ORIGINAL RESEARCH

Comparisons of Rivaroxaban Following Different Dosage Criteria (ROCKET AF or J-ROCKET AF Trials) in Asian Patients With Atrial Fibrillation

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***Background*—**The ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) evaluated rivaroxaban (20/15 mg/d) versus warfarin in patients with atrial fibrillation. A separate trial, J-ROCKET AF (Japanese ROCKET AF), compared rivaroxaban (15/10 mg/d) and warfarin in Japanese patients with atrial fibrillation. Data about rivaroxaban following J-ROCKET AF criteria compared with warfarin and ROCKET AF dosage were limited.

***Methods and Results*—**This retrospective study used medical data from a multicenter healthcare provider in Taiwan that included 3162 patients taking rivaroxaban. Among 2320 patients with an estimated glomerular filtration rate (eGFR) ≥50 mL/min per 1.73 m^2, 384 and 1936 patients followed the ROCKET AF (20 mg/d) and J-ROCKET AF (15 mg/d) recommendation, respectively. Among 842 patients with an eGFR <50 mL/min per 1.73 m^2, 422 and 420 patients followed the ROCKET AF (15 mg/d) and J-ROCKET AF (10 mg/d) recommendation, respectively. A total of 2053 patients with atrial fibrillation receiving warfarin were identified. Rivaroxaban following either ROCKET AF or J-ROCKET AF dosage criteria was associated with a comparable risk of thromboembolism but a lower risk of bleeding than warfarin. For patients with an eGFR ≥50 mL/min per 1.73 m^2, risks of clinical events did not differ significantly between the 2 dosage criteria of rivaroxaban. For patients with an eGFR <50 mL/min per 1.73 m^2, the ROCKET AF dosage was associated with a higher risk of major bleeding compared with the J-ROCKET AF dosage (hazard ratio, 2.70; P=0.0445) without significant differences regarding the risk of ischemic events.

***Conclusions*—**In Asian patients with atrial fibrillation, the J-ROCKET AF dosage was as effective as the ROCKET AF dosage irrespective of renal function. The risk of major bleeding was lower with the J-ROCKET AF dosage in patients with an eGFR <50 mL/min per 1.73 m^2. Compared with warfarin, rivaroxaban following either dosage criteria was effective and even safer.
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Key Words: atrial fibrillation • factor Xa inhibitor • J-ROCKET AF • mortality • rivaroxaban • ROCKET AF • warfarin

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with a global prevalence of 2% to 3%, which significantly increases the risk for thromboembolic events, congestive heart failure, and mortality.[1–3] Stroke prevention with oral anticoagulants is important for the management of patients with AF. Vitamin K antagonist (eg, warfarin) has been recommended for stroke prevention among patients with nonvalvular AF (NVAF) for several decades. Direct oral anticoagulants (DOACs), including dabigatran, rivaroxaban, apixaban, and edoxaban, are effective and safe alternatives to warfarin for stroke prevention in patients with NVAF.[4–7] The global ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition

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Accompanying Tables S1 through S3 and Figure S1 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013053

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Clinical Perspective

What Is New?

- Data about rivaroxaban following J-ROCKET AF (Japanese Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) criteria compared with warfarin and ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) dosage were limited, and compared with warfarin, rivaroxaban following either dosage criteria was effective and even safer.
- The J-ROCKET AF dosage was as effective as the ROCKET AF dosage criteria for the prevention of ischemic stroke/systemic embolism irrespective of renal function.
- Compared with the ROCKET AF dosage, the risk of major bleeding tended to be lower with J-ROCKET AF dosage in patients with impaired renal function.

What Are the Clinical Implications?

- J-ROCKET AF dosage criteria may be reasonable for Asian patients with AF, but should be further tested in prospective and randomized trials.

Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) study evaluated the efficacy and safety of rivaroxaban 20 mg/d (15 mg/d if moderate renal impairment) compared with warfarin therapy for stroke prevention in patients with NVAF. The results indicated that rivaroxaban was associated with comparable efficacy and safety to warfarin in patients with NVAF.[5] J-ROCKET AF (Japanese Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) was a similar but much smaller study comparing the efficacy and safety of rivaroxaban 15 mg/d (10 mg/d if moderate renal impairment) and warfarin in Japanese patients with NVAF, which showed a comparable risk of major bleeding and a strong trend for the reduction in the risk of stroke/systemic embolism with rivaroxaban 15/10 mg/d versus warfarin.[8] Of note, Taiwan is the only country that approved either a standard-dose regimen (20/15 mg/d), following the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) dosage criteria, or low-dose regimen (15/10 mg/d), following the J-ROCKET AF dosage criteria, for stroke prevention in patients with NVAF around the world. However, 2 different dosage recommendations of rivaroxaban have not been previously compared. Also, data about the comparisons of rivaroxaban at the dose following J-ROCKET AF and warfarin in daily practice outside Japan were limited. In the present study, we aimed to compare the effectiveness and safety of rivaroxaban following ROCKET AF (20/15 mg/d) and J-ROCKET AF (15/10 mg/d) among Asians with NVAF. In addition, the safety and efficacy of warfarin and rivaroxaban at either dosage criteria were also compared.

Methods

Study Population

The data that support the findings of this study are available from the corresponding author upon reasonable request. This present study was approved by the institutional review board of the Chang Gung Medical Foundation. In the retrospective cohort study, patient data were obtained from the Chang Gung Memorial Hospital System, which is the largest healthcare provider in Taiwan, which comprises 3 major teaching hospitals and 4 tertiary care medical centers. The healthcare provider has a total of 10 050 beds and admits ≈280 000 patients per year.[9] Informed consent was waived because the original identification number of each patient in the present study is encrypted and deidentified to protect patient privacy by using a consistent encrypting procedure. This study is based in part on data from the Chang Gung Research Database provided by Chang Gung Memorial Hospital. The interpretation and conclusions contained herein do not represent the position of Chang Gung Memorial Hospital.

Study Design

The study design flowchart and patient enrollment are shown in Figure 1. From June 1, 2012, to December 31, 2017, 18 591 patients diagnosed with AF (*International Classification of Diseases, Ninth Revision Clinical Modification* [*ICD-9-CM*] codes [427.31] or *ICD-10-CM codes* [I48]) taking at least 1 prescription filled for oral anticoagulant (edoxaban, apixaban, rivaroxaban, dabigatran, or warfarin) were identified. The index date was defined as the first date of prescribing DOACs or warfarin. The follow-up period was defined as the duration from the index date until the occurrence of study outcomes or until the end date of the study period (December 31, 2017), whichever came first. To establish a cohort of patients with NVAF who took an oral anticoagulant for the primary purpose of stroke prevention, patients were excluded if they had diagnoses indicating venous thromboembolism (deep vein thrombosis or pulmonary embolism) (n=74) or valvular AF (mitral stenosis or history of valvular surgery), or required joint replacement therapy (n=236) within 6 months before the index date. Patients with end-stage renal disease (n=83) were also excluded because NOACs are contraindicated in such patients in Taiwan.

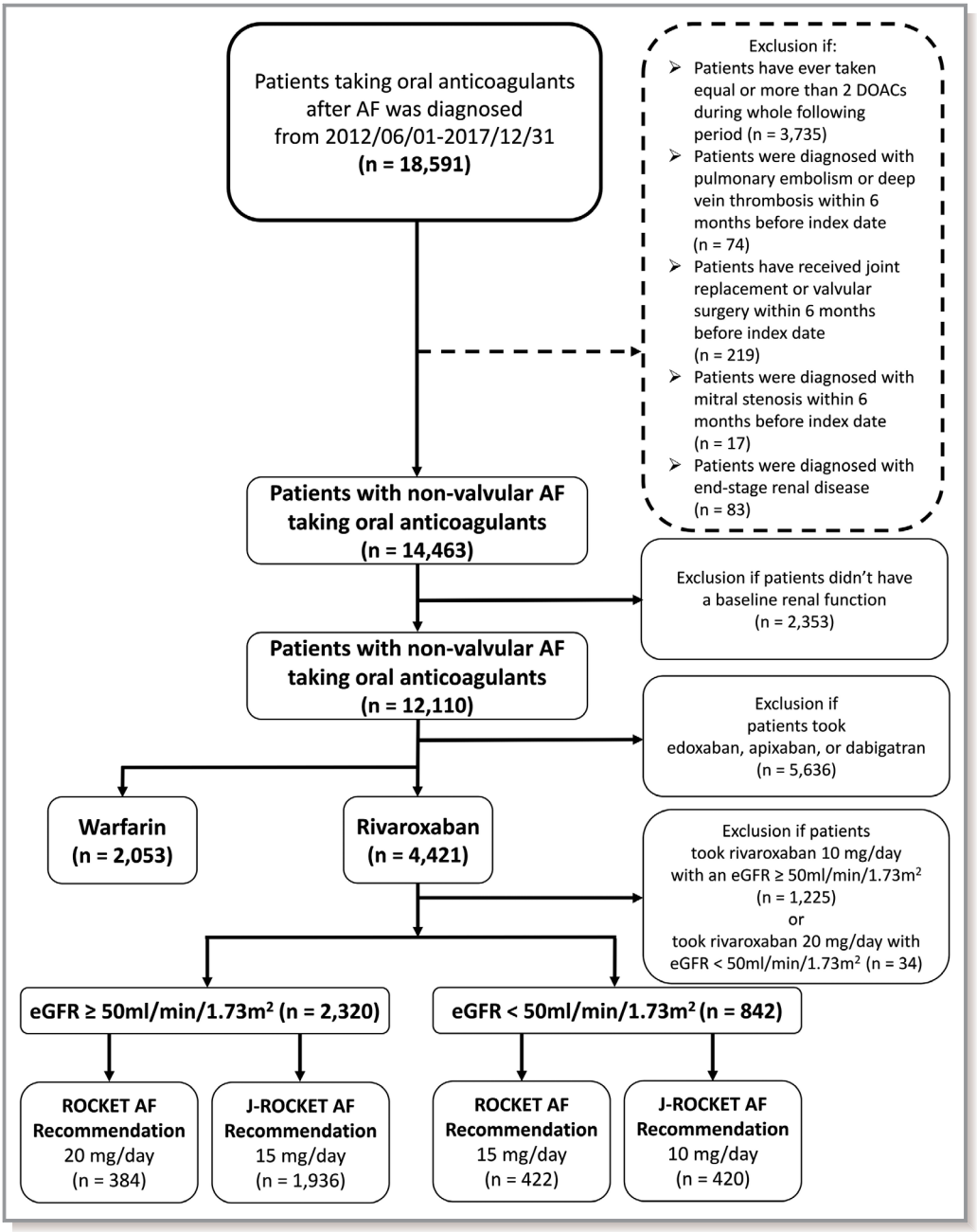

Figure 1. Enrollment of patients with nonvalvular atrial fibrillation (NVAF). There were 2320 and 842 patients with NVAF with estimated glomerular filtration rate (eGFR) ≥50 mL/min per 1.73 m^2 and eGFR <50 mL/min per 1.73 m^2 taking rivaroxaban, respectively, enrolled in this study from June 1, 2012, to December 31, 2017. Among the 2320 patients with eGFR ≥50 mL/min per 1.73 m^2, there were 384 and 1936 patients following the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) (20 mg/d) and J-ROCKET AF (Japanese ROCKET AF) (15 mg/d) dosage criteria, respectively. Among the 842 patients with eGFR <50 mL/min per 1.73 m^2, there were 422 and 420 patients following the ROCKET AF (15 mg/d) and J-ROCKET AF (10 mg/d) dosage criteria, respectively. AF indicates atrial fibrillation.

We specifically focused on rivaroxaban in the present study, and patients taking the other 3 DOACs (n=5636) anytime during the entire study period were excluded. The study identified a total of 4421 patients taking rivaroxaban for stroke prevention whose baseline renal functions were available. Of these, 1225 patients (27.7%) who were prescribed 10 mg of rivaroxaban once daily were excluded. We also excluded 34 patients with an estimated glomerular filtration rate (eGFR) <50 mL/min per 1.73 m^2 who took rivaroxaban 20 mg once daily. Finally, 3162 patients were

eligible for this study and were divided into 2 subgroups: (1) patients with an eGFR ≥50 mL/min per 1.73 m^2 (n=2320), and (2) patients with an eGFR <50 mL/min per 1.73 m^2 (n=842). During the same study period, a total of 2053 patients with AF treated with warfarin for stroke prevention were also identified.

Of note, the present study was performed in an intention-to-treat design, similar to most trials, where each study group was included in the statistical analysis and analyzed according to the group they were originally assigned, regardless of what treatment (if any) they received or changed. For example, patients taking rivaroxaban 20 mg/d with a baseline eGFR ≥50 mL/min per 1.73 m^2 would still be categorized as the ROCKET AF dosing group, even though the daily doses of rivaroxaban were shifted from 20 mg to 15 mg or 10 mg later because of a decline in renal function or physician's intention during the following-up period, and vice versa. Indeed, for 384 patients originally taking rivaroxaban at a daily dose of 20 mg, the dosage was shifted to 15 mg/d and 10 mg/d in 64 and 48 patients, respectively. For 2358 patients originally taking rivaroxaban at a daily dose of 15 mg, the dosage was shifted to 20 mg/d and 10 mg/d in 38 and 339 patients, respectively. For 420 patients originally taking rivaroxaban at a daily dose of 10 mg, the dosage was shifted 15 mg/d in 20 patients and none of them increased the dosage to 20 mg.

Study Outcomes

Six study outcomes were assessed to investigate the effectiveness and safety of rivaroxaban, including ischemic stroke/systemic embolism (IS/SE), acute myocardial infarction (AMI), all-cause mortality, intracranial hemorrhage (ICH), major gastrointestinal bleeding (GIB), and all major bleeding events. All study outcomes were defined on the basis of the discharge diagnosis to avoid misclassification. ICH was defined with the use of codes for atraumatic hemorrhage. Major GIB was defined as a hospitalized primary diagnosis indicating bleeding in the gastrointestinal tract. All major bleeding events were defined as the total number of hospitalized events of ICH, major GIB, and other sites of critical bleeding. The diagnosis codes used in Chang Gung Memorial Hospital System were shifted from *ICD-9-CM* to *ICD-10-CM* after January 1, 2016. The *ICD-9-CM* and *ICD-10-CM* codes used to identify the study outcomes, and the baseline covariates are summarized in Table S1.

Covariates

Baseline covariates referred to any claim record with the above diagnoses or medication codes before the index date. Bleeding history was confined to events within 6 months preceding the index date. A history of any prescription medicine was confined to medications taken at least once within 3 months preceding the index date. Important laboratory data, including serum hemoglobin, platelet count, eGFR, and alanine aminotransferase, were based on the measurements performed within 6 months of the index date. The CHA_2DS_2-VASc score (congestive heart failure, hypertension, age 75 years or older for 2 points, diabetes mellitus, previous stroke or transient ischemic attack for 2 points, vascular disease, age 65–74 years, and female) was computed to represent the predicted risk of IS/SE in patients with AF.[10] The HAS-BLED score (hypertension, abnormal renal/liver function, stroke, bleeding history, labile international normalized ratio [INR], age 65 years or older, and antiplatelet drug/alcohol use) was adopted to represent the risk of bleeding in patients with AF treated with oral anticoagulants.[11]

Statistical Analysis

Data were presented as mean and SD for continuous variables and as proportions for categorical variables. Unpaired 2-tailed *t* test was used to compare the differences between continuous values. Chi-square test was used to compare the differences between nominal variables. Logistic regression analysis was performed to identify factors associated with the prescriptions of rivaroxaban following either ROCKET AF or J-ROCKET AF dosage criteria. Crude incidence rates were computed as the total number of study outcomes during the follow-up time divided by person-years at risk. Cox proportional hazards regression was used to compare the risk of events between ROCKET AF and J-ROCKET AF dosage criteria in patients with an eGFR ≥50 mL/min per 1.73 m^2 and <50 mL/min per 1.73 m^2 separately. The covariates included in the Cox regression models were variables that differed significantly between patients following ROCKET AF and J-ROCKET AF dosage criteria ($P<0.05$). The comparisons between rivaroxaban and warfarin were performed using Cox regression analysis in the same way. Statistical significance was defined as $P<0.05$. All analyses were conducted using SAS 9.2 (SAS Institute).

Results

This study identified a total of 2320 and 842 consecutive rivaroxaban users with an eGFR ≥50 mL/min per 1.73 m^2 and eGFR <50 mL/min per 1.73 m^2, respectively. Among patients with an eGFR ≥50 mL/min per 1.73 m^2, 384 (16.6%) and 1936 (83.4%) of them followed the ROCKET AF (20 mg/d) and J-ROCKET AF (15 mg/d) dosage criteria, respectively. Among patients with an eGFR <50 mL/min per 1.73 m^2, 422 (50.1%) and 420 (49.9%) of them followed the ROCKET AF (15 mg/d) and J-ROCKET AF (10 mg/d) dosage criteria, respectively (Figure 1). The mean drug adherence rate of rivaroxaban, calculated based on proportion of days covered with rivaroxaban during the entire follow-up period for each patient, was 69%.

Rivaroxaban Versus Warfarin

The baseline characteristics of patients taking warfarin and rivaroxaban following either ROCKET AF or J-ROCKET AF dose criteria are shown in Table 1. For patients taking warfarin, the average time in therapeutic ranges (TTRs) of INRs targeted at 2.0 to 3.0 or 1.5 to 2.5 were 22.2±26.1% and 43.2±34.0%, respectively. The patients in the rivaroxaban groups following either ROCKET AF (n=806) or J-ROCKET AF (n=2356) dosage criteria were older and had more comorbidities and higher CHA_2DS_2-VASc and HAS-BLED scores compared with the warfarin group (n=2054). The prevalence rates of concomitant use of antiplatelet agents were lower among patients taking rivaroxaban compared with those taking warfarin (31.1% in ROCKET AF, 29.5% in J-ROCKET AF, and 35.1% in warfarin groups). The baseline eGFRs were 59.5±26.7, 72.3±27.9, and 63.5±37.6 mL/min per 1.73 m^2 for patients taking rivaroxaban following ROCKET AF, J-ROCKET AF dosage criteria, and those taking warfarin, respectively. At the end of the study, the average declines in eGFR were 1.2±20.1, 2.5±25.5, and 3.9±24.8 mL/min per 1.73 m^2 for ROCKET AF, J-ROCKET AF, and warfarin groups, respectively (Table 1). The median follow-up periods for the ROCKET AF, J-ROCKET AF, and warfarin groups were 2.66, 2.48, and 2.35 years, respectively.

Patients taking rivaroxaban following either ROCKET AF or J-ROCKET AF dosage criteria showed a comparable risk of IS/SE and a lower risk of AMI, mortality, ICH, and all major bleeding than those taking warfarin after the adjustments for baseline differences (Figure 2 and Table S2). Among 229 patients who experienced major bleeding, the average blood pressures were 141.8±25.8 mm Hg (142.4±24.9 mm Hg for patients with an eGFR ≥50 mL/min per 1.73 m^2 and 141.6±24.2 mm Hg for those with an eGFR <50 mL/min per 1.73 m^2) at the time when major bleeding occurred. Compared with patients taking warfarin with the top quartile of individual TTR (mean 61.1% for the range of INR between 2.0 and 3.0), patients taking rivaroxaban following either ROCKET AF or J-ROCKET AF dosage criteria showed a comparable risk of IS/SE and a lower risk of mortality, ICH, and all major bleeding, which were generally consistent with the principal analyses (Figure S1).

Baseline Characteristics of Patients Following ROCKET AF Versus J-ROCKET AF Dosage Criteria

The baseline characteristics of patients following ROCKET AF versus J-ROCKET AF dosage criteria are shown in Table 2. In general, patients following the ROCKET AF dosage criteria were younger than those following the J-ROCKET AF dosage criteria (both $P<0.001$). Patients following the ROCKET AF dosage criteria had a higher prevalence of stroke history than those following the J-ROCKET AF dose criteria in patients with an eGFR <50 mL/min per 1.73 m^2 (24.6% versus 13.3%, $P<0.001$). The prevalence rates of concomitant use of antiplatelet agents did not differ significantly between the 2 groups. Of note, patients following the ROCKET AF dosage criteria had a comparable eGFR to those following the J-ROCKET AF recommendation in patients with an eGFR ≥50 mL/min per 1.73 m^2 (81.54±21.88 versus 79.75±24.69 mL/min per 1.73 m^2, $P=0.187$), whereas patients following the ROCKET AF dose criteria had a higher eGFR than those following the J-ROCKET AF recommendation in patients with an eGFR <50 mL/min per 1.73 m^2 (39.51±9.25 versus 37.70±9.84 mL/min per 1.73 m^2, $P=0.006$). The changes of eGFRs at the end of the follow-up were similar between the ROCKET AF and J-ROCKET AF groups.

Patients With an eGFR ≥50 mL/min per 1.73 m^2

For patients with an eGFR ≥50 mL/min per 1.73 m^2, older age and presence of malignancy were independent factors associated with the prescriptions of rivaroxaban following J-ROCKET AF dosage criteria (15 mg/d), while the presence of peripheral artery disease was associated with the prescriptions following ROCKET AF dosage criteria (20 mg/d) (Table 3 [upper panel]). Figure 3 and Table S3 (upper panel) show the adjusted hazard ratios and 95% CIs of the efficacy and safety outcomes for ROCKET AF (20 mg/d) versus J-ROCKET AF (15 mg/d) dosage criteria among patients with an eGFR ≥50 mL/min per 1.73 m^2. Compared with J-ROCKET AF (15 mg/d) dosage criteria (n=1936), ROCKET AF (20 mg/d) dosage criteria (n=384) was associated with a similar risk of IS/SE, AMI, mortality, ICH, major GIB, and all major bleeding after adjustments for baseline differences.

Patients With an eGFR <50 mL/min per 1.73 m^2

For patients with an eGFR <50 mL/min per 1.73 m^2, older age and low platelet count were independent factors associated with the prescriptions following the J-ROCKET AF dosage criteria, whereas previous stroke history was the independent factor associated with the prescriptions following ROCKET AF dosage criteria (Table 3 [lower panel]). Figure 3 and Table S3 (lower panel) show the adjusted hazard ratios and 95% CIs of outcomes for ROCKET AF (15 mg/d) versus J-ROCKET AF (10 mg/d) dosage criteria among patients with an eGFR <50 mL/min per 1.73 m^2. Compared with J-ROCKET AF (10 mg/d) dosage criteria (n=420), ROCKET AF (15 mg/d) dosage criteria (n=422) was associated with a higher risk of all major bleeding (adjusted hazard ratio, 2.70; 95% CI, 1.03–7.13 [$P=0.0445$]) with no significant differences in the risk of IS/SE, AMI, mortality, ICH, and major GIB.

Table 1. Baseline Characteristics of Patients With NVAF Taking Rivaroxaban Following the ROCKET AF or J-ROCKET AF Dose Criteria Versus Patients Taking Warfarin

	ROCKET AF Criteria 20/15 mg/d (n=806)	J-ROCKET AF Criteria 15/10 mg/d (n=2356)	Warfarin (n=2053)	*P* Value ROCKET AF vs Warfarin	*P* Value J-ROCKET AF vs Warfarin
Age, y	72.44±10.67	73.85±9.83	67.03±12.75	<0.001	<0.001
Women, No. (%)	311 (38.6)	975 (41.4)	859 (41.8)	0.111	0.759
CHA_2DS_2-VASc score	3.61±1.67	3.49±1.60	2.71±1.84	<0.001	<0.001
HAS-BLED score	2.94±1.24	2.80±1.19	2.34±1.46	<0.001	<0.001
History, No. (%)					
Chronic lung disease	240 (29.8)	706 (30.0)	484 (23.6)	0.001	<0.001
Chronic liver disease	144 (17.9)	500 (21.2)	417 (20.3)	0.138	0.457
Congestive heart failure	102 (12.7)	227 (9.6)	247 (12.0)	0.647	0.010
Hypertension	647 (80.3)	1809 (76.8)	1351 (65.8)	<0.001	<0.001
Hyperlipidemia	378 (46.9)	1073 (45.5)	746 (36.3)	<0.001	<0.001
Diabetes mellitus	338 (41.9)	849 (36.0)	693 (33.8)	<0.001	0.113
Previous stroke	178 (22.1)	409 (17.4)	146 (7.1)	<0.001	<0.001
Previous TIA	20 (2.5)	42 (1.8)	28 (1.4)	0.036	0.267
Ischemic heart disease	97 (12.0)	258 (11.0)	268 (13.1)	0.462	0.032
Gout	186 (23.1)	402 (17.1)	379 (18.5)	0.005	0.225
Peripheral artery disease	3 (0.4)	3 (0.1)	8 (0.4)	1.000	0.082
Malignancy	110 (13.6)	376 (16.0)	292 (14.2)	0.69	0.109
Laboratory data					
Hemoglobin, g/dL	13.01±2.29	13.05±2.05	12.39±2.41	<0.001	<0.001
Platelet, ×1000/Ul	199.90±66.04	197.84±66.24	196.45±74.49	0.27	0.529
Baseline eGFR, mL/min per 1.73 m^2	59.54±26.72	72.26±27.88	63.53±37.59	0.006	<0.001
Changes of eGFR, mL/min per 1.73 m^2	−1.16±20.11	−2.47±25.54	−3.88±24.79	0.006	0.064
ALT, U/L	27.90±33.92	28.98±94.90	34.16±82.16	0.041	0.061
Medications, No. (%)					
Concomitant APT	251 (31.1)	695 (29.5)	720 (35.1)	0.0459	<0.001
NSAIDs	126 (15.6)	316 (13.4)	252 (12.3)	0.017	0.261
PPIs	96 (11.9)	246 (10.4)	286 (13.9)	0.153	<0.001
ACEIs/ARBs	506 (62.8)	1332 (56.5)	1042 (50.8)	<0.001	<0.001
Loop diuretics	254 (31.5)	660 (28.0)	725 (35.3)	0.054	<0.001
Amiodarone	172 (21.3)	461 (19.6)	548 (26.7)	0.003	<0.001
Dronedarone	23 (2.9)	75 (3.2)	56 (2.7)	0.853	0.374
Quinidine	3 (0.4)	3 (0.1)	8 (0.4)	1.000	0.082
β-Blockers	495 (61.4)	1347 (57.2)	1246 (60.7)	0.722	0.018
Diltiazem	135 (16.7)	447 (19.0)	364 (17.7)	0.534	0.288
Verapamil	35 (4.3)	107 (4.5)	86 (4.2)	0.855	0.568
Digoxin	140 (17.4)	453 (19.2)	417 (20.3)	0.074	0.367
Statins	297 (36.8)	802 (34.0)	532 (25.9)	<0.001	<0.001
Azithromycin/clarithromycin/erythromycin	11 (1.4)	41 (1.7)	32 (1.6)	0.701	0.637

Continued

Table 1. Continued

	ROCKET AF Criteria 20/15 mg/d (n=806)	J-ROCKET AF Criteria 15/10 mg/d (n=2356)	Warfarin (n=2053)	*P* Value ROCKET AF vs Warfarin	*P* Value J-ROCKET AF vs Warfarin
Itraconazole	0 (0.0)	3 (0.1)	1 (0.0)	1.000	0.628
Cyclosporine	1 (0.1)	4 (0.2)	2 (0.1)	1.000	0.692

ACEIs indicates angiotensin-converting enzyme inhibitors; ALT, alanine aminotransferase; APT, antiplatelet agent; ARBs, angiotensin II receptor antagonists; CHA_2DS_2-VASc, congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke/transient ischemic attack, vascular disease, age 65 to 74 years, female; eGFR, estimated glomerular filtration rate; HAS-BLED, hypertension, abnormal renal or liver function, stroke, bleeding history, labile international normalized ratio, age 65 years or older, and antiplatelet drug or alcohol use; J ROCKET AF, Japanese Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; NSAIDs, nonsteroidal anti-inflammatory drugs; NVAF, nonvalvular atrial fibrillation; PPIs, proton pump inhibitors; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; TIA, transient ischemic attack.

Discussion

Main Findings

This is the first study to directly compare the effectiveness and safety between standard-dose (20/15 mg/d) and low-dose (15/10 mg/d) rivaroxaban among Asians with NVAF in real-world practice. This is because Taiwan is the only country that approved either ROCKET AF or J-ROCKET AF dosage criteria for stroke prevention in patients with NVAF. The main findings of this study are as follows: (1) Clinical physicians chose to prescribe rivaroxaban following the J-ROCKET AF rather than ROCKET AF dosage criteria for most Asian AF patients (75%) despite the approval of both dosages for stroke prevention in Taiwan. (2) Use of rivaroxaban following either ROCKET AF or J-ROCKET AF dosage criteria was associated with a similar risk of IS/SE and a significantly lower risk of bleeding compared with warfarin. (3) Older age and presence of malignancy were independent factors associated with prescriptions of rivaroxaban following J-ROCKET AF dosage criteria (15 mg/d) for patients with an eGFR ≥50 mL/min per 1.73 m^2, whereas older age and low platelet count were independent factors associated with the prescriptions following the J-ROCKET AF dosage criteria (10 mg/d) in patients with an eGFR <50 mL/min per 1.73 m^2. On the contrary, the presence of peripheral artery disease was associated with the prescriptions following ROCKET AF dosage criteria (20 mg/d) for patients with an

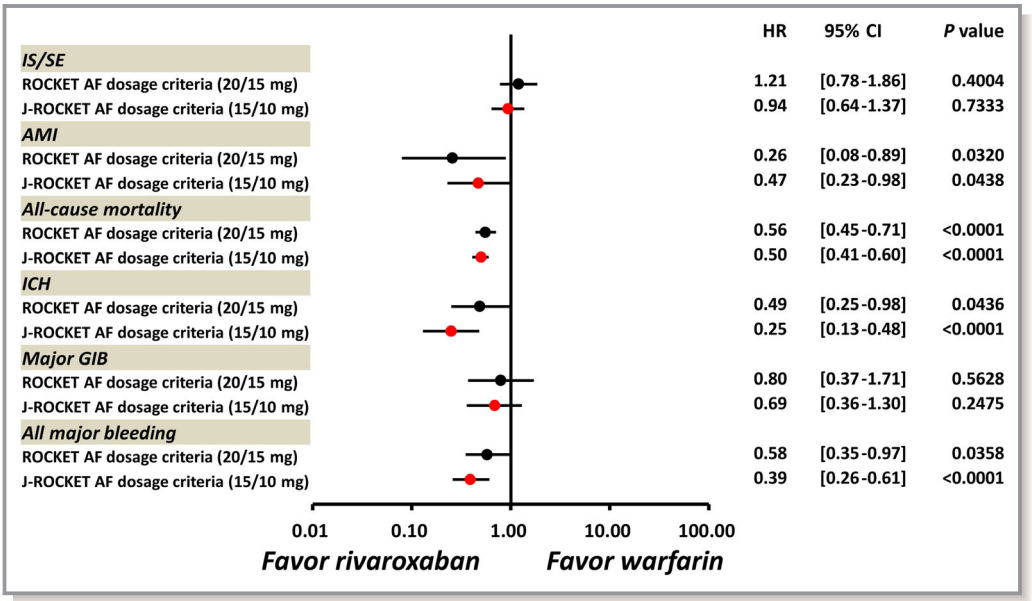

Figure 2. Forest plot of hazard ratio (HR) and 95% CI for patients with nonvalvular atrial fibrillation taking rivaroxaban following the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) dosage criteria or J-ROCKET AF (Japanese ROCKET AF) dosage criteria vs patients taking warfarin. Patients taking rivaroxaban following either the ROCKET AF (20/15 mg/d) or J-ROCKET AF (15/10 mg/d) dosage criteria showed a comparable risk of ischemic stroke or systemic embolism (IS/SE) and a lower risk of acute myocardial infarction (AMI), mortality, intracranial hemorrhage (ICH), and all major bleeding than patients taking warfarin after baseline covariate adjustment. GIB indicates gastrointestinal bleeding.

Table 2. Baseline Characteristics of Patients With NVAF With Normal or Impaired Renal Function Taking Rivaroxaban Following the ROCKET AF or the J-ROCKET AF Dosage Criteria

	eGFR ≥50 mL/min per 1.73 m^2 (n=2320)			eGFR <50 mL/min per 1.73 m^2 (n=842)		
	ROCKET AF Criteria 20 mg/d (n=384)	J-ROCKET AF Criteria 15 mg/d (n=1936)	*P* Value	ROCKET AF Criteria 15 mg/d (n=422)	J-ROCKET AF Criteria 10 mg/d (n=420)	*P* Value
Age, y	68.71±10.46	72.65±9.80	<0.001	75.84±9.69	79.34±7.93	<0.001
Women, No. (%)	120 (31.2)	774 (40.0)	0.001	191 (45.3)	201 (47.9)	0.450
CHA_2DS_2-VASc score	3.00±1.60	3.34±1.59	<0.001	4.16±1.52	4.18±1.43	0.846
HAS-BLED score	2.51±1.16	2.68±1.17	0.009	3.33±1.19	3.34±1.11	0.96
History, No. (%)						
Chronic lung disease	98 (25.5)	540 (27.9)	0.342	142 (33.6)	166 (39.5)	0.077
Chronic liver disease	66 (17.2)	401 (20.7)	0.116	78 (18.5)	99 (23.6)	0.070
Congestive heart failure	33 (8.6)	151 (7.8)	0.599	69 (16.4)	76 (18.1)	0.503
Hypertension	276 (71.9)	1452 (75.0)	0.199	371 (87.9)	357 (85.0)	0.216
Hyperlipidemia	168 (43.8)	855 (44.2)	0.882	210 (49.8)	218 (51.9)	0.534
Diabetes mellitus	134 (34.9)	634 (32.7)	0.414	204 (48.3)	215 (51.2)	0.408
Previous stroke	74 (19.3)	353 (18.2)	0.632	104 (24.6)	56 (13.3)	<0.001
Previous TIA	5 (1.3)	32 (1.7)	0.616	15 (3.6)	10 (2.4)	0.316
Ischemic heart disease	37 (9.6)	192 (9.9)	0.866	60 (14.2)	66 (15.7)	0.543
Gout	61 (15.9)	271 (14.0)	0.335	125 (29.6)	131 (31.2)	0.621
Peripheral artery disease	3 (0.8)	2 (0.1)	0.035	0 (0.0)	1 (0.2)	0.499
Malignancy	37 (9.6)	301 (15.5)	0.003	73 (17.3)	75 (17.9)	0.831
Laboratory data						
Hemoglobin, g/dL	13.73±2.14	13.30±1.98	<0.001	12.38±2.24	11.97±2.03	0.006
Platelet, ×1000/μL	200.26±65.41	199.97±66.05	0.941	199.60±66.66	188.49±66.34	0.019
Baseline eGFR, mL/min per 1.73 m^2	81.54±21.88	79.75±24.69	0.187	39.51±9.25	37.70±9.84	0.006
Changes of eGFR, mL/min per 1.73 m^2	−3.91±23.77	−3.36±27.01	0.707	1.35±15.69	1.63±16.60	0.801
ALT, U/L	28.86±41.99	29.61±103.78	0.893	27.07±24.80	26.17±32.81	0.659
Medications, No. (%)						
Concomitant APT	106 (27.6)	543 (28.1)	0.860	145 (34.4)	152 (36.2)	0.578
NSAIDs	49 (12.8)	250 (12.9)	0.935	77 (18.2)	66 (15.7)	0.328
PPIs	32 (8.3)	188 (9.7)	0.4	64 (15.2)	58 (13.8)	0.576
ACEIs/ARBs	221 (57.6)	1063 (54.9)	0.341	285 (67.5)	269 (64.0)	0.286
Loop diuretics	87 (22.7)	455 (23.5)	0.72	167 (39.6)	205 (48.8)	0.007
Amiodarone	70 (18.2)	364 (18.8)	0.793	102 (24.2)	97 (23.1)	0.713
Dronedarone	6 (1.6)	52 (2.7)	0.198	17 (4.0)	23 (5.5)	0.323
Quinidine	1 (0.3)	1 (0.1)	0.304	2 (0.5)	2 (0.5)	1.000
β-Blocker	243 (63.3)	1090 (56.3)	0.012	252 (59.7)	257 (61.2)	0.662
Diltiazem	65 (16.9)	386 (19.9)	0.173	70 (16.6)	61 (14.5)	0.409
Verapamil	23 (6.0)	93 (4.8)	0.33	12 (2.8)	14 (3.3)	0.681
Digoxin	65 (16.9)	366 (18.9)	0.363	75 (17.8)	87 (20.7)	0.279

Continued

Table 2. Continued

	eGFR ≥50 mL/min per 1.73 m^2 (n=2320)			eGFR <50 mL/min per 1.73 m^2 (n=842)		
	ROCKET AF Criteria 20 mg/d (n=384)	J-ROCKET AF Criteria 15 mg/d (n=1936)	*P* Value	ROCKET AF Criteria 15 mg/d (n=422)	J-ROCKET AF Criteria 10 mg/d (n=420)	*P* Value
Statins	139 (36.2)	629 (32.5)	0.158	158 (37.4)	173 (41.2)	0.265
Azithromycin/clarithromycin/erythromycin	2 (0.5)	35 (1.8)	0.066	9 (2.1)	6 (1.4)	0.440
Itraconazole	0 (0.0)	2 (0.1)	1.000	0 (0.0)	1 (0.2)	0.499
Cyclosporine	0 (0.0)	3 (0.2)	1.000	1 (0.2)	1 (0.2)	1.000

ACEIs indicates angiotensin-converting enzyme inhibitors; ALT, alanine aminotransferase; APT, antiplatelet agent; ARBs, angiotensin II receptor antagonists; CHA_2DS_2-VASc, congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke/transient ischemic attack, vascular disease, age 65 to 74 years, female; eGFR, estimated glomerular filtration rate; HAS-BLED, hypertension, abnormal renal or liver function, stroke, bleeding history, labile international normalized ratio, age 65 years or older, and antiplatelet drug or alcohol use; J ROCKET AF, Japanese Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; NSAIDs, nonsteroidal anti-inflammatory drugs; NVAF, nonvalvular atrial fibrillation; PPIs, proton pump inhibitors; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; TIA, transient ischemic attack.

eGFR ≥50 mL/min per 1.73 m^2, whereas previous stroke history was the independent factor associated with the prescriptions following ROCKET AF dosage criteria (15 mg/d) in patients with an eGFR <50 mL/min per 1.73 m^2. (4) J-ROCKET AF (15 mg/d) dosage criteria was as effective as ROCKET AF (20 mg/d) dose criteria for the prevention of IS/SE among patients with either an eGFR ≥ or <50 mL/min per 1.73 m^2. For patients with an eGFR <50 mL/min per 1.73 m^2, ROCKET AF (15 mg/d) dosage criteria was associated with a significantly higher risk of major bleeding compared with J-ROCKET AF (10 mg/d) dosage criteria.

Low-Dose DOACs in Stroke Prevention

Recent real-world data demonstrated a high prevalence of prescriptions of DOACs at a low dose in patients with NVAF worldwide.[12–15] In the present study, we also observed a high percentage (75%) of patients taking rivaroxaban at a lower dose by following the J-ROCKET AF dosage criteria, which was triggered by older age, presence of underlying malignancy, and low platelet count. These findings suggest that Asian physicians are concerned about the risk of bleeding with oral anticoagulants, and therefore, prefer to choose a lower dose for Asian patients with AF.

Of note, inappropriate prescriptions of low-dose DOACs without following the "labelling" recommendation may result in more thromboembolic events, while failing to reduce the risk of major bleeding.[12] These findings highlight the importance of prescribing DOACs at an "on-label" dose for stroke prevention. However, a debate about the dose of rivaroxaban is whether J-ROCKET AF dosage criteria should be regarded as an "on-label" dosage for Asian patients with AF. The existence of the argument is because the J-ROCKET AF dosage criteria was only supported by the J-ROCKET AF study, with a much smaller sample size than that of the ROCKET AF trial (n=1280 versus 14 264).[5,8] In addition, the target range of the INR in the J-ROCKET AF study (1.6–2.6 for patients aged ≥70 years and 2.0–3.0 for those aged <70 years) is different from that of the ROCKET AF study (2.0–3.0 regardless of patient age). In the present study, we demonstrated that rivaroxaban at a dose following either ROCKET AF or J-ROCKET AF dosage criteria was as effective as warfarin for the prevention of thromboembolic events and was associated with a significantly lower risk of ICH and major bleeding. Rivaroxaban at the J-ROCEKT AF dosage in particular was associated with a lower risk of major GIB compared with warfarin. These findings provide real-world data supporting the use of rivaroxaban following J-ROCKET AF dosage criteria as an alternative choice to warfarin for stroke prevention. However, more prospective and randomized studies are necessary to investigate this issue and confirm our findings.

Different Dosage Criteria of Rivaroxaban for Asians—ROCKET AF Versus J-ROCKET AF

Previous studies have shown that Asian patients with AF have a higher risk of ICH compared with non-Asians treated with DOACs, suggesting that Asians are more prone to bleeding.[16–19] Therefore, clinical physicians in Asia may tend to prescribe a lower dose of DOACs for Asian patients in daily practice. In fact, J-ROCKET dosage criteria is the only dosage regimen approved in Japan for stroke prevention in AF. In addition, even in South Korea where J-ROCKET dosage criteria was not approved, a daily dosage of rivaroxaban at 15 mg rather than 20 mg accounted for almost 60% of the prescriptions.[20] Therefore, it is important to understand the safety and effectiveness of rivaroxaban following J-ROCKET AF dosage criteria compared with that of ROCKET AF. In the present study, we demonstrated that the risk of ischemic stroke did not differ significantly between J-ROCKET AF and ROCKET AF dosage criteria. For patients with an eGFR ≥50 mL/min per 1.73 m^2, ROCKET AF dosage was not associated with a higher

Table 3. Factors for Patients Choosing to Follow the ROCKET AF or the J-ROCKET AF Dosage Criteria

	ROCKET AF vs J-ROCKET AF Univariate OR		ROCKET AF vs J-ROCKET AF Multivariate OR	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
eGFR ≥50 mL/min per 1.73 m^2 (n=2320)				
Age	0.96 (0.95–0.97)	<0.001	0.97 (0.95–0.98)	<0.001
Women	0.68 (0.54–0.86)	0.001		
CHA_2DS_2-VASc score	0.87 (0.81–0.93)	<0.001		
Peripheral artery disease	7.61 (1.27–45.72)	0.026	8.82 (1.43–54.40)	0.019
Malignancy	0.58 (0.40–0.83)	0.003	0.62 (0.42–0.91)	0.014
Hemoglobin, per g/dL	1.12 (1.05–1.18)	<0.001		
Use of β-blockers	1.34 (1.07–1.68)	0.012		
eGFR <50 mL/min per 1.73 m^2 (n=842)				
Age	0.96 (0.94–0.97)	<0.001	0.95 (0.94–0.97)	<0.001
Stroke history	2.13 (1.49–3.04)	<0.001	2.28 (1.56–3.33)	<0.001
Hemoglobin, per g/dL	1.09 (1.03–1.17)	0.007		
Platelet, per 10 000/μL	1.02 (1.00–1.03)	0.020	1.03 (1.01–1.05)	0.018
eGFR, per mL/min per 1.73 m^2	1.02 (1.01–1.03)	0.007		
Use of loop diuretics	0.69 (0.52–0.90)	0.007		

CHA_2DS_2-VASc indicates congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke/transient ischemic attack, vascular disease, age 65 to 74 years, female; eGFR, estimated glomerular filtration rate; J ROCKET AF, Japanese ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; OR, odds ratio; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.

risk of ICH, major GIB, or all major bleeding compared with J-ROCKET dosage. Among patients with an eGFR <50 mL/min per 1.73 m^2, the risk of major bleeding was lower in favor of J-ROCKET AF criteria. Our findings provided good insight into the performance of rivaroxaban following J-ROCKET criteria, which suggested that it may serve as an alternative to ROCKET AF criteria, especially for patients with an eGFR <50 mL/min per 1.73 m^2.

Study Strengths

The strength of our study is the use of a well-defined database with information on baseline hemoglobin, platelet count, liver function, and renal function of patients, which was not reported in most previous real-world studies using registry database. To our knowledge, the present study is the first to directly compare the effectiveness and safety between different dosage recommendations of rivaroxaban in patients with either normal or impaired renal function.

Study Limitations

This study has several limitations. First, although the Taiwan AF guidelines recommend an INR range of 2 to 3 for patients treated with warfarin,[21] the TTR was low in our cohort, and therefore, rivaroxaban following either dosage criteria would be more likely to perform better than warfarin. Indeed, a lower INR and poor TTR for Asian patients with AF receiving warfarin is a common issue. For example, the TTR for warfarin was only 44% for Taiwanese patients with AF even in the RE-LY (Randomized Evaluation of Long-Term Anti-coagulation Therapy) trial.[4] However, even compared with patients treated with warfarin in a top quartile of TTR, rivaroxaban following ROCEKT AF or J-ROCKET AF dosage criteria was still associated with a similar risk of IS/SE and a lower risk of mortality, ICH, and all major bleeding, which were generally consistent with the principal analyses. Therefore, a low TTR in our study may not significantly confound our main findings. Second, both ROCKET AF and J-ROCKET AF adopted the Cockcroft and Gault formula to calculate eGFR of patients to adjust the dose of rivaroxaban, while we used the Modification of Diet and Renal Disease (MDRD) equation to estimate renal function in the present study. Different from the MDRD equation, an important characteristic of the Cockcroft and Gault formula is the inclusion of total body weight in the equation, as a reflection of muscle mass, the main determinant of creatinine generation. However, we did not use the Cockcroft and Gault formula in the present study because of the lack of body weight in the electronic medical data of the Chang Gung Memorial Hospital System. In Taiwan, most

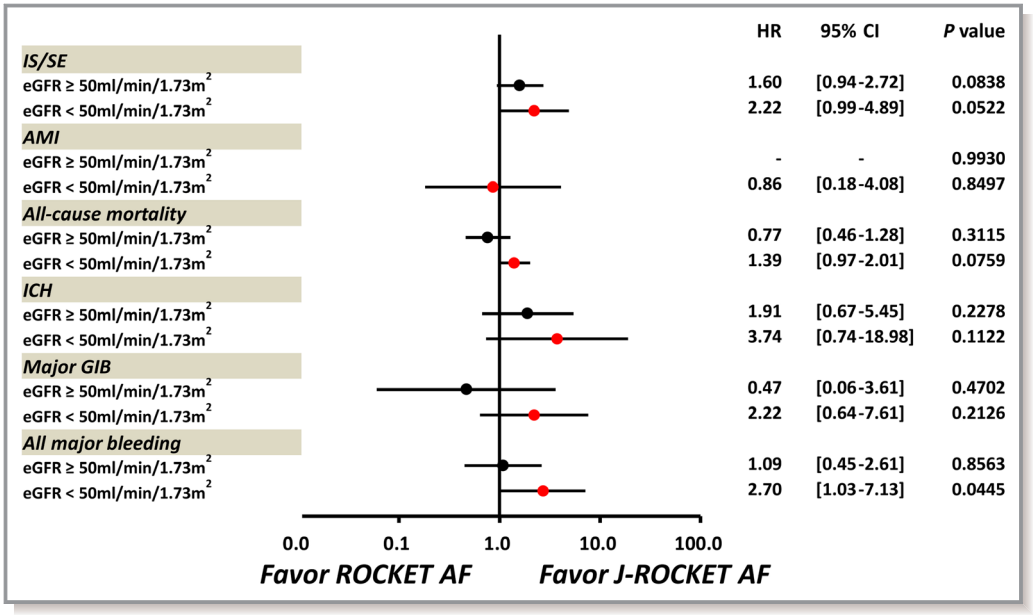

Figure 3. Forest plot of hazard ratio (HR) and 95% CI for rivaroxaban following the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) dosage criteria vs J-ROCKET AF (Japanese ROCKET AF) dosage criteria in patients with nonvalvular atrial fibrillation with estimated glomerular filtration rate (eGFR) ≥50 mL/min per 1.73 m^2 and eGFR <50 mL/min per 1.73 m^2. For patients with eGFR >50 mL/min per 1.73 m^2, following the ROCKET AF dosage criteria (20 mg/d) was associated with a comparable risk of ischemic stroke or systemic embolism (IS/SE) and major bleeding to following the J-ROCKET AF dosage criteria (15 mg/d) after baseline covariate adjustment. For patients with eGFR <50 mL/min per 1.73 m^2, following the ROCKET AF dosage criteria (15 mg/d) was associated with a higher risk of major bleeding than following the J-ROCKET AF dosage criteria (10 mg/d) after baseline covariate adjustment. AMI indicates acute myocardial infarction; GIB, gastrointestinal bleeding; ICH, intracranial hemorrhage.

biochemistry laboratories directly provide an MDRD equation–derived eGFR (mL/min per 1.73 m^2) in keeping with the national guidance, and many physicians adopt the results from the MDRD equation instead of the Cockcroft and Gault formula to estimate the renal function of patients and determine the dose of DOACs. Previous studies indicate that MDRD equation slightly underestimates renal function at higher levels and tends to overestimate at lower levels relative to the Cockcroft and Gault formula. For the case of rivaroxaban, 0.3% would have been incorrectly judged eligible for treatment and 13.5% would have received too high a dose.[22] However, the slight disagreement between Cockcroft and Gault and MDRD estimation may not significantly influence our analysis because we did not focus on the intragroup comparisons within the ROCKET AF (eg 20 versus 15 mg/d) or J-ROCKET AF (eg 15 versus 10 mg/d) groups in the present study. Third, miscoding and misclassification of the underlying comorbidities and outcomes recorded by each physician's choice of treatment constitutes an additional limitation of the present study. Hence, our present study only used primary discharge diagnoses in order to improve the accuracies of clinical outcomes. In addition, such miscoding and misclassification are highly unlikely to be different between patients following ROCKET AF and J-ROCKET AF dosage criteria. Fourth, although the baseline differences of comorbidities between groups have been adjusted by the multivariate regression analysis, residual unmeasured confounding and selective prescribing behavior could not be excluded in the present study. Fifth, our study was performed in an intention-to-treat design, and did not take the changes of dosages of rivaroxaban and eGFRs, which may result in different categorizations of patients into considerations. This important limitation should be kept in mind when interpreting the results we presented here. Sixth, we defined $P<0.05$ as statistically significant without further adjustments for multiplicity, and, therefore, the type I error is possible to be present for some analyses. In our study, the 6 end points we defined were those also commonly tested in prior studies comparing different treatments for stroke prevention in patients with AF, which were prespecified rather than being randomly selected from many other end points. In addition to *P* values, both the point estimates and their 95% CIs were reported for each comparison, which could be helpful for readers to judge and interpret the results. Finally, the present study only enrolled Taiwanese patients; therefore, whether the results can be extrapolated to other countries in Asia remains unclear.

Conclusions

In Asian patients with NVAF taking rivaroxaban for stroke prevention, the J-ROCKET AF dosage criteria (15/10 mg once daily) was as effective as ROCKET AF (20/15 mg once daily) and was associated with a lower risk of major bleeding in patients with impaired renal function. Compared with warfarin, rivaroxaban following either the ROCKET AF or J-ROCKET AF dosage criteria was effective and even safer in Asian patients with AF.

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Disclosures

None.

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Supplemental Material

Table S1. International Classification of Disease (9th and 10th edition) Clinical Modification (ICD 9-CM and ICD 10-CM) codes used to define the co-morbidities and clinical outcome in the study cohort

Disease	ICD-9 Codes	ICD-10 Codes	Diagnosis definition
Atrial fibrillation	427.31	I48	Discharge or outpatient department ≥2
Ischemic stroke	433, 434, 436	I63, I64	Discharge
Systemic embolism	444	I74	Discharge
Transient ischemic attack	435	G45	Discharge
Peripheral arterial occlusive disease	440.2	I70.2-I70.9, I71; I73.9	Discharge
Myocardial infarction	410, 411, 412	I21-I25	Discharge
Congestive heart failure	428	I11.0, I13.0, I13.2, I42.0, I50, I50.1, I50.9	Discharge
Hypertension	401, 402	I10-I16	Outpatient department ≥2
Diabetes mellitus	250	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9	Outpatient department ≥2
Hyperlipidemia	272	E78	Outpatient department ≥2

Chronic gout	274.0, 274.10, 274.11, 274.19, 274.81, 274.82, 274.89, 274.9	M10, M1A	Outpatient department ≥2
Chronic lung disease	490, 491.0, 491.1, 491.20-491.22, 491.8, 491.9, 492.0, 492.8, 493.00-493.02 493.10-493.12, 493.20-493.22, 493.81, 493.82, 493.90-493.92, 494.0, 494.1, 495.8, 495.9, 496, 500, 502, 503, 504, 505, A323, A325	J44	Discharge
Chronic kidney disease	580-589	I12, I13, N00, N01, N02, N03, N04, N05, N07, N11, N14, N17, N18, N19, Q61	Outpatient department ≥2

Chronic liver disease	570, 571, 572	B150, B160, B162, B190, K704, K72, K766, I85	Outpatient department ≥2
Malignancy	140.0-208.9	C	Outpatient department ≥2
Intracranial hemorrhage	430, 431, 432, 852, 853	I60, I61, I62	Discharge
Gastrointestinal bleeding	456.0, 456.2, 455.2, 455.5, 455.8, 530.7, 530.82, 531.0-531.6, 532.0-532.6, 533.0-533.6, 534.0-534.6, 535.0-535.6 537.83, 562.02, 562.03, 562.12 562.13 568.81, 569.3, 569.85, 578.0, 578.1, 578.9	K250, K260, K270, K280, K290	Discharge
Other critical site bleeding	423,0, 459.0, 568.81, 593.81,	D62, J942, H113, H356, H431, N02, N95,	Discharge

	599.7, 623.8, 626.32, 626.6, 719.1, 784.7, 784.8, 786.3	R04, R31, R58	

Table S2. HR and 95% CI of six outcomes for NVAF patient taking rivaroxaban following the ROCKET AF or J-ROCKET AF dose criteria vs. those taking warfarin.

	Event Rate/100 Person-Years (95% CI)		**Crude**		**Adjusted**	
ROCKET AF dose criteria (20/15 mg/day) vs. Warfarin						
	Rivaroxaban (n = 806)	**Warfarin (n = 2,053)**	**HR (95% CI)**	***P* value**	**HR (95% CI)***	***P* value**
IS/SE	1.94 (1.32 - 2.55)	1.35 (1.02 - 1.68)	1.44 (0.97 - 2.16)	0.0727	1.21 (0.78 - 1.86)	0.4004
AMI	0.15 (0.03 - 0.43)	0.62 (0.40 - 0.84)	**0.24 (0.07 - 0.78)**	**0.0180**	**0.26 (0.08 - 0.89)**	**0.0320**
All-cause mortality	4.58 (3.65 - 5.50)	6.59 (5.87 - 7.31)	**0.70 (0.56 - 0.88)**	**0.0025**	**0.56 (0.44 - 0.71)**	**<0.0001**
ICH	0.59 (0.26 - 0.93)	0.83 (0.57 - 1.09)	0.72 (0.38 - 1.38)	0.3260	**0.49 (0.25 - 0.98)**	**0.0436**
Major GIB	0.49 (0.19 - 0.80)	0.58 (0.37 - 0.80)	0.86 (0.42 - 1.78)	0.6893	0.80 (0.37 - 1.71)	0.5628
All-major bleeding	1.14 (0.68 - 1.61)	1.52 (1.17 - 1.87)	0.77 (0.48 - 1.23)	0.2700	**0.58 (0.35 - 0.97)**	**0.0358**
J-ROCKET AF dose criteria (15/10 mg/day) vs. Warfarin						
	Rivaroxaban (n = 2,356)	**Warfarin (n = 2,053)**	**HR (95% CI)**	***P* value**	**HR (95% CI)†**	***P* value**
IS/SE	1.34 (1.04 - 1.64)	1.35 (1.02 - 1.68)	0.99 (0.71 - 1.38)	0.9296	0.94 (0.64 - 1.47)	0.7333
AMI	0.19 (0.08 - 0.30)	0.62 (0.40 - 0.84)	**0.31 (0.15 - 0.61)**	**0.0008**	**0.47 (0.23 - 0.98)**	**0.0438**
All-cause mortality	3.52 (3.04 - 4.00)	6.59 (5.87 - 7.31)	**0.53 (0.44 - 0.63)**	**<0.0001**	**0.50 (0.41 - 0.60)**	**<0.0001**

ICH	0.29 (0.15 - 0.43)	0.83 (0.57 - 1.09)	**0.36 (0.20 - 0.63)**	**0.0004**	**0.25 (0.13 - 0.48)**	**<0.0001**
Major GIB	0.37 (0.21 - 0.52)	0.58 (0.37 - 0.80)	0.62 (0.35 - 1.09)	0.0965	0.69 (0.36 - 1.30)	0.2475
All-major bleeding	0.72 (0.50 - 0.94)	1.52 (1.17 - 1.87)	**0.47 (0.32 - 0.69)**	**0.0001**	**0.39 (0.26 - 0.61)**	**<0.0001**

AMI = acute myocardial infarction; CI = confidential interval; eGFR = estimated Glomerular filtration rate; GIB = gastrointestinal bleeding; HR = hazard ratio; ICH = intracranial hemorrhage; IS/SE = Ischemic stroke or systemic embolism; NVAF = nonvalvular atrial fibrillation.

*Adjusted baseline factors with significant difference between the ROCKET AF group vs. warfarin group in **Table 1**

†Adjusted baseline factors with significant difference between the ROCKET AF group vs. warfarin group in **Table 1**

Table S3. HR and 95% CI of six outcomes for rivaroxaban following the ROCKET AF dose criteria vs. J-ROCKET AF dose criteria in NVAF patients with eGFR ≥ 50 ml/min/1.73m^2 or eGFR < 50 ml/min/1.73m^2

	Event Rate/100 Person-Years (95% CI)		**Crude**		**Adjusted**	
eGFR ≥ 50 ml/min/1.73m^2 (n = 2,320)						
	ROCKET AF Criteria 20 mg/day (n = 384)	**J-ROCKET AF Criteria 15 mg/day (n = 1,936)**	**HR (95% CI)**	***P* value**	**HR (95% CI)***	***P* value**
IS/SE	2.04 (1.12-2.95)	1.37 (1.03 – 1.70)	1.48 (0.89-2.48)	0.1299	1.60 (0.94-2.72)	0.0838
AMI	0.00 (0.00-0.00)	0.14 (0.06 – 0.29)	NA	0.9931	NA	0.9930
All-cause mortality	1.72 (0.90-2.54)	3.02 (2.54 – 3.51)	**0.57 (0.36-0.94)**	**0.0284**	0.77 (0.46-1.28)	0.3115
ICH	0.51 (0.17-1.20)	0.29 (0.14 – 0.43)	1.79 (0.65-4.97)	0.2641	1.91 (0.67-5.45)	0.2278
Major GIB	0.10 (0.01-0.56)	0.35 (0.18 – 0.51)	0.29 (0.04-2.21)	0.2334	0.47 (0.06-3.61)	0.4702
All-major bleeding	0.62 (0.23-1.34)	0.70 (0.46 – 0.93)	0.88 (0.37-2.10)	0.7742	1.09 (0.45-2.61)	0.8563
eGFR < 50 ml/min/1.73m^2 (n = 842)						
	ROCKET AF Criteria 15 mg/day (n = 422)	**J-ROCKET AF Criteria 10 mg/day (n = 420)**	**HR (95% CI)**	***P* value**	**HR (95% CI)†**	***P* value**
IS/SE	1.85 (1.02 – 2.68)	1.18 (0.45 – 1.92)	1.76 (0.82 - 3.80)	0.1490	2.20 (0.99-4.89)	0.0522

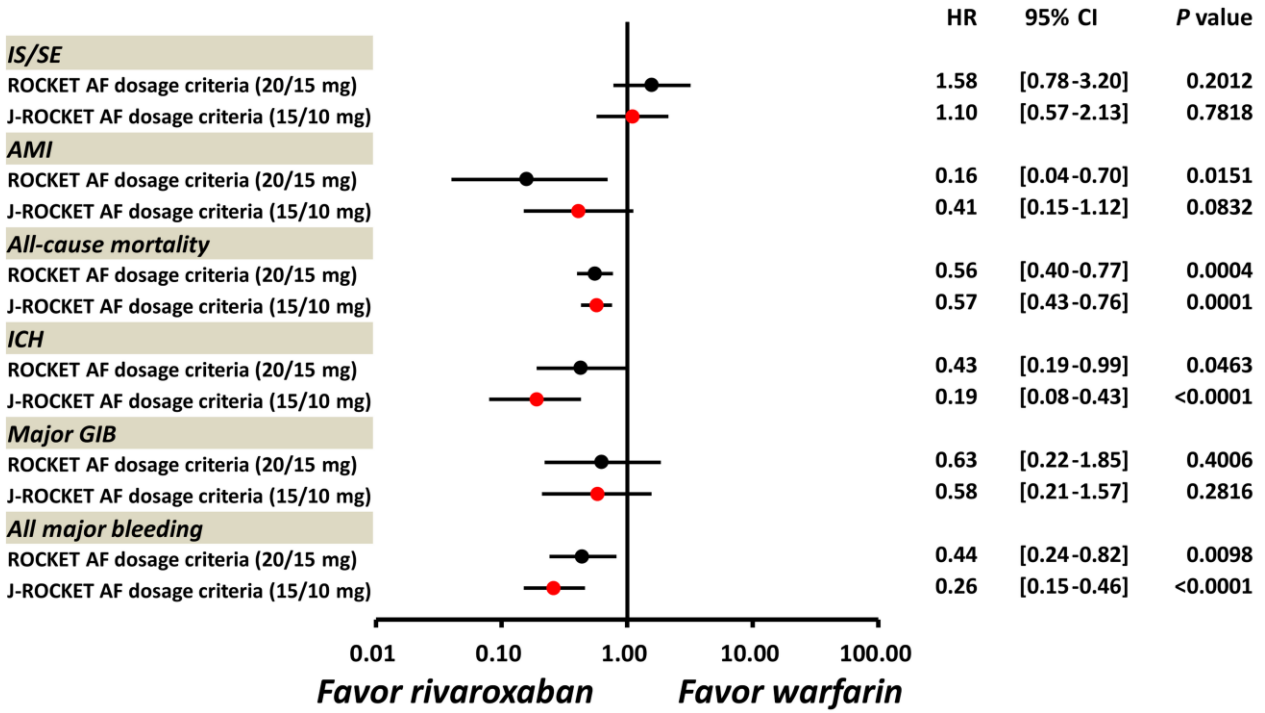
AMI	0.28 (0.06 – 0.82)	0.47 (0.13 – 1.19)	0.71 (0.16 - 3.17)	0.6527	0.86 (0.18-4.08)	0.8497
All-cause mortality	7.23 (5.61 – 8.84)	6.36 (4.68 – 8.04)	1.26 (0.89 - 1.78)	0.1997	1.39 (0.97-2.01)	0.0759
ICH	0.66 (0.27 – 1.36)	0.35 (0.07 – 1.02)	2.03 (0.52 - 7.88)	0.3055	3.74 (0.74-18.98)	0.1122
Major GIB	0.86 (0.39 – 1.63)	0.47 (0.13 – 1.19)	2.22 (0.68 - 7.21)	0.1843	2.20 (0.64-7.61)	0.2126
All-major bleeding	1.64 (0.86 – 2.41)	0.82 (0.33 – 1.68)	2.26 (0.94 - 5.47)	0.0693	**2.70 (1.03-7.13)**	**0.0445**

AMI = acute myocardial infarction; CI = confidential interval; eGFR = estimated Glomerular filtration rate; GIB = gastrointestinal bleeding; HR = hazard ratio; ICH = intracranial hemorrhage; IS/SE = Ischemic stroke or systemic embolism; NVAF = nonvalvular atrial fibrillation.

*Adjusted baseline factors of age, female, CHA_2DS_2-VASc score, peripheral disease, Malignancy, hemoglobin, and use of beta-blocker

†Adjusted baseline factors of age, stroke history, hemoglobin, platelet count, eGFR, and use of loop diuretics

Figure S1. Forest plot of HR and 95% CI for NVAF patients taking rivaroxaban following the ROCKET AF dosage criteria or J-ROCKET AF dosage criteria vs. those taking warfarin with the top quartile of TTR (mean 61.1% for the range of INR between 2.0-3.0).



Compared to patients taking warfarin with the top quartile of individual TTR (mean 61.1% for the range of INR between 2.0-3.0), patients taking rivaroxaban following either ROCKET AF or J-ROCKET AF dosage criteria showed a comparable risk of IS/SE and a lower risk of mortality, ICH, and all major bleeding, which were generally consistent with the principal analyses. AMI = acute myocardial infarction; CI = confidential interval; eGFR = estimated Glomerular filtration rate; GIB = gastrointestinal bleeding; HR = hazard ratio; ICH = intracranial hemorrhage; INR = international normalized ratio; IS/SE = Ischemic stroke or systemic embolism; NVAF = nonvalvular atrial fibrillation; TTR = time in therapeutic range.