Original Article

Rate and Reasons for the Use of Oral Anticoagulants in Patients with Non-Valvular Atrial Fibrillation and a CHA_2DS_2-VASc Score of 0 in Thailand: The COOL-AF Registry

Komsing Methavigul, MD[1], Arjbordin Winijkul, MD[2], Sirin Apiyasawat, MD[3], Ratikorn Methavigul, MD[1], Thanasak Patmuk, MD[4], Pattraporn Srirattana, MD[5], Praprut Thanakitcharu, MD[6], Kulyot Jongpiputvanich, MD[7], Sumon Tangsuntornwiwat, MD[8], Ahthit Yindeengam, BSc[2], Rungroj Krittayaphong, MD[2], for the COOL-AF Investigators

[1] Department of Cardiology, Central Chest Institute of Thailand, Nonthaburi, Thailand

[2] Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

[3] Division of Cardiology, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[4] Ratchaburi Hospital, Ratchaburi, Thailand

[5] Charoen Krung Pracha Rak Hospital, Bangkok, Thailand

[6] Sapphasitthiprasong Hospital, Ubon Ratchathani, Thailand

[7] Faculty of Medicine, Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand

[8] Udon Thani Hospital, Udon Thani, Thailand

Background: A substantial number of patients with non-valvular atrial fibrillation (NVAF) and a CHA_2DS_2-VASc score of 0 (i.e., low-risk group) use oral anticoagulants (OACs).

Objective: To investigate the rate and reasons for OAC use in Thai patients with NVAF and having a CHA_2DS_2-VASc score of 0.

Materials and Methods: A nationwide observational multicenter registry of patients with NVAF was set up in Thailand. The patients' demographic and clinical data were recorded on a case record form and then entered into a web-based data collection and management system.

Results: One hundred seventy-six patients with NVAF and a CHA_2DS_2-VASc score of 0 were included. The average age was 53.9±8.2 years old, and all patients were male. Forty-six (26.1%) of the patients received OACs. NVAF patients receiving OACs had a longer duration of AF, more persistent and permanent AF, and mild left ventricular dysfunction. NVAF patients not receiving OACs were significantly more likely to be taking antiplatelet drugs. The reasons for using OACs in patients with a CHA_2DS_2-VASc score of 0 included thrombus in the left atrial appendage, post-AF ablation, planned cardioversion, hypertrophic cardiomyopathy, hyperthyroidism, and endomyocardial fibrosis. Physicians or patients preferred OAC use despite having a CHA_2DS_2-VASc score of 0 in 24 patients (52.2%). The use of OACs did not decrease clinical events, but it increased the bleeding risk.

Conclusion: Among Thai NVAF patients with CHA_2DS_2-VASc score of 0, OAC was used in 26.1%. Some stroke risk factors were identified but were not included in the current risk scoring tool.

Keywords: Oral anticoagulant, Outcomes, Non-valvular atrial fibrillation, CHA_2DS_2-VASc score, Thailand

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Correspondence to:

Krittayaphong R.

Division of Cardiology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wang Lang Road, Bangkoknoi, Bangkok 10700, Thailand.

Phone: +66-2-4196104, **Fax**: +66-2-4127412

Email: rungroj.kri@mahidol.ac.th

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Non-valvular atrial fibrillation (NVAF) is the most common cardiac arrhythmia in clinical practice. Its prevalence is 1% to 2% in Caucasian populations and approximately 1% in Asian populations, with an increased prevalence in advanced age[1]. The most serious complication of atrial fibrillation (AF) is ischemic stroke. The CHA_2DS_2-VASc score is currently commonly used to predict stroke in this patient population[2-4]. Current clinical practice guidelines recommend oral anticoagulant (OAC) therapy in patients with NVAF that have additional risk factors for stroke[2-5]. Warfarin is the most widely

used OAC in Thailand. Although meta-analysis has shown adjusted-dose warfarin to be associated with a 64% to 68% risk reduction in stroke, it can also cause major bleeding or intracerebral hemorrhage (ICH)[6,7]. Non-vitamin K antagonist oral anticoagulants (NOACs) are now alternatively prescribed in NVAF patients due to having a more favorable safety profile[8-11]. The original study of the CHA_2DS_2-VASc score in the Euro Heart Survey showed that patients with a CHA_2DS_2-VASc score of 0 had a very low (0.0%) risk of ischemic stroke[12]. Validation of the CHA_2DS_2-VASc score in a Swedish AF cohort of 182,678 patients revealed a stroke risk of 0.2% per year[13], which is considered a very low risk. However, stroke risk data in an Asian population demonstrated that patients with a CHA_2DS_2-VASc score of 0 had a stroke risk of 1.15% per year, which is not considered a very low risk[14]. Warfarin is a vitamin-K antagonist (VKA) that is associated with rates of major bleeding and ICH of 1.3% to 3.5% and 0.3% to 1.3% per year, respectively[15]. Previous studies suggested that Asian populations tend to have a greater risk of OAC-related bleeding than Caucasian populations[16-18]. It has been suggested that the threshold of benefit from the use of VKAs is when the ischemic stroke risk is greater than 1.7% per year; however, the threshold of benefit for NOACs is when the ischemic stroke risk is greater than 0.9% per year[19].

Although a previous study showed that approximately 40% of NVAF patients with a CHA_2DS_2-VASc score of 0 were receiving OACs[20], it is possible that some patients with a CHA_2DS_2-VASc score of 0 may be on OACs for reasons other than those associated with the CHA_2DS_2-VASc scoring-related criteria. Accordingly, the primary aim of the present study was to investigate the reasons for OAC use and the treatment outcomes in Thai patients with NVAF and have a CHA_2DS_2-VASc score of 0. The secondary objective of the present study was to explore the outcomes among patients with a CHA_2DS_2-VASc score of 0 comparing between those with and without OAC use.

Materials and Methods

Study population

An observational multicenter prospective registry of patients with NVAF, the COhort of antithrombotic use and Optimal INR Level in patients with non-valvular Atrial Fibrillation in Thailand (COOL-AF Thailand) registry (CREC004/57), was established in Thailand. Patients with NVAF were consecutively recruited. The protocol for the present study was approved by the Institutional Review Board (IRB) of the Thailand Ministry of Public Health and the IRBs of each participating hospital. The study protocol had been previously described[21]. All patients provided written informed consents prior to participation in the present study. Patients aged at least 18 years old diagnosed with AF by standard twelve-lead electrocardiogram (ECG) or ambulatory monitoring were eligible for inclusion. Patients having one or more of the following were excluded, 1) previous ischemic stroke within three months, 2) thrombocytopenia (less than 100,000/mm^3), myeloproliferative disorders, hyperviscosity syndrome, or antiphospholipid syndrome, 3) prosthetic valve or valve repair, 4) rheumatic valve disease or significant valve disease, 5) AF from transient reversible cause (e.g., during respiratory tract infection or bronchospasm), 6) ongoing participation in a clinical trial, 7) life expectancy less than three years, 8) pregnancy, 9) inability to attend scheduled follow-up appointments or who miss follow-ups, 10) refusal to participate in the study, or 11) current hospitalization or a previous history of hospitalization within one month before study enrollment.

Data collection

Baseline demographic and clinical data were collected and recorded. Data relating to cardiovascular events, blood pressure, heart rate, and medications were collected at each follow-up visit. Data from each patient were written on a case record form and then entered into a web-based data collection and management system. The following data were collected, 1) demographic information, 2) history of stroke and bleeding, 3) type and duration of AF, 4) component parameters of the CHA_2DS_2-VASc score for stroke risk, and HAS-BLED score for risk of bleeding, 5) history of medical and cardiovascular disease, 6) antithrombotic medication, 7) reason for not using warfarin in those not taking warfarin, 8) concomitant medications, 9) standard twelve-lead ECG, and 10) current international normalized ratio (INR). The components of CHA_2DS_2-VASc were scored and recorded, as follows, C=congestive heart failure (HF) (1 point), H=hypertension (1 point), A=age ≥75 years old (2 points), D=diabetes (1 point), S=stroke (2 points), V=vascular disease (1 point), A=age 65 to 74 years old (1 point), and Sc=female gender (1 point). The HAS-BLED score was also recorded, as follows, uncontrolled Hypertension (1 point), Abnormal renal or liver function (1 point), history of Stroke (1 point), history

of Bleeding (1 point), Labile INR (1 point), Elderly (age above 65 years old) (1 point), and Drugs or alcohol (1 point). The score for HF was counted when the patient had clinical HF or left ventricular systolic dysfunction (LVSD) (left ventricular ejection fraction [LVEF] of less than 40%)[12,22]. Protocols were established and followed by the data management team and statisticians to ensure the integrity and quality of the data before the final analysis. Random site monitoring was also regularly performed. Approximately 70% of sites were audited. Data were collected between 2014 and 2017 study period. The sample size of the main study was calculated based on the purpose of optimal INR, which was the primary aim of the present study.

Patients were followed-up every six months until 36 months. Data relating to cardiovascular events, vital signs, and medications were recorded. Data from each patient were written on a case record form and transferred into a web-based system. The following clinical events during follow-up were recorded from the medical records, death, ischemic stroke, and major and minor bleeding. All events were evaluated and verified by the adjudication committee. Ischemic stroke was defined as a sudden onset of focal neurologic deficit lasting more than 24 hours. Major bleeding was defined using the International Society of Thrombosis and Hemostasis (ISTH) criteria.

If a patient with a CHA_2DS_2-VASc score of 0 was receiving anticoagulants, the appropriate principal investigator was asked to describe the reason(s) why the anticoagulant was prescribed. Investigators were given the answer choice of either 'physician preference' or 'patient preference' in patients who were prescribed OACs that had no specific indication for OACs.

Statistical analysis

Demographic and clinical data were interpreted using descriptive statistics. Continuous data were presented as mean ± standard deviation, and categorical data were shown as number and percentage. Continuous data were compared by the Student's t-test for unpaired data. Categorical data were compared by the chi-square test or Fisher's exact test. Variables with p-value less than 0.2 from initial analysis were selected for logistic regression analysis. Univariate and multivariate logistic regression analyses with backward stepwise were performed to identify factors significantly associated with anticoagulant use in patients with a CHA_2DS_2-VASc score of 0. A p-value of less than 0.05 was considered statistically significant. Patients with lost to follow-up were excluded from analysis. All statistical analyses were performed using IBM SPSS Statistics, version 20 (IBM Corp., Armonk, NY, USA).

Results

After a review and verification process of the available data relative to CHA_2DS_2-VASc score-related information, the use or non-use of OACs, and the reasons for using OACs, 176 cases from 22 hospitals that had a CHA_2DS_2-VASc score of 0 were included in the analysis. The CHA_2DS_2-VASc score was found to be misclassified in 21 cases. The average age of patients was 53.9±8.2 years old, and all patients were male. AF was paroxysmal in 82 patients (46.6%), persistent in 34 (19.3%), and permanent in 60 (34.1%). The HAS-BLED score was 0, 1, 2, and 3 in 100 (56.8%), 63 (35.8%), 12 (6.8%), and one (0.6%) patients, respectively.

OACs were prescribed in 46 patients (26.1%). Among the patients who were on OACs, VKA, a direct thrombin inhibitor, and factor Xa inhibitor were prescribed in 33 (71.7%), eight (17.4%), and five (10.9%) patients, respectively. Baseline characteristics of the patients who received or did not receive OACs are shown in Table 1. Univariate and multivariate analyses of the factors associated with the prescription of OACs in patients with a CHA_2DS_2-VASc score of 0 are shown in Table 2. Patients who received OACs had a longer duration of AF, more persistent and permanent types of AF, and were more likely to have mild left ventricular dysfunction. Patients that did not receive OACs were prescribed more antiplatelet drugs.

The reasons for OAC use are shown in Figure 1. The reasons for using OACs in patients with a CHA_2DS_2-VASc score of 0 included thrombus in the left atrial appendage (LAA), post-AF ablation, planned cardioversion, hypertrophic cardiomyopathy (HCM), hyperthyroidism, and endomyocardial fibrosis (EMF). Physician or patient preference for OAC use despite a CHA_2DS_2-VASc score of 0 was found in 52.2% of patients using OACs. Two patients were referred from other hospitals after being prescribed OACs without having stroke risk factors identified from their CHA_2DS_2-VASc scores. Mildly impaired left ventricular systolic function with LVEF of less than 50% (but more than 40%) was the reason for OAC use in those five patients (10.9%), which two of these patients were considered HF with preserved ejection fraction (HFpEF), and the other three patients were patients recovered from LVSD.

Table 1. Baseline characteristics of patients with NVAF and a CHA_2DS_2-VASc score of 0 comparing between those taking and not taking OACs

Characteristics	Total (n=176) n (%)	OACs (n=46) n (%)	No OACs (n=130) n (%)	p-value
Age (years); mean±SD	53.9±8.2	54.2±7.4	53.7±8.5	0.720
Sex: male	176 (100)	46 (100)	130 (100)	-
Time after diagnosis of AF (years); mean±SD	2.9±3.7	4.4±4.4	2.3±3.3	0.004*
Type of AF				0.001*
Paroxysmal	82 (46.6)	11 (23.9)	71 (54.6)	
Persistent	34 (19.3)	16 (34.8)	18 (13.8)	
Permanent	60 (34.1)	19 (41.3)	41 (31.5)	
History of heart failure	0 (0.0)	0 (0.0)	0 (0.0)	
History of CAD	0 (0.0)	0 (0.0)	0 (0.0)	
Device	7 (4.0)	2 (4.3)	5 (3.8)	1.000
History of bleeding	5 (2.8)	2(4.3)	3 (2.3)	0.607
LVEF (%); mean±SD	63.3±8.3	59.4±8.3	64.7±7.9	<0.001*
<50	10 (5.7)	6 (13.0)	4 (3.1)	0.048*
Antiplatelet use	48 (27.3)	1 (2.2)	47 (36.2)	<0.001*
Aspirin	46 (26.1)	0 (0.0)	46 (35.4)	<0.001*
$P2Y_{12}$ inhibitors	3 (1.7)	1 (2.2)	2 (1.5)	1.000
HAS-BLED score				0.143
0	100 (56.8)	29 (63.0)	71 (54.6)	
1	63 (35.8)	12 (26.1)	51 (39.2)	
2	12 (6.8)	4 (8.7)	8 (6.2)	
3	1 (0.6)	1 (2.2)	0 (0.0)	

NVAF=non-valvular atrial fibrillation; OACs=oral anticoagulants; AF=atrial fibrillation; CAD=coronary artery disease; LVEF=left ventricular ejection fraction; SD=standard deviation

* A p<0.05 indicates statistical significance

Table 2. Univariate and multivariate analysis for factors independently associated with the use of anticoagulants in patients with a CHA_2DS_2-VASc score of 0

Factors	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Time after diagnosis of AF ≥3 years	3.20 (1.60 to 6.41)	0.001*	4.63 (1.94 to 11.00)	0.001*
Type of AF				
Paroxysmal	-	-	-	-
Persistent	5.74 (2.27 to 14.48)	<0.001*	6.46 (2.15 to 19.38)	0.001*
Permanent	3.0 (1.30 to 6.90)	0.010*	2.86 (1.09 to 7.53)	0.033*
Devices	1.14 (0.21 to 6.07)	0.881		
History of bleeding	1.92 (0.31 to 11.90)	0.481		
LVEF <50%	4.73 (1.27 to 17.59)	0.021*	8.43 (1.46 to 48.63)	0.017*
Taking antiplatelet	0.04 (0.005 to 0.294)	0.002*	0.02 (0.003 to 0.189)	<0.001*
HAS-BLED score ≥2	1.86 (0.58 to 6.00)	0.299		

OR=odds ratio; CI=confidence interval; AF=atrial fibrillation; LVEF=left ventricular ejection fraction

* A p<0.05 indicates statistical significance

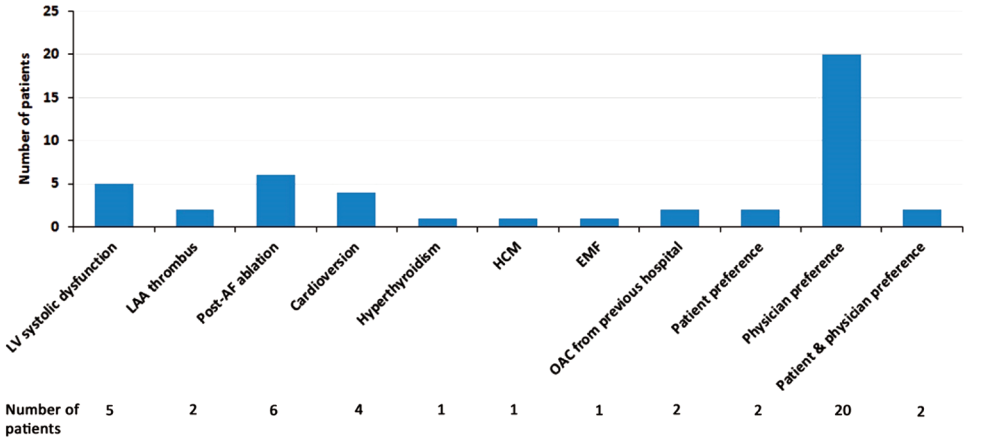

Figure 1. Reasons for oral anticoagulant use in AF patients with a CHA_2DS_2-VASc score of 0.

LV=left ventricular; LAA=left atrial appendage; AF=atrial fibrillation; HCM=hypertrophic cardiomyopathy; EMF=endomyocardial fibrosis

Table 3. Clinical events comparing between patients who did and who did not receive OACs (comprising 173 patients who had available follow-up data)

Events	Total (n=173) n (%)	OACs (n=46) n (%)	No OACs (n=127) n (%)	p-value
Death	2 (1.2)	0 (0.0)	2 (1.6)	0.392
Ischemic stroke	2 (1.2)	1 (2.2)	1 (0.8)	0.451
Major bleeding	1 (0.6)	1 (2.2)	0 (0.0)	0.266
Minor bleeding	3 (1.7)	2 (4.3)	1 (0.8)	0.113
All bleeding	4 (2.3)	3 (6.5)	1 (0.8)	0.027*
Death or ischemic stroke or bleeding	7 (4.0)	3 (6.5)	4 (3.1)	0.320

OACs=oral anticoagulants

* A p<0.05 indicates statistical significance

Follow-up data were available in 173 patients (98.3%). Clinical events in patients with and without OAC use are shown in Table 3. The average follow-up duration was 21.7±10.6 months. The ischemic stroke rate in patients with a CHA_2DS_2-VASc score of 0 in the present study was 1.2%, which was low, accounting for 0.66% per year, and no significant difference was observed between patients taking and not taking OACs. However, the bleeding events were significantly higher in patients with OAC use than in those without OAC use (6.5% versus 0.8% per year, p=0.027).

Discussion

The present study was a nationwide multicenter registry revealed the prevalence of NVAF patients with a CHA_2DS_2-VASc score of 0 between 2014 and 2017 in Thailand. The authors found a prevalence of OAC use of 26.1% among 176 patients with a CHA_2DS_2-VASc score of 0. Factors that predict the use of OACs were AF longer than three years, persistent or permanent types of AF, and mild left ventricular dysfunction. The use of antiplatelets was significantly associated with the non-use of OACs. The reasons for using OAC was physician or patient preference in 52.2% of the patients. Other reasons were thrombus in LAA, post-AF ablation, planned cardioversion, HCM, hyperthyroidism, or EMF.

Data specific to OAC use in Thai NVAF patients with a CHA_2DS_2-VASc score of 0 are scarce. Current clinical practice guidelines recommend no antithrombotic therapy in these patients due to a very low risk of stroke[1,2,23]. However, some stroke risks that are not included in the CHA_2DS_2-VASc score were identified in the present study, including HCM, EMF, atrial stunning resulting from cardioversion, and post-AF ablation. Additionally, some patients may have thrombus in the LAA despite having a CHA_2DS_2-

VASc score of 0. These stroke risks should also be included in the stroke risk stratification algorithm. Certain risk factors, such as impaired renal function, proteinuria, and cardiac biomarkers, which are not included in the CHA_2DS_2-VASc score, have been studied, and the results showed that they can be used to predict ischemic stroke in addition to the $CHADS_2$ or CHA_2DS_2-VASc score[24-27].

Just over half (52.2%) of the patients were prescribed OACs due to physician or patient preference. In addition, one patient with hyperthyroidism and two patients referred from other hospitals were prescribed OACs. Physician or patient preference was due to several possible reasons. First, there were some stroke risks that are not included in the CHA_2DS_2-VASc score, as mentioned prior. Second, a previous Asian study demonstrated that an age of 50 to 64 years old can increase the stroke risk in Chinese patients[28,29]. Some experts suggested modification of the CHA_2DS_2-VASc score by lowering the age threshold for the risk of stroke, especially in Asian populations[29]. In that study, the average age of NVAF patients with a CHA_2DS_2-VASc score of 0 prescribed OACs was 53.7±8.5 years old. This age group may also be at an increased risk of stroke among Thai patients despite no clinical outcome trial yet being conducted in Thai NVAF patients.

It is debatable whether HF in the CHA_2DS_2-VASc score should include those without functional limitation (New York Heart Association or NYHA functional class 1). The authors excluded 19 patients who had a history of HF with functional class 1 from the present analysis. The original $CHADS_2$ score was developed before the CHA_2DS_2-VASc score[30]. The definition of HF in the $CHADS_2$ score is recent HF within 100 days[31]. Additionally, in the Stroke Prevention in Atrial Fibrillation (SPAF) study, investigators recommended the term 'clinical HF' as a stroke risk in patients with AF[22]. The original version of the CHA_2DS_2-VASc score used clinical HF or LVEF of less than 40%. Recent NOAC trials used a different definition of HF as a component in the CHA_2DS_2-VASc score, but they tended to use symptomatic HF or LVSD (LVEF of less than 40%)[32]. It is, therefore, unclear whether patients with HF and NYHA functional class 1 should or should not be included in the CHA_2DS_2-VASc score. The CHA_2DS_2-VASc score is currently widely used in routine clinical practice. Moderate to severe LVSD was found to increase stroke risk, so LVSD (defined as LVEF of less than 40%) was included in the CHA_2DS_2-VASc score[12,33].

Multivariate analysis of the factors associated with anticoagulant use in patients with a CHA_2DS_2-VASc score of 0 revealed a prolonged duration of AF, the types of AF, or LVSD as predictors of anticoagulant use. That same analysis showed antiplatelet use to be a predictor of no anticoagulant use. Previous clinical trials demonstrated that persistent AF is associated with a higher risk of thromboembolism when compared with paroxysmal AF[34-36]. Moreover, persistent or permanent AF was found to be associated with a prolonged duration when compared with paroxysmal AF. In the present study, physicians preferred to prescribe OACs in those with a prolonged duration of AF, especially in patients with a history of AF longer than three years, and in patients with persistent and/or permanent AF. Although there is a scarcity of data specific to the prevention of thromboembolism in patients with mild LVSD (LVEF between less than 40% to 50%), some physicians preferred to prescribe OACs in these patients because of the thrombotic risk in the left ventricle. The fact that antiplatelet use was found to be a predictor of no anticoagulant use was predictable and due to the fact that combined antiplatelet and OAC use is associated with increased bleeding events when compared with OAC or antiplatelet use alone[37]. Patients taking antiplatelet medications may have other indications, such as peripheral artery disease or primary prevention of CAD. Some physicians may use antiplatelets for AF stroke prevention.

Follow-up data from patients with a CHA_2DS_2-VASc score of 0 showed comparable mortality, HF, and ischemic stroke incidence when comparing between those taking and not taking OACs. However, there were more bleeding events among those taking OACs. The annual rate of thromboembolic events was 0.66% among patients with a CHA_2DS_2-VASc score of 0 in the present study, which indicated a very low thromboembolic event rate. More bleeding events in those taking OACs may be due to the fact that most patients taking OACs were prescribed warfarin, while those not taking OACs were mostly prescribed antiplatelets, especially aspirin. Previous trials found that warfarin caused bleeding events more than aspirin[37,38]. These findings demonstrated no difference between warfarin and no OAC use relative to the incidence of ischemic stroke, however, OAC use increased the number of bleeding events. However, few patients were prescribed NOACs. Future studies should be conducted to investigate the efficacy and safety profile of NOACs in these patients, especially in those with LVSD or HF because of the

fewer bleeding events[8,10,11].

Limitation

The present study had some mentionable limitations to note. First, the study enrolled mainly NVAF patients from university hospitals or large general hospitals, which limited the generalizability of the results of the patients in and from other care settings. Second, the sample size of patients with a CHA_2DS_2-VASc score of 0 was relatively small, and this may have limited the power of the present study to identify all the significant differences and associations between groups. Moreover, the number of clinical events that occurred during the follow-up periods may have been too small to compare the benefit of OACs in this group. The strengths of the present study included its prospective design, the fact that the data were collected from across Thailand by board-certified cardiologists, and that is was managed and audited by a centralized data management team.

Conclusion

Among Thai NVAF with CHA_2DS_2-VASc score of 0, OAC was used in 26.1%. Some stroke risk factors were identified that are not included in the current risk scoring tool. Further study should be conducted to identify a better stroke risk scoring system that includes factors other than CHA_2DS_2-VASc score.

What is already known on this topic?

OACs are not indicated in patients with NVAF with a CHA_2DS_2-VASc score of 0 due to the very low risk of ischemic stroke. OACs increase the risk of bleeding. However, several patients with a CHA_2DS_2-VASc score of 0 receive OACs.

What this study adds?

The proportion of NVAF patients with a CHA_2DS_2-VASc score of 0 who receive OACs was 26.1%. The reasons for using OACs in patients with a CHA_2DS_2-VASc score of 0 included thrombus in the LAA, post-AF ablation, planned cardioversion, HCM, hyperthyroidism, and EMF, as well as physicians or patients' preference. The ischemic stroke rate is low. OAC use increases the bleeding risk.

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Investigators list

Buddhachinaraj Hospital: Tomorn Thongsri, MD; Central Chest Institute of Thailand: Kriengkrai Hengrussamee, MD; Chiangrai Prachanukroh Hospital: Wattana Wongtheptien, MD; Chonburi Hospital: Pornchai Ngamjanyaporn, MD; Faculty of Medicine, Chiang Mai University: Arintaya Phrommintikul, MD; Faculty of Medicine, Chulalongkorn University: Smonporn Boonyaratavej, MD; Faculty of Medicine, Naresuan University: Pongpun Jittham, MD; Faculty of Medicine, Prince of Songkla University: Treechada Wisaratapong, MD; Faculty of Medicine Ramathibodi Hospital, Mahidol University: Sirin Apiyasawat, MD; Faculty of Medicine Siriraj Hospital, Mahidol University: Arjbordin Winijkul, MD, Rungroj Krittayaphong, MD; Faculty of Medicine, Thammasat University (Rangsit Campus): Roj Rojjarekampai, MD; Golden Jubilee Medical Center: Somchai Dutsadeevettakul, MD; Srinakarind Hospital, Faculty of Medicine, Khon Kaen University: Chaiyasith Wongvipaporn, MD; Lampang Hospital: Thanita Boonyapiphat, MD; Maharat Nakorn Ratchasima Hospital: Weerapan Wiwatworapan, MD; Nakornping Hospital: Khanchai Siriwattana, MD; Phramongkutklao College of Medicine: Thoranis Chantrarat, MD; Police General Hospital: Kasem Ratanasumawong, MD; Prapokklao Hospital (Chanthaburi): Wiwat Kanjanarutjawiwat, MD; Ratchaburi Hospital: Thanasak Patmuk, MD; Sapphasitthiprasong Hospital: Praprut Thanakitcharu, MD; Surat Thani Hospital: Suchart Arunsiriwattana, MD

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Conflicts of interest

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