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Thromboembolic, Bleeding, and Mortality Risks of Rivaroxaban and Dabigatran in Asians With Nonvalvular Atrial Fibrillation

Yi-Hsin Chan, MD,[a,b] Chi-Tai Kuo, MD,[a,b] Yung-Hsin Yeh, MD,[a,b] Shang-Hung Chang, MD, PhD,[a,b] Lung-Sheng Wu, MD,[a,b] Hsin-Fu Lee, MD,[a,b] Hui-Tzu Tu, MS,[c] Lai-Chu See, PhD[c,d,e]

ABSTRACT

BACKGROUND It is unclear whether the non-vitamin K antagonist oral anticoagulant agents rivaroxaban and dabigatran are superior to warfarin for efficacy and safety outcomes in Asians with nonvalvular atrial fibrillation (NVAF).

OBJECTIVES The aim of this study was to compare the risk for thromboembolic events, bleeding, and mortality associated with rivaroxaban and dabigatran versus warfarin in Asians with NVAF.

METHODS A nationwide retrospective cohort study was conducted of consecutive patients with NVAF taking rivaroxaban (n = 3,916), dabigatran (n = 5,921), or warfarin (n = 5,251) using data collected from the Taiwan National Health Insurance Research Database between February 1, 2013 and December 31, 2013. The propensity score weighting method was used to balance covariates across study groups. Patients were followed until the first occurrence of any study outcome or the study end date (December 31, 2013).

RESULTS A total of 3,425 (87%) and 5,301 (90%) patients were taking low-dose rivaroxaban (10 to 15 mg once daily) and dabigatran (110 mg twice daily), respectively. Compared with warfarin, both rivaroxaban and dabigatran significantly decreased the risk for ischemic stroke or systemic embolism ($p = 0.0004$ and $p = 0.0006$, respectively), intracranial hemorrhage ($p = 0.0007$ and $p = 0.0005$, respectively), and all-cause mortality ($p < 0.0001$ and $p < 0.0001$, respectively) during the short follow-up period. In comparing the 2 non-vitamin K antagonist oral anticoagulant agents with each other, no differences were found regarding risk for ischemic stroke or systemic embolism, intracranial hemorrhage, myocardial infarction, or mortality. Rivaroxaban carried a significantly higher risk for hospitalization for gastrointestinal bleeding than dabigatran ($p = 0.0416$), but on-treatment analysis showed that the risk for hospitalized gastrointestinal bleeding was similar between the 2 drugs ($p = 0.5783$).

CONCLUSIONS In real-world practice among Asians with NVAF, both rivaroxaban and dabigatran were associated with reduced risk for ischemic stroke or systemic embolism, intracranial hemorrhage, and all-cause mortality without significantly increased risk for acute myocardial infarction or hospitalization for gastrointestinal bleeding compared with warfarin. (J Am Coll Cardiol 2016;68:1389–401) © 2016 by the American College of Cardiology Foundation.

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From the [a]Cardiovascular Department, Chang Gung Memorial Hospital, Linkou, Taoyuan, Taiwan; [b]College of Medicine, Chang Gung University, Taoyuan, Taiwan; [c]Department of Public Health, College of Medicine, Chang Gung University, Taoyuan, Taiwan; [d]Biostatistics Core Laboratory, Molecular Medicine Research Center, Chang Gung University, Taoyuan, Taiwan; and the [e]Division of Rheumatology, Allergy and Immunology, Department of Internal Medicine, Chang Gung Memorial Hospital, Linkou, Taoyuan, Taiwan. This study was supported by grants 102-2628-B-182-011-MY3 and 102-2314-B-182A-053-MY3 from the Ministry of Science and Technology and CMRPG3B0991-3, CMRPG3F0041, CMRPG3D1631, and CMRPD1F0251 from the Chang Gung Memorial Hospital (Linkou, Taiwan). The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Chan and Kuo contributed equally to this work.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AMI = acute myocardial infarction

ASMD = absolute standardized mean difference

CI = confidence interval

CKD = chronic kidney disease

GI = gastrointestinal

HR = hazard ratio

ICH = intracranial hemorrhage

INR = international normalized ratio

NHIRD = National Health Insurance Research Database

NOAC = non-vitamin K antagonist oral anticoagulant agent

NVAF = nonvalvular atrial fibrillation

OAC = oral anticoagulant agent

VKA = vitamin K antagonist

Atrial fibrillation (AF) significantly increases the risk for thromboembolic events and death, affecting 2% to 3% of the global population (1,2). Oral anticoagulants (OACs) such as vitamin K antagonists (VKAs) (such as warfarin) effectively decrease the risk for thromboembolic events in patients with AF, while increasing the risk for intracranial hemorrhage (ICH) (3,4). The results of several large trials have suggested that non-VKA OACs (NOACs), such as dabigatran, a direct thrombin inhibitor, and rivaroxaban, a factor Xa inhibitor, are convenient and safe alternatives to VKAs (5,6). NOACs have been shown to be noninferior or superior to VKAs in preventing thromboembolic events, depending strongly on choosing either standard-dose NOAC administration (i.e., 150 mg for dabigatran) or low-dose NOAC administration (i.e., 110 mg for dabigatran). Evaluation of NOAC safety has shown that both dabigatran and rivaroxaban reduced the risk for ICH, while unexpectedly increasing the risk for gastrointestinal (GI) bleeding compared with warfarin (7,8).

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Of particular note, Asians show a higher risk for ICH than non-Asians when taking VKAs (9), but limited data are available to determine whether NOACs are as effective and safe in an Asian population than in non-Asians (10,11). In our recent study of a large nationwide Asian cohort with nonvalvular AF (NVAF) (12), dabigatran administered mainly at a low dose of 110 mg twice daily was associated with reduced risk for ischemic stroke, ICH, and all-cause mortality compared with warfarin, and it did not increase the risk for major GI bleeding compared with warfarin. However, no published data are available to directly compare efficacy and safety outcomes in Asians with AF who are taking rivaroxaban versus dabigatran during the same period. The objective of this study was to evaluate the risk for thromboembolic events, bleeding events, and all-cause mortality associated with the NOACs dabigatran and rivaroxaban versus warfarin in a real-world population of Asians with NVAF.

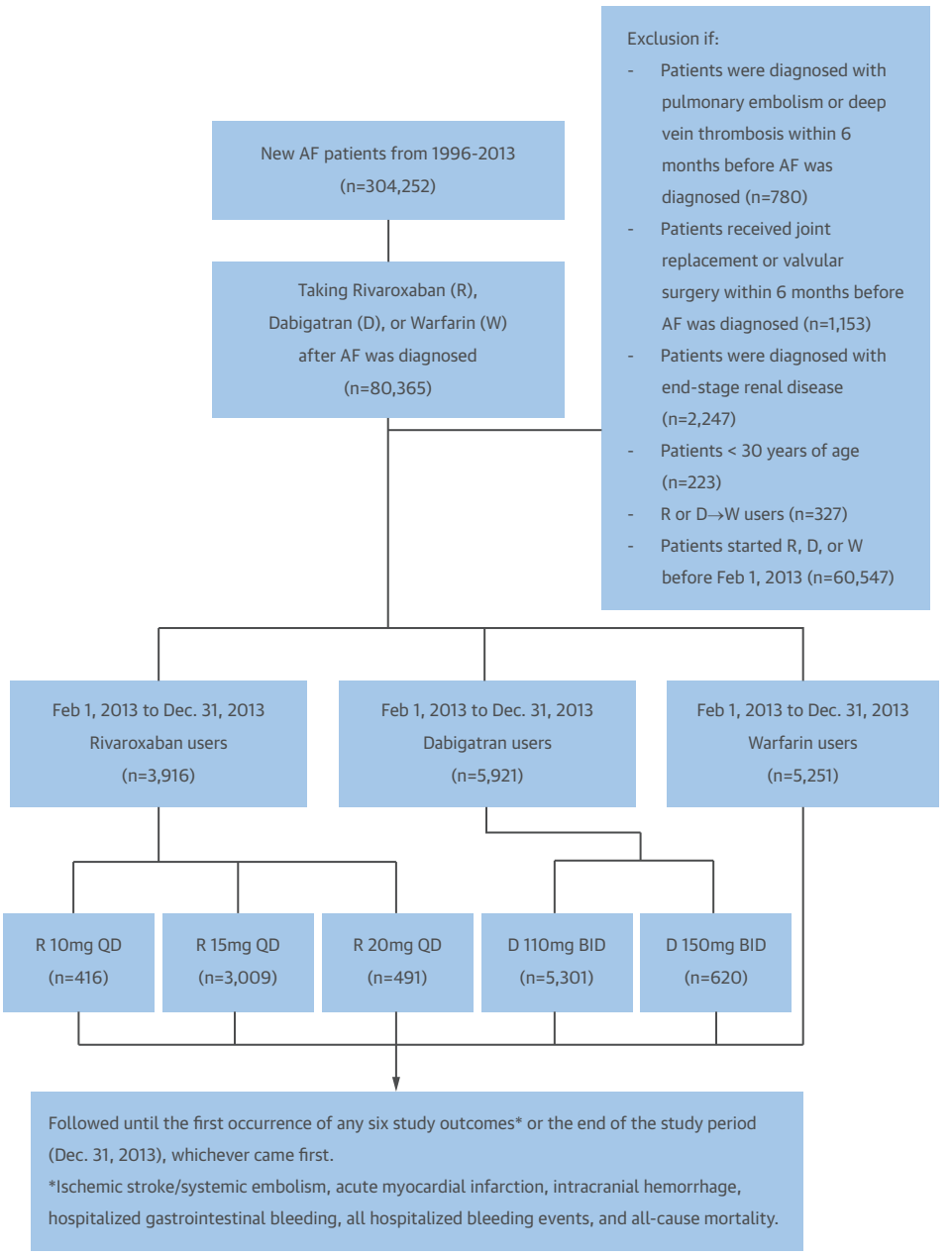
METHODS

In this retrospective cohort study, all patient data were obtained from the Taiwan National Health Insurance Research Database (NHIRD). Taiwan has a mandatory universal health insurance program providing comprehensive medical care coverage to all Taiwanese, currently including >23 million enrollees. The NHIRD is a national billing administrative database of health care services covering >99% of the Taiwanese population in 2014 (13). Because patients' original NHIRD identification numbers are encrypted and deidentified to protect their privacy, informed consent was waived. The consistent data encrypting process made it feasible to link and continuously follow all claims belonging to the same patient within the NHIRD. The study protocol was approved by the Institutional Review Board of Chang Gung Memorial Hospital.

STUDY DESIGN. We studied patients with NVAF treated with rivaroxaban, dabigatran, or warfarin (**Figure 1**). We identified a total of 304,252 patients with new AF using International Classification of Diseases, Ninth Revision, Clinical Modification code 427.31 from January 1, 1996, to December 31, 2013. Among the 304,252 patients, 80,365 patients had at least 1 prescription filled for rivaroxaban, dabigatran, or warfarin after AF was diagnosed. The approval dates of dabigatran and rivaroxaban in Taiwan were June 1, 2012, and February 1, 2013, respectively. We selected 3 study groups taking the first dose of rivaroxaban, dabigatran, or warfarin between February 1, 2013 and December 31, 2013—rivaroxaban (n = 3,916), dabigatran (n = 5,921), and warfarin (n = 5,251)—on the basis of each patient's final anticoagulant status. Some patients had experience with more than 1 of the drugs studied. Thus, the detailed profile of each treatment group was as follows: 1) the dabigatran group included only dabigatran users (n = 2,781), rivaroxaban-experienced dabigatran users (n = 45), and warfarin-experienced dabigatran users (n = 3,095); 2) the rivaroxaban group included only rivaroxaban users (n = 1,441), dabigatran-experienced rivaroxaban users (n = 375), and warfarin-experienced rivaroxaban users (n = 2,100); and 3) the warfarin group included only warfarin users (n = 5,251). Dabigatran- or rivaroxaban-experienced warfarin users (n = 327) were excluded from our analysis. The index date was defined as the date of first prescription of these 2 NOACs or warfarin after February 1, 2013, for each group. The follow-up period was defined as from the index date until the first occurrence of any study outcome or the end date of the study period (December 31, 2013), whichever came first.

STUDY OUTCOMES. Six outcomes were used in the present study to determine the efficacy and safety of NOACs and warfarin, including ischemic stroke or systemic embolism, ICH, hospitalization for GI

FIGURE 1 Study Design



From a total of 304,252 patients with new atrial fibrillation (AF), 3,916 rivaroxaban (R) users, 5,921 dabigatran (D) users, and 5,251 warfarin (W) users were enrolled in this study. BID = twice daily; QD = once daily.

bleeding, acute myocardial infarction (AMI), all hospitalizations for bleeding, and all-cause mortality. To avoid misclassification, all study outcomes were required to be discharge diagnoses. ICH was defined using the codes for atraumatic hemorrhage. Hospitalization for GI bleeding was defined as a hospitalized primary code indicating bleeding in the GI tract. All hospitalizations for bleeding events included ICH, hospitalization for GI bleeding, and other critical site bleeding. The International Classification of Diseases codes for the study outcomes and other baseline covariates are summarized in

Online Table 1. It must be noted that the same patient could have more than 1 study outcome during the study duration, but only the study outcome that occurred first was considered in the study.

Medical history and risk factors for thromboembolic and bleeding events at baseline were referenced to any claim record with the previous diagnoses or medication codes prior to the index date. A history of bleeding was confined to events within 6 months preceding the index date. A history of specific prescribed medications was confined to at least once within 3 months preceding the index date (12).

STATISTICAL ANALYSIS. The propensity score method, which simulates the effect of a randomized clinical trial for observational cohort data, was used to study the effects of NOACs on the 6 study outcomes (14). The propensity score is the predicted probability of treatment conditional on selected covariates using logistic regression. Hence, separate propensity score modes were obtained for the rivaroxaban-warfarin and dabigatran-warfarin comparisons. Inverse probability of treatment weights of propensity scores was used to balance covariates across the 3 study groups regarding time-to-event analyses (incidence rate, log-rank test, and Cox proportional hazards model). Incidence rates were estimated using the total number of study outcomes during the follow-up period divided by person-years at risk. The risk for 6 study outcomes for the 2 NOACs versus warfarin (reference) or rivaroxaban versus dabigatran (reference) was obtained using survival analysis (Kaplan-Meier method and log-rank test for univariate analysis and Cox proportional hazards regression for multivariate analysis). The balance of covariates at baseline among study groups was assessed using the absolute standardized mean difference (ASMD) rather than statistical testing, because balance is a property of the sample and not of an underlying population. An ASMD $\leq$0.1 indicates a negligible difference in potential confounders between the 2 study groups (14). Statistical significance was indicated by a p value $<$ 0.05. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

We enrolled consecutive patients taking rivaroxaban (n = 3,916), dabigatran (n = 5,921), or warfarin (n = 5,251) from February 1, 2013, to December 31, 2013. The mean adherence rates were 65 $\pm$ 28%, 58 $\pm$ 28%, and 63 $\pm$ 31% for rivaroxaban, dabigatran, and warfarin, respectively (p $<$ 0.001 for analysis-of-variance test). The number of dose alterations was limited for either the rivaroxaban or dabigatran group during the study period. For the dabigatran group, 179 patients (3.0%) had dose alterations: 100 were switched from 150 to 110 mg and 79 were increased from 110 to 150 mg. For the rivaroxaban group, 218 patients (5.6%) had dose alterations: 16 and 31 were switched from 20 to 15 or 10 mg, respectively; conversely, 16 and 66 patients were switched from 15 to either 20 or 10 mg, respectively; and, finally, 19 and 70 patients went from 10 to either 20 or 15 mg, respectively.

Before propensity score weighting, both the rivaroxaban and dabigatran groups were older, had higher CHA_2DS_2-VASc and HAS-BLED scores, and had a higher proportion of comorbidities than the warfarin group (**Tables 1** and **2**). After propensity score weighting, the rivaroxaban and dabigatran groups were well balanced in all characteristics (all ASMDs $<$0.1). Both rivaroxaban and dabigatran were associated with significantly reduced risk for ischemic stroke or systemic embolism, ICH, and all-cause mortality compared with warfarin (all p values $<$ 0.05 before and p $<$ 0.001 after propensity score weighting, respectively) (**Table 3**, Online Tables 2 and 3). No differences were found in hospitalized GI bleeding or AMI for the 2 NOAC groups versus the warfarin group. Kaplan-Meier curves showed early separation of event-free curves for ischemic stroke or systemic embolism, ICH, and all-cause mortality for the 2 NOACs versus warfarin (**Figures 2** and **3**).

Because rivaroxaban and dabigatran groups had similar baseline characteristics (all ASMDs $<$0.1), propensity score weighting was not performed when comparing the 2 NOACs with each other for the 6 outcomes. No differences were found in risk for thromboembolic events, ICH, AMI, all hospitalized bleeding, or all-cause mortality between rivaroxaban and dabigatran (**Table 3**). However, rivaroxaban carried a higher risk for hospitalization for GI bleeding than dabigatran (hazard ratio [HR]: 1.60; 95% confidence interval [CI]: 1.11 to 2.51; p = 0.0416). GI bleeding events were further divided into critical and noncritical bleeding, which was defined as receiving or not receiving blood transfusion. A significantly higher rate of noncritical bleeding was found in rivaroxaban users than dabigatran users (1.99 vs. 1.04 events/100 patient-years; HR: 1.82; 95% CI: 1.06 to 3.12; p = 0.0311). No significant differences were found in the critical bleeding rate associated with rivaroxaban versus dabigatran use (0.69 vs. 0.58

TABLE 1 Baseline Characteristics of Patients Using Rivaroxaban Versus Warfarin

	Propensity Score Weighting					
	Before			After		
	Rivaroxaban (n = 3,916)	Warfarin (n = 5,251)	ASMD	Rivaroxaban (n = 3,916)	Warfarin (n = 5,251)	ASMD
Age, yrs	76 ± 9	71 ± 12	0.4551	76 ± 9	76 ± 8	0.0051
<65	11	32		11	11	
65–74	29	26		29	28	
75–84	43	30		43	43	
≥85	17	13		17	17	
Female	46	44	0.0384	54	54	0.0039
CHA_2DS_2-VASc score*	4.12 ± 1.62	3.33 ± 1.82	0.4620	4.12 ± 1.62	4.12 ± 1.50	0.0015
HAS-BLED score†	3.11 ± 1.14	2.69 ± 1.33	0.3375	3.11 ± 1.14	3.14 ± 1.04	0.0275
Chronic kidney disease	22	21	0.0412	22	22	0.0096
Chronic liver disease	27	22	0.1206	27	27	0.0009
Congestive heart failure	16	16	0.0011	16	16	0.0009
Hypertension	87	75	0.2949	87	87	0.0015
Hyperlipidemia	51	42	0.1879	51	50	0.0160
Diabetes mellitus	41	36	0.0978	41	41	0.0069
Previous stroke	29	20	0.2298	29	29	0.0042
Previous TIA	5	2	0.1162	5	4	0.0074
Myocardial infarction	4	3	0.0218	4	4	0.0127
PAOD	0	0	0.0062	0	0	0.0018
History of bleeding	2	2	0.0244	2	3	0.0202
History of NSAIDs	23	26	0.0862	23	23	0.0181
History of antiplatelet agents	41	54	0.2647	41	44	0.0669
History of PPIs	7	7	0.0143	7	7	0.0171
History of steroids	4	6	0.0600	4	4	0.0095
PCI	9	6	0.0857	9	9	0.0044
CABG	1	1	0.0282	1	1	0.0021

Values are mean ± SD or %. *CHA_2DS_2-VASc score awards 1 point each for congestive heart failure, hypertension, diabetes mellitus, vascular disease, age 65 to 74 years, and female (sex category) and 2 points each for age ≥75 years and previous stroke or TIA. †HAS-BLED score awards 1 point each for hypertension, abnormal renal or liver function, stroke, bleeding history, labile INR, age 65 years or older, and antiplatelet drug or alcohol use. (Labile INR could not be determined from claims and was excluded from this scoring.)

ASMD = absolute standardized mean difference; CABG = coronary artery bypass graft; INR = international normalized ratio; NSAID = nonsteroidal anti-inflammatory drug; PAOD = peripheral arterial occlusive disease; PCI = percutaneous coronary intervention; PPI = proton pump inhibitor; TIA = transient ischemic attack.

events/100 patient-years; HR: 1.20; 95% CI: 0.52 to 2.75; p = 0.6701) (**Central Illustration**). On-treatment analysis was based on patients without any drug interruption during the study period; the cohorts included rivaroxaban (n = 2,007), dabigatran (n = 2,387), or warfarin (n = 2,526). On-treatment analysis indicated that the risk for GI bleeding was similar between rivaroxaban and dabigatran (HR: 1.16; 95% CI: 0.68 to 1.99; p = 0.5783). Both rivaroxaban and dabigatran were associated with a lower risk for ICH ($p < 0.05$ for both) and all-cause mortality ($p < 0.005$ for both) versus warfarin for the on-treatment analysis (Online Table 4).

Subgroup analysis was performed to determine whether the NOACs had significant protective effects for 4 outcomes compared with warfarin. A total of 3,425 (87%) and 5,301 (90%) patients were taking low-dose rivaroxaban and dabigatran, respectively. In contrast to low-dose NOACs, neither standard-dose rivaroxaban (n = 491) nor standard-dose dabigatran (n = 620) significantly improved safety and efficacy outcomes compared with warfarin (Online Figures 1 to 4). During the study period, 1,441 (36.8%) and 2,475 (63.2%) patients were OAC-naive and OAC-experienced rivaroxaban users, respectively; 2,781 (47.0%) and 3,140 (53.0%) patients were OAC-naive and OAC-experienced dabigatran users, respectively. Subgroup analysis was performed on the basis of age, presence of chronic kidney disease (CKD), and CHA_2DS_2-VASc and HAS-BLED scores. Rivaroxaban users with previous OAC experience or CKD showed significantly higher risk for GI bleeding than warfarin users (Online Figure 3).

TABLE 2 Baseline Characteristics of Patients Using Dabigatran Versus Warfarin

	Propensity Score Weighting					
	Before			After		
	Dabigatran (n = 5,921)	Warfarin (n = 5,251)	ASMD	Dabigatran (n = 5,921)	Warfarin (n = 5,251)	ASMD
Age, yrs	75 ± 9	71 ± 12	0.4062	75 ± 9	75 ± 10	0.0214
<65	13	32		13	12	
65–74	30	26		30	29	
75–84	42	30		42	43	
≥85	16	13		16	16	
Female	42	44	0.0375	42	42	0.0085
CHA_2DS_2-VASc score*	4.08 ± 1.59	3.32 ± 1.82	0.4412	4.08 ± 1.59	4.12 ± 1.87	0.0215
HAS-BLED score†	3.12 ± 1.14	2.69 ± 1.33	0.3440	3.12 ± 1.14	3.19 ± 1.30	0.0553
Chronic kidney disease	22	21	0.0402	22	22	0.0027
Chronic liver disease	28	22	0.1226	28	28	0.0005
Congestive heart failure	16	16	0.0070	16	16	0.0173
Hypertension	86	75	0.2774	86	86	0.0011
Hyperlipidemia	51	42	0.1898	51	51	0.0056
Diabetes mellitus	41	36	0.1084	41	41	0.0044
Previous stroke	32	20	0.2854	32	32	0.0059
Previous TIA	5	2	0.1387	5	5	0.0137
Myocardial infarction	3	3	0.0133	3	3	0.0063
PAOD	0	0	0.0187	0	0	0.0049
History of bleeding	2	2	0.0048	2	2	0.0171
History of NSAIDs	25	26	0.0257	25	26	0.0163
History of antiplatelet agents	45	54	0.1701	45	49	0.0845
History of PPIs	5	7	0.0820	5	6	0.0111
History of steroids	4	6	0.0546	4	5	0.0145
PCI	7	6	0.0237	7	7	0.0104
CABG	1	1	0.0424	1	1	0.0089

Values are mean ± SD or %. *CHA_2DS_2-VASc score awards 1 point each for congestive heart failure, hypertension, diabetes mellitus, vascular disease, age 65 to 74 years, and female (sex category) and 2 points each for age ≥75 years and previous stroke or TIA. †HAS-BLED score awards 1 point each for hypertension, abnormal renal or liver function, stroke, bleeding history, labile INR, age 65 years or older, and antiplatelet drug or alcohol use. (Labile INR could not be determined from claims and was excluded from this scoring.)

Abbreviations as in Table 1.

DISCUSSION

This was the first population-based study to investigate the efficacy and safety of rivaroxaban and dabigatran with a specific focus on Asians with NVAF taking these NOACs or warfarin during the same period. No previous study had compared the effects of these 2 NOACs directly in Asian patients. The results of the present study showed that nearly 90% patients in this large Asian cohort with NVAF were taking low-dose anticoagulant therapy (10 to 15 mg once daily for rivaroxaban or 110 mg twice daily for dabigatran). Compared with warfarin, the NOACs were associated with lower risk for ischemic stroke or systemic embolism, ICH, and all-cause mortality, without simultaneous increased risk for AMI or hospitalization for GI bleeding. Of note, no differences were found between rivaroxaban and dabigatran in risk for thromboembolic events, ICH, critical GI bleeding, or all-cause mortality. However, rivaroxaban was associated with a higher risk for noncritical GI bleeding than dabigatran in the Asian cohort. Subgroup analysis indicated that rivaroxaban users with previous OAC experience or CKD showed a particularly increased risk for GI bleeding compared with such patients taking warfarin. The risk for GI bleeding was similar between dabigatran and rivaroxaban for the on-treatment analysis.

Our results indicated that physicians tend to prescribe low-dose NOACs to their Asian patients with AF. Several reasons may explain why physicians in Taiwan favor low-dose NOACs. First, the average lower body mass index of adults in Taiwan is approximately 23 kg/m^2, which is much lower than the mean value (~28 kg/m^2) for patients enrolled in

TABLE 3 Outcomes: Incidence Rates and Hazard Ratios

	Incidence Rate (95% CI) (per 100 Person-Years)*		HR† (95% CI) [p Value]	Incidence Rate (95% CI) (per 100 Person-Years)*		HR† (95% CI) [p Value]	HR‡ (95% CI) [p Value]
	Rivaroxaban	Warfarin	Rivaroxaban vs. Warfarin	Dabigatran	Warfarin	Dabigatran vs. Warfarin	Rivaroxaban vs. Dabigatran
Ischemic stroke/systemic embolism	3.07 (2.12–4.02)	5.62 (4.48–6.76)	0.51 (0.35–0.74) [0.0004]	3.65 (2.92–4.39)	5.71 (4.79–6.64)	0.64 (0.49–0.83) [0.0006]	0.78 (0.54–1.13) [0.1914]
Acute myocardial infarction	0.38 (0.12–0.89)	0.56 (0.26–1.05)	0.63 (0.21–1.89) [0.4135]	0.62 (0.31–0.92)	0.60 (0.30–0.89)	1.02 (0.51–2.06) [0.9583]	0.62 (0.22–1.68) [0.3438]
Intracranial hemorrhage	0.77 (0.29–1.24)	2.47 (1.72–3.23)	0.30 (0.15–0.60) [0.0007]	1.00 (0.62–1.38)	2.27 (1.69–2.85)	0.44 (0.28–0.70) [0.0005]	0.73 (0.35–1.51) [0.3947]
Hospitalization for gastrointestinal bleeding	2.68 (1.79–3.57)	1.83 (1.18–2.48)	1.43 (0.88–2.33) [0.1531]	1.62 (1.13–2.10)	1.73 (1.22–2.24)	0.93 (0.61–1.42) [0.7273]	1.60 (1.11–2.51) [0.0416]
Hospitalization for any major bleeding	3.45 (2.44–4.46)	4.33 (3.33–5.33)	0.77 (0.53–1.13) [0.1786]	2.62 (1.99–3.24)	4.03 (3.26–4.81)	0.65 (0.48–0.88) [0.0050]	1.26 (0.87–1.85) [0.2262]
All-cause mortality	3.30 (2.31–4.28)	7.05 (5.77–8.32)	0.47 (0.33–0.67) [<0.0001]	2.65 (2.03–3.28)	6.67 (5.67–7.67)	0.40 (0.30–0.52) [<0.0001]	1.27 (0.86–1.86) [0.2272]

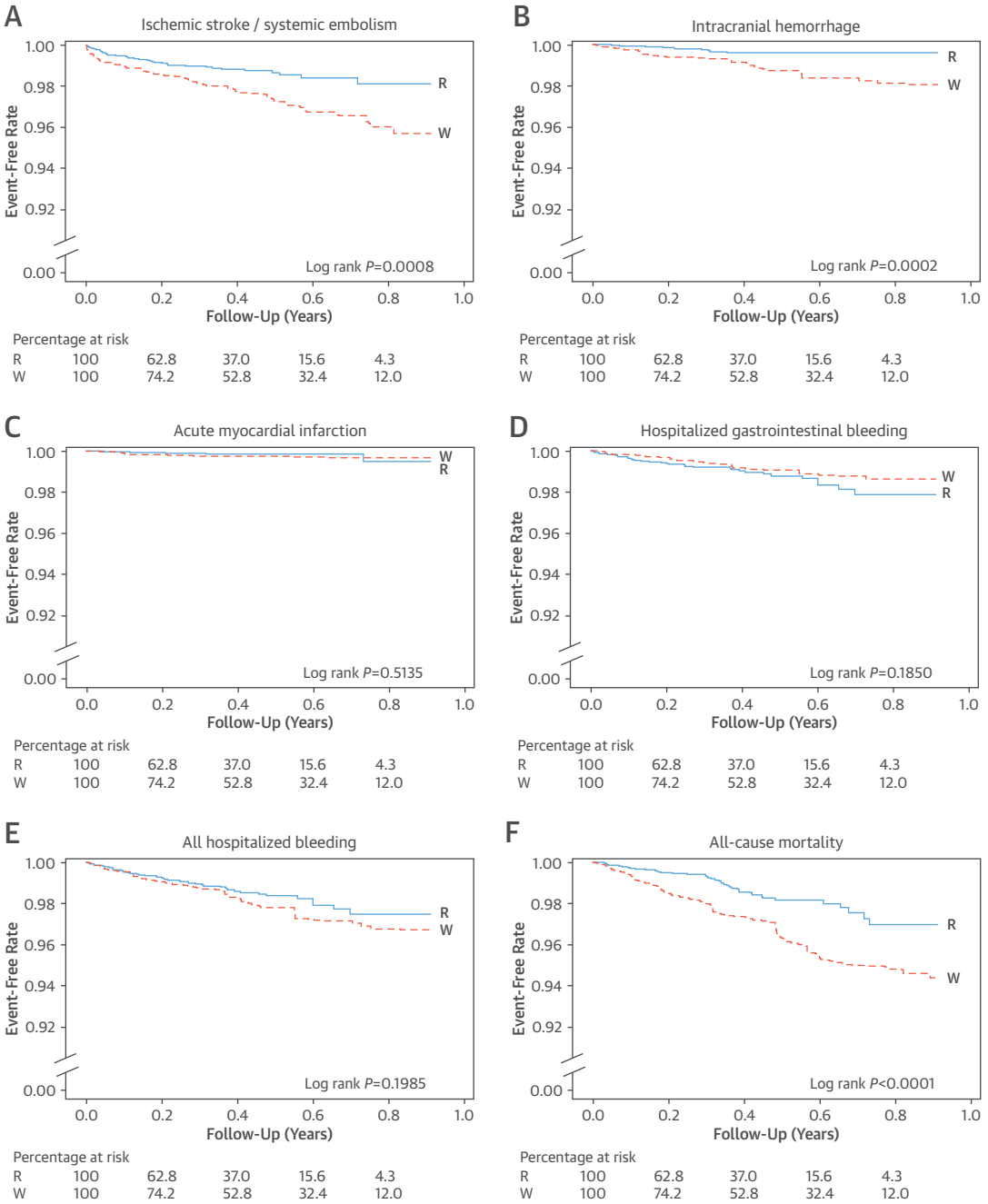
*Obtained using inverse probability of treatment weights of propensity scores. †The warfarin group served as the reference and was obtained using inverse probability of treatment weights of propensity scores. ‡The dabigatran group served as the reference.
CI = confidence interval; HR = hazard ratio.

the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) and ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trials (5,6,12). Therefore, given the lower body size, physicians tend to prescribe low-dose NOACs for their Asian patients. Second, although Taiwanese and Korean stroke guidelines recommend a target international normalized ratio (INR) of 2.0 to 3.0 in patients with AF taking warfarin, the Japanese and Chinese AF guidelines suggest a lower INR of 1.6 to 2.5 for older adult patients with AF (age >70 years) or those with high bleeding risk (15). Accordingly, some physicians may prescribe lower-dose NOACs to mimic the reduced INR of warfarin. Third, NOACs are restricted to older patients (age ≥65 years) with multiple comorbidities by the Taiwan national insurance system because of financial considerations, potentially selecting older patients and those with multiple comorbidities compared with warfarin users (**Table 1**). Physicians appear to be relatively cautious about prescribing standard-dose NOACs for older patients with AF with high CHA_2DS_2-VASc and HAS-BLED scores. Finally, Asian patients are particularly exposed to higher risk for VKA-related ICH than other ethnic groups (9). As a result of this concern, NOACs may be also underdosed in Asian patients.

Although the superior safety of low-dose NOACs versus VKAs has been well documented, the efficacy of low-dose NOACs over VKAs remained questionable until now. The RE-LY trial indicated that dabigatran 110 mg was not different from warfarin for reducing thromboembolic events (5). The ENGAGE-AF (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation) trial showed that edoxaban 30 mg was associated with an unfavorable trend in reducing the risk for ischemic stroke or systemic embolism compared with warfarin (HR: 1.13; p = 0.10) (16). The J-ROCKET AF (Japanese ROCKET AF) study showed a trend (p = 0.05) toward improved efficacy for low-dose rivaroxaban (15 or 10 mg once daily) (17). Correspondingly, a meta-analysis including those trials concluded that low-dose NOACs are similarly effective as VKAs in stroke or systemic embolism prevention for both Asian and non-Asian patients but might not be as effective for protection against ischemic stroke (11). The numbers of Asian patients taking low-dose NOACs in those studies were actually very limited.

In contrast, the present study was the largest ever to examine the efficacy of low-dose NOACs in Asians,

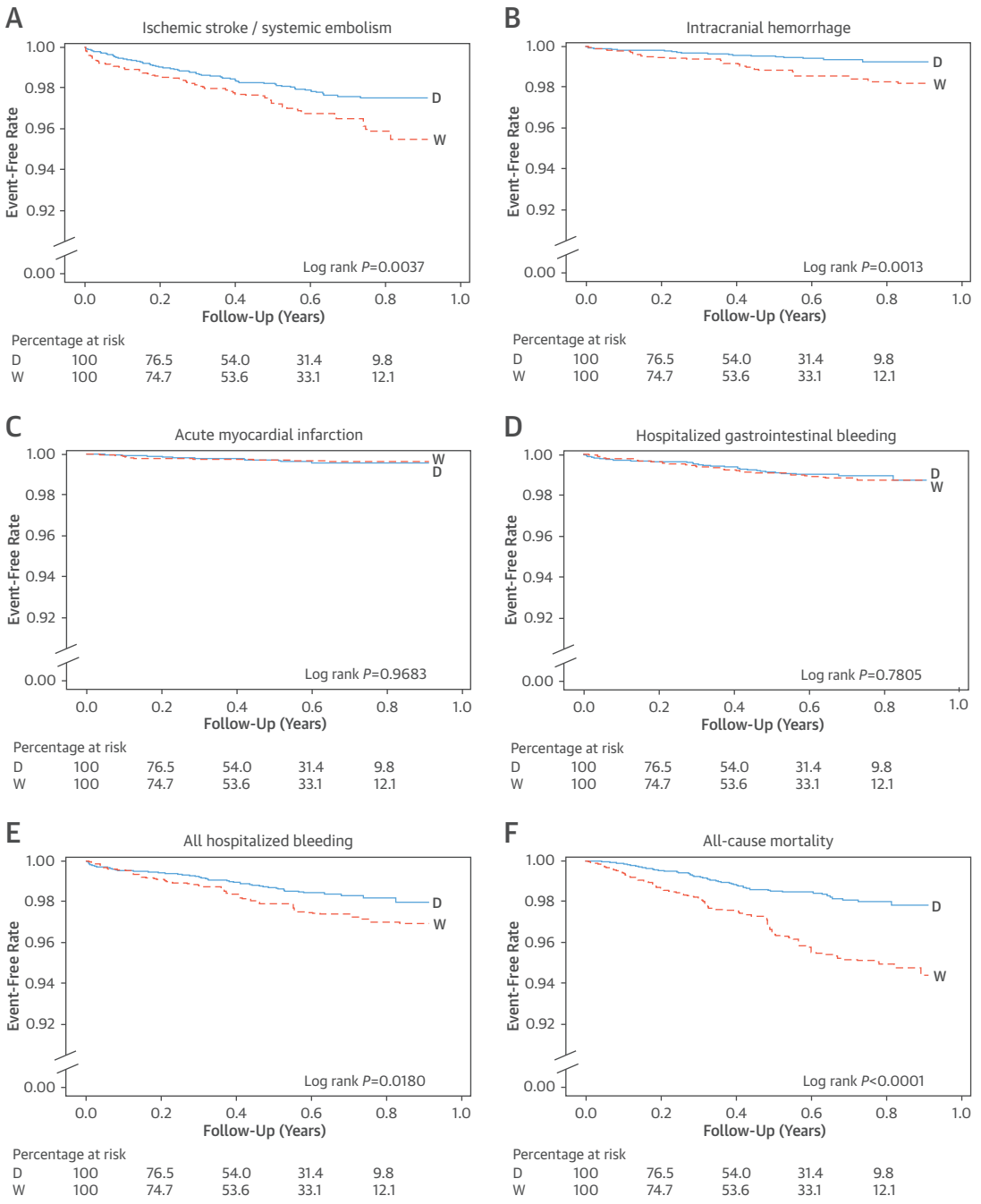
FIGURE 2 Outcomes: Rivaroxaban Versus Warfarin



Rivaroxaban (R) users had a significantly lower risk for ischemic stroke or systemic embolism **(A)**, intracranial hemorrhage **(B)**, and all-cause mortality **(F)**, without increased risk for acute myocardial infarction **(C)**, hospitalized gastrointestinal bleeding **(D)**, or any hospitalized bleeding **(E)** compared with warfarin (W) users.

enrolling a total of 3,425 patients taking low-dose rivaroxaban and 5,301 patients taking low-dose dabigatran; low-dose treatment with either NOAC significantly decreased the risk for ischemic stroke or systemic embolism and all-cause mortality compared with warfarin during the short follow-up period. In general, Asians are smaller in body size and body mass index compared with non-Asians (12).

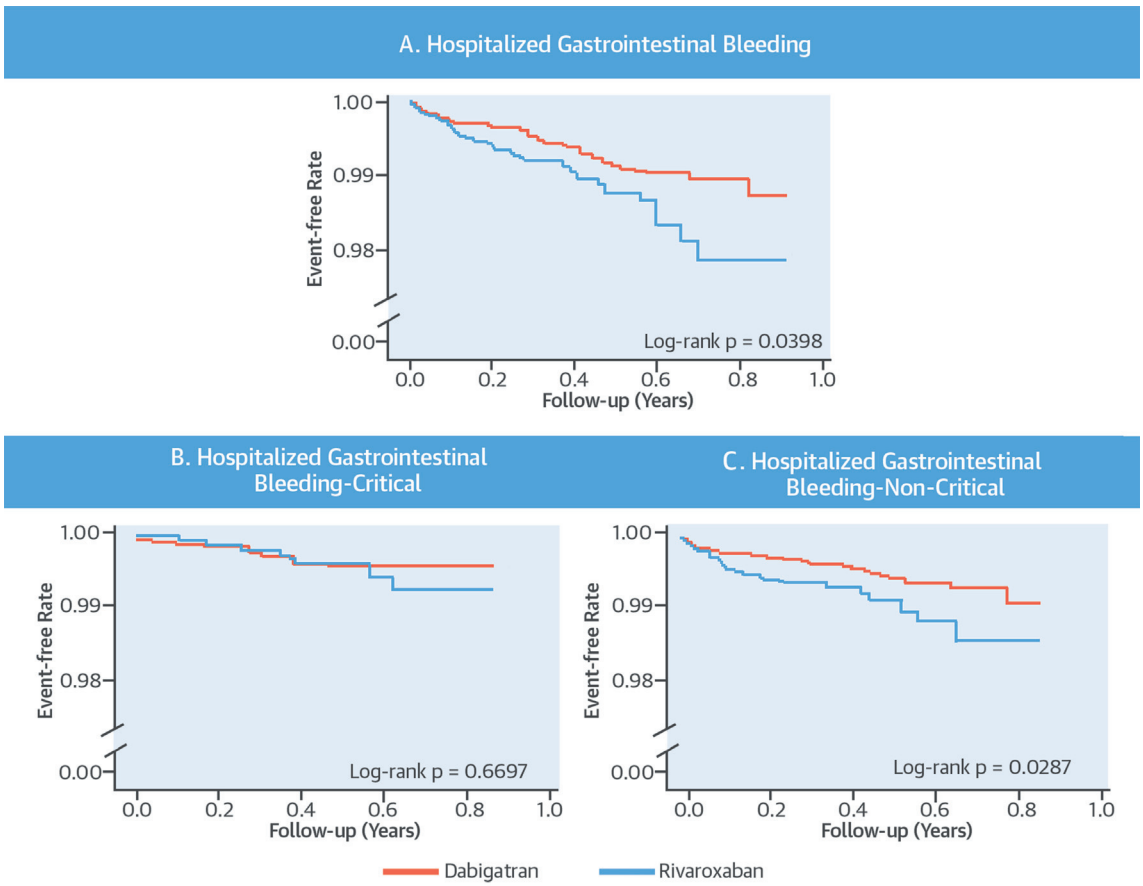
FIGURE 3 **Outcomes: Dabigatran Versus Warfarin**



Dabigatran (D) users had a significantly lower risk for ischemic stroke or systemic embolism **(A)**, intracranial hemorrhage **(B)**, hospitalization for any bleeding **(E)**, and all-cause mortality **(F)** and a similar risk for acute myocardial infarction **(C)** and hospitalization for gastrointestinal bleeding **(D)** compared with warfarin (W) users.

Therefore, low-dose NOACs may be potent enough at reducing thromboembolic events in Asians with low body mass. Another issue is the inadequate time in the therapeutic range of warfarin, which is commonly seen in Taiwan as well as in other Asian countries (18,19). Moreover, warfarin has been known to interact with several herbal drugs and beverages, including dong quai, ginseng, ginger, garlic, ginkgo,

CENTRAL ILLUSTRATION **Hospitalization for Gastrointestinal Bleeding With Non-Vitamin K Antagonist Oral Anticoagulant Agents**



Chan, Y.-H. et al. J Am Coll Cardiol. 2016;68(13):1389–401.

Compared with each other, rivaroxaban carried a significantly higher risk for hospitalization for gastrointestinal bleeding **(A)**, driven by significant differences in noncritical **(C)** rather than critical **(B)** bleeding.

and green tea, which are commonly used in Asian countries (20). The frequent drug-drug interactions may interfere with the stability of INR maintenance in Asians. Furthermore, most physicians in Asia implicitly target the low end of the target range of INR for their patients taking VKAs because of particular concern about the higher risk for ICH seen among Asians compared with non-Asian patients, even when INR is ideally maintained (9,18). Chan et al. (21) recently reported that low-dose dabigatran was associated with a superior reduction in stroke risk and ICH compared with warfarin, which was associated with a time in the therapeutic range ≥55% in older Chinese patients with AF. Those investigators speculated that higher plasma concentration of dabigatran caused by advanced age and reduced creatinine clearance may explain the superior performance of low-dose dabigatran in their patients. This rationale also may help explain findings of the present study, because the indications for NOACs are restricted to older Taiwanese (age ≥65 years), and Taiwanese have been noted to have a high prevalence of CKD (22); we showed higher bleeding with warfarin in patients with CKD in this study. The J-ROCKET AF trial also indicated that the pharmacokinetic profile of a 15-mg dose of rivaroxaban in Japanese patients was similar to that of a 20-mg dose in Caucasian patients (17) and further confirmed that low-dose rivaroxaban

significantly reduced the risk for ischemic stroke. Further study is warranted to define the optimal dose of NOACs in older Asians with AF.

The present study specifically focused on "short-term" outcomes because of 2014 NHIRD data unreleased until now, meaning that the duration of all patients taking OACs was <1 year (February 1 to December 31, 2013). Notably, early thromboembolic and bleeding events can have a major impact on the overall success of treatment in patients with AF, which is closely related to the persistence of long-term treatment (23). However, the results of the present study differed from those of a recent observational study using a French medical-administrative database that found no significant differences in bleeding or thromboembolic risk for dabigatran or rivaroxaban versus VKA during the early phase of treatment (24). In contrast, our analyses indicated that low-dose NOACs can be safer and more effective alternatives to warfarin, specifically in Asians during the early phase of treatment. However, we unexpectedly found that rivaroxaban carried a higher risk for hospitalization for GI bleeding than dabigatran in this large Asian cohort. Recently, results of a large real-world study presented by Tepper et al. (25) indicated that rivaroxaban users (n = 30,529) appear to have higher risk for major GI bleeding than dabigatran (n = 20,963) and apixaban (n = 8,785) users in the first 6 months after treatment initiation. Although the data source of Tepper et al. was from patients with non-Asian ethnicity, our study population was still similar to their cohort, as both study cohorts comprised new NOAC initiators and/or switchers from warfarin; plus, both studies focused specifically on short-term outcomes after NOAC initiation. The age distribution and other baseline characteristics of the cohort in the present study were similar between dabigatran and rivaroxaban groups (**Tables 1** and **2**). The increased risk for GI bleeding in the rivaroxaban group may be explained by several unmeasured confounders, including poor compliance or unmeasured serious comorbidities. One possible explanation is that the rivaroxaban group comprised a higher proportion of switchers from another OAC (~63%) than the dabigatran group (~53%). The ROCKET AF subgroup analysis indicated that VKA-experienced patients have a significantly higher risk for major bleeding than VKA-naive patients (26). In contrast, the RE-LY trial revealed that both VKA-experienced and VKA-naive dabigatran users had similar safety outcomes compared with warfarin (27). Like the subgroup analyses of the RE-LY and ROCKET AF trials, the present study revealed that OAC-experienced rivaroxaban users carried a significantly higher risk for GI bleeding than OAC-naive rivaroxaban users, while the risk for GI bleeding was similar between OAC-experienced and OAC-naive dabigatran users compared with warfarin (Online Figure 3). Further studies enrolling larger cohorts of Asian subjects are necessary to confirm our findings for risk for GI bleeding between dabigatran and rivaroxaban during the early phase of treatment.

STUDY LIMITATIONS. First, renal excretion rates of rivaroxaban and dabigatran are largely different, and the choice of the low dose of NOACs may be guided according to the measurements of serum renal function for each patient. However, the NHIRD does not contain laboratory data, so important information was not available for analysis, including serum hemoglobin, renal and liver function, and INR. Because the coding of CKD depends entirely on each physician's choice in clinical practice, the population of patients with CKD may have been heterogeneously contaminated in our study. Also, although a number of variables were selected in our propensity score model, and a close balance of those factors was achieved, residual confounding by unmeasured factors cannot be excluded. Coding errors of outcomes and comorbidities registered by each physician constitute a limitation of Taiwan's NHIRD. However, only primary discharge diagnoses were used, to improve the outcome accuracy of the present study. Furthermore, the reliability of the AF database for the NHIRD and the diagnostic accuracies of those factors have been validated previously (28–31).

Another potential limitation was the adherence rate of anticoagulant agents in our study, which was calculated on the basis of the prescription period divided by the total follow-up period. The actual adherence rate may have been lower than the prescription rate obtained in the study. Additionally, we did not classify the patient group on the basis of initial anticoagulant regimen, because of the complexity of anticoagulant switching during the treatment course. If patients are grouped on the basis of their initial regimens, it may be hard to conclusively attribute risk for a specific clinical event to a particular anticoagulant regimen or possible switching/bridging gaps between different regimens during follow-up. Instead, we classified each patient on the basis of his or her final anticoagulant regimen and followed from "first prescription of final anticoagulant (the index date)" until the study end date or the occurrence of an event, which might have reduced the contamination of other

anticoagulant agents. However, the possibility of misclassification for patient groups could not be avoided.

Finally, the follow-up period of NOAC administration in our study was short because of 2014 NHIRD data unreleased. Although significant divergence exists for thromboembolic events, ICH, and all-cause mortality between NOACs and warfarin during the early phase of treatment, it is unclear whether the efficacy and safety of NOACs persist after long-term follow-up. Also, other NOACs, such as apixaban and edoxaban, were not included because they were approved after 2014 in Taiwan.

CONCLUSIONS

Low-dose rivaroxaban and dabigatran were associated with reduced risk for ischemic stroke or systemic embolism, ICH, and all cause-mortality compared with warfarin in a large Asian cohort. The 2 NOACs were not associated with significantly higher risk for hospitalization for GI bleeding or AMI than warfarin. Although rivaroxaban carried a higher risk for GI bleeding than dabigatran in this large Asian cohort for the intention-to-treat analysis, in the on-treatment analysis, the risk for GI bleeding was similar between these NOACs. Either rivaroxaban or dabigatran may be a safer and more effective alternative to warfarin in Asian patients with NVAF.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Lai-Chu See, Department of Public Health, College of Medicine, Chang Gung University, Taoyuan, Taiwan. E-mail: lichu@mail.cgu.edu.tw.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Limited data indicated that NOACs may be more effective and safer in Asians than in non-Asians. This was the first population-based study to investigate efficacy and safety with a specific focus on Asians with NVAF taking rivaroxaban, dabigatran, or warfarin during the same period.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Low-dose rivaroxaban and dabigatran were associated with a reduced risk for ischemic stroke or systemic embolism, ICH, and all-cause mortality without increasing risk for AMI or hospitalized GI bleeding compared with warfarin in a national Asian cohort during the early phase of treatment. Although rivaroxaban carried a higher risk for hospitalization for GI bleeding than dabigatran for the intention-to-treat analysis, that risk was similar in the on-treatment analysis.

TRANSLATIONAL OUTLOOK 1: Although this was a relatively short-term study, long-term follow-up of Asians taking NOACs will lead to better understanding of the comparative benefits conveyed by these 2 NOACs versus warfarin.

TRANSLATIONAL OUTLOOK 2: Further study enrolling more Asian subjects is necessary to confirm findings of the present study regarding different levels of risk for hospitalization for GI bleeding between rivaroxaban and dabigatran.

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KEY WORDS direct thrombin inhibitor, factor Xa inhibitor, hemorrhage, mortality, warfarin

APPENDIX For supplemental tables and figures, please see the online version of this article.