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A Retrospective Cohort Study on The Anticoagulation Control of Patients Receiving Warfarin in Queen Elizabeth Hospital (QEH) Sabah

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ABSTRACT

Background: Warfarin is a vitamin K antagonist (VKA) with a narrow therapeutic window prescribed to prevent thromboembolic events. Time in therapeutic range (TTR) is the most recognised way to measure anticoagulation quality over time. High TTR correlates with reduced thromboembolic events and low TTR with increased complications. **Objective:** To evaluate anticoagulation quality for patients receiving warfarin at Queen Elizabeth Hospital. **Method:** A retrospective observational population study was conducted on patients reviewed under the Warfarin Medication Therapy Adherence Clinic (MTAC) from April 2016 to April 2017. Data was collected using a data collection form. Patients who were on warfarin treatment for at least 6 months or at least 5 visits for those newly started with warfarin were included in the study. The primary outcome was the time in therapeutic range (TTR) of 1.8-3.2, calculated using the Rosendaal method. **Results:** 150 patients on warfarin with 1765 clinic visits were evaluated. Most were male (56%), and the mean age was 61.33±13.47. The prevalent indication observed was nonvalvular atrial fibrillation, which accounted for 110 patients (73.3%) of the total. The overall mean TTR (1.8-3.2) was 80.6±20.2%. The wrong/missed warfarin dose was the main reason the International Normalised Ratio (INR) was out of range (150/851 episodes, 17.6%). Hospitalisation rendered most patients defaulting clinic visits (10/34 episodes, 29.4%) and was predominantly non-warfarin related (27/37 episodes, 19 patients). There was a single episode of major bleeding (1 patient). **Conclusion:** A high average TTR was achieved in patients taking warfarin at our institution. Wrong/missed doses and inconsistent diet were the main reasons for INR being out of range. However, the primary reason for INR being out of range remains unknown. A total of 37 cases of hospitalisation were reported, and 72.9% of them were non-warfarin related. No mortality was recorded.

INTRODUCTION

Warfarin is one of the most commonly used oral anticoagulants (OAC) in Malaysia. It is indicated for the treatment and prevention of thromboembolic disorders such as atrial fibrillation, pulmonary embolism and cardiac valve replacement. Anticoagulation with warfarin showed a reduction in the risk of stroke by two-thirds compared to no anticoagulant therapy [1]. However, a significant safety concern associated with warfarin use is the increased risk of bleeding, especially major bleeding, with intracranial haemorrhage (ICH) being the most severe. This is due to the likelihood of mortality or subsequent significant disability being substantially higher in ICH than bleeding at other sites [2]. The challenge is that warfarin has a narrow therapeutic index; its safety and efficacy depend on maintaining the INR within the target range for the indication.

The time in the therapeutic range (TTR) is commonly used to evaluate the quality of warfarin therapy. It is an essential tool for assessing the risks versus benefits of warfarin therapy. TTRs have frequently been assessed by the Rosendaal linear

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interpolation method in clinical studies, which assumes that between-test INR varies linearly [3]. In patients with atrial fibrillation who are taking warfarin for stroke prevention, evidence indicates that prevention of stroke is most effective when the TTR is 70% or above [4]. Other clinical studies show clinical benefits of warfarin when the TTR is 60-65% [5,6]. It is well-known that poor control of anticoagulant intensity increases the risks of thrombotic and haemorrhagic events [4]. In the Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III and V trials, patients with TTR < 60% had higher rates of mortality, major bleeding, and stroke relative to the patients with TTR > 75% [6]. Given the strong association between TTR and outcomes of warfarin therapy, NICE has recommended that any patient with a TTR below 65% should have anticoagulation reassessed [7].

Although new oral anticoagulants are available, warfarin remains viable for many patients because of its availability and cost [8]. Despite extensive data on warfarin with TTR in countries such as the US, Europe and Asia, more data must be assessed on the anticoagulation quality of warfarin in Malaysia. Recently, a comparison study by Subramaniam et al. [9] in Kuala Lumpur Hospital reported a mean TTR of 66.3% for 92 patients monitored by a pharmacist-managed anticoagulation clinic. Assessing TTR allows physicians to estimate the success of warfarin therapy in patients. Therefore, this study aims to evaluate anticoagulation quality for patients receiving warfarin at Queen Elizabeth Hospital.

MATERIAL AND METHOD

Study Design

This is a retrospective, cohort and single-centred study to determine the anticoagulation control of patients receiving warfarin therapy in HQE from 1st April 2016 to 1st April 2017. Ethical approval was obtained from the Clinical Research Centre (CRC) and the Malaysian Research Ethics Committee (MREC). The study is registered in National Medical Research Registry (NMRR) with the ID of NMRR-17-678-35502.

Inclusion and Exclusion Criteria

All adult patients (above 18 years old) receiving uninterrupted warfarin treatment for more than 6 months and a minimum of five clinic visits for newly started warfarin patients were recruited into the study. Conversely, for patients who monitored their INR using Point of Care (POC) device, patients who were pregnant and patients who were completely lost to follow-up were excluded from the study.

Research outcomes

The primary outcome of the study was the TTR, calculated using the Rosendaal method formulated on Microsoft Excel Spreadsheet. This method assumes INR values change in a linear pattern between measurements. In our study, we utilised expanded TTR by accepting INR ± 0.2 from the target range, as this minimal deviation is not clinically significant and does not warrant dosage adjustment. The secondary outcome was to explore factors that may affect the degree of TTR changes. Additionally, we further determined the reasons for out-of-range INR, episodes of hospitalisation/bleeding complications and reasons for defaulting clinic visits.

Data collection

Eligible patients were identified and recruited by reviewing and screening the medical records of patients in the warfarin MTAC. The parameters of interest, such as patient baseline characteristics, were further categorised into demographic and clinical data. The demographic data included age, gender, weight, height, race and occupation, while the clinical data included co-morbidity, smoking status, alcohol status, warfarin indication and target INR. Subsequently, for each patient, we assessed the warfarin-related variables, which included the risk of the bleeding score (HAS-BLED score), risk of thromboembolism (CHAD2DS2-VASC score) and the reasons for sub- or supratherapeutic INR, hospitalisation or bleeding complications and patient defaulting warfarin MTAC review. Major bleeding was defined as fatal bleeding which may lead to dead within 30 days of presentation with anticoagulation-related bleed, loss of haemoglobin level of equal or more than 2 g/dL, requiring blood transfusion of 2 U or more, or bleeding involving anatomical critical sites [10].

Statistical Analysis

A convenience sampling method was applied in this study, and all patients who fulfilled the eligibility criteria were included. Sample size calculation was omitted as this is a population study. Data analysis was conducted using SPSS software version 17.0. Basic descriptive statistics were utilised to display patient demographic data, the reasons for the sub-/supratherapeutic range of INR and the incidence of warfarin-related complications. Data dispersion was evaluated by mean ± standard deviation and median (interquartile range). The factors associated with poor TTR control were studied using simple logistic regression. All statistical analyses were two-tailed and considered significant if the p-value was less than 0.05.

RESULT

A total of 192 patients received warfarin MTAC during the study period from April 2016 to April 2017. Only 150 patients who met the inclusion criteria were recruited into the study. The data of the recruited patients were processed for analysis. Our warfarin MTAC patients' average age was 61, and most were male (56%). Most of the patients were ethnically originating from Kadazan Dusun Murut (31.3%), followed by Chinese (29.3%) and Bajau (14.6%). Malays accounted for 13.3% of the study population, and 13.3% of the patients did not fall into the listed ethnic groups. The top three common comorbidities recorded are hypertension, diabetes mellitus, and dyslipidaemia, as demonstrated in Table I. In our hospital, most patients were anticoagulated with warfarin for non-valvular AF, accounting for two-thirds of our warfarin patients. Less than 10% of study patients were anticoagulated with warfarin for non-listed indications.

The average HAS-BLED score and CHA2DS2-VASc score were 1 and 3, respectively. The overall mean TTR for our patients was 80.6% (SD 20.2%). The mean and median TTR are further described in Table II per different warfarin indications in descending order. Patients anticoagulated with warfarin for non-valvular AF achieved the highest mean TTR (83.65% ± 17.76), while those with haematological disorder and other indications had TTR below the target of 65%.

There were 1765 patient visits in total, and the INR was out of range in 851 of these patient visits. Several notable reasons for out-of-range INR were wrong/missed dose (17.6%) and inconsistent diet (14.2%). However, most reasons could not be identified (38.6%) (refer to Figure I).

There were 37 hospitalisation episodes in 26 patients documented throughout the study period. Most were warfarin-unrelated, 72.90% (n=27), and 27% (n=10) were explicitly linked to warfarin usage (refer to Figure II). Throughout the study, only 1 major bleeding event in 1 patient and 25 minor bleeding cases in 10 patients were reported (refer to Figure III). The average TTR of patients who experienced minor bleeding event(s) was more than 75%. There was a total of 34 defaulted visits, with the majority attributed to hospitalisation (29.4%), while other reasons (not named) accounted for 32.3% of the defaulted visits (refer to Figure IV).

Among non-valvular AF patients. (n=109), there are 11 patients with recorded TTR <65%. In Table 3, we attempted to find the association of anticoagulation quality with patient's demographic data. However, our study showed no significant association.

Table I: Demographics of recruited patients.

Variables		*Population*
Age	Mean ± SD	61.33 ± 13.47
Gender (%)	Male	84 (56)
	Female	66 (44)
Ethnicity (%)	Malay	17 (11.3)
	Chinese	44 (29.3)
	Kadazan Dusun Murut	47 (31.3)
	Bajau	22 (14.7)
	Others	20 (13.3)
Education Level (%)	Unschooled	27 (18)
	Primary	47 (31.3)
	Secondary	59 (39.3)
	Tertiary	17 (11.3)
Occupation Status (%)	Unemployed	40 (26.7)
	Employed	28 (18.7)
	Retired	82 (54.7)
Marital Status (%)	Married	139 (92.7)
	Single	11 (7.3)
Household structure (%)	Family	138 (92)
	Others (alone, nursing home)	12 (8)
Smoking Status (%)	Non-smoker	99 (66)
	Active Smoker	18 (12)
	Ex-smoker	33 (22)
Alcohol Status (%)	Non-drinker	132 (88)
	Drinker	18 (12)
Warfarin Indication (%)	Nonvalvular AF	110 (73.3)
	Valvular AF	14 (9.3)
	Venous Thrombosis	15 (10)
	Cardiac Valve Replacement	4 (2.7)
	Haematological Disorders	3 (2)
	Others	3 (2.7)
		4 (2.7)
Target INR	2.0-3.0	144 (96)
	2.5-3.5	6 (4.0)
Duration	Lifelong	146 (97.3)
	Non-lifelong	4 (2.7)
Co-morbidity (%)	CKD	22 (14.7)
	COPD	12 (8)
	DM	50 (33.3)
	Dyslipidaemia	37 (24.7)
	Hypertension	96 (64)
	Hyper/hypothyroidism	16 (10.7)
	IHD	12 (8)
	CVA	34 (22.7)
	Heart Failure	13 (8.7)
	Others	70 (46.7)
Number of Comorbidities	Median, IQR	3 (1,4)

Table II: Time in Therapeutic Range (TTR) according to the main indication for warfarin.

Indication	TTR (Mean ± SD)	TTR (Median, IQR)	95% CI
Non-valvular AF (n=109)	83.65± 17.76	87.1 (77.8, 97.4)	80.28-87.02
Valvular AF (n=13)	74.26± 34.66	85.2 (77.7, 94.1)	53.31-95.20
Venous Thrombosis (n=14)	72.33± 15.01	70.6 (59.5, 83.1)	63.66-81.00
Cardiac Valve Replacement (n=2)	72.03± 28.90	72.03 (51.6, 92.4)	-
Haematological Disorder (n=2)	64.55± 9.82	64.55 (57.6, 71.5)	-
Others (n=4)	61.85± 25.56	50.85 (47.7, 75.9)	21.17-102.52

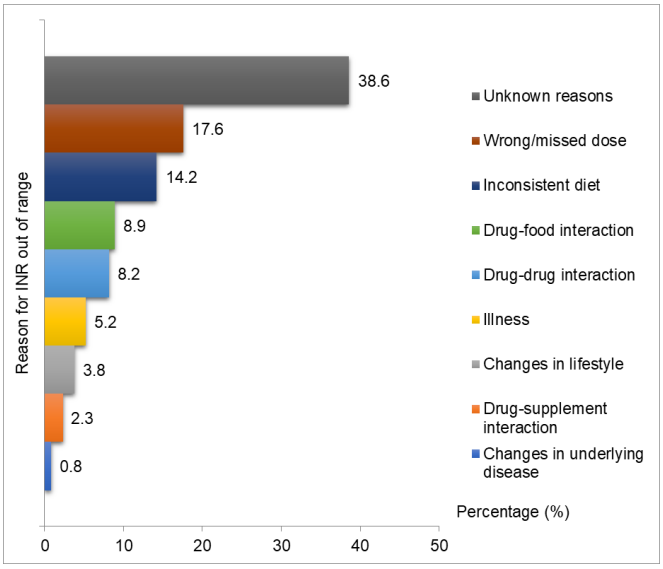

Figure I: Reason for INR being out of range (n=150).

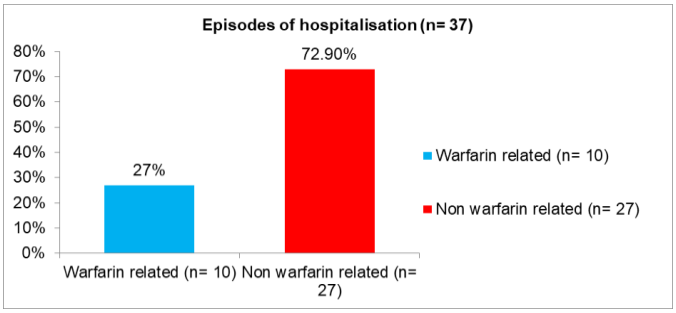

Figure II: Hospitalisation episodes of the patients throughout the study period.

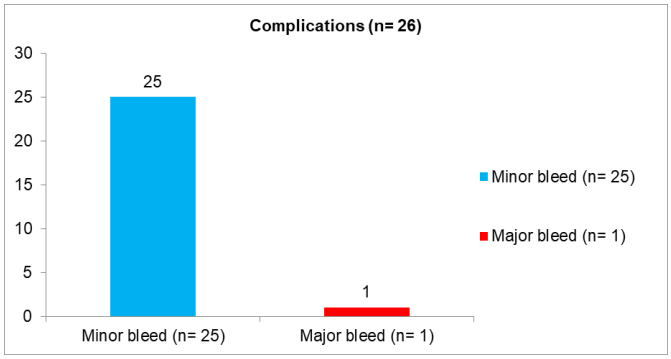

Figure III: Bleeding complications suffered by patients throughout the study period.

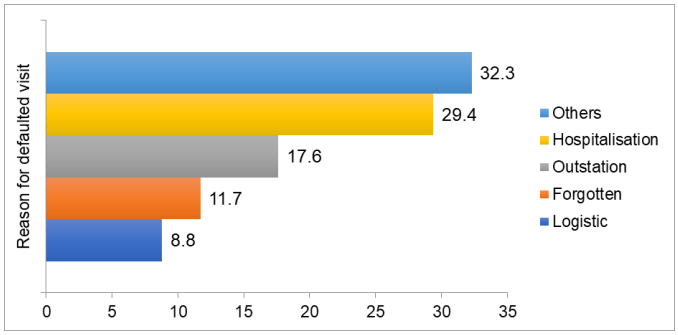

Figure IV: The reasons for defaulted visits.

DISCUSSION

This study represents the inaugural investigation conducted at QEH. It is noteworthy that warfarin remains the primary therapeutic approach for preventing thromboembolism, particularly in cases of AF, venous thrombosis and cardiac valve replacement. It has been observed that there is no significant difference in the favourable net benefit between novel anticoagulants and warfarin when the time in therapeutic range (TTR) of the centre exceeds 65% [11]. However, patients with TTR < 60% have been associated with higher rates of mortality, major bleeding and stroke relative to patients with TTR> 75% [10]. In this study, patients' mean TTR (80.6±20.2%) is higher than the target of >65%. Patients with non-valvular AF achieved the best TTR result with a mean of 83.65% (SD 17.76%), which is higher than that of a study previously conducted in Australia (mean TTR 82.3±15.6%) and Singapore (mean TTR = 57.6±34.2%) [12]. The recent large trials on direct oral anticoagulants, such as ROCKET-AF, ARISTOTLE and RE-LY, have also presented lower anticoagulation control than our centre with a mean TTR of 66%, median TTR of 66% and median TTR of 67.2%, respectively [13]. The superior anticoagulation control of our centre may suggest warfarin could be a mainstay of anticoagulation choice in our setting based on local patients' preference instead of shifting towards DOAC for all the indicated patients.

Table III: Simple Logistic Regression on the Associated Factors Affecting TTR<65% in Non-Valvular AF patients (n=109).

Variable	Regression coefficient (b)	Crude Odds Ratio (95% CI)	P
Age	-0.03	0.966 (0.908,1.029)	0.294
No. of Co-morbidities	-0.15	0.860 (0.538, 1.375)	0.530
CHA_2DS_2-VASc	-0.10	0.901 (0.574, 1.415)	0.654
Gender			
Male	-0.14	1	0.825
Female		0.864 (0.237, 3.150)	
Race			
Non KDM	0.68	1	
KDM		1.982 (0.560, 7.015)	0.288
Education			
Yes	-1.00	1	
No		0.366 (0.044, 3.028)	0.352
Occupation			
Yes	1.05	1	
No		2.878 (0.80, 10.334)	0.105
Marital Status			
Married	0.62	1	
Others (single, divorced, widow)		1.86 (0.197, 17.540)	0.588
Household structure			
Family	0.26	1	
Others (Nursing home, alone)		1.3 (0.144, 11.670)	0.815
Smoking Status			
No	0.31	1	
Yes		1.37 (0.391, 4.819)	0.620
Co-morbidity (Yes vs No)			
CKD	-0.81	0.444 (0.053, 3.696)	0.453
COPD	-0.12	0.88 (0.101, 7.609)	0.908
DM	-0.14	0.864 (0.237, 3.150)	0.825
Dyslipidaemia	-1.48	0.226 (0.027,1.851)	0.166
Hypertension	-1.05	0.347 (0.096,1.247)	0.105
Hyper/hypothyroidism	1.08	2.96 (0.683, 12.869)	0.147
IHD	-0.12	0.88 (0.101, 7.609)	0.908
CVA	-0.53	0.584 (0.118, 2.879)	0.509
Heart Failures	0.78	2.197(0.410,11.773)	0.358
Others	-0.23	0.794 (0.218, 2.892)	0.727

In a previous study done on the assessment of the confidence level of pharmacists in providing anticoagulation therapy, pharmacists who are working in Borneo (where Sabah is located) have demonstrated a higher confidence level (88.3%, p<0.001) in educating patients on warfarin compared to low molecular weight heparins (58.5%, p<0.001) and direct oral anticoagulants (38.9%, p<0.001) [14]. This may be indirectly associated with the impressive TTR results from our study. This may also explain the fewer hospitalisation (Figure I) episodes related to warfarin usage (27%, n=10) compared with non-warfarin-related use (72.9%, n=27). Regarding complications, albeit with reasonable anticoagulation control, most of the bleeding events were considered minor. No mortality was documented throughout the study.

Warfarin is known to have a narrow therapeutic index and multiple interactions with food, drugs and supplements [14,15]. There are 851 visits with sub- or supratherapeutic INR values, which wrong or missed dose (38.6%) and inconsistency in dietary intake (14.2%) have been displayed as the top two leading causes in our study. However, most out-of-range INRs were attributed to unknown reasons (38.6%). This infers that many other potential factors have not been well studied, posing challenges for dose adjustment. One of the potential factors could be a need for more research on quantifying Vitamin K content in the beloved delicacy of our local fruits, such as durian, duku langsat and rambutan and how they influence the INR of patients on warfarin treatment. Additionally, the narrow therapeutic index nature of warfarin necessitates frequent INR monitoring [15]; hence, missed/defaulted warfarin MTAC visit (n=34) is also one of the potential unknown reasons for out-of-range INR.

In the previous study done by Pokorney et al., younger age and comorbidities such as heart failure, CKD, DM and COPD are at risk of low TTR [6]. When investigating the correlation between the baseline demographic and clinical characteristics in non-valvular AF patients with TTR <65%, features described that could affect TTR do not significantly impact our study. This finding limits the applicability of the SAMe-TT2R2 (sex, age, medical history, treatment, tobacco use and race) scoring to predict of anticoagulation quality of patients [16]. This could be due to the relatively smaller size of our study as compared to the data derived and validated in the AFFIRM trial.

Study Limitations

The main limitation is that this is a single-centre study with only a tertiary hospital in Sabah, resulting in a smaller sample size. The majority of warfarin indications were non-valvular AF and less on other indications, such as cardiac valve replacement. We did not consider the indications which pose higher thrombotic risk such as mechanical valve replacement. Throughout the study, missing data is one of the main challenges in obtaining accurate patient information. Future recommendations include a multicentre study to evaluate the TTR for Sabah and a prospective cohort study to avoid recalled bias.

CONCLUSIONS

Albeit the emergence of DOACs, which require minimal lifestyle modification, warfarin would remain one of the treatment options for patients with prosthetic mechanical valves and patients who have contraindications to start DOAC. Our centre has demonstrated an excellent overall anticoagulation quality. The consultation and dose adjustment done in warfarin MTAC must be individualised rather than relying on a simple predictive scoring method.

CONFLICT OF INTEREST

The authors declared no conflict of interest in conducting and writing this research.

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