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The effectiveness and safety of low-dose rivaroxaban in Asians with non-valvular atrial fibrillation

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ABSTRACT

Background: Rivaroxaban (20 mg/15 mg once daily) is an effective and safe alternative to warfarin for stroke prevention in patients with non-valvular AF (NVAF). Low-dose rivaroxaban (15 mg/10 mg once daily) has been only approved for NVAF patients in Japan and Taiwan, although its effectiveness and safety at low doses remain unclear among Asians with NVAF. The objective of the study is to compare the effectiveness and safety of low-dose rivaroxaban to those of warfarin among Asians with NVAF.

Methods: This dynamic cohort study used data from the Taiwan National Health Insurance Database (NHIRD) to enroll 14,971 patients taking 15 mg rivaroxaban, 11,029 patients taking 10 mg rivaroxaban, and 16,000 NVAF patients taking warfarin. Inverse probability of weighting using propensity scores was used to balance covariates across study groups.

Results: The adjusted hazard ratio [95% confidence interval] comparing rivaroxaban 15 and 10 mg with warfarin (reference) was as follows: ischemic stroke/systemic embolism, 0.84 [0.74–0.96; $P = 0.0080$], and 0.84 [0.73–0.96; $P = 0.0097$]; myocardial infarction, 0.53 [0.37–0.74; $P = 0.0002$], and 0.88 [0.65–1.19; $P = 0.3910$]; intracranial hemorrhage, 0.44 [0.34–0.55; $P < 0.0001$], and 0.53 [0.42–0.66; $P < 0.0001$]; major gastrointestinal bleeding, 0.82 [0.67–0.99; $P = 0.0387$], and 0.58 [0.47–0.72; $P < 0.0001$]; all hospitalized major bleeding, 0.63 [0.55–0.73; $P < 0.0001$], and 0.56 [0.48–0.65; $P < 0.0001$]; and all-cause mortality, 0.55 [0.51–0.60; $P < 0.0001$], and 0.58 [0.53–0.63; $P < 0.0001$].

Conclusions: Both low doses of rivaroxaban were associated with a lower risk of ischemic stroke/systemic embolism, intracranial hemorrhage, gastrointestinal bleeding, all major bleeding, and all-cause mortality compared with warfarin in Asian NVAF patients. The 15 mg rivaroxaban dose was associated with a lower risk of acute myocardial infarction compared to warfarin.

1. Introduction

Atrial fibrillation (AF), which affects 2% to 3% of the global population, significantly increases the risk for thromboembolic events, hospitalization, and mortality [1,2]. Warfarin therapy was shown to be very efficacious in reducing the risk of stroke and mortality by 65% and 22%, respectively. However, this therapeutic strategy is compromised by several factors including unpredictable pharmacokinetics due to its frequent food-drug interactions, requirement for regular coagulation monitoring, and increased risk of intracranial hemorrhage [3]. The introduction of non-vitamin K antagonist oral anticoagulants (NOACs) like dabigatran, rivaroxaban, apixaban, and edoxaban has improved rates of stroke prevention in patients with non-valvular AF (NVAF).

Abbreviations: AF, atrial fibrillation; AMI, acute myocardial infarction; ASMD, absolute standardized mean difference; GIB, gastrointestinal bleeding; ICD-9-CM, International Classification of Diseases-Ninth Revision-Clinical Modification; ICD-10-CM, International Classification of Diseases-Tenth Revision-Clinical Modification; ICH, intracranial hemorrhage; IS/SE, ischemic stroke/systemic embolism; NHIRD, National Health Insurance Registry Database; NOAC, non-vitamin K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation.

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The Rocket-AF trial was a global study investigating the safety and efficacy profiles of a daily regimen of 20 mg or 15 mg rivaroxaban compared to warfarin therapy in patients with NVAF. The results indicated that rivaroxaban was an effective and safe alternative to warfarin in patients with NVAF [4]. A similar but much smaller trial (J-ROCKET AF trial) which was designed to address race-based differences in rivaroxaban pharmacokinetics and different target INR of warfarin (INR 1.5–2.5) in Japanese patients, investigated the efficacy and safety profiles of low-dose rivaroxaban (15 mg or 10 mg once daily) versus warfarin in Japanese NVAF patients. Results from this trial showed a marginal trend towards reduction in thromboembolic and major bleeding events in patients treated with 15 mg or 10 mg rivaroxaban compared with warfarin (target INR 1.5–2.5) [5]. It is possible that this lack of statistical significance was due to very limited patient enrollment (n = 1280 patients). The effectiveness and safety profiles of low-dose rivaroxaban among Asian patients with NVAF therefore remain unclear. Currently, Taiwan and Japan are the only two countries where low-dose rivaroxaban (15 mg or 10 mg once daily) has been approved for stroke prevention in NVAF patients. The objective of the present study was to use data from the Taiwan National Health Insurance Database (NHIRD) to investigate the effectiveness and safety of low-dose rivaroxaban to that of warfarin among Asians with NVAF.

2. Methods

2.1. Study population

This study was approved by the Institutional Review Board of the Chang Gung Medical Foundation. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. Informed consent was waived because the original identification number of each patient in the NHIRD is encrypted and de-identified to protect patient privacy by using a consistent encrypting procedure. The National Health Insurance system of Taiwan is a mandatory universal health insurance program which provides comprehensive medical care coverage to all Taiwanese. As of 2014, there were >23 million enrollees and a >99% coverage rate of the entire population [6].

2.2. Study design

This study was designed as a dynamic cohort with study patients assigned to three study groups (rivaroxaban 15 mg once daily, rivaroxaban 10 mg once daily, and warfarin). A flowchart of the study enrollment is shown in Fig. 1. The study identified a total of 279,776 patients diagnosed with AF using *International Classification of Diseases-the ninth revision-Clinical Modification* (*ICD-9-CM*) codes (427.31) between January 1, 2010 and December 31, 2015 or using *ICD-10-CM codes* (I48) between January 1, 2016 and December 31, 2016. The index date was defined as the first date of prescription for rivaroxaban or warfarin after February 1, 2013 for each group. The follow-up period was defined as the duration from the index date until the first occurrence of any study outcome, or until the end date of the study period (December 31, 2016), whichever came first.

2.3. Exclusion criteria

We specifically focused on low-dose rivaroxaban in the present study. The study identified a total of 27,777 patients taking rivaroxaban for stroke prevention. Of these, 1777 patients (6.40%) who were prescribed 20 mg rivaroxaban once daily were excluded from the study. Patients taking other NOACs (e.g. dabigatran, apixaban) anytime during the entire study period were also excluded. Additionally, since rivaroxaban was approved after February 1, 2013, those patients taking first dosage of warfarin before February 1, 2013 were also excluded, in order to achieve the head-to-head comparison with rivaroxaban. To establish a cohort of NVAF patients who took an oral anticoagulant for the primary purpose of ischemic stroke prevention, patients were excluded if they had diagnoses indicating venous thromboembolism (pulmonary embolism or deep vein thrombosis), valvular AF (mitral stenosis or history of valvular surgery), or required joint replacement therapy within 6 months before the index date. Patients with end-stage renal disease were also excluded because NOACs are contraindicated in such patients in Taiwan.

2.4. Study outcomes

The six study outcomes used to determine the effectiveness and safety profiles for NOACs and warfarin included 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 code 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 of NHIRD were shifted from ICD-9-CM to ICD-10-CM after January 1, 2016. The ICD-9-M and ICD-10-CM codes used to identify the study outcomes, and the baseline covariates are summarized in Supplemental Table I. The same patient may have had more than one study outcomes during the study duration, but this study only considered the study outcome that occurred first.

2.5. Covariates

Baseline covariates referred to any claim record with the above diagnoses, or medication codes prior to 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. 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 to 74 years, and female gender) was computed to predict the risk of ischemic stroke/thromboembolic events in AF patients [7]. The HAS-BLED score (hypertension, abnormal renal or liver function, stroke, bleeding history, labile INR, age 65 years or older, and antiplatelet drug or alcohol use) was computed to predict the risk of bleeding in AF patients treated with oral anticoagulants [8].

2.6. Statistical analysis

We used the propensity score method to compare the effectiveness and safety between the three study groups (rivaroxaban 15 mg, rivaroxaban 10 mg and warfarin) [9,10]. Generalized boosted models were used, based on 5000 regression trees, to calculate weights for optimal balance among 3 study groups [11]. The weights were derived to obtain estimates representing average treatment effects in treated patients. The absolute standardized mean difference (ASMD) assessed the balance of potential confounders at baseline (index date) among the three study groups, and ASMD values ≤0.1 indicated a negligible difference in potential confounders between any two study groups [9]. Incidence rates were computed as the total number of study outcomes during the follow-up time divided by person-years at risk. The risk of study outcomes over time among the three study groups was compared using survival analysis (Kaplan-Meier method and log-rank test for univariate analysis and Cox proportional hazards regression for multivariate analysis). Statistical significance was defined as a P value < 0.05. All statistical analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

This study enrolled a total of 14,971, 11,029, and 16,000 consecutive patients taking rivaroxaban 15 mg, rivaroxaban 10 mg, and warfarin, respectively, between February 1, 2013 and December 31, 2016. During the study period, 9220 (61.6%) and 5751 (38.4%) patients were warfarin-naïve and warfarin-experienced rivaroxaban 15 mg users, respectively; 7095 (64.3%) and 3934 (35.7%) patients were warfarin-naïve and warfarin-experienced rivaroxaban 10 mg users, respectively. Before propensity score weighting, patients in the rivaroxaban 10 mg group were older, had a higher proportion of co-morbidities, and had higher CHA_2DS_2-VASc and HAS-BLED scores compared with the rivaroxaban 10 mg or warfarin groups (Supplemental Table II). After propensity score weighting, the three study groups were well-balanced in most characteristics (all ASMD < 0.1) (Table 1).

The medium follow-up period was 1.2, 1.0, and 1.4 years for rivaroxaban 15 mg, rivaroxaban 10 mg, and warfarin groups, respectively. Patients in both rivaroxaban groups had a lower risk of ICH, major GIB, and all major bleeding compared with patients in the warfarin group before as well as after propensity score weighting (all $P < 0.05$ after propensity score weighting, respectively) (Table 2). Before propensity score weighting, patients in both rivaroxaban groups had a similar annual incidence of IS/SE (2.68%/year and 3.08%/year for rivaroxaban 15 mg and 10 mg, respectively) compared with patients in the warfarin group (2.81%.year) ($P = 0.1117$ and $P = 0.6586$, respectively). After the weighting adjustment, the annual incidence rates of IS/SE of the two rivaroxaban groups (2.91%/year and 3.08%/year for the rivaroxaban 15 mg and 10 mg groups, respectively) were significantly lower than that of the warfarin group (3.40%/year; $P = 0.0080$, $P = 0.0097$, respectively). Of note, patients in the 15 mg rivaroxaban group had a lower risk of AMI compared with patients in the warfarin group, before as well as after the weighting adjustment (0.36%/year vs. 0.67%/year; $P = 0.0002$). The cumulative risk showed a clear separation of event curves for ICH, GIB, all major bleeding, and all-cause mortality for

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