Rivaroxaban vs. Warfarin in Japanese Patients With Atrial Fibrillation
– The J-ROCKET AF Study –

Masatsugu Hori, MD, PhD; Masayasu Matsumoto, MD, PhD; Norio Tanahashi, MD; Shin-ichi Momomura, MD; Shinichiro Uchiyama, MD, PhD; Shinya Goto, MD, PhD; Tohru Izumi, MD, PhD; Yukihiko Koretsune, MD, PhD; Mariko Kajikawa, MD, PhD; Masaharu Kato; Hitoshi Ueda, PhD; Kazuya Iwamoto, MD, PhD; Masahiro Tajiri, BSc; on behalf of the J-ROCKET AF study investigators

**Background:** The global ROCKET AF study evaluated once-daily rivaroxaban vs. warfarin for stroke and systemic embolism prevention in patients with atrial fibrillation (AF). A separate trial, J-ROCKET AF, compared the safety of a Japan-specific rivaroxaban dose with warfarin administered according to Japanese guidelines in Japanese patients with AF.

**Methods and Results:** J-ROCKET AF was a prospective, randomized, double-blind, phase III trial. Patients (n=1,280) with non-valvular AF at increased risk for stroke were randomized to receive 15mg once-daily rivaroxaban or warfarin dose-adjusted according to Japanese guidelines. The primary objective was to determine non-inferiority of rivaroxaban against warfarin for the principal safety outcome of major and non-major clinically relevant bleeding, in the on-treatment safety population. The primary efficacy endpoint was the composite of stroke and systemic embolism. Non-inferiority of rivaroxaban to warfarin was confirmed; the rate of the principal safety outcome was 18.04% per year in rivaroxaban-treated patients and 16.42% per year in warfarin-treated patients (hazard ratio [HR] 1.11; 95% confidence interval 0.87–1.42; P<0.001 [non-inferiority]). Intracranial hemorrhage rates were 0.8% with rivaroxaban and 1.6% with warfarin. There was a strong trend for a reduction in the rate of stroke/systemic embolism with rivaroxaban vs. warfarin (HR, 0.49; P=0.050).

**Conclusions:** J-ROCKET AF demonstrated the safety of a Japan-specific rivaroxaban dose and supports bridging the global ROCKET AF results into Japanese clinical practice. ([Circ J 2012; 76: 2104–2111])

**Key Words:** Anticoagulants; Atrial fibrillation; Japanese; Prevention; Stroke

For more than 50 years, vitamin K antagonists (VKAs), primarily warfarin, have been the most effective antithrombotic therapy available for the prevention of ischemic stroke in patients with atrial fibrillation (AF). However, warfarin therapy is associated with numerous issues that limit its use, such as multiple food, drug, and pharmacogenomic interactions, which contribute to its unpredictable pharmacokinetics and pharmacodynamics. Frequent coagulation monitoring and dose adjustment is necessary to maintain warfarin anticoagulation within the therapeutic international normalized ratio (INR) range.²

**Editorial p 2086**

Rivaroxaban is a novel oral, direct Factor Xa inhibitor in advanced clinical development that may overcome the many drawbacks of warfarin. ROCKET AF was a global phase III trial that evaluated the safety and efficacy of rivaroxaban 20mg once daily (o.d.) for the prevention of stroke and systemic embolism in patients with non-valvular AF; a reduced dose of 15mg o.d.
was evaluated in patients with moderate renal impairment, defined as baseline creatinine clearance (CrCl) 30–49 ml/min.3 Patients in Japan were not enrolled into the global ROCK-ET AF trial for 2 reasons. First, pharmacokinetic modeling data indicated that, at steady state, the distribution of both the maximum concentration (Cmax: median: 259.48 μg/L) and area under the curve from 0 to 24 h (AUC0–24: median: 3,193.09 μg·h/L) of rivaroxaban in Japanese patients with AF who received a 15 mg o.d. dose of rivaroxaban would be comparable to the Cmax (median: 289.05 μg/L) and AUC0–24 (median: 3,243.04 μg·h/L), in Caucasian patients with AF who received a 20 mg o.d. dose (Tanigawa et al unpublished data, 2012). Second, lower anticoagulation targets are used in Japanese clinical practice: Japanese guidelines recommend a reduced INR target level of 1.6–2.6 in patients aged ≥70 years, and in practice a tendency for Japanese physicians to favor lower levels of anticoagulation in patients aged <70 years has been reported.8 Accordingly, the 15 mg o.d. dose of rivaroxaban was selected for the phase III J-ROCKET AF study to provide a margin consistent with the lower target INRs recommended for VKA therapy in clinical practice in Japan.5,6

The J-ROCKET AF study was conducted entirely in Japan and was designed specifically to evaluate the safety of the 15 mg o.d. dose of rivaroxaban vs. warfarin comparator dosed according to Japanese practice, with the lower target INR range for patients ≥70 years.4

Methods

Study Design and Enrolment Criteria

J-ROCKET AF was a prospective, randomized, double-blind, double-dummy, parallel-group, active-controlled, multicenter clinical trial that evaluated the safety of rivaroxaban vs. dose-adjusted warfarin. Safety was assessed with respect to on-treatment bleeding events in the safety population (ie, all patients who received ≥1 dose of the study drug). The trial was conducted in accordance with Japanese Good Clinical Practice, the Declaration of Helsinki, and the International Conference on Harmonization guideline E6. The study was approved by the Institutional Review Boards and all patients gave informed consent.

Study Participants

Japanese patients aged ≥20 years with non-valvular AF, documented electrocardiographically ≤30 days before randomization, were recruited from 167 participating sites in Japan. Patients had a history of prior ischemic stroke, transient ischemic attack (TIA), or non-central nervous system (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. Recruitment of patients without prior stroke, TIA, or non-CNS systemic embolism and with only 2 stroke risk factors was limited to 10% of the total number of patients. Detailed inclusion and exclusion criteria are available in Data S1.

Study Treatment

A double-blind, double-dummy design was chosen to minimize bias with respect to concomitant interventions and reporting of clinical events. Patients with AF were randomized to receive either oral rivaroxaban 15 mg o.d. (10 mg o.d. in patients with CrCl 30–49 ml/min at randomization) or warfarin dose-adjusted to a target INR of 2.0–3.0 in patients aged <70 years, or a reduced INR of 1.6–2.6 in patients aged ≥70 years. As part of the double-dummy design, patients in each group also received a tablet of either titrated warfarin placebo or rivaroxaban pla-

cebo, respectively, to preserve the treatment blind. INR monitoring procedures to maintain double-blinding are described in Data S1. Treatment compliance was evaluated by expressing the proportion of days a patient took study medication as a percentage of the total treatment duration.

Study Procedures

The study was divided into several periods: screening, double-blind treatment closing with an end-of-study visit, and a 30-day post-treatment observation period. Patients returned for visits at weeks 2 and 4, and every 4 weeks thereafter for the duration of the double-blind treatment period. The prespecified maximum exposure period, and the expected study duration, were 30 months. At the end-of-study visit, or at an early discontinuation visit, patients were transitioned by the investigator from study medication to open-label warfarin or other appropriate therapy according to usual clinical practice, and a follow-up visit was performed 30 days after the end-of-study or early discontinuation visit.

Adjudication of Clinical Outcomes

An independent clinical endpoint committee adjudicated all suspected strokes, systemic embolisms, myocardial infarctions (MIs), deaths, and bleeding events contributing to the prespecified endpoints. Events taking place from the time of randomization through to the end of the study treatment period and until the end of the 30-day follow-up period were adjudicated.

Safety Outcomes

The principal safety outcome was the composite of major and non-major clinically relevant bleeding assessed by a blinded clinical endpoint committee. Bleeding events adjudicated by the clinical endpoint committee to have met the definition of hemorrhagic stroke were included in the safety outcome analysis as well as the efficacy analysis. Major and non-major clinically relevant bleeding events are defined in the Table S1. Other overt bleeding episodes that did not meet the criteria for major or non-major clinically relevant bleeding were classified as minimal. Treatment-emergent adverse events (AEs), hepatic liver enzyme activity, and total bilirubin were also assessed. Safety outcomes were assessed in the safety population, which included all patients who received ≥1 dose of study drug, using an on-treatment analysis, defined as the period from first dose of study drug up to 2 days after last dose.

Efficacy Endpoints

The primary efficacy endpoint was the composite of adjudicated all-cause stroke (ischemic or hemorrhagic) and non-CNS systemic embolism. Secondary efficacy endpoints included a composite of stroke, systemic embolism, and vascular death and a composite of stroke, systemic embolism, vascular death, and MI. Individual components of the composite secondary endpoints were also included. Definitions of efficacy endpoints and their components are reported in the Table S1).

Statistical Analysis

Safety

The primary objective was to test whether rivaroxaban was non-inferior to warfarin with respect to the principal safety outcome in the safety population, on-treatment, as evaluated by non-stratified Cox proportional hazards modeling. Based on the expected incidence of adjudicated major bleeding events and non-major clinically relevant bleeding events, a sample size of 1,200 patients with 600 per arm was considered sufficient to test the non-inferiority of rivaroxaban with respect to the principal safety outcome, with non-inferiority to be con-
cluded if the upper boundary of the 95% confidence interval (CI) for the hazard ratio (HR) of rivaroxaban to warfarin did not exceed 2.0. This margin was chosen based on studies in Asian patients with AF, which demonstrated at least a 2-fold increase in bleeding risk with warfarin treatment at INRs ≥2.6 compared with <2.6 (Table S6). Therefore in this study, assuming good control of INR, if bleeding resulting from rivaroxaban treatment was less than 2-fold higher compared with that seen with warfarin, rivaroxaban would be at least non-inferior to warfarin treatment at an INR <2.6. Further details are available in Data S1.

**Efficacy**

The study was not powered to test efficacy hypotheses and efficacy endpoints were evaluated in both the per-protocol and intention-to-treat (ITT) populations. The per-protocol population was defined as all patients randomized without any major protocol violations, using an on-treatment analysis as described previously. ITT population analyses included all randomized patients, and were carried out using both an on-treatment analysis (including events occurring up to 2 days after last dose), and an analysis including 30-day follow-up (including events occurring until the 30-day follow-up visit). Events occurring after the 30-day follow-up visit for discontinued patients were not collected in the analysis including 30-day follow-up.

**Time in Therapeutic Range (TTR)**

For each patient receiving warfarin, individual TTR was based on regression analyses, calculated from INR values using linear interpolation. The cumulative total of patient treatment days was the denominator, and the total number of days that INR was in the target range was the numerator. Center TTR was calculated by dividing the total number of INR values within the target range at a center by the total number of INR values from all warfarin-treated patients at the center.

Bayer Yakuhin Ltd funded the trial and was responsible for trial design and study data collection. A Steering Committee, chaired by Dr M. Hori, approved the design of the trial and was responsible for oversight of the conducting of the study. All authors take responsibility for the accuracy and completeness of the data and all analyses presented here.

### Results

**Patients**

A total of 1,439 patients were screened for eligibility and 1,280 were randomized beginning June 8, 2007. The last patient visit was recorded on January 19, 2010. Of the 1,280 randomized patients, 1,278 (639 in each group) received ≥1 dose of study medication and were included in the safety population, and 1,274 patients without major protocol violations were included in the per-protocol population (Figure S1). Baseline demographics were balanced across both treatment arms (Table 1). Mean patient age was 71.1 years. At baseline, moderate renal impairment, defined as CrCl 30–49 ml/min, was present in 22.1% of patients randomized to rivaroxaban; these patients received a reduced 10 mg o.d. rivaroxaban regimen. Mean treatment compliance was >99% for both treatment groups.

**Safety Outcomes**

The principal safety outcomes, the composite of adjudicated major bleeding and non-major clinically relevant bleeding events, eval-
Rivaroxaban vs. Warfarin in Japanese AF Patients

The observed rate of major bleeding events was 3.00% per year in the rivaroxaban arm compared with 3.59% per year in the warfarin arm (HR 0.85; 95% CI 0.50–1.43), and observed rates also tended to be lower with rivaroxaban for all individual components of the major bleeding outcome (Figure 1B), although none of the differences was statistically significant. Non-major clinically relevant bleeding event rates were 15.42% per year in rivaroxaban-treated patients compared with 12.99% per year in warfarin-treated patients (HR 1.20; 95% CI 0.92–1.56), and this difference was also not statistically significant.

Major bleeding from the upper gastrointestinal tract occurred in 6 patients (0.9%) who received rivaroxaban and in 12 patients (1.9%) who received warfarin. Treatment-emergent fatal bleeding events occurred in 1 patient who received rivaroxaban and in 3 patients who received warfarin. In terms of critical organ bleeding, intracranial hemorrhages were observed in 5 patients (0.8%) in the rivaroxaban group and in 10 patients (1.6%) in the warfarin group. These results were not tested for statistical significance. Sites of major bleeding are shown in Figure 2.

No significant differences in principal safety outcome rates were observed between the rivaroxaban and warfarin treatment groups, either in patients with moderate renal impairment (HR 1.22; 95% CI 0.78–1.91) or in patients with mild or no renal impairment and baseline CrCl ≥ 50 ml/min (HR 1.07; 95% CI 0.80–1.43; interaction P-value=0.628) (Table S2).

**Adverse Events**

The observed incidence of treatment-emergent AEs in the safety population, including drug-related AEs, was similar between the 2 treatment groups (Table 2). The incidence of AEs leading to permanent discontinuation of the study drug was 13.1% in the rivaroxaban arm and 15.0% in the warfarin arm. The most frequently reported treatment-emergent bleeding events (ie, those
occurring at a rate \( \geq 10\% \) in either treatment group) were epistaxis (16.3\% in rivaroxaban patients vs. 9.4\% in warfarin patients) and subcutaneous hemorrhage (10.5\% vs. 12.5\%, respectively).

Treatment-emergent serious AEs were reported in 23.6\% and 24.3\% of patients receiving rivaroxaban or warfarin, respectively. Elevations of hepatic enzyme activity and total bilirubin during the study were similar in both treatment groups, and there was no indication of severe liver damage (Table 2).

### Efficacy Endpoints

In the primary efficacy analysis in the per-protocol population, while on treatment, stroke or non-CNS systemic embolism occurred at a rate of 1.26\% per year in patients receiving rivaroxaban, compared with 2.61\% per year in warfarin-receiving patients (HR 0.49; 95\% CI 0.24–1.00; \( P=0.050 \)); Figure 3A, Table 3).

In terms of the secondary efficacy endpoints in the per-protocol population, on-treatment analysis, the observed incidence of the composite of adjudicated stroke, non-CNS systemic embolism, and vascular death was 1.83\% per year in the rivaroxaban group compared with 2.85\% per year in the warfarin group (HR 0.65; 95\% CI 0.34–1.22), and the event rates of the composite of adjudicated stroke, non-CNS systemic embolism, MI, and vascular death were 2.18\% per year and 2.97\% per year for rivaroxaban and warfarin, respectively (HR 0.75; 95\% CI 0.41–1.34; Table 3). All-cause stroke occurred at a lower rate in patients treated with rivaroxaban than with warfarin (HR 0.46; 95\% CI 0.22–0.98), as did primary ischemic stroke (HR 0.40; 95\% CI 0.17–0.96). Primary hemorrhagic stroke occurrence was similar in both treatment arms (HR 0.73; 95\% CI 0.16–3.25). The numbers of MI, vascular death, and all-cause mortality were also low in both treatment groups (Table 3); however, the numbers of each event were too few to permit meaningful statistical analysis.

In the ITT population analysis including 30-day follow-up, the primary efficacy endpoint occurred at a rate of 2.38\% per year and 2.91\% per year in patients receiving rivaroxaban and warfarin, respectively (HR 0.82; 95\% CI 0.46–1.45; Figure S2). In the on-treatment analysis of the ITT population, the primary efficacy endpoint occurred at a rate of 1.26\% per year and 2.60\% per year in patients receiving rivaroxaban and warfarin, respectively (HR 0.48; 95\% CI 0.23–1.00).

The efficacy of rivaroxaban relative to warfarin in the ITT population analysis including 30-day follow-up was lower than in the on-treatment analyses of the per-protocol and ITT populations, partly because of a higher rate of primary efficacy events in the off-treatment period. These data are discussed in Data S1.
TTR
Over the entire treatment period, 65.0% of the INR values of warfarin-treated patients were within the prespecified, age-dependent target range. For those aged ≥70 years, 74.0% of values were within the therapeutic INR range, but for those aged <70 years (for whom guidelines direct that the target INR range should be 2.0–3.0) only 51.8% of values were within this range (Table S3). Nevertheless, HRs for the treatment effect of rivaroxaban vs. warfarin for both the principal safety outcome and primary efficacy endpoints (on-treatment analysis) were consistent across quartiles of center TTR (Table S4, S5).

Discussion
This study was the first double-blind clinical trial conducted entirely in Japan to compare Japanese guideline-directed warfarin therapy for stroke prevention in AF with the newer oral anticoagulant, rivaroxaban, at a dose specifically adjusted for Japanese patient characteristics and Japanese clinical practice.

Safety Outcomes
The primary objective of this trial was met, because non-inferiority of rivaroxaban vs. warfarin was observed with respect to the principal safety outcome of major plus non-major clinically relevant bleeding. Although no significant differences in overall bleeding rates were observed, rivaroxaban use was associated with a non-significant lower major bleeding rate and a slightly higher non-major clinically relevant bleeding rate than with warfarin. In the global ROCKET AF study, there was no significant difference in either the composite of major plus non-maj or clinically relevant bleeding or in the individual components of the composite endpoint. As with the global ROCKET AF study, fewer intracranial hemorrhages were observed with rivaroxaban therapy compared with warfarin therapy, with fewer fatal bleeding events, although there were fewer total events in J-ROCKET AF, limiting the robustness of the analyses of these outcomes. Fewer intracranial hemorrhages with rivaroxaban than warfarin might be attributable to the different mechanisms of inhibition of the coagulation cascade; warfarin sup-

Table 3. Primary and Secondary Efficacy Endpoints

<table>
<thead>
<tr>
<th>Composite efficacy endpoints*</th>
<th>Rivaroxaban (n=637)</th>
<th>Warfarin (n=637)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary efficacy endpoint</strong> (stroke plus non-CNS systemic embolism), n (% per year)</td>
<td>11 (1.26)</td>
<td>22 (2.61)</td>
<td>0.49 (0.24–1.00)</td>
</tr>
<tr>
<td>All-cause stroke, n</td>
<td>10</td>
<td>21</td>
<td>0.46 (0.22–0.98)</td>
</tr>
<tr>
<td>Primary hemorrhagic stroke, n</td>
<td>3</td>
<td>4</td>
<td>0.73 (0.16–3.25)</td>
</tr>
<tr>
<td>Primary ischemic stroke, n</td>
<td>7</td>
<td>17</td>
<td>0.40 (0.17–0.96)</td>
</tr>
<tr>
<td><strong>Secondary efficacy endpoint 1</strong> (stroke, non-CNS systemic embolism and vascular death), n (% per year)</td>
<td>16 (1.83)</td>
<td>24 (2.85)</td>
<td>0.65 (0.34–1.22)</td>
</tr>
<tr>
<td>Secondary efficacy endpoint 2 (stroke, non-CNS systemic embolism, MI and vascular death), n (% per year)</td>
<td>19 (2.18)</td>
<td>25 (2.97)</td>
<td>0.74 (0.41–1.34)</td>
</tr>
<tr>
<td>Other endpoints†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-CNS systemic embolism, n</td>
<td>1</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>MI, n</td>
<td>3</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Vascular death, n</td>
<td>6</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>Stroke with serious residual disability, n</td>
<td>5</td>
<td>10</td>
<td>–</td>
</tr>
<tr>
<td>All-cause mortality, n</td>
<td>7</td>
<td>5</td>
<td>–</td>
</tr>
</tbody>
</table>

*Per-protocol population on treatment. †Too few events occurred to provide a robust statistical evaluation.

HR, hazard ratio; CI, confidence interval; CNS, central nervous system; MI, myocardial infarction.
presses the tissue factor–FVIIa complex and other multiple factors (ie, FIXa, FXa and thrombin), whereas rivaroxaban does not inhibit the tissue factor–FVIIa complex and directly inhibits only FXa. In J-ROCKET AF, despite the lower PT-INR target than in the global ROCKET AF, rivaroxaban also showed a tendency of fewer intracranial hemorrhages compared with warfarin. AE rates were similar across both treatment groups, and there were no significant differences between treatment arms in the elevation of liver enzyme levels.

Major Gastrointestinal Bleeding in J-ROCKET AF and Global ROCKET AF

J-ROCKET AF demonstrated that the major GI bleeding rate of the rivaroxaban group tended to be lower than that of the warfarin group, whereas the global ROCKET AF showed major GI bleeding more frequently in the rivaroxaban group than in the warfarin group. This discrepancy in the rate of GI bleeding between J-ROCKET AF and global ROCKET AF might be attributable to ethnic difference in GI bleeding, or to healthcare divergence by country in the endoscopic diagnosis/treatment for GI tract diseases and different patient awareness of GI bleeding, both of which may influence the entry of patients to the study. The possibility of a lack of robustness of the outcome analysis because of the relatively limited number of patients in J-ROCKET AF can not be excluded.

Bleeding Rates With Warfarin in Japanese Patients With AF

The results of J-ROCKET AF provide additional insight into the Japanese perception of bleeding rates with warfarin, within the wider context of recently published clinical trials of the newer anticoagulants for stroke prevention in AF. Patients receiving warfarin in the standalone J-ROCKET AF trial had their INR levels managed according to Japanese clinical guideline standards. The major bleeding rate in patients in the warfarin group was 3.59% per year in J-ROCKET AF, which was roughly comparable to that observed in warfarin-receiving patients in the subanalysis of the Japanese population in the RE-LY phase III clinical trial of dabigatran etexilate vs. warfarin for stroke prevention in patients with AF (3.31% per year); however, differences in study design (eg, double-blind vs. open-label), patient background (eg, median CHADS2 score), and the protocol-directed target INR ranges for the warfarin group (2.0–3.0 for patients aged <70 years and 2.0–2.6 for patients aged ≥70 years in the RE-LY study) preclude cross-trial comparisons.

EfficacyEndpoints

J-ROCKET AF shared the same efficacy endpoints as the global ROCKET AF study. In the global trial, it was estimated that approximately 14,000 patients would be needed to demonstrate the non-inferiority of rivaroxaban vs. warfarin with regard to the primary efficacy endpoint. However, a total of 1,280 patients were enrolled into J-ROCKET AF. Although J-ROCKET AF was not powered for efficacy, efficacy endpoint data collection was prespecified. The rate at which patients receiving rivaroxaban experienced the primary efficacy endpoint of stroke and non-CNS systemic embolism in the on-treatment analysis was approximately half the rate for patients receiving warfarin, narrowly missing nominal statistical significance. In particular, rivaroxaban was associated with a strong trend towards a reduction in all-cause stroke compared with warfarin; this reduction was driven primarily by a reduction in ischemic stroke, and the hemorrhagic stroke rates were similar in both treatment arms. These results are consistent with those of the global ROCKET AF trial, in which rivaroxaban was non-inferior to warfarin for the primary efficacy endpoint with no significant differences in the rates of either the principal safety outcome, major bleeding, or non-major clinically relevant bleeding (Table S7). Evaluation of the primary efficacy endpoint in the ITT population confirmed these observations, which are discussed further in Data S1.

In terms of the secondary efficacy endpoints and subgroup analyses, absolute event numbers were low, precluding meaningful comparisons between treatment groups. Notably, in the global ROCKET AF trial, which had a 10-fold larger sample size, there was a trend towards fewer MIs in patients while they were receiving treatment with rivaroxaban compared with warfarin (0.9% vs. 1.1%; HR 0.81; 95% CI 0.63–1.06), whereas in J-ROCKET AF there were 3 and 1 MIs in the rivaroxaban and warfarin treatment arms, respectively.

TTR Analyses

Patients assigned to warfarin therapy in this study had an overall mean TTR of 65.0%, which is similar to other clinical trials of the newer oral anticoagulants. Japanese guidelines recommend that patients aged ≥70 years should receive warfarin with a target INR range of 1.6–2.6, or 2.0–3.0 for those aged <70 years. However, the Japanese physicians in this trial tended to anticoagulate to an INR range of 1.6–2.6 regardless of the patient’s age. Patients aged <70 years had a TTR (INR 2.0–3.0) of only 51.8%. Analysis of time spent within the INR range of 1.6–2.6 in patients aged <70 years revealed that 72.7% of the INR values were within the range of 1.6–2.6 (Table S3), a result that was similar to the 74.0% TTR in patients aged ≥70 years. This observation is consistent with Japanese clinical practice, as demonstrated by TTR data from the J-RHYTHM registry, which reported that in patients aged <70 years, most INR values outside the therapeutic range were below the therapeutic range that applied to their age group (ie, below 2.0), reflecting a tendency of Japanese physicians to favor lower levels of anticoagulation. Compared with warfarin, the safety and efficacy of rivaroxaban were consistent across all quartiles of TTR by clinical site, despite the relatively high risk profile.

Renal Impairment Subgroup Analysis

In a similar manner to the global ROCKET AF, a reduced rivaroxaban dose for patients with moderate renal impairment was prospectively assessed in J-ROCKET AF. Patients with a baseline CrCl of 30–49 ml/min received a reduced rivaroxaban dosing regimen of 10 mg o.d. Notably, there was no significant difference in the relative risk of either the principal safety outcome or the primary efficacy endpoint for rivaroxaban vs. warfarin with either dose of rivaroxaban (Table S2).

Overall, the trial results support the use of a reduced dose of rivaroxaban (15 mg o.d.) for evaluation in Japanese patients with non-valvular AF. The results of J-ROCKET AF also supplement and are supported by those of the global ROCKET AF, which demonstrated that, while on treatment, patients receiving rivaroxaban experienced significantly fewer strokes or systemic emboli than patients receiving warfarin, with similar rates of major plus non-major clinically relevant bleeding.

Summary

J-ROCKET AF demonstrated the safety of a Japan-specific dose of rivaroxaban for the prevention of stroke and systemic embolism in Japanese patients with AF and a moderate to high stroke risk; that is, rivaroxaban was non-inferior to warfarin dose-adjusted according to Japanese guideline recommendations with respect to the principal safety outcome. Furthermore, the trial
design had a particular focus on the unique aspects of Japanese clinical practice. Compared with warfarin therapy, there was also a strong trend towards reduction in stroke and non-CNS systemic embolism with rivaroxaban compared with warfarin.

The findings of J-ROCKET AF support bridging of the broader safety and efficacy data from the larger, pivotal, global ROCKET AF study to Japanese patients with AF.

**Acknowledgments**

The authors thank Mark Hillen who provided medical writing services with funding from Bayer HealthCare Pharmaceuticals AG and Janssen Pharmaceuticals, Inc.

**Sources of Funding**

The rivaroxaban clinical development program is co-sponsored by Janssen Pharmaceuticals AG (Raritan, NJ, USA) and Bayer HealthCare Pharmaceuticals AG (Leverkusen, Germany). The trial was funded by Bayer Healthcare Pharmaceuticals AG’s Japanese subsidiary, Bayer Yakuhin Ltd.

**Disclosures**

Drs Iwamoto, Kajikawa and Ueda, and Mr Tajiri and Mr Kato report employment by Bayer Yakuhin. Mr Tajiri reports an equity interest in Bayer HealthCare Pharmaceuticals. Dr Hori has received consultancy fees from Bayer, Boehringer Ingelheim, Bristol Myers-Squibb and Pfizer. Dr Matsumoto and Dr Momomura have received consultancy fees from Bayer. Dr Tanahashi has received consultancy fees from Bayer and Mitsubishi Tanabe, and honoraria from Mitsubishi Tanabe and Sanofi-Aventis. Dr Goto has received research grants from Astellas, AstraZeneca, Daiichi, Eisai, Kowa, Ono, Otsuka, Pfizer, Sanofi-Aventis, and Takeda, and honoraria from Daiichi-Sankyo and Bristol-Myers-Squibb. Dr Uchiyama has received honoraria from Bayer, Boehringer Ingelheim, Daiichi-Sankyo and Bristol-Myers-Squibb. Dr Koretsune has received honoraria from Bayer, Boehringer Ingelheim, Daiichi-Sankyo and Bristol-Myers-Squibb. Dr Uchiyama has received consultancy and research grants from Bayer, Boehringer Ingelheim and research grants from Pfizer. No other conflicts of interest are reported.

**References**


**Supplementary Files**

**Supplementary File 1**

**Data S1.** Online Supplement

**Table S1.** Definitions of Outcome and Endpoint Components

**Table S2.** Renal Impairment Subgroup Analysis for the Primary Safety Outcome and Primary Efficacy Endpoint

**Table S3.** Proportion of INR Values Spent Within Therapeutic (Target) Range in Warfarin-Receiving Patients

**Table S4.** Treatment Comparisons for the Primary Safety Outcome According to Center Time in Therapeutic Range in the Safety Population

**Table S5.** Treatment Comparisons for the Primary Efficacy Endpoint According to Center Time in Therapeutic Range in the Safety Population (on Treatment Analysis)

**Table S6.** Bleeding Event Rates at Different Levels of INR Control in Japanese and Chinese Patients With AF

**Figure S1.** Key Trial Data From the Global ROCKET AF and JROCKET AF Studies

**Figure S2.** Primary efficacy endpoint observed in different populations and analysis periods.

Please find supplementary file(s): http://dx.doi.org/10.1253/circbj.CJ-12-0454