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Sex-Based Differences in Outcomes of Oral Anticoagulation in Patients With Atrial Fibrillation

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ABSTRACT

BACKGROUND Women with atrial fibrillation are at a higher risk of stroke, despite treatment with warfarin. It is unclear if women treated with direct oral anticoagulants (DOACs) have better clinical outcomes, especially when considering the quality of anticoagulation control of warfarin.

OBJECTIVES This study compared the effectiveness and safety outcomes of DOACs versus warfarin in men and women with stratifications for anticoagulation control.

METHODS Patients newly diagnosed with atrial fibrillation and prescribed oral anticoagulants during 2010 to 2015 were identified using the Hong Kong clinical database. Propensity score matching was performed in men and women separately. Further analysis was conducted to stratify warfarin users according to their anticoagulation control. Cox regression was used to compare the risk of ischemic stroke or systemic embolism, intracranial hemorrhage (ICH), gastrointestinal bleeding, and all-cause mortality in the specific sex.

RESULTS There were 4,972 men and 4,834 women successfully matched in our cohort. Compared with warfarin, DOAC use was associated with a lower risk of ICH (hazard ratio [HR]: 0.16; 95% confidence interval [CI]: 0.06 to 0.40) and all-cause mortality (HR: 0.55; 95% CI: 0.39 to 0.77) in women but not in men. The treatment by sex interaction was significant for ICH only, and a significantly lower risk of ICH remained in the DOAC group when compared with warfarin users with good anticoagulation control (HR: 0.13; 95% CI: 0.02 to 1.00) among women only. The risks of ischemic stroke or systemic embolism and gastrointestinal bleeding with DOACs versus warfarin were comparable in both sexes.

CONCLUSIONS DOACs were associated with a lower risk of ICH and all-cause mortality in women only, where the association of lower ICH risk remained when compared with warfarin users with good anticoagulation control.
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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CDARS = Clinical Data Analysis and Reporting System

CI = confidence interval

DOAC = direct oral anticoagulant

GIB = gastrointestinal bleeding

HR = hazard ratio

ICH = intracranial hemorrhage

INR = international normalized ratio

SSE = ischemic stroke or systemic embolism

TTR = time in therapeutic range

Atrial fibrillation (AF) is a global health concern with its growing prevalence, increase in health care burden, and significant morbidity and mortality (1,2). Patients with AF are 5 times more likely to have a stroke (3); hence, oral anticoagulants are recommended for high-risk patients as thromboprophylaxis (4,5). However, the risk of stroke may be heterogeneous between men and women (6–9), raising the possibility of sex-specific anticoagulation management among patients with AF.

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Although epidemiological data demonstrated that men have a higher risk of AF when compared with women, women with AF have a higher risk of stroke (1,2). In particular, female sex was identified as an independent risk factor for stroke in patients with AF even after adjustment for age (10). This is reflected in the female sex component in the CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes, stroke [doubled]-vascular disease, age [65 to 74 years], and sex [female]) score for stroke risk prediction (11). Worse clinical outcomes of stroke were also found to be associated with women who are diagnosed with AF (12). Notably, the higher risk of stroke in women remained in the anticoagulated cohort where warfarin, a vitamin K antagonist, was prescribed (13).

It has been proposed that the worse clinical outcomes of women on warfarin may be due to their poor anticoagulation control as indicated in the low-percentage time in therapeutic range (TTR) (14,15). With the introduction of direct oral anticoagulants (DOACs), it is uncertain whether women have better clinical outcomes when they are prescribed the newer agents, which have a different mechanism of action. There is limited real-world evidence in sex differences in the clinical outcomes of DOACs comparing with the different quality of warfarin treatment. This population-based cohort study was conducted to compare the effectiveness and safety outcomes of DOACs versus warfarin in men and women with stratifications for TTR, with the aim to provide insights into oral anticoagulant treatment choices with respect to the sex of the patients.

METHODS

DATA SOURCE. The data used in this study were collected from the electronic medical records of the Clinical Data Analysis and Reporting System (CDARS), which was developed by the Hospital Authority in Hong Kong. The Hospital Authority is a statutory body that manages public hospitals and outpatient clinics in the region, serving over 7 million people in Hong Kong (16). Clinical information is recorded by healthcare professionals and transferred to CDARS regularly (17,18). All medical records are anonymized with a unique reference number to protect patient confidentiality. Patient demographics and clinical records related to diagnosis, operation and procedure, drug use, accident and emergency visits, outpatient and inpatient visits, and laboratory tests were retrieved from CDARS for data analyses. CDARS has been used to conduct high-quality epidemiological studies in Hong Kong (17,18). International Classification of Diseases-Ninth Revision-Clinical Modification diagnosis codes were used to identify the outcomes and comorbidities (Online Table 1). The reliability of the database was demonstrated by the high coding accuracy for the outcomes measured in this study, with a positive predictive value of 95% for AF, 90% for ischemic stroke, 95% for intracranial hemorrhage (ICH), and 100% for gastrointestinal bleeding (GIB) (17,18). The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (reference no. UW13-468).

STUDY DESIGN. Cohort selection. Patients with a new diagnosis of AF between 2010 and 2015 were identified from CDARS. Due to the lack of specific coding for nonvalvular AF, patients with valvular heart diseases, valve replacement, or hyperthyroidism at or before their first AF occurrence were excluded to select patients with nonvalvular AF only (19). Possible cases of transient or secondary AF were excluded if pericarditis, myocarditis, cardiac surgery, or pulmonary embolism were recorded within 90 days before their first AF occurrence (19). Patients with missing sex or date of birth, under 18 years of age, or who died at their first AF occurrence were also excluded.

The index date was defined as the start date of the first prescription of oral anticoagulants (warfarin, apixaban, dabigatran, or rivaroxaban) after the first AF diagnosis. Patients were assigned into the corresponding treatment groups with respect to the first identified oral anticoagulant prescription regardless of dosage. To select new patients, those who had oral anticoagulants within 180 days before the index date or more than 1 prescription of oral anticoagulants on the index date were excluded.

Outcomes. The primary outcome was defined as the composite of ischemic stroke or systemic embolism (SSE) for the measurement of effectiveness. Secondary

outcomes including ICH, GIB, and all-cause mortality were the safety measures. The follow-up period started from the index date and was censored by the switch of anticoagulation treatment, discontinuation of treatment (i.e., a gap of >5 days between 2 consecutive prescriptions), occurrence of outcomes, date of death, or study end date (i.e., December 31, 2016), whichever came first.

STATISTICAL ANALYSIS. Baseline patient characteristics were retrieved from CDARS for comparison between treatment groups in men and women, respectively. Continuous variables were expressed as mean ± SD while categorical data were reported as frequency (percentage).

Propensity score matching was used to control for the confounding due to nonrandomized treatment decisions (20). Propensity scores were derived from logistic regression using covariates measured on and before the index date. The variables included age, index year, number of inpatient visits at 1 year before the index date, Charlson Comorbidity Index, comorbidities before the index date, and current medication use (i.e., prescription records within 90 days before the index date). CHA_2DS_2-VASc and $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes, stroke [doubled]) scores were calculated for the evaluation of the stroke risk, while modified HAS-BLED (hypertension, abnormal liver or kidney function, stroke history, bleeding history, labile INR [not included], elderly [age >65 years], drug, and alcohol use) score was calculated for the estimation of the bleeding risk (21,22).

Propensity score matching was performed separately in men and women using the greedy variable-ratio matching algorithm (23). DOAC users (apixaban, dabigatran, and rivaroxaban) were matched to warfarin users at a 1:1 ratio with a caliper of 0.2 standard deviations of the propensity score. Two treatment groups were considered to be similar if the standardized difference of the covariates was <0.1 (negligible difference).

The risk of outcomes was compared between DOAC and warfarin groups in the specific sex using Cox proportional hazards regression stratified on propensity score-matched pairs. Results were presented as hazard ratios (HR) with 95% confidence interval (CI). The p value for interaction was calculated as a post hoc analysis to statistically test for any differences in the outcomes with DOACs versus warfarin between men and women. A 2-sided p value of <0.05 was considered statistically significant.

TTR ANALYSIS. TTR was calculated using the Rosendaal method, which was developed with the assumption that international normalized ratio (INR) varies in proportion to time between 2 measurements (24). Due to the fluctuation of INR in the initial warfarin treatment, records measured within 28 days after the index date were excluded. Patients with <28 days of follow-up were excluded from the analysis to allow for a fair comparison. Inpatient INR records were also excluded to reduce the possibilities of patients having other forms of anticoagulation during hospitalization that may affect their INR. The Hospital Authority guideline for warfarin treatment specified that INR should be measured every 8 weeks (25). Therefore, INR records with a gap larger than 60 days were not interpolated for the accuracy of TTR calculation.

Propensity score matching was performed in men and women separately with the aforementioned method. We defined TTR ≥60% as having a good INR control, while TTR <60% was defined as having a poor INR control (18,26,27). Patients who did not have any INR measurement after the 28-day drug initiation period, or did not have a regular INR measurement (i.e., all INR tests measured >60 days apart or not having regular outpatient INR tests) were categorized as "without routine INR monitoring." Matched patients were stratified into 3 subgroups for analysis according to the anticoagulation control: 1) good INR control; 2) poor INR control; and 3) without routine INR monitoring.

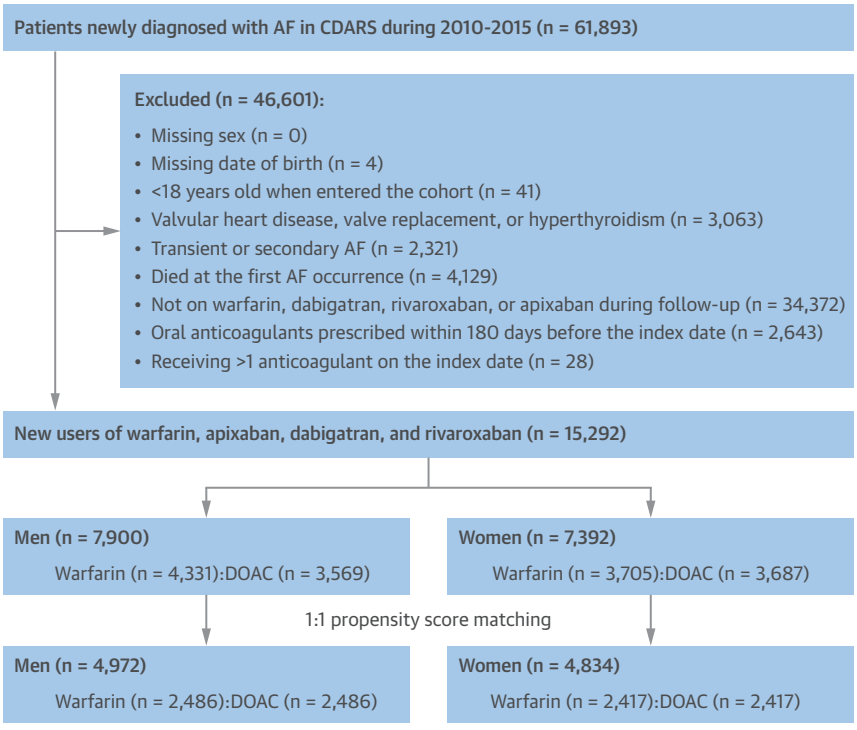
Statistical analyses were conducted independently by 2 coauthors (S.W.Y.L. and W.C.Y.L.) using RStudio 1.0.143 (RStudio, Boston, Massachusetts) and SAS version 9.3 (SAS Institute, Cary, North Carolina). Results were independently cross-checked for quality assurance.

RESULTS

BASELINE CHARACTERISTICS AND TREATMENT CHOICES. There were 61,893 patients with a new diagnosis of AF between 2010 and 2015 in CDARS (**Figure 1**). Following the exclusion criteria, 15,292 patients were included in the analyses, with 48% being women. Among the study cohort, 45% of men and 50% of women were prescribed DOACs after the first diagnosis of AF (Online Table 2). After propensity score matching, 4,972 men and 4,834 women were successfully matched at a 1:1 ratio (**Figure 1**). Both men and women have similar baseline characteristics between the 2 treatment groups, where all standardized differences were <0.1 (**Table 1**).

Among the matched DOAC users, dabigatran (63% of men and 63% of women) was the most commonly used drug, followed by rivaroxaban (28% of men and

FIGURE 1 Cohort Selection for the Main Analysis



AF = atrial fibrillation; CDARS = Clinical Data Analysis and Reporting System; DOAC = direct oral anticoagulant.

27% of women) and apixaban (9% of men and 10% of women). There were 41% of men and 32% of women receiving standard doses (Online Table 3).

The mean age of the matched cohort was 71.7 ± 10.8 years for men and 75.8 ± 10.1 years for women. Both the mean CHA_2DS_2-VASc score and HAS-BLED score were higher in women (4.34 ± 1.79 and 2.74 ± 1.24, respectively) than in men (2.96 ± 1.68 and 2.59 ± 1.27, respectively). The mean follow-up time was 1.23 ± 1.33 years in men and 1.29 ± 1.40 years in women.

MAIN ANALYSIS. Primary outcome. Results of the main analysis before propensity score matching are presented in Online Table 4. After propensity score matching, 152 (6.11%) warfarin users and 140 (5.63%) DOAC users experienced SSE in the men cohort, while 191 (7.90%) warfarin users and 153 (6.33%) DOAC users had SSE in the women cohort. Results from the Cox regression analysis did not show a significant difference in the risk of SSE for DOACs versus warfarin in both sexes (**Table 2**). There was a trend for a lower risk of SSE in women with marginally nonsignificant values (HR: 0.81; 95% CI: 0.63 to 1.03). **Secondary outcomes.** DOAC use was associated with a significantly lower risk of ICH (HR: 0.16; 95% CI: 0.06 to 0.40) and all-cause mortality (HR: 0.55; 95% CI: 0.39 to 0.77) when compared with warfarin in women (**Table 2**). Conversely, there were no significant differences between the treatment groups in all safety outcomes among the men cohort. The p value for interaction was statistically significant for ICH only. Kaplan-Meier curves for ICH and all-cause mortality in men and women are presented in the **Central Illustration**; those for SSE and GIB are presented in Online Figure 1.

TIME IN THERAPEUTIC RANGE ANALYSIS. After excluding 1,540 men and 1,434 women with <28 days of follow-up, 3,972 men and 3,782 women were successfully matched by propensity scores (**Figures 2 and 3**). Among the matched warfarin users, 78.6% of men and 78.9% of women had valid INR records for the calculation of TTR during the follow-up period. The mean TTR was 45.1 ± 29.1% for men and 46.0 ± 29.0% for women. The median INR for men and women were 2.10 (interquartile range: 0.84) and 2.10 (interquartile range: 0.80), respectively.

Results of the TTR analysis before propensity score matching are presented in Online Table 5. After propensity score matching, a significant risk reduction in

TABLE 1 Baseline Characteristics After Propensity Score Matching

	Men			Women		
	Warfarin (n = 2,486)	DOAC (n = 2,486)	Standardized Difference	Warfarin (n = 2,417)	DOAC (n = 2,417)	Standardized Difference
Age, yrs	71.83 ± 10.79	71.58 ± 10.86	0.023	75.87 ± 10.55	75.78 ± 9.63	0.010
CHA_2DS_2-VASc score	2.96 ± 1.68	2.96 ± 1.68	0.005	4.34 ± 1.82	4.34 ± 1.75	<0.001
$CHADS_2$ score	1.98 ± 1.40	1.99 ± 1.39	0.001	2.29 ± 1.53	2.27 ± 1.49	0.016
HAS-BLED score	2.58 ± 1.27	2.59 ± 1.26	0.009	2.73 ± 1.27	2.74 ± 1.21	0.009
Inpatient visits	1.82 ± 1.79	1.84 ± 1.81	0.014	1.90 ± 1.80	1.89 ± 1.94	0.002
CCI	1.48 ± 1.50	1.46 ± 1.48	0.016	1.42 ± 1.46	1.41 ± 1.41	0.003
Comorbidities						
Congestive heart failure	612 (24.6)	603 (24.3)	0.008	641 (26.5)	636 (26.3)	0.005
Hypertension	1,196 (48.1)	1,221 (49.1)	0.020	1,371 (56.7)	1,343 (55.6)	0.023
Stroke	733 (29.5)	737 (29.6)	0.004	741 (30.7)	738 (30.5)	0.003
Vascular disease	601 (24.2)	589 (23.7)	0.011	498 (20.6)	488 (20.2)	0.010
Diabetes	563 (22.6)	562 (22.6)	0.001	568 (23.5)	573 (23.7)	0.005
Intracranial hemorrhage	81 (3.3)	80 (3.2)	0.002	67 (2.8)	63 (2.6)	0.010
Gastrointestinal bleeding	194 (7.8)	192 (7.7)	0.003	173 (7.2)	165 (6.8)	0.013
Other bleeding	230 (9.3)	234 (9.4)	0.006	174 (7.2)	181 (7.5)	0.011
Renal disease	210 (8.4)	203 (8.2)	0.010	171 (7.1)	163 (6.7)	0.013
Medication use within 90 days before the index date						
Antiplatelet	1,791 (72.0)	1,800 (72.4)	0.008	1,769 (73.2)	1,774 (73.4)	0.005
ACE inhibitor/ARB	1,214 (48.8)	1,203 (48.4)	0.009	1,141 (47.2)	1,161 (48.0)	0.017
Beta-blocker	1,421 (57.2)	1,414 (56.9)	0.006	1,508 (62.4)	1,488 (61.6)	0.017
Calcium-channel blocker	1,304 (52.5)	1298 (52.2)	0.005	1,444 (59.7)	1,439 (59.5)	0.004
Amiodarone	251 (10.1)	260 (10.5)	0.012	333 (13.8)	311 (12.9)	0.027
Dronedarone	18 (0.7)	19 (0.8)	0.005	18 (0.7)	16 (0.7)	0.010
Statin	1,264 (50.8)	1,260 (50.7)	0.003	1,177 (48.7)	1,180 (48.8)	0.002
NSAID	148 (6.0)	161 (6.5)	0.022	138 (5.7)	142 (5.9)	0.007
H_2 antagonist	1,295 (52.1)	1,320 (53.1)	0.020	1,366 (56.5)	1,389 (57.5)	0.019
Proton pump inhibitor	663 (26.7)	671 (27.0)	0.007	670 (27.7)	654 (27.1)	0.015
SSRI	31 (1.2)	27 (1.1)	0.015	89 (3.7)	93 (3.8)	0.009
HRT	NA	NA	NA	5 (0.2)	4 (0.2)	0.010

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCI = Charlson comorbidity index; $CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes, stroke (doubled); CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years (doubled), diabetes, stroke (doubled)-vascular disease, age (65 to 74 years), and sex (female); DOAC = direct oral anticoagulant; HAS-BLED = hypertension, abnormal liver or kidney function, stroke history, bleeding history, labile international normalized ratio (not included), elderly (age >65 years), drug, and alcohol use; HRT = hormone replacement therapy; NSAID = nonsteroidal anti-inflammatory drug; SSRI = selective serotonin receptor inhibitor.

SSE among DOAC users when compared with warfarin users without routine INR monitoring was observed in both men (HR: 0.21; 95% CI: 0.08 to 0.55) and women (HR: 0.24; 95% CI: 0.09 to 0.63) (Table 3). There was not a significant difference in the risk of SSE in DOAC and warfarin users with routine INR monitoring in both sexes, irrespective of the quality of INR control (good or poor).

Analyzing safety outcomes, DOAC use was associated with a significantly lower risk of GIB and all-cause mortality when compared with warfarin users without routine INR monitoring in both men (for GIB, HR: 0.08; 95% CI: 0.01 to 0.64; for all-cause mortality, HR: 0.11; 95% CI: 0.03 to 0.35) and women (for GIB, HR: 0.20; 95% CI: 0.06 to 0.69; for all-cause mortality, HR: 0.10; 95% CI: 0.03 to 0.27). Between the 2 sexes, only women on DOACs had a lower risk of ICH when compared with warfarin users with routine INR monitoring (for good INR control, HR: 0.13; 95% CI: 0.02 to 1.00; and for poor INR control, HR: 0.20; 95% CI: 0.04 to 0.91).

DISCUSSION

This study demonstrates sex-specific clinical outcomes for DOACs versus warfarin. Although the risk of SSE with DOACs (vs. warfarin) was comparable among men and women, DOAC use was associated with a lower risk of ICH and all-cause mortality in women but not in men. On stratifications of TTR,

TABLE 2 Risk of Clinical Outcomes in Men and Women After Propensity Score Matching

	Men (n = 4,972)			Women (n = 4,834)			
	Events/Follow-Up Time*/ Incidence†	HR (95% CI)	p Value	Events/Follow-Up Time*/ Incidence†	HR (95% CI)	p Value	p Value for Interaction
Ischemic stroke or systemic embolism							
Warfarin	152/2,942/5.17	Reference		191/3,007/6.35	Reference		–
DOAC	140/3,188/4.39	0.85 (0.65–1.12)	0.247	153/3,252/4.71	0.81 (0.63–1.03)	0.089	0.758
Intracranial hemorrhage							
Warfarin	38/3,123/1.22	Reference		54/3,205/1.68	Reference		–
DOAC	26/3,336/0.78	0.55 (0.27–1.10)	0.091	15/3,426/0.44	0.16 (0.06–0.40)	<0.001	0.037
Gastrointestinal bleeding							
Warfarin	73/3,069/2.38	Reference		97/3,135/3.09	Reference		–
DOAC	86/3,288/2.62	1.13 (0.73–1.74)	0.583	94/3,359/2.80	0.89 (0.63–1.27)	0.528	0.410
All-cause mortality							
Warfarin	137/3,128/4.38	Reference		157/3,218/4.88	Reference		–
DOAC	121/3,348/3.61	0.83 (0.59–1.16)	0.271	98/3,431/2.86	0.55 (0.39–0.77)	<0.001	0.087

*Follow-up time is presented as total number of person-years. †Incidence is presented as number of events per 100 person-years.
CI = confidence interval; DOAC = direct oral anticoagulant; HR = hazard ratio.

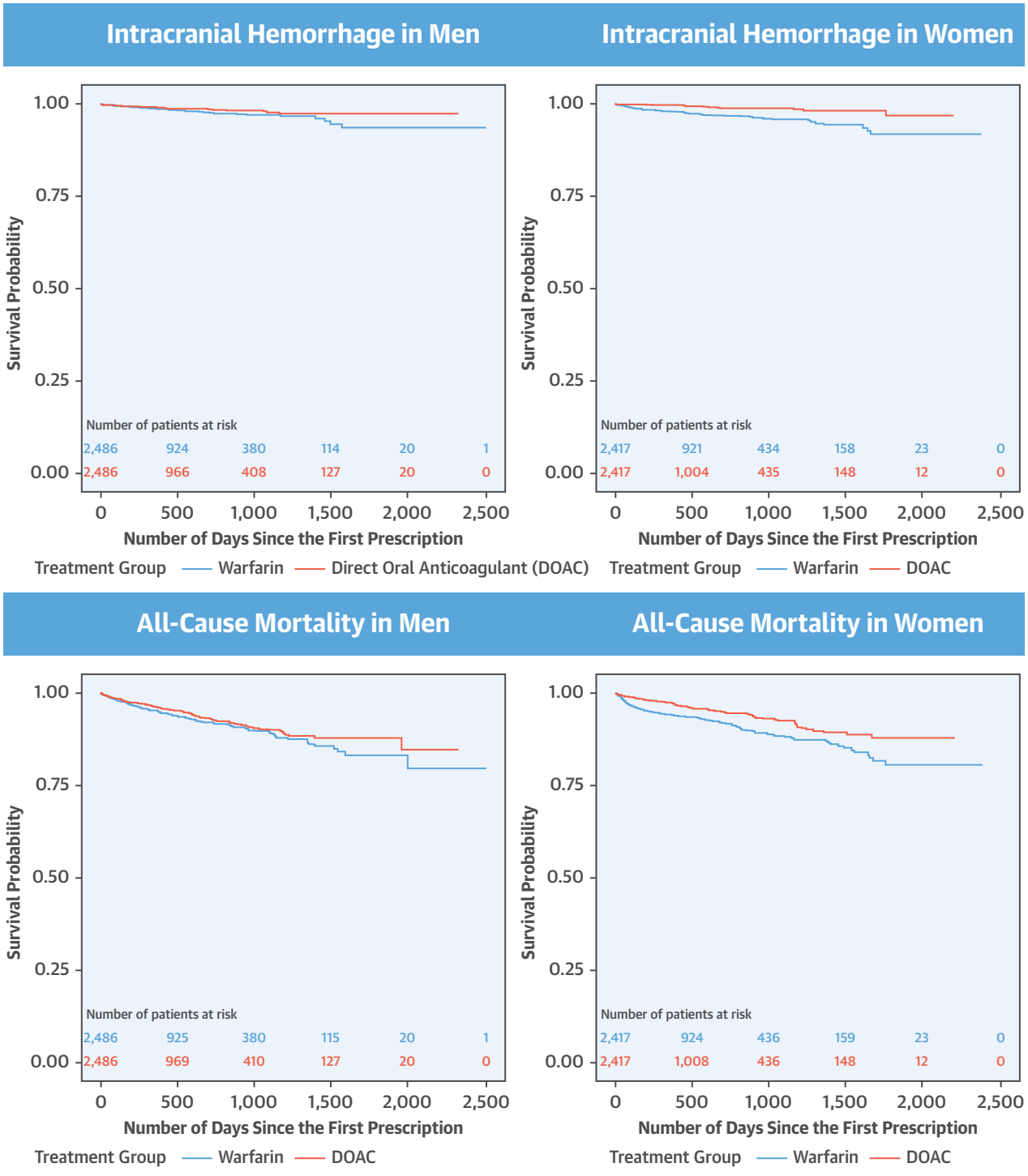
DOAC use was associated with a risk reduction in SSE, GIB, and all-cause mortality when compared with warfarin users without routine INR monitoring in both sexes. The association of a lower risk of ICH in the women cohort remained when comparing DOAC users to warfarin users with routine INR monitoring, regardless of the quality of the anticoagulation control. The significant p value for interaction in the main analysis demonstrates the potential sex difference in ICH outcome.

Women have in general been under-represented in cardiovascular clinical trials. In the previous major trials of warfarin, only 25% of the participants were women (28,29). Despite the increase in the proportion of women to around 40% in the more recent DOAC trials, these trials were not designed to study sex-specific outcomes (29). The lack of trial evidence data makes it difficult to optimize oral anticoagulation therapy with respect to the sex of patients in real-world practice. Sex-specific analysis is particularly important as women appear to have different utilization patterns and metabolism of anticoagulants when compared with men (6,10,30). This highlights the importance of assessing the effectiveness and safety of DOACs versus warfarin in the sexes.

There is limited evidence in the literature investigating sex differences in the treatment outcomes of oral anticoagulants. One meta-analysis pooled the results from 4 landmark randomized controlled trials and found a significant lower risk of stroke or systemic embolism for DOACs versus warfarin in both men and women, and the p value for interaction was not statistically significant (31). However, the benefit of DOACs in stroke or systemic embolism in the meta-analysis was mainly driven by hemorrhagic stroke, which was not included in the SSE outcome in our study. Regarding the safety outcomes, although the p value for interaction was not significant in the major bleeding outcome in the meta-analysis, the significant lower risk of major bleeding was only found in women for DOACs versus warfarin. Of note, major bleeding was a composite of multiple types of bleeding outcomes, which was not directly comparable to the ICH and GIB outcomes in our study.

Two other meta-analyses compared the risk of outcomes for men versus women in the specific treatment groups. Pancholy et al. (13) did not find any differences in stroke or systemic embolism between men and women on DOACs, but there was a lower risk of major bleeding in women when compared with men. Conversely, women on warfarin had a significantly greater risk of stroke or systemic embolism but a similar risk of major bleeding. Therefore, it is concluded that there was a net clinical benefit of DOACs compared with warfarin in women with AF (13). Proietti et al. (32) pooled the results from the DOAC groups of different trials and found that men were more protected from stroke or systemic embolism and women were more protected from major bleeding. With the different study designs, selection of cohort, and definition of outcomes, it is difficult to compare our results with the results of the randomized controlled trials and meta-analyses. However, it is important to note that all major trials of DOACs were not designed or statistically powered to conduct sex-specific analyses (28).

CENTRAL ILLUSTRATION **Sex Differences in Outcomes of Anticoagulants**



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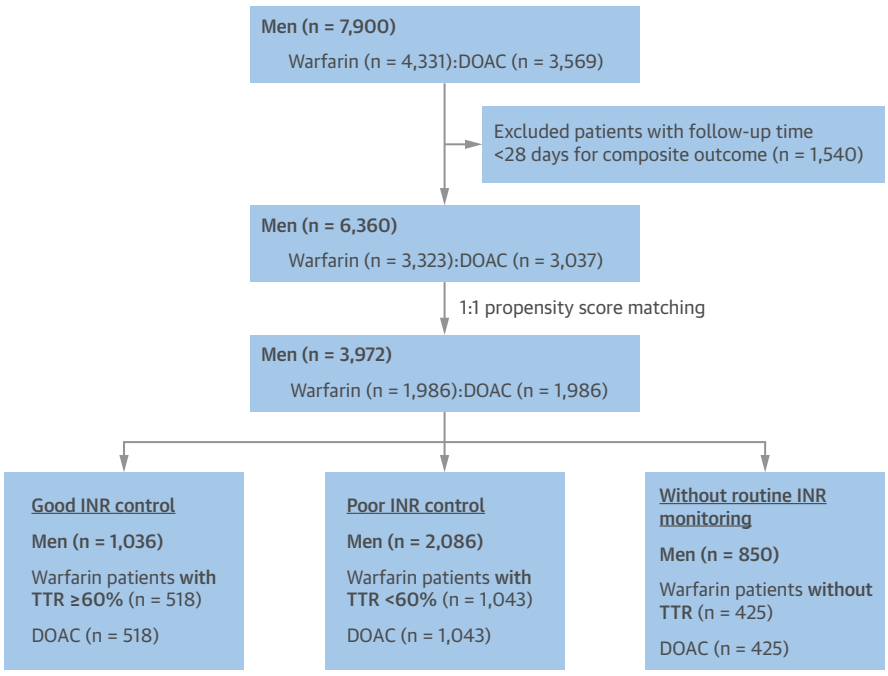
Kaplan-Meier curves for intracranial hemorrhage and all-cause mortality in men and women. DOAC = direct oral anticoagulant.

FIGURE 2 Cohort Selection for Men in the TTR Analysis



INR = international normalized ratio; DOAC = direct oral anticoagulant; TTR = time in therapeutic range.

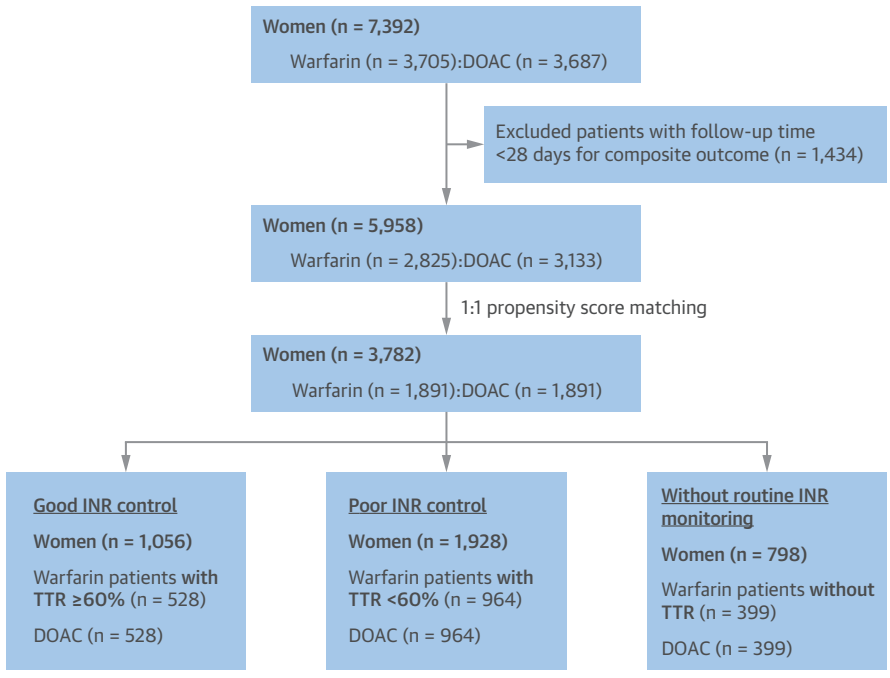
Studies in the real-world population outside the restrictive trial setting are warranted to investigate the actual outcomes of oral anticoagulants in clinical practice.

Two observational studies have described sex differences in the clinical outcomes for DOACs versus warfarin (33,34). However, these studies did not consider the quality of the anticoagulation control or address the class effects of DOACs versus warfarin. In the study using the administrative data in Canada, women on standard-dose dabigatran (150 mg twice daily) had a trend toward a lower risk of stroke but a similar risk of bleeding when compared with warfarin users, while men experienced a similar risk of stroke but a lower risk of bleeding (33). Another cohort study using American data demonstrated a similar risk of stroke and a higher risk of bleeding in women for rivaroxaban versus warfarin, while a lower risk of stroke and similar risk of bleeding was observed in men (34). Analyses for bleeding subtypes showed that dabigatran use was associated with a lower risk of ICH in both sexes in their cohort (34). However, our study using Asian clinical data showed that DOAC use was associated with a lower risk of ICH and all-cause mortality when compared with warfarin users in women only. Although the result was not statistically significant, women on DOACs had a trend for being more protected from SSE when compared with warfarin.

To date, the precise reasons for the different effects of DOACs versus warfarin among men and women remain unknown. It has been proposed that the fluctuation of anticoagulation effects from warfarin may contribute to the sex differences in clinical outcomes of warfarin users (13). In general, women have a lower mean body mass or hepatic fat content (29). This may predispose to the sex differences in the metabolism of warfarin by cytochrome P450 enzymes, leading to a different pharmacological response and outcomes of warfarin among men and women (29). Further prospective studies are required to evaluate the sex differences in the clinical outcomes of DOACs versus warfarin based on the different mechanism of action of the drugs. Indeed, women seem to have a poorer anticoagulation control. Female sex is a component of the SAMe-TT_2R_2 score, a prediction model of poor INR control (35). It is thus important to account for the quality of warfarin treatment in the risk comparison with DOACs.

In the TTR analysis, our results showed that DOACs were more effective in reducing the risk of SSE, GIB,

FIGURE 3 Cohort Selection for Women in the TTR Analysis



Abbreviations as in Figure 2.

and all-cause mortality when compared with patients on warfarin without routine INR monitoring in both men and women. This finding highlights the importance of regular INR measurements for warfarin patients and is in line with the suggestion that regular INR monitoring plays a major role in achieving better clinical outcomes among warfarin users (36).

Among patients on warfarin with routine INR monitoring, statistically significant differences were observed in ICH for DOACs versus warfarin with both good and poor INR control in women only. This finding further strengthens the potential better clinical outcomes of DOACs in women, even after consideration of TTR. However, the risk of stroke was comparable between the 2 treatment groups in both sexes. Indeed, TTR was calculated based on the INR target range of 2.0 to 3.0 as recommended in the guidelines (4,5). With regard to the sex and ethnic differences, a different INR target range may be required for Asians, especially for Asian women. Previous studies have demonstrated that the Asian population may benefit more from a lower INR target if they were prescribed warfarin (37,38); however, these studies have not assessed the quality of anticoagulation control with the use of TTR.

Ethnic differences in stroke and bleeding risk have been suggested, with Asians having a higher risk of stroke and being more prone to bleeding when prescribed warfarin (39). The metabolism of warfarin may be different due to the genetic polymorphism of cytochrome P450 enzymes and vitamin K epoxide reductase complex subunit 1 across different ethnic groups (39). However, clinical trials have only involved a small number of Asian participants and women (29,40). The restrictive environment of the trials may not reflect the complex clinical scenarios in the day-to-day clinical settings, particularly in Asia, where clinical practice may be considered to be more conservative (41). This is partly reflected in our cohort where patients on warfarin had a low TTR and a high percentage of DOAC users received the reduced doses. Nevertheless, the use of Hong Kong Chinese clinical data demonstrated the dosing patterns in the real-life clinical practice, which may not necessarily be the manufacturer recommended dosing patterns.

STUDY STRENGTHS AND LIMITATIONS. To our knowledge, this is the first observational study using the real-world data to present sex differences with consideration of anticoagulation control in

TABLE 3 Risk of Clinical Outcomes Stratified by Time in Therapeutic Range in Men and Women After Propensity Score Matching

		Men (n = 3,972)			Women (n = 3,782)			
		Events/Follow-Up Time*/ Incidence†	HR (95% CI)	p Value	Events/Follow-Up Time*/ Incidence†	HR (95% CI)	p Value	p Value for Interaction
Good INR control (TTR ≥60%)								
SSE	Warfarin	16/1,085/1.47	Reference		23/1,208/1.90	Reference		–
	DOAC	14/786/1.78	1.57 (0.61–4.05)	0.350	14/824/1.70	1.44 (0.62–3.38)	0.396	0.897
ICH	Warfarin	12/1,094/1.10	Reference		15/1,226/1.22	Reference		–
	DOAC	2/804/0.25	0.29 (0.06–1.38)	0.118	1/835/0.12	0.13 (0.02–1.00)	0.050	0.534
GIB	Warfarin	19/1,081/1.76	Reference		30/1,201/2.50	Reference		–
	DOAC	19/787/2.41	1.57 (0.61–4.05)	0.350	20/823/2.43	1.23 (0.59–2.56)	0.578	0.689
All-cause mortality	Warfarin	26/1,095/2.37	Reference		31/1,231/2.52	Reference		–
	DOAC	18/804/2.24	1.40 (0.62–3.15)	0.416	17/837/2.03	1.00 (0.48–2.10)	1.000	0.549
Poor INR control (TTR <60%)								
SSE	Warfarin	35/1,814/1.93	Reference		37/1,773/2.09	Reference		–
	DOAC	33/1,594/2.07	1.13 (0.65–1.98)	0.668	32/1,528/2.09	1.77 (0.90–3.49)	0.100	0.319
ICH	Warfarin	16/1,867/0.86	Reference		18/1,785/1.01	Reference		–
	DOAC	13/1,628/0.80	0.88 (0.32–2.41)	0.796	4/1,560/0.26	0.20 (0.04–0.91)	0.038	0.113
GIB	Warfarin	37/1,838/2.01	Reference		36/1,790/2.04	Reference		–
	DOAC	30/1,615/1.86	1.12 (0.57–2.21)	0.732	32/1,561/2.10	0.95 (0.52–1.76)	0.876	0.720
All-cause mortality	Warfarin	65/1,869/3.48	Reference		49/1,790/2.74	Reference		–
	DOAC	61/1,636/3.73	1.15 (0.72–1.82)	0.559	38/1,561/2.43	1.14 (0.64–2.05)	0.655	0.992
Without routine INR monitoring								
SSE	Warfarin	25/167/14.97	Reference		25/145/17.22	Reference		–
	DOAC	18/633/2.84	0.21 (0.08–0.55)	0.001	19/597/3.18	0.24 (0.09–0.63)	0.004	0.849
ICH	Warfarin	7/207/3.38	Reference		16/170/9.42	Reference		–
	DOAC	2/652/0.31	NA‡	NA‡	4/612/0.65	NA‡	NA‡	NA‡
GIB	Warfarin	15/195/7.70	Reference		17/159/10.71	Reference		–
	DOAC	9/645/1.39	0.08 (0.01–0.64)	0.017	19/596/3.19	0.20 (0.06–0.69)	0.011	0.472
All-cause mortality	Warfarin	34/208/16.35	Reference		47/174/27.01	Reference		–
	DOAC	20/652/3.07	0.11 (0.03–0.35)	<0.001	20/613/3.26	0.10 (0.03–0.27)	<0.001	0.883

*Follow-up time is presented as total number of person-years. †Incidence is presented as number of events per 100 person-years. ‡Results not available due to low number of events.
GIB = gastrointestinal bleeding; ICH = intracranial hemorrhage; INR = international normalized ratio; SSE = ischemic stroke or systemic embolism; TTR = time in therapeutic range; other abbreviations as in Table 2.

warfarin users. The use of propensity score matching, clinical data representing predominantly Asian ethnicity, and comparison of sex-specific outcomes between drug classes adds strength to our study. The availability of INR test results, drug dispensing history, and diagnosis records allowed for reliable calculations of TTR, where similar data were not available in prior studies.

Nonetheless, several limitations of our study should be noted. First, similar to other epidemiological studies, there may be residual confounding as inherent in the observational study design. To overcome this potential limitation, all important confounding factors for which there was adequate information available were included and addressed in this study. Propensity score matching was used and the baseline characteristics were well balanced between the treatment groups in both sexes. Second, DOACs were combined as a group for comparison with warfarin. There could be potential differences in the outcomes between each DOAC; however, there is limited evidence from the current literature to demonstrate the magnitude of the potential differences. This study was conducted based on the pharmacological basis that women may not respond as well when they are prescribed warfarin, a vitamin K antagonist. The approach of combining all DOACs as a single group increased the sample size to achieve adequate statistical power. Third, although the quality of anticoagulation control in the warfarin group was assessed with the use of TTR, the actual adherence in the DOAC group could not be assessed with the use of dispensing records. In particular, similar to other epidemiological studies, the discontinuation of medications was censored using the gap between each dispensing record but not by the actual intake of the medications, which is not available. However, as the mean duration of DOAC use in our cohort was more than 1 year, it is unlikely that patients continued to collect

prescriptions for a drug that they have not been using for such a long period. Finally, our post hoc analysis might not have had sufficient power to demonstrate the significant p value for interaction for all-cause mortality in the main analysis and ICH in the TTR analysis, although the significant lower risk of these outcomes was only found in women. Of note, our per-protocol analysis was to compare the clinical outcomes of DOACs versus warfarin in men and in women, respectively. We aimed to provide sex-specific data to inform oral anticoagulant prescribing with respect to the sex of patients in clinical practice.

CONCLUSIONS

In men, comparable clinical outcomes were observed with DOACs versus warfarin. In women, DOAC use was associated with a lower risk of ICH and all-cause mortality when compared with warfarin. Routine INR monitoring may result in comparable clinical outcomes between DOACs and warfarin in both sexes. However, a lower risk of ICH remained in women on DOACs when they were compared with warfarin users with both good and poor INR control.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The advantage of DOACs over warfarin for prevention of thromboembolism may be greater in women with AF than in men because of lower rates of ICH and all-cause mortality and similar effects on stroke and GIB, which is not observed in men.

TRANSLATIONAL OUTLOOK: More prospective studies are needed to evaluate the mechanisms responsible for sex-based differences in clinical outcomes with DOACs compared with warfarin and how these may relate to the quality and consistency of anticoagulation control.

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KEY WORDS anticoagulant, atrial fibrillation, female, intracranial hemorrhage, sex difference, stroke

APPENDIX For supplemental tables and a figure, please see the online version of this paper.