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ORIGINAL ARTICLE

Effectiveness and Safety of Direct Oral Anticoagulants in an Asian Population with Atrial Fibrillation Undergoing Dialysis: A Population-Based Cohort Study and Meta-Analysis

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Abstract
Purpose Whether direct oral anticoagulants (DOACs) are more effective and safer than warfarin among Asian patients with non-valvular atrial fibrillation (NVAF) undergoing dialysis remains unclear.

Methods We first compared the risks of ischemic stroke/systemic embolism (IS/SE) and major bleeding associated with DOACs compared with warfarin, in NVAF Asians undergoing dialysis using the Taiwan National Health Insurance Research Database (NHIRD) (**Aim 1**). Next, we searched PubMed and Medline from January 1, 2010 until January 31, 2020, to perform a systematic review and meta-analysis of all observational real-world studies comparing DOACs with warfarin specifically focused on NVAF patients with stage 4 or 5 chronic kidney disease undergoing dialysis (**Aim 2**). Finally, we tested the hypothesis whether AF patients undergoing dialysis treated with OACs (warfarin and DOACs) would be associated with lower risk of adverse clinical outcomes as compared to those without OACs using the Taiwan NHIRD (**Aim** 3).

Results From June 1, 2012, to December 31, 2017, a total of 3237 and 9263 NVAF patients comorbid with ESRD receiving oral anticoagulant (OACs) (490 on DOAC, 2747 on warfarin) or no OACs, respectively, were enrolled. Propensity score matching was used to balance covariates across the study groups. For the comparison of DOAC vs. warfarin (**Aim 1**), DOACs had comparable risks of IS/SE and major bleeding to warfarin in our present cohort. From the original 85 results retrieved, nine studies (including our study) with a total of 6490 and 22,494 patients treated with DOACs and warfarin were included in the meta-analysis, respectively. There were 5343 (82%) and 20,337 (90%) patients treated with DOACs and warfarin undergoing dialysis, respectively. The pooled meta-analysis also indicated no difference of the effectiveness (HR:0.90; [95%CI:0.74–1.10]; $P = 0.32$) and safety outcomes (HR:0.75; [95%CI:0.54–1.05]; $P = 0.09$) between DOACs and warfarin (**Aim 2**). For the comparison of OAC (+) vs. OAC (−) (**Aim** 3), OAC-treatment was associated with a higher risk of IS/SE (hazard ratio (HR):1.54;

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[95% confidential interval (CI):1.29–1.84];$P < 0.0001$) and comparable risk of major bleeding compared to those without OAC treatment.

Conclusions DOACs did not provide benefit over warfarin regarding effectiveness and safety in AF patients undergoing dialysis. The use of OAC was not associated with a lower risk of IS/SE in ESRD AF patients when compared to those without OAC use.

Keywords Atrial fibrillation · Direct thrombin inhibitor · Dialysis · Factor Xa inhibitor · Ischemic stroke · Hemorrhage · Mortality · End-stage renal disease · Warfarin

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia worldwide, which is associated with a significant risk of thromboembolic events, hospitalization, and mortality [1]. Oral anticoagulants (OACs) such as vitamin K antagonists (e.g., warfarin) or direct oral anticoagulants (DOACs; e.g., dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended for thromboembolism prevention in patients with AF [2, 3]. However, all DOACs are excreted via the kidney, ranging from 27% with apixaban to as high as 80% for dabigatran [4]. Therefore, patients with severe renal impairment (e.g., serum creatinine clearance (CrCl) < 25–30 mL/min) or end-stage renal disease (ESRD) were excluded from clinical trials with DOACs. To date, guidelines recommend against routine use of DOACs in AF patients undergoing hemodialysis, given that these drugs can bioaccumulate to precipitate bleeding [2, 3, 5]. We aimed to investigate the effectiveness and safety associated with the use of DOACs, compared to warfarin, in a population-based Asian AF population undergoing dialysis. We also performed a meta-analysis on the effectiveness and safety associated with the use of DOACs vs. warfarin incorporating the present study and relevant prior studies. Second, we examined whether ESRD AF patients undergoing dialysis treated with OACs (warfarin and DOACs) were associated with improved clinical outcomes compared to those without OAC treatment.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request. We analyzed the health insurance claims data of the Taiwan National Health Insurance (NHI) system, a mandatory universal health insurance program in Taiwan, which provides comprehensive medical care coverage to >99% of all Taiwanese individuals. As of 2018, the program had more than 23 million enrollees and a more than 99% coverage rate of the entire population [6]. A consistent encryption procedure was used to encrypt and de-identify the original identification number of each patient in the NHI database to protect the patient's privacy. Therefore, the need for informed consent was waived. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (104-8079B and 201801427B0).

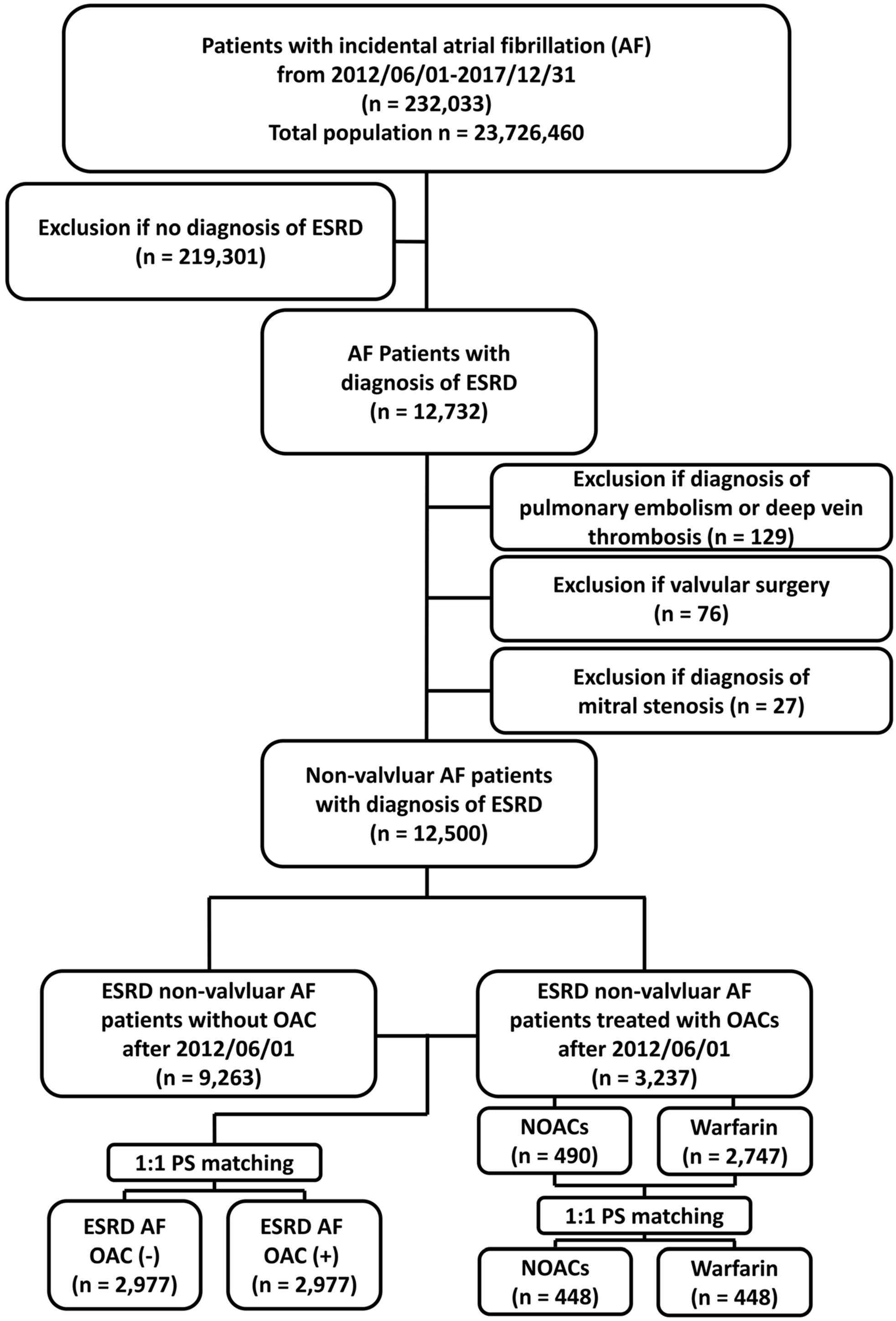
Study Design

A flowchart of the patient enrollment process is shown in Fig. 1. A total of 232,033 patients diagnosed as having AF (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 427.31 from June 1, 2012, to December 31, 2015, or ICD-10-CM code I48 from January 1, 2016 to December 31, 2017) were identified. Among these, 12,732 patients were diagnosed as having ESRD requiring renal replacement therapy. The diagnosis of ESRD requiring dialysis was confirmed by both relevant ICD-9-CM or ICD-10-CM codes and enrollment in the Registry of Catastrophic Illness Patient Database, a subpart of the NHI database. Patients were categorized in the OAC group if they filled at least one prescription for warfarin or any DOAC (dabigatran, rivaroxaban, apixaban, or edoxaban) during the study period. There were 3237 and 9263 ESRD AF patients treated with and without OACs, respectively. Among those treated with OACs, 490 and 2747 patients were treated with DOACs and warfarin, respectively. For those treated with OACs, the index date was defined as the first date of prescription for any DOAC or warfarin after June 1, 2012, for each group. For those without any OAC treatment, the index date was defined as the first diagnosis of AF after June 1, 2012. The follow-up period was defined from the index date until the first occurrence of any study outcome, or the end date of the study period (December 31, 2017), whichever came first.

Exclusion Criteria

Patients with diagnoses indicating venous thromboembolism (pulmonary embolism or deep vein thrombosis), joint replacement therapy within 6 months, or a previous history of valvular AF (mitral stenosis or valvular surgery) before the index date were excluded from the present study in order to establish a cohort of patients with non-valvular AF who were taking OACs for the primary purpose of stroke prevention. The ICD-

Fig. 1 Enrollment of patients with non-valvular atrial fibrillation (AF) and end-stage renal disease (ESRD) undergoing dialysis. From June 1, 2012, to December 31, 2017, a total of 3237, and 9263 non-valvular AF patients comorbid with ESRD receiving oral anticoagulants (OACs) or without OAC treatment, respectively, were enrolled in the present study. Among those treated with OACs, there were 490 and 2747 patients treated with direct oral anticoagulants (DOACs) and warfarin, respectively. Abbreviations: AF = atrial fibrillation; DOAC = direct oral anticoagulants; ESRD = end-stage renal disease; NVAF = non-valvular atrial fibrillation; OAC = oral anticoagulants



9-CM and ICD-10-CM codes used to identify the exclusion criteria are summarized in Supplemental Table 1.

Study Outcomes

Study outcomes were ischemic stroke/systemic embolism (IS/SE), intracranial hemorrhage (ICH), major gastrointestinal bleeding, and all major bleeding. All study outcomes were required to be a discharge diagnosis to avoid misclassification. ICH was defined using codes for atraumatic hemorrhage. Major gastrointestinal bleeding was defined as a hospitalized primary code indicating bleeding in the gastrointestinal tract. All major bleeding events were defined as the total events of ICH, major GIB, and other critical site bleedings that required hospitalization. The diagnosis codes of the National Health Insurance Research Database were shifted from ICD-9-CM to ICD-10-CM after January 1, 2016. The ICD-9-CM and ICD-10-CM codes used to identify the study outcomes and the baseline covariates are summarized in Supplemental Table 1. Although the same patient may have had more than one study outcome, only the outcome that first occurred was considered.

Covariates

Baseline covariates were referred to any claim record with the diagnoses or medication codes prior to the index date. A bleeding history was confined to events within 6 months preceding the index date. A history of prescription for medicine was confined to at least once within 3 months preceding the index date. The CHA_2DS_2-VASc score (congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65 to 74 years, and female gender) was adopted to predict the risk of ischemic stroke/thromboembolic events in patients with AF. The HAS-BLED score (hypertension, abnormal renal or liver function, stroke, bleeding history, labile INR, age 65 years or older, and antiplatelet drug or alcohol use) was used to predict the risk of bleeding in patients with AF who were treated with oral anticoagulants [7, 8]. Labile INR data were not available in NHIRD.

Statistical Analysis

The propensity score (PS) method, which simulates the design of a randomized clinical trial for observational cohort data by balancing the covariates across study groups with different weightings [9], was used to estimate the study outcomes of NOACs and warfarin. The PS method is the predicted probability of treatment conditional on selected covariates in Table 1 using the generalized boosted model (GBM), except for CHA_2DS_2-VASc and HAS-BLED scores, because these scores were a combination of other covariates. GBM was chosen to select the best functional form including interactions and the covariates in the model [10]. PS matching was conducted between the NOAC users and warfarin users. Another separate PS matching was conducted between those treated with OAC (including DOAC and warfarin) and those without any OAC treatment. The PS matching was conducted for a ratio of 1:1 between the two groups of patients who share a similar value of the propensity score. The matching used here was without replacement and the nearest neighbor matching within a caliper width equal to 0.2 of the standard deviation of the logit of the estimated propensity score [11]. The balance of potential confounders at the baseline (index date) between 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 value of ≤ 0.1 indicates a nonsignificant difference in potential confounders between the two study groups [12]. Incidence rates were estimated using the total number of study outcomes during the follow-up period divided by person-years at risk. The risks of study outcomes happening over the follow-up duration for DOACs vs. warfarin (reference) or OAC (+) vs. OAC (−) (reference) were obtained using survival analysis (Kaplan–Meier method and log-rank test, and Cox proportional hazards regression),

Table 1 Baseline characteristics of non-valvular atrial fibrillation (AF) patients undergoing dialysis and treated with direct oral anticoagulants (DOACs) and warfarin after propensity score (PS) matching

	DOACs (*n* = 448)	Warfarin (n = 448)	ASMD
Age			
(mean ± SD)	74.3 ± 10.9	75.2 ± 10.9	0.0833
<65	93 (20.8%)	83 (18.5%)	0.1007
65–74	127 (28.4%)	111 (24.8%)	
75–84	150 (33.5%)	162 (36.2%)	
>85	78 (17.4%)	92 (20.5%)	
Male	222 (49.6%)	213 (47.5%)	0.0402
CHA_2DS_2-VASc (mean ± SD)	4.5 ± 1.9	4.7 ± 1.9	0.0920
HAS-BLED (mean ± SD)	3.7 ± 1.1	3.6 ± 1.2	0.0337
Hypertension	371 (82.8%)	362 (80.8%)	0.0520
Diabetes mellitus	276 (61.6%)	285 (63.6%)	0.0415
Dyslipidemia	236 (52.7%)	248 (55.4%)	0.0537
Chronic liver disease	63 (14.1%)	67 (15%)	0.0253
Chronic lung disease	72 (16.1%)	69 (15.4%)	0.0184
Gout	123 (27.5%)	116 (25.9%)	0.0353
Congestive heart failure	110 (24.6%)	113 (25.2%)	0.0155
Chronic ischemic heart disease	110 (24.6%)	107 (23.9%)	0.0156
Stroke	88 (19.6%)	108 (24.1%)	0.1080
Malignancy	55 (12.3%)	46 (10.3%)	0.0635
PCI	79 (17.6%)	83 (18.5%)	0.0232
CABG	10 (2.2%)	8 (1.8%)	0.0318
History of bleeding	16 (3.6%)	15 (3.4%)	0.0122
Use of NSAIDs	107 (23.9%)	121 (27%)	0.0717
Use of PPI	117 (26.1%)	117 (26.1%)	0.0000
Use of H_2 blocker	183 (40.9%)	184 (41.1%)	0.0045
Use of ACEI, ARB	236 (52.7%)	243 (54.2%)	0.0313
Use of beta-blocker	282 (63%)	272 (60.7%)	0.0459
Use of verapamil or diltiazem	119 (26.6%)	125 (27.9%)	0.0301
Use of statin	139 (31%)	162 (36.2%)	0.1087

ACEI angiotensin-converting-enzyme inhibitor, *AF* atrial fibrillation, *ARB* angiotensin II receptor antagonists, *ASMD* absolute standardized mean difference, *CABG* coronary artery bypass grafting, *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, *DOAC* direct oral anticoagulant, *DM* diabetes mellitus, *HAS-BLED* hypertension, abnormal renal or liver function, stroke, bleeding history, labile INR, age 65 years or older, and antiplatelet drug or alcohol use, *INR* international normalized ratio, *NSAIDs* nonsteroidal anti-inflammatory drugs, *PCI* percutaneous coronary intervention, *PS* propensity score, *SD* standard deviation and presented as hazard ratios (HR) with 95% confidential intervals (CI). Statistical significance was defined as a P value of <0.05. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Meta-Analysis

We conducted a meta-analysis on the effectiveness and safety of DOACs vs. warfarin by including the present study with relevant prior studies. We followed the PRISMA (preferred reporting items for systemic reviews and meta-analyses) and MOOSE (Meta-analyses of Observational Studies in Epidemiology) guidelines when performing the meta-analyses [13, 14]. Two independent reviewers (HF Lee and YH Chan) searched PubMed and MEDLINE for relevant studies from inception to January 31, 2020. The search items were (apixaban OR dabigatran OR rivaroxaban OR edoxaban) AND (atrial fibrillation) AND (warfarin) AND (dialysis OR end stage renal disease OR end stage kidney disease). We only included original articles from peer-reviewed journals to assure the quality of the reported data. Because there were no published randomized controlled trials, we only included retrospective cohort studies that investigated the effectiveness and safety outcomes for DOACs vs. warfarin among AF patients with advanced kidney disease or undergoing dialysis. In all comparisons, warfarin was used as the reference. The outcomes of the present meta-analysis included IS/SE, ICH, major gastrointestinal bleeding, and all major bleeding. Data are presented as hazard ratio (HR) with 95% confidential interval (CI). We performed random-effects model meta-analysis using the reverse invariance method [15]. The statistical heterogeneity was measured by the statistic I^2. Values of <25%, 25–50%, and $\geq$ 50% were defined as low, moderate, and high degree of heterogeneity, respectively. $P < 0.05$ was taken as statistically significant. All analyses were performed using Review Manager Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

Among 3237 patients with AF and ESRD who were on chronic dialysis, we identified a total of 490 and 2747 patients taking DOACs and warfarin, respectively (Fig. 1). Before PS matching, the DOAC group was older, with a higher prevalence of prior stroke, chronic lung disease, and had a higher CHA_2DS_2-VASc score than the warfarin group (ASMD >0.1) (Supplemental Table 2). There was no difference in the female gender and HASBLED score between the two study groups. Among the DOAC group, 88, 150, 19, and 233 patients were taking apixaban, dabigatran, edoxaban, and rivaroxaban, respectively. There were 72 (82%), 138 (92%), 17 (89%), and 224 (96%) treated with low-dose apixaban (2.5 mg twice daily), dabigatran (110 mg twice daily), edoxaban (30 mg once daily), and rivaroxaban (15/10 mg once daily), respectively. After PS matching, both study groups were well-balanced in most characteristics (most ASMD <0.1) (Table 1). DOACs was associated with a comparable risk of IS/SE, gastrointestinal bleeding, ICH, and all major bleeding when compared to warfarin (Fig. 2).

Table 2 Baseline characteristics of non-valvular atrial fibrillation (AF) patients undergoing dialysis treated with oral anticoagulant (OACs) and without OACs after PS matching

	OAC ($n = 2977$)	no-OAC (n = 2977)	ASMD OAC vs. no-OAC
Age			
(mean ± SD)	71.3 ± 11	71.1 ± 11.2	0.0201
<65	838 (28.2%)	855 (28.7%)	0.0254
65–74	952 (32%)	952 (32%)	
75–84	885 (29.7%)	901 (30.3%)	
>85	302 (10.1%)	269 (9%)	
Male	1465 (49.4%)	1479 (49.9%)	0.0094
CHA_2DS_2-VASc (mean ± SD)	4.1 ± 1.8	4.1 ± 1.8	0.0243
HAS-BLED (mean ± SD)	3.6 ± 1	3.6 ± 1.1	0.0307
Hypertension	2527 (85.2%)	2590 (87.4%)	0.0618
Diabetes mellitus	1750 (59%)	1806 (60.9%)	0.0385
Dyslipidemia	1459 (49.2%)	1511 (51%)	0.0351
Chronic live disease	392 (13.2%)	381 (12.9%)	0.0110
Chronic lung disease	357 (12%)	370 (12.5%)	0.0134
Gout	750 (25.3%)	770 (26%)	0.0154
Congestive heart failure	528 (17.8%)	554 (18.7%)	0.0227
Chronic ischemic heart disease	669 (22.6%)	701 (23.6%)	0.0256
Stroke	344 (11.6%)	379 (12.8%)	0.0361
Malignancy	368 (12.4%)	334 (11.3%)	0.0355
PCI	498 (16.8%)	514 (17.3%)	0.0143
CABG	69 (2.3%)	79 (2.7%)	0.0216
History of bleeding	135 (4.6%)	126 (4.3%)	0.0148
Use of NSAIDs	624 (21.1%)	615 (20.7%)	0.0075
Use of PPI	712 (24%)	692 (23.3%)	0.0159
Use of H_2 blocker	1189 (40.1%)	1188 (40.1%)	0.0007
Use of ACEI, ARB	1467 (49.5%)	1479 (49.9%)	0.0081
Use of beta-blocker	1878 (63.3%)	1881 (63.4%)	0.0021
Use of verapamil or diltiazem	820 (27.7%)	826 (27.9%)	0.0045
Use of statin	837 (28.2%)	838 (28.3%)	0.0007

OAC oral anticoagulant

Other abbreviations as in Table 1

Meta-Analysis of DOAC and Warfarin in AF Patients Undergoing Dialysis

We identified 85 articles. A total of nine studies (including the present study) met our inclusion criteria [16–23] (Supplemental Fig. 1). The characteristics of the included studies are shown in

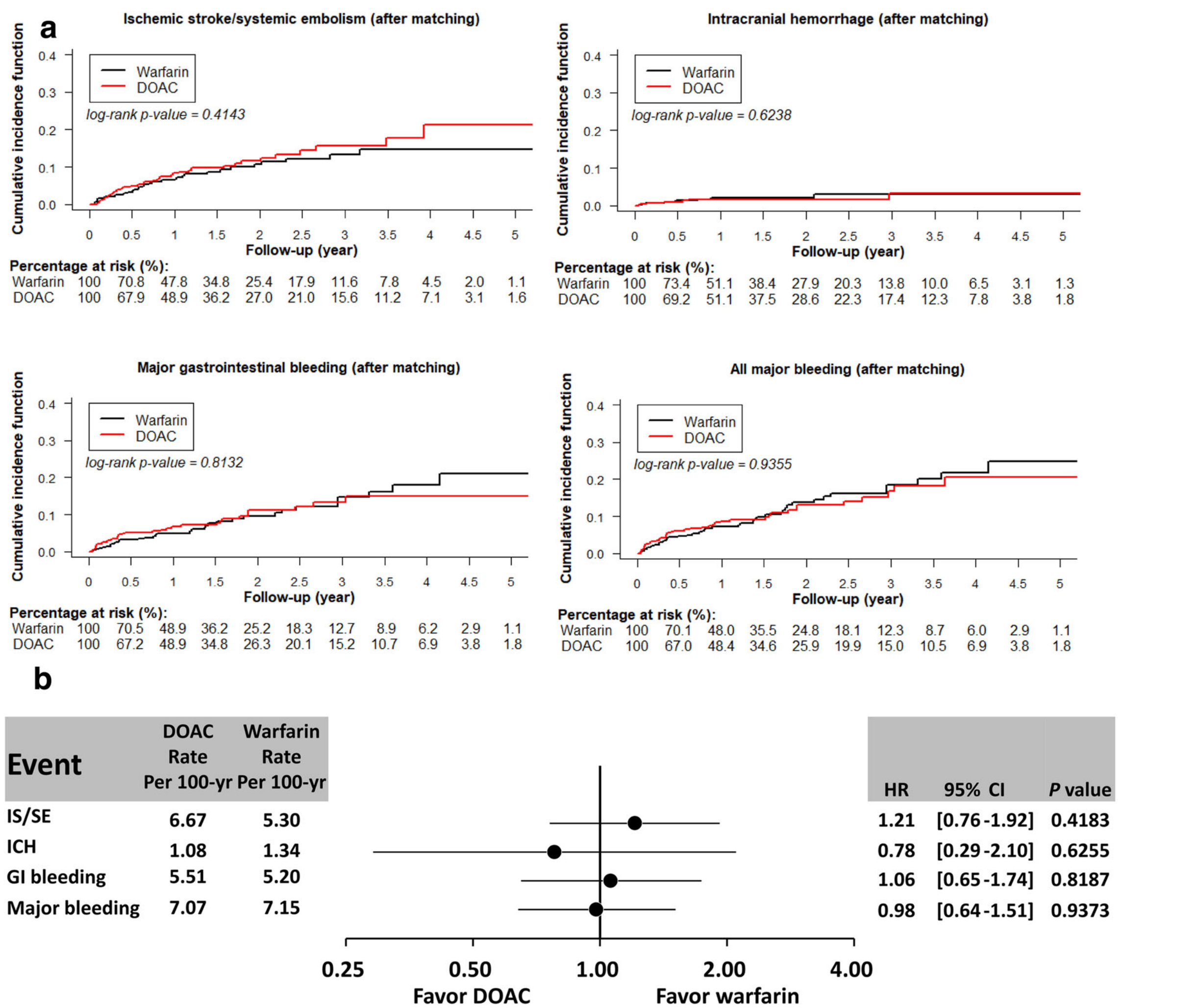


Fig. 2 Cumulative incidence rates and forest plot of hazard ratio (HR) of outcomes for DOACs versus warfarin among AF patients with ESRD taking OACs after propensity score (PS) matching. DOACs was associated with a comparable risk of ischemic stroke/systemic embolism (IS/SE), gastrointestinal bleeding, intracranial hemorrhage (ICH), and all major bleeding when compared to warfarin in ESRD AF patients undergoing dialysis. Abbreviations: AF = atrial fibrillation; CI = confidential interval; DOAC = direct oral anticoagulants; ESRD = end-stage renal disease; HR = hazard ratio; ICH = intracranial hemorrhage; IS = ischemic stroke; OAC = oral anticoagulant; PS = propensity score; SE = systemic embolism

Supplemental Table 3. Among the nine included studies, the present study and two others used the propensity score matching method [18, 21]; one used the propensity score weighting method [17]; one used covariate adjusted Poisson regression [16]; and two used multivariable logistic regression to balance confounding factors between DOACs and warfarin [20, 23]. Apixaban and warfarin were already well-balanced at baseline and no statistical method was used to adjust the baseline covariates in two studies [19, 22]. A bias evaluation is summarized in Supplemental Table 4. Overall, most studies reported a low risk of bias, while two studies had a risk of selection bias [16, 20], two studies had a risk of detection bias [19, 23], three studies had a risk of attrition bias [20–22], and two studies had a risk of reporting bias [16, 19]. Among the nine included studies (including our study), there were a total of 6490 and 22,494 patients treated with DOACs and warfarin included in the meta-analysis, respectively. There were 5343 (82%) and 20,337 (90%) patients treated with DOACs and warfarin undergoing dialysis, respectively. The risk for IS/SE did not differ between patients treated with DOACs and warfarin (pooled HRs of IS/SE was 0.90 ([95%CI: 0.74–1.10]; $P = 0.32$) (Fig. 3a). DOAC was associated with a comparable risk of ICH, major gastrointestinal bleeding, and all major bleeding when compared to warfarin (Fig. 3b to c). There was substantial statistical heterogeneity observed across the studies analyzing the risk of all major bleeding ($I^2 = 84\%$, $P < 0.00001$).

We further analyzed the effectiveness and safety for individual DOACs vs. warfarin in AF patients with advanced kidney disease or undergoing dialysis. We did not analyze edoxaban due to very limited patient numbers ($n = 19$). Apixaban ($n = 2505$; $I^2 = 0\%$, 3 studies), dabigatran ($n = 131$; this study), and rivaroxaban ($n = 2895$; $I^2 = 31\%$, 3 studies)

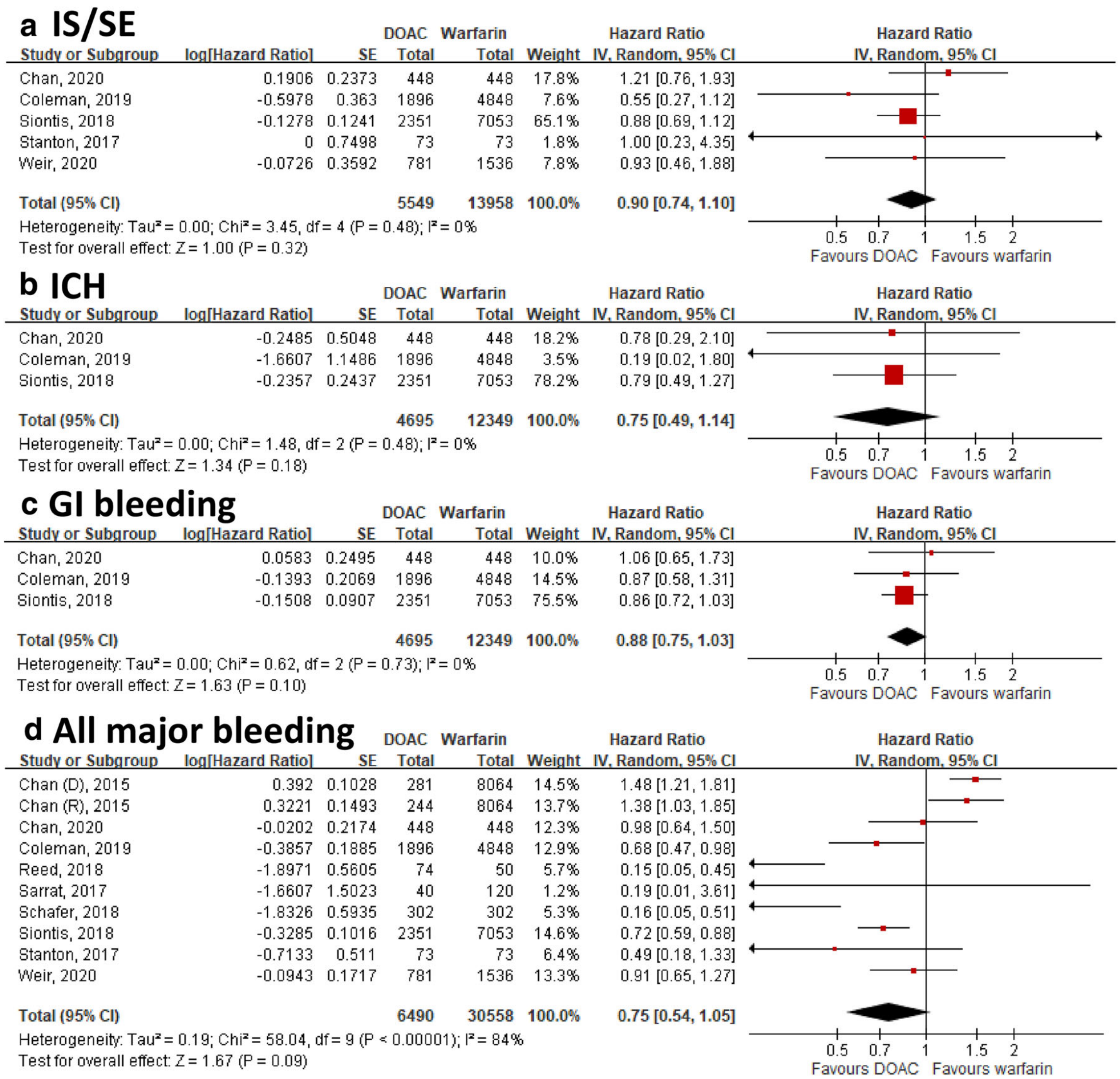


Fig. 3 Meta-analysis of DOACs vs. warfarin for IS/SE, ICH, major gastrointestinal bleeding, and all major bleeding in non-valvular AF patients with advanced kidney disease or undergoing dialysis. The meta-analysis indicated that DOACs was associated with a comparable risk of IS/SE, gastrointestinal bleeding, ICH, and all major bleeding when compared to warfarin in AF patients with advanced kidney disease or undergoing dialysis. The abbreviations are as in Fig. 2.

were all associated with a comparable risk of IS/SE to warfarin. For the safety outcome, apixaban ($n = 2921$) was associated with a lower risk of major bleeding than warfarin (HR: 0.43; [95%CI: 0.22–0.82]; $I^2 = 68\%$, 6 studies); dabigatran ($n = 412$) was associated with a higher risk of major bleeding than warfarin (HR: 1.47; [95%CI: 1.22–1.77]; $I^2 = 0\%$, 2 studies); rivaroxaban ($n = 3139$) was associated with a comparable risk of major bleeding compared to warfarin ($I^2 = 73\%$, 4 studies) (Supplemental Fig. 2).

OAC vs. without OAC

There were 3237 (490 for NOACs and 2747 for warfarin, respectively) and 9263 patients treated with OACs and no OACs, respectively (Fig. 1). Before PS matching, the OAC group had a higher prevalence of most comorbidities and a higher CHA_2DS_2-VASc and HAS-BLED score than those without OAC treatment (ASMD >0.1) (Supplemental Table 5). There was no difference in age and gender between the two study groups. After PS matching, both study groups were well-balanced (ASMD <0.1) (Table 2). ESRD AF patients undergoing dialysis treated with OAC were associated with a significantly higher risk of IS/SE ($P < .0001$) than those without OAC treatment. There was no difference in the risk of major bleeding between the OAC and no-OAC group (Fig. 4). Subgroup analysis showed consistent results for IS/SE and major bleeding for OAC (+) vs. OAC (−) among those patients with a history of stroke, ≥ 75 years of age, the presence of diabetes mellitus, a high CHA_2DS_2-VASc of ≥4 points, and a high HAS-BLED of ≥3 points, consistent with the main analysis (P interaction >0.05) (Supplemental Fig. 3).

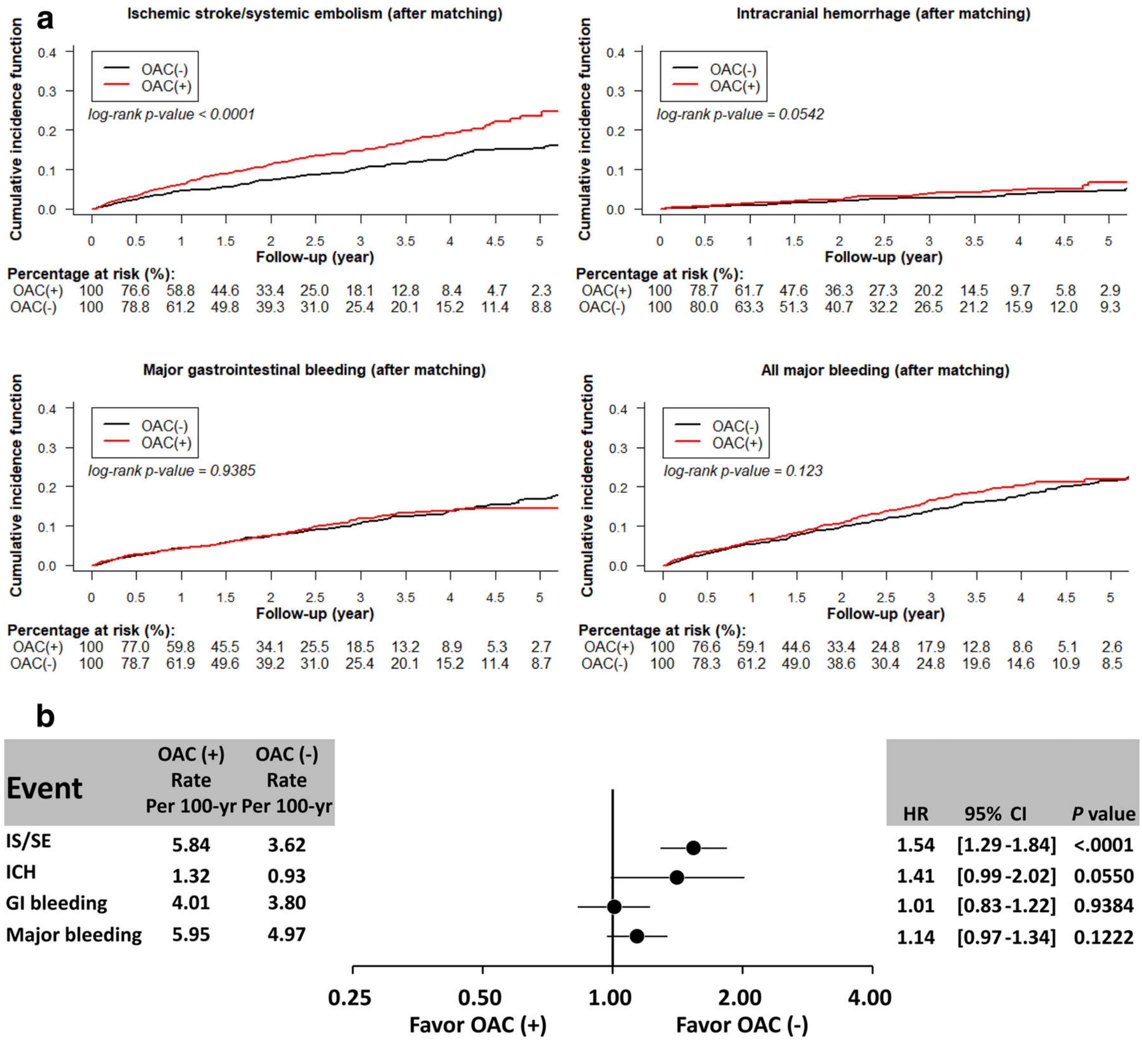


Fig. 4 Cumulative incidence rates and forest plot of HR of outcomes for OAC (+) versus OAC (−) among non-valvular AF patients with ESRD after PS matching. ESRD AF patients undergoing dialysis treated with OAC were associated with a significantly higher risk of IS/SE than those without OACs. There was no difference for the risk of major bleeding between the OAC and no-OAC group. The abbreviations are as in Fig. 2.

Discussion

In this nationwide retrospective cohort study, our principal results show the following: (i) approximately 26% of AF patients undergoing dialysis were treated with OACs, and 15% with DOACs; (ii) DOACs had a comparable risk of IS/SE and all major bleeding when compared to warfarin in ESRD AF patients undergoing dialysis; (iii) the meta-analysis of nine studies (including the present study) enrolling 6490 and 22,494 patients with stage 4 or 5 chronic kidney disease (CKD) undergoing dialysis (89% of patients were undergoing dialysis) treated with DOAC and warfarin, respectively, also revealed no significant difference in the effectiveness and safety outcomes between DOACs and warfarin: all DOACs were associated with comparable risk of IS/SE to warfarin. For the safety outcome, apixaban was associated with a lower risk of major bleeding when compared to warfarin; dabigatran associated with a higher risk; and rivaroxaban associated with a comparable risk; and (iv) AF patients undergoing dialysis treated with OAC were associated with a significantly higher risk of IS/SE than those without any OAC treatment.

OAC or Not in ESRD AF Patients Undergoing Dialysis?

Whether AF patients with ESRD who are undergoing dialysis should receive OACs for stroke prevention remains unclear. The prevalence of warfarin prescription in such patients varies worldwide, possibly owing to a lack of solid evidence to judge the benefit and risk of warfarin in ESRD patients who are on dialysis [24]. Almost all AF patients with ESRD who are undergoing dialysis would have a CHA_2DS_2-VASc score of more than 2, and previous studies have indicated that the risks of AF occurrence, thromboembolic events, and major bleeding are increased with deterioration of renal function [4]. Thus far, few retrospective studies have investigated whether anticoagulants should be used for stroke prevention in patients with AF and ESRD [25, 26]. Meta-analysis of the above retrospective studies indicated that warfarin did not show a consistent reduction in ischemic stroke in the setting of substantial heterogeneity between individual studies. Nevertheless, excess bleeding including hemorrhagic stroke has been associated with warfarin [25, 26].

A recent meta-analysis showed that the use of warfarin was not associated with a lower risk of stroke compared to non-treatment in AF patients undergoing dialysis [25, 27]. Furthermore, some studies indicated that warfarin was even associated with an increased risk of ischemic stroke [28–30]. It was hypothesized that the increased risk of ischemic stroke may be a reflection of warfarin-related acceleration in vascular and valvular calcification in AF patients with ESRD [31–33]. Another rare but serious and life-threatening complication in ESRD patients that has been strongly associated with warfarin use is calciphylaxis, a condition characterized by vascular calcification, metastatic calcified occlusion of small vessels, and consequent cutaneous necrosis [25]. The associated mortality rate is high, primarily caused by secondary infection of the ulcers and sepsis [34]. The incidence of calciphylaxis is estimated to be approximately 1 in 300 per year in ESRD patients and approximately 50% of them have a prior warfarin exposure [35, 36]. In addition, the OAC (+) group had a higher prevalence of most comorbidities, including history of stroke, heart failure, and a higher CHA_2DS_2-VASc score than the OAC (−) group before PS matching. Although the PS matching with several variables allowed the matching of comorbidities among the study groups (Tables 1 and 2), residual confounding by unmeasured variables and selective prescribing behavior could not be excluded in our present study. Therefore, whether the increased risk of IS/SE for AF patients undergoing dialysis receiving OAC (most warfarin) in the present study were really due to drug related acceleration in vascular/valvular calcification and calciphylaxis, or were confounded by other factors remains unclear.

Current guidelines also have inconsistent recommendations. For example, the KDIGO (Kidney Disease: Improving Global Outcomes) guideline does not recommend routine anticoagulation for primary stroke prevention among AF patients with ESRD who are undergoing dialysis [37]. By contrast, the 2014 AHA/ACC/HRS guidelines and its 2019 focused update still recommended the use of warfarin with the INR range of 2.0 to 3.0 among patients with AF having CHA_2DS_2-VASc scores of ≥2 and advanced CKD (CrCl <15 mL/min) or undergoing dialysis, with a class IIb recommendation [3, 38]. Considering international guideline recommendations, the meta-analysis of several observational studies as well as the results in our present study, does not support the routine use of OACs for stroke prevention in all AF patients undergoing dialysis.

DOAC or Warfarin in ESRD AF Patients Undergoing Dialysis?

Although current evidence indicated that DOAC is an effective and safe alternative to warfarin among AF patients with moderate kidney disease (stage 3 CKD) [39], whether the result can be applied to the patients with advanced kidney disease or undergoing dialysis remains unclear. The current guideline recommends against the use of DOACs in AF patients undergoing dialysis, although in the United States, apixaban and rivaroxaban are approved for use in AF patients undergoing dialysis [2, 3, 5]. In the present study, we observed that approximately 15% of anticoagulated AF patients with ESRD were taking DOACs. One observational study in the United States indicated that 5.9% of anticoagulated dialysis patients were started on dabigatran ($n = 281$) or rivaroxaban ($n = 244$); of note, dabigatran and rivaroxaban were associated with a higher risk of hospitalization or death due to major bleeding, compared to warfarin, among patients with ESRD [16]. Dabigatran has a renal clearance of approximately 80% and is thus highly dependent on the kidneys for removal from the body [4]. Our meta-analysis indicates that dabigatran was associated with a higher risk of major bleeding than warfarin in AF patients with ESRD, which is consistent with the recommendations of the 2019 AHA/ACC/HRS focused update against the use of dabigatran in AF patients undergoing dialysis (class III recommendation) [3]. In contrast, a more recent study utilizing a US insurance claims database showed that rivaroxaban ($n = 1896$) was associated with a comparable risk of IS/SE and lower risk of major bleeding (HR; 0.68, [95%CI: 0.47–0.99]) when compared to warfarin ($n = 4848$) among AF patients with stage 5 CKD [17]. Another study utilizing a US insurance claims database showed that rivaroxaban ($n = 781$) was associated with a comparable risk of IS/SE and major bleeding compared to warfarin ($n = 1536$) among AF patients with stage 4–5 CKD [18]. We are unaware of studies comparing the efficacy and safety of dabigatran or rivaroxaban vs. warfarin among AF patients undergoing dialysis. Apixaban and rivaroxaban have been considered in the United States for stroke prevention in AF patients undergoing dialysis [3]. The evidence supporting the consideration of apixaban among patients with ESRD was obtained from limited pharmacokinetic data [40, 41]. Recently, Siontis et al. studied 2351 and 23,172 AF patients with ESRD treated with apixaban and warfarin, respectively [21]. There was no difference in the risk of IS/SE between apixaban and warfarin in a paired matched cohort, but apixaban was associated with a significantly lower risk of major bleeding. It should be noted that annual bleeding incidence, particularly the intracranial bleeding, were both high for apixaban and warfarin in this real-world ESRD AF population. Furthermore, more than two-thirds of patients discontinued OACs within one year in both the apixaban and warfarin groups equally.

To our best of our knowledge, our present study is the first population-based study to investigate the effectiveness and safety for DOACs vs. warfarin specifically focused on an Asian population comorbid with AF and ERSD. Our results reveal that DOACs did not show a reduction of IS/SE and major bleeding events when compared to warfarin in such a high risk AF population with ESRD. Furthermore, our meta-analysis showed no significant difference of the effectiveness and safety outcomes between DOACs and warfarin in AF patients undergoing dialysis, although there was substantial statistical heterogeneity observed across the nine studies for major bleeding, indicating that the comparable safety profile between DOACs and warfarin in AF patients undergoing dialysis should be interpreted with caution.

To date, the RENAL-AF trial is the one single randomized controlled study to compare the efficacy and safety of apixaban vs. warfarin among AF patients with ESRD undergoing dialysis [25]. After enrolling 154 patients (short of the 762 patient target), the RENAL-AF trial was stopped early due to finite resources and slow enrollment. There were comparable risks of major and clinically relevant non-major bleeding between apixaban and warfarin. One ongoing trial in Germany is comparing apixaban to VKA [42].

Limitations

The present study has several limitations. First, our study was performed in an intention-to-treat design, and did not take the changes or discontinuation of OACs during the study period into consideration, which may result in different categorizations of patients. Our study only identified 490 patients treated with DOACs, and whether more patients may show a significant difference between the effectiveness and safety between DOACs and warfarin remains unclear. Second, different DOACs prescribed had varying degrees of renal excretion; thus, decisions regarding the use of a specific DOAC or its dosage may have been guided by the renal function and body weight of each patient, because the information was lacking in the NHIRD. Third, misclassification and miscoding of the underlying covariates and outcomes registered by each physician's choice of treatment constitute an additional limitation of the present study. Similar to most electronic health databases worldwide, miscoding and purposely "upcoding" could be a problem. For example, physicians might tend to upcoding the diagnosis to a more severe one to avoid the refused reimbursement of DOACs by the NHI system in Taiwan. Although large data sets could potentially mitigate this problem, the real impact of the miscoding and misclassification remained unclear. Because the current major guidelines did not make any definite or conclusive recommendation regarding the preferred use of either DOAC, warfarin, or no-OAC treatment for stroke prevention in AF patients undergoing dialysis, it is unlikely that physicians have the motivation for upcoding the diagnoses to get the reimbursement of DOACs in these patient populations. In addition, several validation studies have been performed to evaluate the validity of diagnosis codes in the NHIRD [43]. Most of the validated diagnosis codes included several common diseases such as AF, cancer, ischemic stroke, acute myocardial infarction, heart failure, and cardiovascular risk factors, including hypertension, diabetes, and hyperlipidemia, and the validation showed a modest to high sensitivity and positive predictive values [43]. Furthermore, patients with severe diseases (such as the diagnosis of ESRD undergoing dialysis, ischemic stroke, or ICH in the present study) would qualify for the "catastrophic illness certification" under the current NHI program in Taiwan, so as to be exempted from certain copayments for each patient. All applications for catastrophic illness certification are carefully reviewed by specific experts; therefore, the diagnosis categorized as catastrophic illness can be considered as highly accurate. In addition, only primary discharge diagnoses were adopted in this study to improve the outcome accuracy. Nevertheless, whether the study outcomes in the present study were confounded by these factors cannot not be fully excluded. Fourth, the outcomes of major bleeding events were defined as the total sum events of ICH, major GIB, and other critical site bleedings that required hospitalization. We did not adopt the definition of major bleeding according to the definition provided by the International Society on Thrombosis and Hemostasis (ISTH) [44] due to the lack of important laboratory data (e.g., hemoglobin or blood transfusion unit) in our claim database. The definitions of major bleeding were also not exactly the same for the nine included studies in the meta-analysis [16–23]. Whether the different major bleeding outcome using different criteria may influence the study result remains unclear. Fifth, we used the PS matching method to balance the baseline covariate for the two study groups. Although the PS matching with several variables allowed the matching of comorbidities among the study groups, residual confounding by unmeasured variables and selective prescribing behavior could not be excluded in this study. Sixth, CKD prevalence (e.g., the high prevalence of CKD and ERSD that require dialysis in Taiwan [45]) and prescribing behaviors (e.g., a high prevalence of low-dose DOACs in Asians) would be different from non-Asian cohorts. In our present study, the prevalence of AF in the overall population was approximately 1% (Fig. 1), which was consistent with several Asian cohort studies and registries showing that the prevalence rate of AF is approximately 1% for the adult population in most Asian countries [46]. The prevalence of AF in the Asian population is lower than that in the Western population (approximately 2%) [47, 48]. The relatively low AF prevalence of the overall general population in the present study may affect our study results, and whether our results can be directly extrapolated to Western populations remains unclear. Finally, although most AF patients (89%) in the present meta-analysis were ESRD patients undergoing dialysis, those studies in the meta-analysis did not report outcomes separately for patients with stage 4 CKD or ESRD undergoing dialysis. This important limitation should be kept in mind when interpreting the results we presented here.

Conclusions

DOACs did not provide benefit over warfarin regarding effectiveness and safety in AF patients undergoing dialysis. In addition, the use of OAC was not associated with a lower risk of IS/SE in AF patients undergoing dialysis when compared with those without OAC use.

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Contributions LCS, HFL, and YHC contributed to the conception and design of the study as well as the analysis and interpretation of the data, and they wrote the manuscript and approved its submission. LCS, PRL, and JRL contributed to data acquisition and analysis. LCS, YHC, and GYHL contributed to the analysis of data and provided critical revisions. TFC, LSW, SHC, YHY, and CTK contributed to the conception and design, and they provided critical revisions of the paper for crucial intellectual content. All authors read and approved the final manuscript.

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Data Availability The datasets used in this study were only available from the Health and Welfare Data Center, Taiwan. The SAS programs (codes) involved in this study are available from the corresponding author upon reasonable request.

Compliance with Ethical Standards

Conflict of Interest GYHL: Consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally. The remaining authors have nothing to disclose.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent The identification number and personal information of each patient are encrypted and de-identified by using a consistent encrypting procedure; therefore, informed consent was waived for this study.

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