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ORIGINAL INVESTIGATIONS

Effectiveness and Safety of Standard- and Low-Dose Rivaroxaban in Asians With Atrial Fibrillation

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ABSTRACT

BACKGROUND Low-dose rivaroxaban (10 mg/day) has been widely used in Asia for patients with atrial fibrillation (AF), although there is a lack of evidence regarding its effectiveness. In Asians, it is unclear whether low-dose rivaroxaban is equally effective as that of the standard dose or is associated with less bleeding risk.

OBJECTIVES The aim of this study was to evaluate the effectiveness and safety of standard-dose (15 or 20 mg/day) and low-dose (10 mg/day) rivaroxaban in Asians with AF.

METHODS Using data files from the National Health Insurance Research Database between May 1, 2014, and September 30, 2015, a retrospective population-based cohort study was conducted in patients diagnosed with AF or atrial flutter and treated with low- or standard-dose rivaroxaban. Patients were followed up until the first occurrence of the study outcome or the end of the observation period (December 31, 2015).

RESULTS Among 6,558 eligible patients, a total of 2,373 and 4,185 patients took low- and standard-dose rivaroxaban, respectively. Compared to standard-dose rivaroxaban, low-dose rivaroxaban was associated with a significantly higher risk of myocardial infarction (subdistribution hazard ratio: 2.26; 95% confidence interval: 1.13 to 4.52), with similar risk of ischemic stroke, systemic embolism, major bleeding, and nonmajor clinically relevant bleeding.

CONCLUSIONS Compared to standard-dose rivaroxaban, low-dose rivaroxaban in Asian patients with AF was associated with similar risks of thromboembolism and bleeding except myocardial infarction. (J Am Coll Cardiol 2018;72:477–85)

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CI = confidence interval

MI = myocardial infarction

NHIRD = National Health Insurance Research Database

NOAC = non-vitamin K antagonist oral anticoagulant

SHR = subdistribution hazard ratio

Atrial fibrillation (AF) is associated with a 5-fold increased risk of stroke (1). Warfarin is effective for the prevention of stroke in patients with AF, although its use is limited by numerous food and drug interactions, frequent monitoring and dose adjustment, and bleeding risk. The risk of warfarin-induced hemorrhage, especially intracranial bleeding, is higher in Asians (2), which might result in a high prevalence of the suboptimal use of warfarin in Asians when compared with that of other racial groups, especially in the pre-non-vitamin K antagonist oral anticoagulant (NOAC) era (3). This underdosing behavior exposed a portion of Asian AF patients to a higher risk of embolic events (4).

Rivaroxaban is a NOAC that directly inhibits factor Xa. 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) trial has shown the non-inferiority of rivaroxaban to warfarin in efficacy outcome (i.e., the composite of stroke and systemic embolism), with a similar major bleeding rate (5). Considering the higher risk of bleeding in Asians, a separate trial, J-ROCKET AF, evaluated the reduced dose of rivaroxaban (15 mg/day) in Japanese patients with AF, showing similar results to the global study (6).

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Despite the advantages of NOACs over warfarin, showing comparable or better efficacy and safety, more predictable effects and fewer interactions with drugs and food than warfarin (7), suboptimal oral anticoagulant use and poor compliance with practice guidelines for AF is still common worldwide (3). Possibly a result of previous experience with warfarin treatment, low-dose rivaroxaban (10 mg/day) has been widely used in real-world clinical practice in Asian countries (8–10). Despite the fact that low-dose rivaroxaban has only been tested in patients with renal impairment (creatinine clearance 30 to 49 ml/min) in the J-ROCKET AF trial (6), a low dose was selected for high bleeding risk and advanced age in patients with normal renal function (9). In addition, phase III randomized controlled trials have focused on the comparison of NOAC and warfarin (5,6). There are no studies directly comparing the effectiveness and safety of standard- and low-dose rivaroxaban in Asians.

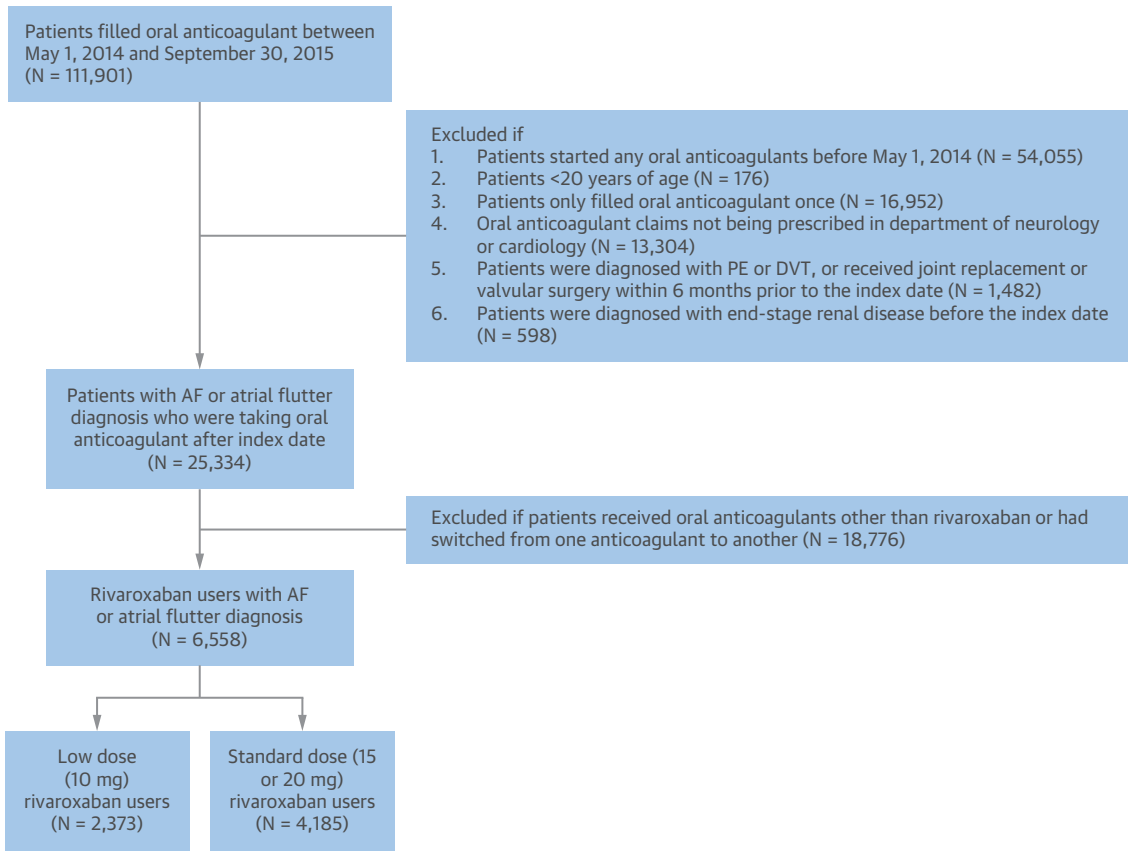
The objective of this study was to investigate the effectiveness and safety of standard- (15 or 20 mg/day) and low-dose (10 mg/day) rivaroxaban in Asians with AF in a real-world setting.

METHODS

STUDY DESIGN AND DATA SOURCES. This retrospective population-based cohort study was conducted using data files from the National Health Insurance Research Database (NHIRD) maintained by the Health and Welfare Data Science Center. The NHIRD is a claims-based database managed by the National Health Insurance Administration of Taiwan, which covers health care use and costs for 99% of residents in Taiwan. The NHIRD files include inpatient, outpatient, pharmaceutical claims, and disease diagnoses, and were coded by the International Classification of Diseases-9th Revision-Clinical Modification. In addition, the enrollment files of beneficiaries and providers were included. The data period used in this study was 2010 to 2015. This study was approved by the Joint Institutional Review Board of Taipei Medical University (TMU-JIRB No. N201701018).

STUDY COHORT. To reduce incomplete or underreported coding of diagnoses using the administrative health care database, which allowed up to 5 diagnoses in NHIRD, we instead used a history of prescription drug claims to select the study cohort. Patients who filled oral anticoagulant prescriptions between May 1, 2014, and September 30, 2015, were first included. The period was chosen to follow the regulations of the National Health Insurance Administration because rivaroxaban was first approved for treating stroke patients with AF after May 1, 2014. Of these patients, we added several exclusion criteria to ensure that the patients were more likely to be new drug users eligible for anticoagulant use: 1) any anticoagulant use before May 1, 2014; 2) age younger than 20 years; 3) oral anticoagulant filled once in the study period; 4) oral anticoagulant claims were not prescribed in the department of neurology or cardiology; 5) diagnosis of pulmonary embolism or deep vein thrombosis or undertaking of joint replacement or valvular surgery within 6 months before the index date that was referred to the first date of the oral anticoagulant claim; and 6) diagnosis of end-stage renal disease before the index date. Among the patients with AF or atrial flutter diagnosis who were taking oral anticoagulants, those who had received oral anticoagulants other than rivaroxaban or had switched from 1 anticoagulant to another were further excluded. Finally, we classified the patients into low-dose (10 mg/day) and standard-dose (15 or 20 mg/day) rivaroxaban groups. **Figure 1** depicts the process of patient selection in detail.

FIGURE 1 Patient Selection Process



Among 6,558 AF patients using rivaroxaban, 2,373 low-dose (10 mg/day) users, and 4,185 standard-dose (15 or 20 mg/day) users were enrolled in this study. AF = atrial fibrillation; DVT = deep vein thrombosis; PE = pulmonary embolism.

COMORBIDITIES AND MEDICATIONS. The disease diagnosis codes for baseline comorbidities and Anatomical Therapeutic Chemical codes for medications are provided in Online Table 1. Baseline thromboembolic and bleeding risk were assessed at the time of inclusion. For quantifying thromboembolic risk, we combined comorbidity information into the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 years, diabetes, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category [female]). To assess the risk of bleeding, we calculated the ORBIT score (age ≥74 years, anemia, bleeding history, chronic kidney disease, treatment with antiplatelet therapy). The ORBIT score had a better ability to predict major bleeding than that of other risk scores and was validated in a large randomized trial (ROCKET-AF) (11). To assess the effect of medication adherence, we calculated medication possession ratio (MPR). MPR is defined as total number of days covered by filled prescriptions divided by a pre-defined period (i.e., 90 days). An MPR of <0.4, 0.4 to <0.8, and ≥0.8 is classified as low, intermediate, and high adherence (12).

STUDY OUTCOMES. The primary safety outcomes were hospitalization for major bleeding and nonmajor clinically relevant bleeding. Major bleeding was defined as fatal bleeding, symptomatic bleeding in a critical area or organ, or bleeding leading to transfusion of >2 U of packed red blood cells. The primary efficacy outcomes were thromboembolic events, including myocardial infarction (MI), ischemic stroke, and systemic embolism. The disease diagnosis codes for study outcomes are provided in Online Table 1.

STATISTICAL ANALYSIS. Baseline characteristics were analyzed using standardized mean difference. A standardized mean difference of >0.1 indicates the

TABLE 1 Baseline Characteristics of Patients Received Low-Dose (10 mg) Versus Standard-Dose (15 or 20 mg) Rivaroxaban

	Before IPTW			After IPTW		
	Low Dose (n = 2,373)	Standard Dose (n = 4,185)	SMD	Low Dose (n = 2,373)	Standard Dose (n = 4,185)	SMD
Male	52.5	56.0	0.071	54.9	54.8	0.003
Age, yrs						
20–64	8.1	15.1	0.220	12.6	12.6	<0.001
65–74	24.7	33.0	0.184	30.1	30.0	0.001
75+	67.2	51.9	0.316	57.4	57.4	0.001
Charlson-Deyo index	1.8 ± 1.6	1.8 ± 1.6	0.028	1.8 ± 1.6	1.8 ± 1.6	0.002
0-1	51.0	52.7	0.034	52.0	52.1	0.002
≥2	49.0	47.3	0.034	48.0	47.9	0.002
CHA_2DS_2-VASc score	3.8 ± 1.5	3.5 ± 1.6	0.170	3.6 ± 1.6	3.6 ± 1.6	0.004
0	0.7	1.6	0.083	1.3	1.3	0.001
1	4.6	6.9	0.100	6.0	6.0	<0.001
2–3	38.6	42.8	0.087	41.3	41.3	<0.001
≥4	56.2	48.7	0.150	51.4	51.4	<0.001
ORBIT score	1.7 ± 1.1	1.5 ± 1.1	0.184	1.5 ± 1.1	1.5 ± 1.1	0.012
0–2	84.5	86.9	0.068	86.0	86.0	0.001
3	8.2	7.8	0.012	8.1	8.0	0.002
≥4	7.3	5.3	0.083	6.0	6.0	0.001
Adherence						
High (MPR ≥0.8)	28.7	29.9	0.026	29.7	29.5	0.005
Intermediate (MPR 0.4–0.8)	52.7	54.6	0.038	53.6	53.9	0.005
Low (MPR <0.4)	18.5	15.4	0.083	16.6	16.6	0.001
Comorbidities						
Ischemic stroke	20.0	20.2	0.006	20.3	20.2	0.003
GI bleeding	6.4	6.0	0.020	6.4	6.2	0.007
Myocardial infarction	3.8	3.2	0.035	3.4	3.4	<0.001
Congestive heart failure	28.4	25.8	0.058	26.5	26.7	0.004
Peptic ulcer disease	16.8	15.8	0.027	16.2	16.2	0.001
Hypertension	72.4	72.8	0.010	72.8	72.7	0.003
Diabetes	26.8	29.1	0.051	28.4	28.3	0.003
Chronic liver disease	5.0	5.7	0.033	5.6	5.5	0.004
Hyperlipidemia	28.0	30.6	0.058	30.1	29.8	0.007
Chronic obstructive pulmonary disease	15.4	13.5	0.053	14.2	14.2	0.001
Mild to moderate valvular heart disease	10.9	11.1	0.007	11.3	11.1	0.007
Malignancy	8.6	8.2	0.015	8.5	8.4	0.002
Chronic kidney disease	16.1	15.7	0.012	16.0	15.9	0.004
Medication use						
Nonsteroidal anti-inflammatory drugs	37.5	41.2	0.076	39.9	39.9	<0.001
Glucocorticoids	8.2	10.2	0.070	9.5	9.5	0.001
Antiplatelet agents	58.3	56.3	0.040	57.3	57.1	0.003
Proton pump inhibitors	5.8	5.2	0.027	5.4	5.4	<0.001
HMG-CoA reductase inhibitors	25.2	24.8	0.009	25.0	24.9	<0.001
Angiotensin-converting enzyme inhibitors	7.0	6.6	0.015	6.7	6.7	0.003
Angiotensin II antagonists	45.8	45.9	0.001	45.7	45.8	0.001
Follow-up period, months	8.9 ± 4.9	9.6 ± 5.0	0.140	8.9 ± 4.9	9.5 ± 5.1	0.113

Values are % or mean ± SD.

CHA_2DS_2-VASc score = congestive heart failure, hypertension, age ≥75 years, diabetes, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category (female); Charlson-Deyo index = myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, diabetes, diabetes with chronic complications, hemiplegia or paraplegia, renal disease, moderate or severe liver disease, acquired immune deficiency syndrome; GI = gastrointestinal; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; IPTW = inverse probability of treatment weighting; MPR = medication possession ratio; ORBIT score = age ≥74 years, anemia, bleeding history, chronic kidney disease, treatment with antiplatelet; SMD = standardized mean difference.

presence of non-negligible difference between 2 groups. Inverse probability of treatment weighting method was performed to adjust for differences of baseline characteristics between 2 cohorts. This approach is highly recommended in observational studies that intend to compare different treatment alternatives, allowing us to estimate the relative treatment effect with minimal bias on time-to-event

outcomes (13,14). Survival analysis was conducted using the Cox proportional hazard regression. The models were adjusted for baseline covariates and medications listed in Table 1. Because the subjects in this study were expected to be at risk of death, we applied competing risk model analyses to estimate the absolute and relative risks of thromboembolic and bleeding events. The follow-up period for each patient started from the index date of rivaroxaban prescription to the date of the event of interest or the end of the observation period (December 31, 2015). Subjects who switched from low-dose rivaroxaban to the high-dose and vice versa during the follow-up period were treated as censored cases in the competing risk model. All analyses were performed using SAS/STAT 9.4 (SAS Institute Inc., Cary, North Carolina) and STATA 14 (Stata Corp LP, College Station, Texas). A $p < 0.05$ was considered significant.

RESULTS

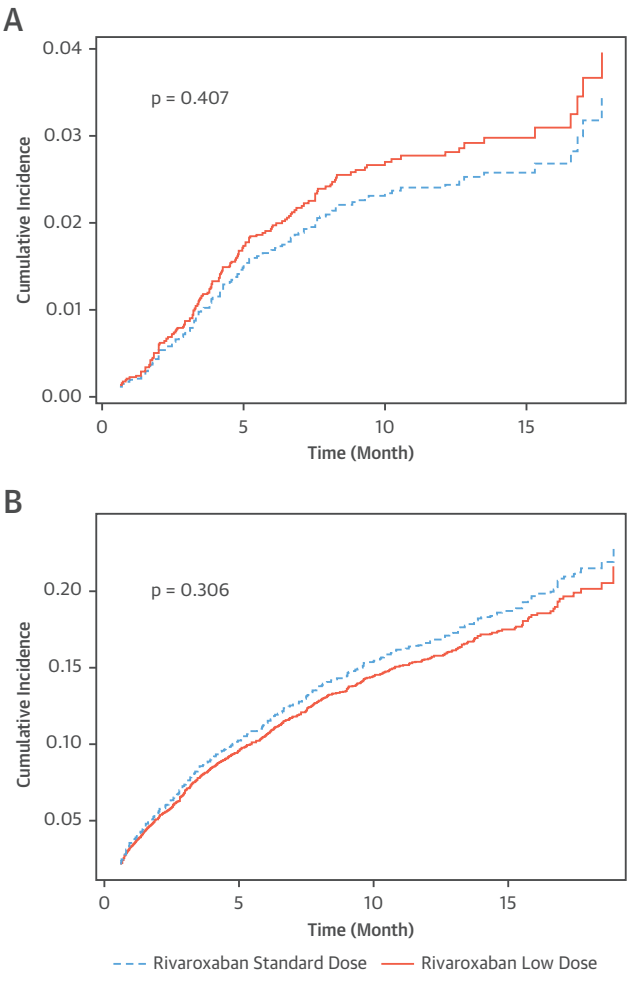
Among 111,901 patients who filled oral anticoagulant prescriptions from May 1, 2014, to September 30, 2015, a total of 6,558 patients met eligibility criteria. These patients were separated into 2 cohorts depending on dosage: 2,373 for low-dose rivaroxaban and 4,185 for standard-dose rivaroxaban, with 887 patients receiving 20 mg/day and 3,298 patients receiving 15 mg/day in the standard-dose group (Figure 1).

Baseline characteristics are shown in Table 1. Before inverse probability of treatment weighting, patients who received low-dose rivaroxaban were older and had higher CHA_2DS_2-VASc and ORBIT scores. After inverse probability of treatment weighting, baseline characteristics were well-balanced between the 2 groups. The mean follow-up period was longer in the standard-dose group.

The cumulative incidence and relative risks of bleeding outcomes are shown in Figure 2 and Table 2. No differences were found in major bleeding between two groups (subdistribution hazard ratio [SHR]: 1.16; 95% confidence interval [CI]: 0.82 to 1.63). The risk of nonmajor clinically relevant bleeding was also similar between the 2 groups (SHR: 0.93; 95% CI: 0.81 to 1.07). We further classified bleeding events into gastrointestinal bleeding, noncritical site bleeding other than gastrointestinal bleeding, noncritical site bleeding requiring transfusions, combined intracranial bleeding, and other critical site bleeding. The incidence of all bleeding types was similar between the 2 groups (Online Table 2).

The cumulative incidence and relative risks of thromboembolic outcomes and are shown in Figure 3 and Table 2. There was a significantly higher risk of MI

FIGURE 2 Bleeding Outcomes: Low-Dose Versus Standard-Dose Rivaroxaban



Low-dose rivaroxaban users had similar risk for major bleeding **(A)** and nonmajor clinically relevant bleeding **(B)** outcomes compared to standard-dose rivaroxaban users.

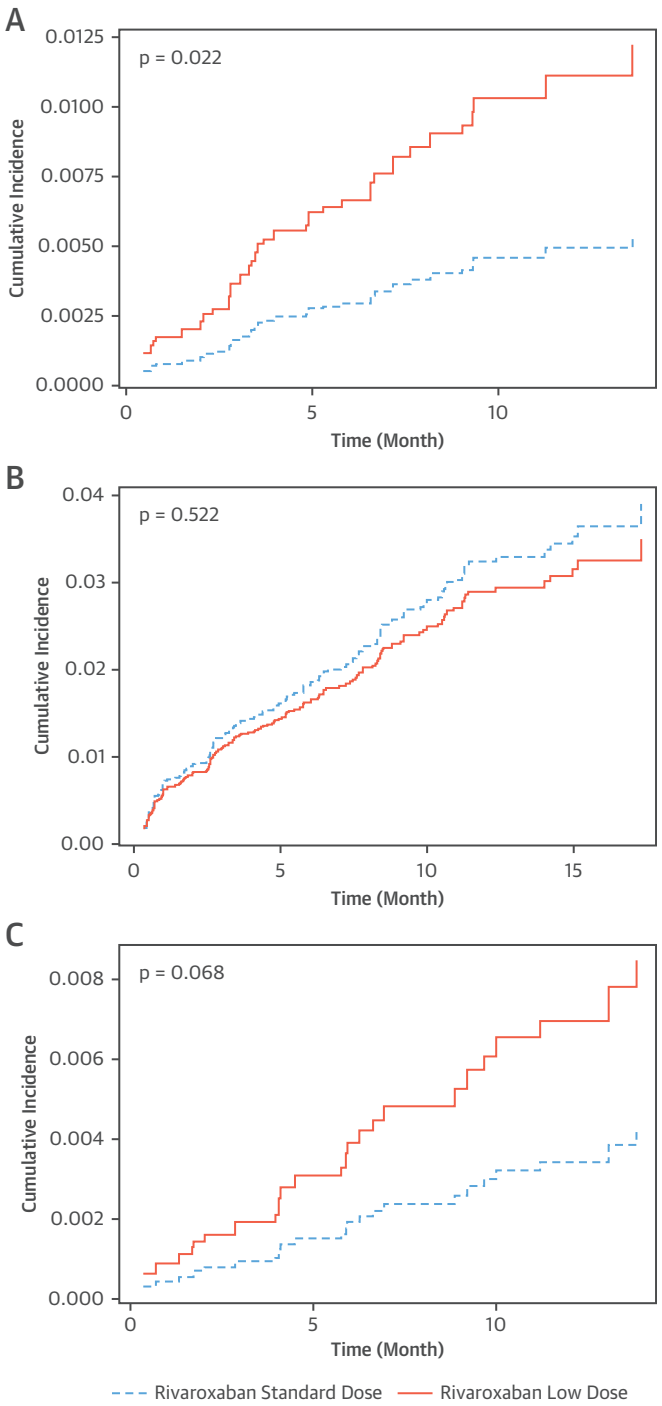
TABLE 2 Subdistribution Hazard Ratio of Bleeding and Thromboembolic Outcomes

Outcomes	SHR (95% CI)	p Value
Major bleeding*	1.16 (0.82–1.63)	0.407
Nonmajor clinically relevant bleeding	0.93 (0.81–1.07)	0.306
Myocardial infarction	2.26 (1.13–4.52)	0.022
STEMI	1.59 (0.31–8.07)	0.574
NSTEMI	2.54 (1.17–5.49)	0.018
Ischemic stroke	0.89 (0.63–1.27)	0.522
Systemic embolism	2.04 (0.95–4.36)	0.068

The standard dose group served as the reference. *Major bleeding is defined as fatal bleeding, symptomatic bleeding in a critical area or organ, or bleeding leading to transfusion more than two units of packed red blood cells.

CI = confidence interval; NSTEMI = non-ST-segment elevation myocardial infarction; SHR = subdistribution hazard ratio; STEMI = ST-segment elevation myocardial infarction.

FIGURE 3 Thromboembolic Outcomes: Low-Dose Versus Standard-Dose Rivaroxaban



Low-dose rivaroxaban users had higher risk for myocardial infraction **(A)** without increased risk for ischemic stroke **(B)** and systemic embolism **(C)** outcomes compared to standard-dose rivaroxaban users.

among the low-dose users (SHR: 2.26; 95% CI: 1.13 to 4.52). **Figure 3A** showed early separation of MI events during the first 6 months. The difference in MI events was primarily driven by non-ST elevation MI (NSTEMI), with a higher event rate in the low-dose group ($p = 0.018$). Moreover, there was a trend toward higher risk of systemic embolism in the low-dose group compared to that in the standard-dose group (SHR: 2.04; 95% CI: 0.95 to 4.36). **Figure 3C** showed early separation of systemic embolism event during the first 6 months. No significant difference was found in ischemic stroke events between the two groups (SHR: 0.89; 95% CI: 0.63 to 1.27) (**Central Illustration**). In patients with CHA_2DS_2-VASc score of ≥2, the risk of stroke was similar between the 2 groups as well (Online Table 3).

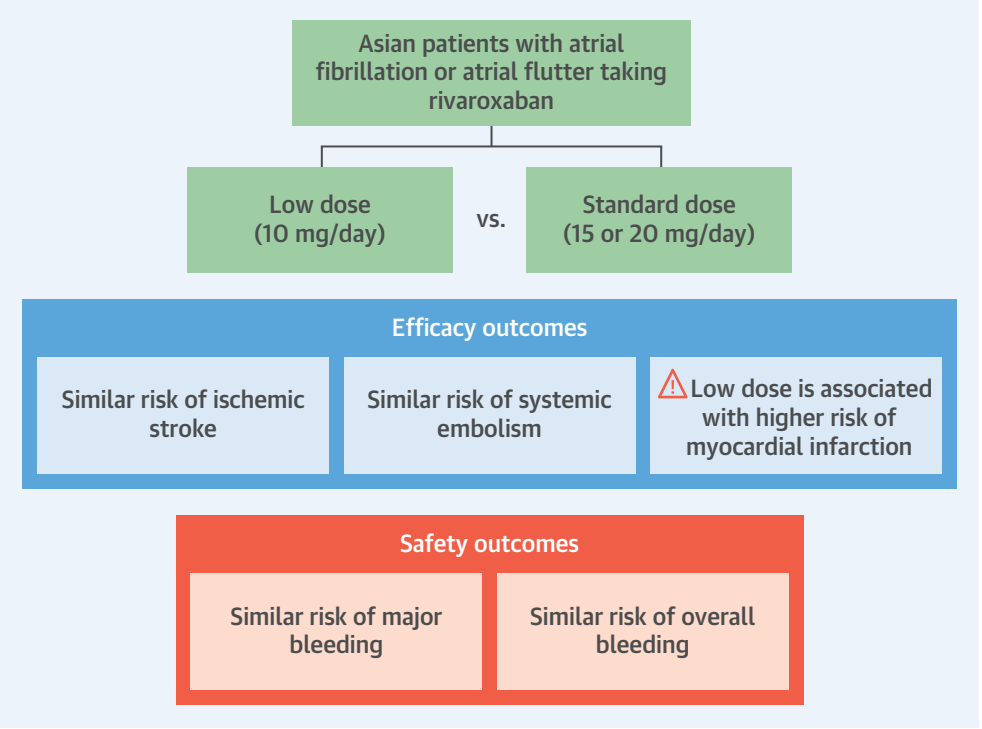
Subgroup analysis was performed on the basis of age, comorbidities, CHA_2DS_2-VASc score, and medications to assess whether the risk of MI varied among different patient populations (Online Figure 1). In patients receiving low-dose rivaroxaban, all subgroups had similar trends toward higher risk of MI than those of the standard-dose group. There were significant interactions between patients with hypertension, chronic kidney disease, ischemic stroke, and those without these comorbidities.

DISCUSSION

To our knowledge, this was the first population-based study to examine the effectiveness and safety of standard- and low-dose rivaroxaban in Asians with AF. No prior studies compared different doses of rivaroxaban directly in an Asian population. In this large-scale analysis, 36% patients in the Asian cohort were taking low-dose (10 mg/day) rivaroxaban. Compared to that of the standard dose, low-dose rivaroxaban was associated with a significantly higher risk of MI, without simultaneous increased risk of ischemic stroke, systemic embolism, or major and nonmajor clinically relevant bleeding. Subgroup analysis indicated that all subgroups receiving low-dose rivaroxaban had similar trends toward higher risk of MI, and the difference of MI events between 2 groups was mainly driven by NSTEMI.

According to drug labeling, dose selection of rivaroxaban should be based on renal function. Our study showed that clinicians often prescribed low-dose NOAC to Asian patients with AF despite the fact that the prevalence of chronic kidney disease was only 16% (**Table 1**). Such a prescribing pattern has been observed in some studies (9,10,15-17) and was associated with

CENTRAL ILLUSTRATION **Comparison of Standard-Dose and Low-Dose Rivaroxaban in Atrial Fibrillation**



Lin, Y.-C. et al. J Am Coll Cardiol. 2018;72(5):477–85.

Compared to that of the standard dose, low-dose rivaroxaban in Asian patients with atrial fibrillation was associated with a significantly higher risk of myocardial infarction. The risks of ischemic stroke, systemic embolism, major bleeding, and nonmajor clinically relevant bleeding were similar between the 2 groups.

adverse outcome (16,17). A large nationwide cohort study in Denmark by Nielsen et al. (17) indicated that low-dose apixaban was associated with a trend toward higher risk of ischemic stroke and systemic embolism than that of warfarin, with no significant difference in bleeding rates. Another large real-world study in the United States performed by Yao et al. (16) showed that in apixaban-treated patients, underdosing was associated with higher risk of stroke and systemic embolism without significant difference in major bleeding. Similarly, our study indicated that low-dose rivaroxaban may be less effective than standard-dose rivaroxaban without lowering the adverse effect of bleeding in an Asian population.

Our study showed that standard-dose rivaroxaban was associated with a significantly lower risk of MI than that of the low dose. According to several prospective cohort studies, AF was associated with increased risk of myocardial infarction in patients without coronary heart disease at baseline (18–20). As MI in AF is mediated by both platelet aggregation with coagulation cascade activation and atrial thrombus embolization, anticoagulants may exert a protective effect against MI (21–25). A Danish registry evaluated the risk of MI in patients with AF without prevalent coronary artery disease (24). Whereas the overall incidence rate of MI is 8.0 per 1,000 person-years, anticoagulation with warfarin was associated with a lower risk of MI with an incidence rate of 5.8 per 1,000 person-years compared to that of aspirin. In particular, for rivaroxaban, the ATLAS ACS 2-TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis In Myocardial Infarction 51) trial showed that rivaroxaban significantly reduced the incidence of spontaneous MI in patients with recent acute coronary syndrome compared to that of placebo (26,27). In a subanalysis of the ROCKET-AF trial (28), patients with AF assigned to rivaroxaban tended to have a lower risk of

cardiovascular death, MI, or unstable angina compared to patients assigned to warfarin. The COMPASS (A Randomized Controlled Trial of Rivaroxaban for the Prevention of Major Cardiovascular Events in Patients With Coronary or Peripheral Artery Disease) study enrolled stable atherosclerotic vascular disease patients; in the study, 62% of patients had prior MI, and patients who received rivaroxaban plus aspirin tended to have a lower rate of MI than patients receiving aspirin alone (29). The reduction of spontaneous MI was significant only in the higher-dose group (5 mg twice daily) in the ATLAS ACS 2-TIMI 51 trial (27), suggesting that the lower dose exerted less of an anticoagulation effect, resulting in less protection against MI.

Regarding systemic embolism events, rivaroxaban significantly reduced risk of systemic embolism in patients with AF in the phase III clinical trial (5). Our study showed a trend toward a higher risk of systemic embolism but did not achieve statistical significance in low-dose users compared to standard dose users. Because the events occurred infrequently, the power to detect statistically significant difference was limited.

STUDY LIMITATIONS. First, the diagnosis of coronary artery disease often requires imaging studies and/or other diagnostic procedures for definite diagnosis. However, the NHIRD did not include imaging studies and diagnostic test results. Therefore, we did not include coronary artery disease as a covariate in the present analysis. Instead, we included MI as one of the covariates, as the coding of MI was confirmed to be accurate in a previous study (30). Second, the choice of low-dose rivaroxaban may be guided by creatinine clearance. Because NHIRD did not include laboratory data, the chronic kidney disease population in this study may be heterogeneous. Third, the possibility of residual confounding might present given the nature of this study even though we used inverse probability treatment of weighting method to balance the differences in many foreseeable confounders between the 2 cohorts. Finally, we only included 6,558 patients in the analysis as we used strict exclusion criteria to minimize confounding effects. Because long-term anticoagulant therapy is required for stroke prevention, low adherence may impact outcomes. Therefore, we eliminated patients who filled only 1 prescription. Additionally, we excluded 4,576 patients who had switched from 1 anticoagulant to another. These patients actually received warfarin temporarily during acute stage of ischemic stroke before switching to rivaroxaban because our national insurance policy does not allow the use of rivaroxaban during the first 14 days of ischemic stroke episode. As there is potential selection bias in the present study, we performed a sensitivity analysis by including these patients, and the results were similar to the main analysis (Online Table 4).

CONCLUSIONS

In this population-based cohort study, in Asian patients with AF, low-dose rivaroxaban was associated with similar risk of thromboembolism except myocardial infarction compared to that of the standard dose. Dose reduction did not alter the risk of major and overall bleeding rates.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Limited data exists for low-dose rivaroxaban, although it has been commonly used in real-world practice in Asia. This was the first population-based study that directly compared the effectiveness and safety of standard- and low-dose rivaroxaban in Asians with AF.

COMPETENCY IN PATENT CARE AND PROCEDURAL SKILLS: In Asian patients with AF, low-dose rivaroxaban was associated with similar risk of thromboembolism except MI compared to that of the standard dose. Dose reduction did not alter the risk of major bleeding and nonmajor clinically relevant bleeding.

TRANSLATIONAL OUTLOOK: Further study is needed to confirm the findings of this study regarding the increased risk of myocardial infarction associated with low-dose rivaroxaban.

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KEY WORDS bleeding, embolism, myocardial infarction, non-vitamin K antagonist oral anticoagulant, stroke

APPENDIX For supplemental tables and a figure, please see the online version of this paper.