Comparative Effectiveness and Safety of Dabigatran and Rivaroxaban in Atrial Fibrillation Patients

Chao-Lun Lai, MD, PhD; Ho-Min Chen, MS; Min-Tsun Liao, MD; Ting-Tse Lin, MD; K. Arnold Chan, MD, ScD

Background—We aimed to examine the comparative effectiveness and safety between dabigatran and rivaroxaban in atrial fibrillation patients.

Methods and Results—We conducted a population-based, retrospective, new-user cohort study based on the National Health Insurance claims database in Taiwan. Adult atrial fibrillation patients who initiated dabigatran (N=10 625) or rivaroxaban (N=4609) between June 1, 2012 and May 31, 2014 were identified as the overall population. A propensity score was derived using logistic regression to model the probability of receipt of rivaroxaban as a function of potential confounders. Altogether, 4600 dabigatran users were matched with 4600 rivaroxaban users to create a propensity score–matched population. The marginal proportional hazards model was applied among the propensity score–matched population as the primary analysis, and the proportional hazards model with adjustment of the quintiles of the propensity score among the overall population was used as the secondary analysis. Rivaroxaban users had a higher risk of all-cause death than dabigatran users (hazard ratio 1.44, 95%CI 1.17-1.78 in the primary analysis and hazard ratio 1.47, 95%CI 1.23-1.75 in the secondary analysis). Rivaroxaban users also possessed a higher risk of gastrointestinal hemorrhage needing transfusion than dabigatran users in the primary analysis (hazard ratio 1.41, 95%CI 1.02-1.95), but the difference diminished in the secondary analysis (hazard ratio 1.20, 95%CI 0.92-1.56). The risks of ischemic stroke, acute myocardial infarction, arterial embolism/thrombosis, and intracranial hemorrhage were similar between the 2 groups.

Conclusions—Rivaroxaban therapy was associated with a statistically significant increase in all-cause death compared with dabigatran therapy in atrial fibrillation patients. (J Am Heart Assoc. 2017;6:e005362. DOI: 10.1161/JAHA.116.005362.)

Key Words: anticoagulant • dabigatran • effectiveness • rivaroxaban • safety
of dabigatran and rivaroxaban using a retrospective cohort study design based on claims data from the National Health Insurance (NHI) program in Taiwan.

Methods

Data Sources

Taiwan has provided compulsory universal NHI coverage for all citizens since 1995 via a single-payer health insurance system. Patient identification number, sex, birthday, dates of outpatient clinic visits, dates of hospital admission and discharge, diagnoses associated with claims, procedures administered, dates of pharmacy dispensing, and drugs dispensed are available in the NHI claims database. Diagnoses are coded according to the International Classification of Diseases Ninth Revision Clinical Modification (ICD-9-CM) system. The Taiwan NHI Administration routinely carries out audits for inappropriate use of drugs or procedures by healthcare institutions, and inappropriate use of drugs or procedures would result in serious penalty. The overall accuracy of diabetes mellitus diagnosis in the Taiwan NHI claims database is 74.6%. The diagnosis of acute ischemic stroke in the Taiwan NHI claims database has a positive predictive value of 88.4%. The diagnosis of acute myocardial infarction has a positive predictive value of 88%, and the positive predictive values for percutaneous coronary intervention, coronary stenting, and antiplatelet prescription in the Taiwan NHI inpatient claims database are 98%, 99%, and 98%, respectively. The patients’ records can be linked to the Taiwan National Death Registry by patients’ identification numbers to obtain the date and cause of death. To comply with Taiwanese privacy regulations, all personal identifiers are encrypted, and all data have to be analyzed anonymously. As a result, the Taiwan NHI claims database has been accepted as an important resource for clinical investigation. This study protocol was approved by the Institutional Review Board of the National Taiwan University Hospital Hsin-Chu Branch (protocol number 104-009-E), which waived requirement for informed consent.

Study Design and Cohort Definition

Dabigatran has been reimbursed by the Taiwan NHI program for stroke prevention in AF patients with an estimated glomerular filtration rate $\geq 30$ mL/min per $1.73$ m$^2$ since June 1, 2012. Although rivaroxaban 10 mg formula has been introduced into the Taiwan market for thromboprophylaxis in patients undergoing knee/hip arthroplasty since January 1, 2012, it was not reimbursed by the NHI program for stroke prevention in AF patients with an estimated glomerular filtration rate $\geq 30$ mL/min per $1.73$ m$^2$ until the launch of 15- and 20-mg formulas on February 1, 2013.

We used the Taiwan NHI claims database covering 2011 to 2014 and applied a retrospective cohort study design. All adult beneficiaries aged $\geq 20$ years with a diagnosis of atrial fibrillation and flutter (ICD-9-CM code 427.3) and prescriptions of study medications within the June 1, 2012 to May 31, 2014 enrollment period were identified. The date of the first prescription of dabigatran or rivaroxaban was operationally defined as the index date. In addition, subjects having diagnoses of deep vein thrombosis (ICD-9-CM codes 451.1, 451.2, 451.81, 453.4, 455.91, 671.3, 671.4), pulmonary embolism (ICD-9-CM codes 415.1, V12.51, 673.2), mitral stenosis (ICD-9-CM codes 746.5, 394.0, 394.2, 396.6, 396.1, 396.8), or procedures including valvular replacement, mitral commissurotomy, heart transplantation, or extracorporeal circulatory support within the 6-month period prior to the index date were excluded. Finally, patients receiving 2 study medications at the same time or having concomitant antiplatelet agents such as aspirin, clopidogrel, ticlopidine, or dipyridamole on the index date were excluded (Figure 1).

Exposures

In our preliminary results, 86% of patients in the dabigatran group received 110 mg; 75% of patients in the rivaroxaban group received 15 mg, 21% received 20 mg, and 4% received 10 mg. Therefore, patients receiving different doses of the same study medication (110 and 150 mg for dabigatran; 10, 15, and 20 mg for rivaroxaban) were pooled into 1 study group for their respective drugs.

Clinical Outcomes

The primary outcome of interest was all-cause death. Secondary outcomes included ischemic stroke (ICD-9-CM codes 433.x1, 434.x1, 435.9, 436, 437.1x, 437.9x), acute myocardial infarction (ICD-9-CM codes 410.x), arterial embolism/thrombosis (ICD-9-CM codes 444.x), intracranial hemorrhage (ICD-9-CM codes 430, 431, 432), and gastrointestinal hemorrhage (ICD-9-CM codes 456.0, 456.20, 530.21, 530.7, 530.82, 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, 534.6, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 537.83, 537.84, 569.85, 569.86, 562.02, 562.03, 562.12, 562.13, 569.3, 578, 586.81) needing transfusion.

Follow-Up

Patients were classified as dabigatran group or rivaroxaban group according to their initial prescription of study medications. All the clinical outcomes were evaluated from the inpatient records of the NHI claims database. All patients
were followed from their index date until death, switching to other oral anticoagulants, discontinuation of study medications (30-day treatment gap), or the end of the study at December 31, 2014, whichever came first.

**Baseline Characteristics and Potential Confounders**

We defined comorbidities as appearance of the specific diagnosis codes at least twice in the outpatient records or once in the inpatient records within the 6-month period prior to the index date and coded as binary variables. Comorbidities were evaluated according to Elixhauser comorbidities except for ischemic stroke (ICD-9-CM codes 433.x1, 434.x1, 435.9, 436, 437.1x, 437.9x), intracranial hemorrhage (ICD-9-CM codes 430, 431, 432), myocardial infarction (ICD-9-CM codes 410.x, 412.x), and vascular disease (ICD-9-CM codes 410.x, 412.x, 093.0, 437.3, 440.x, 441.x, 443.1-443.9, 447.1, 557.1, 557.9, V43.4). Only comorbidities with a prevalence of more than 0.5% were retained for further
Analysis. Medications that had ever been prescribed within the 6-month period prior to the index date were extracted from the NHI claims database. The list of medications included warfarin, aspirin, clopidogrel, ticlopidine, dipyriramole, digoxin, amiodarone, dronedarone, β-blockers, verapamil, diltiazem, dihydropyridine calcium-channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, loop diuretics, thiazide diuretics, spironolactone, statins, oral antidiabetic drugs, insulin, proton-pump inhibitors, H2 blockers, and nonsteroidal anti-inflammatory drugs. We also calculated the total number of physician visits and total number of hospitalizations within the 6-month period prior to the index date for each study subject. Finally, CHADS2 score14 and CHA2DS2-VASc score15 were evaluated according to baseline characteristics. In addition to sex and age, all the baseline characteristics mentioned above were included as potential confounders for further analysis (Table 1).

Statistical Analysis
Categorical data are presented in contingency tables, and continuous variables are presented as mean values with standard deviations or medians with interquartile ranges. With the χ2 test used for categorical variables and the 2-sample t test for normally distributed continuous variables, the baseline characteristics between the dabigatran group and the rivaroxaban group in the overall population were compared. We also used standardized difference to measure covariate balance, whereby an absolute standardized difference greater than 0.10 represents meaningful imbalance.16

A propensity score (PS) was derived using logistic regression to model the probability of receipt of rivaroxaban (or dabigatran) as a function of all the potential confounders listed in Table 1 (age was incorporated as categorical data) (Figure 2).17 Based on the PS, rivaroxaban users were matched to dabigatran users according to caliper measurements of <0.2 standard deviations of the logit of the PS at a 1:1 ratio to create a PS-matched population. The balance in baseline characteristics between the dabigatran group and the rivaroxaban group in the PS-matched population was assessed by the Mantel-Haenszel test for categorical variables and the paired t test for normally distributed continuous variables. Incidence rates of various clinical outcomes are presented as cases per 100 person-years among the overall population and the PS-matched population, respectively. To account for the correlated nature of the survival data in the PS-matched population, the marginal proportional hazards model developed by Lee et al18 was applied for estimation of the relative risks (hazard ratios, [HRs]) of various clinical outcomes between the dabigatran group and the rivaroxaban group among the PS-matched population as the primary analysis. Switching to other oral anticoagulants, discontinuation of study medications, or end of follow-up were treated as censoring. When we explored the relative hazards concerning clinical outcomes other than all-cause death, we treated death as a competing risk instead of as a censoring event.19 The cumulative incidences for various clinical outcomes among the PS-matched population were plotted using the Fine and Gray subdistribution method to estimate cumulative incidence function.19

To examine the robustness of the results of the primary analysis, we used the proportional hazards model with adjustment of the quintiles of the PS among the overall population20 as the secondary analysis. To explore the homogeneity of relative hazards of clinical outcomes between 2 study medications among patients with different background characteristics, 2 subgroup analyses stratified by previous experience of warfarin exposure and low (<3)/high (≥3) CHA2DS2-VASc score21 were conducted, with PS-matched analysis performed within each subgroup separately. P value for interaction was assessed by addition of an interaction term between the NOAC group and stratifying factors into the proportional hazards model of the secondary analysis. All analysis was performed using SAS software, version 9.4 (SAS Institute, Inc, Cary, NC). All P values reported are 2-sided, and the significance level was set at <0.05.

Results
Characteristics of Study Subjects in the Overall Population
A total of 15 234 subjects were included in our study with 10 625 incident users of dabigatran and 4609 incident users of rivaroxaban. The mean age was 75.2 ± 9.7 years (median 76, interquartile range 69-82), and the mean follow-up duration was 10.8 ± 7.8 months. Although there were numerical differences between dabigatran users and rivaroxaban users with respect to the distributions of sex, prior ischemic stroke, history of congestive heart failure, history of depression, previous warfarin exposure, clopidogrel, dronedarone, loop diuretics, spironolactone, proton-pump inhibitors, H2-blockers, nonsteroidal anti-inflammatory drugs, and the CHADS2 score, the 2 study groups had no statistically significant difference evaluated by the standardized differences except more prior ischemic strokes in dabigatran users (Table 1).

Characteristics of Study Subjects in the PS-Matched Population
After applying a PS-matching procedure, 4600 dabigatran users were matched to 4600 rivaroxaban users successfully. The PS-matching procedure further improved balance.
Table 1. Covariate Distribution by Treatment Groups in the Overall Population and the PS-Matched Population

|                                      | Overall Population | PS-Matched Population | P Value* | STD | STD |
|--------------------------------------|--------------------|-----------------------|----------|-----|-----|
|                                      | Dabigatran N=10 625 (%) | Rivaroxaban N=4 609 (%) |          |     |     |
|                                      |                     |                       |          |     |     |
| Sex                                  | Female              | 43.3                  | 0.022    | 0.040 | 45.4 | 45.2 | 0.86 | 0.003 |
|                                      | Age, y              | Mean (SD)             | 75.1 (9.7) | 0.10 | 75.4 (9.5) | 0.037 | 75.4 (9.6) | 0.95 | 0.001 |
|                                      | Median (IQR)        | 76 (69-82)            | 76 (70-82) |     | 76 (70-82) |     |     |     |
|                                      | Age group, y        | <65                   | 12.9     | 0.27 | 12.0 | 0.027 | 11.6 | 0.067 | 0.013 |
|                                      |                     | 65 to 74              | 29.8     | 0.15 | 30.5 | 0.004 | 30.1 | 0.03 | 0.009 |
|                                      |                     | ≥75                   | 57.3     | 0.04 | 57.6 | 0.004 | 58.4 | 0.017 |
|                                      | Ischemic stroke     | 23.8                  | <0.001   | 0.106 | 19.1 | 0.004 | 19.5 | 0.60 | 0.009 |
|                                      |                      |                       |          |     |     |
|                                      | Myocardial infarction | 1.1                   | 0.34     | 0.017 | 1.4 | 0.84 | 1.2 | 0.65 | 0.009 |
|                                      | Vascular disease    | 3.5                   | 0.84     | 0.003 | 3.3 | 0.79 | 3.4 | 0.73 | 0.007 |
|                                      | Congestive heart failure | 24.4               | 0.010    | 0.046 | 26.1 | 0.79 | 26.3 | 0.79 | 0.005 |
|                                      | Valvular heart disease | 9.6                 | 0.21     | 0.022 | 10.0 | 0.73 | 10.3 | 0.73 | 0.007 |
|                                      | Pulmonary circulation disorders | 0.6             | 0.41     | 0.014 | 0.7 | 1.00 | 0.7 | 1.00 | 0.000 |
|                                      | Hypertension        | 49.0                  | 0.41     | 0.014 | 49.4 | 0.76 | 49.7 | 0.76 | 0.006 |
|                                      | Chronic pulmonary disease | 14.2               | 0.27     | 0.019 | 15.2 | 0.72 | 14.9 | 0.72 | 0.007 |
|                                      | Diabetes mellitus   | 20.2                  | 1.00     | 0.000 | 20.4 | 0.77 | 20.2 | 0.77 | 0.006 |
|                                      | Hypothyroidism      | 2.0                   | 0.21     | 0.023 | 1.6 | 0.74 | 1.7 | 0.74 | 0.007 |
|                                      | Renal failure       | 4.7                   | 0.89     | 0.002 | 4.8 | 0.80 | 4.7 | 0.80 | 0.005 |
|                                      | Liver disease       | 1.9                   | 0.62     | 0.009 | 2.2 | 0.56 | 2.0 | 0.56 | 0.012 |
|                                      | Peptic ulcer disease excluding bleeding | 8.4       | 0.57     | 0.010 | 8.2 | 0.97 | 8.2 | 0.97 | 0.001 |
|                                      | Solid tumor without metastasis | 5.7          | 0.89     | 0.002 | 5.3 | 0.41 | 5.7 | 0.41 | 0.017 |
|                                      | Rheumatoid arthritis/collagen vascular diseases | 1.8      | 0.37     | 0.016 | 2.2 | 0.72 | 2.0 | 0.72 | 0.008 |
|                                      | Fluid and electrolyte disorders | 2.5       | 0.89     | 0.003 | 2.5 | 0.79 | 2.5 | 0.79 | 0.006 |
|                                      | Depression          | 2.6                   | 0.003    | 0.05  | 3.7 | 0.48 | 3.4 | 0.48 | 0.014 |
|                                      | Medications used previously Warfarin | 51.0     | 46.3     | <0.001 | 0.095 | 46.2 | 46.3 | 0.94 | 0.001 |
|                                      | Aspirin             | 42.8                  | 44.3     | 0.09  | 0.03 | 44.3 | 44.3 | 1.00 | 0.000 |
|                                      | Clopidogrel         | 8.1                   | 9.5      | 0.004 | 0.05 | 9.2 | 9.5 | 0.61 | 0.010 |
|                                      | Ticlopidine         | 2.6                   | 2.7      | 0.77  | 0.005 | 2.6 | 2.7 | 0.85 | 0.004 |
|                                      | Dipyridamole        | 8.2                   | 9.0      | 0.10  | 0.029 | 8.6 | 9.0 | 0.55 | 0.012 |
|                                      | Digoxin             | 26.3                  | 25.0     | 0.11  | 0.028 | 24.8 | 25.0 | 0.75 | 0.007 |
|                                      | Amiodarone          | 17.4                  | 18.7     | 0.05  | 0.034 | 19.0 | 18.7 | 0.70 | 0.008 |
|                                      | Dronedarone         | 2.4                   | 4.2      | <0.001 | 0.098 | 4.0 | 4.2 | 0.61 | 0.008 |
|                                      | β-Blockers          | 52.3                  | 53.9     | 0.06  | 0.033 | 53.7 | 53.8 | 0.85 | 0.004 |
|                                      | Verapamil           | 3.5                   | 4.0      | 0.20  | 0.022 | 3.5 | 3.9 | 0.28 | 0.023 |
|                                      | Diltiazem           | 20.4                  | 20.2     | 0.74  | 0.006 | 19.9 | 20.2 | 0.69 | 0.008 |

Continued
of the observed characteristics between dabigatran users and rivaroxaban users (Table 1). The mean age was 75.4±9.6 years (median 76, interquartile range 70-82), and the mean follow-up duration was 10.3±7.3 months among the PS-matched population.

Primary Analysis
Among the overall population, the incidence rates of all-cause death were 3.59/100 person-years in dabigatran users and 5.73/100 person-years in rivaroxaban users (Tables 2 and 3). These figures did not change substantially after application of the PS-matching procedure (3.86/100 person-years in dabigatran users and 5.72/100 person-years in rivaroxaban users among the PS-matched population). Among the PS-matched population, the risk of all-cause death in rivaroxaban users was higher than that in dabigatran users (HR 1.44, 95%CI 1.17-1.78). Rivaroxaban users also possessed a higher risk of gastrointestinal hemorrhage needing transfusion than dabigatran users (1.42/100 person-years in dabigatran users and 2.38/100 person-years in rivaroxaban users, HR 1.41, 95%CI 1.02-1.95). The risks of ischemic stroke, acute myocardial infarction, arterial embolism/thrombosis, and intracranial hemorrhage were similar between the 2 study groups among the PS-matched population (Table 3). The cumulative incidences for various clinical outcomes are depicted in Figure 3.

Secondary Analysis
Among the overall population, the risk of all-cause death in rivaroxaban users remained significantly higher than that in dabigatran users (HR 1.47, 95%CI 1.23-1.75) with adjustment of the quintiles of the PS. Also, we found no difference in the risks of ischemic stroke, acute myocardial infarction, arterial embolism/thrombosis, and intracranial hemorrhage between the 2 study groups. In contrast with the primary analysis, the difference in risk of gastrointestinal hemorrhage needing transfusion between the 2 study groups diminished (HR 1.20, 95%CI 0.92-1.56) in the secondary analysis (Table 3).

Subgroup Analyses
The main findings did not change substantially in the subgroup analysis concerning previous experience of warfarin...
exposure (Figure 4). In the subgroup analysis stratified by different CHA2DS2-VASc score (<3/≥3), the only significant interaction found was for the risk of acute myocardial infarction (Figure 5). The rivaroxaban group possessed a lower risk for acute myocardial infarction (HR 0.15, 95%CI 0.02-1.20) in patients with low CHA2DS2-VASc score (<3) but a higher risk of acute myocardial infarction (HR 1.30, 95%CI 0.68-2.50) in patients with high CHA2DS2-VASc score (≥3) (P for interaction=0.039).

Discussion

Through the nationwide insurance claims database in Taiwan, we collected clinical data from more than 15 000 ethnic Chinese patients with incident usage of dabigatran and rivaroxaban for AF. We found that rivaroxaban users were associated with a significantly higher risk of all-cause death than dabigatran users. The risk of gastrointestinal hemorrhage needing transfusion was moderately higher in rivaroxaban users compared with dabigatran users. The 2 study medications had similar risks of ischemic stroke, acute myocardial infarction, arterial embolism/thrombosis, and intracranial hemorrhage.

Dabigatran is a direct thrombin inhibitor. In the Randomized Evaluation of Long-Term Anticoagulation Therapy study, 18 113 AF patients with a mean age of 71 years and a CHADS2 score of 2.1 were randomly assigned to receive dabigatran or warfarin therapy. After a median follow-up of 2.0 years, the relative risk of stroke/systemic embolism was reduced by 34% in the dabigatran 150-mg group in comparison with the warfarin group. The relative risk of hemorrhagic stroke was reduced by 69% in the dabigatran 110-mg group and 74% in the dabigatran 150-mg group. Rivaroxaban is a direct factor Xa inhibitor. The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) enrolled 14 264 patients with non-valvular AF. The median age was 73 years, and mean CHADS2 score was 3.5. After a median follow-up period of 707 days, rivaroxaban was shown to be not inferior to warfarin concerning prevention of stroke or systemic embolism but to have a reduced risk of intracranial hemorrhage than the warfarin group. Lip and colleagues have conducted an indirect comparison between dabigatran and rivaroxaban using data from the Randomized Evaluation of Long-Term Anticoagulation Therapy study and the ROCKET-AF. They found that dabigatran 150 mg was associated with a significantly lower risk of stroke and systemic embolism compared with rivaroxaban, as well as less hemorrhagic stroke. However, both 110- and 150-mg doses of dabigatran were associated with an increase in the risk of myocardial infarction compared to rivaroxaban. Another indirect comparison study extracting patients with a CHADS2 score ≥3 from the Randomized Evaluation of Long-Term Anticoagulation Therapy study and the ROCKET-AF showed that dabigatran 150 mg and rivaroxaban 20 mg resulted in statistically similar rates of stroke and systemic

Table 2. Causes of Death for the Overall Study Population Provided by the Taiwan National Death Registry

| Category* | Total | Dabigatran | Rivaroxaban |
|-----------|-------|------------|-------------|
|           | n (%) | n (%)      | n (%)       |
| Total     | 572 (100.0) | 363 (100.0) | 209 (100.0) |
| Circulatory system diseases | 259 (45.3) | 161 (44.4) | 98 (46.9) |
| Respiratory system diseases | 80 (14.0) | 43 (11.8) | 37 (17.7) |
| Cancer    | 72 (12.6) | 47 (12.9) | 25 (12.0) |
| Endocrine system diseases | 43 (7.5) | 29 (8.0) | 14 (6.7) |
| Infectious diseases | 27 (4.7) | 19 (5.2) | 8 (3.8) |
| Genitourinary system diseases | 22 (3.8) | 16 (4.4) | 6 (2.9) |
| Digestive system diseases | 20 (3.5) | 15 (4.1) | 5 (2.4) |
| External causes | 20 (3.5) | 15 (4.1) | 5 (2.4) |
| Ill-defined conditions | 13 (2.3) | 6 (1.7) | 7 (3.3) |
| Musculoskeletal system diseases | 6 (1.0) | ...† | ...† |
| Nervous system diseases | 6 (1.0) | ...† | ...† |
| Others | 4 (0.6) | 4 (0.6) | 0 (0.0) |

*Based on the Statistics Canada (http://www.statcan.gc.ca/pub/82-003-x/2009004/article/11034/Tables/tbla-eng.htm). 
†In accordance with privacy regulations in Taiwan, the exact number of patients is not specified if it is less than 3.
Although our subgroup analysis suggested heterogeneity concerning risk of acute myocardial infarction between the dabigatran group and the rivaroxaban group among patients with different CHA2DS2-VASc scores, the results should be interpreted with caution. Because of the small number of events in patients with low CHA2DS2-VASc scores and a wide confidence interval of the HR, the results could just be a play of chance.

A new-user cohort study from Danish registries with a median follow-up time of 1.08 years found that the stroke rate was similar between the rivaroxaban group and the dabigatran group. Nevertheless, the rivaroxaban 15-mg group (N=776) was associated with a significantly higher risk of all-cause death (HR 1.43, 95%CI 1.13-1.81) and an insignificant trend toward higher bleeding rate (HR 1.28, 95%CI 0.82-2.01) in comparison with the dabigatran 110-mg group (N=3588).23 Our findings complemented the Danish study through a much larger Asian population and illustrated for the first time that the difference in death rate between dabigatran and rivaroxaban was similar across patients with different experience of warfarin exposure and patients with different CHA2DS2-VASc scores (<3/≥3). Adequately powered, randomized, controlled trials are necessary to provide conclusive results regarding the difference in clinical safety between dabigatran and rivaroxaban. Besides, further research is also needed to clarify whether these findings represent a class effect between a direct thrombin inhibitor and a direct factor Xa inhibitor or not.

Graham and colleagues enrolled 118 891 patients with nonvalvular AF from the US fee-for-service Medicare system to conduct a retrospective new-user cohort study. Their data showed that treatment with rivaroxaban 20 mg once daily was associated with statistically significant increases in intracranial hemorrhage and major extracranial bleeding, including major gastrointestinal bleeding, compared with dabigatran 150 mg twice daily.24 Chan and colleagues collected 3425 patients with low-dose rivaroxaban (10-15 mg once daily) and 5301 patients with low-dose dabigatran (110 mg twice daily) from the Taiwan NHI Research Database. They found that rivaroxaban carried a significantly higher risk for hospitalization for gastrointestinal bleeding than dabigatran, but the difference vanished with on-treatment analysis.25 In our study, rivaroxaban users were associated with a higher risk of gastrointestinal hemorrhage needing transfusion than dabigatran users in the primary analysis, but this difference diminished in the secondary analysis.

**Table 3.** Incidences and Relative Risks of Various Clinical Outcomes Between Study Groups Among the Overall Population and the PS-Matched Population

|                          | Overall Population | PS-Matched Population |
|--------------------------|--------------------|-----------------------|
|                          | Dabigatran (N=10 625) | Rivaroxaban (N=4609) | Dabigatran (N=4600) | Rivaroxaban (N=4600) |
| All-cause death          | PY | Event Number | IR* | PY | Event Number | IR* | aHR† | 95% CI          |
|                          | 10 116 | 363 | 3.59 | 3645 | 209 | 5.73 | 1.47 | 1.23 to 1.75 |
| Ischemic stroke          | 9944 | 310 | 3.12 | 3602 | 115 | 3.19 | 0.97 | 0.78 to 1.20 |
| Acute myocardial infarction | 10 091 | 48 | 0.48 | 3641 | 22 | 0.6 | 1.17 | 0.71 to 1.94 |
| Arterial embolism/thrombosis | 10 083 | 64 | 0.63 | 3637 | 28 | 0.77 | 1.09 | 0.69 to 1.72 |
| Intracranial hemorrhage  | 10 065 | 51 | 0.51 | 3630 | 25 | 0.69 | 1.34 | 0.83 to 2.16 |
| Gastrointestinal hemorrhage | 9957 | 176 | 1.77 | 3580 | 85 | 2.37 | 1.20 | 0.92 to 1.56 |
|                          | PY | Event Number | IR* | PY | Event Number | IR* | aHR‡ | 95% CI          |
| All-cause death          | 4254 | 164 | 3.86 | 3638 | 208 | 5.72 | 1.44 | 1.17 to 1.78 |
| Ischemic stroke          | 4182 | 130 | 3.11 | 3595 | 115 | 3.2 | 0.95 | 0.74 to 1.23 |
| Acute myocardial infarction | 4241 | 22 | 0.52 | 3634 | 22 | 0.61 | 1.11 | 0.61 to 2.01 |
| Arterial embolism/thrombosis | 4244 | 22 | 0.52 | 3630 | 28 | 0.77 | 1.47 | 0.83 to 2.61 |
| Intracranial hemorrhage  | 4235 | 22 | 0.52 | 3623 | 25 | 0.69 | 1.26 | 0.71 to 2.25 |
| Gastrointestinal hemorrhage | 4194 | 68 | 1.62 | 3574 | 85 | 2.38 | 1.41 | 1.02 to 1.95 |

aHR indicates adjusted hazard ratio; CI, confidence interval; IR, incidence rate; PS, propensity score; PY, person-year.
*Per 100 person-years.
†Using the proportional hazards model with adjustment of the quintiles of the propensity score as the secondary analysis.
‡Using the marginal proportional hazards model as the primary analysis.
analysis. Our results were derived from a more clinically relevant context in contrast with the very short duration of follow-up in these 2 studies (mean duration of follow-up 108-111 days in the US study and only using database from February 1, 2013 to December 31, 2013 in the Taiwan study).

**Study Limitations**

Several limitations of our study have to be acknowledged. First, most of our study subjects received relatively lower dosages of anticoagulants, such as 110 mg of dabigatran and 15 mg of rivaroxaban. Therefore, different dosages of

Figure 3. Cumulative incidences of clinical outcomes in the propensity score–matched population: (A) all-cause death, (B) ischemic stroke, (C) acute myocardial infarction, (D) arterial embolism/thrombosis, (E) intracranial hemorrhage, and (F) gastrointestinal hemorrhage needing transfusion.

Figure 4. Forest plot summarizing results of the subgroup analysis concerning previous experience with warfarin exposure. HR indicates hazard ratio.
individual drugs could not be analyzed separately due to inadequate sample size. In the J-ROCKET AF study conducted in Japan, 15 mg once-daily rivaroxaban (10 mg daily in patients with a creatinine clearance of 30-49 mL/min) was shown to be not inferior to warfarin in patients with nonvalvular AF. Second, the relatively lower dosage of NOACs used in Taiwanese reflects the impact of the J-ROCKET AF study on Asian populations. Second, this study was a retrospective design with data derived from insurance claims data; thus, certain essential laboratory data such as prothrombin time, international normalized ratio, and creatinine clearance could not be obtained from the database, and there was a concern about lack of standardized data collection during construction of the database. Third, the HAS-BLED score (hypertension, abnormal renal/liver function, stroke, bleeding history of predisposition, labile international normalized ratio, elderly >65 years, and drugs/alcohol taken concomitantly) can provide a practical tool to assess the bleeding risk in patients with AF. Because labile international normalized ratio and alcohol use could not be obtained from the NHI claims database, we did not calculate the full HAS-BLED score but included all of its other components (hypertension, renal failure/liver disease, prior ischemic stroke, intracranial hemorrhage, peptic ulcer, age, and exposures to major drugs) into our list of potential confounders during construction of the PS. Fourth, we evaluated baseline characteristics of study subjects within the 6-month period prior to the index date. Misclassification of baseline characteristics such as previous experience of warfarin exposure could not be ruled out. Fifth, because this study was derived from an Asian population, we recommend caution in extrapolating these findings to Western populations. Finally, apixaban was not reimbursed by the Taiwan NHI program until June 1, 2014 and was not included in this study owing to inadequate sample size and short follow-up duration.

Conclusions

Based on a large Asian population, our study illustrated that rivaroxaban therapy was associated with a statistically significant increase in all-cause death compared with dabigatran therapy among patients with AF. We also found a modest increase in gastrointestinal hemorrhage needing transfusion in patients receiving rivaroxaban. No statistically significant difference could be found in the risks of ischemic stroke, acute myocardial infarction, arterial embolism/thrombosis, and intracranial hemorrhage between dabigatran and rivaroxaban groups. These findings need to be confirmed by clinical trials.

Acknowledgments

All the data used in this study were released and approved by the Health and Welfare Data Science Center, Ministry of Health and Welfare, Executive Yuan, Taiwan. We thank professor Por-Jau Huang of the Far Eastern Polyclinic, Taipei, Taiwan, for his help in the revision of this manuscript.
Sources of Funding

This work was supported by grants from the National Taiwan University Hospital, Hsin-Chu Branch (105-HCH016 and 105-HCH003). The funding source did not have any input in study design, data analysis, or interpretation of findings or in the decision to submit the manuscript for publication.

Disclosures

Dr Lai reports receiving lecture fees from AstraZeneca, Bayer, Pfizer, Novartis, Actelion, Excelsior, Sanofi-Aventis, Boehringer Ingelheim, Tanabe, Daiichi-Sankyo, and MSD. The other authors report no relationships that could be construed as a conflict of interest.

References

1. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P, ESC Committee for Practice Guidelines (CPG). 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J. 2012;33:2719–2747.

2. Lip GY, Hart RG, Conway DS. Antithrombotic therapy for atrial fibrillation. BMJ. 2002;325:1022–1025.

3. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekwok MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS Guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014;64:e1–e76.

4. Connolly SJ, Ezekwok MD, Yusuf S, Elkemob J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themele A, Harrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis B, Darius H, Diener H, Joyner CD, Wallentin L, RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139–1151.

5. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Polsini JF, Berkowitz SD, Fox KA, Calif RF, ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883–891.

6. Lin CC, Lai MS, Syu CY, Chang SC, Tseng FY. Accuracy of diabetes diagnosis in health insurance claims data in Taiwan. J Formos Med Assoc. 2005;104:157–163.

7. Hsieh CY, Chen CH, Li CY, Lai ML. Validating the diagnosis of acute ischemic stroke in a National Health Insurance claims database. J Formos Med Assoc. 2015;114:254–259.

8. Cheng CL, Kao YH, Lin SJ, Lee CH, Lai ML. Validation of the National Health Insurance Research Database with ischemic stroke cases in Taiwan. Pharmacoepidemiol Drug Saf. 2011;20:236–242.

9. Cheng CL, Lee CH, Chen PS, Li YH, Lin SJ, Yang YH. Validation of acute myocardial infarction cases in the National Health Insurance Research Database in Taiwan. J Epidemiol. 2014;24:500–507.

10. Lu TH, Lee MC, Chou MC. Accuracy of cause-of-death coding in Taiwan: types of miscoding and effects on mortality statistics. Int J Epidemiol. 2000;29:336–343.

11. Hsing AW, Ioannidis JP. Nationwide population science: lessons from the Taiwan National Health Insurance Research Database. JAMA Intern Med. 2015;175:1527–1529.

12. Ross JS. Global drug safety insights from Taiwan. JAMA Intern Med. 2015;175:1847.

13. Quan H, Sundararajan V, Halfon F, Fong A, Burnand B, Luthje JC, Saunders LD, Beck CA, Feasby TE, Ghali WA. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005;43:1130–1139.

14. Gage BF, Waterman AD, Shannon W, Boehringer, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA. 2001;285:2864–2870.

15. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. Chest. 2010;137:263–272.

16. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. Commun Stat Simul Comput. 2009;38:1228–1234.

17. D’Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med. 1998;17:2265–2281.

18. Lee EW, Wei LJ, Amato DA. Cox-type regression for large numbers of small groups of correlated failure time observations. In: Klein JP, Goel PK, eds. Survival Analysis: State of the Art. Dordrecht, The Netherlands: Kluwer Academic Publishers; 1992:237–247.

19. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94:496–509.

20. Lin TT, Chan AK, Chen HM, Lai CL, Lai MS. Class effect of beta-blockers in survivors of ST-elevation myocardial infarction: a nationwide cohort study using an insurance claims database. Sci Rep. 2015;5:13692.

21. Schneeweiss S, Gagne JI, Patrick AR, Choudhry NK, Avorn J. Comparative efficacy and safety of new oral anticoagulants in patients with atrial fibrillation. Circ Cardiovasc Qual Outcomes. 2012;5:480–486.

22. Lip GY, Larsen TB, Skjeth F, Rasmussen LH. Indirect comparisons of new oral anticoagulant drugs for efficacy and safety when used for stroke prevention in atrial fibrillation. J Am Coll Cardiol. 2012;60:738–746.

23. Gorst-Rasmussen A, Lip GY, Bjergregaard Larsen T. Rivaroxaban versus warfarin and dabigatran in atrial fibrillation: comparative effectiveness and safety in Danish routine care. Pharmacoeconom Drug Saf. 2016;25:1236–1244.

24. Graham DJ, Reichman ME, Wemecke M, Hsuheh YH, Iem R, Southworth MR, Wei Y, Liao J, Goulding MR, Mott K, Cliffarge Y, MacCundy TE, Worrall C, Kelman JA. Stroke, bleeding, and mortality risks in elderly Medicare beneficiaries treated with dabigatran or rivaroxaban for nonvalvular atrial fibrillation. JAMA Intern Med. 2016;176:1662–1671.

25. Chan YH, Kuo CT, Yeh YH, Chang SH, Wu LS, Lee HF, Tu HT, See LC. Thromboembolic, bleeding, and mortality risks of rivaroxaban and dabigatran in Asians with nonvalvular atrial fibrillation. J Am Coll Cardiol. 2016;110:1389–1401.

26. Hori M, Matsumoto M, Tanahashi N, Momomura S, Uchiyama S, Goto S, Izumi T, Koresuto S, Kajikawa M, Kato M, Ueda H, Iwamoto K, Tajiri M; J-ROCKET AF Committee and Investigators. Dabigatran versus warfarin in Japanese patients with atrial fibrillation—the J-ROCKET AF study. Circ J. 2012;76:2104–2111.

27. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010;138:1093–1100.