Original Article

Vajira Med J
Journal of Urban Medicine

Appropriate Use of Anticoagulants among Nonvalvular Atrial Fibrillation Patients at a University Hospital in Thailand

Phanthaphan Sureeyathanaphat MD[1], Padoemwut Teerawongsakul MD[1], Teetouch Ananwattanasuk MD[1]

[1] *Cardiology Division, Department of Internal Medicine, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok 10300, Thailand*

ABSTRACT

OBJECTIVE: Warfarin is primarily used for stroke prevention in atrial fibrillation (AF) patients in Thailand. Novel oral anticoagulants (NOACs) are used less commonly due to their high cost. This study aimed to evaluate the appropriate use of anticoagulants and clinical outcomes among nonvalvular AF (NVAF) patients.

METHODS: This retrospective study collected data from the electronic medical records of patients who were diagnosed with NVAF between January 2014 and December 2019 at the Faculty of Medicine, Vajira Hospital. Baseline characteristics, prescribed indication, types and doses of anticoagulant, and ischemic and hemorrhagic outcomes were recorded and analyzed.

RESULTS: We analyzed 783 patients with NVAF in this study. Of these, 539 (68.90%) were treated with oral anticoagulants (OAC), including 344 patients (43.90%) with warfarin therapy and 195 (24.90%) with NOACs. Meanwhile, 492 (73.10%) patients with CHA_2DS_2VASC score ≥ 2 received OAC therapy that was suitable for their indication. Of the 344 patients who received warfarin, 112 patients (32.60%) had an optimal time in therapeutic range (TTR) level of ≥ 65%. Of the 195 NOAC patients, only 98 (50.30%) received appropriate doses of NOACs. There was no statistically significant difference in the overall incidence rates of ischemic stroke/systemic embolism, bleeding, cardiovascular death, and all-cause death between the warfarin and NOACS groups. Appropriate TTR levels in the warfarin group was associated with significantly lower incidence rates of cardiovascular death (hazard ratio: 0.14; 95% CI: 0.02–0.79; p = 0.02) and all-cause death (hazard ratio: 0.36; 95% CI: 0.12–0.87; p = 0.01), than inappropriate TTR levels.

CONCLUSION: Most NVAF patients received oral anticoagulants with the appropriate indication. Warfarin is the most prescribed oral anticoagulant for patients with NVAF. About half of the patients received inappropriate doses of oral anticoagulants that potentially adversely affected the study outcomes of cardiovascular and all-cause deaths.

KEYWORDS: nonvalvular atrial fibrillation, novel oral anticoagulant, warfarin

INTRODUCTION

Atrial fibrillation (AF) is a common arrhythmia worldwide. In the general Thai population, the prevalence of AF is relatively low at 0.36%[1], while it is 1.90% in adults older than 65 years[2]. AF patients are at five times greater risk of developing stroke and systemic embolism (SE) than the normal population without AF[3].

Corresponding author: Teetouch Ananwattanasuk, teetouch@nmu.ac.th
Received: 30 November 2023
Revised: 9 February 2024
Accepted: 16 February 2024
Vajira Med J 2024;68(1):e266163
http://dx.doi.org/10.62691/vmj.2024.266163

The aim of AF treatment with oral anticoagulants (OAC) is to prevent complications, such as ischemic stroke and SE[4-5]. Over the past ten years, the use of novel anticoagulants (NOACs) in patients with nonvalvular AF (NVAF) has increased globally. In Asia, only 60.70% of AF patients with a high risk of stroke received OAC treatment[6]. In Thailand, historical data show that 75.30% of AF patients received oral anticoagulants. Of these, 90.10% received warfarin and only 9.10% received NOACs[7].

Warfarin has several disadvantages including the need for close monitoring of the international normalized ratio (INR) level, which creates an extra burden for physicians and patients. NOACs, on the other hand, require no monitoring. However, they are more expensive than warfarin and are not covered by the country's public healthcare scheme. Therefore, they are not affordable for many patients. The aim of this study was to investigate the appropriateness of anticoagulant use in NVAF patients and compare the incidence of stroke, SE, and bleeding between anticoagulated and nonanticoagulated patients.

METHODS

This study was a single center, retrospective longitudinal descriptive study that collected data from the Vajira electronic database (Ephis) from January 2014 to December 2019. The trial was designed and led by three investigators. The study was approved by the ethics committee of the Faculty of Medicine, Vajira Hospital, Navamindradhiraj University (COA number 165/61). Eligible patients were those diagnosed with NVAF or atrial flutter who had been followed up at the Vajira outpatient clinic for at least three months and were more than 18 years old. All eligible patients were included in this study. We excluded patients with valvular AF, including moderate to severe rheumatic mitral stenosis and prosthetic valve disease. Baseline characteristics collected included age, sex, body weight, height, systolic blood pressure, diastolic blood pressure, heart rate, date of diagnosis, type of AF, first clinical presentation, underlying medical illnesses including coronary artery disease (CAD), heart failure, previous stroke or transient ischemic attack (TIA), peripheral arterial disease, thyroid disease, liver disease, chronic kidney disease, sick sinus syndrome and heart block, cancer, history of bleeding, OAC use (type and dose), antiplatelet use, and other medications. The investigators also gathered baseline laboratory investigations including serum creatinine, hemoglobin level, and platelet count. Patients with liver cirrhosis were noted along with the Child–Turcotte–Pugh classification. The CHA_2DS_2-VASc score (consisting of heart failure, hypertension, age, diabetes mellitus, peripheral arterial disease or CAD, and female sex) was then calculated for all patients. The investigators were able to determine the appropriateness of anticoagulant use by physicians at Vajira Hospital during the study period as a primary outcome based on 1) indications for OAC use in NVAF patients and 2) the standard dosage of OACs prescribed. According to standard guidelines, OAC is indicated in NVAF patients with a CHA_2DS_2-VASc score ≥ 2 in males and greater than and ≥ 3 in females. Antiplatelets or anticoagulants are not recommended for patients with a CHA_2DS_2-VASc score of zero (including women without other stroke risk factors)[8]. Based on such indications, the investigator was able to categorize all patients studied into two groups: those whose indication was appropriate for OAC use and those whose indication was inappropriate. Regarding the prescribed dosage of OACs, both the warfarin and NOACs groups were studied. In the warfarin group, the appropriate drug dosage was determined by time in therapeutic range (TTR) at the optimal INR level of 2–3[8] based on the most recent three or more consecutive INR levels. A TTR of greater than 65% was appropriate for the warfarin dose[9-10]. The TTR was calculated using the Rosendaal et al. method[11]. In the NOACs group, the dosing was considered appropriate if adhering to adjusted dose criteria as outlined in the current standard guideline recommendations[4-5,8] which based on the patients' creatinine clearance (CrCl) calculated by the Cockcroft–Gault Equation,

ml/min, and based on the Child–Turcotte–Pugh score in liver cirrhosis patients. Based on the dosage, the investigator was able to categorize all patients on OAC therapy into appropriate and inappropriate dosage groups. In addition to the primary outcome, this study's other primary outcomes were the incidence rates of ischemic stroke or SE, cardiovascular death, all-cause death and bleeding events. We compared anticoagulated patients with nonanticoagulated patients and appropriate OAC dose with inappropriate OAC dose. Patients in the study were followed up from the date of diagnosis of AF or OAC start date until the index date that was defined as the date of the first event or the end of the study period, December 11, 2019, whichever came first. AF was categorized into 1) paroxysmal, 2) persistent, 3) long-standing persistent, and 4) permanent[12]. The definition of bleeding used was in accordance with the global use of strategies to open occluded arteries (GUSTO) bleeding definition[13]. Sample size calculations were based on estimating the single proportion from a reported prevalence of NVAF[9] and based on two independent proportions, to find the correlation of stroke incidence between anticoagulated and nonanticoagulated patients. With a statistical power of 80%, two-sided p-value of 0.05, and a 4.54% difference of incidence of ischemic stroke between NVAF patients in the anticoagulant and nonanticoagulant groups[14], the appropriate sample size was 768 patients. SPSS version 23 and STATA version 13 were used for statistical analysis.

RESULTS

From January 2014 to December 2019, 783 patients were included in the study. The consort diagram is shown in Figure 1 for more details. The median follow-up period was 47 months.

The mean participant age was 74.08 (± 11.49) years; 416 patients (53.10%) were women. Regarding AF type, 557 (71.10%) patients had paroxysmal AF, 193 (24.60%) had permanent AF. 16 (20.00%) had persistent AF and 13 (1.70%) had long-standing persistent AF. Atrial flutter was present in 5.40% of patients. The median CHA_2DS_2-VASc score was 4.0 (IQR 3–5). Overall, there were statistical differences in baseline characteristics between OAC and non-OAC patients, in weight, clinical presentation, history of hypertension, previous stroke/TIA, valvular heart disease, baseline LVEF, CHA_2DS_2-VASc score and HAS-BLED score (table 1). The distribution of the CHA_2DS_2-VASc score and HAS-BLED score by choice of anticoagulation are shown in Figure 2 and 3.

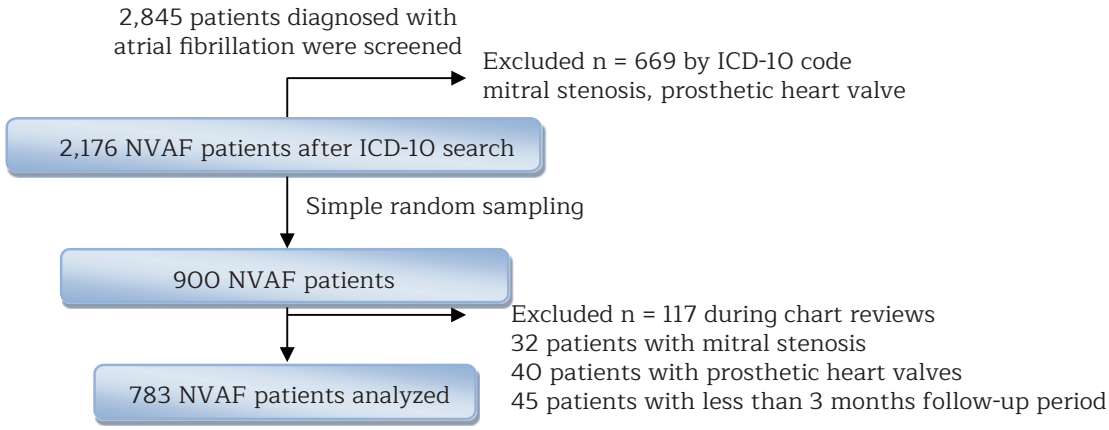
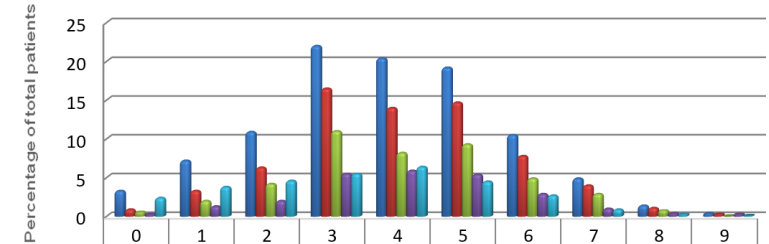


Figure 1 Consort diagram of study patients

Table 1 Baseline characteristics of patients with nonvalvular atrial fibrillation

Variables	Total (n = 783)	OAC (n = 539)	No OAC (n = 244)	P-value
Age (years)	74.08 ± 11.49	74.45 ± 0.47	73.26 ± 0.82	0.18
Female sex	53.10%	54.54%	50.00%	0.23
Weight (kg)	62.82 ± 14.20	63.64 ± 14.80	60.95 ± 12.60	0.01
Heart rate	77 ± 17	77 ± 17	77 ± 17	0.63
Type of AF				
Paroxysmal	557 (71.10%)	72.20%	68.90%	0.12
Persistent	16 (20.00%)	2.60%	0.80%	
Long standing persistent	13 (1.70%)	2.00%	0.80%	
Permanent	193 (24.60%)	22.80%	28.70%	
Previous diseases				
Hypertension	67.90%	72.20%	58.60%	0.00
Diabetes	31.90%	33.60%	28.30%	0.16
Hyperlipidemia	37.30%	39.30%	32.80%	0.08
Previous stroke or TIA	27.70%	33.20%	15.60%	0.00
Thromboembolic event	1.70%	2.00%	0.80%	0.22
CKD	17.50%	18.40%	15.60%	0.34
Peripheral arterial disease	1.40%	1.70%	0.80%	0.35
Coronary artery disease	25.80%	26.90%	23.40%	0.29
LVEF < 40%	26.90%	29.60%	19.70%	0.03
Valvular heart disease	11.00%	10.20%	5.30%	0.03
Permanent pacemaker implantation	9.60%	8.70%	11.90%	0.17
Sick sinus syndrome	10.00%	8.20%	14.30%	0.01
Thyroid disease	11.90%	11.70%	11.70%	0.81
Liver disease	2.30%	2.40%	2.00%	0.75
CHA_2DS_2 VASC score	4 (3,5)	4 (3,5)	3 (2,5)	0.00
HAS-BLED score	2 (2,3)	3 (2,4)	2 (1,5)	0.00
LVEF	50.97 ± 26.10	49.22 ± 26.33	55.88 ± 24.88	0.01
Left atrial dimension (cm)	3.85 ± 1.90	3.94 ± 1.90	3.60 ± 1.90	0.12
Creatinine clearance (ml/min)	51.34 ± 30.79	49.64 ± -27.05	49.36 ± 29.44	0.90

Abbreviations: AF, atrial fibrillation; CKD, chronic kidney disease; cm, centimeter; kg, kilogram; LVEF, left ventricular ejection fraction; min, minute; ml: milliliter; n, number; OAC, oral anticoagulant; TIA, transient ischemic attack
Data with normal distribution are mean (± 2SD), with skew distribution are median (IQR), categorical data n(%)



	0	1	2	3	4	5	6	7	8	9
Total	3.3	7.2	10.9	22	20.4	19.2	10.5	4.9	1.4	0.4
OAC	0.9	3.3	6.3	16.5	14	14.7	7.8	4	1.1	0.3
Warfarin	0.6	2	4.2	11	8.2	9.3	4.9	2.9	0.8	0
NOACs	0.3	1.3	2	5.5	5.9	5.4	2.9	1	0.4	0.3
No OAC	2.4	3.8	4.6	5.5	6.4	4.5	2.7	0.9	0.3	0.1

Figure 2 Distribution of CHA2DS2-VASc score by choice of anticoagulation

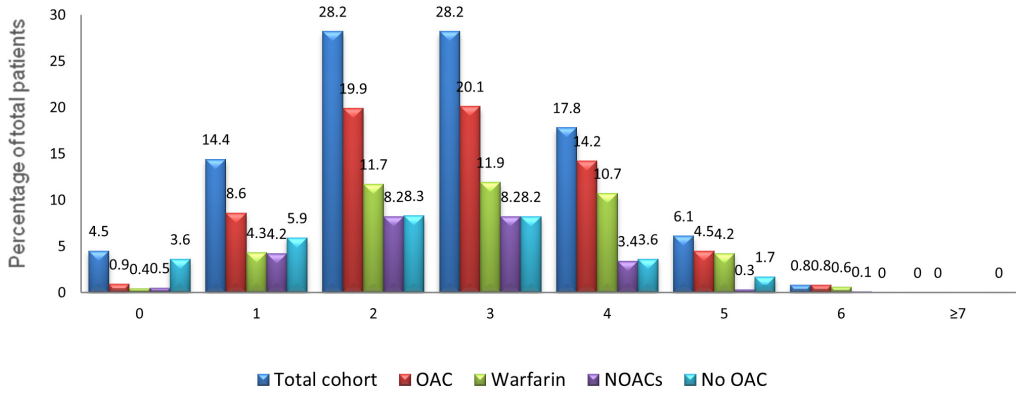


Figure 3 Distribution of HAS-BLED score by choice of anticoagulation

Regarding anticoagulant and antiplatelet therapy received, of the total 783 patients, most (539 patients, 68.92%) were treated with OAC therapy, and of these, 344 (63.80%) received warfarin therapy while 195 (36.20%) received NOAC therapy. Of the 195 patients who received NOACs, dabigatran was the most prescribed NOAC with 86 patients (44.10% of those on NOAC therapy) while rivaroxaban was prescribed for 77 patients (39.50% of those on NOACs therapy). Apixaban was prescribed for 32 patients (16.40% of those on NOAC therapy). Edoxaban was not available at the hospital at the time of the study. Antiplatelets were used in 211 of the 783 patients (26.90% of the total patients). There were 99 patients (12.60% of 783 patients) who received a combination of antiplatelet and OAC. Overall, 132 patients (16.90% of 783 patients) did not receive any antiplatelet or anticoagulant therapy (table S1).

Regarding the appropriateness of the OAC therapy use according to indication, of the 783 patients, there were 701 NVAF patients with a CHA2DS2-VASC score ≥ 2 (including women with two additional risk factors). Of these, 492 patients (70.20%) received OAC therapy, while 209 patients (29.80%) did not receive it despite having a CHA_2DS_2-VASC score ≥ 2 although 98 of them received antiplatelet therapy (from other indications) instead of OAC therapy. There were 48 patients with a CHA_2DS_2-VASC score of 0 (including women without additional stroke risk factors). Of these, 16 patients (33.30% of 48 patients) received OAC therapy that was not in accordance with the indication for OAC use (figure 2 and table S2).

Regarding the appropriate dose of warfarin, the mean TTR of target INR 2–3 in the warfarin group was 45.33 (± 30.71). Only one third of patients on warfarin treatment (112, 32.60% of 344 patients) had an optimized TTR level of more than 65%, and 57.30% of the 344 patients had a TTR less than 50% (figure S1).

Regarding the appropriate dose of NOACs, among the 195 patients who were on NOAC therapy, 98 patients (50.30%) received appropriate doses of NOACs, while 97 patients (49.70%) did not. Of these, 80 patients (82.40%) received less than the appropriate dose, while 14 patients (14.40%) received higher than appropriate dose. Three patients (3.20%) received NOACs despite not meeting the criteria for use (figure S2 and table S3).

The overall incidence rate of ischemic stroke or SE in the total study population during the follow-up period was 1.47/100 person-years. The incidence rates of stroke/SE in the warfarin, NOACs, and no anticoagulant groups were 1.83, 1.28, and 1.20 per 100 person-years, respectively. No significant difference in the incidence rate of ischemic stroke or SE was observed between different treatment groups, except for the warfarin group and NOACS group at 1 year with a hazard ratio (HR) of 7.49 (95% CI: 1.33–42.13,

p = 0.0172) (table S4, S5). In the warfarin group, 11 of 13 patients with ischemic stroke or SE that occurred at 1 year had a TTR lower than 65%. No statistically significant difference of incidence rate of ischemic stroke or SE was observed in patients receiving the appropriate dose, compared with inappropriate dose of NOACs therapy and within the warfarin group (table 2).

Bleeding occurred in 72 (18.80%) of 382 patients. The overall incidence rate of bleeding in the study patients during the follow-up period was 1.76/100 person-years. The incidence rates of bleeding in the warfarin, NOACs, and no anticoagulant groups were 2.81, 1.79, and 0.56 per 100 person-years, respectively. During the entire study period, bleeding occurred in the warfarin group more often than in the NOACs group but this was not statistically different (HR 1.54, 95% CI: 0.81–2.94, p = 0.18). In addition, at the 1-year and 5-year follow-up, the patients on warfarin had a higher incidence of bleeding than patients on NOACs with HR 6.42; 95% CI:1.58–56.29; p = 0.002 and HR 1.89; 95% CI: 0.96–4.06.29; p = 0.05 respectively (table S5). Among the patients who received warfarin, bleeding events occurred less often in those with an appropriate TTR but with no statistical difference (HR 0.77, 95% CI 0.43–1.38, p = 0.39). Among the patients who received NOAC therapy, bleeding events occurred in those with appropriate dose less often than in those with an inappropriate dose of NOACs therapy but with no statistical difference (HR 0.48, 95% CI: 0.15–1.61, p = 0.26) (table 2).

The overall incidence rate of cardiovascular death in the study patients during the follow-up period was 0.66/100 person-years. The incidence rates of cardiovascular death in the warfarin, NOACs, and no anticoagulant groups were 0.72, 0.31, and 0.70 per 100 person-years, respectively. There was no difference of incidence rate of cardiovascular death between the warfarin, NOACs and No OAC group. However, in patients in the warfarin group, there were fewer cardiovascular deaths in patients with a TTR ≥ 65% than in those with an inappropriate TTR. This was statistically significant (HR 0.14, 95% CI: 0.02–0.79, p = 0.02). For NOACs patients, no statistically significant differences in the incidence rate of cardiovascular death was observed between patients on an appropriate dose and those on an inappropriate dose of NOACs.

Table 2 The incidence of efficacy and safety outcomes in NVAF patients

	Stroke or SE	Bleeding	Cardiovascular death	All-cause death
Warfarin (n = 344)	No. of events/ Incidence rate*	No. of events/ Incidence rate*	No. of events/ Incidence rate*	No. of events/ Incidence rate*
Appropriate TTR ≥ 65	9/1.33	16/2.43	1/0.15	6/0.94
Inappropriate TTR < 65	26/2.13	38/3.13	13/1.06	31/2.64
Hazard ratio of IR (appropriate/inappropriate TTR)	0.62 (0.29-1.32), 0.22	0.77 (0.43-1.38), 0.39	0.14 (0.02-0.79), 0.02	0.36 (0.12-0.87), 0.01
NOAC (n = 195)				
Appropriate dose	3/1.03	4/1.20	1/0.30	6/0.80
Inappropriate dose	6/1.79	7/2.49	1/0.34	12/2.29
Hazard ratio of IR (appropriate/inappropriate dose)	0.57 (0.15-2.25), 0.45	0.48 (0.15-1.61), 0.26	0.87 (0.54-13.77), 0.93	0.44 (0.13-1.25), 0.10
No OAC (n = 244)	19/1.20	9/0.56	11/0.70	29/2.14

Abbreviations: IR, incidence rate; n, number; NOAC, novel oral anticoagulant; NVAF, nonvalvular atrial fibrillation; SE, systemic embolism; TTR, time in therapeutic range
*Incidence rate in 100-person year

The overall incidence rate of all-cause death in total patients was 1.97/100 person-years. The incidence rates of all-cause death in the warfarin, NOACs, and nonanticoagulated groups were 2.00, 1.69, and 2.14 per 100 person-years, respectively. In the warfarin group, there were fewer all-cause deaths in patients with an appropriate TTR, < 65%, than in those with an inappropriate TTR. This was a statistically significant difference (HR 0.23, 95% CI: 0.08–0.68, p = 0.003). For NOAC patients, no statistically significant difference in incidence rates of all-cause death was observed between patients on an appropriate dose and those on an inappropriate dose of NOACs (table 2).

According to the univariate analysis performed to determine factors for predicting the ischemic and hemorrhagic outcomes, previous ischemic stroke, peripheral arterial disease, $CHA_2DS_2VASc \geq 2$, HAS-BLED ≥ 3 and labile INR were the predictive factors for ischemic stroke outcome. After the multivariate analysis, diabetes and a history of stroke/TIA were the statistically significant independent predictive factors for ischemic stroke or SE outcome. For the bleeding outcome, an age of more than 65, previous ischemic stroke, $CHA_2DS_2VASc \geq 2$, HAS-BLED ≥ 3, CrCl < 30 and labile INR were the predictive factors. However, after the multivariate analysis, there was no significant correlation between the above factors and the bleeding outcome. A post-hoc analysis comparing the efficacy and safety outcome between the NOACs and warfarin group, stratified by various predictive factors, showed no statistically significant differences in the incidence rate of ischemic stroke/SE or bleeding outcome between the two groups (table 3).

Table 3 Factors that influenced the risk of stroke/SE and bleeding in patients with nonvalvular atrial fibrillation

	Stroke/SE					Any Bleeding				
	Univariate		Multivariate		Hazard ratio NOAC vs Warfarin, P- value	Univariate		Multivariate		Hazard ratio NOAC vs Warfarin, P-value
	OR (95% CI)	P-value	OR (95% CI)	P-value		OR (95% CI)	P-value	OR (95% CI)	P-value	
Age > 65	1.48 (0.73-2.98)	0.33			0.71 (0.33-1.54), 0.81	2.87 (1.29-6.38)	0.007	1.42 (0.50-4.03)	0.51	0.65 (0.30-1.26), 0.19
Female Sex	1.09 (0.62-1.89)	0.79			0.83 (0.25-2.27), 0.74	1.11 (0.68-1.81)	0.71	0.81 (0.43-1.53)		
Diabetes	1.36 (0.79-2.34)	0.31			0.39 (0.09-1.58), 0.22	0.93 (0.55-1.58)	0.90	0.92 (0.46-1.84)		
Hypertension	1.60 (0.86-2.97)	0.15			0.99 (0.41-2.19), 1.01	1.01 (0.60-1.69)	1.00	0.47 (0.20-1.07)		
Previous stroke	3.32 (1.95-5.67)	0.00	1.89 (1.19-3.02)	0.007	0.51 (0.13-1.49), 0.20	2.00 (1.22-3.29)	0.008	1.16 (0.79-1.69)	0.45	0.84 (0.29-2.49), 0.53
CAD	1.37 (0.77-2.42)	0.28			1.07 (0.28-4.12), 0.59	1.30 (0.77-2.20)	0.33	1.12 (0.53-2.38)		0.73 (0.24-2.22), 0.73
PAD	4.7 (1.21-18.22)	0.05	2.06 (0.18-23.83)	0.56	1.97 (0.03-154.43), 0.67	3.82 (0.99-14.73)	0.07	4.1 (0.59-28.5)		
Liver disease	1.52 (0.34-6.79)	0.64			0	1.24 (0.28-5.51)	0.68	0.47 (0.05-4.89)		
CHA_2DS_2 VASc ≥ 2	10.47 (1.44-76.39)	0.002	1.62 (0.31-8.54)	0.57	0.74 (0.31-1.56), 0.42	2.98 (1.06-8.34)	0.03	1.98 (0.37-10.72)	0.43	0.57 (0.29-1.12), 0.26
HAS-BLED score ≥ 3	2.20 (1.24-3.90)	0.007	1.38 (0.35-5.36)	0.65	0.68 (0.20-1.76), 0.40	2.74 (1.57-4.66)	0.000	1.97 (0.64-6.04)	0.24	0.94 (0.45-1.93), 0.18
CrC < 30	1.59 (0.89-2.86)	0.14			0.30 (0.04-2.05), 0.32	1.93 (1.51-3.25)	0.02	1.87 (0.89-3.95)	0.09	0.70 (0.21-2.37), 0.91
Labile INR	1.98 (1.15-3.39)	0.016	1.57 (0.14-17.41)	0.72	-	2.42 (1.48-3.97)	0.001	0.45 (0.10-1.95)	0.29	-
TTR < 65%	1.89 (0.80-4.51)	0.17			-	1.14 (0.6-2.15)	0.75	1.78 (0.39-8.02)	0.45	-
Antiplatelet use	1.28 (0.73-2.26)	0.45			1.56 (0.35-5.6), 0.46	0.82 (0.47-1.45)	0.58	0.63 (0.26-1.54)		

Abbreviation: AF, atrial fibrillation; CAD, coronary artery disease; CrC, creatinine clearance; INR, international normalized ratio; NOAC, novel oral anticoagulant; OR, odd ratio; PAD, peripheral arterial disease; SE, systemic embolism; TIA, transient ischemic attack; TTR, therapeutic range

DISCUSSION

The results of this study showed that the majority of NVAF patients received OAC therapy with most receiving OAC with the appropriate indication. Regarding choice of anticoagulants used, warfarin was more commonly prescribed at Vajira Hospital (63.90%) than NOACs (26.10%). The Thailand registry reported the use of warfarin in 90.90% of the country's registered patients and NOACs use in 9.10% of patients[8]. This implies more NOAC than warfarin use in NVAF patients in recent years. Moreover, the results from this study showed that most patients on warfarin therapy did not achieve the target TTR level of > 65%. In contrast to warfarin, the prescription of NOACs was low at our center due to its high price with prescription limited to subspecialists. We found that only half of NOACs patients received appropriate doses. Physicians tended to prescribe below the recommended dose of NOACs more than they prescribed higher than the recommended dose. Regarding the efficacy and safety outcome results, there was no statistical difference in the incidence of ischemic stroke or SE among different OACs and between appropriate and inappropriate doses of OAC. This may result from the low target TTR in this study population, inappropriate doses of NOACs in some patients and inadequate power in this study to differentiate the efficacy outcomes. However, among warfarin group, patients with inappropriate TTR of < 65% were associated with a significantly increased incidence of both cardiovascular and non-cardiovascular deaths, compared to those with a TTR ≥ 65%. Our study has a consistent result with a previous Thailand registry reported poor TTR control is associated with adverse clinical outcome, including ischemic events, major bleeding, intracranial hemorrhage and death[15]. The underlying reasons for the higher incidence rate of cardiovascular and all-cause death in inappropriate TTR patients could be from warfarin level fluctuations leading to bleeding and subsequently to discontinuation of the drug, which then leads to the adverse events. Regard to NOACs dosing and clinical outcome, out findings

This study has several limitations. Due to its retrospective design, the subjects were not fully randomized. Because of the study's limited duration, its sample size is relatively small compared with prior studies. Some data were missing due to the retrospective nature of the study and the electronic medical records. Furthermore, due to inadequate power regarding the ischemic and bleeding outcomes, we are unable to determine differences in the efficacy and safety outcomes between different patient groups. A larger prospective cohort or randomized study with a longer follow-up period are suggested for further study.

CONCLUSION

Most NVAF patients received OACs with appropriate indications. Warfarin was used for patients with NVAF more than NOACs were. About half of the patients received an inappropriate dose of OACs (both warfarin and NOACs). A suboptimal TTR, < 65%, was associated with significantly higher cardiovascular and all-cause mortality than an optimal TTR.

CONFLICT OF INTEREST

The authors have no financial interest in any of the products mentioned in this article.

ACKNOWLEDGEMENT

None

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to restrictions.

REFERENCES

1. Kiatchoosakun S, Pachirat O, Chirawatkul A, Choprapawan C, Tatsanavivat P. Prevalence of cardiac arrhythmias in Thai community. J Med Assoc Thai 1999;82(7):727-33.

2. Phrommintikul A, Detnuntarat P, Prasertwitayakij N, Wongcharoen W. Prevalence of atrial fibrillation in Thai elderly. J Geriatr Cardiol 2016;13(3):270-3.
3. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol 1998;82(8A):2N-9N.
4. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association task force on practice guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014;64(21):e1-76.
5. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, et al. The 2018 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J 2018;39(16):1330-93.
6. Huisman MV, Rothman KJ, Paquette M, Teutsch C, Diener HC, Dubner SJ, et al. Antithrombotic treatment patterns in patients with newly diagnosed nonvalvular atrial fibrillation: the GLORIA-AF registry, phase II. Am J Med 2015;128(12):1306-13.e1.
7. Krittayaphong R, Winijkul A, Methavigul K, Wongtheptien W, Wongvipaporn C, Wisaratapong T, et al. Risk profiles and pattern of antithrombotic use in patients with non-valvular atrial fibrillation in Thailand: a multicenter study. BMC Cardiovasc Disord 2018;18(1):174.
8. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37(38):2893-962.
9. Lip GYH, Banerjee A, Boriani G, Chiang CE, Fargo R, Freedman B, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. Chest 2018;154(5):1121-201.
10. Urbonas G, Valius L, Šakalytė G, Petniūnas K, Petniūnienė I. The quality of anticoagulation therapy among warfarin-treated patients with atrial fibrillation in a primary health care setting. Medicina (Kaunas) 2019;55(1):15.
11. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993;69(3):236-9.
12. Molteni M, Polo Friz H, Primitz L, Marano G, Boracchi P, Cimminiello C. The definition of valvular and non-valvular atrial fibrillation: results of a physicians' survey. Europace 2014;16(12):1720-5.
13. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123(23):2736-47.
14. Yu AY, Malo S, Wilton S, Parkash R, Svenson LW, Hill MD. Anticoagulation and population risk of stroke and death in incident atrial fibrillation: a population-based cohort study. CMAJ Open 2016;4(1):E1-6.
15. Krittayaphong R, Chantrarat T, Rojjarekampai R, Jittham P, Sairat P, Lip GYH. Poor time in therapeutic range control is associated with adverse clinical outcomes in patients with non-valvular atrial fibrillation: a report from the Nationwide COOL-AF Registry. J Clin Med 2020;9(6):1698.