Rivaroxaban versus Warfarin in Japanese Patients with Nonvalvular Atrial Fibrillation for the Secondary Prevention of Stroke: A Subgroup Analysis of J-ROCKET AF

Norio Tanahashi, MD, PhD,* Masatsugu Hori, MD, PhD,† Masayasu Matsumoto, MD, PhD,‡ Shin-ichi Momomura, MD,§ Shinichiro Uchiyama, MD, PhD,‖ Shinya Goto, MD, PhD,¶ Tohru Izumi, MD, PhD,# Yukihiro Koretsune, MD, PhD,** Mariko Kajikawa, MD, PhD,†† Masaharu Kato, MSc,†† Hitoshi Ueda, PhD,†† Kazuya Iwamoto, MD, PhD,†† and Masahiro Tajiri, BSc,†† on behalf of the J-ROCKET AF Study Investigators

Background: The overall analysis of the rivaroxaban versus warfarin in Japanese patients with atrial fibrillation (J-ROCKET AF) trial revealed that rivaroxaban was not inferior to warfarin with respect to the primary safety outcome. In addition, there was a strong trend for a reduction in the rate of stroke/systemic embolism with rivaroxaban compared with warfarin. *Methods:* In this subanalysis of the J-ROCKET AF trial, we investigated the consistency of safety and efficacy profile of rivaroxaban versus warfarin among the subgroups of patients with previous stroke, transient ischemic attack, or non–central nervous system systemic embolism (secondary prevention group) and those without (primary prevention group). *Results:* Patients in the secondary prevention group were 63.6% of the overall population of J-ROCKET AF. In the secondary prevention group, the rate of the principal safety outcome (% per year) was 17.02 in rivaroxaban-treated patients and 18.26 in warfarin-treated patients (hazard ratio [HR] 0.95; 95% confidence interval [CI] 0.70-1.29), while the rate of the primary efficacy endpoint was 1.66 in rivaroxaban-treated patients and 3.25 in warfarin-treated patients (HR 0.51; 95% CI 0.23-1.14). There were no significant interactions in the principal safety and the primary efficacy endpoints of rivaroxaban compared to warfarin between the primary and secondary prevention groups (P = .090 and .776 for both interactions, respectively). *Conclusions:* The safety and efficacy profile of rivaroxaban compared with warfarin was consistent among patients in the primary prevention group and those in the secondary prevention group. **Key Words:** Ischemic stroke—J-ROCKET AF—rivaroxaban—secondary prevention warfarin.

From the *Department of Neurology, Saitama Medical University International Medical Center, Saitama; †Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka; ‡Department of Clinical Neuroscience and Therapeutics, Hiroshima University, Hiroshima; §Division of Cardiovascular Medicine, Saitama Medical Center, Jichi Medical University, Saitama; ‖Department of Neurology, Tokyo Women's Medical University, Tokyo; ¶Department of Medicine (Cardiology), Tokai University School of Medicine, Kanagawa; #Department of Cardio-angiology, Kitasato University School of Medicine, Kanagawa; **Institute for Clinical Research, Osaka National Hospital, Osaka; and ††Bayer Yakuhin Ltd, Osaka, Japan.

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Address correspondence to Norio Tanahashi, MD, PhD, Saitama Medical University, International Medical Center, 1397-1 Yamane, Hidaka City, Saitama 350-1298, Japan. E-mail: tanahasi@saitama-med.ac.jp.

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Patients with atrial fibrillation (AF) are known to have an approximately 5-fold higher risk of thrombosis and stroke compared to with those without AF.[1,2] Among patients with AF, those having a previous history of stroke or transient ischemic attack (TIA) are at an additional increased risk of stroke.[3] The treatment efficacy of warfarin has been established for the prevention of stroke in patients with AF.[4] According to the guidelines, warfarin is recommended for the prevention of stroke in AF patients both with and without previous stroke or TIA.[5,6]

Rivaroxaban is a new anticoagulant agent that attenuates generation of thrombin by selectively and directly inhibiting factor Xa, which is located at the junction between the intrinsic and extrinsic coagulation cascades.[7-9] This drug has different mechanisms of action from those of warfarin and several advantages, including rapid anticoagulation based on its shorter half-life, no requirement of dose adjustment by coagulation monitoring, and few interactions with other drugs.

The rivaroxaban versus warfarin in Japanese patients with atrial fibrillation (J-ROCKET AF) trial was a randomized, double-blind clinical trial that was conducted in Japan comparing a Japan-specific reduced dose of rivaroxaban (15 mg once daily in patients with creatinine clearance [CrCl] ≥50 mL/min or 10 mg once daily in patients with CrCl 30-49 mL/min) with dose-adjusted warfarin according to the Japanese guidelines in 1280 patients with nonvalvular AF,[10] evaluating the safety and efficacy of rivaroxaban for patients with AF and investigating the feasibility to extrapolate global ROCKET AF data by comparing the safety and efficacy results between this Japanese study and the global ROCKET AF study.[11] The results revealed the noninferiority of rivaroxaban against warfarin in terms of its safety. There was a strong trend for a reduction in the rate of stroke/systemic embolism with rivaroxaban compared with warfarin (Fig 1).[10] Although the study was not powered for efficacy, a post hoc analysis revealed that rivaroxaban significantly reduced the rate of all-cause stroke and the rate of ischemic stroke compared to warfarin (Fig 2).

In the J-ROCKET AF trial, many AF patients with a history of stroke, transient ischemic attack (TIA), or non–central nerve system (CNS) systemic embolism who were considered to be at high risk of both bleeding and recurrence of stroke were enrolled. In this subanalysis, we investigated the consistency of safety and efficacy profile of rivaroxaban versus warfarin among the subgroups of patients with previous stroke, TIA, or non-CNS systemic embolism (secondary prevention group) and those without (primary prevention group).

Methods

Study Design, Participants, and Procedure

The design and results of J-ROCKET AF have been described previously.[10] 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 to dose-adjusted warfarin in accordance with Japanese guideline in patients with nonvalvular AF. The study was approved by the institutional review boards of all participating locations, and all patients provided informed consent. The trial was conducted in accordance with the Japanese Good Clinical Practice guidlines.

Japanese patients ≥20 years of age with nonvalvular AF documented electrocardiographically ≤30 days before enrollment were randomized at 167 participating facilities in Japan. Patients had a history of ischemic stroke, TIA, or non-CNS systemic embolism or had ≥2 of the following risk factors for thromboembolism: congestive heart failure and/or left ventricular ejection fraction of ≤35%, hypertension (defined as the use of antihypertensive medications ≤6 months before the screening visit or persistent systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg), age ≥75 years, or diabetes mellitus (i.e., a history of type 1 or type 2 diabetes mellitus or the use of antidiabetic medications within 6 months before the screening visit). Randomization of patients without previous stroke, TIA, or non-CNS systemic embolism and with only 2 stroke risk factors was limited to 10% of the total number of target patients. Patients with a CrCl <30 mL/min were excluded.

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 of 2.0 to 3.0 in patients <70 years of age or a reduced target international normalized ratio of 1.6 to 2.6 in patients ≥70 years of age according to the Japanese guidelines. The prespecified 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-ups of patients were completed at the follow-up visit performed 30 days after the end of study or early discontinuation visit.

Outcomes

The primary safety endpoint was the composite of major bleeding and non-major clinically relevant bleeding. The primary efficacy endpoint was the 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 prespecified endpoints.

Statistical Analysis

The primary objective of J-ROCKET was to test whether rivaroxaban was noninferior to warfarin with respect to