Rivaroxaban vs. Warfarin in Japanese Patients With Non-Valvular Atrial Fibrillation in Relation to Age

– Insight From J-ROCKET AF –

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Background: The J-ROCKET AF study found that rivaroxaban was non-inferior to warfarin with respect to the principal safety outcome in patients with atrial fibrillation (AF). The aim of this subgroup analysis was to assess the safety and efficacy of rivaroxaban and warfarin in relation to patient age.

Methods and Results: A total of 39.0% were elderly (aged ≥ 75 years). In elderly patients, the principal safety outcome occurred at 25.05%/year with rivaroxaban vs. 16.95%/year on warfarin (hazard ratio [HR], 1.49; 95% confidence interval [CI]: 1.02–2.16), whereas the primary efficacy endpoint occurred at 2.18%/year vs. 4.25%/year (HR, 0.51; 95% CI: 0.20–1.27), respectively. There were significant interactions in the principal safety outcomes of rivaroxaban compared with warfarin between the elderly and non-elderly groups, but not in the primary efficacy endpoints ($P=0.04$ and 0.82 for both interactions, respectively). Furthermore, in elderly patients, in the rivaroxaban group there was a trend to increase the principal safety outcome regardless of renal function. In elderly patients with preserved renal function, however, patients on rivaroxaban had a marginally favorable trend in the primary efficacy endpoint incidence rate compared with patients on warfarin.

Conclusions: There is a need to carefully consider the risks and benefits of therapy with rivaroxaban in elderly patients with non-valvular AF. (*Circ J* 2014; **78**: 1349–1356)

Key Words: Atrial fibrillation; Elderly; Oral anticoagulation; Stroke prevention

The number of patients with atrial fibrillation (AF) continues to increase, and AF is a very common cardiac arrhythmia with a prevalence of approximately 30% in the population aged ≥ 80 years.¹ The presence of AF independently increases the risk of mortality and morbidity with stroke, thromboembolism, congestive heart failure, and impaired quality of life, resulting in expanded health-care concerns.² Anticoagulant therapy for stroke prophylaxis is considered essential for patients with AF, but this therapy is underused and poorly controlled, partly because of the concern of bleeding risk, particularly in elderly patients.³ Older age, however, is a

component of not only the CHADS₂ score for stroke risk,⁴ but also the HAS-BLED score for bleeding risk.⁵ Therefore, we need to refine the strategy that maximizes the benefits of anticoagulant therapy for stroke prevention while minimizing the risks of major hemorrhage for each individual patient.

Until recently, warfarin was the only clinically available oral anticoagulant that could effectively reduce the risk of stroke and systemic embolism in patients with AF. In recent years, however, rivaroxaban has been launched as a new oral anticoagulant. Rivaroxaban can inhibit thrombosis by the direct inhibition of Factor Xa via a mechanism of action that differs

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Table. Baseline Patient Characteristics

Characteristic	Age <75 years			Age ≥75 years		
	Rivaroxaban (n=387)	Warfarin (n=393)	P-value	Rivaroxaban (n=252)	Warfarin (n=246)	P-value
Mean age (years)	66	66	0.29	79	79	0.84
Female (%)	14.5	14.5	0.99	21.0	33.3	<0.01
Mean body weight (kg)	66.7	67.5	0.34	60.7	58.7	<0.05
CrCl <50 ml/min (%)	10.1	7.9	0.28	40.5	45.5	0.25
Mean CHADS ₂ score	3.0	3.0	0.74	3.7	3.6	0.33
CHF (%)	37.7	34.9	0.41	46.8	48.8	0.66
Hypertension (%)	77.5	77.9	0.90	82.5	82.1	0.91
Diabetes mellitus (%)	42.1	43.3	0.75	34.1	27.2	0.10
Prior stroke/TIA or systemic embolism (%)	71.6	71.2	0.92	52.0	50.8	0.79

CHADS₂, 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; CHF, congestive heart failure; CrCl, creatinine clearance; TIA, transient ischemic attack.

Figure 1. Principal safety outcomes in the safety group on treatment analysis according to age (≥75 years or younger). Safety group, on treatment. †Major or non-major clinically relevant bleeding. CI, confidence interval; N/A, not applicable.

from that of warfarin.^{6–8} In J-ROCKET AF, the safety and efficacy of rivaroxaban were compared with those of dose-adjusted warfarin in accordance with the Japanese AF guidelines from the Japanese Circulation Society for Japanese patients with AF (a target international normalized ratio [INR] range of 1.6–2.6 for patients aged ≥70 years, or 2.0–3.0 for those aged <70 years).⁹ J-ROCKET AF targeted patients with a mean age of 71.1 years, with moderate or higher risk for thromboembolism and a CHADS₂ score of ≥2. In the present subgroup analysis,

we investigated the safety and efficacy of rivaroxaban vs. dose-adjusted warfarin in elderly patients (aged ≥75 years) or non-elderly patients (aged <75 years) with non-valvular AF in J-ROCKET AF.

Methods

Study Design, Participants, and Procedure

The design and results of J-ROCKET AF have been described

previously.⁹ In brief, J-ROCKET AF was a prospective, randomized, double-blind, double-dummy, parallel-group, active-controlled, multicenter clinical trial comparing the safety of rivaroxaban vs. dose-adjusted warfarin in accordance with the Japanese guidelines in patients with non-valvular AF. The study was approved by the institutional review boards, and all patients gave informed consent. The trial was conducted in accordance with Japanese Good Clinical Practice. 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 (CNS) systemic embolism, or had a CHADS₂ score ≥2 based on the following risk factors for thromboembolism: congestive heart failure and/or left ventricular ejection fraction ≤35%, hypertension (defined as use of anti-hypertensive medications within 6 months before the screening visit or persistent systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg), age ≥75 years, or diabetes mellitus (ie, history of type 1 or type 2 diabetes mellitus or use of anti-diabetic medications within 6 months before the screening visit). Randomization of patients without prior stroke, transient ischemic attack, or non-CNS systemic embolism and with only 2 stroke risk factors limited the patient number to <10% of those enrolled. Patients with creatinine clearance (CrCl) <30 ml/min were also excluded.

Eligible patients were randomized to the rivaroxaban and warfarin treatment groups in accordance with the Japanese AF guidelines. Rivaroxaban was given orally once daily at a dose of 15 mg/day, or 10 mg/day for patients with CrCl 30–49 ml/min at randomization. Dose-adjusted warfarin was given at a target

INR of 2.0–3.0 and 1.6–2.6 to patients aged <70 years and those aged ≥70 years, respectively. The pre-specified maximum exposure period was 30 months. At the end-of-study visit or at an earlier discontinuation visit, patients were transitioned from study medication to open-label warfarin or other appropriate therapy by the investigator in accordance with the clinical guideline. Follow-up was completed at the follow-up visit 30 days after the end-of-study visit or at the early discontinuation visit.

Outcomes

The principal safety outcomes were defined as a composite of major and non-major clinically relevant bleeding. The primary efficacy endpoint was defined as a composite of stroke and non-CNS systemic embolism.

An independent clinical endpoint committee adjudicated all suspected strokes, systemic embolisms, myocardial infarctions, deaths, and bleeding events contributing to the pre-specified endpoints.

Time in Therapeutic Range (TTR)

For each patient who received warfarin, individual TTR was based on regression analysis, calculated from INR 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.

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

Figure 3. Most frequent major bleeding site in patients aged ≥75 years or younger. Safety group, on treatment. GI, gastrointestinal.

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 model. The study was not intended to test efficacy hypotheses, but efficacy endpoints were evaluated on treatment, in the per protocol patients (patients in the safety group without any major protocol violations) in an exploratory manner.

The event rates (% per year) of the principal safety outcome and primary efficacy endpoint were calculated by treatment group and by age ≥75 years and <75 years. In addition, the hazard ratio (HR; rivaroxaban/warfarin) and 95% confidence interval (CI) were calculated for the treatment group aged ≥75 years and <75 years based on the Cox proportional hazard model that included the treatment group as a covariate. Two-sided P-value for the interaction of the treatment group aged ≥75 years and <75 years based on the Cox proportional hazard model, aging, and their interaction as covariates was provided. For the principal safety outcome, cumulative event rates were summarized using the Kaplan-Meier method.

Results

Patient Characteristics

Baseline characteristics according to age are listed in Table. The overall proportion of elderly patients (aged ≥75 years) was 39.0%. Patients aged ≥75 years tended to have lower body weight, and approximately 40% had impaired renal function (CrCl <50 ml/min). Their CHADS₂ scores were >3.0, with the

mean score being 3.6–3.7; many had complications of congestive heart failure and hypertension, and a few had complications of diabetes mellitus and prior stroke, transient ischemic attack, or non-CNS embolism.

Safety Outcomes

In elderly patients, the event rate (%/year) of the principal safety outcome was 25.05 for the rivaroxaban group and 16.95 for the warfarin group, indicating a tendency to a higher event rate in the rivaroxaban group (Figures 1,2). In non-elderly patients, however, the event rate was 14.18 for the rivaroxaban group and 16.13 for the warfarin group, which showed a statistically significant interaction ($P=0.04$).

Sites of major bleeding are given in Figure 3. In elderly patients, intracranial hemorrhage (ICH) occurred in 4 patients on rivaroxaban and in 6 patients on warfarin, whereas in non-elderly patients, ICH occurred in 1 patient and in 4 patients, respectively.

Efficacy Endpoints

In elderly patients, the event rate of the primary efficacy endpoint was 2.18 for the rivaroxaban group and 4.25 for the warfarin group (HR, 0.51; 95% CI: 0.20–1.27), whereas in non-elderly patients, the event rate was 0.72 for the rivaroxaban group and 1.67 for the warfarin group (HR, 0.44; 95% CI: 0.13–1.42), with no statistically significant interaction ($P=0.82$). These results indicate that efficacy of rivaroxaban compared with warfarin was consistent irrespective of age (Figures 4,5).

Figure 4. Primary efficacy endpoint according to age (≥75 years or younger). Per protocol, on treatment. †Stroke plus non-central nervous system systemic embolism. CI, confidence interval; N/A, not applicable.

Figure 5. Kaplan-Meier curve of incidence of stroke or systemic embolism according to age (≥75 years or younger). Per protocol, on treatment. HR, hazard ratio.

Elderly Patients and Renal Function

Further analysis by renal function in elderly patients with AF is shown in **Figure 6**. In patients with preserved renal function (CrCl ≥50 ml/min), the principal safety outcome occurred in 23.31%/year with rivaroxaban vs. 13.19%/year on warfarin (HR, 1.75; 95% CI: 1.02–3.00). In those with moderate renal impairment, it occurred in 27.66%/year vs. 21.71%/year (HR,

1.30; 95% CI: 0.77–2.20), respectively. No significant interaction was observed between those with preserved renal function and those with moderate renal impairment (P=0.43 for interaction).

Furthermore, in patients with preserved renal function, the primary efficacy endpoint occurred in 1.03%/year with rivaroxaban vs. 4.22%/year on warfarin (HR, 0.24; 95% CI: 0.05–

Figure 6. Safety and efficacy according to treatment group and renal function in patients aged ≥ 75 years. †Major or non-major clinically relevant bleeding; ‡stroke or systemic embolism. CI, confidence interval; CrCl, creatinine clearance.

1.16), and in 3.92%/year on rivaroxaban vs. 4.28%/year on warfarin in those with moderate renal impairment (HR, 0.91; 95% CI: 0.28–2.99). No significant interaction was observed between those with preserved renal function and those with moderate renal impairment ($P=0.19$ for interaction).

TTR

For overall J-ROCKET AF, 65.0% of the INR of warfarin-treated patients were within the pre-specified, age-dependent target range. For those aged ≥ 75 years, 69.3% of values were within the therapeutic INR range, but for those aged < 75 years only 57.3% of values were within this range (Table S1).

Discussion

The subgroup analysis of the J-ROCKET AF study by age has found that bleeding events rates were higher in the rivaroxaban group in patients aged ≥ 75 years compared with the warfarin group. In contrast to the safety, the incidence rate of stroke or systemic embolism was lower in the rivaroxaban group compared with the warfarin group regardless of age, indicating that careful judgment is required for physicians with regard to the risk and benefit of rivaroxaban treatment in elderly patients.

Net Clinical Benefit (NCB) of Anticoagulation in Elderly AF Patients

The most important issue in the treatment of AF patients with anticoagulants is the optimization of the balance between efficacy and safety. Unfortunately, complications of bleeding in warfarin treatment are common in elderly patients. Particularly, ICH is a serious problem. Although the incidence rate of ICH is low,¹⁰ it has been reported that approximately 90% of warfarin-related deaths and disabilities in survivors are associated with ICH, indicating that ICH is the most serious outcome.¹¹ Singer et al advocated the NCB of anticoagulants by giving a weighting of 1.5 to ICH.¹² They noted a positive NCB of warfarin in older patients with AF, but not in younger ones, and also a positive NCB of warfarin in patients with AF with

CHADS₂ scores ≥ 2 .¹² Aging is an important component of the CHADS₂ score, and patients aged ≥ 75 years inevitably have a CHADS₂ score ≥ 1 . Moreover, in elderly patients, the number of patients with other complications such as hypertension and diabetes mellitus is higher. Also the mean CHADS₂ score in the present patients aged ≥ 75 years was 3.7 compared with 3.0 in those aged < 75 years. Furthermore, in a subgroup analysis using the results of J-ROCKET AF, according to the NCB calculated by the method advocated by Singer et al, rivaroxaban was significantly favorable compared to warfarin in patients with CHADS₂ score ≥ 2 .¹³ Thus, rivaroxaban is considered more suitable for anticoagulant therapy in elderly patients with a high CHADS₂ score compared with warfarin.

Stroke Prevention With Anticoagulation in Elderly AF Patients

Warfarin is the gold-standard for stroke prevention in patients with AF. In a meta-analysis, warfarin was clearly shown to reduce the incidence rate of stroke in patients with AF by 64% relative to placebo or control.¹⁴ Despite this evidence, however, warfarin is underused and poorly managed, particularly in elderly patients, who carry the highest burden of disease owing to stroke.¹⁵ Several studies have suggested that warfarin is prescribed to only two-thirds of individuals with AF who are eligible for anticoagulant.¹⁶ In contrast, in the clinical setting in the J-RHYTHM Registry, the largest registry study in Japan, anticoagulant therapy was carried out in a large number of patients aged ≥ 70 years, with 89.2% being prescribed warfarin.^{17–19} The reason for the higher prescription rate is the difference in the background of the recruited patients. The J-RHYTHM registry recruited patients only from cardiovascular centers throughout Japan. In addition, with regard to the other clinical practice data in Japan, the Fushimi AF registry is a community-based survey of AF patients.²⁰ Compared with the J-RHYTHM registry, the warfarin prescription rate was much lower; 48.5% vs. 89%, respectively. In the Fushimi AF registry there was a total of 76 institutions, a large proportion of which were private clinics of general practitioners. Therefore,

as in the previous reports,¹⁶ the Fushimi AF registry may most likely reflect real clinical practice in Japan. These data suggested that the prescription rate of anticoagulants for patients with AF is still low. Another barrier to optimal warfarin therapy is poor management of INR in clinical practice. To maximize the benefit of warfarin treatment, Japanese AF 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. The primary analysis of J-ROCKET AF, however, showed that 72.7% of the INR in patients aged < 70 years were within the range 1.6–2.6.⁹ In this subgroup analysis of the J-ROCKET AF study, patients aged < 75 years had a lower TTR (eligible INR 2.0–3.0 for < 70 years and 1.6–2.6 for ≥ 70 years) of only 57.3% (Table S1). It has already been reported that the decrease in interpolated percentage TTR of INR increases the risk of stroke.²¹ In addition, the results of the EURO Heart Survey suggest that anti-thrombotic undertreatment of high-risk patients with AF was associated with a higher cardiovascular mortality during 1 year, whereas overtreatment was not associated with a higher risk for major bleeding.²² Despite this strong evidence for warfarin management, it seems that many physicians are too much concerned about the possible bleeding risk and tend to underestimate the potential benefits of warfarin therapy.²³ Compared with warfarin, rivaroxaban is easier to use with the fixed dose regimen, without the need for monitoring for dose adjustment, and fewer interactions with concomitant drugs and food containing vitamin K. It might be particular beneficial for clinicians to provide this therapeutic option for older patients.

Renal Function in Elderly AF Patients

Renal impairment is an independent risk factor for both stroke and bleeding in AF patients.^{24,25} Among elderly AF patients, renal impairment is more often observed than in the general population. Indeed, in this subgroup analysis, patients aged ≥ 75 years had approximately more than 4-fold impaired renal function (CrCl < 50 ml/min; Table). Therefore, we further analyzed the safety and efficacy outcomes in elderly patients with renal impairment according to treatment. As shown in Figure 6, in elderly patients, the primary safety outcome occurred more frequently in those on rivaroxaban compared to warfarin regardless of renal function. In particular, in patients with preserved renal function, major bleeding events occurred in 8 patients on rivaroxaban and in 4 patients on warfarin. With regard to bleeding at critical sites, however, ICH occurred in 2 patients on rivaroxaban and in 3 patients on warfarin, and fatal bleeding occurred in 1 patient on warfarin. Although bleeding events occurred more frequently in patients on rivaroxaban, the number of critical bleeding events such as fatal bleeding or ICH was lower in the rivaroxaban arm compared with the warfarin arm. In contrast, in elderly patients with preserved renal function, patients on rivaroxaban had a marginally favorable trend in incidence rate of primary efficacy endpoint compared with patients on warfarin. One possible explanation for these differences is the intensity of warfarin treatment, which is a reduced target INR of 1.6–2.6 in patients aged ≥ 70 years according to the Japanese guideline. This might relatively affect the lower rate of bleeding events on warfarin than on rivaroxaban. From the aspect of efficacy, the potential effects of anticoagulant therapy for stroke prophylaxis might be insufficient in the lower intensity of warfarin treatment. Aging is known to be an independent risk factor not only for bleeding during anti-thrombotic therapy, but also for ischemic stroke and systemic embolism in AF patients. Because the bleeding event rate was higher in the rivaroxaban group in patients aged ≥ 75 years compared to

the warfarin group, treatment would need to be personalized based on the risk and benefit of anticoagulant therapy, especially for elderly patients with AF.

Study Limitations

J-ROCKET AF was not sufficiently powered to evaluate efficacy due to the limited number of patients. This trial was also not primarily designed to detect interactions between study drug and patient age. Thus, the present data should be interpreted with caution because the number of patients is limited for further subgroup analyses, such as between study drug and renal function in the younger or older subgroups. Another limitation is that, in this subgroup analysis, patients aged ≥ 75 years tended to have lower body weight and higher CHADS₂ score, and approximately 40% had impaired renal function (CrCl < 50 ml/min). The proportion of women was higher in the patients aged ≥ 75 years. Also, the concomitant disorders varied greatly between elderly patients and non-elderly patients. Therefore, it should be noted that these co-founding factors other than age may affect safety and efficacy in this subgroup analysis. Furthermore, the present results were derived from a selected patient group for the clinical trial, which may deviate from an unselected patient population in the real world.

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Supplementary Files

Supplementary File 1

Table S1. Proportion of INR within therapeutic target range in the warfarin group

Please find supplementary file(s);
<http://dx.doi.org/10.1253/circj.CJ-13-1324>