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Acute Kidney Injury in Asians With Atrial Fibrillation Treated With Dabigatran or Warfarin

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ABSTRACT

BACKGROUND Whether dabigatran is associated with a lower risk of acute kidney injury (AKI) in patients with nonvalvular atrial fibrillation (NVAF) remains unknown.

OBJECTIVES The authors compared the risk of AKI in Asians with NVAF who were prescribed dabigatran versus warfarin.

METHODS The authors analyzed patients enrolled in the Taiwan nationwide retrospective cohort study from June 1, 2012, to December 31, 2013. Dabigatran and warfarin were taken by 7,702 and 7,885 NVAF patients without a history of chronic kidney disease (CKD) and 2,256 and 2,089 NVAF patients with a history of CKD, respectively. A propensity-score weighted method was used to balance covariates across study groups.

RESULTS A total of 6,762 (88%) and 940 (12%) CKD-free patients and 2,025 (90%) and 231 (10%) CKD patients took dabigatran 110 mg and 150 mg twice daily, respectively. Dabigatran was associated with a lower risk of AKI than warfarin for either the CKD-free (hazard ratio [HR]: 0.62; 95% confidence interval [CI]: 0.49 to 0.77; $p < 0.001$) or CKD (HR: 0.56; 95% CI: 0.46 to 0.69; $p < 0.001$) cohort. As the increment in CHA_2DS_2-VASc score (a risk score based on congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke/transient ischemic attack, vascular disease, aged 65 to 74 years, and female sex) increased from 0/1 to 6+ points, the incidence of AKI for the dabigatran group was relatively stable (1.87% to 2.91% per year for the CKD-free cohort; 7.31% to 13.15% per year for the CKD cohort) but increased obviously for patients taking warfarin for either CKD-free (2.00% to 6.16% per year) or CKD cohorts (6.82 to 26.03% per year). The warfarin group had a significantly higher annual risk of AKI than the dabigatran group for those with a high CHA_2DS_2-VASc score (≥4 for the CKD-free cohort and ≥3 for the CKD cohort). Subgroup analysis revealed that among dabigatran users, those taking either low-dose or standard-dose dabigatran, those with a warfarin-naïve or warfarin-experienced history, those with or without diabetes, and those with CHA_2DS_2-VASc ≥4 or HAS-BLED ≥3 (risk score based on hypertension, abnormal renal and liver function, stroke, prior major bleeding, labile international normalized ratios, age 65 years or older, drugs or alcohol usage history) all had a lower risk of AKI than those taking warfarin.

CONCLUSIONS Among Asians with NVAF, dabigatran is associated with a lower risk of AKI than warfarin.

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Oral anticoagulant drugs (OACs), like vitamin K antagonists (e.g., warfarin), have been shown to decrease the risk of thromboembolic events and all-cause mortality in patients with atrial fibrillation (AF) (1). OACs can also increase the risk of hemorrhage caused by coagulopathy. Although warfarin has been commonly used for more than 60 years, its harmful effects on renal function (so-called warfarin-related nephropathy [WRN]) have only recently been recognized (2,3). It is estimated that as many as 20.5% of all patients taking warfarin have experienced at least 1 episode of WRN during their treatment course, with most cases occurring within 1 year after the initiation of treatment (3,4). Dabigatran, a competitive direct thrombin inhibitor, is increasingly used for the prevention of ischemic stroke and systemic embolism in patients with nonvalvular AF as a safer alternative to warfarin with a lower risk of intracranial hemorrhage and other causes of major bleeding (5).

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Dabigatran is excreted primarily from the kidney; however, little is known about its effects on kidney function. In animal models, dabigatran has been shown to produce acute kidney injury (AKI) and hematuria, similar to warfarin (6). Although the incidence of AKI was not significantly different between dabigatran and warfarin in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial, there have been some case reports of AKI occurring with dabigatran use (7,8). Interestingly, the post hoc analysis of RE-LY indicated that patients with AF receiving dabigatran exhibited a slower decline in renal function than those taking warfarin, and the decline of renal function was amplified by previous warfarin use and the presence of diabetes mellitus (9). The magnitude of AKI risk associated with dabigatran and warfarin as administered to AF patients remains unknown in the real-world clinical setting. The objective of this study was to compare the risk of AKI associated with dabigatran versus warfarin among patients with nonvalvular AF.

METHODS

STUDY POPULATION. This was a nationwide retrospective cohort study in which all patient data were obtained from the Taiwan National Health Insurance Registry Database (NHIRD). The National Health Insurance program is a mandatory universal health insurance system in Taiwan, which has contracts with 97% of the hospitals in Taiwan and provides comprehensive medical care coverage to 99% of the 23.74 million Taiwanese. Because the original NHIRD identification number belonging to each patient is encrypted and de-identified to protect their privacy, informed consent was waived for this study. The claims for each individual patient could be linked and continuously followed because of the consistent data encryption process used. Diagnoses were coded according to the International Classification of Diseases-Ninth Revision-Clinical Modification (ICD-9-CM). The study protocol was approved by the Institutional Review Board of Chang Gung Memorial Hospital, Taiwan.

STUDY DESIGN AND OUTCOME. A cohort with 2 study groups (dabigatran and warfarin) was used in this study. A flowchart of the study cohort enrollment is shown in **Figure 1**. A total of 304,252 new AF patients (ICD-9-CM code 427.31) were identified from January 1, 1996, to December 31, 2013. Among these 304,252 patients, 89,705 had at least 1 prescription filled for dabigatran or warfarin after AF was diagnosed. The approval date for dabigatran in Taiwan was June 1, 2012. The index date was defined as the first date of prescribing dabigatran or warfarin after June 1, 2012. Patients were excluded if they had pulmonary embolism or deep vein thrombosis within 6 months before AF diagnosis (n = 1,618), received joint replacement or valvular surgery within 6 months before AF diagnosis (n = 2,747), had end-stage renal disease before the index date (n = 9,651), were <30 years of age (n = 223), had taken dabigatran first and then switched to warfarin (n = 284), or had started taking warfarin before June 1, 2012, and did not shift to dabigatran after June 1, 2012 (n = 55,250). In total, 19,932 patients were eligible for this study. Of these, 15,587 did not have a history of chronic kidney disease (CKD) compared with 4,345 who did before the index date. Patients with CKD history were defined as those who were diagnosed with ICD-9-CM codes 580 through 589 at least twice at an outpatient clinic or at discharge (10). Among patients without any history of CKD, 7,702 and 7,885 patients took the first dose of dabigatran or warfarin, respectively, from June 1, 2012, to December 31, 2013, based on each patient's final anticoagulant status. Among patients with a history of CKD, 2,256 and 2,089 patients took the first dose of dabigatran or warfarin, respectively, during the same time period.

The follow-up period was defined from the index date until the first occurrence of AKI or the end

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AKI = acute kidney injury

ASMD = absolute standardized mean difference

CHA_2DS_2-VASc = congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke/transient ischemic attack, vascular disease, age 65 to 74 years, female

CKD = chronic kidney disease

GFR = glomerular filtration rate

HAS-BLED = hypertension, abnormal renal and liver function, stroke, prior major bleeding, labile INRs, aged 65 years or older, drugs or alcohol usage history

ICD-9-CM = International Classification of Diseases-Ninth Revision-Clinical Modification

INR = international normalized ratio

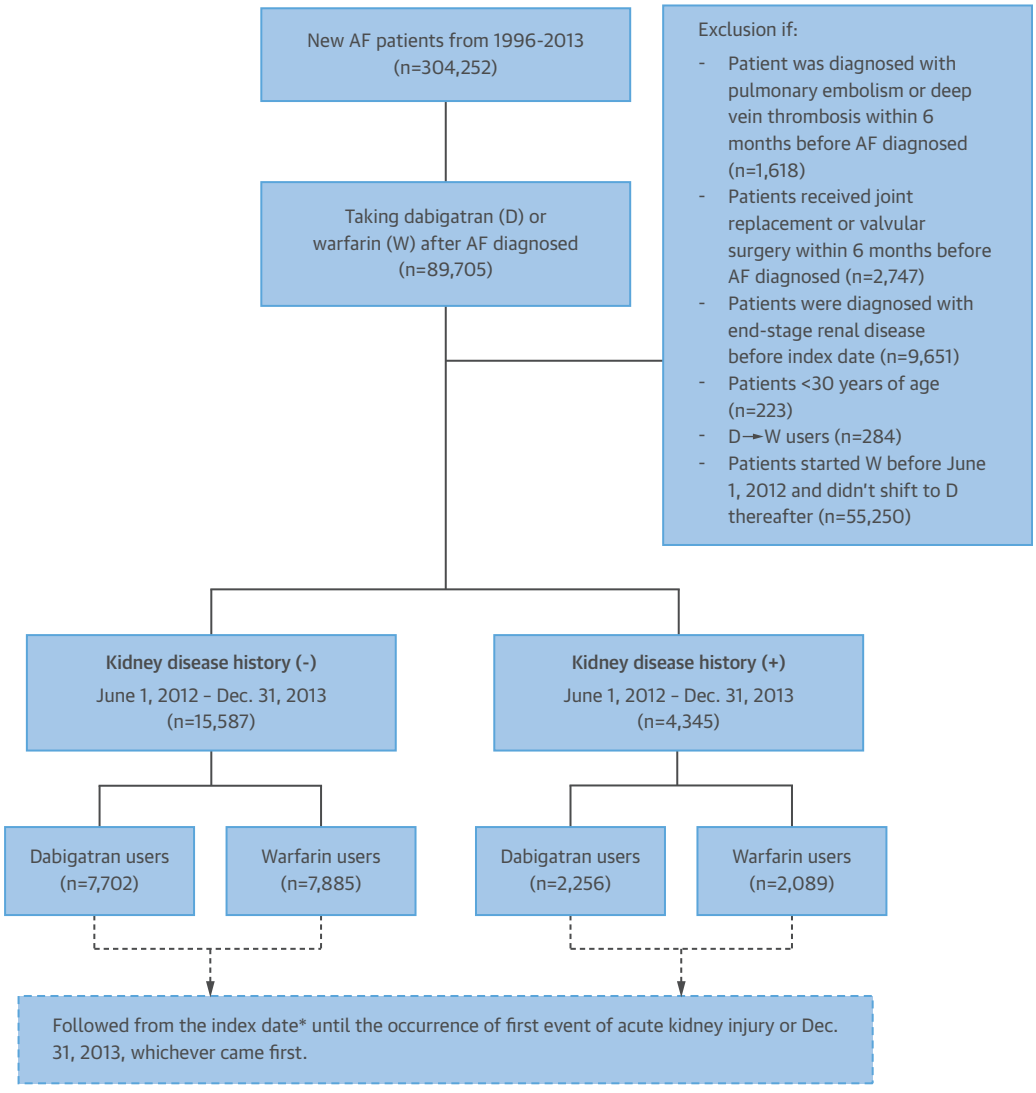
NHIRD = National Health Insurance Registry Database

NOAC = non-vitamin K antagonist oral anticoagulant

OAC = oral anticoagulant

WRN = warfarin-related nephropathy

FIGURE 1 Enrollment of Patients With Nonvalvular AF



From June 1, 2012, to December 31, 2013, this study evaluated a total of 7,702 dabigatran versus 7,885 warfarin users who had nonvalvular atrial fibrillation (AF) and no previous history of chronic kidney disease (CKD). Another study cohort of 2,256 dabigatran and 2,089 warfarin users with previous history of CKD was also enrolled during the same study period. *The index date was defined as the first date of prescribing dabigatran or warfarin after June 1, 2012 for each group. D = dabigatran; W = warfarin.

date of the study period (December 31, 2013), whichever came first. The outcome of AKI was defined as those who received a diagnosis coded as ICD-9-CM 580.X, 584.X, or 586 during hospitalization or during at least 1 outpatient visit. The validation of ICD-9-CM codes for identifying AKI was performed previously, and the positive predictive value of AKI was 0.96 compared with the clinical diagnosis of AKI based on the Acute Kidney Injury Network criteria (11,12). The definition of AKI using the Acute Kidney Injury Network criteria was an absolute increase in serum creatinine of ≥0.3 mg/dl, a percentage increase in serum creatinine of ≥50%, or a reduction in urine output (documented oliguria of <0.5 ml/kg/h for more than 6 h) within 48 h (12). Other studies have also validated the diagnostic accuracy of AKI records in the NHIRD (13,14). ICD-9-CM codes used for the study outcomes and other baseline covariates are summarized in Online Table 1.

VALIDATION. We also validated the ICD-9-CM codes for identifying AKI by analyzing the medical records of 372 consecutive AF patients in the inpatient claims database of Chang Gung Memorial Hospital, Linkou, the largest medical center in Taiwan, between January 2010 and December 2015. Clinical diagnosis of AKI was determined according to the Acute Kidney Injury Network criteria (12). There were 130 confirmed cases of AKI during the hospital course, and 119 could be identified by an ICD-9-CM code indicating AKI (580.X, 584.X, and 586) in the discharge claims. The sensitivity, specificity, positive predictive value, and negative predictive value of ICD-9-CM code to indicate AKI versus a clinical diagnosis of AKI based on the Acute Kidney Injury Network criteria were 0.92, 1.00, 1.00, and 0.96, respectively. The following equations were used: sensitivity = [TP / (TP + FN)], specificity = [TN / (TN + FP)], positive predictive value = [TP / (TP + FP)], and negative predictive value = [TN / (TN + FN)], where TP is true positive, TN is true negative, FP is false positive, and FN is false negative.

COVARIATES. Risk factors for kidney injury, including age, comorbidities, previous bleeding history, and medication history, such as use of nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, aminoglycoside, and steroids at baseline, were referenced to any claim record with the previously mentioned diagnoses or medication codes before the index date. A specific medication history was confined to at least 1 prescription within 3 months preceding the index date. A bleeding history was confined to events within 6 months preceding the index date (15). The CHA_2DS_2-VASc score was calculated based on the summation of the following risk factors: 2 points for age 75 years or older or previous stroke/transient ischemic attack and 1 point each for congestive heart failure, hypertension, diabetes mellitus, vascular disease, age 65 to 74 years, and female sex (15). The HAS-BLED score was calculated according to the summation of the following risk factors (1 point for each risk factor if present): hypertension, abnormal renal and liver function, stroke, prior major bleeding, labile international normalized ratios (INRs), age 65 years or older, and history of drug or alcohol use (15).

STATISTICAL ANALYSIS. The risk of AKI for dabigatran versus warfarin (reference) was obtained using incidence rate and survival analysis (Kaplan-Meier method and log-rank test for univariate analysis, and Cox proportional hazards regression for multivariate analysis). Incidence rates were calculated using the total number of study outcomes during the follow-up period divided by person-years at risk. The propensity score method, which simulates the randomized allocation in a clinical trial for observational cohort data, was used to examine the effects of dabigatran and warfarin on AKI.

The propensity score is the predicted probability of treatment conditioned on selected covariates using logistic regression. In this study, all baseline characteristics in **Tables 1 and 2** were included in the logistic regression to obtain the propensity score, except for CHA_2DS_2-VASc and HAS-BLED scores, because these latter 2 variables are a combination of some of the comorbidities in **Tables 1 and 2**. The inverse probability of treatment weights of propensity scores was used to balance covariates between dabigatran users and warfarin users with regard to time-to-event analyses (Cox proportional hazards model, log-rank test, and incidence rate). The balance of covariates at baseline between dabigatran users and warfarin users was assessed with the absolute standardized mean difference (ASMD) rather than statistical testing, because balance is a property of the sample and not of an underlying population. ASMD $\leq$0.1 indicates a negligible difference in potential confounders between the dabigatran and warfarin groups (16). Subgroup analysis was performed to determine whether the risk of AKI in the dabigatran group compared with the warfarin group was similar in subgroups. Note that propensity score was reobtained for each subgroup analysis to allow covariate balance in the 2 user groups. Statistical significance was defined as a $p < 0.05$. All statistical analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, North Carolina).

RESULTS

A total of 7,702 and 7,885 consecutive patients without a previous history of kidney disease who were taking dabigatran and warfarin, respectively, between June 1, 2012 and December 31, 2013, were eligible. The median follow-up period was 0.69 years for dabigatran users and 0.79 years for warfarin users. Before propensity score weighting, the dabigatran group was older, had higher CHA_2DS_2-VASc and HAS-BLED scores, and had a higher proportion of comorbidities than the warfarin group (**Table 1**). After propensity score weighting, the dabigatran and warfarin groups were well balanced for most characteristics (ASMD <0.1) (**Table 1**). For the CKD cohort, the medium follow-up period was 0.69 years for dabigatran users (n = 2,256) and 0.71 years for warfarin users (n = 2,089). Similar to the CKD-free cohort, the dabigatran group was older and had higher CHA_2DS_2-VASc and

TABLE 1 Baseline Characteristics of Patients With Nonvalvular Atrial Fibrillation Without Kidney Disease History Taking Dabigatran and Warfarin, Before and After Propensity Score Weighting

	Propensity Score Weighting					
	Before			After		
	Dabigatran (n = 7,702)	Warfarin (n = 7,885)	ASMD	Dabigatran (n = 7,702)	Warfarin (n = 7,885)	ASMD
Age, yrs	75 ± 10	70 ± 12	0.4059	75 ± 10	75 ± 10	0.0321
<65	14	33		14	13	
65–74	30	27		30	29	
75–84	42	29		42	43	
>85	14	12		14	15	
Male	57	55	0.0447	57	56	0.0133
CHA_2DS_2-VASc	4.02 ± 1.59	3.20 ± 1.79	0.4810	4.02 ± 1.59	4.06 ± 1.73	0.0283
HAS-BLED	2.87 ± 0.99	2.46 ± 1.16	0.3779	2.87 ± 0.99	2.94 ± 1.07	0.0687
Chronic liver disease	24	19	0.1317	24	24	0.0019
Congestive heart failure	14	13	0.0250	14	14	0.0034
Hypertension	85	73	0.3002	85	85	0.0136
Hyperlipidemia	48	37	0.2156	48	48	0.0062
Diabetes mellitus	38	31	0.1406	38	38	0.0074
Previous stroke	33	20	0.3005	33	33	0.0094
Previous TIA	5	2	0.1547	5	5	0.0139
Myocardial infarction	3	3	0.0026	3	3	0.0038
History of bleeding	1	1	0.0160	1	1	0.0207
Use of NSAIDs	25	28	0.0841	25	26	0.0242
Use of antiplatelet agents	47	61	0.2901	47	53	0.1134
Use of aminoglycoside	2	4	0.1161	2	2	0.0109
Use of ACEI/ARB	63	60	0.0579	63	62	0.0039
Use of steroids	5	9	0.1608	5	6	0.0173
PCI	7	5	0.0608	7	7	0.0212
CABG	1	1	0.0355	1	1	0.0080

Values are mean ± SD or %.

ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin II receptor antagonists; ASMD = absolute standardized mean difference; CABG = coronary artery bypass graft; CHA_2DS_2-VASc = congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke/transient ischemic attack, vascular disease, age 65 to 74 years, female (15); HAS-BLED = hypertension, abnormal renal or liver function, stroke, bleeding history, labile international normalized ratio, age 65 years or older, and antiplatelet drug or alcohol use (15) (labile international normalized ratio could not be determined from claims and was excluded from our scoring); PCI = percutaneous coronary intervention; NSAIDs = nonsteroidal anti-inflammatory drugs; TIA = transient ischemic attack.

HAS-BLED scores than the warfarin group before propensity score weighting (**Table 2**).

In the CKD-free cohort, the incidence rate for AKI was 2.17 (95% CI: 1.78 to 2.56) and 3.47 (95% CI: 2.99 to 3.95) per 100 person-years for the dabigatran and warfarin groups, respectively. In the CKD cohort, the incidence rate for AKI was 9.28 (95% CI: 7.76 to 10.79) and 16.21 (95% CI: 14.22 to 18.19) per 100 person-years for the dabigatran and warfarin groups, respectively. In the CKD-free cohort, there were 71% and 68% inpatient diagnoses of AKI in the dabigatran and warfarin groups, respectively. In the CKD cohort, there were 53% and 47% inpatient diagnoses of AKI in the dabigatran and warfarin groups, respectively. The mortality rate was 3.09% per year (95% CI: 2.62% to 3.56% per year) versus 5.92% per year (95% CI: 5.30% to 6.54% per year) in the CKD-free cohort and 5.52% per year (95% CI: 4.37% to 6.66% per year) versus 12.52% per year (95% CI: 10.84% to 14.20% per year) in the CKD cohort, respectively, in the dabigatran and warfarin groups. The incidence of need for renal replacement therapy was 0.00% per year (95% CI: 0.00% to 0.00% per year) versus 0.03% per year (95% CI: 0.00% to 0.12% per year) in the CKD-free cohort and 0.37% per year (95% CI: 0.14% to 0.81% per year) versus 1.43% per year (95% CI: 0.86% to 2.00% per year) in the CKD cohort, respectively, for the dabigatran and warfarin groups. Early separation of cumulative event curves for AKI, renal replacement therapy, and mortality after propensity score weighting in the 2 study groups were noted for both the CKD-free and CKD cohorts (**Central Illustration**, Online Figures 1 and 2). Dabigatran was associated with a significantly lower risk of AKI than warfarin in both the CKD-free and CKD cohorts (hazard ratio [HR]: 0.62; 95% CI: 0.49 to 0.77; $p < 0.001$ for the CKD-free cohort and HR: 0.56; 95% CI: 0.46 to 0.69; $p < 0.001$ for the CKD cohort, respectively).

TABLE 2 Baseline Characteristics of Patients With Nonvalvular AF With Kidney Disease History Taking Dabigatran and Warfarin, Before and After Propensity Score Weighting

	Propensity Score Weighting					
	Before			After		
	Dabigatran (n = 2,256)	Warfarin (n = 2,089)	ASMD	Dabigatran (n = 2,256)	Warfarin (n = 2,089)	ASMD
Age, yrs	77 ± 9	75 ± 10	0.1839	77 ± 9	77 ± 9	0.0191
<65	7	16		7	7	
65-74	26	25		26	26	
75-84	48	39		48	48	
>85	19	20		19	19	
Male	62	59	0.0690	62	62	0.0057
CHA_2DS_2-VASc score	4.52 ± 1.51	4.17 ± 1.64	0.2265	4.52 ± 1.51	4.50 ± 1.63	0.0126
HAS-BLED score	4.24 ± 0.93	4.11 ± 1.00	0.1307	4.24 ± 0.93	4.28 ± 1.04	0.0456
Chronic liver disease	41	38	0.0672	41	41	0.0075
Congestive heart failure	21	24	0.0679	21	21	0.0011
Hypertension	94	92	0.0695	94	94	0.0060
Hyperlipidemia	66	61	0.0994	66	66	0.0070
Diabetes mellitus	54	53	0.0317	54	54	0.0059
Previous stroke	33	23	0.2341	33	32	0.0278
Previous TIA	7	4	0.1225	7	7	0.0058
Myocardial infarction	4	5	0.0435	4	4	0.0139
History of bleeding	1	1	0.0091	1	2	0.0271
Use of NSAIDs	30	33	0.0503	30	32	0.0334
Use of antiplatelet agents	49	64	0.3191	49	52	0.0718
Use of aminoglycoside	3	4	0.0935	3	3	0.0084
Use of ACEI/ARB	68	67	0.0203	68	68	0.0045
Use of steroids	7	12	0.1798	7	7	0.0112
PCI	10	9	0.0158	10	10	0.0027
CABG	1	2	0.0795	1	1	0.0059

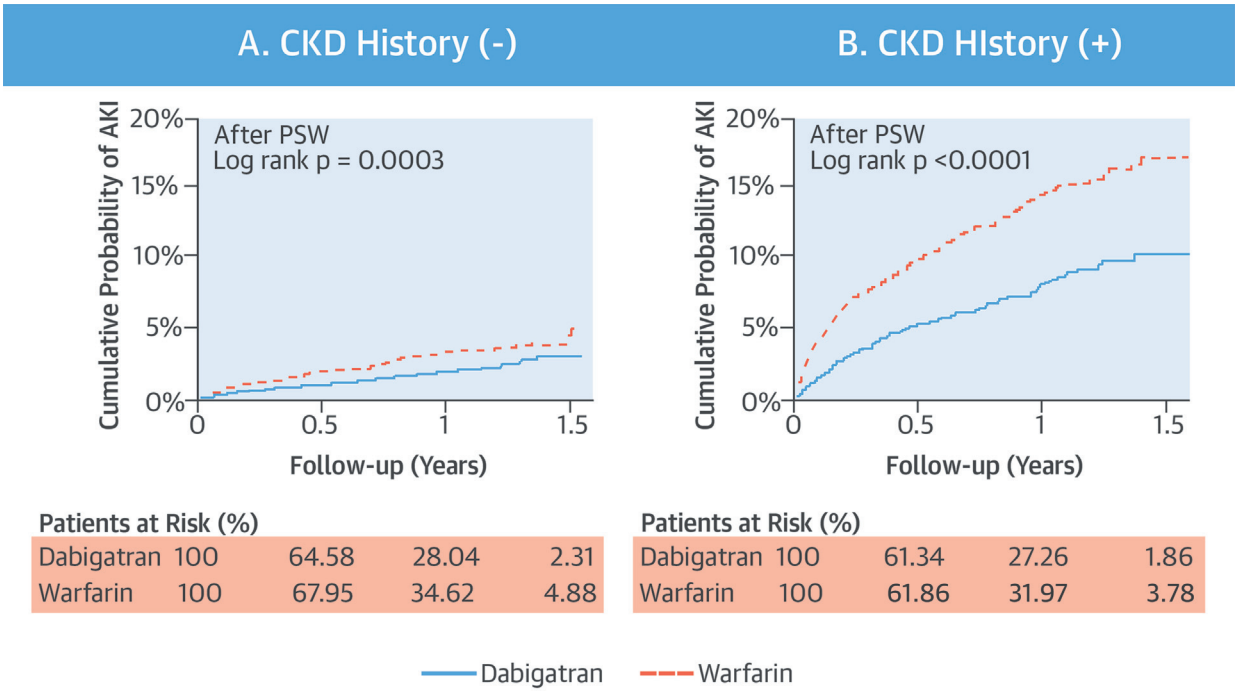
Values are mean ± SD or %.
Abbreviations as in Table 1.

Of note, the annual incidence of AKI for the warfarin group increased obviously with incremental CHA_2DS_2-VASc score for both the CKD-free and CKD cohorts, but the annual incidence of AKI for the dabigatran group was consistent irrespective of the CHA_2DS_2-VASc score after propensity score weighting. The annual risk of AKI for the warfarin group increased from 2.00% (95% CI: 1.13% to 2.86%) to 6.16% (95% CI: 4.33% to 7.99%) and from 6.82% (95% CI: 2.39% to 15.25%) to 26.03% (95% CI: 20.13% to 31.93%) for the CKD-free and CKD cohorts, respectively, whereas the CHA_2DS_2-VASc score increased from 0/1 to ≥6 points. It was noted that the warfarin group had a significantly higher annual risk of AKI than the dabigatran group for those with high CHA_2DS_2-VASc scores (Figure 2).

Subgroup analysis was performed to determine whether the dabigatran group had a lower risk of AKI than the warfarin group. In the CKD-free cohort, a total of 6,762 (88%) and 940 (12%) patients were taking dabigatran 110 mg and 150 mg twice daily, respectively. There were 4,192 patients (54%) with previous warfarin experience among the dabigatran group. Among the dabigatran users, those taking low or standard doses, with or without previous treatment with warfarin, older or younger than 75 years of age, and with or without diabetes all had a lower risk of AKI than those taking warfarin. In contrast to patients with low CHA_2DS_2-VASc (<4) or HAS-BLED (<3) scores, dabigatran users with high CHA_2DS_2-VASc (≥4) or HAS-BLED (≥3) scores had a lower risk of AKI than with warfarin (Figure 3). For the CKD cohort, there were 2,025 (90%) and 231 (10%) patients taking dabigatran 110 mg and 150 mg twice daily, respectively. Likewise, the results indicated that dabigatran was associated with a lower risk of AKI in most subgroups (Figure 4).

A Cox model was performed without propensity score weighting to identify the independent risk factors for new-onset AKI for those patients taking OACs. Among CKD-free patients taking OACs, age (HR: 1.03; 95% CI: 1.02 to 1.04; $p < 0.0001$), use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (HR: 1.37; 95% CI: 1.07 to 1.75; $p = 0.0112$), use of steroids (HR: 1.55; 95% CI: 1.10 to 2.17; $p = 0.0114$),

CENTRAL ILLUSTRATION **AKI in Patients With Nonvalvular AF Treated With Dabigatran or Warfarin: Cumulative Probability After PSW**



Chan, Y.-H. et al. J Am Coll Cardiol. 2016;68(21):2272–83.

Dabigatran users **(solid line)** had a significantly lower risk of acute kidney injury (AKI) than warfarin users **(dashed line)** after propensity score weighting (PSW) in both the chronic kidney disease (CKD)-free **(A)** and CKD **(B)** cohorts. AF = atrial fibrillation.

and presence of congestive heart failure (HR: 1.91; 95% CI: 1.47 to 2.48; $p < 0.0001$) were independent risk factors for new-onset AKI. It was noted that dabigatran was still associated with a lower risk of AKI than with warfarin after multivariate adjustment (HR: 0.61; 95% CI: 0.49 to 0.77; $p < 0.0001$) (Online Table 2). For the CKD cohort, age (HR: 1.02; 95% CI: 1.01 to 1.03; $p = 0.0002$), congestive heart failure (HR: 1.90; 95% CI: 1.54 to 2.34; $p < 0.0001$), diabetes (HR: 1.23; 95% CI: 1.01 to 1.50; $p = 0.0442$), use of dabigatran versus warfarin (HR: 0.55; 95% CI: 0.45 to 0.68; $p < 0.0001$), and steroid use (HR: 1.88; 95% CI: 1.44 to 2.45; $p < 0.0001$) were independent determinants of new-onset AKI (Online Table 3).

DISCUSSION

This is the first and largest population-based study to investigate the risk of AKI from OACs with a specific focus on Asians with nonvalvular AF taking dabigatran or warfarin during the same period. Our study showed that dabigatran was associated with a lower risk of AKI than warfarin, whether or not patients had any prior kidney disease. Patients who took warfarin had an increased risk of AKI as the CHA_2DS_2-VASc score increased in both the CKD-free and CKD cohorts. By contrast, the annual incidence of AKI for dabigatran users remained stable despite the increment in CHA_2DS_2-VASc score. It was noted that the warfarin group had a significantly higher annual risk of AKI than the dabigatran group for those patients with high CHA_2DS_2-VASc scores (≥4 for CKD-free cohort and ≥3 for CKD cohort). Subgroup analysis indicated that dabigatran users (either low dose or standard dose and with or without a previous history of taking warfarin) had a lower risk of AKI than warfarin users.

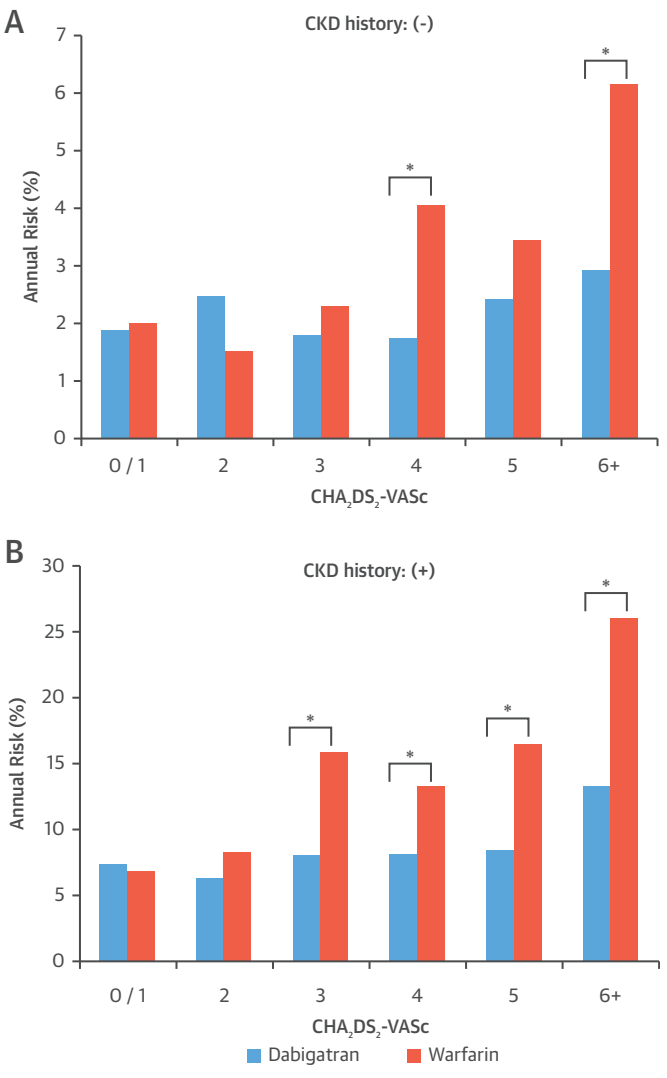
WRN is a common but underdiagnosed complication related to treatment with anticoagulant drugs that is associated with increased mortality and renal morbidity (3,4). The mechanisms underlying WRN are complicated and multifactorial, but supratherapeutic doses of warfarin with an INR >3.0 can result in glomerular hemorrhage and consequent tubular injury caused by obstructive tubular red blood cell

casts and heme-induced free radical injury (2,17). Warfarin also facilitates renal vascular calcification and the consequent decline in renal function via inhibition of the activation of matrix G1a protein and growth arrest-specific gene 6 (18–20). Furthermore, warfarin use has been correlated to other rare renal complications, including allergic interstitial nephritis, spontaneous atheromatous embolism, and renal pelvis/ureteral hematomas (21,22).

Dabigatran and other non-vitamin K antagonist oral anticoagulant drugs (NOACs) have a predictable dose-response effect and a lower risk of major bleeding events than with warfarin in AF patients. However, the question of the potential renal toxicity from NOACs remains unanswered. A few case reports describing dabigatran-related AKI have been reported (7,8). Ryan et al. (6) recently studied the effects of dabigatran on renal function in the 5/6 nephrectomy rat model with CKD. They demonstrated that dabigatran resulted in a dose-dependent increase in serum creatinine and hematuria in both control and CKD rats (6). It was noted that the histological findings in CKD rats treated with dabigatran were similar to those found in rats with WRN, involving acute tubular injury with red blood cell casts in the tubules. Furthermore, kidney injury was also seen in the control rats treated with dabigatran. Of note, both CKD and control rats took high doses of dabigatran, and thus, their results might not be directly applicable to humans. Ware et al. (23) also reported that both dabigatran and warfarin increased systolic blood pressure in a dose-dependent manner in their CKD rat models, and such increases in blood pressure could indirectly cause long-term kidney injury. A recent meta-analysis indicated that the risk of renal failure from the use of NOACs (dabigatran, apixaban, or rivaroxaban) was similar to that with traditional anticoagulant drugs such as warfarin or low-molecular-weight heparin (24); however, it was noted that rivaroxaban was associated with an increased risk of creatinine elevation in the J-ROCKET and RECORD 1-2 trials (25–27). Nevertheless, regular monitoring of renal function is important to avoid prescribing dabigatran or other NOACs at inappropriately high doses, especially when renal function has deteriorated, which can occur in AF patients with multiple well-known risk factors independent of NOAC administration.

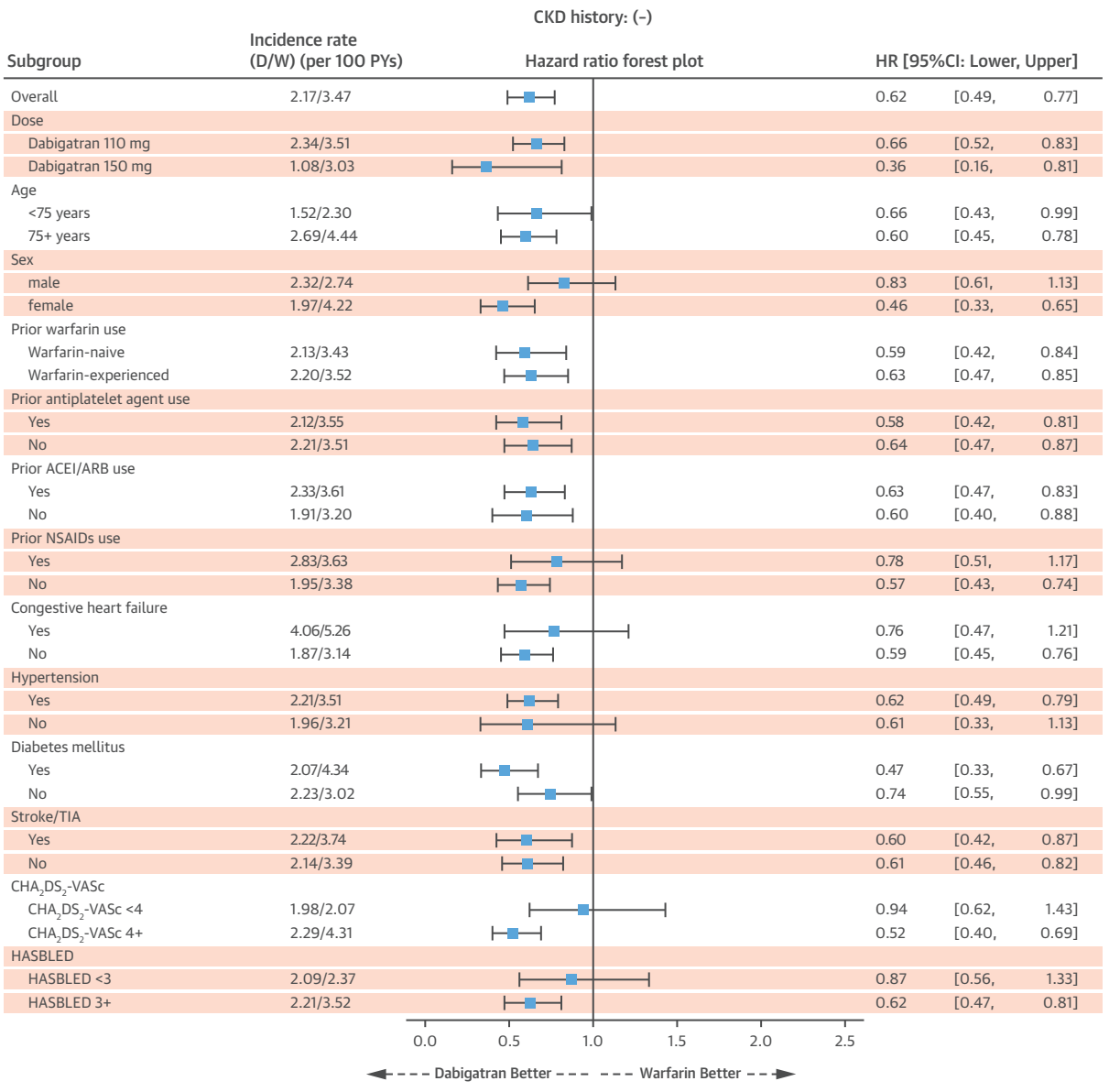
Several things might explain why dabigatran conferred a lower risk of AKI than warfarin in our Asian cohort. The RE-LY subgroup analysis indicated that dabigatran, at either low dose or standard dose, was associated with a lower risk of major bleeding events in Asian patients, and a major bleeding event is a common cause of acute renal failure (28,29). Our recent study of a large nationwide Asian cohort with nonvalvular AF also indicated that dabigatran was associated with a reduced risk of ischemic stroke, intracranial hemorrhage, and all hospitalized major bleeding, whereas it did not increase the risk of major gastrointestinal bleeding compared with warfarin over the same time period (15). The reduced number of thromboembolic events (e.g., renal infarction) and

FIGURE 2 Annual Risk of Acute Kidney Injury for Patients With Nonvalvular Atrial Fibrillation Who Were Treated With Dabigatran or Warfarin for Different CHA_2DS_2-VASc Scores After Propensity Score Weighting



Dabigatran users had a significantly lower annual risk of acute kidney injury than warfarin users with CHA_2DS_2-VASc score ≥4 for the chronic kidney disease (CKD)–free cohort **(A)** and CHA_2DS_2-VASc score ≥3 for the CKD cohort **(B)**. CHA_2DS_2-VASc score = congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke/transient ischemic attack, vascular disease, age 65 to 74 years, female (15). *$p < 0.05$.

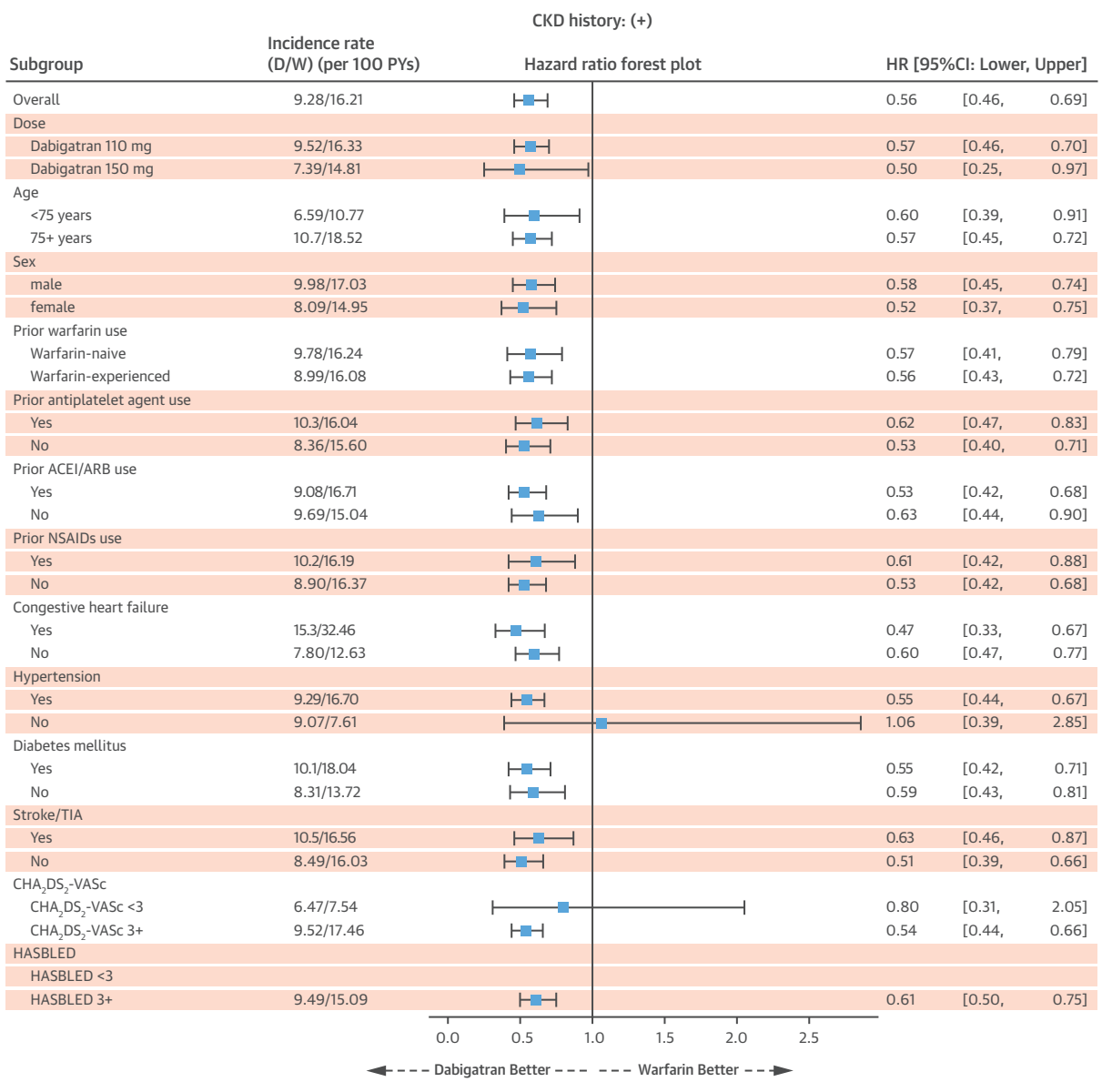
FIGURE 3 **Forest Plot of Hazard Ratio of Acute Kidney Injury for Patients With Nonvalvular Atrial Fibrillation Without Chronic Kidney Disease History Taking Dabigatran Versus Warfarin After Propensity Score Weighting**



Dabigatran users taking either low or standard dose and with or without warfarin experience and a high CHA_2DS_2-VASc (≥4) or HAS-BLED (≥3) score had a lower risk of acute kidney injury than with warfarin. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor antagonist; CI = confidence interval; HAS-BLED = hypertension, abnormal renal or liver function, stroke, bleeding history, labile international normalized ratio, age 65 years or older, and antiplatelet drug or alcohol use (15) (labile international normalized ratio could not be determined from claims and was excluded from our scoring); HR = hazard ratio; NSAIDs = nonsteroidal anti-inflammatory drugs; PYs = person years; TIA = transient ischemic attack; other abbreviations as in Figures 1 and 2.

major bleeding events for dabigatran versus warfarin might thus contribute to a lower risk of AKI. In addition, the post hoc analysis from the RE-LY trial indicated that warfarin was associated with a greater decline in glomerular filtration rate (GFR) than either low-dose or standard-dose dabigatran (9). Of note, patients outside the therapeutic range of INR control (mainly above the target range) and those dabigatran users with previous warfarin experience had a more obvious decline in GFR than with warfarin. In addition, patients with diabetes or older patients had a more obvious decline in GFR. The authors

FIGURE 4 Forest Plot of Hazard Ratio of Acute Kidney Injury for Patients With Nonvalvular Atrial Fibrillation With Chronic Kidney Disease History Taking Dabigatran Versus Warfarin After Propensity Score Weighting



Dabigatran use was associated with a lower risk of acute kidney injury than warfarin use in most subgroups. Abbreviations as in Figure 3.

hypothesized that calcification of renal arteries, vascular inflammation, and increased plaque load mediated by the inhibition of vitamin K by warfarin explained the greater decline in GFR than with dabigatran, which was amplified by several atherosclerotic factors, including diabetes and old age. Our results indicated that patients taking warfarin were at an increased risk of AKI compared with those with higher CHA_2DS_2-VASc score, which also supports the notion that warfarin-related acute renal injury was precipitated by multiple risk factors related to atherosclerosis. Finally, it was noted that physicians tended to prescribe the 110 mg dose (n = 6,762; 88%) of dabigatran in our Asian population, possibly because of the smaller body size and greater number of comorbidities within our Asian cohort (15). If dose-dependent dabigatran-related nephropathy exists, as demonstrated by Ryan et al. (6), then a lower dose of

dabigatran might result in less kidney damage than with warfarin. Prospective validation of our results in a future study is warranted.

STUDY LIMITATIONS. First, the NHIRD does not contain important laboratory data, including serum hemoglobin, renal and liver function, and INR for analysis, which is a common limitation of most health insurance databases around the world. The favorable renal outcomes of patients taking dabigatran might have been attributable in part to a higher baseline GFR due to a selection bias. However, it is unreasonable to assume those dabigatran users who are older and have a higher prevalence of hypertension, diabetes, dyslipidemia, and other comorbidities (**Tables 1 and 2**) would have a higher baseline GFR than the warfarin group. Second, the definition of AKI was based on the ICD-9-CM coding indicating acute kidney disease, which depends completely on each physician's choice in clinical practice. Although the coding indicating AKI in the NHIRD had been validated previously (11,13,14), heterogeneous contamination of the AKI population cannot be excluded. In addition, coding errors for other comorbidities registered by each physician's choice of treatment constitute a limitation in the Taiwan NHIRD. Third, the dabigatran group had significantly more comorbidities than the warfarin group. Hence, we used a propensity score model with several variables to balance the comorbidities of the 2 cohorts and still obtained a positive result both before and after weighting. However, residual confounding by unmeasured factors cannot be excluded. Fourth, the National Health Insurance program in Taiwan restricts dabigatran claims to 1) AF patients with a history of ischemic stroke, transient ischemic attack, or symptomatic heart failure; 2) AF patients >65 years of age with at least 1 risk factor, including hypertension, diabetes, or coronary artery disease; or 3) AF patients >75 years of age. Therefore, the baseline diagnostic codes were not totally blinded with respect to the use of a specific anticoagulant drug. Finally, the follow-up period for dabigatran administration was short in our study because the 2014 NHIRD was unavailable. Although significant divergence exists for AKI risk between dabigatran and warfarin users during the early phase of treatment, it is unclear whether the beneficial effect of dabigatran persists during long-term follow-up.

CONCLUSIONS

Dabigatran was associated with a reduced risk of AKI compared with warfarin in a large Asian cohort either with or without a history of kidney disease. Either low-dose or standard-dose dabigatran might be a safer alternative to warfarin in patients with nonvalvular AF to avoid the risk of anticoagulant-related AKI. Of note, warfarin conveyed a significantly higher risk of AKI than dabigatran for those patients with high CHA_2DS_2-VASc scores.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In a large Asian cohort with or without chronic kidney disease, dabigatran was associated with a lower risk of acute kidney injury than warfarin, particularly among those with higher CHA_2DS_2-VASc stroke risk scores.

TRANSLATIONAL OUTLOOK: Long-term prospective studies are necessary to assess the risks of acute kidney injury during anticoagulation with other target-specific oral anticoagulant drugs (e.g., rivaroxaban, apixaban, and edoxaban).

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KEY WORDS acute kidney injury, atrial fibrillation, direct thrombin inhibitor, warfarin

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