Anti-Factor Xa Activity of Standard and Japan-Specific Doses of Rivaroxaban in Thai Patients With Non-Valvular Atrial Fibrillation

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Background: Recommended rivaroxaban doses for stroke prevention in atrial fibrillation (SPAF) are 20 and 15 mg/day in patients with normal and reduced renal function, respectively, but lower doses (15 and 10 mg) have been tested and approved in Japan. It is not known whether 15 and 10 mg rivaroxaban are appropriate in other Asian populations. This study compared the anti-Factor Xa (FXa) activity of 20 and 15 mg rivaroxaban in Thai patients with normal renal function and 15 and 10 mg rivaroxaban in patients with reduced renal function.

Methods and Results: Sixty non-valvular atrial fibrillation patients receiving rivaroxaban (mean ±SD age 69.3±9.1 years, mean creatinine clearance 59.2±22.7 mL/min) were enrolled. The anti-FXa activity of standard rivaroxaban and Japan-specific doses was measured at peak and trough concentrations. Median anti-FXa activity at peak concentrations was significantly higher for the standard than Japan-specific dose. Median anti-FXa activity measured at the trough was significantly higher for the standard dose only in those with impaired renal function. A higher proportion of patients receiving the Japan-specific rather than standard dose had anti-FXa activity at peak concentrations within the expected range (87.7% vs. 64.4%; P=0.001). One-third of those receiving the standard dose had anti-FXa activity higher than the expected range.

Conclusions: A significantly higher proportion of Thai patients receiving the Japan-specific dose of rivaroxaban had anti-FXa activity at peak concentrations within the expected range.

Key Words: Anti-factor Xa activity; Direct oral anticoagulant; Direct Xa inhibitor; Non-vitamin K oral anticoagulant; Rivaroxaban
Thai patients with non-valvular AF have a lower CrCl and body mass index (BMI) than Caucasian patients. It is not known whether the Japan-specific or standard dose of rivaroxaban is appropriate for use in Thai patients with non-valvular AF.

Previous studies have shown that inhibition of anti-Factor Xa (FXa) activity by rivaroxaban is closely correlated to its plasma concentration. Consequently, anti-FXa activity can be measured as an indication of rivaroxaban exposure. Thus, the aim of the present study was to compare anti-FXa activity between standard and Japan-specific doses of rivaroxaban to determine the appropriate dose of rivaroxaban for use in Thai patients with non-valvular AF.

**Methods**

The present study was a prospective cohort study. The study was approved by the Institutional Research Board of the Faculty of Medicine, Chiang Mai University (Approval no. 205/2561) and all procedures followed the Declaration of Helsinki and ethical standards of the responsible committee on human experimentation. The study was registered in the Thai Clinical Trials Registry (TCTR; ID TCTR20181104002).

The study was conducted in Maharaj Nakorn Chiang Mai Hospital from June 2018 to January 2019. All patients provided written informed consent before study entry. Patients aged ≥18 years with non-valvular AF who had been receiving rivaroxaban were included in the study. Patients were excluded from the study if they had severe renal impairment (CrCl <15 mL/min) or poor compliance to medications.

Standard doses of rivaroxaban were defined as 20 mg once daily in patients with normal and impaired renal function, respectively; Japan-specific doses of rivaroxaban were 15 and 10 mg, once daily, in patients with normal and impaired renal function, respectively.

At steady state, anti-FXa activity was measured at peak and trough concentrations for both the standard and Japan-specific doses of rivaroxaban. Because platelets could affect the FXa activity, serum was collected only from the upper half of the collection tube to avoid platelet contamination.

After patients had been on a standard dose of rivaroxaban for at least 1 week, anti-FXa activity was measured at peak (2–4 h after oral intake of rivaroxaban) and trough (22–24 h after the last dose of rivaroxaban) concentrations. Then, patients were instructed to reduce their dose of rivaroxaban to the Japan-specific dose for at least 1 week, after which anti-FXa activity was again measured at peak and trough concentrations (Figure 1). All patients were instructed to take the rivaroxaban tablets with a meal to increase drug bioavailability.

The primary outcome was anti-FXa activity in Thai patients with non-valvular AF measured at peak and trough concentrations following administration of 20 and 15 mg rivaroxaban once daily in patients with CrCl ≥50 mL/min or 15 and 10 mg rivaroxaban once daily in patients with CrCl 15–49 mL/min.

According to previous clinical pharmacokinetic studies,
the 5th–95th percentiles for trough and peak concentrations are 12–137 and 178–419 μg/L, respectively. In the present study, the anti-FXa activity of rivaroxaban was specifically calibrated and translated into values of blood rivaroxaban concentration (i.e., μg/L). As such, we defined the expected range of anti-FXa activity at trough and peak rivaroxaban concentrations as 12–137 and 178–419 μg/L, respectively, and determined the proportion of patients receiving the standard and Japan-specific doses with anti-FXa activity in the expected range.

The anti-FXa activity of rivaroxaban in plasma samples was measured using the BIOPHEN DiXal kit (chromogenic anti-FXa; Dasit, Milan, Italy) and analyzed on a Sysmex CS 2500 System (Siemens Health Care, Milan, Italy). All reagents and instruments were used in accordance with the manufacturers’ instructions.

**Statistical Analysis**

Continuous variables are presented as the mean ± SD or as the median (IQR) or 5th–95th percentile range, as appropriate. Categorical variables are presented as percentages. Normally distributed continuous variables were compared between groups using t-tests; for non-normally distributed variables, comparisons were made using the Mann-Whitney U-test. Paired t-tests were used to compare the anti-FXa activity of different doses of rivaroxaban within the same renal function group. Proportions were compared by Chi-squared or Fisher’s exact tests as appropriate. Correlations were analyzed using non-parametric (Spearman) correlation and are expressed as Spearman’s $\rho$. Two-tailed $P<0.05$ was considered significant.

**Results**

**Baseline Characteristics of the Study Population**

In all, 60 patients were enrolled in the study. The baseline characteristics of the study population are given in **Table 1**. The mean age of the study population was 69.4 ± 9.2 years, 63.3% were male, and mean body weight was 64.0 ± 14.1 kg. The median BMI was 24.4 kg/m² (IQR 21.5–26.9 kg/m²) and mean CrCl was 59.0 ± 22.8 mL/min. For the 39 patients (65%) with CrCl $\geq$ 50 mL/min, mean CrCl was 72.1 ± 16.9 mL/min, whereas for the 21 patients (34%) with CrCl 15–49 mL/min, median CrCl was 34.9 ± 7.0 mL/min. Twenty-eight patients (46.7%) had persistent or permanent AF and 32 (53.3%) had paroxysmal AF. The median duration of rivaroxaban use before study enrollment was 707.5 days (IQR 348.3–1,219.8 days).

**Anti-FXa Activity of Rivaroxaban**

Of the 60 patients, 4 had received inappropriate rivaroxaban dosing: 1 patient with CrCl <50 mL/min had received inappropriate overdosing (20 mg once daily) and 3 patients with CrCl $\geq$ 50 mL/min had received inappropriate underdosing (10 mg once daily).

The anti-FXa activity of rivaroxaban with appropriate dosing (20 or 15 mg once daily in those with normal renal function; 15 or 10 mg once daily in those with impaired renal function) is summarized in **Table 2**. In patients with normal renal function (CrCl $\geq$ 50 mL/min), anti-FXa activity measured at the peak concentration was significantly higher after administration of the standard 20-mg dose than the Japan-specific 15-mg dose (median [5th–95th percentile] anti-FXa activity 364 [154–636] and

| Table 1. Baseline Characteristics of the Study Patients (n=60) |
|-----------------|------------------|
| Age (years)     | 69.4±9.2         |
| Male sex        | 38 (63.3)        |
| Body weight (kg)| 64.0±14.1        |
| Body mass index (kg/m²) | 24.4 [21.5–26.9] |
| Creatinine (mg/dL) | 1.1±0.3         |
| Creatinine clearance (mL/min) | 59.0±22.8       |
| CHADS² score    | 2 [1–2]          |
| CHA²DS²-VASC score | 3 [2–4]      |
| HAS-BLED score  | 2 [1–2]          |
| Underlying diseases                                      |
| Hypertension    | 46 (76.7)        |
| Congestive heart failure                                | 15 (25.0)       |
| Ischemic heart disease                                  | 8 (13.3)        |
| Diabetic        | 16 (26.7)        |
| Dyslipidemia    | 35 (58.3)        |
| Ischemic stroke  | 7 (11.7)         |
| Concomitant drugs                                       |
| Amiodarone      | 1 (1.7)          |
| Dronedarone     | 3 (5.0)          |
| Antiviral drug (Ledipasvir/Sofosbuvir) +Ribavirin       | 1 (1.7)         |
| Aspirin (81 mg) | 1 (1.7)          |
| Clopidogrel (75 mg)                                    | 1 (1.7)         |

Data are given as the mean ± SD, median [interquartile range], or n (%).

| Table 2. Anti-FXa Activity of Rivaroxaban at Peak and Trough Concentrations According to Dose and Renal Function |
|---------------------------------------------------------------|
| Anti-FXa activity (µg/L) |
| Peak                  | Trough                |
|-----------------------|-----------------------|
| Normal renal function (CrCl $\geq$ 50 mL/min)                 |
| 20 mg once daily (standard dose; n=35)                        | 364 (154–636)       |
| 15 mg once daily (Japan-specific dose; n=35)                  | 298 (150–474)*      |
| Impaired renal function (CrCl 15–49 mL/min)                   |
| 15 mg once daily (standard dose; n=21)                        | 331 (222–652)       |
| 10 mg once daily (Japan-specific dose; n=21)                  | 263 (121–439)*      |

Data are presented as the median (5th–95th percentile range). *$P<0.05$ compared with the standard dose within the same renal function group. CrCl, creatinine clearance; FXa, Factor Xa.
298 [150–474] µg/L, respectively; P=0.001). Similarly, in those with impaired renal function (CrCl 15–49 mL/min), anti-FXa activity measured at peak concentration was significantly higher after administration of the standard 15-mg dose than the Japan-specific 10-mg dose (median [5th–95th percentile] anti-FXa activity 331 [222–652] and 263 [121–439] µg/L, respectively; P<0.001).

In contrast, anti-FXa activity measured at the trough did not differ between the 20-mg (standard) and 15-mg (Japan-specific) doses, with median anti-FXa activity 263 [121–439] and 298 [150–474] µg/L, respectively; P=0.001).

Figure 2. Median anti-Factor Xa (FXa) activity of different doses of rivaroxaban at (A) peak and (B) trough in patients with normal and impaired renal function (creatinine clearance ≥50 and <50 mL/min, respectively). The boxes show the interquartile range, with the median value indicated by the horizontal line; whiskers show the range. Circles indicate outliers.

Figure 3. Individual changes in anti-Factor Xa (FXa) activity between standard and Japan-specific doses of rivaroxaban at (A) peak and (B) trough. Standard doses were 20 and 15 mg rivaroxaban, once daily, in patients with normal and impaired renal function, respectively; Japan-specific doses of rivaroxaban were 15 and 10 mg, once daily, in patients with normal and impaired renal function, respectively.
Anti-FXa Activity of Different Rivaroxaban Doses

After the anti-FXa activity of rivaroxaban has been assessed at the standard and Japan-specific doses, all patients continued with the standard dose of rivaroxaban. At the 1-year follow-up, 1 patient had developed ischemic stroke; in this patient, anti-FXa activity measured at peak was above the expected range, whereas anti-FXa activity measured at trough was within the expected range. Three patients experienced major bleeding while on rivaroxaban. In these patients, anti-FXa activity measured at peak was within the expected range in 1 and above and below the expected range in the remaining 2 patients. Because of the small sample size and relatively low event rate, correlations between anti-FXa activity and clinical outcomes were not evaluated.

Discussion

Rivaroxaban, an orally administered direct inhibitor of Factor Xa, was proved in ROCKET-AF to be non-inferior to warfarin in reducing stroke and systemic embolism, as well as in terms of the occurrence of major bleeding, in patients with non-valvular AF.7 In addition, rivaroxaban is associated with a lower risk of fatal bleeding and intracranial hemorrhage than warfarin.7 The doses of rivaroxaban used in the ROCKET-AF trial were 20 mg once daily in patients with normal renal function and 15 mg once daily in patients with moderate renal impairment. A previous simulation pharmacokinetic study in Caucasian patients with AF showed similar exposure between 15 mg rivaroxaban once daily in patients with CrCl ≥50 mL/min.18

J-ROCKET AF is similar to ROCKET-AF, but was conducted exclusively in Japan. The J-ROCKET AF investigators decided to use lower doses of rivaroxaban in their study, namely 15 mg once daily in patients with nor-
nal renal function and 10 mg once daily in patients with moderate renal impairment.\textsuperscript{9} This decision was based on pharmacokinetic modeling data that indicated that the anti-FXa activity of rivaroxaban 15 mg once daily in Japanese AF patients was comparable to that of 20 mg once daily in Caucasian AF patients. The median anti-FXa activity measured at peak and trough for the 15-mg once daily dose in the Japanese AF population was reported to be 259 and 44 \( \mu \text{g/L} \), respectively, at steady state. Similarly, the median anti-FXa activity measured at peak and trough following administration of 20 mg rivaroxaban once daily in a Caucasian population was reported to be 289 and 32 \( \mu \text{g/L} \), respectively.\textsuperscript{10}

The efficacy and safety of the Japan-specific dose of rivaroxaban were proven in J-ROCKET AF. Caucasian patients with non-valvular AF receiving the Japan-specific dose of rivaroxaban had a similar rate of major bleeding, a non-significantly lower rate of stroke and systemic thromboembolism, and a significantly lower rate of intracranial bleeding than patients taking warfarin.\textsuperscript{11} The large cohort study in Japan also showed that patients receiving the Japan-specific dose had a lower risk of major bleeding than those receiving warfarin.\textsuperscript{12}

It has been shown that approximately one-third of rivaroxaban is excreted unchanged via the kidney.\textsuperscript{13,14} Correspondingly, previous studies demonstrated that moderate renal impairment increased exposure to rivaroxaban.\textsuperscript{15,16} Several observational studies found that Asian patients with AF had lower CrCl than their Caucasian counterparts.\textsuperscript{17,18} Therefore, it is possible that Asian populations may need lower doses of rivaroxaban than Caucasian populations.

In the present study, we demonstrated that median anti-FXa activity measured at the peak was significantly higher for the standard than Japan-specific dose of rivaroxaban. Interestingly, the median anti-FXa activity measured at the peak for the 20-mg once daily dose reported in a Caucasian AF population (289 \( \mu \text{g/L} \))\textsuperscript{16} seems to be more comparable to that of the 15-mg once daily dose (298 \( \mu \text{g/L} \)), rather than the 20-mg once daily dose (364 \( \mu \text{g/L} \)), in Thai AF patients with normal renal function in the present study. Furthermore, a higher proportion of patients receiving the Japan-specific dose of rivaroxaban in the present study had anti-FXa activity measured at peak within the expected range than patients receiving the standard dose. Of importance, one-third of patients receiving the standard dose of rivaroxaban in the present study had anti-FXa activity measured at peak that was higher than the expected range (>419 \( \mu \text{g/L} \)). Testa et al demonstrated that concentrations of NOACs were associated with clinical outcome, with high anti-FXa activity measured at peak associated with increased bleeding events and low anti-FXa activity measured at trough associated with increased thromboembolic events.\textsuperscript{21,22} Taking all these findings into consideration, the Japan-specific dose of rivaroxaban may be appropriate for use in the Thai population with non-valvular AF.

Several retrospective cohort studies from Asian countries have examined the efficacy and safety of different doses of rivaroxaban in patients with non-valvular AF. In these studies, AF patients receiving either 15 or 20 mg rivaroxaban once daily had a significantly lower risk of ischemic stroke and a lower risk of intracranial bleeding than those receiving warfarin.\textsuperscript{23,24,25} A cohort study from Taiwan showed that the risks of stroke and bleeding were similar in patients receiving 10 mg rivaroxaban once daily and those receiving 15–20 mg once daily.\textsuperscript{26} Nevertheless, patients receiving the 10-mg once daily dose had a higher risk of myocardial infarction than those receiving the 15–20 mg once daily dose. However, the renal function of patients in that study was not reported.\textsuperscript{27}

A recent cohort study explored the efficacy and safety of the standard and Japan-specific doses of rivaroxaban in a Taiwanese AF population.\textsuperscript{28} Renal function was examined in all patients. The investigators demonstrated that the efficacy of stroke and systemic thromboembolism prevention was similar between the Japan-specific and standard doses regardless of renal function.\textsuperscript{29} However, in patients with impaired renal function (estimated glomerular filtration rate <50 mL/min/1.73 m\(^2\)), the standard dose of rivaroxaban was associated with a higher risk of bleeding than the Japan-specific dose.\textsuperscript{28} These results are in accordance with the present findings that anti-FXa activity measured at peak and trough concentrations following administration of the standard dose was significantly higher than after administration of the Japan-specific dose in patients with CrCl 15–49 mL/min.

Another study reported that inappropriate underdosing of rivaroxaban (10 mg once daily in those with normal renal function) was associated with an increased risk of ischemic stroke compared with appropriate dosing (either standard dose or Japan-specific dose).\textsuperscript{29} These results are consistent with the findings of the present study. In the present study, all 3 patients who had inappropriately received 10 mg rivaroxaban once daily despite normal renal function had anti-FXa activity measured at peak below the expected range and had anti-FXa activity measured at trough below 20 \( \mu \text{g/L} \). Furthermore, the previous study found no difference in the risk of intracranial hemorrhage between inappropriate underdosing and appropriate dosing of rivaroxaban.\textsuperscript{28} These findings illustrate that the use of 10 mg rivaroxaban once daily in patients with normal renal function should be avoided in clinical practice.

The definition of the expected range of anti-FXa activity of the standard dose of rivaroxaban used in the present study was derived mostly from Caucasian patients.\textsuperscript{15,16} Nevertheless, a pharmacokinetic study indicated that average rivaroxaban exposure was comparable between a 15-mg dose of rivaroxaban in Japanese patients and a 20-mg dose in non-Japanese patients.\textsuperscript{30} There have been several studies on the anti-FXa activity of the Japan-specific dose of rivaroxaban in the Japanese population.\textsuperscript{30,31} A previous study in 96 Japanese patients reported that the mean anti-FXa activity of the Japan-specific dose of rivaroxaban measured at peak and trough was 351 \( \mu \text{g/L} \) (90% interval 79–585 \( \mu \text{g/L} \)) and 24 \( \mu \text{g/L} \) (90% interval 2–129 \( \mu \text{g/L} \)).\textsuperscript{32} Another study in 119 Japanese patients demonstrated that the mean anti-FXa activity of a 15-mg once-daily dose of rivaroxaban in patients with normal renal function measured at peak and trough was 248±112 and 28±13 \( \mu \text{g/L} \), respectively, whereas the mean anti-FXa activity of the 10-mg once-daily dose in patients with moderate

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renal impairment measured at peak and trough was 202±92 and 28±20 μg/L, respectively. In addition, the anti-FXa activity of the standard dose of rivaroxaban has been assessed in 30 Singaporeans. In that study, the mean anti-FXa activity of the standard dose of rivaroxaban measured at peak and trough in Singaporeans was lower than the expected range derived from Caucasians. This is in contrast with the observations in the present study and other previous Japanese studies, and the disparity may be due to the fact that the Singaporeans in the study had a higher mean BMI (29 kg/m²) that the present study population and the Japanese population in the previous study (BMI 24 kg/m²).

The present study has several limitations. First, the sample size is relatively small. High interindividual variability in rivaroxaban concentrations has been reported. A larger study is needed to confirm the results reported here. Second, we did not examine correlations between anti-FXa activity and clinical outcomes due to the very low event rate. Therefore, further studies, particularly randomized controlled trials, are warranted to confirm the efficacy and safety of the Japan-specific dose of rivaroxaban in other Asian populations.

Conclusions
The anti-FXa activity measured at the peak of the standard rivaroxaban dose in Thai patients with non-valvular AF was higher than that measured for the Japan-specific dose. A higher proportion of patients taking the Japan-specific dose than the standard dose had anti-FXa activity within the expected range. Thus, it may be appropriate to use the Japan-specific dose of rivaroxaban in the Thai population with non-valvular AF. Randomized studies are needed to confirm the efficacy and safety outcomes of the Japan-specific dose in other Asian populations.

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Conflict of Interest
The authors declare no competing interests for this work.

IRB Information
The Institutional Research Board of the Faculty of Medicine, Chiang Mai University approved this study (Approval no. 205/2561).

Data Availability
Deidentified participant data will not be shared.

Author Contributions
W.W., P.P. designed the study, recruited the patients, performed the statistical analyses, evaluated the results, and drafted the paper. W.W., P.P., L.N. and S.G. collected the data and contributed substantially to data preparation and quality assurance. A.P. participated in the conception and design of the study, and revised the paper for important intellectual content.

Authorship
All authors had access to the data used in this study and participated in writing the manuscript.

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