ORIGINAL RESEARCH

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

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***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

Atrial fibrillation (AF) is a common cardiac arrhythmia that increases in prevalence with aging. Nonvalvular AF is associated with a 5-fold risk of ischemic stroke and a 3-fold incidence of congestive heart failure.[1] It is well established that vitamin K antagonist therapy confers thromboprophylaxis in patients with AF. Adjusted dose warfarin can reduce the risk of ischemic stroke by about 60%.[2] Despite the evidence for the efficacy of warfarin, many physicians are reluctant to prescribe warfarin therapy for patients with AF due to fears of bleeding complications and logistic problems of prothrombin time international normalized ratio monitoring.[2]

Several non–vitamin K antagonist oral anticoagulants (NOACs) have been developed for thromboprophylaxis of AF. Dabigatran is the first NOAC approved by the US Food and Drug Administration (October 19, 2010) for prevention of ischemic stroke and systemic embolism in patients with nonvalvular AF and is a direct thrombin inhibitor.[3] Rivaroxaban, a direct factor Xa inhibitor, is the second NOAC approved by the US Food and Drug Administration (November 4, 2011) for reduction of risk of stroke and systemic embolism in patients with nonvalvular AF.[3] Both dabigatran and rivaroxaban have been shown to be at least not inferior to warfarin concerning efficacy in prevention of stroke and systemic embolism with a significantly lower risk of intracranial hemorrhage in large-scale randomized controlled trials.[4,5] However, a head-to-head comparison between dabigatran and rivaroxaban has never been conducted with large-scale clinical trials.

The aim of this study was to provide real-world data concerning the comparative effectiveness and clinical safety

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Received January 9, 2017; accepted March 15, 2017.

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%.[6] The diagnosis of acute ischemic stroke in the Taiwan NHI claims database has a positive predictive value of 88.4%.[7,8] 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.[9] The patients' records can be linked to the Taiwan National Death Registry by patients' identification numbers to obtain the date and cause of death.[10] 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.[11,12] 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 ≥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 ≥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 ≥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, 459.1, 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, 396.0, 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 dypyridamole 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, 568.81) 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

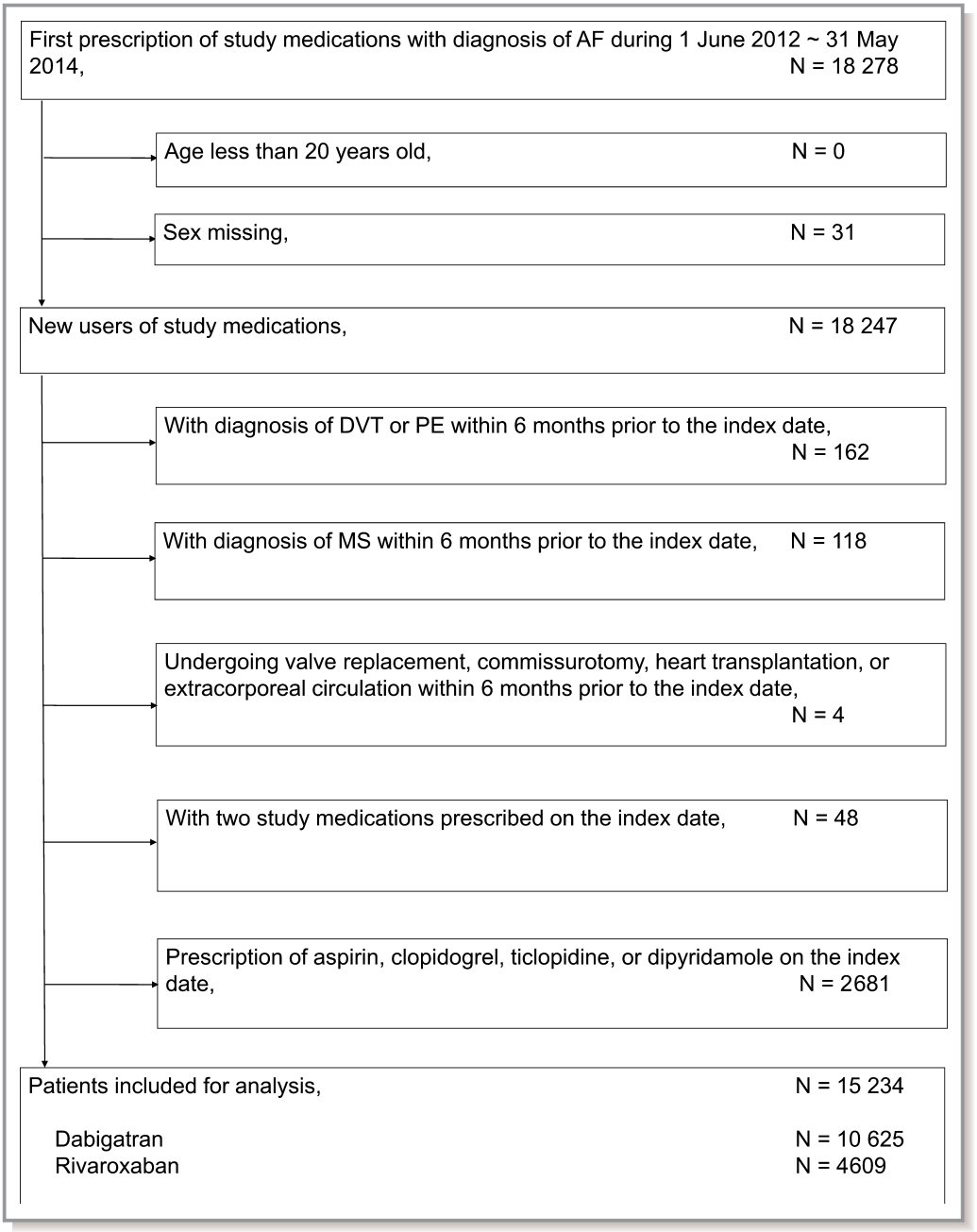

Figure 1. Patient flow diagram. AF indicates atrial fibrillation; DVT, deep vein thrombosis; MS, mitral stenosis; PE, pulmonary embolism.

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[13] 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, dipyridamole, 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, H_2 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, $CHADS_2$ score[14] and CHA_2DS_2-VASc score[15] 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 χ^2 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 al[18] 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 population[20] 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) CHA_2DS_2-VASc score[21] 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, H_2-blockers, nonsteroidal anti-inflammatory drugs, and the $CHADS_2$ 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			
	Dabigatran	Rivaroxaban			Dabigatran	Rivaroxaban		
	N=10 625 (%)	N=4609 (%)	*P* Value*	STD	N=4600 (%)	N=4600 (%)	*P* Value†	STD
Sex								
Female	43.3	45.3	0.022	0.040	45.4	45.2	0.86	0.003
Age, y								
Mean (SD)	75.1 (9.7)	75.4 (9.6)	0.10	0.037	75.4 (9.5)	75.4 (9.6)	0.95	0.001
Median (IQR)	76 (69-82)	76 (70-82)			76 (70-82)	76 (70-82)		
Age group, y								
<65	12.9	12.0	0.27	0.027	11.6	12.0	0.67	0.013
65 to 74	29.8	30.5		0.015	30.1	30.5		0.009
≥75	57.3	57.6		0.004	58.4	57.5		0.017
Ischemic stroke	23.8	19.4	<0.001	0.106	19.1	19.5	0.60	0.009
Intracranial hemorrhage	1.1	1.2	0.82	0.004	1.1	1.2	0.84	0.004
Myocardial infarction	1.1	1.3	0.34	0.017	1.4	1.3	0.65	0.009
Vascular disease	3.5	3.4	0.84	0.003	3.3	3.4	0.82	0.005
Congestive heart failure	24.4	26.4	0.010	0.046	26.1	26.3	0.79	0.005
Valvular heart disease	9.6	10.3	0.21	0.022	10.0	10.3	0.73	0.007
Pulmonary circulation disorders	0.6	0.7	0.41	0.014	0.7	0.7	1.00	0.000
Hypertension	49.0	49.7	0.41	0.014	49.4	49.7	0.76	0.006
Chronic pulmonary disease	14.2	14.9	0.27	0.019	15.2	14.9	0.72	0.007
Diabetes mellitus	20.2	20.2	1.00	0.000	20.4	20.2	0.77	0.006
Hypothyroidism	2.0	1.7	0.21	0.023	1.6	1.7	0.74	0.007
Renal failure	4.7	4.7	0.89	0.002	4.8	4.7	0.80	0.005
Liver disease	1.9	2.0	0.62	0.009	2.2	2.0	0.56	0.012
Peptic ulcer disease excluding bleeding	8.4	8.2	0.57	0.010	8.2	8.2	0.97	0.001
Solid tumor without metastasis	5.7	5.7	0.89	0.002	5.3	5.7	0.41	0.017
Rheumatoid arthritis/collagen vascular diseases	1.8	2.1	0.37	0.016	2.2	2.0	0.72	0.008
Fluid and electrolyte disorders	2.5	2.5	0.89	0.003	2.5	2.5	0.79	0.006
Depression	2.6	3.5	0.003	0.05	3.7	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

Table 1. Continued

	Overall Population				PS-Matched Population			
	Dabigatran	Rivaroxaban			Dabigatran	Rivaroxaban		
	N=10 625 (%)	N=4609 (%)	*P* Value*	STD	N=4600 (%)	N=4600 (%)	*P* Value†	STD
Dihydropyridine CCBs	34.7	33.5	0.13	0.027	33.3	33.4	0.91	0.002
ACEIs	14.4	13.6	0.19	0.023	13.8	13.5	0.69	0.008
ARBs	53.1	52.2	0.33	0.017	51.4	52.2	0.44	0.016
Loop diuretics	30.1	33.9	<0.001	0.083	33.3	33.8	0.55	0.012
Thiazides	7.1	6.5	0.22	0.022	6.5	6.5	1.00	0.000
Spironolactone	12.3	14.7	<0.001	0.071	14.6	14.6	0.97	0.001
Statins	28.1	28.2	0.88	0.003	27.7	28.2	0.59	0.011
OADs	23.8	23.6	0.75	0.006	23.0	23.6	0.52	0.013
Insulin	6.6	6.9	0.44	0.014	6.9	6.9	1.00	0.000
PPIs	11.0	12.3	0.021	0.04	12.1	12.3	0.84	0.004
H_2-blockers	29.0	30.6	0.042	0.036	30.5	30.6	0.89	0.003
NSAIDs	55.5	58.0	0.005	0.049	57.6	57.9	0.73	0.007
Ever hospitalized	29.1	30.0	0.30	0.018	29.8	29.8	1.00	0.000
	Mean (SD)	Mean (SD)			Mean (SD)	Mean (SD)		
Number of physicians visits	19.0 (12.4)	19.1 (12.4)	0.41	0.01	19.4 (12.6)	19.1 (12.4)	0.27	0.023
Number of hospitalizations	0.4 (0.8)	0.4 (0.8)	0.17	0.04	0.4 (0.8)	0.4 (0.8)	0.24	0.025
$CHADS_2$	1.9 (1.3)	1.9 (1.3)	0.004	0.048	1.9 (1.2)	1.9 (1.3)	0.96	0.001
CHA_2DS_2-VASc	3.3 (1.5)	3.3 (1.5)	0.22	0.022	3.3 (1.5)	3.3 (1.5)	0.94	0.001

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; OAD, oral antidiabetic drug; PPI, proton pump inhibitor; PS, propensity score; SD, standard deviation; STD, standardized difference.
*The χ^2 test for categorical variables and the 2-sample t test for continuous variables.
†The Mantel-Haenszel test for categorical variables and the paired t test for continuous variables.

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 (1.62/100 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

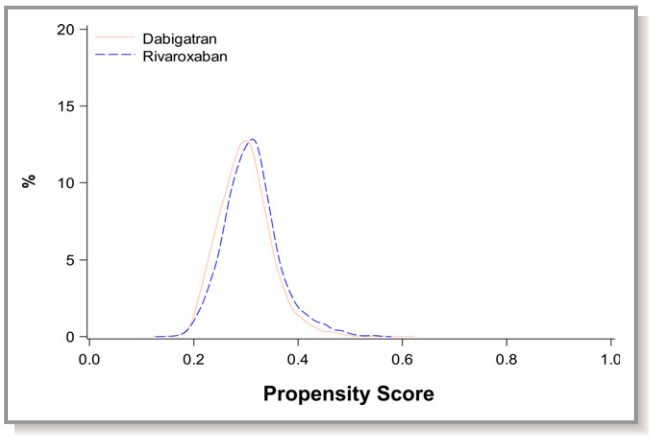

Figure 2. Estimated density of the propensity scores concerning the probability of receiving rivaroxaban among new users of dabigatran and rivaroxaban.

exposure (Figure 4). In the subgroup analysis stratified by different CHA_2DS_2-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 CHA_2DS_2-VASc score (<3) but a higher risk of acute myocardial infarction (HR 1.30, 95%CI 0.68-2.50) in patients with high CHA_2DS_2-VASc score (≥3) (*P* for interaction=0.039).

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

Category*	Total n (%)	Dabigatran n (%)	Rivaroxaban 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.

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 $CHADS_2$ 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.[4] 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 nonvalvular AF. The median age was 73 years, and mean $CHADS_2$ 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.[5]

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.[22] Another indirect comparison study extracting patients with a $CHADS_2$ 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 3. Incidences and Relative Risks of Various Clinical Outcomes Between Study Groups Among the Overall Population and the PS-Matched Population

	Dabigatran			Rivaroxaban				
	N=10 625			N=4609				
Overall Population	PY	Event Number	IR*	PY	Event Number	IR*	aHR†	95% CI
All-cause death	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
	Dabigatran			Rivaroxaban				
	N=4600			N=4600				
PS-Matched Population	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.

embolism.[21] Although our subgroup analysis suggested heterogeneity concerning risk of acute myocardial infarction between the dabigatran group and the rivaroxaban group among patients with different CHA_2DS_2-VASc scores, the results should be interpreted with caution. Because of the small number of events in patients with low CHA_2DS_2-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 CHA_2DS_2-VASc scores ($<3/\geq 3$). 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

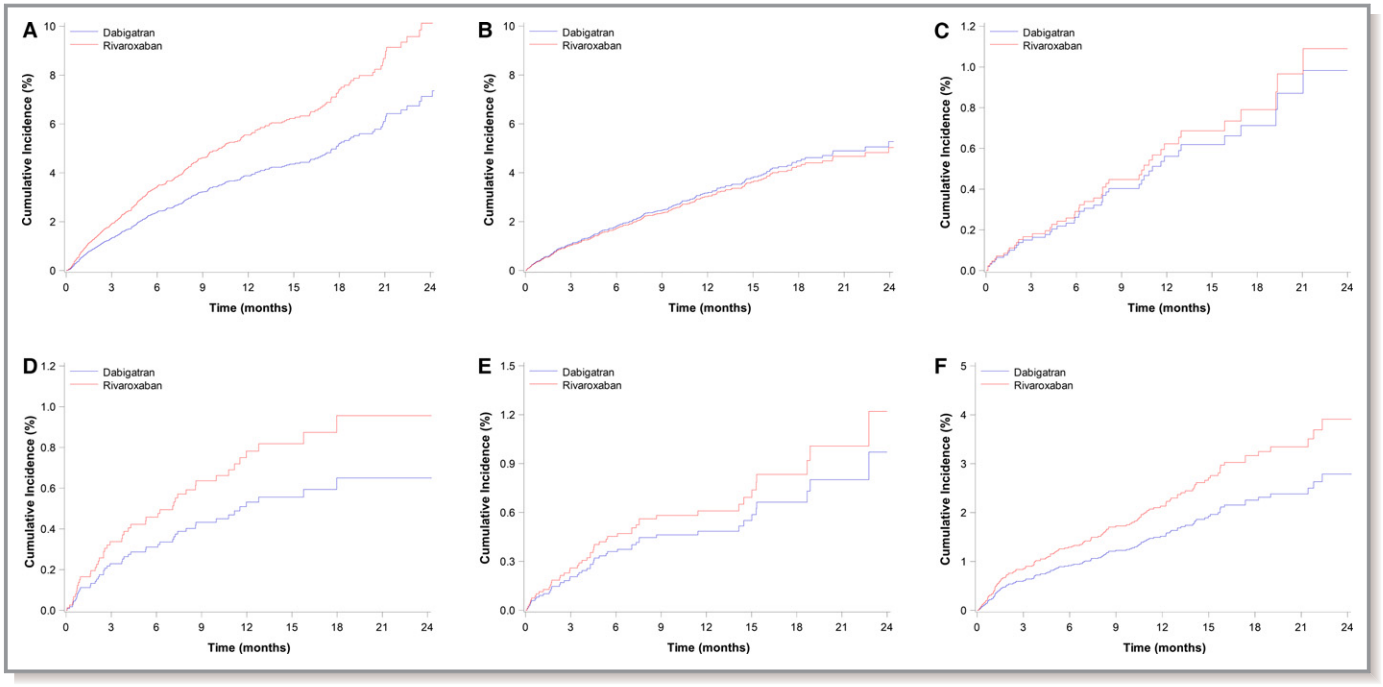

Figure 3. Cumulative incidences of clinical outcomes in the propensity score–matched population: (A) all-cause death, (B) ischemic stroke, (C) acute myocardial infarction, (D) arterial embolism/thrombosis, (E) intracranial hemorrhage, and (F) gastrointestinal hemorrhage needing transfusion.

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[24] and only using database from February 1, 2013 to December 31, 2013 in the Taiwan study[25]).

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

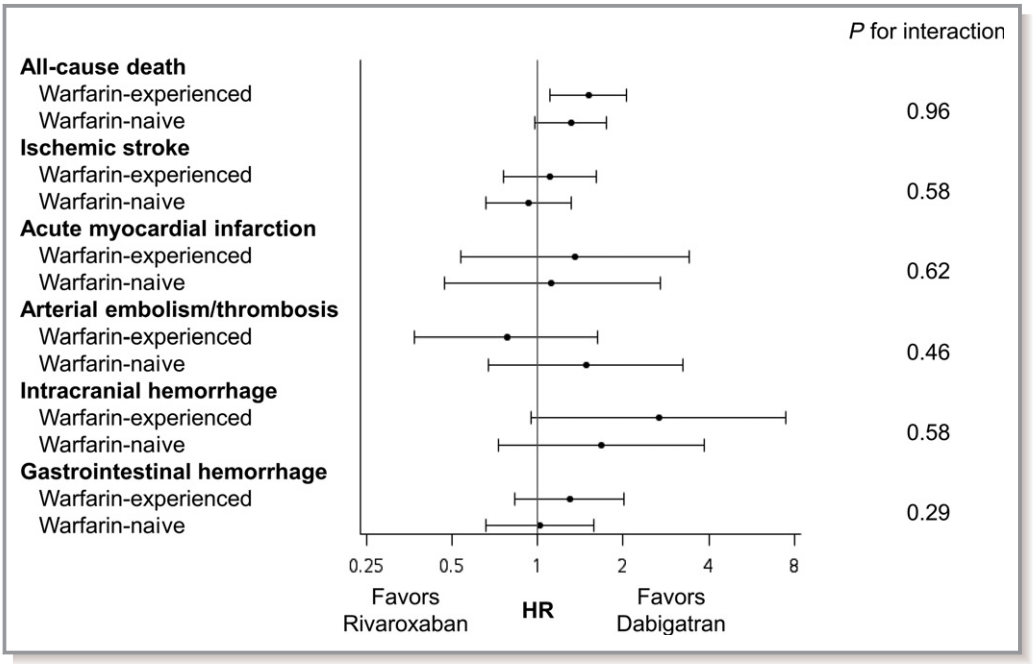

Figure 4. Forest plot summarizing results of the subgroup analysis concerning previous experience with warfarin exposure. HR indicates hazard ratio.

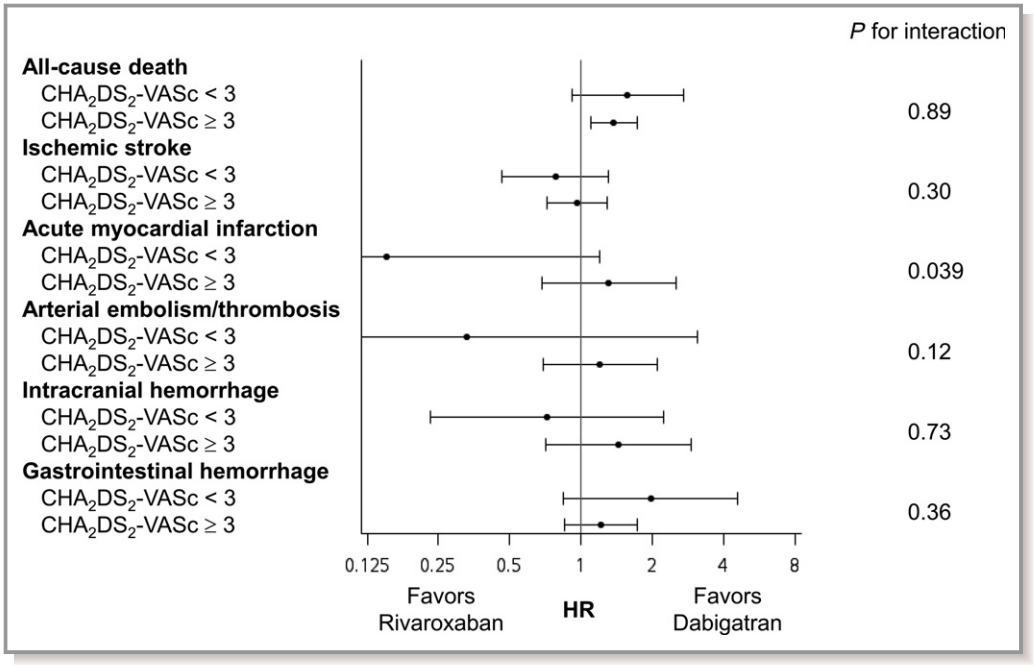

Figure 5. Forest plot summarizing results of the subgroup analyses concerning different CHA_2DS_2-VASc scores. HR indicates hazard ratio.

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.[26] 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.[27] Because labile international normalized ratio and alcohol use could not be obtained from the NHI claims database, we did not calculate the 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.

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