Factor Xa inhibitors in clinical practice: Comparison of pharmacokinetic profiles

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ABSTRACT

Background: The anticoagulant actions of oral direct factor Xa (FXa) inhibitors can be inferred from their observed plasma concentrations; however, the steady-state pharmacokinetics (PK) of different FXa inhibitors have not been compared in clinically.

Methods: The sensitivity of the rivaroxaban, apixaban, and edoxaban in the STA-Liquid Anti-FXa assay were compared, and the anti-FXa plasma concentrations were measured for PK assessments. Nonlinear mixed-effects modeling was used to assess population PK in 329 patients with nonvalvular atrial fibrillation or venous thromboembolism. Patients were followed up for an average of 3.6 years.

Results: Sensitivity was similar among the three drugs in this assay, which could directly compare plasma concentrations instead of anti-FXa activities. Overall exposure was greatest in 5 mg BID apixaban relative to other drugs ($p < 0.001$). The geometric mean AUC for the 0 to 24-h interval was 4550 ng·h/mL for apixaban, 2710 ng·h/mL for 15 mg QD rivaroxaban, and 1290 ng·h/mL for 60 mg QD edoxaban. The PKs of 2.5 mg BID apixaban or 15 mg QD rivaroxaban were associated with hemorrhagic events.

Conclusions: Apixaban was associated with greater exposure, higher trough concentrations in plasma compared with rivaroxaban or edoxaban. Furthermore, a higher plasma concentration may partially predict hemorrhagic events.

Keywords: Apixaban, Rivaroxaban, Edoxaban, Atrial fibrillation, Venous thromboembolism, anti-FXa activity, Plasma concentration, Population pharmacokinetics.

1. Introduction

Rivaroxaban, apixaban, and edoxaban are available in clinical practice as direct oral anticoagulants that reversibly inhibit activated factor X (FXa) and show predictable pharmacokinetic (PK) properties [1–4]. Thus, routine anticoagulation monitoring is not required to guide dosages, and those that result in anticoagulation are determined according to their observed plasma concentration and are generally first proposed based on their pharmacokinetic (PK) properties [5]. Although the half-life of these drugs in serum is ~12 h, the administration frequency and dosages are not necessarily consistent among each type of FXa inhibitor [6]. Moreover, the rivaroxaban dosage in Japan differs from the standard dosage used worldwide because simulated mean plasma concentrations from PK modeling of this drug at 15 mg in Japanese patients coincide with those at 20 mg in Caucasian patients [7, 8]. Conversely, no differences have been observed between the PKs of single doses of apixaban or edoxaban in healthy Japanese and Caucasian adults [9–11]. Thus, the dosages of these two drugs are consistent worldwide.

The direct comparisons of rivaroxaban at 10 and 20 mg/d (QD), and apixaban at 2.5 mg and 5 mg twice/d (BID), showed similar areas under the plasma drug concentration-time curves (AUCs) for both drugs, and the time-course of anti-FXa activity mirrored their plasma concentration–time profile in healthy Caucasian volunteers [12, 13]. Moreover, direct

relationship between the anti-FXa activity and the plasma concentration of each drug was noted, and the slope of regression lines was almost similar [13]; however, these studies on healthy Caucasian volunteers used the worldwide standard dosage of 20 mg QD rivaroxaban, but not the standard Japanese dosage of 15 mg QD and might not predict PK of this drug in Japanese patients with nonvalvular atrial fibrillation (NVAF) or venous thromboembolism (VTE).

The primary objective was to examine whether the plasma concentrations measured by the anti-FXa activity, which was one of pharmacodynamic (PD) properties of rivaroxaban, apixaban, and edoxaban, can be compared with each other or not.

The secondary objective was to compare the steady-state PK of rivaroxaban, apixaban, and edoxaban. The time to peak concentration of FXa inhibitors can vary widely among patients according to renal function, age, body weight, sex, feeding conditions, and other factors. Thus, an analysis of the population PK (PPK) was conducted to predict peak concentrations and AUCs at a steady state using three previously described PPK models [8, 14, 15].

The third objective was to examine whether clinical events (e.g., stroke, systemic embolization, bleeding) could be predicted using these PK parameters, especially considering that a standard clotting test for monitoring anti-FXa inhibitors is not available.

2. Materials and Methods

2.1. Anti-FXa chromogenic assay, assay sensitivity, and liquid chromatography–tandem mass spectrometry

Anti-FXa activity was determined using the validated STA-Liquid Anti-Xa assay kit with STA-rivaroxaban [17] and STA-apixaban calibrators and controls [18, 19] (CE Marked, Diagnostica Stago, Asnières, France) and a Stago STA Compact Coagulation Analyzer (Diamond Diagnostics, Holliston, MA, USA). Calibrated rivaroxaban and apixaban plasma concentrations were expressed in ng/mL, and the working range was 20–500 ng/mL. Because an edoxaban-specific calibrator [20] was not available at the time of the study, the raw data for optical density (OD)/min were used to determine edoxaban sensitivity in the STA-Liquid Anti-Xa assay. These data were plotted against the corresponding plasma concentrations that were separately measured by liquid chromatography–tandem mass spectrometry (LC–MS/MS) (LSI Medience Corporation, Tokyo, Japan) to construct a calibration curve. The edoxaban plasma concentrations as indicted by LC–MS/MS and STA-Liquid Anti-Xa assays with the STA-rivaroxaban calibrators and controls [17] were confirmed to be correlated and had high coincidence rates (Supplementary Fig. 1).

2.2. Clinical study design and patient

Patients were recruited from April 1, 2016, to March 31, 2017. A physician chose rivaroxaban, apixaban, or edoxaban based on a personal assessment of the best drug for prevention of

NVAF and VTE in patients with these conditions. A prospective drug-intervention observational study was conducted at three centers and six ambulatory clinics to compare plasma drug concentrations in a steady state and clinical events. All patients provided written informed consent. Baseline medical history and patient characteristics were reviewed, and physical examinations and laboratory tests were conducted. Patients received apixaban, rivaroxaban or edoxaban, and all patients were followed up without any changes in their medication regimens throughout the study period. The study complied with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee of Dokkyo Medical University (approval number: 26088; approval date: December 10, 2015).

2.3. Blood sample collection and dosing

Patients were prescribed rivaroxaban or edoxaban QD at enrollment in the study and took the drugs each morning after breakfast. Patients prescribed apixaban BID took the drug each morning after breakfast and each evening after dinner. Following at least 4 weeks of treatment, the patients visited a hospital or clinic after their morning dose, and blood samples were collected at least once and up to three times over different days in citrate-containing tubes to measure plasma concentrations. The timing of drug ingestion and blood sampling were also recorded. Blood was sampled. After centrifuging the blood samples at 1600 ×*g* for 10 min, the platelet-poor plasma was collected, quickly frozen, and stored at −80°C until drug assessment. Apixaban, rivaroxaban, or edoxaban doses were adjusted in accordance with

current package insert labeling [16, 21, 22].

2.4. PK evaluation methods

PPK models for rivaroxaban, edoxaban, and apixaban were constructed by using previously reported models [8, 14, 15].

The models reported by Kaneko et al. [8] for rivaroxaban and Ueshima et al. [14] for apixaban one-compartment open models with first-order absorption, were used to describe the PK properties, respectively. The model reported by Shimizu et al. [15], a two-compartment open model with first-order absorption, was used to describe the PK properties for edoxaban. Only the population mean for clearance and the volume of distribution were estimated; whereas, all other parameters, including both inter- and intraindividual variances, were fixed to the reported values. The relationship among the conditional weighted residuals (CWRES), the time after the last dose, and predicted population concentrations was evaluated to justify the goodness-of-fit for the final models. The visual predictive check was verified using 200 simulations for predicting the performance by the model [23]. PK parameters for each individual were assessed using the estimated parameters as follows: AUC in the steady state was calculated by dose/clearance, half-life ($T_{1/2}$) elimination was estimated by 0.693/(CL/V), and the maximum concentration (C_{max}) and time to peak concentration (T_{max}) were calculated based on simulated concentration profiles, which were estimated at 0.1-h interval. All analyses were conducted

using Phoenix® NLME™ 8.1 (Certara LP, Princeton, NJ, USA) and the first-order conditional estimation method.

2.5. Clinical events

The observation period for the incidence of clinical events, such as stroke, systemic embolism, and bleeding, was at least 1-year after administration of the drug. Stroke was defined as an abrupt episode of a focal neurological deficit within the general distribution area of a single brain artery that lasted at least 24 h. Systemic embolism was defined as an abrupt episode of arterial insufficiency associated with clinical or radiological evidence of arterial occlusion. Major bleeding was defined according to criteria set by the International Society on Thrombosis and Haemostasis [24]. Nonmajor bleeding was defined as acute or subacute clinically overt bleeding that did not satisfy the criteria for major bleeding but led to admission to a hospital.

2.6. Statistical analyses

Results are presented as the mean ± standard deviation for continuous data and as numbers and percentages for categorical data. Data were compared by one-way analysis of variance for continuous variables. Multiple comparisons were conducted using the Bonferroni correction. Patient and clinical characteristics and plasma concentrations were analyzed using the dosage of each drug. Correlation coefficients were calculated for paired data. $P < 0.05$ was considered significant. All calculations were performed using JMP v.10.0 (SAS Institute,

Cary, NC, USA).

3. Results

3.1. Sensitivity of the anti-FXa chromogenic assay

As shown in Fig. 1, the anti-FXa activity assessed using a colorimetric test was inversely proportional to the drug concentration. The calibration lines for apixaban, rivaroxaban, and edoxaban in this assay were similar, and the 95% confidence interval (CI) overlapped for the three drugs, as shown in the gray areas in Fig. 1. These data suggested that anti-FXa activities are similar when the plasma concentrations are nearly equal in these drugs in this assay. Thus, this assay may be able to directly compare plasma concentrations instead of anti-FXa activities among these drugs.

3.2. Patients

Table 1 shows the clinical characteristics of the 329 patients. The proportion of males in the standard dosage groups was higher than that of females ($p < 0.01$). The mean age, $CHADS_2$ and $CHADS_2$-VASc scores were significantly higher in reduced dosage groups than in standard dosage groups in the apixaban or rivaroxaban ($p < 0.01$, respectively), however those did not differ among patients receiving standard dosages of the three drugs. In contrast, these scores were significantly higher after administration of reduced dosages of apixaban compared with those of rivaroxaban or edoxaban and for rivaroxaban compared with

edoxaban ($p < 0.01$, respectively).

Creatinine clearance (CCr) was lower in patients with dosages reduced relative to the standard dosages for all drugs ($p < 0.01$, respectively), and it was lower in the apixaban group than in the rivaroxaban or edoxaban groups in the standard and reduced dosages ($p < 0.01$, respectively).

Of the 329 patients, 294 (89.4%) received the dosage recommended on the drug label from the manufacturer (90.7% for apixaban, 85.7% for rivaroxaban, and 92.9% for edoxaban).

3.3 PK models of apixaban, rivaroxaban, and edoxaban

As measured by the anti-FXa chromogenic assay, 183 apixaban, 162 rivaroxaban, and 137 edoxaban plasma concentration values were obtained from 140, 119, and 70 patients, respectively. The final PPK parameters for the concentration data on apixaban, rivaroxaban, and edoxaban are shown in Supplementary Table 1. The goodness-of-fit plots for the final models are shown in Fig. 2. Population and individual predictions appeared to be reasonably correlated with observation values because they were evenly distributed and centered as shown by the 1:1 dotted line in Fig. 2 for the three drugs. Systematic deviation was not observed in the relationship between CWRES and time after the last dose or population prediction values because each isometric line between these values was 0 (Supplementary Fig. 2). As shown in Fig. 3, the observation values fell close to the 95th percentile prediction

interval of the simulated concentrations of the final model. Thus, the final model reasonably predicted the observed concentrations.

Detailed PK parameters are summarized in Table 2. The predicted C_{max} was higher for the standard dosages than for the reduced dosages of apixaban and edoxaban ($p < 0.001$, respectively); however, C_{max} values for the standard and reduced dosages of rivaroxaban did not differ. C_{max} was the lowest for edoxaban among the reduced dosages of the three drugs (Table 2). The predicted C_{min} was also significantly higher for the standard dosages than for the reduced dosage of apixaban and for both dosages of apixaban than for any dosage of either rivaroxaban or edoxaban, which did not differ (Table 2) because the number of administrations was BID for only apixaban; therefore, the predicted 24-h AUC was greater for the standard dosages than for the reduced dosages of apixaban and rivaroxaban ($p < 0.001$, respectively), although the same values were not observed for edoxaban. AUC was greatest at the standard dosage of apixaban compared with that for all other dosages of each of the three drugs ($p < 0.001$, respectively) and was significantly smaller for both dosages of edoxaban than for both dosages of apixaban ($p < 0.001$, respectively). This pattern was not observed for rivaroxaban (Table 2). Lower C_{max}, lower AUC values, shorter T_{max}, and longer $T_{1/2}$ were exhibited for edoxaban, even at the highest dosages among the three drugs (Table 2). This is most likely explained by the fast absorption and large volume of distribution of edoxaban compared with those of apixaban or rivaroxaban (Supplementary Table 1).

3.4. *Clinical events and plasma concentrations*

Major and minor clinical events throughout an average follow-up period of 3.6 years are shown in Supplementary Table 2. Two patients developed cerebral infarction following treatment with 2.5 mg BID apixaban; two patients who received 5 mg BID apixaban also developed cerebral infarction. Thus, the stroke rate was 2.9% (4/140 patients). All average plasma concentrations in these patients were within a 95% CI. Among the patients administered 2.5 mg of BID apixaban, the one who received dual antiplatelet therapy developed cerebral bleeding and died, and two had gastrointestinal bleeding, including one who received a nonsteroidal anti-inflammatory drug (NSAID). Moreover, one patient developed traumatic peritoneal hematoma and another had epistaxis and underwent emergency surgery. Thus, the major bleeding rate was 3.6% (5/140 patients). Also, seven patients who received 5.0% apixaban (three at 2.5 mg BID and four at 5 mg BID) experienced nonmajor bleeding. Although individual plasma concentrations in these patients were within nearly a 95% CI (data not shown), C_{max} and AUCs were significantly greater in patients with major or minor bleeding than in those without bleeding in the group receiving 2.5 mg BID apixaban ($p < 0.01$, $p < 0.05$, respectively), as shown in Fig. 4. The high plasma concentrations in these hemorrhagic patients were associated with low CCr ($p = 0.03$) and low BW ($p = 0.09$).

Within the rivaroxaban treatment group, one patient with chronic CHF who received 10

mg QD rivaroxaban developed cerebral infarction and died. One patient with hypertrophic cardiomyopathy who received 15 mg QD rivaroxaban developed renal infarction, and another developed cerebral infarction. Thus, the overall stroke and systemic embolism rate was 2.5% (3/119 patients). The average plasma concentrations in these patients were also within a 95% CI. Within the group receiving 15 mg QD rivaroxaban, one patient who also received an NSAID for 1 month developed gastrointestinal bleeding, one patient developed a small thalamic cerebral hemorrhage with no sequelae, and one patient with chronic CHF who was also treated with 100 mg aspirin developed gastrointestinal bleeding. Thus, the major bleeding rate was 2.5% (3/119 patinets). Nonmajor bleeding occurred in eight patients who were administered 6.7% rivaroxaban (four at 10 mg QD and four at 15 mg QD). Patients with major or nonmajor bleeding had an average plasma concentration of rivaroxaban within the 95% CI, except for one who had epistaxis (nonmajor bleeding) at 15 mg QD; however, C_{max} and AUC were significantly greater in patients with major or minor bleeding than in those with no bleeding in the group receiving 15 mg QD rivaroxaban ($p < 0.01$, $p < 0.05$, respectively), as shown in Fig. 4. Within these patients with bleeding, high C_{max} and AUCs were more frequently observed in females than in males ($p < 0.01$); however, there was no observed threshold of plasma concentration related to bleeding events within any treatment group (Fig. 4).

No incidences of stroke or major bleeding were observed in the edoxaban group;

however, there were four nonmajor bleeding events (5.7%) observed in the group receiving 60 mg QD edoxaban. The average plasma concentrations were within the 95% CI, and C_{max}, C_{min}, and AUC did not differ between patients with or without bleeding (Fig. 4).

4. Discussion

The sensitivity of the heparin-calibrated chromogenic anti-Xa assay for direct FXa inhibitors differs significantly among manufacturers, methods, and inhibitors, and an assessment of the sensitivities of these assays and calibrators for different direct FXa inhibitors has been recommended [25]. However, we found that the validated STA-Liquid Anti-Xa assay using calibrator kits for apixaban and rivaroxaban and LC–MS/MS data for edoxaban had similar calibration lines for the three drugs evaluated in this study. Thus, the sensitivities of the STA-Liquid Anti-Xa assay for apixaban, rivaroxaban, and edoxaban were nearly the same, which was most likely the result of their similar molecular weights (apixaban, 459.5; rivaroxaban, 435.9; and edoxaban, 548.1). If the plasma concentrations measured by this assay kit are the same for these three FXa inhibitors, their anti-FXa activities against exogenous FXa should also be similar. Therefore, a PD comparison may be replaced with a PK comparison among different drugs when PD is defined by the measurements of the drugs' anti-FXa activity against exogenous FXa using the STA-Liquid Anti-Xa kit.

In this study, a PPK model was constructed using multicenter cohorts from hospitals and clinics where plasma concentrations were measured using anti-FXa assays. With these data, the PK population models of apixaban, rivaroxaban, and edoxaban were constructed by using previously reported models [8, 14, 15]. One- or two-compartment models with moderate inter- and intraindividual variabilities for both the clearance and volume of distribution were used, in which absorption rate constants, intercompartment clearance (Q) only for edoxaban, volume of peripheral compartment (Vp) only for edoxaban, and inter- and intraindividual variabilities were fixed using the values derived from previous reports because the construction of a PPK model using a limited amount of data in this study was considered inadequate to estimate each PK parameter. For the validity of the analyzed results, the plots of the observed versus predictive values were evenly distributed and centered on a 1:1 line for the three drugs (Fig. 2) and systematic deviation was not observed in the relationship between CWRES and time after the last dosage or population prediction values (Supplementary Fig. 2). Moreover, the predictive interval of the plasma concentration curve obtained using the bootstrap method and individual observed values was superimposed for the three drugs (Fig. 3). This model accurately predicted the observed plasma concentration values. Thus, these results validated the analysis by the PPK model using a nonlinear mixed-effects model. Furthermore, the predicted C_{max}, C_{min}, AUC, T_{max}, and $T_{1/2}$ for the three FXa inhibitors were comparable with those of previously reports [7,10-12].

Notably, AUC for 5 mg BID apixaban throughout 1 d was the highest among the standard dosages of the other drugs when the age, $CHADS_2$, and $CHADS_2$-Vasc did not differ among them. Actually, a larger population-based PK analysis, including data from Phase II and III clinical trials in patients with AF, suggested that clearance of apixaban was 15% lower in Japanese patients than in the overall population, which corresponded with an 18% higher exposure [26]. With regard to the lower CCr observed in our apixaban group, Chang et al. [27] have evaluated apixaban PK in both subjects with renal impairment and healthy subjects following a single10-mg oral dose. The regression analysis showed that decreasing renal function resulted after mildly increasing apixaban dosage (genomic mean AUC 1.161 and 1.292 times when the CCr 65 and 40 mL/min compared with 100 mL/min, respectively), but that C_{max} was not affected. The predicted AUC of the median CCr values (i.e., 74.7 mL/min) after standard dosages of the three FXa inhibitors used in this study, which were calculated using the regression lines between CCr and the estimated AUC for each drug, was 4293 ng·h/mL in 5 mg BID apixaban, 2675 ng·h/mL in 15 mg QD rivaroxaban, and 1399 ng·h/mL in 60 mg QD edoxaban (data not shown); therefore, the limited influence of renal dysfunction on apixaban PK values might not affect the main results of our study.

The phase II APROPOS study [28] of apixaban for VTE indicated that its efficacy is associated with trough concentration, whereas its safety is related to AUC throughout 1 d. In contrast, Ruff et al. [29] have demonstrated a linear increase in the risk of major bleeding

with increasing trough concentration in the plasma after edoxaban treatment. Thus, with edoxaban treatment, safety was related to trough concentration.

Considering these studies, high AUC in apixaban and high trough concentration in plasma after edoxaban treatment might be associated with increased bleeding from these FXa inhibitors. Interpreting our data from this perspective, AUCs throughout 1 d and trough concentrations in plasma were significantly greater with 5 mg BID apixaban than with 15 mg QD rivaroxaban or 60 mg QD edoxaban. These data differ from those calculated on a worldwide scale for the standard dose of 20 mg rivaroxaban; however, it is expected that AUC might be lower for 15 mg QD rivaroxaban than for 5 mg BID apixaban because the AUC was similar for 20 mg QD rivaroxaban and 5 mg BID apixaban [13].

Although stroke or systemic embolic events were observed in seven patients in this study, statistical analyses of these events were difficult because of their low occurrences in our study population. Conversely, C_{max}, and AUC after treatment with 2.5 mg BID apixaban or 15 mg QD rivaroxaban were significantly greater in patients with major or minor bleeding than in those with no bleeding. Without this analysis, measuring C_{max} would be difficult because T_{max} exhibited individual variability; therefore, the occurrence of major or nonmajor bleedings appeared to be related to the plasma concentration of both drugs, at least at both of those dosages. Moreover, the hemorrhagic events would be related to CCr and BW even if the dosage of apixaban were reduced and would be related to females with the standard

dosage of rivaroxaban. The reason that similar results were not observed in 5 mg BID apixaban was most likely that the group receiving 2.5 mg BID apixaban was prone to bleeding, considering that the $CHADS_2$ and $CHADS_2$-Vasc scores were greatest and CCr was lowest in this group. In other words, the exposure to high plasma concentrations might not be associated with bleeding complications in the group receiving 5 mg BID apixaban because it was at a low risk of bleeding.

Unlike previous reports [29], C_{min} (trough) for edoxaban was not associated with bleeding events in this study. C_{min} of edoxaban was at a lower detection limit of ~20 ng/mL and would exhibit large variations in the STA-Liquid Anti-Xa assay; therefore, the detectable difference might have been less pronounced in this study.

Theoretically, a high plasma concentration can induce bleeding, which might also be influenced by each patient's risk factors. In large-scale prospective observational studies, such as post-marketing surveillance studies, differences in plasma concentrations among the three FXa inhibitors might be reflected in the rates of bleeding events. The major bleeding event rate of 2.1/100 patient-years from the international XANTUS study [30] (international standard dosage of 20 mg QD rivaroxaban) was higher than the 1.2/100 patient-years in the Japanese EXPAND study [31] (standard dose of 15 mg QD rivaroxaban). The authors speculate that these differences are related to patient characteristics, including race and ethnicity, and to rivaroxaban dosage.

In a large post-marketing study in Japan, the major rate of hemorrhagic events was higher in the STANDARD trial [32] than in the XAPASS [33] or ETNA-AF trials [34] at 2.36, 1.8, and 0.92/100 patient-years, respectively; however, the rate of stroke events was lower in the STANDARD than in the XAPASS trials at 0.91 and 1.6/100 patient-years, respectively. Interestingly, the patient characteristics in those three post-marketing studies were nearly similar.

Taken together, these results suggest that the exposure to apixaban appears high in real-world practical medicine in Japan. Our study was underpowered for a direct conclusion that the risk of hemorrhagic events is associated with increased plasma concentrations of the drugs or with anti-FXa activity. Despite our limitations in statistical power, these data could be valuable to post-marketing surveillance studies.

5. Limitations

This study was a nonrandomized, prospective, longitudinal, observational, multicenter cohort study. Accordingly, there was selection bias, such as the differences in renal function among FXa inhibitors, and the reduction criteria for each drug was not met in several patients.

Comparing the three drugs by their anti-Xa activities instead of their plasma concentrations is the most straightforward method; however, the STA® line analyzer automatically expresses plasma concentration.

Although newer oral anticoagulants were reported to have predictable PKs, the variability in PK parameters for these is not considered negligible [35, 36]; however, no systematic deviations were observed in the relationship between CWRES and time after the last dose or predicted population value, and the visual check resulted in a reasonable predictability of the final model.

For edoxaban, the comparison between anti-Xa activity and the results of LC–MS/MS require consideration of the potential M4 metabolite because this metabolite is pharmacologically active and will interfere with the assay, even at elevated edoxaban concentrations in contrast to the LC–MS/MS measurements [37]. The calibration curve in this study did indeed account for the presence of the potential M4 metabolite. VTE patients, who can harbor relatively low plasma concentrations compared with non-VTE patients, were included only in the edoxaban group [38]; however, blood samples were obtained during a steady state to avoid inclusion of the acute VTE patients. Another potential limitation was the small patient population available for clinical-event analyses, especially in the edoxaban group. A future study using a larger sample size would be beneficial for confirming the association between drug concentrations and clinical events.

6. Conclusion

Apixaban was associated with greater exposure, higher troughs in plasma concentration, and

higher anti-FXa activities compared with rivaroxaban or edoxaban in Japanese patients with NVAF or VTE. Although the PKs of the reduced apixaban dosage and standard rivaroxaban dosage were associated with hemorrhagic events, no cutoff value was detected for plasma concentrations of the drugs in relation to the onset of bleeding events.

Author Contributions

Dr. Horinaka conceived of and designed the study. Dr. Goto and Dr. Horinaka analyzed and interpreted the data. Dr. Goto, Dr. Horinaka, and Dr. Katou corrected and assembled the data Dr. Goto and Dr. Horinaka drafted the article. Dr. Ishimitsu and Dr. Horinaka revised the article. Dr. Horinaka provided final approval of the article.

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Conflict of Interest

SH has received honoraria for lectures from Bristol-Myers Squibb Company, Bayer Yakuhin, Ltd., and Daiichi-Sankyo, Ltd. There are no other potential conflicts of interest relevant to this article.

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Figure Legends

Figure 1. Calibration lines for apixaban, rivaroxaban, and edoxaban in the STA-Liquid Anti-Xa assay.

Rivaroxaban and apixaban curves were created using commercial STA-apixaban and STA-rivaroxaban calibrator kits. For edoxaban, raw data (OD/min) were measured using the STA-Liquid Anti-Xa assay and plotted against the corresponding plasma concentrations that were separately measured by liquid chromatography–tandem mass spectrometry (LC–MS/MS). The 95% confidence interval (CI) of each calibration line for the three drugs is shown in light gray.

Notes: OD, optical density; min, minute; concentration; n, number of samples.

Figure 2. Goodness-of-fit plots for the observed versus predicted population concentrations or predicted individual concentrations for apixaban, rivaroxaban, and edoxaban.

The center line shows a 1:1 ratio.

Figure 3. The observed plasma apixaban, rivaroxaban, and edoxaban concentrations and the predicted plasma concentration–time curves of the 5th, 50th, and 95th percentiles from the final population PK model.

Each circle point corresponds to an actual observed plasma concentration at a specific sampling time after oral ingestion.

Notes: Red lines, 5th and 95th percentile curves; blue line, 50th percentile curve (median); BID, twice daily; QD, once daily.

Figure 4. C_{max}, C_{min}, and $AUC_{0–24h}$ in patients with or without hemorrhagic events are presented for the three FXa inhibitors.

Notes: Bleeding, observed hemorrhagic events; none, no hemorrhagic events were observed; n, number of patients. C_{max}, maximum concentration; C_{min}, minimum concentration; AUC, area under the curve.

Supplementary Table and Figure Legends

Supplementary Table 1. Population estimates for the final pharmacokinetic model of apixaban, rivaroxaban, and edoxaban.

Supplementary Table 2. Relationship between the clinical events and the observed plasma concentrations or predicted C_{max}, C_{min}, and area under the curve (AUC) for apixaban, rivaroxaban and edoxaban.

Notes: C_{max}, maximum concentration; C_{min}, minimum concentration.

Supplementary Figure 1. Edoxaban plasma concentrations obtained by liquid chromatography–tandem mass spectrometry and STA-Liquid Anti-Xa assays with STA-rivaroxaban calibrators and controls.

Supplementary Figure 2. Relationship between conditional weighted residuals (CWRES), time after the last dose and predicted population concentrations for the apixaban, rivaroxaban, and edoxaban treatment groups.

Open circles indicate the observed values. Each dotted line shows a line of identity.