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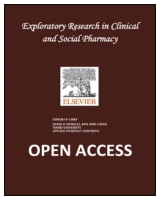

Appropriateness of direct oral anticoagulant dosing in patients with atrial fibrillation at a tertiary care hospital in Thailand

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ABSTRACT

Background: Appropriate dosing of direct oral anticoagulants (DOACs) has been associated with clinical efficacy and safety. Several studies have shown that DOAC dosing are often inconsistent with guideline recommendations. Little is known about this issue in Thailand. This study aimed to evaluate the appropriateness of DOAC dosing in Thai hospitalized patients with atrial fibrillation (AF).

Method: This was a retrospective descriptive study conducted on hospitalized patients at Rajavithi Hospital, a tertiary care hospital in Thailand. Inpatients diagnosed with AF and treated with DOACs between February 2021 and February 2023 were enrolled in the study. The appropriate dosing of DOACs was assessed according to the recommendation of the 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation (EHRA). Descriptive statistics were used to analyze the data; median (interquartile range) for continuous variables, and numbers and percentages for categorical variables.

Results: A total of 120 patients with AF were evaluated for dosing. The patients received rivaroxaban in 47 cases (39.2 %), apixaban in 32 cases (26.7 %), edoxaban in 31 cases (25.8 %), and dabigatran in 10 cases (8.3 %). Most of the patients were elderly, with a median age of 77.5 (68–84) years. Females were predominant (57.5 %). Our findings indicate that the prevalence of appropriate dosing of DOACs was 63.3 %. However, approximately one-third of patients received inappropriate dosing, with 24 (20.0 %) being overdosed, and 20 (16.7 %) being underdosed. The highest overdosing and underdosing rates were seen in dabigatran (90.0 %) and apixaban (21.9 %), respectively.

Conclusion: Inappropriate dosing of DOACs according to the 2021 EHRA recommendations was high in 36.7 %, with overdosing mostly occurring in 20.0 %. The high number of inappropriate dosing highlights the need for implementation of optimal strategies to select the appropriate dose of DOACs in Thai hospitalized patients with AF.

1. Introduction

Stroke is a major health burden and the leading cause of death and long-term disability in Thailand, especially ischemic stroke accounting for approximately 80 % of cases.[1] In Thailand, cardioembolism was the common cause of ischemic strokes varied from 9 % to 29 %.[2,3] Atrial fibrillation (AF) remains the most common cause of cardioembolic stroke, especially in elderly. The prevalence of AF in Thai population has been reported to be 0.4 % for those aged ≥30 years, 1.9 % for those aged ≥65 years, and 3.46 % among hypertensive patients.[4–6] Anticoagulant therapy is widely used in AF to prevent stroke and systemic embolism. Nowadays, DOACs are recommended for patients with nonvalvular atrial fibrillation (NVAF) over warfarin by national guidelines in developed countries due to better clinical outcomes.[7,8] Additionally, the rapid onset, less frequent laboratory monitoring, fewer drug-drug interactions, and drug-food interactions of DOACs can lead to improved patient compliance.[9–11] However, inappropriate prescribing of DOACs has been reported in 8.4 % to 28.9 % of hospitalized patients.[12]

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Table 1
Dose recommendation and adjustment criteria for direct oral anticoagulants used in the study.

	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Standard dose	20 mg once daily	5 mg twice daily	60 mg once daily	150 mg twice daily
Reduced dose	15 mg once daily	2.5 mg twice daily	30 mg once daily	110 mg twice daily
Dose reduction criteria		≥2 of the following		
Renal function	CrCl 15 to 49 mL/min	Serum creatinine ≥1.5 mg/dL	CrCl 15 to 49 mL/min	CrCl 30 to 50 mL/min
Age		≥ 80 years		≥ 80 years
Body weight		≤ 60 kg	≤ 60 kg	
Concomitant drug use	Dronedarone Erythromycin Itraconazole Ketoconazole	Itraconazole Ketoconazole	Dronedarone Erythromycin Itraconazole Ketoconazole	Verapamil
Contraindication	CrCl <15 mL/min	CrCl <15 mL/min	CrCl <15 mL/min	CrCl <30 mL/min

In developing countries, including Thailand, the use of DOACs is still limited since they have not been listed in the National List of Essential Medicines (NLEM) and are not considered cost-effective for the Thai AF population.[13] However, DOACs are increasingly used for stroke prevention in Thai AF patients. In a real-world retrospective study of Thai AF patients, DOACs were associated with effectiveness and safety advantages compared to warfarin.[14,15] Despite the advantages of DOACs, the criteria for dose reduction are more complex based on certain patient characteristics, such as age, weight, and renal function. Recent studies have reported common inappropriate dosing of DOACs, and deviations from standard dosing or lack of dose reduction being associated with a higher risk of poor outcomes.[16–20] There have been a few studies evaluating DOAC dosing in Thailand. The rate of inappropriate dosing ranged from 22 % to 50 %.[21–23] Nevertheless, there are no study focusing on AF inpatients. Therefore, the objective of this study was to assess the appropriate dosing of DOACs in Thai hospitalized patients with AF according to the 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation (EHRA).

2. Methods

2.1. Study design and participants

This study was a retrospective descriptive study conducted at Rajavithi Hospital, a tertiary care hospital in the central region of Thailand. DOACs were prescribed from specialist such as cardiologist and neurologist. Adult inpatients (age ≥ 18 years) who were diagnosed AF and received either edoxaban, apixaban, dabigatran or rivaroxaban between February 2021 and February 2023 were included. We excluded patients with deep vein thrombosis (DVT) and pulmonary embolism (PE). Incomplete medical records were also excluded. To identify patients, we screened for the first recorded prescription of a DOAC in hospitalized patients and then identified those with an atrial fibrillation/flutter diagnosis by International Statistical Classification of Diseases (ICD) 10.

Participants were categorized into appropriate dosing and inappropriate dosing (overdose or underdose). Inappropriate dosing of DOACs was defined as a deviation of the recommended dose from the 2021 EHRA. Overdose and underdose were defined as the administration of a higher or lower dose than the recommended dose of DOACs. Overdose included prescribing a standard dose of a DOAC despite the patient meeting the criteria for dose reduction, while underdose included prescribing a reduced dose despite the patient not meeting the criteria for dose reduction. The recommended dose criteria are presented in Table 1.

2.2. Data collection

Data were collected from the electronic medical record (EMR), including baseline characteristics, comorbidities, CHA2DS2-VASc score, HAS-BLED score, and serum creatinine levels around the time of DOACs initiation, used to calculate creatinine clearance (CrCl) using Cockcroft–Gault (C-G) equation. In addition, concomitant medications that are strong inhibitors of the P-glycoprotein (P-gp) and/or cytochrome P450 3A4 (CYP3A4) pathways were collected as a recommendation for dose reduction criteria (Table 1). Three pharmacy students, knowledgeable in the disease and DOAC therapy, were involved in data collection. These students received training that emphasized the study objectives and the operation of the data collection tool. Training sessions detailed the variables to be collected, operational definitions, and

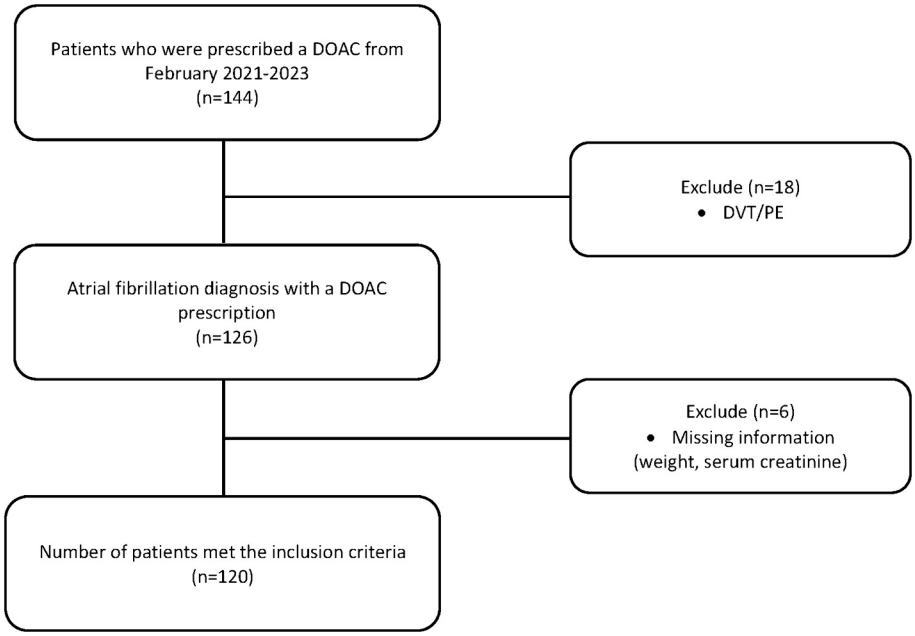

Fig. 1. The flow diagram of study participant.

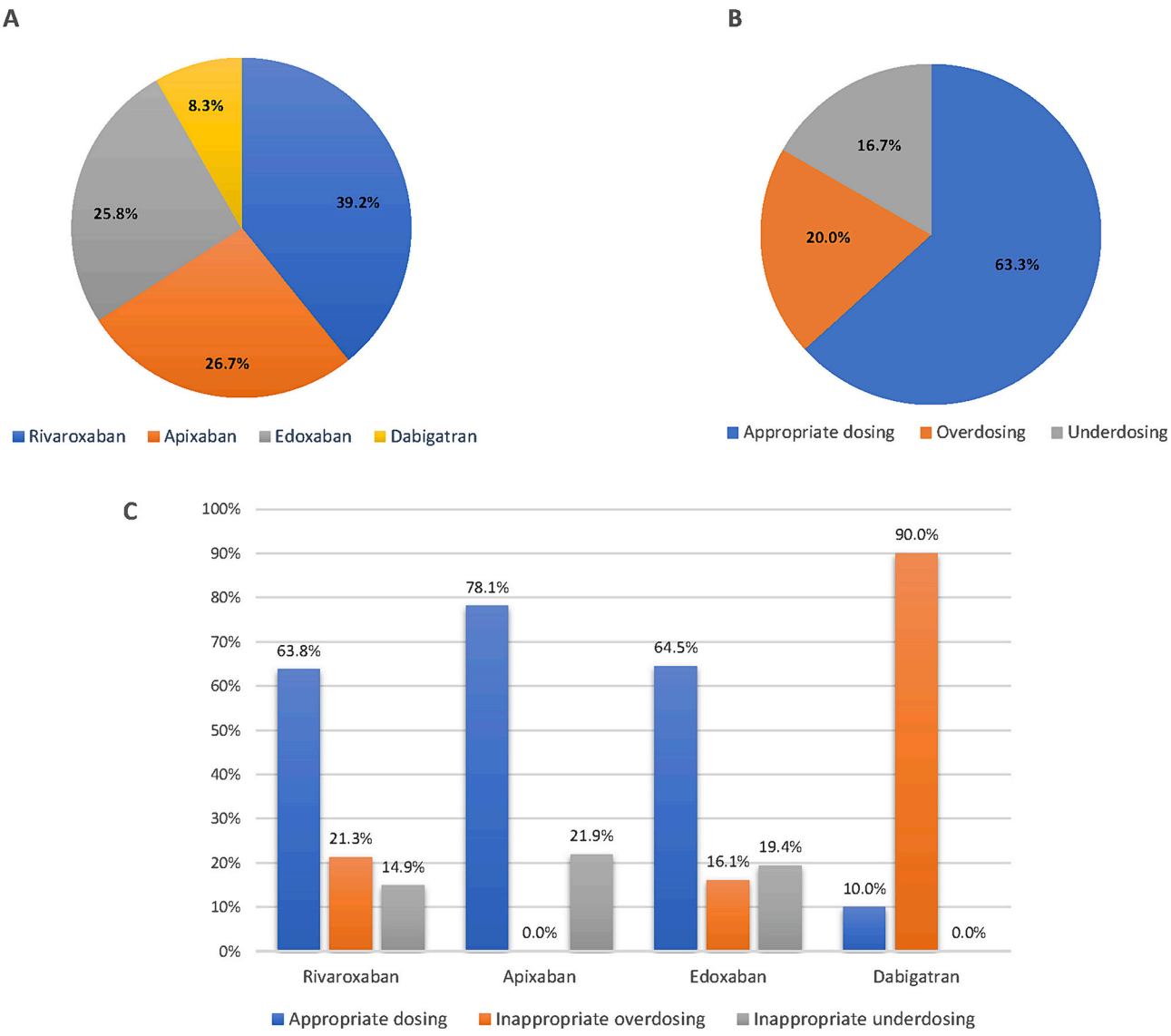

Fig. 2. (A) The proportion of DOAC prescriptions; (B) The proportion of appropriate dosing vs inappropriate dosing of DOACs; (C) The proportion of appropriate dosing, inappropriate underdosing and overdosing for each DOAC.

criteria for data extraction based on guideline referenced in the methodology. A standardized Excel form with dropdown lists for various data points was employed to minimize entry errors and ensure uniformity. Discrepancies in data collection were managed through a review process where each form underwent cross-checking by another data collector or the primary data analyst. Data analysis was conducted by a single analyst responsible for all data cleaning and analytical tasks. This centralized approach to data handling ensured consistency throughout the data cleaning and statistical analysis phases, reinforcing the accuracy and reliability of the results.

2.3. Recruitment and sample size

The study aimed to provide a descriptive analysis of the appropriateness of DOAC dosing in inpatients over a defined period at a single tertiary care center in Thailand. A comprehensive sampling approach was adopted, including all consecutive inpatient cases treated with DOACs from February 2021 to February 2023. The use of consecutive sampling from the hospital database ensured an accurate representation of the inpatient population receiving DOAC therapy. Given the descriptive nature of the research, there was no comparator group. The total number of patients during the study period who were administered DOACs constituted the sample base. This sample of 120 patients, extracted from the hospital database, includes all cases managed by the hospital during the study period. This dataset allows for a detailed description of the DOAC usage patterns and the appropriateness of dosing among the inpatient population.

2.4. Data analysis

We analyzed the data using descriptive statistics. Categorical variables were presented as frequencies and percentages, while continuous variables were characterized by median (interquartile range). The Chi-square test and Fisher's exact test were used to compare categorical variables. A significance level of 0.05 was used. Statistical analysis was performed using SPSS software version 21.

2.5. Ethics approval

The study was approved by Human Research Ethics Committee of Rajavithi Hospital (Research code:66065).

Table 2
Baseline characteristics of patients receiving DOACs.

Characteristics	Overall (n = 120)	Rivaroxaban (n = 47)	Apixaban (n = 32)	Edoxaban (n = 31)	Dabigatran (n = 10)
Sex					
Male	51 (42.5)	20 (42.6)	13 (40.6)	12 (38.7)	6 (60.0)
Female	69 (57.5)	27 (57.4)	19 (59.4)	19 (61.3)	4 (40.0)
Age in year, median (IQR)	77.5 (68–84)				
≤64	20 (16.7)	12 (25.5)	1 (3.1)	6 (19.4)	1 (10.0)
65–69	12 (10.0)	5 (10.6)	1 (3.1)	5 (16.1)	1 (10.0)
70–74	17 (14.1)	11 (23.5)	3 (9.4)	1 (3.2)	2 (20.0)
75–79	20 (16.7)	4 (8.5)	9 (28.1)	5 (16.1)	2 (20.0)
≥80	51 (42.5)	15 (31.9)	18 (56.3)	14 (45.2)	4 (40.0)
Weight in kg, median (IQR)	60 (50–71)				
≤60	63 (52.5)	26 (55.3)	19 (59.4)	12 (38.7)	6 (60.0)
>60	57 (47.5)	21 (44.7)	13 (40.6)	19 (61.3)	4 (40.0)
CrCl in mL/min, median (IQR)	51.5 (35–75)				
≥50	63 (52.5)	26 (55.3)	12 (37.5)	21 (67.7)	4 (40.0)
30–49	38 (31.7)	15 (32.0)	11 (34.4)	7 (22.6)	5 (50.0)
15–29	16 (13.3)	5 (10.6)	7 (21.9)	3 (9.7)	1 (10.0)
≤14	3 (2.5)	1 (2.1)	2 (6.2)	0 (0)	0 (0)
Comorbidities					
Hypertension	65 (54.2)	27 (57.4)	16 (50.0)	15 (12.5)	7 (70.0)
Heart failure	13 (10.8)	7 (14.9)	4 (12.5)	1 (3.2)	1 (10.0)
Dyslipidemia	32 (26.7)	13 (27.6)	9 (28.1)	7 (22.6)	3 (30.0)
Diabetes mellitus	32 (26.7)	13 (27.6)	7 (21.9)	6 (19.4)	6 (60.0)
Cerebrovascular disease	6 (5.0)	1 (2.1)	1 (3.1)	3 (9.7)	1 (10.0)
CHA_2DS_2-VASc score, median (IQR)	3 (2–4)				
0–1	16 (13.3)	6 (12.8)	2 (6.3)	6 (19.4)	2 (20.0)
2–3	54 (45.0)	26 (55.3)	14 (43.7)	12 (38.7)	2 (20.0)
≥4	50 (41.7)	15 (31.9)	16 (50.0)	13 (41.9)	6 (60.0)
HAS-BLED score, median (IQR)	1 (1–2)				
0–2	114 (95.0)	46 (97.9)	29 (90.6)	31 (100)	8 (80.0)
≥3	6 (5.0)	1 (2.1)	3 (9.4)	0 (0)	2 (20.0)

3. Results

During the study period, 144 patients were screened for eligibility (Fig. 1). A total of 120 patients were evaluated, including 47 (39.2 %), 32 (26.7 %), 31 (25.8 %), and 10 (8.3 %) of patients receiving rivaroxaban, apixaban, edoxaban, and dabigatran, respectively (Fig. 2A). The majority of patients were elderly (≥ 65 years), with the median age of 77.5 (68–84) years. Females were predominant (57.5 %). The median weight was 60 (50–71) kg. The median CrCl was 51.5 (35–75) mL/min. The median scores on CHA2DS2-VASc and HAS-BLED were 3 and 1, respectively. The most common comorbidity was hypertension (54.2 %), followed by dyslipidemia (26.7 %) and diabetes mellitus (26.7 %). Baseline characteristics of patients receiving DOACs are presented in Table 2.

Our findings indicate that the appropriate dosing of DOACs was 63.3 %. However, approximately one-third of patients received inappropriate dosing, with 24 (20.0 %) being overdosed, and 20 (16.7 %) being underdosed (Fig. 2B). Baseline characteristics of patients were compared between those with appropriate dosing and those with inappropriate dosing are shown in Table 3. The highest overdosing and underdosing rates were seen in dabigatran (90.0 %) and apixaban (21.9 %), respectively. The results of evaluated DOAC dosing by each drug are shown in Fig. 2C. Additionally, DOACs use were contraindicated in four patients due to low CrCl (less than 15 mL/min for rivaroxaban and apixaban, and less than 30 mL/min for dabigatran). These patients were deemed to be overdosed. No drug interactions meeting the criteria for dose reduction were found in the study.

4. Discussion

This is the first study to evaluate DOAC dosing that deviated from the 2021 EHRA guideline in Thai hospitalized patients. Our study found that most of prescribed DOACs were appropriate doses (63 %). However, inappropriate dosing occurred in a high rate at nearly one-third of patients; overdosing (20.0 %) was more common than underdosing (16.7 %). This consistent with a study in Thailand, Wattanaruengchai et al. reported that inappropriate dosing of DOACs was found in approximately 33 % of cases, with underdosing being the most common (22 %), which was associated with an increase in adverse clinical outcomes.[21] While the study of Sureeyathanaphat et al., reported the higher rate of inappropriate dosing of DOACs (50 %) among Thai AF patients who were followed up at the outpatient clinic. Of these patients, 82.4 % received less than the appropriate dose.[22] Another study in Thailand, DOACs used in outpatient settings were inappropriately dosed in 22 %, mostly underdosing (10 %).[23] Several previous studies have reported that inappropriate dosing of DOACs is common, with underdosing occurring more frequently than overdosing.[19–26] The prevalence of inappropriate dosing varies among studies, which may be due to differences in criteria for evaluation, such as US Food and Drug Administration labeling, manufacturer labeling recommendations, summaries of

Table 3
Comparison of baseline characteristics of patients between the appropriate dosing and the inappropriate dosing of DOACs.

Characteristics	Appropriate dosing ($n = 76$)	Inappropriate dosing ($n = 44$)	*P* value
Sex			0.91
Male	32 (42.1)	19 (43.2)	
Female	44 (57.9)	25 (56.8)	
Age in year			0.26
≤64	15 (19.7)	5 (11.4)	
65–69	9 (11.8)	3 (6.8)	
70–74	12 (15.9)	5 (11.4)	
75–79	9 (11.8)	11 (25.0)	
≥80	31 (40.8)	20 (45.4)	
Weight in kg			0.24
≤60	33(43.4)	24(54.5)	
>60	43(56.6)	20(45.4)	
CrCl in mL/min			0.28
≥50	39 (51.3)	24 (54.5)	
30–49	23 (30.3)	15 (34.1)	
15–29	12 (15.8)	4 (9.1)	
≤14	2 (2.6)	1 (2.3)	
Comorbidities			
Hypertension	37 (48.7)	28 (63.6)	0.11
Heart failure	7 (9.2)	6 (13.6)	0.45
Dyslipidemia	15 (19.7)	17 (38.6)	0.02
Diabetes mellitus	20 (26.3)	12 (27.3)	0.34
Cerebrovascular disease	4 (5.2)	2 (4.5)	0.66
CHA2DS2-VASc score			0.31
0–1	12 (15.8)	4 (9.1)	
2–3	36 (47.4)	18 (40.9)	
≥4	28 (36.8)	22 (50.0)	
HAS-BLED score			0.66
0–2	72 (94.8)	42 (95.5)	
≥3	4 (5.2)	2 (4.5)	

product characteristics, and the EHRA guideline. Moreover, characteristics of population can influence on prescribing practices.

Potentially inappropriate dosing of DOACs was associated with older age, history of renal failure, and higher CHA2DS2-VASc score.[26] In our study, the majority of patients were older (≥ 65 years), had lower HAS-BLED scores (0–1), and higher CHA2DS2-VASc score (≥ 2), indicating an increased risk of stroke. Additionally, the elderly and low renal function may be lead to inappropriate overdosing of prescribers. From real-world data of the ORBIT-AF2 registry, patients receiving overdosing of DOACs were older, more likely to be women, and had a higher CHA2DS2-VASc score.[27] In addition, physician's perception to risk of stroke or bleeding may influence their selection of DOAC dose. Physicians may tailor the doses of DOACs based on the specific underlying risks of individual patients.

All patients classified as overdosing due to receiving the standard dose despite meeting the criteria for a reduced dose. Likewise, underdosing in patients who did not require a reduced dose. Some patients received a reduce dose that was inconsistent with the dose reduction criteria. Another important issue was that almost all patients receiving dabigatran (9/10) were considered overdose because they were prescribed 150 mg twice daily, even though 110 mg twice daily should be considered based on their characteristics. Dabigatran 150 mg, 110 mg, and 75 mg are available in Thailand. In the study setting, dabigatran 150 mg is available as non-essential drug in which a patient need to be affordable. The cost is likely one important barrier. However, dabigatran 110 mg is available in this setting for prescribing individual case requesting to use medicine. It can only be prescribed in case of approving from the hospital director. The simple accessibility of dabigatran 110 mg in a patient who meet the dose reduction criteria remains challenge on the hospital policy. When excluding patients receiving dabigatran, approximately 32 % of patients had inappropriate dosing, with underdosing became more common than overdosing. Similar to the findings of Lavoie K et al., 61.3 % of dabigatran were prescribed 150 mg despite a lower dose was indicated.[28] Previous reports suggest that Asian races are at an increased risk of bleeding from DOACs compared to other races.[29–32] Therefore, our patients may be at a higher risk of bleeding from overdosing. In addition, prescription of non-recommended doses of DOACs is also associated with an increased rate of mortality as cardiovascular complications.[33] Interestingly, clinical pharmacist's interventions can reduce inappropriate DOAC prescribing.[19,34,35] We recommend implementation of DOAC stewardship program in this setting to promote the optimal use during hospitalization. In addition, the impact of clinical pharmacist's intervention on drug related problems of DOACs and clinical outcomes should be studied prospectively.

5. Limitation

This study has some limitations as follows. First, this study is a retrospective descriptive study in which analysis using data collected from medical record. A prospective study could provide more comprehensive data to clarify the results. Second, this study population was enrolled from inpatients of a single center. The results might not be generalized to others. Lastly, this study did not explore factors associated with inappropriate dosing of DOACs. Further research is needed to determine the causes of inappropriate prescribing and its impact on clinical outcomes.

6. Conclusion

The prevalence of inappropriate dosing of DOACs according to 2021 EHRA recommendations was high in 36.7 %, with overdosing was commonly occurred in 20.0 %. These results could provide further insights for clinicians to tailor DOAC dosing. Additionally, clinical pharmacist as part of a multidisciplinary approach in DOAC stewardship program could contribute to improve prescribing. Optimal strategies for selecting the appropriate dose of DOACs in Thai hospitalized patients with AF need to be implemented.

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CRediT authorship contribution statement

Chayanat Pongsathabordee: Writing – original draft, Visualization, Supervision. **Piyachat Saringkarn:** Supervision, Project administration, Methodology, Conceptualization. **Kanjana Ratanapornsompong:** Supervision, Resources, Methodology, Conceptualization. **Ratiya Rungruang:** Supervision, Resources, Methodology. **Saranporn Srithonrat:** Investigation, Formal analysis. **Pimlada Tangkaotong:** Investigation, Formal analysis. **Salintip Sena:** Investigation, Formal analysis. **Taniya Paiboonvong:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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