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Renal function decline in Asian patients with atrial fibrillation with warfarin and non-vitamin K antagonist oral anticoagulants: A report from the COOL-AF registry

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Abstract

Background: The objective of this study was to compare the risk of estimated glomerular filtration rate (eGFR) decline between atrial fibrillation (AF) patients with direct oral anticoagulants (DOACs) and warfarin.

Methods: We studied patients with nonvalvular AF from a prospective multicenter national AF registry in Thailand. Patients with missing eGFR data or eGFR less than 30 mL/min/1.73 m^2 were excluded. Follow-up data including eGFR were collected every 6 months until 3 years. eGFR decline was assessed by eGFR slope. We compared eGFR slope between patients who received DOACs and warfarin at baseline. In the warfarin group, we assessed the impact of good anticoagulation control by time in the therapeutic range (TTR).

Results: A total of 1708 patients were studied (mean age 68.1 years; 42.6% female). Patients with DOACs had a significantly slower rate of eGFR decline compared to warfarin. The eGFR slope was 2.32 mL/min/1.73 m^2 per year in the warfarin group (95% CI: 3.09 to 1.55), and 1.31 mL/min/1.73 m^2 per year in the DOAC group (95% CI: 1.97 to 0.64). The effect of OAC type on the eGFR slope remained significant even after the adjustment of baseline variables including baseline eGFR. There was no difference in GFR decline as reflected by eGFR slope when comparing warfarin patients with TTR <65% and ≥65%.

Conclusion: In this prospective cohort of Asian patients with AF, DOACs were associated with a slower rate of eGFR decline when compared with warfarin. In the latter group, this was irrespective of the quality of anticoagulation control.

KEYWORDS
atrial fibrillation, chronic kidney disease, estimated glomerular filtration rate, non-vitamin K antagonist oral anticoagulants, oral anticoagulants

1 | INTRODUCTION

Majority of patients with atrial fibrillation (AF) require oral anticoagulants (OAC) for stroke prevention.[1,2] International guidelines recommend direct oral anticoagulants (DOACs) over warfarin when choosing the type of OAC.[3–6] When using warfarin, guidelines recommend that the time in therapeutic range (TTR) should be at least 65%–70%.[3,6,7] However, the TTR can be influenced by many factors, including drugs and diet, as well as certain comorbidities.

AF patients tend to be older and have an increased risk of chronic kidney disease (CKD).[8] AF patients generally have a more rapid decline in renal function or estimated glomerular filtration rate (eGFR) than the non-AF population.[9] Also, data from Rotterdam study found a bidirectional association of AF and eGFR decline.[10] Renal dysfunction is also associated with poor anticoagulation control, which is related to adverse outcomes.[11] In addition, warfarin is associated with a more rapid renal function decline compared with DOACs.[12,13] Both abnormal baseline renal function has been shown to be a prognostic indicator in patients with AF.[8] The eGFR slope has been recommended as a good marker to assess eGFR decline and to predict future renal failure.[14,15] Nevertheless, prospective data from Asian cohorts on these aspects linking renal function decline with DOACs versus warfarin or with the quality of anticoagulation control assessed by TTR is limited.

The primary objective of this study was to compare the rate of GFR decline between AF patients with warfarin and DOACs in the Asian population in a real-world setting national AF registry. Second, we also investigated the association between the rate of GFR decline and TTR.

2 | METHODS

2.1 | Study population

This is a prospective multicenter registry of patients with nonvalvular AF aged at least 18 years. Patients were enrolled from 27 hospitals during 2014–2017. Patients need to have documented ECG for AF. The exclusion criteria were as follows: (i) rheumatic mitral stenosis; (ii) mechanical heart valve; (iii) AF from a transient cause; (iv) life expectancy of less than 3 years; (v) hematologic conditions that increase the risk of bleeding; (vi) Ischemic stroke within 3 months; (vii) cannot have follow-up data; (viii) participating in clinical trials using pharmaceutical products; (ix) no baseline eGFR data; (x) baseline eGFR result <30 mL/min/1.73 m^2; (xi) did not receive OAC; and (xii) did not have follow-up data.

This study was approved by the Institutional Review Board of the Central Research Ethic Committee (CREC) with the Certificate of Approval (COA) number CREC 003/2014.

All patients gave written informed consent prior to participation. The study was conducted in accordance with the principles set forth in the Declaration of Helsinki and the International Conference on Harmonization for Good Clinical Practice Guidelines. The study protocol has been previously published.[1]

2.2 | Data collection

Data were collected from medical records and patient's interview. The following baseline data were recorded: demographic, body weight, height, body mass index (BMI), vital signs, AF types and symptoms, cardiovascular risk factors, and comorbid conditions [including T2D, hypertension, dyslipidemia, smoking, heart failure (HF), and coronary artery disease (CAD)], laboratory data, ECG and echocardiographic results, other investigations, and medications. Components of CHA_2DS_2-VASc score[16] and HAS-BLED score[17] were recorded. The data were recorded on the web-based system. The investigators at the data management site verified the data and made queries to the site investigators for clarification. Site monitoring was performed for every study site to confirm the data quality and to ensure that the study was conducted in accordance with good clinical practice. eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.[18,19]

Patients were followed up every 6 months for 3 years. Data on the presence or absence of clinical outcomes and the details of the events were recorded on the web-based system. All available laboratory data including eGFR were recorded. Source documents used to support the events were uploaded into the web system. All events were verified by the adjudication committee.

2.3 | Outcome

The study endpoint was eGFR slope, which was estimated based on the method described in a previous publication.[12] The linear mixed regression models were used for the estimation. The treatment group, time of eGFR test, and the interaction between treatment group and time of eGFR test were included as fixed factors. Each individual was included as a random factor. Fixed factors also included age, gender, BMI, baseline eGFR, T2D, hypertension, dyslipidemia, HF, CAD, and smoking.

2.4 | Statistical analysis

Descriptive statistics were the mean and standard deviation for continuous data and the number and percentages for categorical data. Comparisons of continuous data were made by the student's *t*-test for unpaired data and the chi-square test for categorical data. eGFR slope was compared between patients using warfarin and DOACs.

Sensitivity analyses were performed first, using propensity score matching methods to adjust for the baseline difference of patients

with DOACs and warfarin, and for the comparison between DOACs and warfarin, and second, for the comparison between patients with DOACs and warfarin for a GFR decline of at least 30%. GFR decline of at least 30% (based on the clinical relevance from a previous study[12,20]) was calculated from the percentage of reduction of eGFR of the baseline GFR and last GFR data and third the effect of DOACs and warfarin on eGFR slope between patients with T2D and non-T2D and between patients with CKD and non-CKD. CKD was defined as an eGFR of less than 60 mL/min/1.73 m^2. Because our study utilized data from a prospective registry, it is possible

TABLE 1 Baseline characteristics of study population.

Variables	All (*N* = 1708)	Warfarin (*N* = 1530)	DOACs (*N* = 178)	*p*-value
Age (years)	68.1 ± 11.0	68.9 ± 10.7	68.5 ± 10.6	0.658
Female gender	727 (42.6%)	651 (42.5%)	76 (42.7%)	0.970
Time after diagnosis of AF (years)	3.4 ± 4.3	3.5 ± 4.3	3.9 ± 5.0	0.257
Atrial fibrillation				**<0.001**
Paroxysmal	530 (31.0%)	444 (29.0%)	86 (48.3%)	
Persistent	346 (20.3%)	316 (20.7%)	30 (16.9%)	
Permanent	832 (48.7%)	770 (50.3%)	62 (34.8%)	
Symptomatic AF	1327 (77.7%)	1190 (77.8%)	137 (77.0%)	0.806
History of heart failure	513 (30.0%)	479 (31.3%)	34 (19.1%)	**0.001**
History of coronary artery disease	293 (17.2%)	263 (17.2%)	30 (16.9%)	0.910
Cardiac implantable electronic device	205 (12.0%)	172 (11.2%)	33 (18.5%)	**0.005**
History of ischemic stroke/TIA	372 (21.8%)	341 (22.3%)	31 (17.4%)	0.136
Hypertension	1275 (74.6%)	1154 (75.4%)	121 (68.0%)	**0.031**
Diabetes mellitus	497 (29.1%)	454 (29.7%)	43 (24.2$)	0.125
Smoking	336 (19.7%)	302 (19.7%)	34 (19.1%)	0.840
Hypercholesterolemia	1052 (61.6%)	944 (61.7%)	108 (60.7%)	0.790
Dementia	21 (1.2%)	17 (1.1%)	4 (2.2%)	0.266
CKD	923 (54.0%)	841 (55.0%)	82 (46.1%)	**0.024**
History of bleeding	184 (10.8%)	171 (11.2%)	13 (7.3%)	0.115
CHA_2DS_2-VASc score	3.4 ± 3.0	3.4 ± 1.6	3.0 ± 1.7	**0.001**
Low	58 (3.4%)	42 (2.7%)	16 (9.0%)	**<0.001**
Intermediate	220 (12.9%)	190 (12.4%)	30 (16.9%)	
High	1430 (83.7%)	1298 (84.8%)	132 (74.2%)	
HAS-BLED score	1.6 ± 1.0	1.6 ± 1.0	1.1 ± 0.8	**<0.001**
0	231 (13.5%)	191 (12.5%)	40 (22.5%)	
1-2	1204 (70.5%)	1077 (70.4%)	127 (71.3%)	
≥3	273 (16.0%)	262 (17.1%)	11 (6.2%)	
Antiplatelet	221 (12.9%)	209 (13.7%)	12 (6.7%)	**0.009**
GFR	66.4 ± 18.4	66.2 ± 18.6	68.0 ± 17.3	0.217
Beta-blocker	1276 (74.7%)	1134 (74.1%)	142 (79.8%)	0.100
Calcium channel blockers	522 (30.6%)	465 (30.4%)	57 (32.0%)	0.655
Digitalis	286 (16.7%)	258 (16.9%)	28 (15.7%)	0.702
Mineralocorticoid receptor antagonist	161 (9.4%)	152 (9.9%)	9 (5.1%)	**0.035**
Statin	1128 (66.0%)	1008 (65.9%)	120 (67.4%)	0.683
ACEI/ARB	923 (54.0%)	841 (55.0%)	82 (46.1%)	**0.024**
NSAID/Cox-2 inhibitor	30 (1.8%)	23 (1.5%)	7 (3.9%)	**0.020**

Note: Bold indicates statistical significance.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin receptor blockers; CKD, chronic kidney disease; DOAC, non-vitamin K antagonist anticoagulants TIA, transient ischemic attack.

that there are some differences in the baseline characteristics between the DOACs and the warfarin groups. Therefore, we created a propensity-matched population to minimize the differences. To generate the propensity-matched population, we matched one patient from the DOACs group to four patients from the warfarin group based on the same method as described in the matched-pair approach. Our study employed propensity score matching by the nearest neighbor method with logistic regression from the MatchIt package in R (27). Each DOAC patient was matched with four warfarin patients based on all variables, including age, gender, BMI, duration after AF diagnosis, AF symptoms, type of AF, history of HF, history of revascularization, implanted cardiac device, peripheral arterial disease, carotid occlusive disease, ischemic stroke or transient ischemic attack (TIA), hypertension, dyslipidemia, T2D, smoking, renal replacement therapy, dementia, history of bleeding, and antiplatelet use.

Sensitivity analysis was performed to assess the difference of eGFR slope in patients with warfarin with a TTR <65% and ≥65%. TTR was calculated by the Rosendaal method.[21] Sankey diagram was performed to demonstrate changes in the grading of eGFR from baseline to last follow-up visit. eGFR is classified into four grades; ≥60, 45–60, 30–45, and <30 mL/min/1.73 m^2. eGFR decline was defined as the deterioration of eGFR by at least 1 grade. Proportion of patients in warfarin and DOAC groups with eGFR decline as shown by worsening in eGFR grade was compared by the chi-square test. Multivariable analysis was performed using the Cox proportional hazard model to determine the risk factors for eGFR decline. The variables that were included in the multivariable model were age, gender, type 2 diabetes, hypertension, dyslipidemia, smoking, HF, and CAD, antihypertensive agents [calcium channel blocker, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB)], diuretics, non-steroidal anti-inflammatory drugs, types of AF, and baseline eGFR.

Comparisons of eGFR slope between warfarin and DOACs were made by the lmerTest of the lmerTest package of R version 4.2.3. The lmerTest package provides *p*-values in type I, II, or III ANOVA for linear mixed models (lmer model fits cf. lme4) via Satterthwaite's degrees of freedom method. The analyses were performed both for unadjusted and adjusted approaches. The adjusted variables were age, gender, type 2 diabetes, hypertension, dyslipidemia, smoking, HF, CAD, antihypertensive agents (calcium channel blocker, ACEI or ARB), diuretics, non-steroidal anti-inflammatory drugs, types of AF, and baseline eGFR. A *p*-value of less than 0.05 was considered statistically significant.

3 | RESULTS

A total of 1708 patients were studied. The mean age was 68.1 ± 11.0 years; 727 (42.6%) were female. Mean CHA_2DS_2-VASc and HAS-BLED scores were 3.4 ± 3.0 and 1.6 ± 1.0. Baseline characteristics of patients using DOACs and warfarin are shown in Table 1. The types of DOACs in this study were dabigatran, rivaroxaban, apixaban, and edoxaban in 64 (36.0%), 82 (46.1%), 30 (16.9%), and 2 (1.1%). The flow diagram of the study population is shown in Figure 1.

3.1 | Analysis of eGFR slope

Baseline eGFR was 66.4 ± 18.4 mL/min/1.73 m^2; 231 (13.5%), 430 (25.2%), 847 (49.6%), and 200 (11.7%) had eGFR 30–45, 45–60, 60–90, and >90 mL/min/1.73 m^2, respectively. The average time from start date to the last available eGFR was 2.47 years (2.46 years in warfarin group and 2.61 years in DOAC group). Patients in the DOAC group had a significantly slower rate of eGFR decline when compared to the warfarin group. The eGFR slope was 2.32 mL/min/1.73 m^2 per year in the warfarin group (95% CI: 3.09 to 1.55), and 1.31 mL/min/1.73 m^2 per year in the DOAC group (95% CI: 1.97 to 0.64) (Figure 2A and Table 2). The effect of OAC type on the eGFR slope remained significant after the adjustment of baseline variables including age, gender, type 2 diabetes (T2D), hypertension, dyslipidemia, smoking, HF, CAD, antihypertensive agents (calcium channel blocker, ACEI or ARB), diuretics, non-steroidal anti-inflammatory drugs, types of AF, and baseline eGFR (Figure 2A and Table 2). Figure 3A,B shows unadjusted and adjusted analysis of GFR decline in patients with warfarin and DOACs during the study time in patients with DOAC and warfarin.

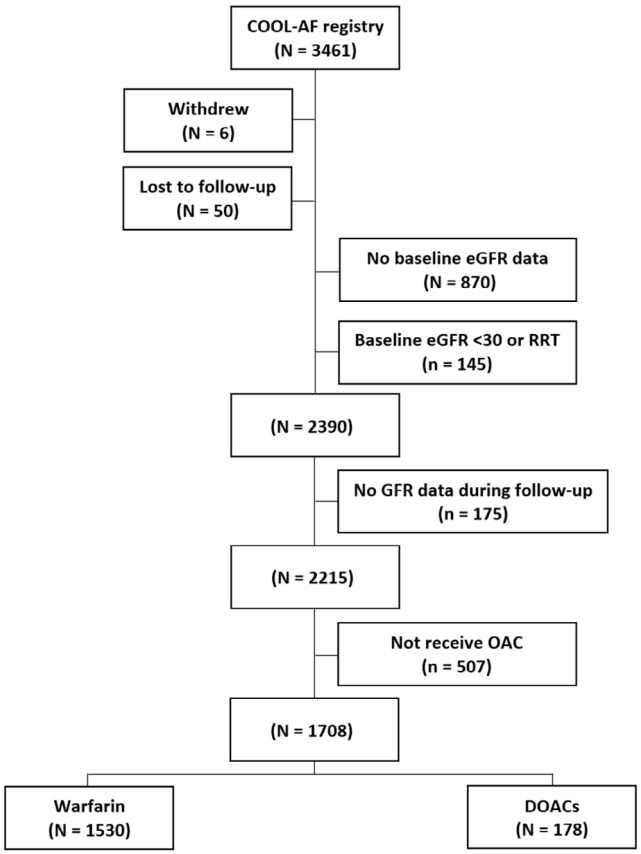

FIGURE 1 Flow diagram of the study population (DOACs, direct oral anticoagulants; eGFR, estimated glomerular filtration rate; OAC, oral anticoagulants; RRT, renal replacement therapy).

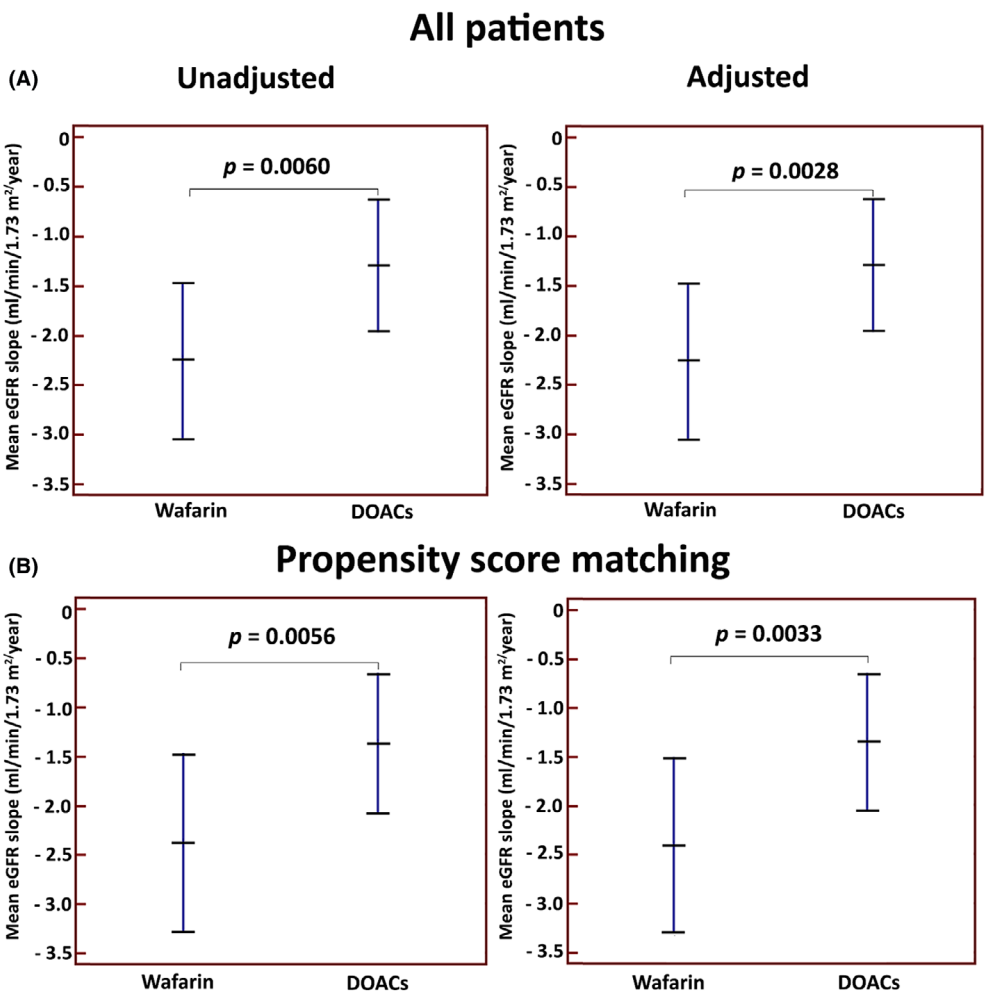

FIGURE 2 Unadjusted and adjusted analysis of the estimated glomerular filtration rate (eGFR) slope of warfarin and direct oral anticoagulants (DOACs). (A) All patients and (B) propensity score-matching dataset.

TABLE 2 Unadjusted and adjusted analysis of the eGFR slope of warfarin and non-vitamin K antagonist oral anticoagulant (DOACs) (A) all patients and (B) propensity score matching dataset.

	N	eGFR slope (95% CI)	Difference (95% CI)	*p*-value
All patients				
Unadjusted				
Warfarin	1530	−2.2507 (−3.0356 to −1.4659)	Ref.	
DOACs	178	−1.3029 (−1.9789 to −0.6269)	0.9478 (0.2718 to 1.6238)	0.0060
Adjusted				
Warfarin	1530	−2.3187 (−3.0891 to −1.5499)		
NOACs	178	−1.3098 (−1.9729 to −0.6454)	1.0089 (0.3458 to 1.6733)	0.0029
Propensity score matching				
Unadjusted				
Warfarin	712	−2.3805 (−3.2975 to −1.4638)	Ref.	0.0056
DOACs	178	−1.3677 (−2.0843 to −0.6510)	1.0128 (0.2962 to 1.7295)	
Adjusted				
Warfarin	712	−2.4039 (−3.3048–1.5052)	Ref.	
DOACs	178	−1.3465 (−2.0497 to −0.6413)	1.0574 (0.3542 to 1.7626)	0.0033

Note: The adjusted variables were age, gender, type 2 diabetes, hypertension, dyslipidemia, smoking, history of heart failure, stroke, coronary artery disease, antihypertensive agents (calcium channel blocker, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker), diuretics, non-steroidal anti-inflammatory drugs, types of atrial fibrillation, and baseline eGFR.

Abbreviations: CI, confidence interval; DOAC, non-vitamin K antagonist anticoagulants; eGFR, estimated glomerular filtration rate.

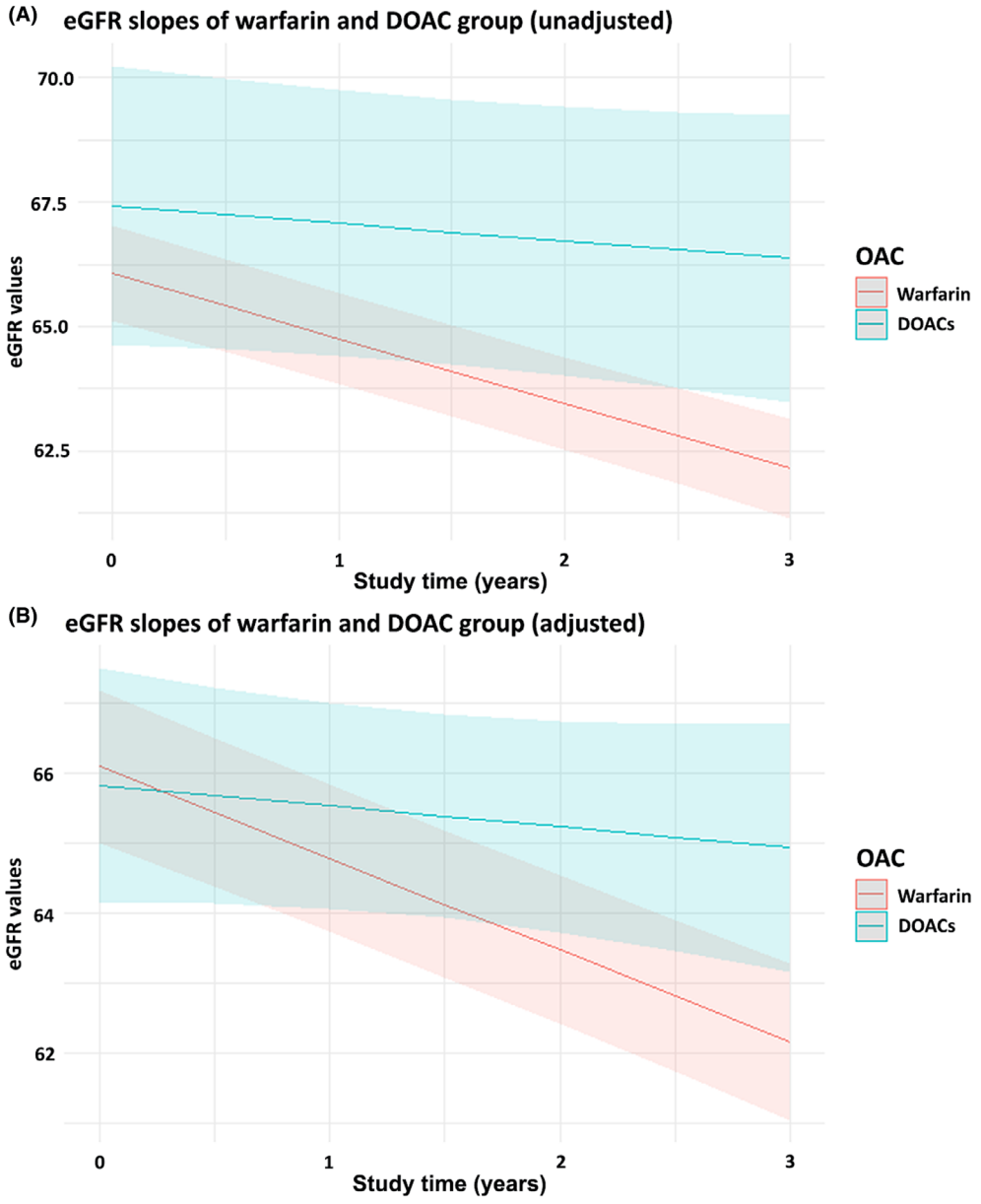

FIGURE 3 Estimated glomerular filtration rate (eGFR) decline in patients with warfarin and direct oral anticoagulants (DOACs) during the study time in patients with DOACs and warfarin. (A) Unadjusted analysis and (B) adjusted analysis.

3.2 | Sensitivity analysis

Propensity score matching was performed with the DOAC: Warfarin ratio of 1:4. Comparisons of baseline characteristics of 178 patients with DOACs and 712 patients with warfarin showed no statistically significant differences (Table S1). The results of the analysis of eGFR in the propensity score matching dataset showed that warfarin had a more rapid GFR decline compared to DOACs as demonstrated in Figure 2B.

Sensitivity analysis was performed on the exploratory subpopulation of T2D versus non-T2D and CKD versus non-CKD in all patients as well as the propensity score dataset. The results are shown in Table S2 for T2D versus non-T2D and Table S3 for CKD versus non-CKD. The greater GFR decline in patients with warfarin compared to DOACs is seen in patients with non-T2D but was not different in patients with T2D. For CKD versus non-CKD, the effect of warfarin on GFR decline is seen in both patients with CKD and non-CKD. There was no difference in GFR decline as reflected by eGFR slope in warfarin patients with TTR <65% and ≥65%. Patients who were on DOACs had a slower rate of GFR decline compared to warfarin in both groups with TTR <65% and ≥65% (Table 3).

Patients in the warfarin group had a greater proportion of GFR decline of >30% when compared to the DOAC group (10.1% vs. 3.9%, $p=0.008$). A Sankey diagram was performed to demonstrate changes in the grading of eGFR from baseline to the last follow-up visit (Figure 4). Patients with worsening eGFR grade were

TABLE 3 Unadjusted and adjusted differences in eGFR slope in warfarin patients with time in the therapeutic range (TTR) <65% and ≥65% as well as differences in non-vitamin K antagonist oral anticoagulants (DOACs) and warfarin with TTR <65% and ≥65%.

	N	eGFR slope (95% CI)	Difference (95% CI)	*p*-value
Unadjusted				
Warfarin TTR <65%	962	−1.358 (−2.062 to −0.655)	Ref.	
Warfarin TTR ≥65%	527	−1.324 (−1.805 to −0.843)	0.035 (−0.446 to 0.515)	0.8878
Adjusted				
Warfarin TTR <65%	962	−1.361 (−2.048 to −0.673)	Ref.	
Warfarin TTR ≥65%	527	−1.334 (−1.805 to −0.864)	0.027 (−0.444 to 0.497)	0.9097
Unadjusted				
Warfarin TTR <65%	962	−2.292 (−3.156 to −1.429)	Ref.	
DOAC	178	−1.324 (−2.021 to −0.627)	0.969 (0.272 to 1.666)	0.0065
Adjusted				
Warfarin TTR <65%	962	−2.356 (−3.204 to −1.510)	Ref.	
DOAC	178	−1.330 (−2.014 to −0.644)	1.026 (0.342 to 1.712)	0.0034
Unadjusted				
Warfarin TTR ≥65%	527	−2.226 (−3.220 to −1.232)	Ref.	
DOAC	178	−1.290 (−2.035 to −0.546)	0.936 (0.191 to 1.680)	0.0138
Adjusted				
Warfarin TTR ≥65%	527	−2.329 (−3.304 to −1.360)	Ref.	
DOAC	178	−1.313 (−2.039 to −0.582)	1.016 (0.290 to 1.747)	0.0063

Note: Adjusted variables: Age, gender, body mass index, baseline eGFR, type 2 diabetes, hypertension, dyslipidemia, heart failure, coronary artery disease, smoking.

342 (22.4%) patients in the warfarin group, which was significantly greater than 28 (15.7%) patients in the DOAC group ($p = 0.027$).

Multivariable analysis using the Cox proportional hazard model was performed to explore the risk factors for eGFR decline. The results of the multivariable analysis showed that the variables and hazard ratio (95%CI) in the final model for the prediction of eGFR decline were age [1.027 (1.013, 1.027)], diabetes [1.762 (1.366, 2.274)], ACEI or ARB [1.414 (1.101, 1.817)], diuretics [1.649 (1.286, 2.114)], baseline eGFR [0.977 (0.969, 0.984)], and warfarin [1.536 (1.101, 2.367)].

4 | DISCUSSION

The results of this prospective multicenter nationwide AF registry from Thailand demonstrated that patients who used DOACs had a slower rate of renal function decline as assessed by the eGFR slope compared to those who used warfarin. Second, we show there was no difference in GFR decline as reflected by eGFR slope even in patients with good anticoagulation control.

A significant proportion of AF patients had impaired kidney function. The results of the COOL-AF registry indicated that CKD accounts for approximately 64% of AF patients.[8] The risk of AF-related complications such as ischemic stroke and major bleeding was higher in patients with CKD compared with non-CKD.[22,23] Data from Taiwan indicated that AF patients had a more rapid renal function decline compared to the non-AF population, and an increased CHA_2DS_2-VASc score is an important factor associated with renal function decline.[9] The median annual decline of eGFR of the warfarin group from previous studies from Italy[13] and the United Kingdom[12] was − 2.11 and − 2.03 mL/min/1.73 m^2, respectively. Patients in the warfarin group of our study had a median annual decline in eGFR of −1.52 mL/min/1.73 m^2. The results in the DOACs group were as follows: −0.27 (dabigatran); −1.21 (rivaroxaban); and − 1.32 (apixaban) mL/min/1.73 m^2 from Italy study, while it was −1.65 (rivaroxaban) mL/min/1.73 m^2 from the United

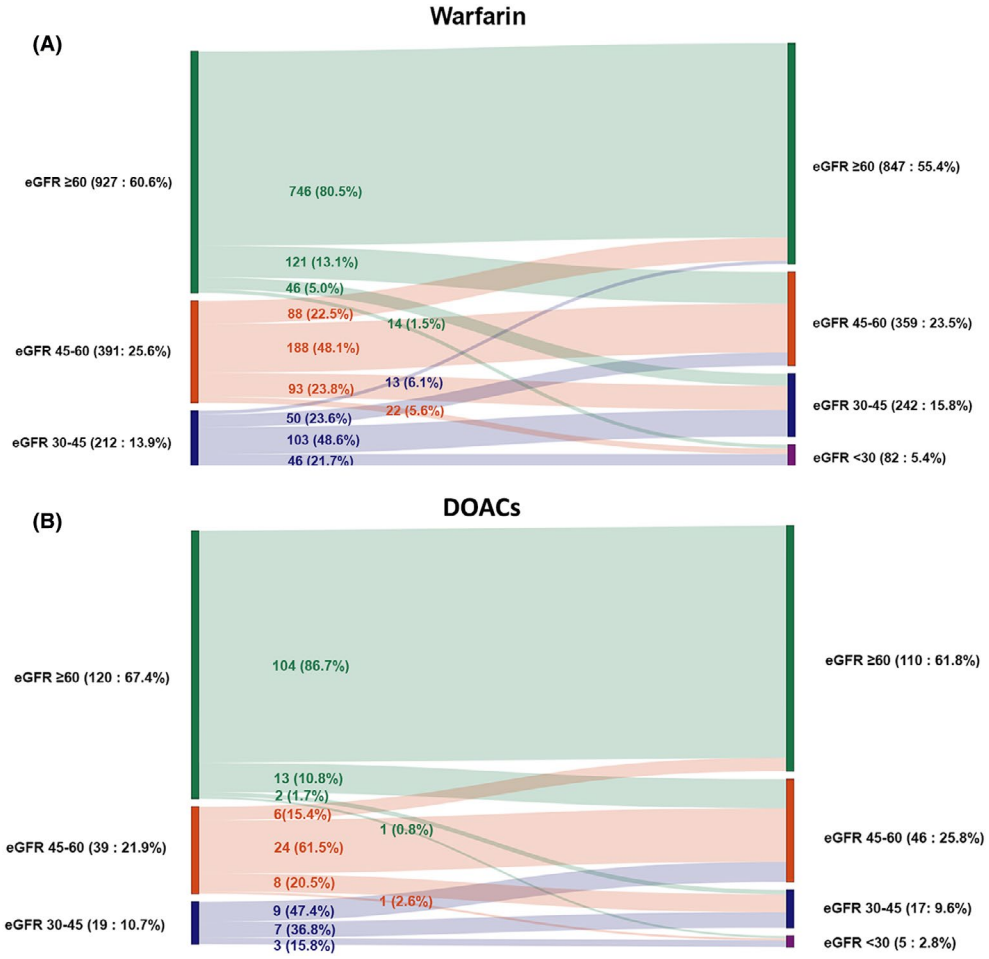

FIGURE 4 Sankey diagram of changes in grading of estimated glomerular filtration rate (eGFR) from baseline to last follow-up visit. eGFR is classified into four groups: ≥60, 45–60, 30–45, and <30 mL/min/1.73 m^2. (A) Warfarin (B) direct oral anticoagulants (DOACs).

Kingdom study, in comparison with −0.57 mL/min/1.73 m^2 from our study. Although the absolute numbers for the warfarin and DOAC groups may show slight differences, the results of these studies show the same directional trends. A study from the national database of the Taiwanese AF population showed that dabigatran had a lower risk of acute kidney injury (AKI) compared with warfarin.[24]

The results of the differential effects of DOAC and warfarin among different DOACs may be similar[13] but Yao et al. demonstrated the benefit of rivaroxaban over warfarin but did not show a similar benefit for apixaban.[20] The postulated mechanism of the differential effects of DOAC versus warfarin on renal function decline may be related to the action of warfarin in the inhibition of vitamin-K dependent matrix gamma-carboxyglutamic acid protein, thereby, promoting renal vascular calcification and progressive renal dysfunction.[25–27] DOACs may also have a protective effect due to the reduction of vascular inflammation mediated by factor Xa and thrombin inhibition.[28]

A previous study showed that renal function decline was greater in patients with warfarin with poor TTR control compared with those with good TTR control.[11] However, the results of our study showed no difference between GFR decline in patients with good and poor TTR control, and patients with DOACs had a slower GFR decline compared to warfarin with TTR <65% and ≥65%.

4.1 | Strengths and limitations

The strength of this study is that this is a well-designed prospective multicenter nationwide registry. We collected follow-up data every 6 months for the duration of 3 years. As a result, we are able to use eGFR data at baseline and each follow-up visit to calculate eGFR slope, which was not available in prior studies.

Nonetheless, there are some limitations of this study. First, this is a prospective multicenter AF registry with the majority being large-sized hospitals. Hence, there is limited generalizability. Second, patients in this registry were enrolled during 2014–2017. The national policy in Thailand was to restrict the use of the (expensive) DOACs, and the majority of our patients were on warfarin, which was the mandated OAC of choice in our healthcare system. Third, the number of patients receiving DOACs limited the analysis of individual DOAC medications. Fourth, this study focuses on eGFR decline and does not aim to evaluate key clinical outcomes such as end-stage kidney disease and dialysis initiation. Therefore,

despite the data collection on the eGFR during follow-up, we did not collect data on the dialysis requirement. However, we have data on the change in eGFR during follow-up and mortality data. The number of patients who developed ESRD was 15 (0.88%) and 178 (10.4%) died during the follow-up. All 15 patients who developed ESRD belong to the warfarin group, and none of the DOAC group developed ESRD. We also combined the ESRD and mortality outcomes which happened in 182 patients (10.7%) and ran the analysis. The results showed that warfarin had a higher chance of developing ESRD or mortality outcomes compared to DOACs [171 (11.2%) vs. 11 (6.2%), ($p = 0.041$)].

5 | CONCLUSION

In this prospective cohort of Asian patients with AF, DOACs were associated with a slower rate of eGFR decline when compared with warfarin. In the latter group, this was irrespective of the quality of anticoagulation control.

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CONFLICT OF INTEREST STATEMENT

GYHL: Consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally. Other authors hereby declare no personal or professional conflicts of interest relating to any aspect of this particular study.

DATA AVAILABILITY STATEMENT

The dataset that was used to support the conclusion of this study is included in the manuscript. Any other additional data will be made available upon request to the corresponding author.

ETHICS STATEMENT

This study was approved by the Institutional Review Board of the Central Research Ethic Committee (CREC) (Certificate of Approval number 003/2014). The study was performed following the principles of the Declaration of Helsinki and the International Conference on Harmonization for Good Clinical Practice Guidelines.

PATIENT CONSENT STATEMENT

All patients gave written informed consent before participation.

CLINICAL TRIAL REGISTRATION

The trial has been registered with the Thai Clinical Trials Registry (TCTR), which complied with the WHO International Clinical Trials Registry Platform dataset. The registration number is TCTR20160113002 (05/01/2016).

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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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