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Direct Comparison of Low-Dose Dabigatran and Rivaroxaban for Effectiveness and Safety in Patients with Non-Valvular Atrial Fibrillation

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Background: We aimed to examine the comparative effectiveness and safety between low-dose dabigatran and rivaroxaban in atrial fibrillation (AF) patients.

Methods: Using the National Health Insurance claims database in Taiwan, we conducted head-to-head comparisons among adult non-valvular AF patients prescribed with dabigatran 110 mg or rivaroxaban 15 mg between June 1, 2012 and May 31, 2015. A propensity score was derived using logistic regression to model the probability of receiving different non-VKA oral anticoagulants (NOACs) as a function of potential confounders, and an inverse-probability-of-treatment-weighted (IPTW) pseudo-cohort was created. A Cox proportional hazards model was used to compare clinical outcomes in the IPTW pseudo-cohort as the primary analysis. The propensity score-matched analysis was applied as the secondary analysis.

Results: Overall, 13505 dabigatran 110 mg users and 6551 rivaroxaban 15 mgusers were identified. In the primary analysis, the rivaroxaban 15 mg users had a higher risk of all-cause death [hazard ratio (HR) 1.19, 95% confidence interval (CI) 1.02-1.38]. In addition, the rivaroxaban 15 mg users had an increased risk of all-cause death (HR 1.25, 95% CI 1.05-1.50) in the secondary analysis. The risks of ischemic stroke, intracranial hemorrhage and gastrointestinal hemorrhage were similar between the 2 study groups in both the primary and secondary analyses.

Conclusions: For non-valvular AF patients, rivaroxaban 15 mg seemed to be associated with an increased risk of all-cause death compared with dabigatran 110 mg. This was a retrospective data analysis and the results should not be over-interpreted to guide the choice of different NOACs.

Key Words: Anticoagulant • Dabigatran • Death • Effectiveness • Rivaroxaban • Safety

INTRODUCTION

The prevalence of atrial fibrillation (AF) increases with age.[1] It is estimated that one tenth of the population in Taiwan over 80 years of age will suffer from AF.[2] Atrial fibrillation is associated with several common medical conditions such as hypertension, obesity, diabetes, and even insomnia in Taiwan.[3-5] Furthermore, patients with AF are associated with higher risks of embolic stroke, congestive heart failure, and mortality.[6]

Prior studies have confirmed the efficacy of vitamin K antagonist (VKA) in stroke prevention.[7] However, in Asia, many physicians are reluctant to prescribe VKA due to its drug-drug, drug-food interactions, and the documented higher risk of intracranial bleeding compared to Western countries.[8]

Non-VKA oral anticoagulants (NOACs) have been

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shown to be at least non-inferior to warfarin regarding their effectiveness in embolic stroke prevention with a lower risk of bleeding, especially intracranial hemorrhage.[9-12] In our previous study focusing on Taiwanese patients, rivaroxaban was associated with a statistically significant increase in all-cause mortality compared with dabigatran.[13] However, there is a prevalence of prescribing low-dose NOACs in Taiwan, and large-scale head-to-head clinical trials concerning this prescription behavior are lacking.[13-15] In addition, in our previous study, different dosages of rivaroxaban and dabigatran were pooled into one group for analysis.[13] Accordingly, this study was designed to compare the clinical effectiveness and safety specifically between low-dose dabigatran (110 mg twice daily) and rivaroxaban (15 mg once daily) in real world practice using a retrospective cohort study design based on claims data from the National Health Insurance (NHI) program in Taiwan.

METHODS

Data sources

The data sources and clinical setting were the same as in our previous publication.[13] Briefly, Taiwan launched a universal NHI program for all citizens in 1995. Patient identification number, gender, birth date, dates of medical services, diagnoses made by physicians, procedures administered, and drugs dispensed are available in the NHI claims database. All diagnoses are coded using International Classification of Diseases Ninth Revision Clinical Modification (ICD-9-CM) codes. The patients' records can be linked to the Taiwan National Death Registry to obtain the exact date of death and the officially speculated main cause of death.[16] To comply with Taiwanese privacy regulations, all personal identifiers are encrypted and all data are analyzed anonymously. The study protocol was approved by the Institutional Review Board of the National Taiwan University Hospital Hsin-Chu Branch which waived the requirement for informed consent.

Study design and cohort definition

The Taiwan NHI program has reimbursed dabigatran and rivaroxaban for stroke prevention in non-valvular AF patients with an estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2 since 1 June 2012 and 1 February 2013, respectively. This retrospective cohort study used the Taiwan NHI claims database from 2011 to 2015. All AF patients aged ≥ 20 years who initiated NOACs within the 1 June 2012 to 31 May 2015 enrollment period were identified. The date of the first prescription of study medications was defined as the index date. Subjects having diagnoses of deep vein thrombosis, pulmonary embolism, mitral stenosis (Supplementary Table 1) or procedures including valvular replacement, mitral commissurotomy, heart transplantation or extracorporeal circulatory support within 6 months prior to the index date were excluded. Patients receiving concomitant warfarin therapy, concomitant antiplatelet agents such as aspirin, clopidogrel, ticlopidine, ticagrelor, dipyridamole, or cilostazol (prasugrel has never been launched in Taiwan) on the index date, or receiving more than one NOAC at the same time were excluded. Subjects whose daily dosage of NOACs could not be clarified at the index date were also excluded. The remaining dabigatran 110 mg users and rivaroxaban 15 mg users were enrolled as our study population (Figure 1).

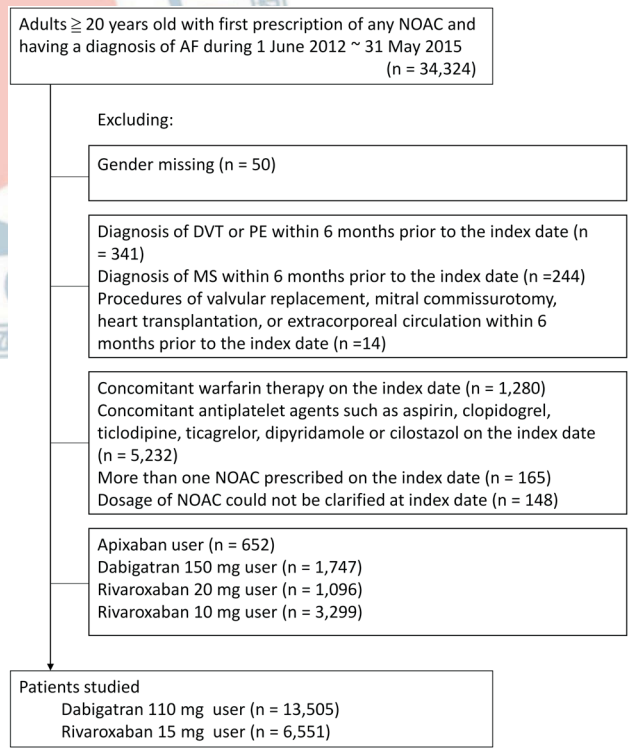

Figure 1. *Patient flow diagram. AF, atrial fibrillation; DVT, deep vein thrombosis; MS, mitral stenosis; NOAC, non-vitamin K antagonist oral anticoagulant; PE, pulmonary embolism.*

Clinical outcomes

The clinical outcomes of interest were all-cause death, ischemic stroke, intracranial hemorrhage, and gastrointestinal hemorrhage needing transfusion.[13] We also included respiratory diseases and osteoporotic fractures as negative controls to explore the possible residual confounding effects (Supplementary Table 1).[17,18]

Follow-up

Patients were classified according to their initial prescriptions of different study medications (dabigatran 110 mg or rivaroxaban 15 mg). All of the clinical outcomes were evaluated from the in-patient records of the NHI claims database. To adhere to as-treated analysis,[19] all patients were followed from their index date until death, change of dosage of the initial study medications, switching to other oral anticoagulants, discontinuation of the study medications (30-day treatment gap), or the end of the study (31 December 2015), whichever occurred first.

Background characteristics and potential confounders

Age was ascertained at the index date. We used the Taiwan NHI insurance premium for each subject as a proxy of socioeconomic status, and quartiles of the insurance premium among the overall study population were used as cut-off levels for categorization. We evaluated comorbidities according to the Elixhauser Comorbidity Index except for ischemic stroke, intracranial hemorrhage, myocardial infarction, and vascular disease (Supplementary Table 1).[20] For each specific comorbidity, at least two records of the corresponding diagnosis codes in the out-patient records or one in-patient record within a 6-month period prior to the index date was defined as the existence of the specific comorbidity and was coded as a binary variable. Patients who had ever received nasogastric intubation within a 6-month period prior to the index date were identified by specific NHI procedure codes. Data on medications were extracted from the NHI claims database within a 6-month period prior to the index date. We calculated the total number of hospitalizations and total number of physician visits within the 6-month period prior to the index date for each study subject. $CHADS_2$ score and CHA_2DS_2-VASc score were calculated based on background characteristics.[21,22] Sex, age, and all of the background characteristics mentioned above with a prevalence of more than 1.0% were retained in the statistical analysis.

Statistical analysis

We used standardized differences to assess the balance of covariates between different treatment groups, whereby an absolute standardized difference of greater than 0.10 represented a meaningful imbalance.[23] A propensity score (PS) was derived using logistic regression to model the probability of receiving different study medications as a function of all potential confounders (as listed in Table 1 and Supplementary Table 2; age was incorporated as categorical data).[24] For the primary analysis, an inverse-probability-of-treatment-weighted (IPTW) pseudo-cohort was created by means of the PS.[25] A Cox proportional hazards model was used to estimate the relative risks [hazard ratios, (HRs)] of developing various clinical outcomes between the patients receiving different study drugs among the IPTW pseudo-cohort. Changes in dosage of the initial study medications, switching to other oral anticoagulants, discontinuation of the study medications, or the end of follow-up were treated as censoring. When exploring the relative hazards concerning clinical outcomes other than all-cause death, death was treated as a competing risk instead of censoring.[26]

For the secondary analysis, we applied the PS-matching procedure to create a PS-matched subcohort. Based on the individual PS, subjects belonging to different treatment groups were matched according to a caliper measurement of < 0.2 standard deviation of the logit of the PS. A marginal proportional hazards model was applied within the PS-matched subcohort to account for the correlated nature of the survival data.[27] Kaplan-Meier survival curves were used to illustrate the incidence rates of various clinical outcomes among different treatment groups.

As 3299 patients received a 10 mg dosage of rivaroxaban (Figure 1), we included rivaroxaban 10 mg into our rivaroxaban group, and compared dabigatran 110 mg users with rivaroxaban 15/10 mg users as the sensitivity analysis. All analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Baseline characteristics

Overall, the cohort comprised 13505 subjects using

Table 1. Covariate distribution in the overall population and the inverse-probability-of-treatment weighted pseudo-cohort

	Overall population			IPTW pseudo-cohort		
	Dabigatran 110 mg (n = 13505)	Rivaroxaban 15 mg (n = 6551)	STD	Dabigatran 110 mg (n = 13508)	Rivaroxaban 15 mg (n = 6547)	STD
Female gender (%)	43.8	45.4	0.032	44.4	44.3	0.001
Age group (%)						
< 65	11.8	13.5	0.050	12.4	12.5	0.001
65-74	29.7	32.7	0.064	30.7	30.6	0.001
≥ 75	58.4	53.8	0.093	56.9	56.9	0
Quartiles of insurance premium (%)						
Q1	30.7	29.2	0.032	30.2	30.3	0.001
Q2	23.1	16.4	0.170	20.9	20.9	0.001
Q3	21.6	30.7	0.208	24.6	24.6	0.001
Q4	24.6	23.8	0.020	24.3	24.2	0.002
Comorbidities-1* (%)						
Ischemic stroke	21.5	18.6	0.071	20.5	20.4	0.002
Intracranial hemorrhage	1.2	1.5	0.024	1.3	1.3	0.003
Myocardial infarction	1.1	1.5	0.035	1.2	1.2	0.001
Vascular disease	3.4	3.4	0.002	3.4	3.3	0.003
Comorbidities-2# (%)						
Congestive heart failure	23.7	24.4	0.017	23.9	24.1	0.003
Cardiac arrhythmias	71.6	68.8	0.061	70.7	70.7	0
Valvular disease	9.2	9.7	0.019	9.4	9.6	0.005
Peripheral vascular disorders	2.4	2.0	0.026	2.2	2.2	0.004
Hypertension	49.9	50.3	0.009	50.0	50.1	0.001
Chronic pulmonary disease	14.7	14.6	0.002	14.7	14.7	0.001
Diabetes mellitus	20.5	20.3	0.006	20.4	20.3	0.003
Hypothyroidism	1.8	1.8	0.002	1.8	1.8	0
Renal failure	5.1	5.2	0.006	5.1	5.2	0.001
Liver disease	2.1	2.1	0.002	2.1	2.1	0.003
Peptic ulcer disease excluding bleeding	8.4	8.1	0.012	8.3	8.4	0.001
Solid tumor without metastasis	6.0	5.8	0.008	6.0	5.9	0.002
Rheumatoid arthritis/collagen vascular diseases	2.1	2.1	0.006	2.1	2.1	0.001
Fluid and electrolyte disorders	2.7	2.8	0.006	2.7	2.8	0.003
Depression	2.8	3.1	0.022	2.9	2.9	0
History of NG intubation	6.7	9.8	0.115	7.7	7.8	0.001
Medication exposure history (%)						
Warfarin	36.3	32.4	0.083	35.0	35.0	0.001
Aspirin	44.2	46.8	0.053	45.1	45.0	0.002
Clopidogrel	8.1	9.4	0.046	8.6	8.5	0.002
Ticlopidine	2.8	2.6	0.011	2.7	2.8	0.002
Dipyridamole	8.6	9.0	0.014	8.7	8.8	0.003
Digoxin	24.7	23.0	0.040	24.2	24.3	0.003
Amiodarone	17.9	19.2	0.034	18.4	18.4	0.002
Dronedarone	2.4	3.8	0.083	2.9	2.9	0
Beta-blockers	52.0	53.9	0.038	52.6	52.5	0.003
Verapamil	3.5	3.7	0.013	3.6	3.6	0
Diltiazem	20.3	19.8	0.012	20.2	20.1	0.003
Dihydropyridine CCBs	35.5	34.9	0.013	35.2	35.1	0.002

Table 1. Continued

	Overall population			IPTW pseudo-cohort		
	Dabigatran 110 mg (n = 13505)	Rivaroxaban 15 mg (n = 6551)	STD	Dabigatran 110 mg (n = 13508)	Rivaroxaban 15 mg (n = 6547)	STD
ACEIs	14.2	13.0	0.036	13.8	13.9	0.001
ARB	52.1	52.6	0.009	52.2	52.1	0.003
Loop diuretics	29.6	30.9	0.027	30.1	30.2	0.002
Thiazide diuretics	7.0	6.2	0.033	6.8	6.8	0.001
Spironolactone	12.1	13.0	0.027	12.4	12.6	0.005
Statins	28.2	30.0	0.039	28.8	28.7	0.002
NSAIDs	56.5	58.6	0.041	57.3	57.4	0.003
OADs	23.9	23.7	0.005	23.8	23.7	0.001
Insulin	6.5	6.9	0.015	6.6	6.7	0.002
PPIs	11.3	12.3	0.029	11.7	11.7	0.001
H_2-blockers	30.4	32.8	0.052	31.2	31.3	0.002
Ever hospitalization (%)	29.4	30.0	0.014	29.7	29.9	0.004
Mean number of hospitalization (SD)	0.4 (0.8)	0.4 (0.8)	0.037	0.4 (0.8)	0.4 (0.8)	0.017
Mean number of physician visit (SD)	18.9 (12.3)	19.1 (12.4)	0.011	19.0 (12.3)	19.0 (12.5)	0.005
Mean $CHADS_2$ score (SD)	1.9 (1.3)	1.8 (1.3)	0.077	1.9 (1.3)	1.9 (1.3)	0.006
Mean CHA_2DS_2-VASc score (SD)	3.3 (1.5)	3.2 (1.5)	0.063	3.2 (1.5)	3.2 (1.5)	0.002

* Defined specifically for this study. Refer to supplementary Table 1. # According to Elixhauser's comorbidities. Refer to supplementary Table 1.

ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; IPTW, inverse-probability-of-treatment weighted; NG, nasogastric; NSAID, nonsteroidal anti-inflammatory drug; OAD, oral antidiabetic drug; PPI, proton pump inhibitor; SD, standard deviation; STD, standardized difference.

110 mg dabigatran and 6551 using 15 mg rivaroxaban. The mean age was 75.4 ± 9.5 years in the dabigatran group and 74.7 ± 9.7 years in the rivaroxaban group. The mean follow-up duration was 11.1 ± 10.9 months in the dabigatran group and 9.8 ± 8.5 months in the rivaroxaban group. The two study groups differed significantly in the distribution of insurance premium and previous history of nasogastric intubation. The imbalance in background covariates was improved in the IPTW pseudo-cohort (Table 1).

Primary analysis

In the IPTW pseudo-cohort, the incidence rates of all-cause death were 3.94/100 person-years in the dabigatran users and 4.78/100 person-years in the rivaroxaban users (Table 2). The risk of all-cause death in the

Table 2. Incidences and relative risks of various clinical outcomes between study groups in the inverse-probability-of-treatment weighted pseudo-cohort

Outcome	Dabigatran 110 mg (n = 13508)		Rivaroxaban 15 mg (n = 6547)		HR	95% CI
	Event No.	IR*	Event No.	IR*		
All-cause death	484	3.94	261	4.78	1.19	(1.02, 1.38)
Ischemic stroke	302	2.49	140	2.59	1.00	(0.82, 1.22)
Intracranial hemorrhage	61	0.5	31	0.56	1.12	(0.73, 1.74)
Gastrointestinal hemorrhage	212	1.73	114	2.1	1.14	(0.91, 1.43)
Respiratory diseases	1370	11.79	663	12.78	1.03	(0.94, 1.13)
Osteoporotic fracture	149	1.22	67	1.23	0.99	(0.74, 1.32)

* Per 100 person-years.

CI, confidence interval; HR, hazard ratio; IR, incidence rate.

rivaroxaban users was significantly higher than that in the dabigatran users [HR 1.19, 95% confidence interval (CI) 1.02-1.38]. No difference was noted regarding the risks of ischemic stroke, intracranial hemorrhage, gastrointestinal hemorrhage needing transfusion, respiratory diseases and osteoporotic fractures between the rivaroxaban users and dabigatran users.

Secondary analysis

The PS-matched subcohort also showed balance in background covariates (Supplementary Table 2). The findings in the secondary analysis were essentially identical to those in the primary analysis. The rivaroxaban 15 mg users had an increased risk of all-cause death (HR 1.25, 95% CI 1.05-1.50) in the PS-matched analysis (Supplementary Table 3).

Survival curves

The Kaplan-Meier survival curves for various clinical outcomes by study groups among the overall population are shown in Figure 2.

Supplementary analyses

The main causes of death in the overall population are listed in Table 3. We conducted additional sensitivity analysis to compare the dabigatran 110 mg users with

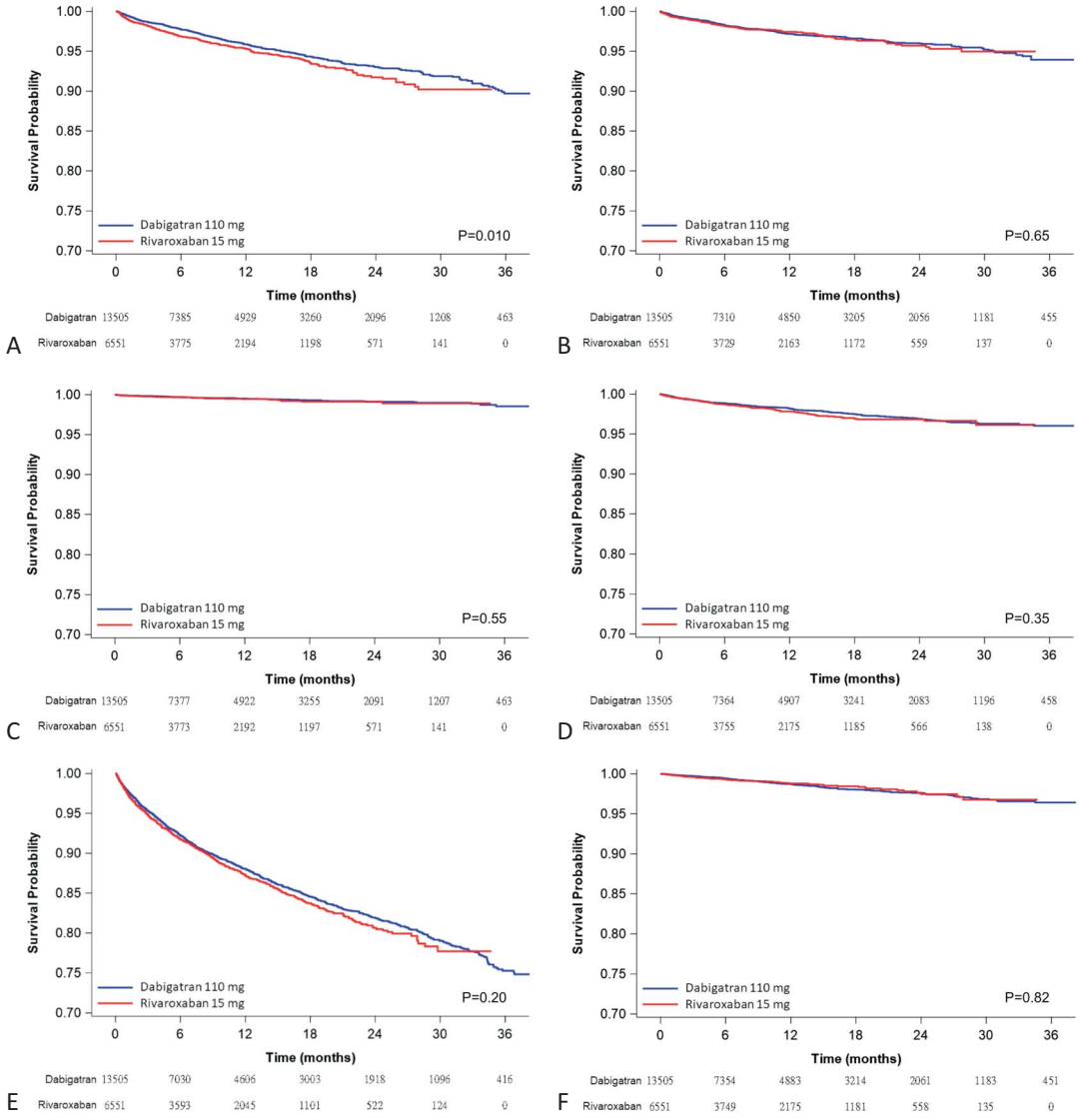

Figure 2. *Kaplan-Meier survival curves for various clinical outcomes by study groups among the overall population: (A) all-cause death, (B) ischemic stroke, (C) intracranial hemorrhage, (D) gastrointestinal hemorrhage, (E) respiratory diseases, and (F) osteoporotic fracture.*

Table 3. Causes of death in the overall study population

	Total		Dabigatran 110 mg		Rivaroxaban 15 mg	
	n	(%)	n	(%)	n	(%)
	895	(100)	487	(100)	262	(100)
Circulatory system diseases	418	(46.7)	225	(46.2)	125	(47.7)
Respiratory system diseases	129	(14.4)	68	(14.0)	43	(16.4)
Cancer	113	(12.6)	59	(12.1)	36	(13.7)
Endocrine system diseases	58	(6.5)	33	(6.8)	17	(6.5)
External causes	36	(4.0)	24	(4.9)	4	(1.5)
Genitourinary system diseases	35	(3.9)	18	(3.7)	8	(3.1)
Infectious diseases	34	(3.8)	19	(3.9)	9	(3.4)
Digestive system diseases	30	(3.4)	20	(4.1)	7	(2.7)
Ill-defined conditions	19	(2.1)	9	(1.8)	8	(3.1)
Nervous system diseases	9	(1.0)	3	(0.6)	3	(1.1)
Musculoskeletal system diseases	6	(0.7)	3	(0.6)	1	(0.4)
Others	5	(0.6)	4	(0.8)	0	
Mental disorders	3	(0.3)	2	(0.4)	1	(0.4)

rivaroxaban 15/10 mg users, and the findings remained largely the same (Supplementary Table 4 and Supplementary Table 5).

DISCUSSION

Given that AF is an increasing health burden in Asia, NOACs may become a cornerstone of treatment of AF-associated stroke. Since warfarin is associated with higher risks of major bleeding and intracranial hemorrhage in Asians compared to non-Asians, the benefit of NOACs seems to be especially robust in Asian patients with AF.[8] On the other hand, low-dose NOACs are more popular than warfarin in Asian populations and are often prescribed in everyday practice.[13,15] In addition, the non-inferiority of low-dose rivaroxaban compared with warfarin was demonstrated in the J-ROCKET AF study conducted in Japan.[28] Our study directly compared the effectiveness and safety between the two most commonly prescribed dosages of NOACs in Taiwan, 110 mg dabigatran and 15 mg rivaroxaban, and showed that the rivaroxaban 15 mg users had a significantly higher risk of all-cause death than the dabigatran 110 mg users. However, the risk of ischemic stroke was similar in the two groups. Likewise, there were no significant differences in the risks of intracranial hemorrhage and gastrointestinal hemorrhage needing transfusion between the two study groups.

An increasing number of studies have evaluated the effectiveness and safety of different NOACs in a head-to-head comparisons using insurance claims databases.[13,15,29] These studies concluded that the use of rivaroxaban was related to an increased risk of bleeding events.[13,29] Specifically, Asian users of rivaroxaban have a higher risk of gastrointestinal hemorrhage needing hospitalization.[15] Although these studies mixed different dosages for each medication during analysis, most of the subjects included in these studies used low-dose NOACs.[13,15] Our study directly compared low-dose dabigatran (110 mg) and rivaroxaban (15 mg) users. With regards to safety events, compared with the RELY and ROCKET-AF trials, our study revealed a similar incident rate of intracranial hemorrhage but higher rate of gastrointestinal bleeding events.[10,30] On the other hand, Chan and colleagues reported a hospitalization rate of 1.62% per year for gastrointestinal bleeding in dabigatran users, which is similar to our results (1.73% annual rate for gastrointestinal hemorrhage needing transfusion).[15] However, the rate of gastrointestinal hemorrhage in the rivaroxaban users was lower in our cohort compared with their results (2.1% vs. 2.68%). Chan et al. defined gastrointestinal hemorrhage as events along with hospitalization.[15] In our analysis, the definition of gastrointestinal hemorrhage was more rigorous as gastrointestinal hemorrhage with hospitalization plus blood component transfusion. This may explain the lower incidence of gastrointestinal hemorrhage in our rivaroxaban cohort. In this regard, our findings are consistent

with previous investigations that the rivaroxaban 15 mg users had a higher risk of gastrointestinal hemorrhage needing hospitalization but the same risk of gastrointestinal hemorrhage needing blood transfusion, which reflects more severe cases, compared with the dabigatran 110 mg users.

There was no increased risk of ischemic stroke in the rivaroxaban users compared with the dabigatran users. However, an increased mortality rate was noted in the rivaroxaban group with an annual incidence rate of up to 4.78%. Our findings are consistent with several observational studies.[13,29,31,32] Bai et al. reported that the pooled HR of mortality was 1.23 in their meta-analysis, and concluded that rivaroxaban was associated with an increased risk of all-cause death compared with dabigatran, regardless of whether or not a low dose was used.[33] As all of the other comparisons concerning different clinical outcomes between dabigatran and rivaroxaban in our study revealed no significant differences, further research is needed to clarify the cause of increased mortality in rivaroxaban 15 mg users compared with dabigatran 110 mg users.

In our previous study,[13] we used the Taiwan NHI claims database between 2012 and 2014 to compare the clinical effectiveness and safety between mixed doses of dabigatran (110 mg and 150 mg, n = 10625 total) and rivaroxaban (10 mg, 15 mg, and 20 mg, n = 4609 total). The primary analysis of the previous study was PS-matched analysis, while the secondary analysis was regression adjustments of the quintiles of the PS. In this study, we retrieved data between 2012 and 2015 in the same database to increase the sample size, and focused on the single most used dosages (dabigatran 110 mg, n = 13505; rivaroxaban 15 mg, n = 6551). In addition, we used IPTW analysis as the primary analysis to maintain an adequate sample size, with PS-matched analysis as the secondary analysis. We still found a higher mortality rate in the rivaroxaban 15 mg users compared with the dabigatran 110 mg users, which is consistent with the findings of our prior work.[13]

Strengths of this study

To explore possible residual confounding effects, we included respiratory diseases and osteoporotic fractures as clinical outcomes. Because the risks of both respiratory diseases and osteoporotic fractures are similar between rivaroxaban 15 mg users and dabigatran 110 mg users with HRs approaching 1.0, we believe that the residual confounding effect was minimal. In addition, the mean follow-up duration in our cohort was up to 11 months, in contrast with the very short duration (about 110 days) of follow-up in a previously published US observational study,[29] and a shorter follow-up period of only until 31 December 2013 with a smaller sample size in a previously published Taiwan study.[15]

Study limitations

Our study was subject to several limitations. First, some patient characteristics, such as weight, height, habits, laboratory results including international normalized ratio (INR) and eGFR, are not available in the Taiwan NHI database. Accordingly, we could not calculate the HAS-BLED score (hypertension, abnormal renal/liver function, stroke, bleeding history of predisposition, labile INR, elderly > 65 years, and drugs/alcohol taken concomitantly), which is a practical tool to assess the risk of bleeding.[6] However, we tried to balance all of the other components of HAS-BLED score in our analytical model as far as possible. In addition, dabigatran is excreted mainly by the kidneys (80%), while only one third of rivaroxaban is excreted by the kidneys.[34] Physicians may be prone to prescribe rivaroxaban in patients with a low eGFR, thus introducing selection bias into our study. Nevertheless, we included a previous diagnosis of renal failure during construction of the PS. As shown in Table 1, the percentage of patients having a previous diagnosis of renal failure in both groups (5.1% vs. 5.2%) was similar with a low standardized difference of 0.006, which was statistically insignificant (< 0.10). Thus, it seems that renal failure did not play a significant role when comparing two groups.

Second, insurance claims data do not include information of the patients' adherence to therapy, which may have been higher in the rivaroxaban group because of the once-daily regimen. Our findings showed increased mortality in the rivaroxaban group but no differences in the risks of ischemic stroke and bleeding between the two NOAC groups, implying a better benefit-risk ratio in real-world clinical practice of dabigatran than rivaroxaban. Third, our study did not include apixaban. Although apixaban has been reimbursed by the Taiwan Bureau of NHI since June 2014, the sample size was too

small to be included in our analysis (Figure 1).

CONCLUSIONS

In real-world practice among an Asian AF population, dabigatran 110 mg and rivaroxaban 15 mg demonstrated similar effectiveness in preventing ischemic stroke and comparable risks of intracranial and gastrointestinal hemorrhage. However, all-cause death was higher in the rivaroxaban 15 mg users compared with the dabigatran 110 mg users. As this was a retrospective data analysis and the detailed reasons behind the increased risk of mortality with rivaroxaban are unknown, the results of our work should be regarded as hypothesis-generating and should not be over-interpreted to guide the choice of different NOACs directly.

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CONFLICTS OF INTEREST

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

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REFERENCES

1. Miyasaka Y, Barnes ME, Bailey KR, et al. Mortality trends in patients diagnosed with first atrial fibrillation: a 21-year community-based study. *J Am Coll Cardiol* 2007;49:986-92.
2. Chiang CE, Wu TJ, Ueng KC, et al. 2016 Guidelines of the Taiwan Heart Rhythm Society and the Taiwan Society of Cardiology for the management of atrial fibrillation. *J Formos Med Assoc* 2016; 115:893-952.
3. Chiang CE, Wang TD, Lin TH, et al. The 2017 Focused Update of the Guidelines of the Taiwan Society of Cardiology (TSOC) and the Taiwan Hypertension Society (THS) for the management of hypertension. *Acta Cardiol Sin* 2017;33:213-25.
4. Lee HH, Chen YC, Chen JJ, et al. Insomnia and the risk of atrial fibrillation: a population-based cohort study. *Acta Cardiol Sin* 2017;33:165-72.
5. Kawada T. Insomnia and atrial fibrillation: risk assessment. *Acta Cardiol Sin* 2018;34:192.
6. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur J Cardiothorac Surg* 2016;50:e1-88.
7. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;146:857-67.
8. Chiang CE, Wang KL, Lin SJ. Asian strategy for stroke prevention in atrial fibrillation. *Europace* 2015;17:ii31-9.
9. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361: 1139-51.
10. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883-91.
11. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; 365:981-92.
12. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369: 2093-104.
13. Lai CL, Chen HM, Liao MT, et al. Comparative effectiveness and safety of dabigatran and rivaroxaban in atrial fibrillation patients. *J Am Heart Assoc* 2017;6(4):e005362.
14. Ruff CT. The reality of "real-world" data: more questions than answers. *J Am Coll Cardiol* 2016;68:1402-3.
15. Chan YH, Kuo CT, Yeh YH, et al. Thromboembolic, bleeding, and mortality risks of rivaroxaban and dabigatran in Asians with nonvalvular atrial fibrillation. *J Am Coll Cardiol* 2016;68:1389-401.
16. 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;29:336-43.
17. Lip GY, Skjoth F, Nielsen PB, et al. Effectiveness and safety of standard-dose nonvitamin K antagonist oral anticoagulants and warfarin among patients with atrial fibrillation with a single stroke

risk factor: a nationwide cohort study. *JAMA Cardiol* 2017;2: 872-81.
18. Statistics Canada. https://www150.statcan.gc.ca/n1/pub/82-003-x/2009004/article/11034/tables/tbla-eng.htm.
19. Schneeweiss S. A basic study design for expedited safety signal evaluation based on electronic healthcare data. *Pharmacoepidemiol Drug Saf* 2010;19:858-68.
20. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;43:1130-9.
21. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;285:2864-70.
22. Lip GY, Nieuwlaat R, Pisters R, et al. 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;137:263-72.
23. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Stat Simul Comput* 2009:1228-34.
24. 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;17:2265-81.
25. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000;11: 550-60.
26. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496-509.
27. 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, 1992:237-47.
28. Hori M, Matsumoto M, Tanahashi N, et al. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation - the J-ROCKET AF study. *Circ J* 2012;76:2104-11.
29. Graham DJ, Reichman ME, Wernecke M, et al. Stroke, bleeding, and mortality risks in elderly medicare beneficiaries treated with dabigatran or rivaroxaban for nonvalvular atrial fibrillation. *JAMA Intern Med* 2016;176:1662-71.
30. Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation* 2011;123:2363-72.
31. Gorst-Rasmussen A, Lip GY, Bjerregaard Larsen T. Rivaroxaban versus warfarin and dabigatran in atrial fibrillation: comparative effectiveness and safety in Danish routine care. *Pharmacoepidemiol Drug Saf* 2016;25:1236-44.
32. Hernandez I, Zhang Y. Comparing stroke and bleeding with rivaroxaban and dabigatran in atrial fibrillation: analysis of the US Medicare Part D data. *Am J Cardiovasc Drugs* 2017;17:37-47.
33. Bai Y, Deng H, Shantsila A, Lip GY. Rivaroxaban versus dabigatran or warfarin in real-world studies of stroke prevention in atrial fibrillation: systematic review and meta-analysis. *Stroke* 2017;48: 970-6.
34. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. *Eur Heart J* 2012;33:2719-47.

SUPPLEMENT

Supplementary Table 1. Diagnosis codes used in this study

Diagnosis	ICD-9-CM codes
Specific to this study*	
Atrial fibrillation and flutter	427.3
Deep vein thrombosis	451.1, 451.2, 451.81, 453.4, 459.1, 671.3, 671.4
Pulmonary embolism	415.1, v12.51, 673.2
Mitral stenosis	746.5, 394.0, 394.2, 396.0, 396.1, 396.8
Ischemic stroke	433.x1, 434.x1, 435.9, 436, 437.1x, 437.9x
Intracranial hemorrhage	430, 431, 432
Gastrointestinal hemorrhage	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
Respiratory diseases[#]	460-519
Osteoporotic fracture[†]	820.x, 805.x
Myocardial infarction	410.x, 412.x
Vascular disease	410.x, 412.x, 093.0, 437.3, 440.x, 441.x, 443.1-443.9, 447.1, 557.1, 557.9, v43.4
According to Elixhauser's comorbidities[‡]	
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428.x
Cardiac arrhythmias	426.0, 426.13, 426.7, 426.9, 426.10, 426.12, 427.0-427.4, 427.6-427.9, 785.0, 996.01, 996.04, V45.0, V53.3
Valvular disease	093.2, 394.x-397.x, 424.x, 746.3-746.6, V42.2, V43.3
Peripheral vascular disorders	093.0, 437.3, 440.x, 441.x, 443.1-443.9, 447.1, 557.1, 557.9, V43.4
Hypertension	401.x, 402.x-405.x
Chronic pulmonary disease	416.8, 416.9, 490.x-505.x, 506.4, 508.1, 508.8
Diabetes mellitus	250.0-250.3, 250.4-250.9
Hypothyroidism	240.9, 243.x, 244.x, 246.1, 246.8
Renal failure	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x
Liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 456.0-456.2, 570.x, 571.x, 572.2-572.8, 573.3, 573.4, 573.8, 573.9, V42.7
Peptic ulcer disease excluding bleeding	531.7, 531.9, 532.7, 532.9, 533.7, 533.9, 534.7, 534.9
Solid tumor without metastasis	140.x-172.x, 174.x-195.x
Rheumatoid arthritis/collagen vascular diseases	446.x, 701.0, 710.0-710.4, 710.8, 710.9, 711.2, 714.x, 719.3, 720.x, 725.x, 728.5, 728.89, 729.30
Fluid and electrolyte disorders	253.6, 276.x
Depression	296.2, 296.3, 296.5, 300.4, 309.x, 311

* Reference: Lai CL, Chen HM, Liao MT, et al. Comparative effectiveness and safety of dabigatran and rivaroxaban in atrial fibrillation patients. *J Am Heart Assoc* 2017;6:e005362.

[#] Reference: The Statistics Canada (https://www150.statcan.gc.ca/n1/pub/82-003-x/2009004/article/11034/tables/tbla-eng.htm).

[†] Reference: Lau WC, Chan EW, Cheung CL, et al. Association between dabigatran vs warfarin and risk of osteoporotic fractures among patients with nonvalvular atrial fibrillation. *JAMA* 2017;317:1151-1158.

[‡] Reference: Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;43:1130-1139.

ICD-9-CM, International Classification of Diseases Ninth Revision Clinical Modification system.

Supplementary Table 2. Covariate distribution between study groups in the propensity score-matched subcohort

	Dabigatran 110 mg (n = 6535)	Rivaroxaban 15 mg (n = 6535)	STD
Female gender (%)	45.3	45.4	0.003
Age group (%)			
< 65	12.9	13.5	0.016
65-74	33.2	32.7	0.011
≥ 75	53.9	53.8	0.001
Quartiles of insurance premium (%)			
Q1	30.1	29.3	0.018
Q2	16.0	16.4	0.011
Q3	30.5	30.5	0
Q4	23.4	23.8	0.009
Comorbidities-1* (%)			
Ischemic stroke	17.9	18.7	0.019
Intracranial hemorrhage	1.5	1.5	0.001
Myocardial infarction	1.5	1.5	0
Vascular disease	3.2	3.4	0.012
Comorbidities-2# (%)			
Congestive heart failure	24.2	24.4	0.003
Cardiac arrhythmias	69.0	68.8	0.003
Valvular disease	9.7	9.7	0
Peripheral vascular disorders	1.8	2.0	0.016
Hypertension	50.4	50.3	0.001
Chronic pulmonary disease	15.0	14.7	0.011
Diabetes mellitus	20.8	20.2	0.014
Hypothyroidism	1.8	1.8	0.002
Renal failure	5.3	5.2	0.002
Liver disease	2.0	2.1	0.005
Peptic ulcer disease excluding bleeding	7.9	8.1	0.007
Solid tumor without metastasis	5.4	5.8	0.018
Rheumatoid arthritis/collagen vascular diseases	2.2	2.1	0.007
Fluid and electrolyte disorders	2.8	2.8	0.000
Depression	3.0	3.1	0.006
History of NG intubation	9.3	9.7	0.013
Medication exposure history (%)			
Warfarin	32.4	32.4	0.000
Aspirin	47.3	46.7	0.011
Clopidogrel	9.3	9.4	0.004
Ticlopidine	2.9	2.6	0.017
Dipyridamole	8.9	9.0	0.002
Digoxin	22.8	23.0	0.004
Amiodarone	19.3	19.2	0.002
Dronedarone	3.7	3.7	0.002
Beta-blockers	53.5	53.9	0.007
Verapamil	3.7	3.7	0.002
Diltiazem	19.6	19.8	0.007
Dihydropyridine CCBs	34.9	34.8	0.002
ACEIs	13.4	13.0	0.011
ARB	52.1	52.6	0.01
Loop diuretics	30.4	30.8	0.009
Thiazide diuretics	5.9	6.2	0.014
Spironolactone	13.1	13.0	0.003
Statins	30.1	29.9	0.003
NSAIDs	58.3	58.6	0.005
OADs	24.3	23.6	0.015

Supplementary Table 2. Continued

	Dabigatran 110 mg (n = 6535)	Rivaroxaban 15 mg (n = 6535)	STD
Insulin	6.8	6.8	0.001
PPIs	12.0	12.2	0.008
H_2-blockers	31.6	32.7	0.025
Ever hospitalization (%)	29.4	29.9	0.010
Mean number of hospitalization (SD)	0.4 (0.8)	0.4 (0.8)	0.021
Mean number of physician visit (SD)	18.9 (12.2)	19.1 (12.4)	0.016
Mean $CHADS_2$ score (SD)	1.8 (1.2)	1.8 (1.3)	0.002
Mean CHA_2DS_2-VASc score (SD)	3.2 (1.5)	3.2 (1.5)	0.006

* Defined specifically for this study. Refer to supplementary Table 1. # According to Elixhauser's comorbidities. Refer to supplementary Table 1.
ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; NG, nasogastric; NSAID, nonsteroidal anti-inflammatory drug; OAD, oral antidiabetic drug; PPI, proton pump inhibitor; SD, standard deviation; STD, standardized difference.

Supplementary Table 3. Incidences and relative risks of various clinical outcomes between study groups in the propensity score-matched subcohort

Outcome	Dabigatran110 mg (n = 6535)		Rivaroxaban15 mg (n = 6535)		HR	95% CI
	Event No.	IR*	Event No.	IR*		
All-cause death	220	3.81	261	4.9	1.25	(1.05, 1.50)
Ischemic stroke	149	2.61	141	2.68	0.99	(0.79, 1.24)
Intracranial hemorrhage	28	0.49	30	0.56	1.15	(0.68, 1.93)
Gastrointestinal hemorrhage	89	1.55	109	2.06	1.23	(0.93, 1.63)
Respiratory diseases	667	12.24	663	13.12	1.03	(0.92, 1.14)
Osteoporotic fracture	67	1.17	64	1.21	1.00	(0.71, 1.41)

* per 100 person-years.
CI, confidence interval; HR, hazard ratio; IR, incidence rate.

Supplementary Table 4. Sensitivity analysis-1. Incidences and relative risks of various clinical outcomes between study groups in the inverse-probability-of-treatment weighted pseudo-cohort while including rivaroxaban 10 mg into rivaroxaban group

Outcome	Dabigatran 110 mg (n = 13514)		Rivaroxaban 15/10 mg (n = 9843)		HR	95% CI
	Event No.	IR*	Event No.	IR*		
All-cause death	493	4.06	397	5.18	1.23	(1.07, 1.40)
Ischemic stroke	301	2.51	193	2.54	0.95	(0.79, 1.14)
Intracranial hemorrhage	62	0.51	44	0.57	1.08	(0.73, 1.59)
Gastrointestinal hemorrhage	215	1.78	154	2.03	1.05	(0.85, 1.29)
Respiratory diseases	1390	12.14	1013	13.94	1.07	(0.99, 1.16)
Osteoporotic fracture	148	1.23	91	1.19	0.94	(0.72, 1.22)

* Per 100 person-years.
CI, confidence interval; HR, hazard ratio; IR, incidence rate.

Supplementary Table 5. Sensitivity analysis-2. Incidences and relative risks of various clinical outcomes between study groups in the propensity-score matched subcohort while including rivaroxaban 10 mg into rivaroxaban group

Outcome	Dabigatran 110 mg (n = 9285)		Rivaroxaban 15/10 mg (n = 9285)		HR	95% CI
	Event No.	IR*	Event No.	IR*		
All-cause death	328	4.09	372	5.27	1.22	(1.05, 1.42)
Ischemic stroke	210	2.65	182	2.6	0.92	(0.76, 1.13)
Intracranial hemorrhage	43	0.54	43	0.61	1.10	(0.72, 1.69)
Gastrointestinal hemorrhage	145	1.81	138	1.96	0.99	(0.78, 1.26)
Respiratory diseases	933	12.31	953	14.24	1.08	(0.98, 1.18)
Osteoporotic fracture	100	1.26	92	1.31	1.02	(0.77, 1.36)

* Per 100 person-years.
CI, confidence interval; HR, hazard ratio; IR, incidence rate.