ORIGINAL ARTICLE

Real-World Clinical Outcomes of Warfarin Use Among Patients with Chronic Kidney Disease in Thailand

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Background: Warfarin has been extensively used for a long time under various conditions. However, comprehensive evidence is scarce regarding the effectiveness and safety of warfarin in each group of chronic kidney disease (CKD) among Thai patients.

Objective: The present study used real-world data from Thailand to determine the incidence of thromboembolism and bleeding among patients with CKD with different estimated glomerular filtration rates (eGFRs).

Materials and Methods: A retrospective cohort study was conducted among Thai patients with CKD who used warfarin at three tertiary-care hospitals between January 2015 and December 2019. Patients were included and divided into five groups according to their eGFRs as N1 to N5 with eGFR greater than 60, 30 to 59, 15 to 29, less than 15 and not receiving dialysis, and less than 15 mL/minute/1.73 m^2 with dialysis, respectively. The incidence density was analyzed to report thromboembolism and bleeding outcomes.

Results: During the follow-up period, 2.28 per 100 person-years of patients developed thromboembolism with N1 to N5 at 2.00, 2.27, 3.68, 4.66, and 1.70 per 100 person-years, respectively. Furthermore, 2.33 per 100 person-years of patients developed major bleeding with N1 to N5 at 1.17, 2.25, 4.03, 11.37, and 5.12 per 100 person-years, respectively.

Conclusion: The present study found that the incidence of thromboembolism and major bleeding among patients with CKD increased across different eGFR groups who used warfarin. Interestingly, patients with CKD in the N4 group had a higher incidence of thromboembolism and major bleeding than the other groups. Thus, close monitoring and frequent follow-up are recommended for this group.

Keywords: Vitamin K antagonist; Bleeding; Thromboembolism; Chronic kidney disease

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Warfarin or vitamin K antagonist (VKA) is an orally administered anticoagulant that has long been prescribed by physicians because of its preventive effect against brain embolism and other thromboembolism events in patients with atrial fibrillation (AF), venous thromboembolism (VTE), and prosthetic valve replacement. Warfarin has complex pharmacokinetics, and factors can affect the level of the international normalized ratio (INR), such as age, race, drug interactions, diet, diseases, and patient conditions. Previous evidence reported that warfarin could reduce the incidence of stroke and other thromboembolism events in patients with non-end-stage chronic kidney disease (CKD) [(1)]. Nevertheless, the clinical efficacy of warfarin remains controversial for patients having end-stage renal disease (ESRD) and those who received renal replacement therapy (RRT) from hemodialysis (HD), peritoneal dialysis (PD), and kidney transplant. Studies have found no correlation between the administration of warfarin and the reduction of risk for stroke in patients with ESRD[(2,3)]. Moreover, patients with low estimated glomerular filtration rate (eGFR), particularly those who received RRT, were highly susceptible to stroke or thromboembolism[(4,5)]. Meanwhile, other studies have shown that warfarin

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treatment might be associated with increased bleeding, particularly in patients with CKD[6-10]. At present, CKD represents a significant public health concern not only in Thailand but also in other countries. CKD often coexists with notable major comorbidities of cardiovascular diseases (CVD), including AF and VTE. Consequently, these patients may require oral anticoagulants, and warfarin is commonly used, particularly for those experiencing severe renal impairment. Therefore, the present study aimed to determine the incidence of thromboembolism and bleeding among Thai patients with CKD who received warfarin and the maintenance dose of warfarin at each eGFR stage.

Materials and Methods

Study population

The present study was a multicenter, retrospective cohort study conducted among patients with CKD who received warfarin between January 2015 and December 2019 in three tertiary-care public hospitals in Thailand, which are Phramonkutklao Hospital, Rajavithi Hospital, and Vajira Hospital. All patients diagnosed with CKD were identified based on the International Classification of Disease, Tenth Revision (ICD-10) for CKD-related terms. Patients aged 18 years or older, taking warfarin, and followed up at each hospital were included. However, patients were excluded if the following conditions were met, history of stroke and bleeding within one year before patient selection, incomplete information, less than one visit for follow-up, and absence of INR monitoring. The study protocol was approved by the Ethics Committee of the Institutional Review Board of the Royal Thai Army Medical Department (Reference no. Q018h/63), Rajavithi Hospital (Reference no. Exp.63172), and Vajira Hospital (Reference no. 020/64 E).

Variable definition

The CKD epidemiology collaboration (CKD-EPI) equation was used to calculate eGFR. Patients were recruited and divided into different groups according to their eGFR with N1 at 60 mL/minute/1.73 m^2 or more, N2 at 30 to 59 mL/minute/1.73 m^2, N3 at 15 to 29 mL/minute/1.73 m^2, N4 at less than 15 mL/minute/1.73 m^2 and not receiving dialysis, and N5 at less than 15 mL/minute/1.73 m^2 with HD or PD. Bleeding outcomes were defined by the International Society on Thrombosis and Haemostasias (ISTH) Criteria as follows, 1) major was defined as fatal bleeding and/or symptomatic bleeding in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red cells, and 2) clinically relevant non-major (CRNM) bleeding was defined as any overt bleeding requiring a medical intervention such as hospitalization, surgery or interventional procedure, further diagnostic imaging, laboratory test, or specialist evaluation, and/or treatment discontinuation and not meeting any of the criteria for major bleeding[11].

The primary effectiveness outcomes were the incidence of thromboembolism events, including ischemic stroke and systemic embolism events (SEE). The primary safety outcome was the incidence of major bleeding. Data were censored when an outcome occurred or at the end of this study. The secondary outcomes were a composite of thromboembolism, total bleeding, and all-cause mortality, including maintenance doses of warfarin, in each eGFR group.

Statistical analysis

The following data were collected from the hospital databases after the patients had been identified: age, gender, comorbidities, indication, maintenance dose of warfarin, comedications, eGFR, and laboratory data. The collected data were analyzed using IBM SPSS Statistics, version 27.0 (IBM Corp., Armonk, NY, USA). All variables were analyzed using descriptive statistics. Categorical variables were reported as frequency with percentages. Continuous variables were reported as mean ± standard deviations or median with interquartile range (IQR). The authors compared and analyzed the mean incidences of thromboembolism, bleeding, and maintenance doses across the eGFRR groups using the one-way analysis of variance and Kruska-Wallis tests for normal and nonnormal distributions, respectively. Cox regression analysis was conducted to adjust for confounding effects. Covariates such as congestive heart failure, hypertension, age, diabetes mellitus, stroke/transient ischemic attack (TIA) history, vascular disease, and gender category were selected for the adjusted hazard ratio (HR) in thromboembolism outcomes. In addition, hypertension, abnormal liver function, stroke, bleeding history, time in the therapeutic range (TTR) of less than 60%, age, and antiplatelet use were selected for adjusted HR in safety outcomes.

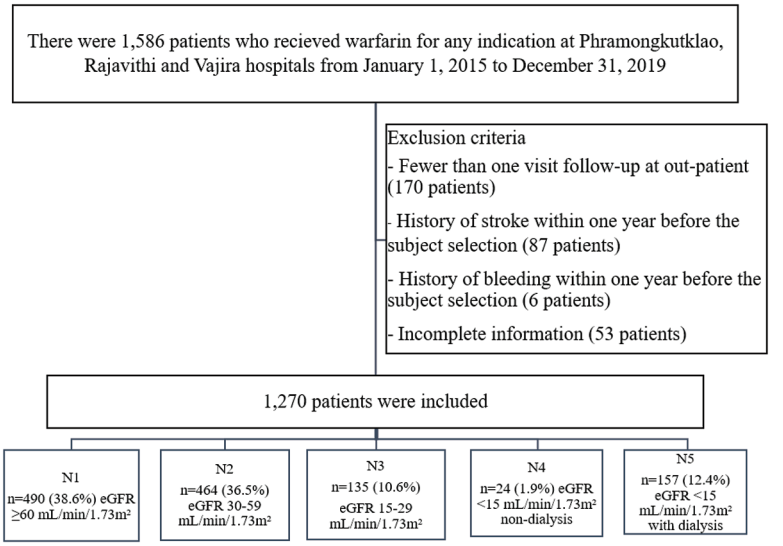

Figure 1. Details of the selected patients.

Results

Baseline characteristics

One thousand two hundred seventy patients were identified from the computerized hospital database between January 2015 and December 2019 in three hospitals. The details of the patient selection are provided in Figure 1. All patients were divided into each group by eGFR as follows: N1 with 490 patients (38.6%), N2 with 464 (36.4%), N3 with 135 (10.6%), N4 with 24 (1.9%), and N5 with 157 (12.4%). Moreover, 144 (11.3%) and 13 (1.0%) of the patients were receiving HD and PD, respectively. The median study period was 1.94 years. The median age was 69 (IQR of 59 to 77) years. More than half of the patients were male at 54.3%. The majority of indications for warfarin use were AF for 68.4%, followed by prosthetic heart valve for 20.6% and DVT for 11.3%. The median scores of CHA_2DS_2VASc and HASBLED were 4 (IQR 3 to 5) and 2 (IQR 1 to 3) points, respectively. Approximately 72.0% had TTR of less than 60%. The baseline characteristics of patients in each stage of CKD are shown in Table 1.

Incidence of thromboembolism and bleeding events

Overall, thromboembolism was found in 64 patients (5.04%, 2.28 per 100 person-years). The incidents occurred at 2.00, 2.27, 3.68, 4.66, and 1.70 per 100 person-years for the N1 to N5 groups, respectively. Compared with the N1 group, the reference group, the incidence of thromboembolism was higher in the group with reduced eGFR. However, no significant differences were found in the incidence rate of thromboembolism.

Major bleeding events were experienced by 66 patients with CKD who received warfarin (5.20%, 2.33 per 100 person-years). The incidences of major bleeding events were 1.17, 2.25, 4.03, 11.37, and 5.12 per 100 person-years for the N1 to N5 groups, respectively. The incidence of major bleeding events was higher in the N4 group than in the other eGFR groups. The authors observed statistically significant differences in the incidence of major bleeding events between the N1 and N2, N3, N4, and N5 groups ($p<0.05$, <0.001, <0.001, and <0.001, respectively). This study also found statistically significant differences in the incidence of CRNM bleeding events between the N1 and N2, N3, N4, and N5 groups ($p<0.04$, <0.05, <0.001, and <0.01, respectively). Overall, most major bleeding events were found in major organs, such as the upper gastrointestinal tract for 1.73%, the subdural hematoma for 0.94%, and the intracerebral hemorrhage for 0.87%. The primary and secondary outcomes are presented in Table 2 and 3, respectively.

Maintenance dose of warfarin classified by CKD stage

Overall, the median maintenance dose of warfarin was 3.00 (IQR 2.00 to 3.43) mg/day and that classified by CKD stages was 3.00 (IQR 2.57 to 4.11), 2.57 (IQR 2.00 to 3.29), 2.57 (IQR 1.71 to 3.00), 2.36 (IQR 1.93 to 3.57), and 2.50 (IQR 1.50 to 3.00) mg/day for the N1, N2, N3, N4, and N5 groups, respectively. The comparison of warfarin

Table 1. Baseline characteristics

Characteristic	Stage of CKD						p-value
	N1 (n=490, 38.6%)	N2 (n=464, 36.4%)	N3 (n=135, 10.6%)	N4 (n=24, 1.9%)	N5 (n=157, 12.4%)	Total (n=1,270, 100%)	
Demographics							
Age (years); median (IQR)	61 (51 to 71)	73 (66 to 79)	77(70 to 82)	73 (66 to 79)	65(57 to 75)	69 (59 to 77)	<0.001[a,b,c,d]
Male	51.0%	62.3%	44.4%	50.0%	50.3%	54.3%	<0.001[a]
Weight (kg); median (IQR)	62 (54.2 to 74.0)	65 (57.0 to 75.0)	63 (55.3 to 73.0)	60 (55.5 to 73.0)	60.5 (54.0 to 68.0)	63 (55.0 to 73.8)	0.009[a]
Time in therapeutic range; median (IQR)	44.1 (21.2 to 65.3)	46.1 (26.8 to 65.2)	45.4 (26.1 to 60.3)	38.2 (21.2 to 51.6)	30.6 (9.5 to 49.9)	42.7 (22.8 to 62.5)	0.001[d]
<60%	69.6%	68.3%	74.1%	83.3%	84.1%	71.7%	
>60%	30.4%	31.7%	25.9%	16.7%	15.9%	28.3%	
Indication of warfarin use							
Atrial fibrillation	53.3%	79.1%	83.0%	79.2%	70.1%	68.4%	<0.014[a,b,c,d]
Prosthetic heart valve	30.8%	16.6%	10.4%	8.3%	10.8%	20.6%	<0.020[a,b,c,d]
Deep vein thrombosis	15.9%	6.5%	9.6%	8.3%	12.7%	11.3%	<0.001[a]
Pulmonary embolism	5.3%	2.4%	1.5%	0.0%	1.9%	3.3%	<0.020[a]
Others	6.5%	4.7%	0.7%	4.2%	7.6%	5.4%	0.008[b]
Medical history							
Hypertension	50.8%	81.7%	82.2%	83.3%	86.0%	70.4%	<0.002[a,b,c,d]
Diabetes mellitus	23.3%	40.9%	62.2%	54.2%	55.4%	38.4%	<0.001[a,b,c,d]
Ischemic heart disease	16.3%	30.8%	33.3%	33.3%	33.8%	25.9%	<0.050[a,b,c,d]
Dyslipidemia	37.1%	51.1%	56.3%	50.0%	51.6%	46.3%	<0.001[a,b,d]
Congestive heart failure	25.9%	31.9%	28.9%	54.2%	33.1%	29.8%	0.042[b], 0.002[c]
Thyroid dysfunction	4.9%	3.7%	5.9%	4.2%	7.0%	4.8%	1.000[a,b,c,d]
Cirrhosis	1.2%	1.1%	0.0%	0.0%	1.9%	1.1%	1.000[a,b,c,d]
Cancer	5.1%	6.7%	5.2%	4.2%	6.4%	5.8%	1.000[a,b,c,d]
Medication							
Aspirin	11.0%	18.5%	21.5%	25.0%	27.4%	17.2%	<0.050[a,b,c,d]
P2Y12 receptor antagonist	3.7%	10.3%	20.0%	29.2%	16.6%	9.9%	<0.001[a,b,c,d]
DAPT	1.8%	3.9%	5.9%	12.5%	6.4%	3.8%	<0.016[b,c,d]
Laboratory parameters; median (IQR)							
eGFR (mL/min/1.73 m^2)	83 (70.1 to 98.0)	45 (39.0 to 52.8)	24 (19.9 to 27)	11.27 (9.4 to 14.0)	7.18 (5.3 to 9.4)	69 (59.0 to 77.0)	<0.001[a,b,c,d]
Hemoglobin (g/dL)	12.6 (11.4 to 13.8)	12.4 (11.1 to 13.7)	11.2 (9.8 to 12.6)	11.0 (10.4 to 2.5)	10.2 (9.5 to 11.2)	12.0 (10.6 to 13.4)	<0.001[a,b,c,d]
Platelet (*10^9/L)	243 (192 to 306)	214 (167 to 265)	219 (167 to 261)	252 (210 to 285)	223 (168 to 289)	224 (177 to 281)	<0.001[a,b,d]
Serum albumin (g/dL)	4.1 (3.7 to 4.4)	4.0 (3.6 to 4.4)	3.8 (3.4 to 4.2)	3.7 (3.3 to 4.1)	3.7 (3.4 to 4.1)	4.0 (3.6 to 4.3)	<0.01[a,b,c,d]
Blood urea nitrogen (mg/dL)	13.0 (10.2 to 16.0)	20.0 (16.0 to 25.0)	32.3 (27.0 to 39.3)	50.8 (38.4 to 93.2)	45.0 (31.0 to 59.0)	19.0 (13.4 to 28.0)	<0.001[a,b,c,d]
Serum creatinine (mg/dL)	0.8 (0.7 to 1.0)	1.4 (1.3 to 1.6)	2.3 (2.0 to 2.5)	4.4 (3.3 to 5.5)	6.4 (5.2 to 8.2)	1.3 (0.9 to 1.9)	<0.001[a,b,c,d]
Hemoglobin (g/dL)	12.6 (11.4 to 13.8)	12.4 (11.1 to 13.7)	11.2 (9.8 to 12.6)	11.0 (10.4 to 12.5)	10.2 (9.5 to 11.2)	12.0 (10.6 to 13.4)	<0.001[a,b,c,d]
CHA_2DS_2VASc score (point); median (IQR)	3 (2 to 4)	4 (3 to 5)	5 (4 to 6)	4 (3.5 to 5)	4 (3 to 5)	4 (3 to 5)	<0.006[a,b,c,d]
Low (0)	3.4%	0.0%	0.0%	0.0%	0.9%	1.2%	
Intermediate (1)	14.9%	4.4%	2.7%	5.3%	6.4%	7.6%	
High (>2)	81.6%	95.6%	97.3%	94.7%	92.7%	91.3%	
HASBLED score (point); median (IQR)	1 (1 to 2)	2 (1 to 2)	3 (2 to 3)	3 (3 to 4)	3 (2 to 4)	2 (1 to 3)	<0.001[a,b,c,d]
Low (0)	10.0%	3.5%	0.0%	0.0%	0.0%	4.5%	
Moderate (1 to 2)	77.8%	73.0%	41.1%	21.1%	29.1%	63.6%	
High (>3)	12.3%	23.4%	58.9%	78.9%	70.9%	31.9%	

CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; DAPT=dual antiplatelet therapy; IQR=interquartile range

N1: eGFR >60 mL/min/1.73 m^2; N2: eGFR 30 to 59 mL/min/1.73 m^2; N3: eGFR 15 to 29 mL/min/1.73 m^2; N4: eGFR <15 mL/min/1.73 m^2 and not receiving dialysis; N5: eGFR <15 mL/min/1.73 m^2 with HD or PD

A p-value ≤0.05 is statistically significant; [a] CKD N2 versus N1; [b] CKD N3 versus N1; [c] CKD N4 versus N1; [d] CKD N5 versus N1

dosages between the groups using the Kruskal-Wallis test with post-hoc analysis showed that the median maintenance doses of warfarin in all five groups of patients with CKD were statistically different (p<0.001). Furthermore, patients in the N1 group with eGFR of more than 60 mL/minute/1.73 m^2 had

Table 2. Primary outcomes classified by the CKD stage

Outcomes	No. of event	Incidence rate (per 100 PY)	Crude HR (95% CI)	Adjusted HR (95% CI)
Primary effectiveness outcome				
Thromboembolism*				
• Total	64	2.28		
• N1	22	2.00	1.00 (Ref.)	1.00 (Ref.)
• N2	27	2.27	1.13 (0.65 to 2.00)	1.13 (0.65 to 2.00)
• N3	9	3.68	1.84 (0.85 to 3.99)	1.84 (0.85 to 3.99)
• N4	2	4.66	2.33 (0.55 to 9.91)	2.33 (0.55 to 9.91)
• N5	4	1.70	0.85 (0.29 to 2.46)	0.85 (0.29 to 2.46)
Primary safety outcomes				
Major bleeding**				
• Total	66	2.33		
• N1	13	1.17	1.00 (Ref.)	1.00 (Ref.)
• N2	27	2.25	1.92 (0.99 to 3.73)	2.16 (1.03 to 4.55)
• N3	10	4.03	3.45 (1.51 to 7.86)	4.15 (1.64 to 10.52)
• N4	4	11.37	9.73 (3.17 to 29.84)	14.65 (4.59 to 46.70)
• N5	12	5.12	4.38 (2.00 to 9.61)	6.03 (2.60 to 13.95)

PY=person-years; HR=hazard ratio; CI=confidence interval

N1: eGFR >60 mL/min/1.73 m^2; N2: eGFR 30 to 59 mL/min/1.73 m^2; N3: eGFR 15 to 29 mL/min/1.73 m^2; N4: eGFR <15 mL/min/1.73 m^2 and not receiving dialysis; N5: eGFR <15 mL/min/1.73 m^2 with HD or PD

* HR adjusted for congestive heart failure, hypertension, age, diabetes mellitus, stroke/TIA history, vascular disease, and sex; ** HR adjusted for hypertension, abnormal liver function, stroke, bleeding history, TTR <60%, age, and antiplatelet use

Table 3. Composite endpoints of thromboembolism, total bleeding, and all-cause mortality

Secondary outcomes	No. of event	Incidence rate (per 100 PY)	Crude HR (95% CI)	Adjusted HR† (95% CI)
Total	263	9.96		
N1	64	6.02	1.00 (Ref)	1.00 (Ref)
N2	110	10.03	1.67 (1.23 to 2.27)	1.59 (1.14 to 2.22)
N3	38	16.15	2.69 (1.80 to 4.01)	2.74 (1.80 to 4.26)
N4	11	38.43	6.39 (3.37 to 12.12)	6.66 (3.39 to 13.06)
N5	40	18.60	3.09 (2.08 to 4.59)	3.05 (2.01 to 4.62)

PY=person-years; HR=hazard ratio; CI=confidence interval

N1: eGFR >60 mL/min/1.73 m^2; N2: eGFR 30 to 59 mL/min/1.73 m^2; N3: eGFR 15 to 29 mL/min/1.73 m^2; N4: eGFR <15 mL/min/1.73 m^2 and not receiving dialysis; N5: eGFR <15 mL/min/1.73 m^2 with HD or PD

† HR adjusted for congestive heart failure, hypertension, age, diabetes mellitus, stroke/TIA history, vascular disease, sex category, abnormal liver function, bleeding history or predisposition, labile INR, and antiplatelet use

statistically different dosages compared with those in the N2, N3, N4, and N5 groups ($p<0.001$, <0.001, <0.03, and <0.001, respectively) as shown in Figure 2.

Discussion

The present study found the overall incidence of thromboembolism was 2.28 per 100 person-years, which is similar to the finding reported by Chantrarat et al., who studied the occurrence of CVD in Asian patients with AF and CKD receiving anticoagulant therapy[12]. In addition, these results are consistent with those of Olesen et al., who reported the incidences of thromboembolism in patients without CKD, patients with non-end-stage CKD, and patients with end-stage CKD who required RRT were 3.61, 6.44, and 5.61 per 100 person-years, respectively[13]. Notably, the patients in the present study were divided into five groups according to their eGFR, which indicated obvious differences in thromboembolism events in each stage of CKD[3,13,14]. Differences in clinical outcomes in each group were shown through this division.

The frequency of thromboembolic events increased in patients with reduced renal function as measured by a decreased eGFR. Interestingly, the N4 group, with eGFR of less than 15 mL/minute/1.73 m^2

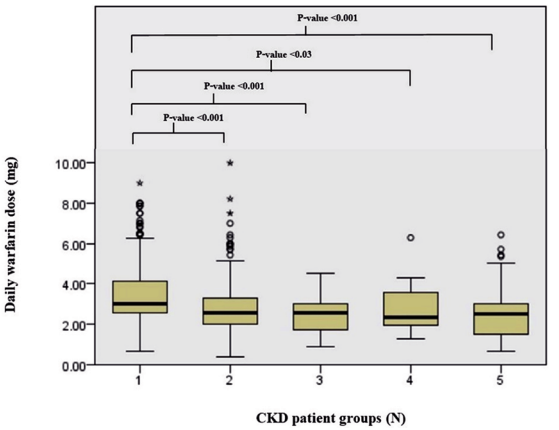

Figure 2. Maintenance dose of warfarin classified by CKD stage.

without RRT, had a higher risk of thromboembolism than the N5 group with eGFR of less than 15 mL/minute/1.73 m² with RRT. Theoretically, patients with lower eGFR would have a higher risk of thromboembolism caused by protein-bound uremic toxins, such as indoxyl sulfate or paracresol sulfate, which are catalysts for oxidative stress[15]. Oxidative stress is a significant inducer of peripheral vascular dysfunction and has a unique characteristic of causing impaired endothelial function and increased risk of atherosclerosis, vascular calcification, stroke, and thromboembolism in patients with end-stage CKD[15]. The risk for thromboembolism was higher for patients in the N4 group than those in the N5 group because they did not have RRT, which could cause accumulation of uremic toxins and thereby lead to thromboembolism.

In addition, as for the baseline characteristics in the present study, the blood urea nitrogen (BUN) level of the N4 group was higher than that in the N5 group. The median BUN differences were 50.8 (IQR 38.4 to 93.2), and 45.0 (IQR 31.0 to 59.0) mg/dL for the N4 and N5 groups, respectively. When compared with the N1 to N3 groups, the median TTR values in patients with eGFR 15 mL/minute/1.73 m² with or without RRT were lower. This result is consistent with the findings of the previous studies, which showed that eGFR correlated with TTR and predicted stroke and bleeding outcomes[16,17].

In addition, 27.4% of the patients in the N5 group had received aspirin concomitant with warfarin to prevent ischemic stroke and CVD. The group also included 144 patients subjected to HD (91.7%) who received heparin during the HD procedures. This might be the reason for the fewer thromboembolism events in the N5 group than in the N4 group, whereas more than half of the patients in the N4 group had under-coagulation.

A previous report using real-world data compared the incidence of bleeding in patients with AFs without CKD, AF with non-end-stage CKD, and AF that required RRT. The results showed that the incidence was 3.54 per 100 person-years in patients having AF without CKD. Meanwhile, the incidences were higher among patients with non-end-stage CKD at 8.77 per 100 person-years, and those with AF requiring RRT at 8.89 per 100 person-years[13]. This finding is consistent with the study by Chantrarat et al., which reported the rates of major bleeding events in patients with eGFR of less than 60 mL/minute/1.73 m² and of more than 60 mL/minute/1.73 m² to be 5.6% and 3.5%, respectively[12].

In the present study, the results were consistent with the previous reports[12,13]. The decline in eGFR could cause major bleeding events in patients with CKD who received warfarin. Furthermore, CKD may affect the quality of treatment using warfarin. Dreisbach et al. reported that CKD could reduce the albumin protein level, leading to an increased level of free-form warfarin[18]. In addition, CYP2C9 activity could be lowered by 50% in patients with CKD, particularly those with end-stage CKD where there was decreased metabolism of S-form warfarin[19]. Interestingly, the present study reported that the N4 group had the highest incidence of major bleeding when compared with the other groups. There may have been more patients in the N4 group who received concomitant warfarin with dual antiplatelets than in the other groups. In addition, platelet dysfunction in patients with uremia is due to uremic toxins being responsible for bleeding tendencies in patients with advanced CKD and ESRD[20,21]. Previous studies have reported that dialysis could decrease uremic toxins. Moreover, the skin-bleeding time after the second dialysis was significantly shorter than that before dialysis[22,23].

In the present study, the major bleeding event was common in upper gastrointestinal tract, followed by subdural hematoma. This finding is consistent with bleeding events in patients prescribed anticoagulant medications[1,24]. In addition, composite outcomes, including the incidence rates of thromboembolism and total bleeding and all-cause mortality rate in patients with CKD using warfarin, were consistent with the previous evidence[25]. In the present study, although the N4 group had a higher incidence rate of major bleeding than the N5 group, 11.30% of the

N5 group received heparin during HD. Therefore, close and careful monitoring is necessary in both groups.

Notably, the authors performed an exploratory analysis to compare the maintenance dose of warfarin in each CKD stage. The maintenance dose of warfarin in each CKD group was calculated only in patients with TTR greater than 60%. The present study showed that the maintenance dose of warfarin directly varied with eGFR, where the N1 group required a higher maintenance dose than the other groups. The maintenance dose of warfarin was reduced when the eGFR decreased. This finding conformed with the previous studies conducted in Asian and white patients with CKD who used warfarin[26,27]. However, the maintenance dose of warfarin in the present study was lower than that in other studies[26,28]. Ichihara et al. reported that the maintenance doses of warfarin were 3.54±1.44, 2.88±1.42, and 2.33±1.04 mg/day for patients with eGFR greater than 60, 30 to 59, and less than 30 mL/minute/1.73 m², respectively. Sakaan et al. reported that the average daily doses of warfarin to maintain a therapeutic INR were 5.6±1.7, 4.3±1.6, 4.6±1.9, and 4.8±1.9 mg in the normal kidney function group, CKD stage 3, CKD stage 4 and 5, and ESRD, respectively[28]. These results showed that the dosage of warfarin decreased in patients with worsening renal function.

Limitation

The present study has limitations. First, similar to other real-world studies, missing data for thromboembolism and bleeding events were found because of the retrospective design. Second, the sample size of the patients included in the study was small, particularly in the N4 group. Therefore, additional multicenter studies are necessary. Finally, the short duration of follow-up may have led to an underestimation of thromboembolism events and mortality.

Conclusion

The present study determined the effectiveness and safety profile of warfarin among patients with CKD in real-world practice in Thailand. The results revealed the incidence of thromboembolism and bleeding increased with each CKD stage, particularly in patients with eGFR of less than 15 mL/minute/1.73 m² and not receiving dialysis. Therefore, individualized INR monitoring is necessary to ensure warfarin efficacy and safety.

What is already known about this topic?

Warfarin use in patients with concomitant CKD results in worse clinical outcomes. However, comprehensive evidence is scarce regarding the effectiveness and safety of warfarin in each group of CKD among Thai patients.

What does this study add?

This study results showed that the incidence of thromboembolism and bleeding increased with each CKD stage, particularly in patients with eGFR of less than 15 mL/minute/1.73 m² and not receiving dialysis. Therefore, individualized INR monitoring is importance to ensure warfarin efficacy and safety.

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Availability of data and materials

The datasets used in this study are available from the corresponding author on reasonable request.

Authors' contributions

Conceptualization: KT, PB, and SL (Sarawuth Limprasert); methodology: KT, PB, MP, SL (Sarawuth Limprasert), and WS (Wichai Santimaleeworagun); patient data and outcomes of interest validation; KT, PB, SL (Sutee Limcharoen), and SY; formal analysis: KT, MP, SL (Sarawuth Limprasert), and WS (Weerayuth Saelim); writing—original draft preparation: KT, SL (Sarawuth Limprasert), and PB. All authors have read and approved the published version of the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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