ORIGINAL ARTICLE

Bleeding Risk in Anticoagulated Patients with Non-Valvular Atrial Fibrillation and Chronic Kidney Disease in Thai Population

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Objective: Atrial fibrillation (AF) and chronic kidney disease (CKD) both increase the risk of stroke, cardiovascular morbidity, and mortality. Oral anticoagulants are effective in preventing stroke in AF patients but are associated with increased risk of bleeding, especially in those with comorbid CKD. The present study aimed to compare the incidence of bleeding events in patients with non-valvular atrial fibrillation (NVAF), either with or without CKD, receiving either warfarin or nonvitamin K antagonist oral anticoagulants (NOACs).

Materials and Methods: This retrospective cohort study enrolled NVAF patients between January 2016 and March 2021. Baseline characteristics and type and dosage of anticoagulants received were analyzed. Data were presented as mean ± standard deviation (SD) and compared using Chi-square tests. Cox proportional hazard models were used to assess the incidence of bleeding events.

Results: A total of 218 patients were included, of whom 122 (56.0%) were female. The average age was 72 years. There were 95 (43.6%) patients with CKD, mostly stage 3a 20.6%. Warfarin was given to 121 patients (55.5%), while NOACs were given to 97 patients (44.5%). The mean time in therapeutic range (TTR) in warfarin groups for patients with and without CKD was equal (34.2 vs. 34.7, p=0.74). There was no significant difference between patients with and without CKD in the incidence of overall major bleeding (12.8% vs. 7.3%, p=0.18), gastrointestinal bleeding (7.4% vs. 5.7%, p=0.60), intracranial hemorrhage (1.1% vs. 0.8%, p=0.85), or other major bleeding (4.2% vs. 0.8%, p=0.10), The incidence of major bleeding events was not significantly different between patients treated with NOACs and warfarin (11.5% vs. 8.3%, adjusted HR 0.72, p=0.45).

Conclusion: The bleeding risk in anticoagulated NVAF patients with mild to moderate CKD is not significantly different from that in those with normal kidney function.

Keywords: Atrial fibrillation; Chronic kidney disease; Major bleeding, Oral anticoagulants

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Atrial fibrillation (AF) is the most common form of sustained arrhythmia worldwide. It is associated with an increased risk of thromboembolic stroke and a higher incidence of all-cause mortality[1]. Chronic kidney disease (CKD), which is defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2, affects up to 15% of adults and is associated with increased cardiovascular disease (CVD) risk[2-4]. AF is an important and frequent cardiovascular complication in patients with CKD, with an incidence two to threefold higher than that in the general population[5]. CKD and AF share many risk factors, including hypertension, diabetes mellitus, and coronary artery disease[1,5,6]. The presence of CKD in patients with AF is associated with a substantial increase in the incidence of thromboembolism, ischemic stroke, and bleeding events[7,8]. Oral anticoagulants (OACs), including vitamin K antagonists (e.g., warfarin) and non-vitamin K antagonist oral anticoagulants (NOACs: dabigatran, rivaroxaban, apixaban, and edoxaban) are indicated for stroke/ systemic embolism prevention in AF patients with one or more stroke risk factors[2]. However, there is limited data on the effects of OACs in patients with comorbid AF and CKD, particularly in end-stage renal disease, kidney transplant recipients, and patients undergoing dialysis, who have been excluded from randomized trials of these agents[8].

The CHA2DS2-VASc is a clinical assessment tool

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developed to predict the risk of stroke and systemic embolism in patients with AF. It is an acronym for the risk factors, with each factor assigned one point except those followed by the number two, which are assigned two points. It stands for congestive heart failure; hypertension; age ≥75 years; diabetes mellitus; prior stroke, transient ischemic attack, or thromboembolism; vascular disease (prior myocardial infarction [MI], peripheral artery disease, or aortic plaque); age; sex category. Scores range from 0 to 9, with higher scores indicating higher risk. A CHA2DS2-VASc score ≥2 indicates high risk, and a score of 2.69% or higher indicates a high risk of ischemic stroke or thromboembolism within a year. Patients with such scores should be considered for anticoagulant therapy[9,10]. The HAS-BLED assessment tool was developed to predict the risk of bleeding events in AF patients[11]. HAS-BLED is an acronym for hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition (e.g., anemia), labile international normalized ratio (INR), elderly (age >65), drugs or alcohol (including therapeutic drugs that increase bleeding risk, such as antiplatelet agents and nonsteroidal anti-inflammatory drugs [NSAIDs]). Patients are given one point for each of these risk factors. A HAS-BLED score ≥3 indicates a high risk of major bleeding events (≥5.8% probability)[11].

Most anticoagulants are excreted through the kidneys and must be dose-adjusted in patients with impaired renal function. Although CKD does not affect warfarin excretion, it may downregulate the metabolism of hepatic cytochrome P450 (CYP450), reducing warfarin dosage requirement in patients with moderate to severe CKD[12]. Well-controlled anticoagulation with a mean time in therapeutic range (TTR) ≥65% is essential to optimize the effects of OACs such as warfarin[8]. Randomized clinical trials of NOACs in patients with AF have found that the direct thrombin inhibitor dabigatran (RELY)[13]; and the direct factor Xa inhibitors rivaroxaban (ROCKET AF)[14], apixaban (ARISTOTLE)[15], and edoxaban (ENGAGE AF-TIMI 48)[16] are either superior or equivalent to warfarin in stroke prevention efficacy but exhibit better safety profiles[8,17].

The present study aimed to compare the bleeding risks of anticoagulated patients with AF with and without comorbid CKD and of those within these two patient groups treated with warfarin with those treated with NOACs. CKD was an eGFR <60 ml/min/1.73 m^2.

Materials and Methods

Study design and population

This retrospective cohort study enrolled patients with NVAF between January 2016 and March 2021 at the Vajira Hospital. These patients were then classified into two groups according to their renal function: patients with an eGFR ≥60 ml/min/1.73 m^2 and those with an eGFR <60 ml/min/1.73 m^2. The study design is illustrated in Figure 1. The investigators reviewed and collated data from the institution's electronic medical record database. The study was approved by the institutional review board.

Study population

The inclusion criteria were age ≥18 years, diagnosed with NVAF, electrocardiogram (ECG) findings in the medical record system, and administered either warfarin or NOACs for stroke prevention. The minimum follow-up time was one year. The exclusion criteria were moderate to severe mitral stenosis or mechanical prosthetic valve replacement, a history of venous thromboembolism, end-stage renal disease (ESRD) and on renal replacement therapy, and the discontinuation of anticoagulants for an unknown reason during the study period.

Data collection

The authors extracted baseline characteristics from the electronic medical records, including age, sex, body mass index (BMI), underlying diseases, CHA2DS2-VASc scores, HAS-BLED bleeding risk scores, laboratory test results such as creatinine, eGFR, INR, and TTR, medical history, warfarin and NOAC doses, follow-up information on clinical outcomes, major and minor bleeding events, and thromboembolic events.

Endpoints and definition

The primary outcome was the major bleeding risk of anticoagulated AF patients with (eGFR <60 ml/min/1.73 m^2) and without CKD (eGFR ≥60 ml/min/1.73 m^2). The secondary outcomes were the incidences of minor bleeding, ischemic stroke, systemic thromboembolism, all-cause mortality, and composite events of major bleeding, minor bleeding, ischemic stroke, systemic thromboembolism,

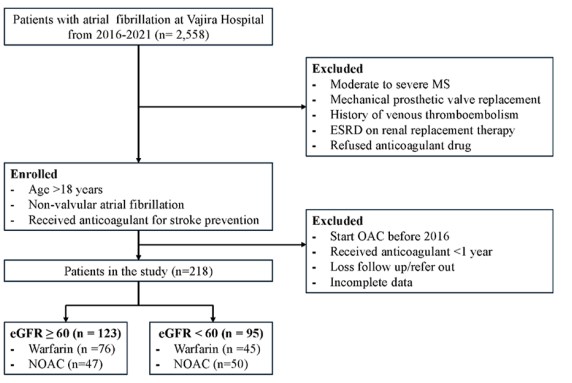

Figure 1. Study design.

eGFR=estimated glomerular filtration rate; ESRD=end stage renal disease; MS=mitral stenosis; NOAC=nonvitamin K antagonist oral anticoagulants; OAC=oral anticoagulants

and all-cause mortality in the CKD and non-CKD groups.

Major bleeding: was defined as any bleeding requiring hospitalization and/or causing a decrease in hemoglobin of at least 2 g/L and/or requiring transfusion of at least two units of packed blood cells or bleeding into a critical site such as intracranial, retroperitoneal, or intrapericardial hemorrhage[11].

Minor bleeding: was defined as any bleeding that does not meet the criteria for major bleeding.

CKD: was defined as abnormalities of kidney structure or function with health implications, present for >3 months, and a GFR <60 ml/min/1.73 m^2[4,18].

Statistical analysis

The sample size for each group was 110 patients (a total of 220 patients) using G*Power software, version 3.1.9.4, with a power of 80% and an alpha value of 0.1. This calculation was based on a study assessing the incidence of major bleeding in patients with atrial fibrillation, both with and without CKD[19].

Normally distributed continuous data were presented as the mean and standard deviation (SD). Nonnormally distributed continuous data were presented as the median and interquartile range (IQR). Categorical data were expressed as numbers and percentages and compared using the Chi-square and Fisher's exact tests. The primary endpoint, overall major bleeding events, and the secondary endpoints, total bleeding events, major bleeding events, minor bleeding events, overall bleeding, ischemic stroke, and death, were estimated using a Cox proportional hazards regression model. The p-values <0.05 were considered statistically significant. Survival analysis was used to determine the differences in the primary and secondary endpoints between patients with and without CKD (eGFR ≥60 ml/min/1.73 m^2). Chi-square tests were used to compare the incidences of total bleeding events, major bleeding events, and minor bleeding events between groups. Stata version 15.0 software, version 17.0 (Stata Corp, College Station, TX, USA) was used to analyze all statistics.

Ethical considerations

The present study was approved by the Faculty of Medicine Vajira Hospital, Navamindradhiraj University Human Research Ethics Committee (COA119/2564) and conducted in accordance with the tenets of the Declaration of Helsinki's 2013 revision.

Results

Study population

Between January 2016 and March 2021, 2,558 patients with AF were treated at the Faculty of Medicine Vajira Hospital. Of these, 218 patients met the inclusion criteria and were not excluded per the exclusion criteria. These 218 constituted our study sample.

The average age of the patients with CKD was significantly higher than that of patients without CKD (76.7±9.0 vs. 72.1±11.0 years, p<0.01). Within the study sample, 122 (56%) patients were female. The average BMI was 25.0±5.0, with no significant difference between groups (p=0.55). There were 95 (43.6%) patients with CKD, and 20.6% of these were at stage 3a[4,20]. Warfarin was given to 121 (55.5%) patients, and NOACs were given to 97 patients (44.5%). The mean TTRs of patients with and without CKD were roughly equivalent in the warfarin groups (34.2±23.6 vs. 34.7±22.7, p=0.74). The CHA2DS2-VASc and HAS-BLED scores were significantly higher in patients treated with NOACs than those treated with warfarin (p<0.01). Most patient characteristics and laboratory results showed no significant differences between groups. Comparisons of these data are provided in Table 1 and Table 2.

Risk of bleeding

There was no significant difference between patients with and without CKD in the risk of overall major bleeding (12.8% vs. 7.3%, p=0.18), gastrointestinal bleeding (7.4% vs. 5.7%, p=0.60), intracranial hemorrhage (1.1% vs. 0.8%, p=0.85), or other major bleeding (4.2% vs. 0.8%, p=0.10). Thus, the primary endpoint did not differ between CKD and non-CKD patients (Table 3). Similarly, there were no significant differences between those with and without CKD in the secondary endpoints of minor bleeding (5.3% vs. 2.4%, p=0.27) or overall bleeding (17.9% vs. 9.8%, p=0.08) (Table 3). Patients receiving NOACs had a slightly higher rate of major bleeding events than those treated with warfarin, but the difference was insignificant (11.5% vs. 8.3%, p=0.43). The incidence of overall bleeding was nearly equal between the NOACs and warfarin groups (13.4% vs. 13.2%, p=0.97).

There was no significant difference between those with and without CKD treated with both NOACs and warfarin in the risk of overall major bleeding (14.3% vs. 8.5%, p=0.38, 11.1% vs. 6.6%, p=0.38, respectively) or overall bleeding (16% vs. 10.6%, p=0.44, 20% vs. 9.2%, p=0.09, respectively) (Table 4).

Survival analysis evaluating the probability of major bleeding between patients with CKD and those without CKD receiving anticoagulants showed no significant difference over 72 months (log-rank test, p=0.16).

A univariate Cox proportional hazards regression model was conducted, including variables such as age >65, hypertension, chronic kidney disease, history of liver disease, cancer, history of stroke, history of bleeding, Cr >2.26 mg/dl, antiplatelet use, and labile INR (Table 5). None of these factors showed a significant association with

Table 1. Demographic and baseline characteristics of participants

	All participants			p-value
	Total (n=218)	Non-CKD (n=123)	CKD (n=95)	
Age (years)	72.1±10.9	68.4±11.0	76.7±9.0	<0.01
Female	122 (56.0%)	71 (57.7%)	51 (53.7%)	0.55
BMI (kg/m^2)	25.0±5.0	25.1±4.5	24.8±5.5	0.34
SBP (mmHg)	133.3±22.2	133.7±22.2	132.7±22.2	0.87
DBP (mmHg)	75.8±13.9	77.5±13.7	73.6±13.9	0.07
HR (bpm)	81.9±23.6	84.1±24.9	79.0±21.6	0.12
Underlying disease				
T2DM	73 (33.5%)	42 (34.1%)	31 (32.6%)	0.81
HT	209 (95.9%)	115 (93.5%)	94 (98.9%)	<0.05
DLP	171 (78.4%)	94 (76.4%)	77 (81.1%)	0.41
IHD	47 (21.6%)	27 (22.0%)	20 (21.1%)	0.87
DCM	10 (4.6%)	3 (2.4%)	7 (7.4%)	0.09
SSS	18 (8.3%)	3 (2.4%)	15 (15.8%)	<0.01
Cancer	14 (6.4%)	9 (7.3%)	5 (5.3%)	0.54
Liver disease	7 (3.2%)	3 (2.4%)	4 (4.2%)	0.46
Others	54 (24.8%)	31 (25.2%)	23 (24.2%)	0.87
History of stroke	56 (25.7%)	29 (23.6%)	27 (28.4%)	0.42
History of bleeding	24 (11.0%)	5 (4.1%)	19 (20.0%)	<0.01
CHADS2VASc score	4.1±1.5	3.8±1.5	4.6±1.5	0.01
HAS-BLED score	2.3±0.9	2.1±0.9	2.6±0.9	<0.01
Lab				
eGFR (ml/min/1.73 m^2)	63.4±24.3	80.2±15.4	41.6±14.3	<0.01
Warfarin (mg/week)	16.2±5.9	16.3±6.5	16.0±4.8	0.91
TTR	34.5±23.0	34.7±22.7	34.2±23.6	0.74
Antiplatelet	42 (19.2%)	24 (19.5%)	18 (18.9%)	0.92

BMI=body mass index; DCM=dilated cardiomyopathy; DLP=dyslipidemia; HT=hypertension; IHD=ischemic heart disease; SSS=sick sinus syndrome; Time in Therapeutic range (TTR); T2DM=type 2 diabetic mellitus

major bleeding. Although the incidence of major bleeding in patients with CKD was higher than in those without CKD (4.60 vs. 2.42 bleeds per 100 person-years, HR 1.86, 95% CI: 0.78 to 4.43, p=0.16), the difference was not statistically significant. Regarding major bleeding across different types of anticoagulants, NOACs showed a trend toward higher bleeding rates compared to warfarin (4.30 vs. 2.66 bleeds per 100 person-years, HR 0.66, 95% CI: 0.28 to 1.56, p=0.34). However, this difference was also not statistically significant (Table 6).

Risk of stroke

As shown in Table 3, 12 patients (5.5%) had ischemic stroke despite taking anticoagulants, five (5.2%) of whom were receiving NOACs, and seven (5.8%) receiving warfarin. These 12 patients were nearly equally distributed between the CKD and non-CKD groups (5.3% vs. 5.7%, p=0.89). A greater number of the patients treated with warfarin did not have CKD, but this was not a significant difference (7.9% vs. 2.2%, p=0.20). NOACs were more often prescribed to CKD patients (8% vs. 2.1%, p=0.19), but the difference was not significant (Table 4). The risk of stroke was not significantly different between those with different levels of kidney function or between those treated with the two types of anticoagulants.

All-cause mortality

In the present study, 15 of 218 patients (6.9%) died. Patients with CKD had an increased risk of all-cause mortality (8.4% vs. 5.7% p=0.43) than patients without CKD (Table 3). The number of patients receiving NOACs was higher than those receiving warfarin (10.3% vs. 4.1%, p=0.07). CKD is associated with an increased risk of all-cause mortality in NOACs groups (14% vs. 6.4% p=0.22), whereas in warfarin groups are lower (2.2% vs. 5.3%, p=0.42) but not statistically significant, as illustrated in Table 4

Discussion

Our study aimed to evaluate the risk of bleeding in patients with NVAF, either with or without CKD, receiving either warfarin or NOACs, especially in the Thai population.

Table 2. Demographic and baseline characteristics of participants on NOACs and warfarin

	NOACs				Warfarin			
	Total, n=97	**Non-CKD, n=47**	**CKD, n=50**	**p-value**	**Total, n=121**	**Non-CKD, n=76**	**CKD, n=45**	**p-value**
Age (years)	75.6±10.3	71.1±10.3	79.9±8.3	<0.01	69.2±10.7	66.8±11.1	73.2±8.6	<0.01
Female	58 (59.8%)	30 (63.8%)	28 (56.0%)	0.43	64 (52.9%)	41 (53.9%)	23 (51.1%)	0.76
BMI (kg/m^2)	25.7±5.0	25.3±4.2	25.2±6.0	0.45	24.7±4.8	25.0±4.7	24.3±4.9	0.47
SBP (mmHg)	132.1±22.5	134.0±21.8	130.3±23.3	0.4	134.2±21.9	133.5±22.7	135.4±20.8	0.50
DBP (mmHg)	73.8±13.9	75.8±12.5	71.9±13.8	0.17	77.4±14.3	78.5±14.4	75.5±14.0	0.34
HR (bpm)	78.3±20.2	80.1±22.7	76.7±17.5	0.51	84.7±25.7	86.6±26.0	81.6±25.3	0.26
Underlying disease								
T2DM	32 (33.2%)	14 (29.8%)	18 (36.0%)	0.52	41 (33.9%)	28 (36.8%)	13 (28.9%)	0.37
HT	92 (94.8%)	43 (91.5%)	49 (98.0%)	0.15	117 (96.7%)	72 (94.7%)	45 (100.0%)	0.12
DLP	84 (86.6%)	40 (85.1%)	44 (88.0%)	0.68	87 (71.9%)	54 (71.1%)	33 (73.3%)	0.79
IHD	20 (20.6%)	8 (17.0%)	12 (24.0%)	0.4	27 (22.3%)	19 (25.0%)	8 (17.8%)	0.36
DCM	4 (4.1%)	1 (2.1%)	3 (6.0%)	0.34	6 (5.0%)	2 (2.6%)	4 (8.9%)	0.13
SSS	9 (9.3%)	1 (2.1%)	8 (16.0%)	0.02	9 (7.4%)	2 (2.6%)	7 (15.6%)	<0.01
Cancer	7 (7.2%)	3 (6.4%)	4 (8.0%)	0.76	7 (5.8%)	6 (7.9%)	1 (2.2%)	0.20
Liver diseases	5 (5.2%)	3 (6.4%)	2 (4.0%)	0.60	2 (1.7%)	0 (0.0%)	2 (4.4%)	0.06
History of stroke	26 (26.8%)	11 (23.4%)	15 (30.0%)	0.46	30 (24.8%)	18 (23.7%)	12 (26.7%)	0.71
History of bleeding	18 (18.6%)	4 (8.5%)	14 (28.0%)	0.01	6 (5.0%)	75 (98.7%)	40 (88.9%)	0.02
CHADS2VASc score	4.5±1.6	4.0±1.5	4.8±1.5	0.01	3.9±1.5	3.7±1.4	4.2±1.4	0.05
HAS-BLED score	2.4±0.9	2.2±0.9	2.6±0.7	0.01	2.2±1.0	2±0.9	2.5±1.0	0.02
Lab								
eGFR (ml/min/1.73 m^2)	58.9±23.0	77.3±15.3	41.5±13.7	<0.01	67.0±24.7	82±15.3	41.7±15.1	<0.01
Warfarin dose (mg/week)					16.2±5.9	16.3±6.5	16.0±4.8	0.03
TTR					34.5±23.0	34.7±22.7	34.2±23.6	0.74
Antiplatelet	18 (18.6%)	8 (17.0%)	10 (20.0%)	0.71	24 (19.8%)	16 (21.0%)	8 (17.8%)	0.69

BMI=body mass index; DCM=dilated cardiomyopathy; DLP=dyslipidemia; HT=hypertension; IHD=ischemic heart disease; NOACs=Non-vitamin K antagonist oral anticoagulants; SSS=sick sinus syndrome; Time in Therapeutic Range (TTR); T2DM=Type 2 Diabetic mellitus

Table 3. Secondary endpoint: kidney function and types of anticoagulants

	Total, (n=218)	non-CKD vs. CKD			Anticoagulants		
		non-CKD, (n=123)	CKD, (n=95)	p-value	NOACs, (n=97)	Warfarin, (n=121)	p-value
Major bleeding	21 (9.7%)	9 (7.3%)	12 (12.8%)	0.18	11 (11.5%)	10 (8.3%)	0.43
GI bleeding	14 (6.5%)	7 (5.7%)	7 (7.4%)	0.60	8 (8.3%)	6 (5.0%)	0.32
ICH	2 (0.9%)	1 (0.8%)	1 (1.1%)	0.85	1 (1.0%)	1 (0.8%)	0.86
Other major bleeding	5 (2.3%)	1 (0.8%)	4 (4.2%)	0.10	2 (2.1%)	3 (2.5%)	0.84
Minor bleeding	8 (3.7%)	3 (2.4%)	5 (5.3%)	0.27	2 (2.1%)	6 (5.0%)	0.26
Overall bleeding	29 (13.3%)	12 (9.8%)	17 (17.9%)	0.08	13 (13.4%)	16 (13.2%)	0.97
Ischemic stroke	12 (5.5%)	7 (5.7%)	5 (5.3%)	0.89	5 (5.2%)	7 (5.8%)	0.84
Systemic thromboembolism	1 (0.5%)	0 (0.0%)	1 (1.1%)	0.25	0 (0.0%)	1 (0.8%)	0.37
Death from any cause	15 (6.9%)	7 (5.7%)	8 (8.4%)	0.43	10 (10.3%)	5 (4.1%)	0.07
All events	63 (28.9%)	30 (24.4%)	33 (34.7%)	0.10	27 (27.8%)	36 (29.8%)	0.76

GI bleeding=Gastrointestinal bleeding; ICH=Intracranial hemorrhage; NOACs=Non-vitamin K antagonist oral anticoagulants

Table 4. Secondary endpoint: Compare kidney function in NOACs vs. Warfarin

	NOACs				Warfarin			
	Total, (n=97)	Non-CKD, (n=47)	CKD, (n=50)	p-value	Total, (n=121)	Non-CKD, (n=76)	CKD, (n=45)	p-value
Major bleeding	11 (11.5%)	4 (8.5%)	7 (14.3%)	0.38	10 (8.3%)	5 (6.6%)	5 (11.1%)	0.38
GI bleeding	8 (8.3%)	3 (6.4%)	5 (10.2%)	0.50	6 (5.0%)	4 (5.3%)	2 (4.4%)	0.84
ICH	1 (1.0%)	1 (2.1%)	0 (0.0%)	0.30	1 (0.8%)	0 (0.0%)	1 (2.2%)	0.19
Other major bleeding	2 (2.1%)	0 (0.0%)	2 (4.0%)	0.17	3 (2.5%)	1 (1.3%)	2 (4.4%)	0.29
Minor bleeding	2 (2.1%)	1 (2.1%)	1 (2.0%)	0.97	6 (5.0%)	2 (2.6%)	4 (8.9%)	0.13
Overall bleeding	13 (13.4%)	5 (10.6%)	8 (16.0%)	0.44	16 (13.2%)	7 (9.2%)	9 (20.0%)	0.09
Ischemic stroke	5 (5.2)	1 (2.1%)	4 (8.0%)	0.19	7 (5.8%)	6 (7.9%)	1 (2.2%)	0.20
Systemic thromboembolism	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA	1 (0.8%)	0 (0.0%)	1 (2.2%)	0.19
Death from any cause	10 (10.3%)	3 (6.4%)	7 (14.0%)	0.22	5 (4.1%)	4 (5.3%)	1 (2.2%)	0.42
All events	27 (27.8%)	9 (19.1%)	18 (36.0%)	0.06	36 (29.8%)	21 (27.6%)	15 (33.3%)	0.51

GI bleeding=Gastrointestinal bleeding; ICH=Intracranial hemorrhage; NOACs=Non-vitamin K antagonist oral anticoagulants

The key findings of our study are as follows: First, the overall major bleeding (including gastrointestinal bleeding, intracranial hemorrhage, and other major bleeding) was no significant difference between patients with and without CKD who were receiving OACs. Second, the probability of major bleeding between patients with CKD and those without CKD receiving anticoagulants also did not differ over 72 months. Third, there was no significant difference in the risk of major bleeding or overall bleeding between patients with and without CKD treated with NOACs and warfarin. Fourth, the risk of stroke and all-cause mortality were not significantly different between patients with and without CKD treated with both NOACs and warfarin.

In the case of warfarin, this study yields aligned results to a previous randomized controlled study (Stroke Prevention in Atrial Fibrillation III study) that included patients with stage 3 CKD (42%) and analyzed warfarin compared to the population with normal renal function. Data analysis in the CKD subgroup shows that well-adjusted doses reduce the risk of ischemic stroke and systemic embolism by 76% and 67%, respectively, without statistically significant differences in major bleeding rates[8]. Additional information regarding warfarin comes from registries and observational studies that include CKD subgroups. In general, the outcomes remain consistent in terms of effectiveness in reducing thromboembolic risk, the risk of fatal stroke, and mortality[21]. Meta-analyses further support the efficient and safe utilization of warfarin in individuals with non-dialysis-dependent CKD[22].

The major randomized controlled trials investigating NOACs, such as dabigatran (RELY)[13], rivaroxaban (ROCKET AF)[14], apixaban (ARISTOTLE)[15], and edoxaban (ENGAGE AF-TIMI 48)[16], demonstrate the effectiveness of NOACs in reducing the risk of bleeding compared to warfarin in individuals with mild to moderate CKD. Guidelines from organizations like the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) recommend anticoagulation therapy for patients with moderate CKD based on their risk assessment[23,24]. Our results are consistent with findings

from these key studies, indicating that using NOACs is safe in patients with mild to moderate CKD.

Our major bleeding rate is slightly higher than estimated by the HAS-BLED score, particularly in patients with CKD. For a HAS-BLED score of two, the expected bleeding rate is approximately 1.88 bleeds per 100 patient-years, and for a score of three, it is 3.72 bleeds per 100 patient-years. However, our cohort shows 2.42 bleeds per 100 patient-years in patients without CKD (HAS-BLED score = 2.1±0.9) and 4.60 bleeds per 100 patient-years in patients with CKD (HAS-BLED score = 2.6±0.9). Additionally, patients with CKD are older than those without CKD, which may contribute to the higher bleeding risk in this group[25]. In the Thai population, the COOL-AF registry demonstrated increased risks of major cardiovascular outcomes, including ischemic stroke/TIA, major bleeding, and death in AF patients with CKD[19]. This finding aligns with our results, which showed a trend toward increased major bleeding, though it was not statistically significant. The lack of significance may be due to the smaller study population, which lacked sufficient power to detect a difference, and the lower rate of TTR[19] .A higher bleeding rate was observed with NOACs compared to warfarin. However, the difference was insignificant (4.30 bleeds per 100 patient-year in NOACs and 2.66 bleeds per 100 patient-year in warfarin, p=0.34). The trend toward increased bleeding may be attributed to the higher mean HAS-BLED score in patients receiving NOACs, the lower TTR in those on warfarin, and the lower BMI in Thai patients than in the previous landmark study[13-16]. Another possible reason for the higher bleeding rate could be inappropriate dosing not aligned with guideline recommendations[23,24,26,27].

Table 5. Univariate Analysis of Major Bleeding with Potential Affecting Factors

Factor	B-value*	95% CI	p-value
Age >65 years	1.215	0.569 to 2.593	0.62
Hypertension	1.085	0.211 to 5.585	0.92
CKD	1.568	0.811 to 3.032	0.18
Liver disease	3.123	0.633 to 15.396	0.16
History of cancer	1.868	0.568 to 6.141	0.30
Previous stroke	1.312	0.660 to 2.608	0.44
Previous bleeding	1.397	0.523 to 3.726	0.51
Cr >2.26 mg/dl	1.152	0.257 to 5.152	0.85
Antiplatelet used	0.927	0.423 to 2.035	0.85
Labile INR+	1.621	0.863 to 3.043	0.13

* B-value is the coefficient of a predictor variable in a simple linear regression model. It represents the slope of the regression line, indicating the change in the dependent variable (outcome) for each unit change in the independent variable (predictor) + Labile INR is Time in Therapeutic Range (TTR) less than 60%

CKD=chronic kidney disease; Cr=creatinine; INR=international normalized ratio

Limitations

Our study had several limitations. The effectiveness of warfarin depends on the time in therapeutic range (TTR)[28]. In our study, the TTR is lower than in the main study, particularly in the NOACs trial. However, this reflects the real-world scenario in Thailand and countries with low TTR. Since we excluded patients with valvular AF, a history of venous thromboembolism, and ESRD patients undergoing renal replacement therapy, the study had a small sample size and a limited number of major bleeding events. It may have insufficient power to evaluate effectiveness, including the risk of stroke and all-cause mortality.

As this was an observational cohort study, the risks to the study population may have been underestimated as a result of patient use of over-the-counter drugs that affect anticoagulants. The bleeding outcomes were restricted to those bleeding events resulting in hospitalization or death. These were gastrointestinal, intracranial, or airway bleeding or bleeding from the urinary tract. Our results cannot be generalized to include the risk of other types of bleeding as some bleeding events (particularly minor bleeding) may have been missed. The study was also limited by missing data and loss of follow-up during the COVID-19 outbreak.

Conclusion

In the Thai population, the use of anticoagulants in patients with NVAF and mild to moderate CKD is common. While anticoagulation offers stroke prevention benefits, it also increases the risk of bleeding. The study demonstrated that anticoagulated NVAF patients with mild to moderate CKD do not

Table 6. Factors associated with overall major bleeding

Endpoint	Hazard ratio	p-value	Incidence Rate (95%CI), bleeds per 100 Person-year	
			Non-CKD	CKD
Major bleeding	1.86 (0.78 to 4.43)	0.16+	2.42 (1.26 to 4.67)	4.60 (2.62 to 8.10)
			NOACs	Warfarin
Major bleeding	0.66 (0.28 to 1.56)	0.34++	4.30 (2.38 to 7.76)	2.66 (1.43 to 4.96)

Non-CKD is the reference. ‡ NOACs group is the reference. Incidence rate refers to the first events.
CKD=chronic kidney disease; NOACs=Non-vitamin K antagonist oral anticoagulants

exhibit significantly different bleeding risks compared to those with normal kidney function.

What is already known on this topic?

AF patients with chronic kidney disease have a higher risk of thromboembolism and stroke. NOACs have proven effective in reducing stroke, intracranial hemorrhage, and mortality rates. These drugs also reduce the incidence of major bleeding to a rate equivalent to that of individuals with normal kidney function. However, these drugs' metabolism largely depends on kidney elimination, and clinical trials often exclude those with reduced GFR, leaving gaps in our understanding.

What this study adds?

The present study provides evidence that anticoagulants are effective and safe for patients with and without mild to moderate CKD in the Thai population. This is demonstrated over intermediate and long-term follow-up. These findings support the use of oral anticoagulants in these patient groups.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Kumar S, Lim E, Covic A, Verhamme P, Gale CP, Camm AJ, et al. Anticoagulation in concomitant chronic kidney disease and atrial fibrillation: JACC Review topic of the week. J Am Coll Cardiol 2019;74:2204-15.
2. Chan YH, See LC, Tu HT, Yeh YH, Chang SH, Wu LS, et al. Efficacy and safety of apixaban, dabigatran, rivaroxaban, and warfarin in Asians with nonvalvular atrial fibrillation. J Am Heart Assoc 2018;7:e008150.
3. Krishna PR, Naresh S, Krishna GS, Lakshmi AY, Vengamma B, Kumar VS. Stroke in chronic kidney disease. Indian J Nephrol 2009;19:5-7.
4. Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int 2011;80:17-28.
5. Carrero JJ, Trevisan M, Sood MM, Bárány P, Xu H, Evans M, et al. Incident atrial fibrillation and the risk of stroke in adults with chronic kidney disease: The Stockholm CREAtinine Measurements (SCREAM) project. Clin J Am Soc Nephrol 2018;13:1314-20.
6. Watanabe H, Watanabe T, Sasaki S, Nagai K, Roden DM, Aizawa Y. Close bidirectional relationship between chronic kidney disease and atrial fibrillation: the Niigata preventive medicine study. Am Heart J 2009;158:629-36.
7. Olesen JB, Lip GY, Kamper AL, Hommel K, Køber L, Lane DA, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. N Engl J Med 2012;367:625-35.
8. Potpara TS, Ferro CJ, Lip GYH. Use of oral anticoagulants in patients with atrial fibrillation and renal dysfunction. Nat Rev Nephrol 2018;14:337-51.
9. Lane DA, Lip GY. Use of the CHA(2)DS(2)-VASc and HAS-BLED scores to aid decision making for thromboprophylaxis in nonvalvular atrial fibrillation. Circulation 2012;126:860-5.
10. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010;137:263-72.
11. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010;138:1093-100.
12. Kaatz S, Mahan CE. Stroke prevention in patients with atrial fibrillation and renal dysfunction. Stroke 2014;45:2497-505.
13. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51.
14. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-91.
15. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981-92.
16. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093-104.
17. Turakhia MP, Blankestijn PJ, Carrero JJ, Clase CM, Deo R, Herzog CA, et al. Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Eur Heart J 2018;39:2314-25.
18. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013;3:5-6.
19. Chantrarat T, Krittayaphong R. Oral anticoagulation and cardiovascular outcomes in patients with atrial fibrillation and chronic kidney disease in Asian Population, Data from the COOL-AF Thailand registry. Int J Cardiol 2021;323:90-9.
20. Stevens PE, Levin A. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med 2013;158:825-30.
21. Dahal K, Kunwar S, Rijal J, Schulman P, Lee J. Stroke, major bleeding, and mortality outcomes in warfarin users with atrial fibrillation and chronic kidney disease: A meta-analysis of observational studies. Chest

2016;149:951-9.
22. Su X, Yan B, Wang L, Lv J, Cheng H, Chen Y. Oral anticoagulant agents in patients with atrial fibrillation and CKD: A systematic review and pairwise network meta-analysis. Am J Kidney Dis 2021;78:678-89.e1.
23. Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haeusler KG, et al. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. Europace 2021;23:1612-76.
24. Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, Cronin EM, et al. 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2024;149:e1-156.
25. Torn M, Bollen WL, van der Meer FJ, van der Wall EE, Rosendaal FR. Risks of oral anticoagulant therapy with increasing age. Arch Intern Med 2005;165:1527-32.
26. Ruiz Ortiz M, Muñiz J, Raña Míguez P, Roldán I, Marín F, Asunción Esteve-Pastor M, et al. Inappropriate doses of direct oral anticoagulants in real-world clinical practice: prevalence and associated factors. A subanalysis of the FANTASIIA Registry. Europace 2018;20:1577-83.
27. Caso V, de Groot JR, Sanmartin Fernandez M, Segura T, Blomström-Lundqvist C, Hargroves D, et al. Outcomes and drivers of inappropriate dosing of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with atrial fibrillation: a systematic review and meta-analysis. Heart 2023;109:178-85.
28. Apostolakis S, Sullivan RM, Olshansky B, Lip GYH. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: the SAMe-TT_2R_2 score. Chest 2013;144:1555-63.