Safety and Efficacy of Adjusted Dose of Rivaroxaban in Japanese Patients With Non-Valvular Atrial Fibrillation

– Subanalysis of J-ROCKET AF for Patients With Moderate Renal Impairment –

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Background: In the Japanese Rivaroxaban Once-daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (J-ROCKET AF) study, rivaroxaban 15 mg once daily was given to patients with creatinine clearance (CrCl) ≥50 ml/min (preserved renal function), and was reduced to 10 mg once daily in patients with CrCl 30–49 ml/min (moderate renal impairment). The aim of this subanalysis was to assess the safety and efficacy of the adjusted dose of rivaroxaban compared with warfarin in a cohort with moderate renal impairment.

Methods and Results: Compared with patients with preserved renal function, those with moderate renal impairment (22.2% of all randomized patients) had higher rates of bleeding and stroke events irrespective of study treatment. Among those with moderate renal impairment, the principal safety endpoint occurred at 27.76%/year with rivaroxaban vs. 22.85%/year with warfarin (hazard ratio [HR], 1.22; 95% confidence interval [CI]: 0.78–1.91) and the rate of the primary efficacy endpoint was 2.77%/year vs. 3.34%/year (HR, 0.82; 95% CI: 0.25–2.69), respectively. There were no significant interactions between renal function and study treatment in the principal safety and the primary efficacy endpoints (P=0.628, 0.279 for both interactions, respectively).

Conclusions: The safety and efficacy of rivaroxaban vs. warfarin were consistent in patients with moderate renal impairment and preserved renal function. (Circ J 2013; 77: 632–638)

Key Words: Atrial fibrillation; Renal impairment; Rivaroxaban; Stroke; Warfarin

Atrial fibrillation (AF) is the most common cardiac rhythm disorder and is associated with an increased risk of ischemic stroke and thromboembolism. Warfarin has been widely used as the most effective anti-thrombotic therapy for stroke prevention in patients with AF and has the advantage that it can be dose-adjusted according to the patient’s risk for bleeding and thromboembolism. The use of warfarin, however, has many limitations, including multiple food and drug interactions, a narrow therapeutic window, the need for frequent coagulation status monitoring, and an increased risk of bleeding events. In an attempt to overcome these drawbacks, new anticoagulants, which are effective, safe,
and convenient to use, have been developed and tested in recent clinical trials.7,8

**Editorial p596**

Rivaroxaban is a novel oral direct factor Xa inhibitor, with a once-daily fixed dose, and is expected to provide more consistent and predictable anticoagulation effects than warfarin.9–11 The Rivaroxaban Once-daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) ROCKET AF study was an international multicenter study comparing rivaroxaban 20 mg once daily with warfarin for the prevention of stroke and systemic embolism in 14,264 patients with AF.12 Rivaroxaban was non-inferior to warfarin even on intention-to-treat analysis for the prevention of stroke and systemic embolism, and the superiority of rivaroxaban over warfarin while patients were receiving investigational drugs was demonstrated. There was no significant difference in either the composite of major and non-major clinically relevant bleeding or in the individual components of the composite endpoint. Fewer cases of intracranial hemorrhage were observed with rivaroxaban compared with warfarin, with fewer fatal bleeding events.

In the global ROCKET AF study, 20 mg once-daily rivaroxaban was selected for patients with creatinine clearance (CrCl) ≥50 ml/min.12 (CrCl was determined by the Cockcroft-Gault formula.13) Kubitz et al reported that in patients with moderate renal impairment (CrCl 30–49 ml/min), the maximum serum concentration of rivaroxaban was 25–30% higher than in healthy controls14 and pharmacokinetic models projected that a 25% dose reduction would lead to similar exposure and trough levels in patients with moderate renal impairment.15 Therefore, patients with moderate renal impairment were treated with an adjusted dose of rivaroxaban (15 mg once daily) to adjust exposure in the global ROCKET AF study.

In Japan, based on pharmacokinetic data indicating that rivaroxaban exposure in Japanese patients receiving a 15-mg once-daily dose is comparable to that in Caucasian patients receiving a 20-mg once-daily dose,16 a separate study, J-ROCKET AF, was conducted comparing a Japan-specific adjusted dose of rivaroxaban with an adjusted dose of warfarin in patients with AF. In the J-ROCKET AF study, 15 mg rivaroxaban once daily was used for patients with CrCl ≥50 ml/min and a further reduced dose (10 mg rivaroxaban once daily) was used for Japanese patients with moderate renal impairment. Non-inferiority of rivaroxaban as opposed to warfarin in terms of the principal safety endpoint (major or non-major clinically relevant bleeding) was demonstrated.

The present subanalysis assessed the risks and benefits of this adjusted dose of rivaroxaban compared with warfarin in a high-risk cohort of patients with moderate renal impairment and examined the validity of the dose setting of rivaroxaban 10 mg once daily for patients with moderate renal impairment.

**Methods**

**Study Design, Participants and Procedure**

The design and main results of the J-ROCKET AF study have been reported previously.17 In brief, this was a prospective, randomized, double-blind, double-dummy, parallel-group, active-controlled, multicenter clinical trial comparing the safety of rivaroxaban (15 mg once daily in patients with CrCl ≥50 ml/min or 10 mg once daily in patients with CrCl 30–49 ml/min at baseline) vs. dose-adjusted warfarin, in accordance to Japanese guidelines for patients with non-valvular AF. The trial was conducted in accordance with Japanese Good Clinical Practice. The study was approved by the Institutional Review Boards and all patients provided their informed consent. Japanese patients aged ≥20 years with non-valvular AF, documented electrocardiographically ≤30 days before enrollment, were randomized at 167 participating facilities in Japan. Patients had a history of prior ischemic stroke, transient ischemic attack, or non-central nervous system (non-CNS) systemic embolism, or had ≥2 of the following risk factors for thromboembolism: congestive heart failure and/or left ventricular ejection fraction ≤35%, hypertension, age ≥75 years, or diabetes mellitus. Patients with CrCl <30 ml/min were excluded. Randomization of patients without prior stroke, transient ischemic attack, or non-CNS systemic embolism and with only 2 stroke risk factors was limited to 10% of the total number of target patients.

Patients were randomized to receive either oral rivaroxaban 15 mg once daily (10 mg once daily in patients with CrCl 30–49 ml/min at randomization) or dose-adjusted warfarin to a target international normalized ratio (INR) of 2.0–3.0 in patients aged <70 years or a reduced target INR of 1.6–2.6 in patients aged ≥70 years. The pre-specified maximum exposure period was 30 months. At the end-of-study visit (or at an early discontinuation visit) patients were transitioned from study medication to open-label commercial warfarin or other appropriate therapy by the investigator according to usual clinical practice. Follow-up was completed at the follow-up visit performed 30 days after the end-of-study visit or early discontinuation visit.

**Outcomes**

An independent clinical endpoint committee adjudicated all suspected strokes, systemic embolisms, myocardial infarctions, deaths, and bleeding events that contributed to pre-specified endpoints. The principal safety endpoint was a composite of major and non-major clinically relevant bleeding. Bleeding events involving the CNS that satisfied the definition of stroke were classified as hemorrhagic strokes and were included in both the principal safety and the primary efficacy endpoints. Adverse events (AEs) were also assessed.

The primary efficacy endpoint was the composite of adjudicated all stroke (ischemic or hemorrhagic) and non-CNS systemic embolism.

**Statistical Analysis**

The primary objective of J-ROCKET AF was to test whether rivaroxaban was non-inferior to warfarin with respect to principal safety outcome in the safety group, which included all patients who received ≥1 dose of the investigational drug, on treatment, which was defined as the period from the first dose of study drug up to 2 days after the last dose, as evaluated on Cox proportional hazard modeling.

In this subanalysis, rivaroxaban-treated patients were divided according to dose, 10 mg or 15 mg based on CrCl at baseline. Event rates by treatment arm and renal function group are presented as %/year. The homogeneity of treatment effects across renal dysfunction status (30–49 ml/min and ≥50 ml/min) regarding the occurrence of principal safety and primary efficacy endpoints was tested based on the Cox model including treatment group, renal dysfunction status and their interaction.

Point estimates and 95% confidence intervals (CI) for hazard ratio (HR) for rivaroxaban vs. warfarin, within levels of renal dysfunction based on the previous model are presented in the safety group, on-treatment for the safety endpoints, and in the per-protocol group, on-treatment for the efficacy end-
served renal function (CrCl ≥ 30–49 ml/min). The median age was 78 years in those with safety group, 284 (22.2%) had moderate renal impairment (CrCl
Table 1.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CrCl 30–49 ml/min</th>
<th>CrCl ≥50 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rivaroxaban 10mg</td>
<td>Warfarin</td>
</tr>
<tr>
<td></td>
<td>o.d. (n=141)</td>
<td>(n=143)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>78 (74–81)</td>
<td>78 (75–82)</td>
</tr>
<tr>
<td>Female</td>
<td>25.5</td>
<td>33.6</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>56.0 (50.8–62.5)</td>
<td>56.1 (48.1–63.0)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>129 (118–138)</td>
<td>126 (118–138)</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>29.8</td>
<td>34.5</td>
</tr>
<tr>
<td>Prior ASA use</td>
<td>43.3</td>
<td>39.9</td>
</tr>
<tr>
<td>Prior VKA use</td>
<td>89.4</td>
<td>88.1</td>
</tr>
<tr>
<td>CHADS2 score (mean)</td>
<td>3.56</td>
<td>3.52</td>
</tr>
<tr>
<td>Prior stroke/TIA or systemic embolism</td>
<td>56.7</td>
<td>57.3</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>52.5</td>
<td>51.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>82.3</td>
<td>82.5</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>36.2</td>
<td>25.9</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>9.9</td>
<td>11.9</td>
</tr>
</tbody>
</table>

Data given as median (IQR) or %.

ASA, acetylsalicylic acid; CHADS2, a clinical prediction rule for estimating the risk of stroke for patients with atrial fibrillation, it was calculated by assigning 1 point for diagnoses of congestive heart failure, hypertension, age 75 years or older, and diabetes mellitus and 2 points for prior stroke or transient ischemic attack; CrCl, creatinine clearance; o.d., once daily; SBP, systolic blood pressure; TIA, transient ischemic attack; VKA, vitamin K antagonist.

points. Statistical analysis was performed by Bayer Yakuhin using SAS version 9.1 (SAS Institute, Cary, NC, USA).

Results

Patient Characteristics

Baseline patient characteristics randomized to rivaroxaban or warfarin are given in Table 1. Of the 1,278 patients in the safety group, 284 (22.2%) had moderate renal impairment (CrCl 30–49 ml/min). The median age was 78 years in those with moderate renal impairment and 70 years in those with preserved renal function (CrCl ≥50 ml/min). The proportion of women was higher in the moderate renal impairment group compared to the preserved renal function group. In addition, patients with moderately impaired renal function had lower body weight and higher CHADS2 scores than those with preserved renal function.

Safety Outcomes

The overall primary safety analysis for J-ROCKET AF showed that a composite of major bleeding and non-major clinically relevant bleeding events occurred in 138 patients on rivaroxaban (18.04%/year) and in 22 on warfarin (2.61%/year; HR, 0.49; 95% CI: 0.24–1.00). As shown in Figure 1B, in patients with moderate renal impairment, intracranial hemorrhage occurred in 11 patients on rivaroxaban-treated patients. Epistaxis and gingival bleeding were more frequent in the rivaroxaban group than in the warfarin group irrespective of renal function.

AEs

Table 2 lists the 10 most frequent AEs observed in the rivaroxaban-treated patients. Epistaxis and gingival bleeding were more frequent in the rivaroxaban group than in the warfarin group irrespective of renal function.

Efficacy Outcomes

The primary efficacy analysis for overall J-ROCKET AF showed that the composite of adjudicated all stroke and non-CNS systemic embolism occurred in 11 patients on rivaroxaban (1.26%/year) and in 22 on warfarin (2.61%/year; HR, 0.49; 95% CI: 0.24–1.00).
Rivaroxaban in AF Patients With Renal Impairment

Figure 1. Safety outcomes according to treatment group and renal function; safety group, on treatment. (A) Kaplan-Meier curve of time until first major bleeding or non-major clinically relevant bleeding event. (B) Components of the principal safety outcomes: major and non-major clinically relevant bleeding. *Major or non-major clinically relevant bleeding. †Rivaroxaban 15 mg once daily. ‡Rivaroxaban 10 mg once daily. CI, confidence interval; CrCl, creatinine clearance; PRBC, packed red blood cells.

3.34%/year with warfarin (HR, 0.82; 95% CI: 0.25–2.69), and in 0.87%/year with rivaroxaban 15 mg once daily vs. 2.41%/year with warfarin in those with preserved renal function (HR, 0.36; 95% CI: 0.14–0.93). The primary efficacy endpoint occurred more frequently in patients with moderate renal impairment than in those with preserved renal function irrespective of study treatment. When compared between the 2 treatment groups, the rate of primary efficacy endpoint was lower in the rivaroxaban group than in the warfarin group irrespective of renal function. Although HR was numerically
In contrast, renal impairment is a risk factor for bleeding during anti-thrombotic therapy. \cite{21-23} Warfarin, the current standard anticoagulant for prevention of stroke in AF patients, is used with adjusted dose according to its pharmacodynamics (PD) parameter, prothrombin time-international normalized ratio (PT-INR). In the guidelines, the same target PT-INR is applied regardless of renal function. \cite{3-24} That is to say, the current anticoagulant therapy for renally impaired AF patients is based on the concept of obtaining similar anticoagulation status by “PD adjusted dose” to that of patients with preserved renal function. However, an absolute difference between patients with moderate renal impairment and those with preserved renal function, there was no significant interaction (P=0.279 for interaction).

**Discussion**

Among patients with AF, renal impairment is common and progressively worsens with advancing age. Such patients have a greater prevalence of thromboembolic risk factors (eg, hypertension, diabetes) than the general population. \cite{18} Renal impairment is also known to be an independent risk factor for ischemic stroke and systemic embolism in AF patients. \cite{19,20} In contrast, renal impairment is a risk factor for bleeding during anti-thrombotic therapy. \cite{21-23} Warfarin, the current standard anticoagulant for prevention of stroke in AF patients, is used with adjusted dose according to its pharmacodynamics (PD) parameter, prothrombin time-international normalized ratio (PT-INR). In the guidelines, the same target PT-INR is applied regardless of renal function. \cite{3-24} That is to say, the current anticoagulant therapy for renally impaired AF patients is based on the concept of obtaining similar anticoagulation status by “PD adjusted dose” to that of patients with preserved renal func-

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**Figure 2.** Bleeding sites of major bleeding according to renal function; safety group, on treatment. CrCl, creatinine clearance; GI, gastrointestinal.

**Table 2. Primary Adverse Events vs. Renal Function†**

<table>
<thead>
<tr>
<th>Adverse event (%)</th>
<th>CrCl 30–49ml/min</th>
<th>CrCl ≥50ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rivaroxaban 10mg</td>
<td>Warfarin</td>
</tr>
<tr>
<td></td>
<td>o.d. (n=141)</td>
<td>(n=143)</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban 15mg</td>
<td>Warfarin</td>
</tr>
<tr>
<td></td>
<td>o.d. (n=498)</td>
<td>(n=496)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>23.4</td>
<td>37.8</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>19.1</td>
<td>11.2</td>
</tr>
<tr>
<td>Subcutaneous hemorrhage</td>
<td>10.6</td>
<td>18.2</td>
</tr>
<tr>
<td>Contusion</td>
<td>13.5</td>
<td>10.5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9.9</td>
<td>5.6</td>
</tr>
<tr>
<td>URTI</td>
<td>8.5</td>
<td>10.5</td>
</tr>
<tr>
<td>Gingival bleeding</td>
<td>6.4</td>
<td>3.5</td>
</tr>
<tr>
<td>Back pain</td>
<td>9.2</td>
<td>14.7</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5.7</td>
<td>2.8</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>14.2</td>
<td>11.9</td>
</tr>
</tbody>
</table>

† Ten most frequent adverse events observed in the rivaroxaban-treated patients.
CrCl, creatinine clearance; o.d., once daily; URTI, upper respiratory tract inflammation.
tion. The net effect of anticoagulation in patients with renal impairment is still not well understood and there is no consensus on the optimal balance between risk and benefit of the therapy. Novel anticoagulants, however, which have become available in this clinical setting recently, should provide at least comparable net effect to that of current standard treatment warfarin.

Novel oral anticoagulants have stable and predictive pharmacokinetic and PD profiles, do not require routine coagulation monitoring and are fixed-dose formulations. But the doses of novel oral anticoagulants also should be adjusted to maintain the balance between efficacy and safety. While rivaroxaban is predominantly metabolized by the liver, approximately one-third is cleared renally. Therefore, renal clearance of rivaroxaban is anticipated to decrease with increasing renal impairment. We estimated rivaroxaban exposure based on the differences in CrCl, a marker for renal function.

In the global ROCKET-AF study and the Japanese-specific J-ROCKET AF study, the dose of rivaroxaban was set at 20 mg once daily for patients with preserved renal function, and at 15 mg once daily and 10 mg once daily respectively for those with moderate renal impairment. The key concept of the dose schedule was to keep the exposure similar for each patient, by adjusting the dose of rivaroxaban based on CrCl. CrCl was determined by the Cockcroft-Gault formula, which takes into account the age, weight, sex and serum creatinine level of the patient. By keeping the exposure similar for each patient, the safety and efficacy of rivaroxaban, compared to warfarin, was expected to be maintained even in patients with moderate renal impairment who are at high risk of bleeding and thromboembolism. As a result of this subanalysis, patients with preserved renal function, those with moderate renal impairment had higher rates of bleeding events irrespective of study treatment. In each subgroup divided by renal function, the rate of the principal safety endpoint was comparable between rivaroxaban and warfarin, showing no significant interaction between the 2 subgroups. The event rate of efficacy events was lower in the rivaroxaban group than in the warfarin group, although the number of cases was limited. Thus, adjusting the dose of rivaroxaban, originally a fixed-dose formulation, to 10 mg once daily according to CrCl was considered appropriate for achieving comparable efficacy to warfarin without increasing the risk of bleeding. This validated the dose setting strategy to adjust rivaroxaban exposure.

In addition, the results obtained in this subanalysis of the J-ROCKET AF study are consistent with those reported in the subgroup analysis of the global ROCKET AF study, as the primary analysis of the J-ROCKET AF study was consistent with that of the global ROCKET AF study. This additionally validated the dose setting strategy of rivaroxaban.

**Study Limitations**

In general, patients with renal impairment have a greater prevalence of thromboembolic and bleeding risk factors (eg, high age and low body weight). Also in this subanalysis, patients with moderate renal impairment had a higher prevalence of those risk factors; the median age and body weight in the moderate renal impairment group were 78 years old and 56 kg, respectively, whereas in the preserved renal function group were 70 years old and 66 kg, respectively. J-ROCKET AF was not primarily designed to compare the safety and efficacy of rivaroxaban between patients with moderate impairment and those with preserved renal function. Consequently, these confounding factors may have affected the safety and efficacy outcome of this subanalysis in addition to renal function.

**Conclusion**

In this subanalysis of J-ROCKET AF, the safety and efficacy of rivaroxaban vs. warfarin were consistent in patients with moderate renal impairment and those with preserved renal function. The validity of the dose schedule of rivaroxaban 10 mg once daily for Japanese patients with moderate renal impairment is confirmed.

**Acknowledgments**

The rivaroxaban clinical development program is co-sponsored by Janssen Pharmaceuticals (Raritan, NJ, USA) and Bayer HealthCare Pharmaceuticals (Leverkusen, Germany). The trial was funded by the Bayer Healthcare Pharmaceuticals Japanese subsidiary, Bayer Yakuhin. Drs Iwamoto, Kajikawa and Ueda, and Mr Tajiri and Mr Kato report employment by Bayer Yakuhin. Dr Hori received consultation fees from Bayer, Boehringer

### Table: Efficacy according to treatment group and renal function; per-protocol group, on treatment

<table>
<thead>
<tr>
<th>Clinical endpoint</th>
<th>Event rate (%/year)</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value (interaction)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rivaroxaban (N=499)</td>
<td>Warfarin (N=494)</td>
<td>rivaroxaban vs Warfarin</td>
</tr>
<tr>
<td></td>
<td>CrCl ≥50 ml/min¹</td>
<td>CrCl 30–49 ml/min²</td>
<td></td>
</tr>
<tr>
<td>Primary efficacy</td>
<td>0.87</td>
<td>2.41</td>
<td>0.30 (0.14–0.93)</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.77</td>
<td>3.34</td>
<td>0.82 (0.25–2.69)</td>
</tr>
<tr>
<td></td>
<td>CrCl ≥50 ml/min¹</td>
<td>CrCl 30–49 ml/min²</td>
<td></td>
</tr>
<tr>
<td>All stroke</td>
<td>0.72</td>
<td>2.41</td>
<td>0.30 (0.11–0.82)</td>
</tr>
<tr>
<td></td>
<td>2.77</td>
<td>2.78</td>
<td>0.99 (0.29–3.42)</td>
</tr>
<tr>
<td></td>
<td>CrCl ≥50 ml/min¹</td>
<td>CrCl 30–49 ml/min²</td>
<td></td>
</tr>
<tr>
<td>Primary haemorrhagic stroke</td>
<td>0.14</td>
<td>0.45</td>
<td>0.32 (0.03–3.08)</td>
</tr>
<tr>
<td></td>
<td>1.11</td>
<td>0.56</td>
<td>1.98 (0.18–21.8)</td>
</tr>
<tr>
<td></td>
<td>CrCl ≥50 ml/min¹</td>
<td>CrCl 30–49 ml/min²</td>
<td></td>
</tr>
<tr>
<td>Primary Ischaemic stroke</td>
<td>0.58</td>
<td>1.96</td>
<td>0.30 (0.10–0.91)</td>
</tr>
<tr>
<td></td>
<td>1.66</td>
<td>2.22</td>
<td>0.74 (0.17–3.31)</td>
</tr>
</tbody>
</table>

*Figure 3.* Efficacy according to treatment group and renal function; per-protocol group, on treatment. *Stroke plus non-CNS systemic embolism. †Rivaroxaban 15 mg once daily. ‡Rivaroxaban 10 mg once daily. CI, confidence interval; CrCl, creatinine clearance.
References


