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A Retrospective Study on the Use of Direct Oral Anticoagulants in Atrial Fibrillation Patients at Cardiac Outpatient Setting, Sarawak Heart Centre

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ABSTRACT

Introduction: Atrial fibrillation (AF) increases stroke risk up to five-fold, but anticoagulants have been shown to reduce that risk. Compliance with direct oral anticoagulants (DOAC) improved thromboembolic outcomes and was superior to warfarin in decreasing all-cause mortality. This study evaluated the compliance with the CHA_2DS_2VASc scoring system for DOAC prescribing, the pre-initiation, and post-initiation monitoring practices, and the pattern of use of DOAC in AF patients undergoing follow-ups at the Cardiac Clinic of Sarawak Heart Centre.

Methods: This retrospective study involved 55 eligible AF patients undergoing follow-ups at the Cardiac Clinic of Sarawak Heart Centre between 1st January 2020 and 30th June 2021.

Results: Based on the CHA_2DS_2VASc scoring system, most of the participants were indicated for DOAC as per guidelines, [male (n=26, 72.2%); female: (n=15, 78.9%)]. Before DOAC initiation, liver functions tests (n=32, 58.2%) were absent in most monitoring parameters, which was then followed by the absence of renal function tests (n=11, 20.0%) and coagulation profiles (n=22, 40.0%). For routine post-initiation monitoring, 15 patients (27.3%) did not have their renal profile repeated within one year of post-DOAC initiation. In terms of the pattern of use, Dabigatran 150mg was more commonly initiated in patients below 80 years old (n=29, 59.2%) and those with a Creatine Clearance (CrCl) of 50 mL/min or higher (n=22, 64.7%). On

the other hand, Dabigatran 110mg was preferred for patients aged 80 years and above (n=4, 66.7%) and those with a CrCl ranging from 15 mL/min to 49 mL/min (n=5, 50.0%).

Conclusion: Prescribers adhered to the CHA_2DS_2VASc scoring system when initiating DOAC. Age and creatinine clearance were considered before the initiation of DOAC. Complete monitoring, including renal function tests, liver function tests, and coagulation profiles is crucial before and after initiating DOAC therapy to ensure effectiveness, safety, and appropriate selection of DOAC.

Keywords: Atrial fibrillation, direct oral anticoagulants

INTRODUCTION

Atrial fibrillation (AF) is one of the most common arrhythmias manifested by uncoordinated electrical activation of the atrium, resulting in ineffective atrial contraction (1). Ischemic stroke remains the major complication of AF (2). The risk of stroke in AF depends on various risk factors. The thromboembolic risk of AF can be quantified based on Congestive heart failure, Hypertension, Age, Diabetes, Stroke, Vascular disease and Sex category (CHA_2DS_2VASc) score (1). Anticoagulant is indicated for patients with CHA_2DS_2VASc scores of two and above among males, while three and above among females (3,4). On the other hand, uncontrolled Hypertension, Abnormal renal/ hepatic function, Stroke, Bleeding history, Labile International Normalised Ratio (INR), Elderly, and Drug/ excessive alcohol use (HAS-BLED) score has been used to assess bleeding risks. A HAS-BLED score of 3 or greater indicates regular clinical review and follow-ups, but it should not be a reason for discontinuing oral anticoagulant (3).

Oral anticoagulants available for thromboembolic prophylaxis are vitamin K antagonists or warfarin and direct oral anticoagulants (DOAC), such as Dabigatran, Rivaroxaban, and Apixaban (3). Warfarin has been the gold standard for anticoagulation in AF for many decades. However, DOAC have been proven to improve thromboembolism outcomes with lower all-cause mortality compared to warfarin (5). The safety and efficacy of DOAC are widely established and have been given class IA recommendations in European and American Guidelines for thromboembolic prophylaxis in AF (3,4).

In the era of DOAC use, clinicians face multiple challenges including the selection of appropriate agents, monitoring parameters, availability of reversal agents, and use in special populations, such as in geriatrics. Age and renal functions are the two main criteria taken into account during the initiation or continuation of DOAC (6). Other parameters such as haemoglobin levels and liver function are closely monitored to ensure the appropriate use of DOAC.

In Malaysia, DOAC checklists have been in been use in public healthcare facilities to ensure the rational and safe use of DOAC. The checklists includes complete medication history, laboratory parameters, and contraindications to anticoagulation. The checklist enables clinicians and pharmacists to evaluate the appropriateness of DOAC in thromboembolic prophylaxis. Baseline monitoring during pre-initiation of DOAC included clinical parameters

such as coagulation profiles, full blood counts, renal function tests and liver function tests. Thromboembolic and bleeding risks were assessed by CHA_2DS_2-VASc & HAS-BLED scores, respectively. On the other hand, post-initiation monitoring included repeated renal or liver function tests. Creatinine clearance (CrCl) monitoring of at least once or twice a year for patients with CrCl ≥ 50ml/min or every 6 months for patients with CrCl ≤ 50ml/min were encouraged by the Anticoagulation Medication Therapy Adherence Clinic (ACMTAC) protocol (7).

The Sarawak Heart Centre, a government cardiology referral centre in Sarawak, has the highest DOAC quota for use in the state. Hence, this study aimed to analyse the compliance with the CHA_2DS_2-VASc scoring system for DOAC prescribing for AF patients at Sarawak Heart Centre. Besides, we also evaluated the pre-initiation and post-initiation monitoring practice, and the pattern of use of DOAC.

METHODS

Study Type and Design

This was a retrospective, cross-sectional study that investigated the data extracted from the clinical case notes of non-valvular AF patients undergoing follow-ups in the Cardiac Clinic of Sarawak Heart Centre between 1st January 2020 and 30th June 2021. Data collection started on 1st July 2022 and data collection forms were used to collect and record the patients' demographic details, criteria of CHA_2DS_2VASc and HAS-BLED scores, renal function tests, liver function tests and coagulation profiles.

Study Population, Sampling and Sample Size

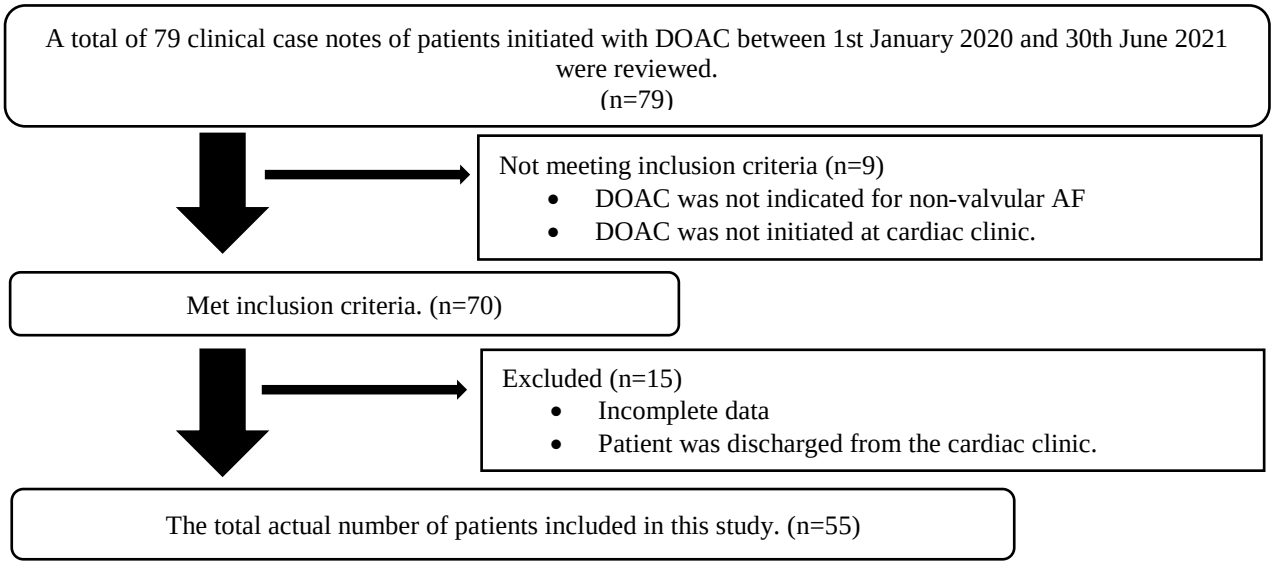
All non-valvular AF patients who were initiated with either one of the three DOAC (Dabigatran, Rivaroxaban, or Apixaban) between 1st January 2020 and 30th June 2021, and were under follow-ups at Cardiac Clinic of Sarawak Heart Centre were included in the study. Patients with valvular AF or bioprosthetic or mechanical heart valve, did not have their DOAC initiated at the cardiac clinic, or non-valvular AF patients who self-purchased their DOAC were excluded to ensure drug congruity in such cases. Study participants with incomplete data, such as a lack of laboratory profiles, indication information, default follow-up, or discharge from the cardiac clinic, were also excluded from the study.

Due to the limited targeted population, this study included all AF patients who fulfilled the inclusion criteria during study period.

Data Collection

Figure 1 summarises the data collection process. A total of 55 eligible patients were included in the study.

Figure 1: Summary of data collection process



Definition of Study Variables

The definitions of the variables used in this study is listed in Table 1.

Table 1: Definitions of variables

Variables	**Definition**
BMI Classification (8)	18.4 or lower (Underweight)
	18.5-24.9 (Normal)
	25-29.9 (Overweight)
	30.0 or greater (Obese)
CHA_2DS_2VASc Score (1)	Male more than or equal to 2: Appropriate (Class IA)
	Male less than 2: Inappropriate
	Female more than or equal to 3: Appropriate
	Female less than 3: Inappropriate

Table 1: *continued*

Variables	Definition
HAS-BLED Score (3)	0 indicates low risk, 1–2 indicates moderate risk ≥3 indicates high risk
Switching therapy	Switching from warfarin to DOAC therapy

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) version 26 was used for data analysis. Descriptive statistics were employed to analyse various aspects of the data, including patient demographic data, anticoagulant therapy status, and the choice of anticoagulant therapy. An independent t-test was utilised for normally distributed data to calculate the mean, while the Mann-Whitney test was employed for non-normally distributed data to calculate the median. Categorical data was analysed using the Pearson Chi-square test. A P-value of less than 0.05 was considered statistically significant.

Ethical Approval

The study protocol was registered in National Medical Research Register (NMRR), reviewed, and approved by the Malaysian Research Ethics Committee (MREC) (NMRR ID-22-01296-LFN). Researchers adhered to the principles of the Declaration of Helsinki and the Malaysian Good Clinical Practice Guidelines. All personal information collected was treated with full confidentiality.

RESULTS

Characteristics of Patients Initiated with DOAC (Dabigatran, Rivaroxaban, Apixaban)

A total of 55 non-valvular AF patients were involved in this study. All the patients were initiated with DOAC as thromboprophylaxis therapy. Most study participants were of Chinese ethnicity (n=23, 41.8%), had the mean age of 65.98 ± 11.82 years old. Most of the study participants had normal BMI (n=22, 40.0%), non-smokers (n=38, 69.1%), non-alcoholic drinkers (n=52, 94.5%), and were switched from another anticoagulant (n=30, 54.5%). Table 2 summarises these findings.

For the CHA_2DS_2VASc scoring, most study participants were male (65.5%), had no history of stroke (94.5%), vascular disease (81.8%) and congestive heart failure (69.1%), but were diagnosed with hypertension (69.1%), diabetes (70.9%), and aged above 65 years (60.0%).

Table 2: Demographic & clinical characteristics (n=55)

Item	Characteristics	n (%)	Mean (SD)
Ethnicity	Malay	19 (34.5)	
	Chinese	23 (41.8)	
	Bumiputera	12 (21.8)	
	Others	1 (1.8)	
Age (years)			65.98 (11.82)
BMI (kg/m^2)	Underweight	2(3.6)	
	Normal	22 (40.0)	
	Overweight	13 (23.6)	
	Obese	18 (32.7)	
Smoking	Yes	17 (30.9)	
	No	38 (69.1)	
Alcohol Intake	Yes	3(5.5)	
	No	52 (94.5)	
Status of DOAC	Switching	30 (54.5)	
	Naive	25 (45.5)	
Criteria of CHA_2DS_2VASc	Yes	17 (30.9)	
Congestive Heart Failure	No	38 (69.1)	
Criteria of CHA_2DS_2VASc	Yes	38 (69.1)	
Hypertension	No	17 (30.9)	
Criteria of CHA_2DS_2VASc	<65	22 (40.0)	
Age (years)	65-74	19 (34.5)	
	>75	14 (25.5)	
Criteria of CHA_2DS_2VASc	Yes	16 (29.1)	
Diabetes Mellitus	No	39 (70.9)	
Criteria of CHA_2DS_2VASc	Yes	3 (5.5)	
Stroke	No	52 (94.5)	

Table 2: *continued*

Item	Characteristis	n (%)	Mean (SD)
Criteria of CHA_2DS_2VASc	Yes	10 (18.2)	
Vascular disease	No	45 (81.8)	
Criteria of CHA_2DS_2VASc	Female	19 (34.5)	
Sex	Male	36 (65.5)	
Criteria of HAS-BLED	Yes	4 (7.3)	
Uncontrolled Hypertension	No	51 (92.7)	
Criteria of HAS-BLED			
Abnormal renal/Hepatic	Yes	2 (3.6)	
Function	No	53 (96.4)	
Criteria of HAS-BLED	Yes	3 (5.5)	
Stroke	No	52 (94.5)	
Criteria of HAS-BLED	Yes	5 (9.1)	
Bleeding History	No	50 (90.9)	
Criteria of HAS-BLED	Yes	2 (3.6)	
Labile INR	No	53 (96.4)	
Criteria of HAS-BLED	Yes	33 (60)	
Elderly	No	22 (40)	
Criteria of HAS-BLED			
Drug/Excessive Alcohol	Yes	5 (9.1)	
Use	No	50 (90.9)	

Table 3 tabulates the CHA_2DS_2VAC and HAS-BLED scores stratification between gender. Most of the male patients scored 2 whereas most females scored 3-4. Majority of the patients had moderate bleeding risk, 63.9% and 68.4% for the male and female groups respectively.

Table 3: CHA_2DS_2VAC and HAS-BLED scores between gender (n=55)

Score	Classification	Gender, n (%)	
		Male (n=36)	Female (n=19)
CHA_2DS_2VACS	1	10 (18.2)	1 (1.8)
Score	2	13 (23.6)	3 (5. 5)

Table 3: *continued*

Score	Classification	Gender, n (%)	
		Male (n=36)	Female (n=19)
CHA_2DS_2VACS Score	3-4	10 (18.2)	10 (18.2)
	5 and above	3 (5.5)	5 (9.1)
HAS-BLED Score	0	10 (27.8)	6 (31.6)
	1-2	23 (63.9)	13 (68.4)
	≥3	3 (8.3)	0 (0.0)

Compliance with the CHA_2DS_2VASc Scoring System for DOAC Prescribing

Based on CHA_2DS_2VASc score, DOAC were appropriately initiated in most of the study participants (male: n=26, 72.2%; female: n=15, 78.9%) (Table 4).

Table 4: CHA_2DS_2VAC assessment and initiation of DOAC (n=55)

Gender	n (%)		X^2 Statistic	P-value
	Appropriate	Inappropriate		
Male	26 (72.2)	10 (27. 8)	0.296	0.586[a]
Female	15 (78.9)	4 (21.1)		

[a] Pearson Chi Square

Pre- and post-initiation Monitoring Practices

Prior to the initiation of DOAC, most of the participants were monitored for renal function (n=44, 80.0%). However, less than half of the study participants (n=23, 41.8%) were monitored for liver function and only around three-fifth of the participants had their coagulation profiles monitored (n=33, 60.0%). The pre-initiation monitoring varies among patients and the parameters monitored also differ between patients.

On the other hand, after DOAC was initiated, renal function monitoring were done in only two-third of the participants (n=40, 72.7%). However, only around half of the participants were monitored for liver function (n=28, 50.9%). There were less patients monitored for coagulation profile post-initiation of DOAC (n=19, 34.5%). Table 5 summarises the observation.

Table 5: Pre- and post-initiation monitoring of DOAC

Monitoring Parameters	Characteristics	n (%)	
		Pre-initiation monitoring	Post-initiation monitoring
Renal Function	Yes	44(80.0)	40 (72.7)
	No	11 (20.0)	15 (27.3)
Liver Function	Yes	23 (41.8)	28 (50.9)
	No	32 (58.2)	27 (49.1)
Coagulation Profile	Yes	33 (60.0)	19 (34.5)
	No	22 (40.0)	36 (65.5)

The renal function of the participants were monitored by measuring their CrCl level. The median CrCl level of male was 63.40 mL/min, whereas for female was 61.50 mL/min. However, the findings showed that creatinine clearance level was not statistically significant among gender group.

The alanine transaminase (ALT) and aspartate aminotransferase (AST) level were parameters used to monitor the participants' liver function. There was a significant difference (P=0.010) in AST level, in which female participants had a higher mean AST level. Table 6 shows the renal and liver function parameters of the participants.

Table 6: Baseline clinical parameters among male and female

Monitoring Parameters	Characteristics	Mean (SD)		Median (IQR)		P-value
		Male	Female	Male	Female	
Renal Profile	CrCl (ml/min)			63.40 (38.50)	61.50 (38.50)	0.726[b]
Liver Profile	ALP (U/L)	79.22 (27.80)	53.67 (9.14)			0.501[c]
	ALT (U/L)	25.33 (14.47)	28.20 (9.32)			0.096[c]
	AST (U/L)	28.06 (9.32)	30.65 (18.10)			0.010[c]

[b] Mann-Whitney test

[c] Independent T-test

Pattern of Use of DOAC in AF Patients

Table 7 demonstrates that dabigatran 150mg (n=29, 59.2%) is the preferred choice of DOAC among study participants who were 79 years old and below. For those above the age of 80, dabigatran 110mg (n=4, 66.7%) was the first choice of DOAC. The results showed that the dose-reduction criteria for dabigatran with regards to the age of the participants were well adhered to.

Table 7: Age and choice of DOAC (n=55)

Choice of DOAC	**Age Group, n (%)**	
	79 and below (n=49)	**80 and above (n=6)**
Dabigatran 110mg	14 (28.6)	4 (66.7)
Dabigatran 150mg	29 (59.2)	0 (0.0)
Rivaroxaban 15mg	0 (0.00)	1 (16.7)
Rivaroxaban 20mg	3 (6.1)	0 (0.0)
Apixaban 2.5mg	2 (4.1)	1 (16.7)
Apixaban 5mg	1 (2.0)	0 (0.0)

Table 8 shows the choice of DOAC with regards to the CrCl level of the study participants. The CrCl level is divided into 2 groups; ie 15-49 ml/min and 50ml/min and above. The results show that dabigatran 150mg was mostly initiated among participants with CrCl level of 50 mL/min and above. It was also noted that one of the patients was initiated inappropriately on rivaroxaban as dose reduction was required when the CrCl level is between 15 mL/min and 49 mL/min.

Table 8: Pre-initiation creatinine clearance and choice of DOAC (n=44)

CrCl (ml/ min)	**n (%)**					
	Dabigatran 110mg	Dabigatran 150mg	Rivaroxaban 15mg	Rivaroxaban 20mg	Apixaban 2.5mg	Apixaban 5mg
15-49 (n=10)	5 (50.0)	2 (20.0)	1 (10.0)	1 (10.0)	1 (10.0)	0 (0.0)
>50 (n=34)	9 (26.5)	22 (64.7)	0 (0.0)	1 (2.9)	1 (2.9)	1 (2.9)

DISCUSSION

Compliance with the CHA_2DS_2VASc Scoring System for DOAC Prescribing

Based on the European Society of Cardiology (ESC) guideline, anticoagulant is indicated for patients with CHA_2DS_2VASc score of two and above in male, and three and above in female (Class IA recommendation) (1,4). Thus, most of the participants in this study were initiated on DOAC as recommended. If the CHA_2DS_2VASc score is 1 in male or 2 in female, DOAC should be considered as a Class IIa recommendation for stroke prevention. The initiation of DOAC in most participants with the aforementioned scores was also done as recommended. However, the initiation of DOAC on 1 female participant with a CHA_2DS_2VASc of 1 was done against the recommendation. In this case, the clinicians decided to initiated DOAC on the patient not as the CHA2DS2VASc score is not the definitive determinant for anticoagulation therapy and other clinical parameters have to be taken into account, too. For instance, clinical parameters such as transthoracic echocardiography (TTE) findings can also play a role in the decision-making process (9). Transesophageal echocardiography (TTE) offers a prompt, secure, and fairly extensive evaluation of cardiac structure and function, which aids in determining the underlying cause of atrial fibrillation (AF) and assessing the risk of complications (9).

Pre- and Post-initiation Monitoring Practices (Coagulation Profile)

There was a sharp decline in the number of patients who had their coagulation profiles monitored prior to (n=33, 60.0%) and after DOAC initiation (n=19, 34.5%). This can be explained by the fact that DOAC are promoted for their advantage over current anticoagulants by eliminating the need for routine laboratory monitoring for post initiation DOAC (10,11). Furhtermore, DOAC did not have significant impact on INR value as compared to warfarin (12). Ciurus et al agreed that coagulation monitoring is not essential, but patients should be followed up on a frequent basis to detect situations that may lead to changes in the predicted efficacy or safety (12).

In certain clinical scenarios, it has become increasingly important to determine the quantitative or qualitative presence of DOAC. These scenarios include such instances whereby patients are presented with major bleeding or require urgent surgery, where the need for a reversal or hemostatic agent arises, as well as cases involving extremes of body weight or failed therapy. To assess drug compliance, qualitative coagulation assays like activated partial thromboplastin time, thrombin time and prothrombin time are recommended as the initial tests. The choice of

coagulation assay depends on the DOAC being used. Additionally, although not clinically significant due to the lack of evidence for therapeutic range and correlation with clinical outcomes, quantitative measures such as anti-factor Xa levels (for apixaban and rivaroxaban) and ECT (for dabigatran) can also be employed to evaluate the anticoagulation effects. However, it should be noted that quantitative measurements are currently unavailable in this facility.

Pre-initiation Monitoring Practices (Renal and Liver Function)

In this study, most of the study participants underwent renal function monitoring before initiating DOAC. Guidelines recommended against initiating both dabigatran and rivaroxaban in non-valvular AF patients with a CrCl level below 30 mL/min, as this patient group was excluded from the trials and the efficacy in this population is still unknown (13,14). For example, the RE-LY trial, a large trial comparing the efficacy of dabigatran and warfarin, excluded patients with severe renal impairment (CrCl $\leq$ 30 mL/min) (15). As for apixaban, patients with impaired renal function and a CrCL level of 15-29 mL/min should be initiated with a lower dose of 2.5 mg twice daily instead of 5 mg twice daily (1). Anticoagulation with apixaban should be avoided in patients with end-stage kidney disease and non-valvular AF due to limited data (16).

The findings revealed that incompleteness of clinical monitoring occurred mainly in absence of liver function tests. Less than half of the study participants underwent liver function monitoring before starting DOAC. With regards to the dosage adjustment for dabigatran based on liver function, there is no available recommendation as consistent changes in exposure or pharmacodynamics were not observed in studies involving patients with moderate liver impairment. The use of rivaroxaban should be avoided in patients with moderate to severe hepatic impairment (Child-Pugh class B and C) and any hepatic disease with coagulopathy (17). For apixaban, caution should be exercised in patients with moderate liver impairment (Child-Pugh class B), but no dosage adjustment is necessary. However, its use is not recommended in patients with severe liver impairment (Child-Pugh class C) (10). Since most DOAC have limited impact on liver function, routine liver monitoring is typically not required before DOAC initiation. However, caution should be exercised when using DOAC in patients with significant liver disease or impaired liver function, and appropriate assessments should be conducted. Additionally, a patient's overall medical condition and specific risk factors should

be taken into consideration, as certain serious comorbidities can affect the metabolism or elimination of DOAC.

Post-initiation Monitoring Practices (Renal and Liver Function)

Nearly three quarters of the study participants had their renal function monitored closely after DOAC initiation (n=40, 72.7%), whereas only half of them were closely monitored for liver function post-initiation (n=28, 50.9%). Close monitoring on both parameters should be done as DOAC such as apixaban and rivaroxaban can cause significant adverse effects such as kidney and hepatic impairment (18–22). Another study highlights the significance of monitoring renal function in post-initiation DOAC patients to prevent bleeding events. The study suggests that patients receiving DOAC therapy should undergo regular renal function monitoring, at least once a year, particularly if there are suspicions of renal dysfunction due to factors such as acute myocardial infarction, acute decompensated heart failure, diabetes, diuretic use, specific co-medications, dehydration, or hypovolemia. If relevant impairment is detected, dosage adjustment or discontinuation of the medication may be necessary (11).

One of the reasons for failure for post-initiation monitoring is due to a lack of awareness and practices in the facility. Anticoagulant Medication Therapy Adherence Clinic (ACMTAC) is a subset of Medical Therapy Adherence Clinic services provided by the Pharmacy Practice and Development Division, Ministry of Health (7). ACMTAC works with doctors to manage the patients on anticoagulant therapy. In ACMTAC, pharmacists can play their roles by preparing DOAC post-initiation checklist for all the prescribers who are going to see the patients for follow-ups. The post-initiation monitoring of DOAC should also focus on potential adverse effects such as those related to the patients' renal and liver function. The overall bleeding risk should also be taken into consideration to ensure the appropriateness of ongoing DOAC therapy. Regular follow-up visits are essential to monitor DOAC therapy and the frequency of follow-up visits depends on every patient's condition and needs.

Nonetheless, a high HAS-BLED score that equals or greater than 3 means that there is a need for regular clinical review and follow-ups, but it should not be a reason for discontinuing oral anticoagulant (3). Therefore, our finding aligns with the recommendation that high-risk participants should continue taking oral anticoagulants with ongoing monitoring, including renal function assessment and clinical evaluation for abnormal bleeding. This is further

supported by the fact that none of the subjects included in our data collection experienced hospital admissions due to thromboembolic or hemorrhagic events.

Pattern of Use of DOAC (Age and Choice of DOAC)

Age is crucial when deciding whether to initiate a reduced dose of DOAC. The results of the study demonstrated that the dose-reduction criteria for age were well adhered to. According to the study by Lauw MN et.al, the effects of dabigatran on extracranial major bleeding were found to vary with age, supporting the use of dabigatran 110 mg twice daily in elderly patients (age ≥80 years) (23). Another study also recommended a reduced dose of dabigatran to 110 mg in patients aged 80 years or older to minimise the risk of major bleeding risk (24). Both studies align with our findings that Dabigatran 110mg twice daily was most preferred initiated in aged 80 years and above.

Based on our findings, we observed that only one patient initiated the use of a reduced dose of Apixaban, aged 80 years and above, while two patients were aged 79 years and below. Among the available DOAC, the guidelines recommend Apixaban 2.5mg twice daily as the preferred first choice for individuals aged 80 years and above (1). A dose reduction to Apixaban 2.5mg twice daily is recommended if at least two criteria are met, such as age over 80 years, body weight of 60 kg or less, and serum creatinine level of 1.5 mg/dL (133 μmol/L) or higher (1). The study by DK et al. also supports the use of DOAC in elderly patients (aged ≥75 years), demonstrating a reduced incidence of stroke or systemic embolism and significant bleeding compared to warfarin (25). This explains the initiation of a reduced dose of Apixaban in patients aged 79 years and below in our study. Therefore, according to the ESC guideline, apixaban should be the preferred anticoagulant for stroke prevention in elderly patients with AF (1,25). Consequently, the usage of a reduced dose of Apixaban at 2.5mg twice daily may become more prevalent in future clinical practice.

In terms of rivaroxaban, although there are no age restrictions for its use, elderly patients with AF are often prescribed a reduced off-label dose. However, only one patient aged 80 years and above was initiated on the reduced dose. However, the study conducted in South Korea suggested that reducing the dose of rivaroxaban to 15 mg did not provide any benefits in elderly patients without renal dysfunction and carried a similar risk of thromboembolic and

hemorrhagic events. Therefore, it was concluded that using rivaroxaban 20 mg in elderly Korean patients with AF is beneficial (26).

Pre-initiation Creatinine Clearance and Choice of DOAC

The finding reported that dabigatran was mostly initiated among participants with creatinine clearance level of 50 ml/min and above. The finding was in line with ESC guidelines. The dosing of dabigatran indicated for AF is either 110mg BD or 150mg BD. Based on the ESC Guidelines 2020, it supported that dose reduction to 110mg BD is indicated for patients older than 80 years old, patients taking verapamil concomitantly, and patients with increased bleeding risk (1). Moreover, the study also supported that patient with moderate renal impairment (CrCl 30–50 mL/min) should receive dose reduction of 110mg BD (24). However, RE-LY trial had demonstrated that AF patients with severe renal impairment of CrCl level which less than 30 ml/min should be excluded for treatment with dabigatran (15). Dabigatran should also be avoided in patients with severe obesity with body mass index of more than 40 kg/m^2 or body weightof more than 120kg (27).

For rivaroxaban, dose indicated for AF is either 15mg OD or 20mg OD. However, it was noted that one of the patients was initiated inappropriately on rivaroxaban 20mg OD as dose reduction is required when the CrCl level is between 15 mL/min and 49 mL/min. The guideline supported that a reduced dose of 15mg OD is indicated for patient with CrCl level of between 15 to 49 ml/min (1). Rocket-AF trial also demonstrated that patients with a CrCl level of less than 30mL/minute was excluded (14). A population pharmacokinetic analyses with simulations on virtual patient populations with AF had demonstrated that 15mg OD dose of rivaroxaban in patients with CrCl level of 30 to 49 mL/min would achieve the same AUC and Cmax values compared to those with normal renal function who took the 20mg OD dose (28).

Lastly, apixaban 5mg BD and reduced dose 2.5mg BD are also indicated for AF (30). The findings revealed that 1 patient was initiated on the reduced dose of apixaban with a CrCl level between 15 to 49 ml/min. The findings revealed that 1 patient was initiated on the reduced dose of apixaban with a CrCl level between 15 to 49 ml/min. This finding aligns with the ESC guidelines, which recommended dose reduction to 2.5mg twice daily if at least two criteria are met: age over 80 years old, body weight less than or equal to 60 kg, and serum creatinine level greater than or equal to 1.5mg/dL (133µmol/L) (1). Apixaban exhibits minimal renal clearance,

but the clinical significance of this is uncertain and there are varying recommendations regarding when to dose adjust (27). Thus, CrCl is also one of the indicators to decide on the choice of DOAC used.

LIMITATIONS AND RECOMMENDATIONS

There were a few limitations in this study. First and foremost, it was a single-center study, so it may not be possible to generalise the findings to the entire Malaysian AF population. Therefore, a multi-center study that includes private hospitals is recommended to provide more accurate and reliable data. Furthermore, this research was retrospective in nature. The retrospective study design has the drawback of incomplete data in patients' medical records and the potential for patients being lost to follow-up during treatment or discharge from the clinic. Additionally, the study had a small sample size as it only included patients who received DOAC from the hospital pharmacy and excluded patients who self-purchased DOAC and those who defaulted on follow-up during the COVID-19 pandemic.

Hence, future research, prospective in nature and conducted at multiple centers to evaluate the use of all DOAC in AF patients, monitoring parameters required, availability of reversal agents, and use in special populations, such as in geriatrics is recommended.

CONCLUSION

In conclusion, prescribers adhered to the CHA_2DS_2VASc scoring system when initiating DOAC. Age and creatinine clearance were considered during initiation of DOAC. However, pre- and post-initiation monitoring practices such as coagulation profiles, renal function tests, and liver function tests were not strictly followed. Complete monitoring, including all relevant parameters, is crucial both before and after initiating DOAC therapy to ensure effectiveness, safety, and appropriate selection of DOAC. To improve adherence to guidelines, pharmacists may need to provide additional interventions or reinforce the use of the DOAC checklist during DOAC initiation.

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CONFLICT OF INTERESTS

All study investigators declared that they have no conflict of interests.

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REFERENCES

1. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the Europe. Eur Heart J. 2021 Feb;42(5):373–498.
2. Nantsupawat T, Nugent K, Phrommintikul A. Atrial fibrillation in the elderly. Drugs Aging. 2013 Aug;30(8):593–601.
3. Camm AJ, Lip GYH, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J. 2012 Nov;33(21):2719–47.
4. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JCJ, et al. 2019 AHA/ACC/HRS Focused Update of the 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 Clinical Practice Guidelines and the Heart . J Am Coll Cardiol. 2019 Jul;74(1):104–32.
5. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383(9921):955–62.
6. George D, Devaraj NK, Shakirin S, Sahimi M, Noraini M. A national audit on the utilisation and documentation of dabigatran checklist for patients initiated on dabigatran. Med J Malaysia. 2019;74:425–30.
7. Mohamad RB, Haron NHB, Wah ATM, Rahmat SBS. Anticoagulation MTAC (AC-MTAC) protocol. Minist Heal Malaysia. 2020;18–87.

8. Classification of body mass index - UpToDate [Internet]. [cited 2023 May 25]. Available from: https://www.uptodate.com/contents/image?imageKey=OBGYN%2F97661
9. Troughton RW, Asher CR, Klein AL. The role of echocardiography in atrial fibrillation and cardioversion. Heart. 2003 Dec;89(12):1447–54.
10. Jarboe L, Dadlani A, Bandikatla S, Wade R, Barve A. Drug Use Evaluation of Direct Oral Anticoagulants (DOAC) in Patients With Advanced Cirrhosis. Cureus. 2022 Apr;14(4):e24029.
11. Dunois C. Laboratory Monitoring of Direct Oral Anticoagulants (DOAC). Biomedicines. 2021 Apr;9(5).
12. Ciurus T, Sobczak S, Cichocka-Radwan A, Lelonek M. New oral anticoagulants - a practical guide. Kardiochirurgia i torakochirurgia Pol = Polish J cardio-thoracic Surg. 2015 Jun;12(2):111–8.
13. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuünemann HJ. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):7S-47S.
14. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011 Sep;365(10):883–91.
15. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009 Sep;361(12):1139–51.
16. Chang S-H, Wu C-C V, Yeh Y-H, Kuo C-F, Chen Y-L, Wen M-S, et al. Efficacy and Safety of Oral Anticoagulants in Patients With Atrial Fibrillation and Stages 4 or 5 Chronic Kidney Disease. Am J Med. 2019 Nov;132(11):1335-1343.e6.
17. Graff J, Harder S. Anticoagulant therapy with the oral direct factor Xa inhibitors rivaroxaban, apixaban and edoxaban and the thrombin inhibitor dabigatran etexilate in patients with hepatic impairment. Clin Pharmacokinet. 2013 Apr;52(4):243–54.
18. Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. Am J Med. 1998 Aug;105(2):91–9.
19. Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, et al. A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation

and Risk Factors in Atrial Fibrillation) Study. J Am Coll Cardiol. 2011 Jul;58(4):395–401.

20. Gage BF, Yan Y, Milligan PE, Waterman AD, Culverhouse R, Rich MW, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). Am Heart J. 2006 Mar;151(3):713–9.
21. Hylek EM, Held C, Alexander JH, Lopes RD, De Caterina R, Wojdyla DM, et al. Major bleeding in patients with atrial fibrillation receiving apixaban or warfarin: The ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation): Predictors, Characteristics, and Clinical Outcomes. J Am Coll Cardiol. 2014 May;63(20):2141–7.
22. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010 Nov;138(5):1093–100.
23. Lauw MN, Eikelboom JW, Coppens M, Wallentin L, Yusuf S, Ezekowitz M, et al. Effects of dabigatran according to age in atrial fibrillation. Heart. 2017 Jul;103(13):1015–23.
24. Dabigatran – Reduced dose recommendations [Internet]. [cited 2023 Apr 6]. Available from: https://www.medsafe.govt.nz/profs/PUArticles/June2019/Dabigatran-Reduced-dose-recommendations.htm
25. Deng K, Cheng J, Rao S, Xu H, Li L, Gao Y. Efficacy and Safety of Direct Oral Anticoagulants in Elderly Patients With Atrial Fibrillation: A Network Meta-Analysis. Frontiers in medicine. 2020 Apr;7(7):7-107.
26. Kim SS, Lee KH, Yoon NS, Park HW, Cho JG. What is Standard Dose of Rivaroxaban in Elderly Asian Patients with Atrial Fibrillation: 20mg versus. 15mg? Clin Appl Thromb Off J Int Acad Clin Appl Thromb. 2021;27:10760296211061148.
27. Chen A, Stecker E, Warden BA. Direct oral anticoagulant use: A practical guide to common clinical challenges. J Am Heart Assoc. 2020;9(13):1–18.
28. Mueck W, Stampfuss J, Kubitza D, Becka M. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. Clin Pharmacokinet. 2014 Jan;53(1):1–16.