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Cardiac and renal outcomes of direct oral anticoagulants in patients with atrial fibrillation

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Abstract

Background: Oral anticoagulation therapy with warfarin or direct oral anticoagulants (DOACs) is the mainstay for stroke prevention in patients with non-valvular atrial fibrillation (AF). The DOACs might have a lower risk of declining renal function than warfarin. This study aimed to compare renal outcomes among rivaroxaban, edoxaban, dabigatran, and warfarin.

Method: This cohort study identified 2203 adults with AF who started anticoagulation therapy between 1 July 2013 and 31 December 2020, in a clinical database at a single centre. Inverse probability of treatment weighting was adopted to balance baseline characteristics among four anticoagulants treatment groups. The primary outcome was a composite of cardiac and renal outcomes, involving a ≥30% decline in estimated glomerular filtration rate (eGFR), renal failure and cardiovascular death.

Results: After propensity score weighting, dabigatran was associated with significantly lower risks of a ≥30% decline in eGFR (hazard ratio [HR]: .69, 95%

Yu-Ting Wang and Jo-Hsin Chen contributed equally to this work and share first authorship.

Direct oral anticoagulants are the mainstay for stroke prevention in patients with non-valvular atrial fibrillation (AF). Some evidence suggested that direct oral anticoagulants might have a lower risk of declining renal function than warfarin. Therefore, this study aims to compare the cardiac and renal outcomes among edoxaban, rivaroxaban, dabigatran and warfarin. This study contributes to the literature as follows. First, this study provides real-world evidence of the cardiac and renal outcomes of oral anticoagulants in patients with AF, especially in the Asian population, which is generally assumed to have a higher bleeding risk. Second, dabigatran was associated with a lower risk of composite cardiac and renal outcome and renal function declining than warfarin, while rivaroxaban and edoxaban were not. Lastly, this study's findings may yield clinical implications for clinicians when choosing oral anticoagulants for patients with AF with a higher risk of renal impairment.

confidence interval [CI]: .497–.951, $p = .0237$), doubling of the serum creatinine level (HR: .49, 95% CI: .259–.927, $p = .0282$) and the cardiac and renal outcome composite (HR: .67, 95% CI: .485–.913, $p = .0115$) than warfarin. Rivaroxaban and edoxaban did not show significant protective effects on renal outcomes compared to warfarin.

Conclusion: In this study, patients treated with dabigatran had significantly reduced risks of declining renal function and composite cardiac and renal events than those treated with warfarin. However, rivaroxaban and edoxaban were not associated with lower risks of any renal outcomes than warfarin. More studies are warranted to investigate and compare the impact of renal function between different DOACs in patients with AF.

KEYWORDS

acute kidney injury, atrial fibrillation, direct oral anticoagulants, renal failure, renal function, warfarin

1 | BACKGROUND

Warfarin or direct oral anticoagulants (DOACs) are the mainstay of anticoagulation treatment for thromboembolism prophylaxis in patients with non-valvular atrial fibrillation (AF). Subgroup analyses from clinical trials investigating the effect of DOACs and warfarin on renal function have reported heterogeneous results. The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial reported a greater decline in renal function in patients treated with warfarin than with dabigatran.[1] In the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial, similar rates of renal function decline were observed in the warfarin (26%) and rivaroxaban (27%) groups.[2] However, the warfarin group showed a significantly greater decline in creatinine clearance. An analysis from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in AF (ARISTOTLE) trial showed no difference in the decline in renal function over time between apixaban and warfarin.[3]

Several studies have used real-world data to compare the effects of dabigatran, rivaroxaban, apixaban and warfarin on renal outcomes, including changes in the estimated glomerular filtration rate (eGFR) and serum creatinine and the occurrence of acute kidney injury (AKI) and renal failure (RF) events, in different countries. Some studies have reported that dabigatran and rivaroxaban were associated with a lower risk of eGFR decline than warfarin.[4–9] A retrospective cohort study conducted in Taiwan showed that warfarin was associated with a significantly higher risk of AKI than DOACs. However, a comparison of dabigatran with other anti-factor Xa inhibitors indicated no difference.[10] Furthermore, changes in the eGFR did not differ between the warfarin and DOAC groups. However, few studies have examined changes in renal function in patients treated with edoxaban, the latest approved DOAC. Because of the close links between cardiac events and renal dysfunction, increased attention has focused on renal function decline, particularly in patients with AF.[11,12]

Therefore, we conducted this real-world retrospective cohort study to estimate the risk of using rivaroxaban, edoxaban, dabigatran and warfarin as oral anticoagulation treatments based on a composite of cardiac and renal outcomes and four meaningful renal outcomes (a ≥30% decline in the eGFR, doubling of the serum creatinine level, AKI incidence and RF incidence) in patients with non-valvular AF.

2 | MATERIALS AND METHODS

2.1 | Study population and follow-up

This observational, retrospective, single-centre cohort study extracted data from the Taipei Medical University Clinical Research Database (TMUCRD), which includes complete medical records of patients attending this medical center, including disease diagnoses, clinical laboratory examinations, pathology reporting, medications, surgeries and self-paid treatments.

A total of 5362 patients were diagnosed with AF according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 427.31 or International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code I48 between 1 July 2012 and 31 December 2020. Patients who received rivaroxaban, edoxaban, dabigatran or warfarin as their first anticoagulant treatment between 1 July 2013

and 31 December 2020, were identified, and the date of their first prescription was set as the index date. Patients with a history of receiving any anticoagulation therapy or who received an RF diagnosis 1 year before the index date were excluded. Moreover, we excluded patients whose eGFR data during the follow-up period were unavailable. Because apixaban was unavailable in our centre, we only identified patients who were administered warfarin, rivaroxaban, edoxaban and dabigatran as their first anticoagulant treatment. The incidence of study outcomes was noted for 2 years from the index date. The end of follow-up was the date of outcome occurrence, drug discontinuation or switching, death, end of the 2-year observation or 31 December 2020, whichever came first. The study flow chart is shown in Figure 1.

This study was approved by Taipei Medical University's Institutional Review Board (TMU-eJIRB N202112044). Because we used de-identified data, this study did not require informed consent to be obtained.

2.2 | Baseline characteristics and variables for propensity scoring

Baseline characteristics of clinical variables, including the patients' medication and comorbidities, were collected up to 1 year before the index date. ICD-9-CM and ICD-10-CM codes for diagnosing comorbidities are listed in Table S1. The most recent serum creatinine level and eGFR measured within 1 year before the index date were used as baseline values. The eGFR was calculated using the Modification of Diet in Renal Disease GFR equation. The CHA_2DS_2-VASc score was calculated to evaluate patients' thromboembolic risk based on sex; age at the index date; and the status of congestive heart failure (HF), hypertension, diabetes mellitus (DM), stroke, transient ischemic attack, thromboembolism and vascular disease.

Covariates, including demographic variables and health status, were considered potential determinants for patients prescribed rivaroxaban, edoxaban, dabigatran or warfarin. To reduce confounding through indication bias, we derived a propensity score for each patient based on their age, sex, CHA_2DS_2-VASc score, serum creatinine level, eGFR, medical history (i.e. HF, hypertension, hyperlipidaemia, DM, thromboembolism, major bleeding, myocardial infarction, peripheral arterial disease, liver disease, anaemia, chronic kidney disease [CKD], AKI, chronic obstructive pulmonary disease, cancer, hypothyroidism and thyrotoxicosis) and mediation (i.e. antiplatelet drugs, nonsteroidal anti-inflammatory drugs [NSAIDs], angiotensin-converting enzyme inhibitors [ACEIs] or angiotensin II receptor blockers [ARBs], aminoglycosides, sodium-glucose cotransporter-2 inhibitors [SGLT2is], glucagon-like peptide-1 receptor agonists [GLP1RAs], statins and diuretics) to estimate the corresponding probabilities of rivaroxaban, edoxaban, dabigatran or warfarin treatment. The propensity scores were used for further analyses.

2.3 | Study outcomes

The primary outcome was a composite of cardiac and renal outcomes: a ≥30% decline in eGFR, RF and cardiovascular death. The renal outcomes of interest were

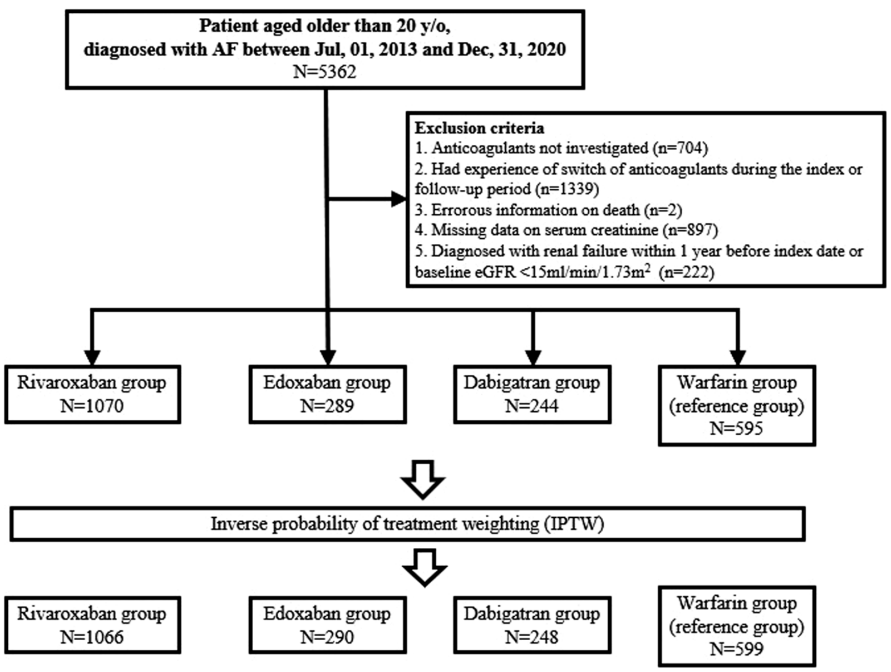

FIGURE 1 Flow chart of eligible patients.

a ≥30% decline in eGFR, a doubling of the serum creatinine level, and AKI and RF incidence, which were analysed across the four drug groups. We collected the baseline eGFR and serum creatinine level. The follow-up time period was every 3–6 months after the index date and the follow-up duration was 24 months. Doubling of the serum creatinine level has been used as an established endpoint of kidney disease progression in clinical trials. However, it may occur relatively late and require long-term observation. Therefore, the United States Food and Drug Administration recommends using a 30% or 40% decline in the eGFR as a valid surrogate endpoint. This surrogate endpoint has been adopted in other clinical studies.[13] An AKI event was defined as an emergency department visit or hospitalisation recorded using the diagnosis codes of ICD-9-CM (584.9, 584.5, 584.6, 584.7, 584.8 or 584.9) or ICD-10-CM (N17). RF was defined as an eGFR of <15 mL/min/1.73 m^2, the presence of end-stage renal disease, or kidney transplant treatment with the diagnosis codes of ICD-9-CM (586 or 996.81) or ICD-10-CM (V42.0, N18.6, N19, T86.1 or Z94.0).

2.4 | Subgroup analyses

Patients treated with rivaroxaban may be prescribed different doses based on their renal function. Based on the ROCKET-AF and J-ROCKET-AF trials, which examined global and Japanese patients, respectively, two treatment doses of rivaroxaban are recommended in the US and Asian populations.[14,15] Because this study included Asians, we adopted the standard dose in the J-ROCKET-AF trial for the Asian population.[14] The standard doses of rivaroxaban, calculated using the Cockcroft–Gault formula, were 15 and 10 mg/day when the patient's creatinine clearance was >50 mL/min and 15–50 mL/min, respectively. An off-label dose was defined as one that did not correspond to these creatinine clearance levels, including higher or lower doses. We conducted a subgroup analysis comparing the standard and off-label doses of rivaroxaban with those of warfarin.

A prespecified subgroup analysis of composite cardiac and renal events between the DOAC and warfarin groups was also conducted. The subgroups of patients were stratified based on sex; creatinine clearance; CHA_2DS_2-VASc score; the absence or presence of HF, hypertension, DM or thromboembolism; and treatment with NSAIDs, ACEIs/ARBs, SGLT2is, GLP1RAs or statins. This subgroup analysis identified interactions between prespecified subgroups and different anticoagulants.

2.5 | Statistical analysis

We evaluated the effect of the anticoagulants (i.e. warfarin, rivaroxaban, edoxaban and dabigatran) on the incidence of various cardiac and renal outcomes. Differences in characteristics between the drug groups were assessed using the chi-squared test for categorical variables and analysis of variance for continuous variables. Kaplan–Meier survival analysis was used to examine differences in the incidence of cardiac and renal outcomes stratified by drug use. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the effects of the anticoagulants.

Confounding through indication bias may exist in this study because of the different probabilities of patients being prescribed a particular anticoagulant based on their baseline characteristics, comorbidities, or medications. The propensity score first proposed by Rosenbaum and Rubin[16] was derived to account for this bias.[17] Because this study investigated four treatments, we conducted propensity score weighting rather than pairwise propensity score matching to prevent the problem of multiple comparisons.[17] We first included variables influencing anticoagulant prescription in a (multinomial) logistic regression to estimate the predicted probability (propensity score) of receiving a specific drug. Second, the inverse probability of treatment weighting (IPTW) approach was applied, and the original population was weighted with the inverse propensity score to create a pseudo-population for subsequent analyses. Imbalances among treatment groups were well controlled in the pseudo-population, resulting in virtual randomisation on warfarin, rivaroxaban, edoxaban or dabigatran group.[17–19] Third, the weights used for the IPTW were stabilised by the sample size of the original population to prevent the extreme inflation of pseudo-population size due to the inverse of a small propensity score, resulting in an elevated Type I error rate.[20] Finally, the risk of cardiac and renal events according to different drug types was evaluated with the conventional Cox proportional hazards model using the pseudo-population.[17,19] Statistical analyses were two-sided, and the level of significance was .05. All statistical analyses were performed using SAS software (version 9.4; SAS Institute).

3 | RESULTS

3.1 | Characteristics of study groups

The baseline demographic variables and covariates of patients treated with anticoagulants are presented in Table 1. The study groups comprised 2198 patients with AF, which differed significantly in age; NSAID, ACEI/ARB, statin and

TABLE 1 The baseline characteristics of patients stratified by the drug before and after IPTW.

	Before IPTW					After IPTW				
	Warfarin (*N* = 595)	**Rivaroxaban (*N* = 1070)**	**Edoxaban (*N* = 289)**	**Dabigatran (*N* = 244)**	***p* Value**	**Warfarin (*N* = 599)**	**Rivaroxaban (*N* = 1066)**	**Edoxaban (*N* = 290)**	**Dabigatran (*N* = 248)**	***p* Value**
Age	74.7 ± 13.3	78.6 ± 10.9	77.5 ± 12.3	75.9 ± 10.6	<.0001*	77.2 ± 12.8	76.9 ± 11.7	77.1 ± 12.7	77.2 ± 11.0	.980
Serum creatinine	1.07 ± 0.46	1.04 ± 0.39	1.05 ± 0.44	0.94 ± 0.31	.0006*	1.03 ± 0.41	1.03 ± 0.39	1.02 ± 0.41	1.07 ± 0.47	.509
eGFR	74.37 ± 28.30	74.38 ± 29.77	77.30 ± 33.02	81.07 ± 26.76	.0069*	75.91 ± 28.04	75.85 ± 30.04	76.32 ± 29.10	74.83 ± 30.57	.946
CHA_2DS_2-VASc	3.4 ± 1.8	3.6 ± 1.5	4.0 ± 1.7	3.5 ± 1.5	.0023*	3.5 ± 1.7	3.4 ± 1.7	3.6 ± 1.8	3.6 ± 1.6	.867
Male	323 (54.3)	565 (52.8)	175 (60.6)	133 (54.5)	.1377	335 (55.8)	581 (54.5)	156 (53.8)	141 (56.7)	.861
Medical history										
HF	203 (34.1)	433 (40.5)	97 (33.6)	63 (25.8)	<.0001*	210 (35)	381 (35.7)	101 (34.9)	86 (34.6)	.981
HTN	300 (50.4)	550 (51.4)	151 (52.3)	135 (55.3)	.626	313 (52.2)	555 (52)	150 (51.5)	130 (52.2)	.998
Hyperlipidemia	193 (32.4)	376 (35.1)	107 (37)	83 (34)	.541	213 (35.5)	367 (34.4)	103 (35.4)	81 (32.6)	.864
DM	204 (34.3)	361 (33.7)	106 (36.7)	77 (31.6)	.654	206 (34.3)	356 (33.4)	97.2 (33.5)	96.3 (38.8)	.431
Thromboembolism[a]	124 (20.8)	108 (10.1)	54 (18.7)	60 (24.6)	<.0001*	107 (17.9)	167 (15.6)	64 (21.9)	41 (16.4)	.846
Major bleeding[b]	101 (17)	148 (13.8)	46 (15.9)	42 (17.2)	.28	85 (14.2)	161 (15.1)	41 (14.2)	33 (13.4)	.891
MI	15 (2.5)	27 (2.5)	15 (5.2)	6 (2.5)	.091	20 (3.3)	28 (2.7)	7 (2.4)	6 (2.5)	.853
PAD	16 (2.7)	31 (2.9)	5 (1.7)	4 (1.6)	.539	14 (2.3)	26 (2.5)	5 (1.7)	6 (2.3)	.902
Liver disease	62 (10.4)	130 (12.2)	30 (10.4)	23 (9.4)	.512	64 (10.7)	119 (11.1)	43 (14.9)	30 (12.1)	.281
Anaemia	25 (4.2)	54 (5.1)	17 (5.9)	8 (3.3)	.458	26 (4.4)	53 (5)	15 (5.2)	17 (7)	.461
CKD	23 (3.9)	72 (6.7)	41 (14.2)	17 (7)	<.0001*	46 (7.7)	74 (7)	20 (7)	16 (6.6)	.936
Proteinuria	15 (2.5)	31 (2.9)	16 (5.5)	9 (3.7)	.093	17 (2.8)	34 (3.2)	8 (2.7)	7 (3)	.954
TKD	11 (1.9)	35 (3.3)	13 (4.5)	11 (4.5)	.091	19 (3.1)	34 (3.2)	10 (3.5)	6 (2.5)	.925
AKI	53 (8.9)	102 (9.5)	38 (13.2)	19 (7.8)	.143	63 (10.6)	107 (10)	28 (9.7)	24 (9.5)	.957
COPD	96 (16.1)	221 (20.7)	59 (20.4)	46 (18.9)	.147	120 (20.1)	209 (19.6)	57 (19.6)	46 (18.5)	.967
Cancer	35 (5.9)	96 (9.0)	28 (9.7)	26 (10.7)	.056	50 (8.3)	90 (8.4)	26 (8.9)	17 (6.8)	.82
Hypothyroidism	35 (5.9)	51 (4.8)	16 (5.5)	11 (4.5)	.736	30 (5)	55 (5.1)	12 (4.2)	13 (5.1)	.934
Thyrotoxicosis	23 (3.9)	56 (5.2)	21 (7.3)	9 (3.7)	.123	24 (3.9)	56 (5.2)	12 (4.3)	11 (4.3)	.649
Medication										
Antiplatelet	331 (55.6)	635 (59.4)	161 (55.7)	137 (56.2)	.407	340 (56.7)	608 (57)	165 (56.9)	137 (55.3)	.969
NSAID	198 (33.3)	484 (45.2)	156 (54.0)	124 (50.8)	<.0001*	271 (45.1)	467 (43.8)	131 (45.2)	107 (43.1)	.914
ACEIs or ARBs	286 (48.1)	664 (62.1)	205 (70.9)	164 (67.2)	<.0001*	361 (60.2)	639 (59.9)	176 (60.6)	145 (58.4)	.959
Aminoglycoside	13 (2.2)	28 (2.6)	4 (1.4)	17 (7)	.0003*	22 (3.7)	27 (2.5)	15 (5.2)	6 (2.3)	.091

(Continues)

TABLE 1 (Continued)

	Before IPTW					After IPTW				
	Warfarin (N = 595)	Rivaroxaban (N = 1070)	Edoxaban (N = 289)	Dabigatran (N = 244)	p Value	Warfarin (N = 599)	Rivaroxaban (N = 1066)	Edoxaban (N = 290)	Dabigatran (N = 248)	p Value
SGLT2i	3 (0.5)	12 (1.1)	6 (2.1)	4 (1.6)	.137	7 (1.1)	13 (1.2)	3 (0.9)	2 (1)	.966
GLP1RA	3 (0.5)	4 (0.4)	3 (1)	0 (0)	.324	2 (0.4)	5 (0.4)	1 (0.4)	0 (0)	.794
Statin	126 (21.2)	345 (32.2)	127 (43.9)	110 (45.1)	<.0001*	191 (31.8)	342 (32)	96 (33.1)	74 (30)	.892
Diuretic	238 (40)	566 (52.9)	159 (55)	110 (45.1)	<.0001*	308 (51.3)	525 (49.2)	144 (49.5)	125 (50.2)	.869

Note: Values are the mean ± standard deviation or number (%).

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HF, heart failure; HTN, hypertension; IPTW, inverse probability of treatment weighting; MI, myocardial infarction; NSAID, nonsteroid anti-inflammatory drug; PAD, peripheral artery disease; TKD, tubulointerstitial kidney disease.

[a]Thromboembolism includes transient ischemic attack and stroke.

[b]Major bleeding includes patients who require blood transfusion and those with a haemoglobin level of >2 mg/dL.

*Statistically significant difference ($p < .05$).

diuretic treatment history; and thromboembolism and CKD complications before propensity score weighting. All baseline demographic characteristics and clinical variables were balanced in the weighted cohort after weighting (Table 1).

3.2 | Cardiac and renal outcomes of DOACs and warfarin

In the original study cohort, the crude incidence rates of the composite cardiac and renal events were 25.7, 37.6, 30.1 and 19.3 per 100 person-years in patients treated with warfarin, rivaroxaban, edoxaban and dabigatran, respectively.

After propensity score weighting, dabigatran was associated with a significantly lower risk of the composite of cardiac and renal events (HR: .67, 95% CI: .485–.913, $p = .0115$) than warfarin (Table S2).

In addition, dabigatran was associated with a significant beneficial effect on renal outcomes after propensity score weighting, including a ≥30% decline in the eGFR (HR: .69, 95% CI: .497–.951, $p = .0237$) and doubling of serum creatinine levels (HR: .49, 95% CI: .259–.927, $p = .0282$). Rivaroxaban and edoxaban were associated with a higher risk of a ≥30% decline in the eGFR than warfarin in the original cohort but was not observed in the weighted cohort (HR: 1.04, 95% CI: .861–1.260 and HR: 1.20, 95% CI: .920–1.571, respectively).

None of the three DOACs were associated with significantly lower risks of AKI or RF (Table S2). The Kaplan–Meier curves for the composite of cardiac and renal events, ≥30% decline in the eGFR, doubling of serum creatinine levels, AKI incidence and RF incidence after propensity score weighting are shown in Figure 2.

3.3 | Subgroup analyses

Over 50% of the patients in the rivaroxaban group were treated using the standard dose with guided dose adjustment based on renal function. An off-label dose of rivaroxaban was associated with a significantly higher risk of the composite of cardiac and renal events (HR: 1.269, 95% CI: 1.017–1.585, $p = .0353$) and a ≥30% decline in the eGFR (HR: 1.346, 95% CI: 1.073–1.689, $p = .0103$). The effects of the standard rivaroxaban dose on all outcomes did not differ significantly from those of warfarin (Table 2).

Because dabigatran was associated with a significantly lower risk of the composite cardiac and renal outcome in the primary analysis, we conducted a subgroup analysis comparing dabigatran's cardiac and renal protective effects in prespecified patient groups. As summarised in Figure 3, dabigatran showed the consistency of cardiac and renal protective effects in most subgroups.

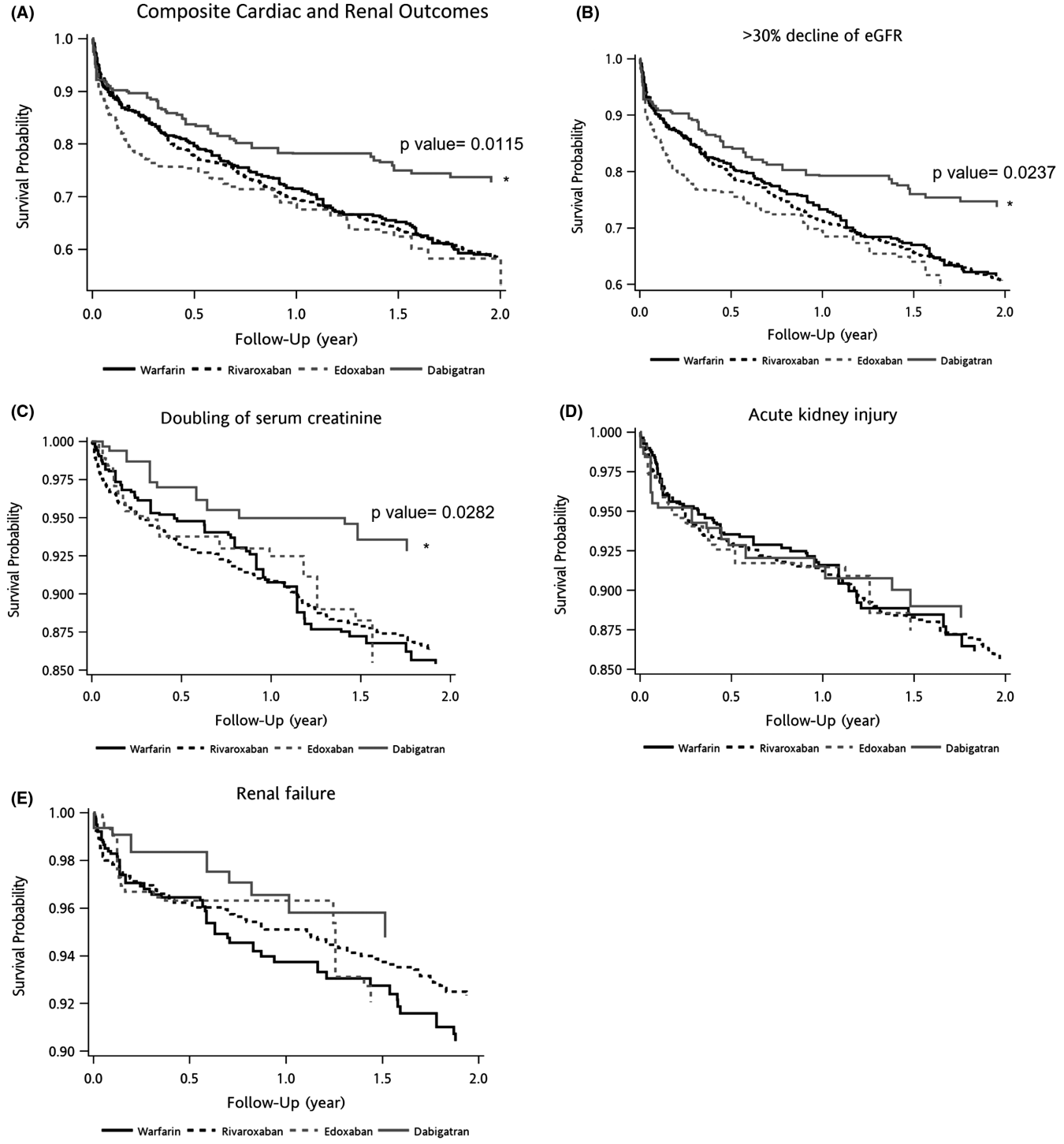

FIGURE 2 Kaplan–Meier plot of the composite of cardiac and renal outcomes (A), ≥30% decline in eGFR (B), doubling of serum creatinine (C), acute kidney injury (D) and renal failure (E). *Significant difference to warfarin.

4 | DISCUSSION

This retrospective cohort study analysing clinical real-world data had the following principal findings: First, renal function decline was common in patients with AF receiving oral anticoagulants; second, compared with warfarin, dabigatran was associated with a lower risk of the composite of cardiac and renal events, ≥30% decline in eGFR and doubling of serum creatinine levels.; and third, rivaroxaban and edoxaban did not show significant protective effects on any renal outcomes compared to warfarin.

TABLE 2 Subgroup analysis of rivaroxaban stratified by dose in the weighted cohort.

	No. of events	HR (95% CI)	*p* Value
Composite of cardiac and renal events			
Warfarin	163	Ref.	
Rivaroxaban, standard dose	198	1.054 (.856–1.2970)	.6224
Rivaroxaban, off-label dose	150	1.269 (1.017–1.5850)	.0353
≥30% decline in eGFR			
Warfarin	152	Ref.	
Rivaroxaban, standard dose	180	1.03 (.831–1.281)	.7777
Rivaroxaban, off-label dose	147	1.346 (1.073–1.6890)	.0103
Doubling of serum creatinine			
Warfarin	51	Ref.	
Rivaroxaban, standard dose	59	.947 (.650–1.380)	.7777
Rivaroxaban, off-label dose	53	1.388 (.945–2.0370)	.0943
Acute kidney injury			
Warfarin	50	Ref.	
Rivaroxaban, standard dose	59	.996 (.684–1.452)	.9839
Rivaroxaban, off-label dose	53	1.406 (.956–2.0670)	.0831
Renal failure			
Warfarin	34	Ref.	
Rivaroxaban, standard dose	35	.857 (.545–1.374)	.5226
Rivaroxaban, off-label dose	23	.905 (.535–1.5320)	.7112

Note: After IPTW, 599, 550, and 354 patients were treated with warfarin, the standard rivaroxaban dose and the off-label rivaroxaban dose, respectively.

Abbreviations: eGFR, estimated glomerular filtration rate; IPTW, inverse probability of treatment weighting.

Our findings with dabigatran are consistent with those of a post-hoc analysis in the RE-LY trial that compared changes in renal function between dabigatran and warfarin groups, showing a significant decline in the eGFR in the warfarin group.[1] A large cohort study in the United States using an administrative database and linked laboratory results reported lower risks of a ≥30% decline in the eGFR and AKI in patients treated with dabigatran than with warfarin.[4] The mechanism was that warfarin might induce glomerular haemorrhage, tubular obstruction by red blood cell casts and renal artery calcification by inhibiting the vitamin K-dependent protein matrix, increasing the risk of renal function decline.[21–26] In contrast, DOACs protect renal function by inhibiting the coagulation factor Xa and thrombin, which are associated with vascular inflammation.[7,27,28]

The thrombin inhibitor dabigatran showed a greater tendency to exert significant renal protective effects than warfarin. Furthermore, in the subgroup with creatinine clearance <80 mL/min, the patients treated with dabigatran had a significantly lower risk of cardiac and renal events and a decline in the eGFR than those treated with warfarin. However, the results of studies on factor Xa inhibitors, including rivaroxaban and edoxaban, and their effect on renal function have been inconclusive. These conflicting findings are perhaps related to different anticoagulation mechanisms. Factor Xa and thrombin are associated with vascular inflammation involving the protease-activated receptor 2 (PAR2), which can induce interleukin (IL)-8 production and thereby lead to the recruitment of inflammatory cells to atherosclerotic plaques. However, only thrombin inhibitors have been shown to reduce advanced atherosclerotic plaque burden and improve endothelial function in animal models of atherosclerosis. Their possible mechanism may be inhibiting protease-activated receptor 1 (*PAR1*) expression and transforming growth factor-beta (TGF-ß)- and snail family transcriptional repressor 2 (SNAI2)-induced epithelial–mesenchymal transition.[1]

This study found no significant differences in study outcomes between factor Xa DOACs and warfarin. Other studies found that rivaroxaban was associated with lower risks of a ≥30% decline in the eGFR, doubling of serum creatinine levels, and AKI than warfarin.[2,4,6–9] When we stratified patients treated with the standard and off-label rivaroxaban doses to those treated with warfarin to compare their effects on renal function, we found that those treated with the off-label rivaroxaban dose had significantly higher risks of the composite of cardiac and renal events and a ≥30% decline in the eGFR than those treated with warfarin. This effect was not observed in patients treated with the standard rivaroxaban dose. Notably, the rivaroxaban dose was adjusted according to the patient's renal function. However, the prescribed off-label dose may vary depending on the physician's concern about the patient's age, bleeding risk, or other reasons affecting medication prescription behaviour. Therefore, whether the standard treatment rivaroxaban dose is administered may be a crucial factor affecting renal function decline. Our findings suggest that the clinical implications of whether the standard rivaroxaban dose is prescribed according to patients' renal function must be examined and that renal function must be carefully monitored.

This study found that the trends with edoxaban were consistent with rivaroxaban for all the study outcomes, including the composite of cardiac and renal events and

	No. of events	Warfarin, n (event rate %)	Dabigatran, n (event rate %)	HR (95% CI)	*p* value
Sex					0.6386
Female	110	265 (32.09)	107 (23.34)	0.736 (0.474–1.142)	
Male	104	334 (23.52)	141 (18.16)	0.646 (0.409–1.020)	
Creatinine clearance					0.0201
<50 mL/min	107	249 (34.50)	93 (22.99)	0.572 (0.345–0.949)	
50–79 mL/min	64	166 (30.49)	83 (16.67)	0.501 (0.278–0.903)	
≥80 mL/min	30	98 (19.81)	35 (32.59)	1.830 (0.911–3.678)	
CHA_2DS_2-VASc score					0.1785
0 or 1	13	68 (17.55)	25 (5.50)	0.335 (0.072–1.548)	
2	32	106 (19.91)	43 (25.65)	1.264 (0.606–2.637)	
≥3	168	426 (30.71)	180 (21.19)	0.580 (0.400–0.843)	
Heart failure					0.2398
No	115	390 (23.29)	162 (15.33)	0.564 (0.365–0.872)	
Yes	98	209 (34.80)	86 (30)	0.842 (0.524–1.353)	
Hypertension					0.3860
No	104	286 (27.01)	119 (22.52)	0.787 (0.506–1.223)	
Yes	110	313 (27.59)	129 (18.46)	0.576 (0.365–0.911)	
Diabetes mellitus					0.5984
No	128	394 (25.22)	152 (19.32)	0.711 (0.473–1.069)	
Yes	85	205 (31.31)	96 (22.11)	0.583 (0.350–0.970)	
Thromboembolism					0.4898
No	186	492 (28.98)	207 (21.16)	0.702 (0.495–0.996)	
Yes	27	107 (19.62)	41 (16.55)	0.500 (0.227–1.101)	
Antiplatelet					0.8599
No	91	259 (26.68)	111 (20.39)	0.680 (0.423–1.094)	
Yes	122	340 (27.79)	137 (20.41)	0.660 (0.431–1.012)	
NSAID					0.3683
No	117	329 (26.05)	141 (22.26)	0.758 (0.513–1.120)	
Yes	377	270 (28.85)	107 (17.94)	0.566 (0.329–0.973)	
ACEI/ARB					0.4909
No	81	238 (25.53)	103 (19.57)	0.764 (0.477–1.225)	
Yes	133	361 (28.49)	145 (21)	0.600 (0.391–0.923)	
SGLT-2i					
No	213	593 (27.62)	246 (20.24)	0.655 (0.476–0.900)	
Yes	0	6 (0)	2 (37.20)	-	
GLP-1RA					
No	213	597 (27.27)	248 (20.40)	0.667 (0.486–0.917)	
Yes	0	2 (37.46)	0 (0)	-	
Statin					0.4743
No	163	408 (30.42)	174 (22.65)	0.725 (0.509–1.031)	
Yes	50	191 (20.65)	74 (15.17)	0.523 (0.258–1.059)	

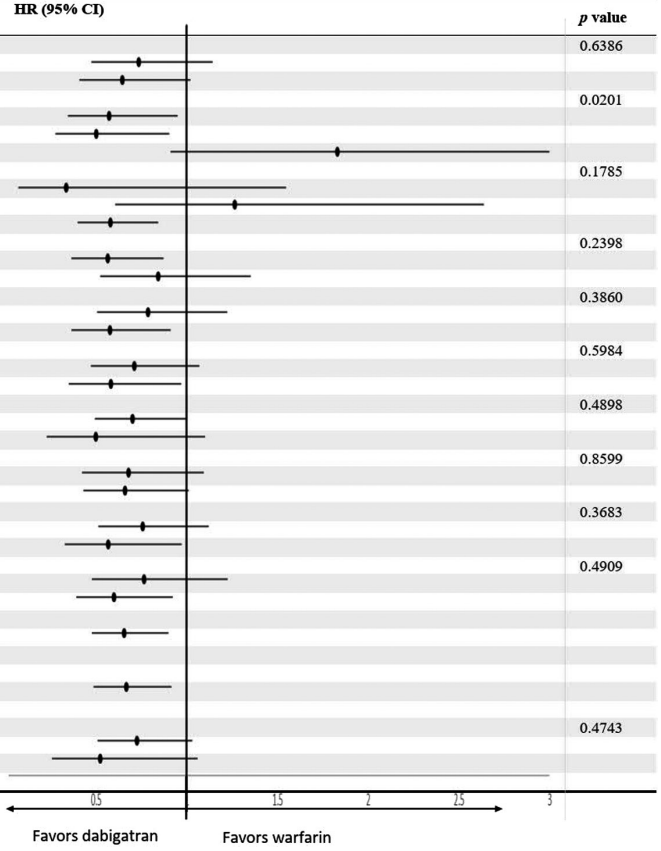

FIGURE 3 Composite of cardiac and renal outcomes for dabigatran versus warfarin according to the subgroup analysis.

the incidences of a ≥30% decline in the eGFR, doubling of the creatinine level, AKI and RF, which did not differ significantly from warfarin. The edoxaban dose is adjusted based on creatinine clearance, body weight, and concomitant use of P-glycoprotein inhibitors such as cyclosporine, dronedarone, erythromycin, and ketoconazole. In our database, it was impossible to define the "standard dose" given the incomplete body weight data and lack of medication records from other medical institutions.

While this analysis focused on the decline in renal function with DOACs compared to warfarin, the associations with clinical events, especially stroke, merit future consideration in larger prospective studies as patients with AF remain at high residual risk of major adverse cardiovascular events despite taking oral anticoagulants.[29,30] Therefore, there is a need for a more holistic or integrated care approach to AF management,[31] which has been associated with improved clinical outcomes,[32] leading to its incorporation into guidelines.[33] Finally, at the other extreme of renal function, there are concerns about a numerical (but nonstatistically significant) increase in ischaemic stroke in patients with very high eGFR (>90 mL/min) taking factor Xa inhibitors compared to warfarin indicated in subgroup analyses from clinical trials[2,3] or real-world data.[34] Such a concern is not evident for dabigatran, despite its greater renal dependency for excretion.[1]

4.1 | Limitations

This study had several limitations. First, while it used ICD-9-CM and ICD-10-CM codes to identify AKI, the TMUCRD only contains the records of the first 10 codes for each patient, possibly leading to the underestimation of AKI incidence. This underestimation may underlie the inconsistency between our findings and other studies indicating DOACs were associated with a lower AKI incidence than warfarin.[4–6]

Second, early drop-out may have caused the underreporting of adverse renal effects. We censored patients who were switched from their first anticoagulant to another and ceased follow-up with these patients at the time of the switch. Conversion between anticoagulants may result from renal function change and can occur before the renal outcomes of interest in this study. Therefore, we may not have observed renal outcome events during patients' original anticoagulant therapy, causing further underestimation of the incidence of the study outcomes.

Finally, we could not calculate the time in the therapeutic range (TTR) to evaluate the effect of the international normalised ratio (INR) on the outcomes of interest. One study indicated that patients treated with warfarin and a supratherapeutic INR range (>3) had markedly higher risks of a ≥30% decline in eGFR, doubling of serum creatinine levels and AKI. Patients treated with DOACs still had lower risks than those treated with warfarin whose INR was in the subtherapeutic (<2) or therapeutic[2,3] range.[4] Therefore, further studies must consider the TTR for a more precise estimation of the renal protective effects of DOACs.

5 | CONCLUSION

In this retrospective study, renal function decline was common in patients with AF taking oral anticoagulants. Patients with AF treated with dabigatran had significantly reduced risks of cardiac and renal events and a decline in renal function than those treated with warfarin. However, rivaroxaban and edoxaban were not associated with lower risks of renal outcomes compared to warfarin. More studies are warranted to investigate and compare the impact of renal function between different DOACs in patients with AF.

6 | CLINICAL PERSPECTIVES

This study provided insight into cardiac and renal outcomes in patients with AF given anticoagulative treatment using four drugs: edoxaban, rivaroxaban, dabigatran and warfarin. One of the more significant findings from this study was that dabigatran had a greater tendency to exert significant renal protective effects than warfarin. However, there were no significant differences in the study outcomes between factor Xa inhibitors and warfarin. These findings may have clinical implications for clinicians when choosing oral anticoagulants to treat patients at higher risk of renal impairment. This study also contributed real-world evidence in Asian patients, who are generally assumed to have a higher bleeding risk. This study indicates that further studies are needed to understand better the differences between thrombin and factor Xa inhibitors.

AUTHOR CONTRIBUTIONS

Y-TW, J-HC, Y-JC and J-SY contributed to the study's conception and design. S-FL performed the statistical analysis. Y-TW, J-HC and S-FL wrote the manuscript draft. All authors contributed to the manuscript revision and read and approved the final published version.

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CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data supporting this study's findings are available in the TMUCRD. However, restrictions apply to their availability, and they are not publicly available; this study used them under licence. However, the data are available from the authors upon reasonable request and with the permission of the TMUCRD administrators.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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