty (TKA), unicompartmental knee arthroplasty (UKA), and proximal hip fracture surgery (HFS) for the management of osteoporosis are increasing with the aging of the population. All these surgeries are classified as procedures with a high risk of venous thromboembolism (VTE) [1].

Conventionally, low-molecular-weight heparin and unfractionated heparin have been used as standard drugs for VTE prophylaxis after orthopedic surgery of the lower extremities. However, the administration of these drugs is complicated because they are injectables. In Japan, dabigatran, apixaban, and rivaroxaban are not indicated for the prevention of VTE after lower limb orthopedic surgery. Edoxaban tosylate hydrate (edoxaban) was launched in 2011 and is the only direct oral anticoagulant available for VTE prophylaxis after lower limb orthopedic surgery in Japan. Although edoxaban 30 mg/day is usually used for VTE prophylaxis after orthopedic surgery of the lower extremities, the package insert in Japan states, "In patients with creatinine clearance (Ccr) of 30 mL/min or more but less than 50 mL/min, the dosage should be reduced to 15 mg once daily after assessing each patient's risk of developing venous thromboembolism and bleeding." However, in the STARS-J-V and STARS-E3 studies [2, 3], phase III trials of edoxaban in patients scheduled to undergo THA and TKA, respectively, edoxaban 15 mg was not useful, and its clinical efficacy could not be confirmed.

Several studies have evaluated the efficacy of edoxaban 15 mg in patients with normal renal function [4, 5]. However, to our knowledge, no study has evaluated its efficacy in patients with reduced renal function. Therefore, in this study, we investigated the efficacy and safety of edoxaban 15 mg for the prevention of VTE after orthopedic surgery of the lower limbs in patients with impaired renal function.

Methods

Target patients

Patients who underwent THA, TKA, HFS, or UKA between January 1, 2018, and December 31, 2020, at the Department of Orthopedics at Kariya Toyota General Hospital (henceforth referred to as "our hospital") were considered. Of these patients, those with 30 mL/min ≤ Ccr < 50 mL/min and who received edoxaban 15 mg, and those with 50 mL/min ≤ Ccr and who received edoxaban 30 mg for VTE prophylaxis were included in the study. Patients with Ccr < 30 mL/min or who did not use edoxaban with preoperative DVT or with unknown DVT were excluded.

Investigation method

This retrospective study was conducted using electronic medical records. Data for the following background characteristics were collected: age, sex, weight, body mass index, renal function, medical history, and concomitant medications. Ccr was calculated using the Cockcroft–Gault equation: Ccr (mL/min) = (140−age) × weight/(72 × serum creatinine value); for female patients, the value was multiplied by 0.85. Furthermore, a history of intracranial hemorrhage, stroke, gastrointestinal bleeding, VTE, and malignancy was investigated.

The concomitant medications that were taken included P-glycoprotein inhibitors (quinidine sulfate hydrate, verapamil hydrochloride, erythromycin, cyclosporine, azithromycin, clarithromycin, itraconazole, diltiazem, amiodarone hydrochloride, and HIV protease inhibitors), antiplatelet agents (low-dose aspirin, ticlopidine hydrochloride, clopidogrel, prasugrel hydrochloride, ticagrelor, and cilostazol), HMG-CoA reductase inhibitors, low-dose estrogen preparations, selective estrogen receptor modulators (raloxifene hydrochloride and bazedoxifene acetate), corticosteroids, tranexamic acid, antidepressants (serotonin noradrenergic reuptake inhibitors, selective serotonin reuptake inhibitors, noradrenergic and specific serotonergic antidepressants, tricyclic antidepressants, tetracyclic antidepressants, and lithium carbonate), and antipsychotics (phenothiazines, butyrophenones, benzamides, serotonin-dopamine antagonists, multi-acting receptor-targeted antipsychotics, and aripiprazole).

Efficacy was assessed by the incidence of new VTE on postoperative day 7 based on lower extremity ultrasonography. Safety was assessed based on the presence or absence of bleeding during edoxaban treatment and liver function endpoints. Regarding the incidence of hemorrhagic events, entries related to bleeding were extracted from the electronic medical records.

Bleeding was divided into major bleeding, clinically relevant non-major (CRNM) bleeding, and minor bleeding, with major bleeding ascertained according to the International Society on Thrombosis and Hemostasis criteria [6]. CRNM bleeding was defined as bleeding that did not meet the criteria for major bleeding but was associated with a hematoma (at least 5 cm in length), nosebleed, or gingival bleeding (for at least 5 min), gastrointestinal bleeding, or gross hematuria (persistent after 24 h), or bleeding assessed as clinically significant. Regarding minor bleeding, all other bleeding events, including microscopic hematuria, that were not categorized as major or CRNM bleeding, were considered. Liver function endpoints were investigated by determining aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels by blood sampling on

postoperative day 10 to check if they exceeded 1.5- or threefold the institutional standard.

Sample size

To detect a 17% difference in the incidence of VTE between the edoxaban 15- and 30-mg groups, a sample size of 132 patients (66 in each group) was estimated to achieve a statistical power of 80% based on the estimates of 3% and 20% risk of VTE in the edoxaban 30- and 15-mg groups, respectively. The incidence of VTE in patients who received edoxaban 30 mg was estimated from a previous report [3]. The incidence of VTE in patients with impaired renal function who received edoxaban 15 mg was estimated to be approximately 20%, expecting the same efficacy as that of edoxaban 30 mg in patients with normal renal function, which has been reported in the past [5]. The risk of VTE in the absence of thromboprophylaxis after orthopedic surgery varies widely; however, it was reported to be 60–70% in a previous study conducted among Asian patients [7]. The type I error (α) was 0.05.

Statistical methods

EZR version 1.54 (Jichi Medical University Saitama Medical Center, Japan) was used for statistical analysis [8]. Mann–Whitney U test and Student's *t*-test were used for comparing continuous variables after confirming the normality and distribution of data for two-group comparisons, as appropriate. Fisher's exact test was used to compare nominal variables. Statistical significance was set at $p < 0.05$. Multivariate analysis was performed using a logistic regression model.

Adjustment for patient background characteristics

Any significant differences in patients' background characteristics between the two groups were corrected for by multivariate analysis.

Ethical considerations

This study was conducted according to the Declaration of Helsinki 1964 and per subsequent revisions (https://www.wma.net/), the "Medical Guidelines for Medical and Health Research Involving Human Subjects," and the "Guide for the Appropriate Handling of Personal Information for Medical and Nursing Care Professionals." Approval was obtained from the hospital's ethics review committee, and adequate consideration was given to the protection of personal data (approval no. 577).

Results

Patient characteristics

The patient inclusion flowchart for the study is shown in Fig. 1, and the patients' background data are shown in Table 1. The 15-mg group had 23 patients with impaired renal function, and the 30-mg oral group comprised 209 patients with normal renal function. The Ccr of the 15-mg group was significantly lower than that of the 30-mg group; furthermore, the patients in the 15-mg group were also significantly older than those in the

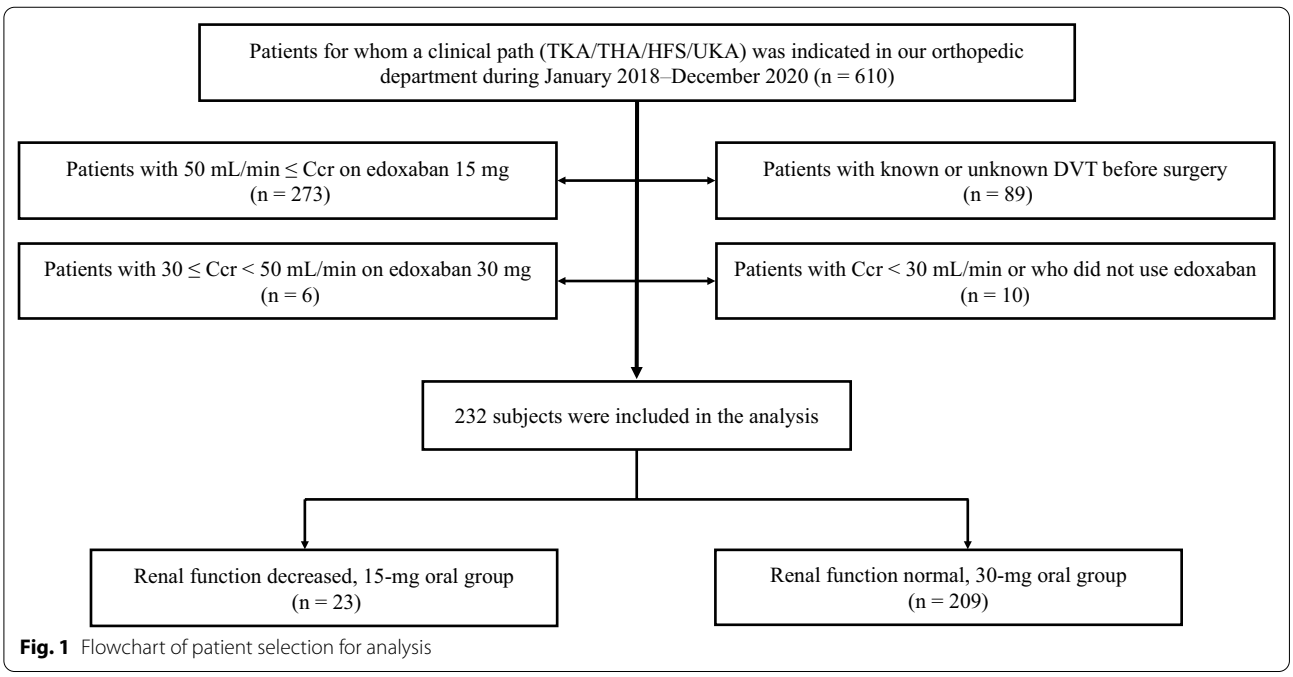

Fig. 1 Flowchart of patient selection for analysis

Table 1 Characteristics of the patients

	Edoxaban 15 mg (n = 23)	Edoxaban 30 mg (n = 209)	*p* value
Sex			
Male	6 (26.1%)	51 (24.4%)	0.80
Female	17 (73.9%)	158 (75.6%)	
Age (years), median (IQR)	81 (77.5–86.5)	71 (65–78)	< 0.01
Body weight (kg), median (IQR)	55 (51.7–65.3)	60.4 (51.0–69.1)	0.31
Body mass index, median (IQR)	23.8 (21.8–29.8)	25.8 (22.1–28.2)	0.73
Creatinine clearance (mL/min), median (IQR)	44.5 (38.1–47.0)	101.4 (79.4–125.1)	< 0.01
Surgical intervention			
TKA	10 (43.5%)	65 (31.1%)	0.56
THA	9 (39.1%)	94 (45.0%)	
HFS	3 (13.0%)	25 (12.0%)	
UKA	1 (4.3%)	25 (12.0%)	
Medical history			
Intracranial hemorrhage	1 (4.3%)	6 (2.9%)	0.52
Gastrointestinal bleeding	1 (4.3%)	4 (1.9%)	0.41
Venous thromboembolism	0	3 (1.4%)	1.00
Malignant tumor	1 (4.3%)	18 (8.6%)	0.70
Concomitant medication			
P-glycoprotein inhibitor	1 (4.3%)	2 (1.0%)	0.27
Antiplatelet agent	3 (13.0%)	11 (5.3%)	0.15
Statin	9 (39.1%)	59 (28.2%)	0.33
Estrogen	0	0	1.00
SERM	0	6 (2.9%)	1.00
Adrenal corticosteroid	2 (8.7%)	8 (3.8%)	0.26
Antipsychotic drug	2 (8.7%)	5 (2.4%)	0.15
Antidepressant	3 (13.0%)	8 (3.8%)	0.08
Tranexamic acid	0	3 (1.4%)	1.00

HFS, hip fracture surgery; SERM, selective estrogen receptor modulator; THA, total hip arthroplasty; TKA, total knee arthroplasty; UKA, knee arthroplasty single granule replacement

Table 2 Treatment outcomes

	Edoxaban 15 mg (*n* = 23)	Edoxaban 30 mg (*n* = 209)	*p* value	OR (95% CI)
Proximal DVT	0	0	1.00	0
Distal DVT	2 (8.7%)	18 (8.6%)	1.00	0.99(0.22–4.56)
PTE	0	0	1.00	0

CI, confidence interval; DVT, deep venous thrombosis; OR, odds ratio; PTE, pulmonary thromboembolism

30-mg group. However, intergroup differences in other background characteristics were not significant.

Treatment outcomes

Table 2 shows the incidence of VTE in the two groups. The incidence of VTE in the 15- and 30-mg groups was 8.7% (2/23 patients) and 8.6% (18/209 patients), respectively, and there was no significant difference between the groups. Furthermore, all VTE cases involved patients with distal DVT ($p = 1.00$). After adjusting for significant differences in patients' background characteristics between the two groups (age [continuous variable], renal function [continuous variable], and edoxaban dose [15 mg or 30 mg]), the incidence of VTE increased 1.07-fold with each additional year of age (adjusted OR 1.07; 95% CI 1.00–1.15, $p = 0.05$) and the edoxaban dose was found to not be a significant factor associated with the incidence of VTE (adjusted OR 2.31; 95% CI 0.39–13.8, $p = 0.36$) (Table 3).

Table 4 shows the data on the presence of bleeding and AST/ALT elevation as a measure of safety. Although nine patients in the 30-mg group experienced bleeding while taking edoxaban, bleeding was minor in all cases, and the intergroup difference was not significant. Furthermore, there was no difference in the increase in AST and ALT levels between the groups.

Table 3 Univariate and multivariate analyses (logistic regression analysis)

Parameters	Crude OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value
Age	1.07(1.01–1.13)	0.02	1.07(1.00–1.15)	0.05
Creatinine clearance	0.99(0.98–1.00)	0.18	1.00(0.98–1.02	0.78
Edoxaban 30 mg	0.99(0.22–4.56)	0.99	2.31(0.39–13.80)	0.36

CI, confidence interval

Table 4 Adverse events

	Edoxaban 15 mg ($n=23$)	Edoxaban 30 mg ($n=209$)	*p* value	OR (95% CI)
Major bleeding	0	0	1.00	
CRNM bleeding	0	2 (1%)	1.00	
Minor bleeding	0	7 (3.3%)	1.00	
AST or ALT level $\geq 1.5 \times$ ULN	4 (17.4%)	26 (12.4%)	0.51	1.48 (0.34–4.95)
AST or ALT level $\geq 3 \times$ ULN	3 (13.0%)	14 (6.7%)	0.39	2.07 (0.35–8.37)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; OR, odds ratio; ULN, upper limit of normal

Discussion

In this study, we compared the efficacy and safety of VTE prophylaxis after orthopedic surgery of the lower extremities in two groups: the edoxaban 15-mg oral group with impaired renal function and the edoxaban 30-mg oral group with normal renal function. The comparison was based on VTE incidence, bleeding, and liver function test parameters. However, there was no significant difference between the groups in terms of any of the items evaluated. Approximately 50% of edoxaban is excreted by the kidneys [9], and body weight and renal function have been reported as factors that increase drug exposure [10]. In addition, the pharmacokinetics of the drug are linear [9], and factor Xa (FXa) activity, which has been reported as a marker of anticoagulant capacity by blood coagulation FXa inhibitors, has been suggested to be proportional to the blood concentration of the FXa inhibitor [11, 12].

Previous studies [4, 5] examining the required dose of edoxaban for VTE prophylaxis reported that the higher the dose, the lower the incidence of VTE. It has also been suggested that the incidence of VTE decreases with an increase in the doses of other FXa inhibitors such as apixaban and rivaroxaban [13–15]. These results suggest that FXa inhibitors do not exert anticoagulant effects unless sufficient blood levels are achieved. Furthermore, it has been reported that the administration of 15 mg edoxaban to patients with impaired renal function results in the same blood concentration as that achieved with 30 mg edoxaban when administered to patients with normal renal function [16, 17]. When used for atrial fibrillation, even a 15 mg edoxaban dose is effective in elderly individuals [18]. In the present study, the 15-mg group was older and had a lower Ccr than did the 30-mg group, suggesting that the two groups had similar blood levels of edoxaban. Multivariate analysis in this study showed that old age was a significant risk factor for VTE. Although the 15-mg group had a higher risk of VTE than did the 30-mg group, similar blood levels were obtained in the two groups, which may be one of the reasons for the similarity in the incidence of VTE.

Regarding the safety evaluation, there was no significant difference in AST and ALT levels, which are used as markers of liver damage, between the groups. Hepatotoxicity caused by heparin (heparin is traditionally used for VTE prophylaxis) is considered transient and reversible [19] and rarely causes major problems. Edoxaban is associated with a lower risk of hepatotoxicity than is heparin [20], and in our clinical pathway, the duration of edoxaban treatment was only 10 days. Therefore, the effect of hepatotoxicity was considered to be small. In terms of bleeding, no major bleeding or CRNM bleeding occurred in either group. Four patients in the 30-mg oral group presented with minor bleeding and could continue taking the medication.

In the present study, the 15-mg group was older and had poorer renal function than did the 30-mg group. The risk of anticoagulant-induced bleeding is higher in older patients [21], and decreased renal function is associated with the risk of developing VTE and bleeding [22, 23]. It has been suggested that high blood levels of FXa inhibitors contribute to increased bleeding [24], and reduction in the edoxaban dose to 15 mg to prevent excessive increases in blood levels may have reduced the incidence

of bleeding events. In general, edoxaban is used for a short duration (10–14 days) after orthopedic surgery of the lower extremities, and VTE often develops in the early postoperative period [1]. Hence, it is desirable to avoid edoxaban dose reduction based on weight loss that does not meet the weight loss criteria and reduced renal function. However, it has also been pointed out that an overdose of anticoagulants can increase the risk of major bleeding [25]. In terms of both efficacy and safety, edoxaban 15 mg is expected to be a useful option for VTE prevention after orthopedic surgery of the lower limbs in patients with impaired renal function.

This study has some limitations. Off-label underdosing was prevalent in many cases, and not enough patients with reduced renal function could be included (inadequate sample size). In addition, this was a retrospective observational study, and we did not have detailed information such as activity level before admission, foot pump use, and time to the start of postoperative rehabilitation; the calculation of renal function without correction for serum creatinine levels even in elderly and underweight patients; and assessment of thrombus on postoperative day 7 and not thereafter. Other limitations of this study were that a placebo was not used in the target group and factor Xa concentration was not measured to predict the drug effect.

Although causality was not fully investigated, there was no significant difference in the efficacy and safety of edoxaban tosylate 15 mg in patients with impaired renal function compared with those of edoxaban tosylate 30 mg in patients with normal renal function. Therefore, edoxaban 15 mg may be an option for patients with reduced renal function and needs to be tested on a larger scale.

Conclusions

Our results suggest that edoxaban tosylate 15 mg is an effective option for preventing VTE after orthopedic surgery of the lower extremities in patients with impaired renal function; nevertheless, our findings should be validated in a larger-scale study.

Abbreviations

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; Ccr: Creatinine clearance; CRNM: Clinically relevant non-major; DVT: Deep venous thrombosis; FXa: Factor Xa; HFS: Hip fracture surgery; PTE: Pulmonary thromboembolism; THA: Total hip arthroplasty; TKA: Total knee arthroplasty; UKA: Unicompartmental knee arthroplasty; VTE: Venous thromboembolism.

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Authors' contributions

TK and SO conceived and designed this study. YT, SF, and AI assisted with the research design. TK provided epidemiological data and performed the statistical analyses. AI, MS, and ST assisted with performing the statistical analyses. TK, SO, TS, and NT wrote the manuscript. All authors have read and approved the final version of the manuscript.

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Availability of data and materials

Not applicable.

Declarations

Ethical approval and consent to participate

This study was approved by the hospital's ethics review committee, and adequate consideration was given to the protection of personal data (approval no. 577).

Consent for publication

Not applicable.

Competing interests

Teruhisa Kinoshita has received lecture fees from Daiichi Sankyo Company, Limited. The other authors declare no conflict of interest.

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References

1. Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, et al. Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e278S-325S.
2. Fuji T, Wang CJ, Fujita S, Kawai Y, Nakamura M, Kimura T, et al. Safety and efficacy of edoxaban, an oral factor Xa inhibitor, versus enoxaparin for thromboprophylaxis after total knee arthroplasty: the STARS E-3 trial. Thromb Res. 2014;134:1198–204.
3. Fuji T, Fujita S, Kawai Y, Nakamura M, Kimura T, Fukuzawa M, et al. Efficacy and safety of edoxaban versus enoxaparin for the prevention of venous thromboembolism following total hip arthroplasty: STARS J-V. Thromb J. 2015;13:27.
4. Fuji T, Fujita S, Tachibana S, Kawai Y. A dose-ranging study evaluating the oral factor Xa inhibitor edoxaban for the prevention of venous thromboembolism in patients undergoing total knee arthroplasty. J Thromb Haemost. 2010;8:2458–68.
5. Raskob G, Cohen AT, Eriksson BI, Puskas D, Shi M, Bocanegra T, et al. Oral direct factor Xa inhibition with edoxaban for thromboprophylaxis after elective total hip replacement. A randomised double-blind dose-response study. Thromb Haemost. 2010;104:642–9.
6. Schulman S, Kearon C. Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005;3:692–4.
7. Dhillon KS, Askander A, Doraismay S. Postoperative deep-vein thrombosis in Asian patients is not a rarity: a prospective study of 88 patients with no prophylaxis. J Bone Joint Surg Br. 1996;78:427–30.
8. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013;48:452–8.
9. Ogata K, Mendell-Harary J, Tachibana M, Masumoto H, Oguma T, Kojima M, et al. Clinical safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel factor Xa inhibitor edoxaban in healthy volunteers. J Clin Pharmacol. 2010;50:743–53.
10. Salazar DE, Mendell J, Kastrissios H, Green M, Carrothers TJ, Song S, et al. Modelling and simulation of edoxaban exposure and response relationships in patients with atrial fibrillation. Thromb Haemost. 2012;107:925–36.

11. Kreutz R, Persson PB, Kubitza D, Thelen K, Heitmeier S, Schwers S, et al. Dissociation between the pharmacokinetics and pharmacodynamics of once-daily rivaroxaban and twice-daily apixaban: a randomized crossover study. J Thromb Haemost. 2017;15:2017–28.
12. Yin OQP, Antman EM, Braunwald E, Mercuri MF, Miller R, Morrow D, et al. Linking endogenous factor Xa activity, a biologically relevant pharmacodynamic marker, to edoxaban plasma concentrations and clinical outcomes in the ENGAGE AF-TIMI 48 trial. Circulation. 2018;138:1963–73.
13. Eriksson BI, Borris LC, Dahl OE, Haas S, Huisman MV, Kakkar AK, et al. A once-daily, oral, direct factor Xa inhibitor, rivaroxaban (BAY 59–7939), for thromboprophylaxis after total hip replacement. Circulation. 2006;114:2374–81.
14. Eriksson BI, Borris LC, Dahl OE, Haas S, Huisman MV, Kakkar AK, et al. Dose-escalation study of rivaroxaban (BAY 59–7939)—an oral, direct factor Xa inhibitor—for the prevention of venous thromboembolism in patients undergoing total hip replacement. Thromb Res. 2007;120:685–93.
15. Lassen MR, Davidson BL, Gallus A, Pineo G, Ansell J, Deitchman D. The efficacy and safety of apixaban, an oral, direct factor Xa inhibitor, as thromboprophylaxis in patients following total knee replacement. J Thromb Haemost. 2007;5:2368–75.
16. Koretsune Y, Yamashita T, Kimura T, Fukuzawa M, Abe K, Yasaka M. Short-term safety and plasma concentrations of edoxaban in Japanese patients with non-valvular atrial fibrillation and severe renal impairment. Circ J. 2015;79:1486–95.
17. Shimizu T, Tachibana M, Kimura T, Kumakura T, Yoshihara K. Population pharmacokinetics of edoxaban in Japanese atrial fibrillation patients with severe renal impairment. Clin Pharmacol Drug Dev. 2017;6:484–91.
18. Okumura K, Akao M, Yoshida T, Kawata M, Okazaki O, Akashi S, et al. Low-dose edoxaban in very elderly patients with atrial fibrillation. N Engl J Med. 2020;383:1735–45.
19. Carlson MK, Gleason PP, Sen S. Elevation of hepatic transaminases after enoxaparin use: case report and review of unfractionated and low-molecular-weight heparin-induced hepatotoxicity. Pharmacotherapy. 2001;21:108–13.
20. Caldeira D, Barra M, Santos AT, de Abreu D, Pinto FJ, Ferreira JJ, et al. Risk of drug-induced liver injury with the new oral anticoagulants: systematic review and meta-analysis. Heart. 2014;100:550–6.
21. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrøm J. Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost. 2007;5:692–9.
22. Goto S, Haas S, Ageno W, Goldhaber SZ, Turpie AGG, Weitz JI, et al. Assessment of outcomes among patients with venous thromboembolism with and without chronic kidney disease. JAMA Netw Open. 2020;3:e2022886.
23. Wattanakit K, Cushman M, Stehman-Breen C, Heckbert SR, Folsom AR. Chronic kidney disease increases risk for venous thromboembolism. J Am Soc Nephrol. 2008;19:135–40.
24. Bernier M, Lancrerot SL, Parassol N, Lavrut T, Viotti J, Rocher F, et al. Therapeutic drug monitoring of direct oral anticoagulants may increase their benefit-risk ratio. J Cardiovasc Pharmacol. 2020;76:472–7.
25. Chan YH, Chao TF, Chen SW, Lee HF, Yeh YH, Huang YC, et al. Off-label dosing of non-vitamin K antagonist oral anticoagulants and clinical outcomes in Asian patients with atrial fibrillation. Heart Rhythm. 2020;17:2102–10.

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