Original Article

Assessment of the quality of anticoagulation management with warfarin in a tertiary care center

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ABSTRACT

الأهداف: تقييم جودة عيادة منع تخثر الدم في مستشفى من الدرجة الثالثة وتحديد العوامل التي تؤثر على الوقت في النطاق العلاجي (TTR) وعلاقته بالمضاعفات المختلفة.

المنهجية: أجريت هذه الدراسة بأثر رجعي من مركز واحد خلال الفترة من مارس 2015م حتى يونيو 2016م وشملت 1914 مريضًا يتلقون العلاج بالوارفارين. تم تقسيمها إلى 4 مجموعات للوارفارين: الرجفان الأذيني غير الصمامي (العدد=403)، الصمامات الأذينية (العدد=227)، والصمامات الاصطناعية (العدد= 700)، والانسداد الوريدي أو الرئوي (العدد=584).

النتائج: كان متوسط العمر 56 (25 ، 75 في المائة: [45، 67]) عام، و 53.2% من الإناث، وبمتوسط 0.52 (0.28، 0.76). أثر انخفاض الهيموجلوبين (0.007) وارتفاع مستويات الفوسفاتيز القلوية (0.020) سلبيًا على TTR. ارتبط الانصمام الخثاري الوريدي (VTE) بانخفاض TTR. حدث نزيف طفيف في 64 (3.35%)، ونزيف معدي معوي في 14 (0.7%)، وسكتة في 41 (2.2%) مريضاً، مع عدم وجود اختلافات بين المجموعات. لم يرتبط TTR مع النزيف الطفيف (نسبة الأرجحية = 0.49 ؛ p=0.09)، أو نزيف الجهاز الهضمي (نسبة الأرجحية = 0.29 ؛ p=0.18) ، أو السكتة الدماغية (نسبة الأرجحية = 1.15 ؛ p=0.79) .

الخلاصة: تعكس تجربة الحياة الواقعية للتحكم في منع تخثر الدم، ينفق مرضانا أقل من نصف TTR داخل INR. الزم انخفاض معدل الهدف (TTR) إلى تحسين جودة الخدمة وعوامل التحكم التي تؤثر على TTR، بما في ذلك مستويات الهيموغلوبين والزيارات المنتظمة لمرضى VTE.

Objectives: To evaluate the quality of an anticoagulation clinic in a tertiary hospital and identified factors affecting the time in the therapeutic range (TTR) and its relation to different complications.

Methods: This single-center retrospective study conducted between March 2015 and June 2016 included 1914 patients receiving warfarin therapy. They were divided into 4 warfarin indication groups: non-valvular atrial fibrillation (AF) (n=403), valvular AF (n=227), prosthetic valves (n=700), and venous or pulmonary embolism (n=584).

Results: The median age was 56 (25th, 75th percentiles: [45, 67]) years, and 53.2% were female. The median TTR was 0.52 (0.28, 0.76). Low hemoglobin (0.007) and high alkaline phosphatase (0.020) levels negatively affected the TTR. Venous thromboembolism (VTE) was associated with low TTRs. Minor bleeding occurred in 64 (3.35%), gastrointestinal bleeding in 14 (0.7%), and stroke in 41 (2.2%) patients, with no inter-group differences. The TTR was not associated with minor bleeding (odds ratio [OR]=0.49; *p*=0.09), gastrointestinal bleeding (OR=0.29; *p*=0.18), or stroke (OR=1.15; *p*=0.79).

Conclusion: Reflecting the real-life experience of anticoagulation control, our patients spend less than half the TTR within the INR. The low target TTR mandates the need to improve service quality and control factors affecting the TTR, including hemoglobin levels and regular visits for patients with VTE.

Keywords: warfarin, anticoagulation, time in therapeutic range

Thrombosis prevention is a top priority in managing patients with a high risk of thromboembolic events, such as patients with atrial fibrillation (AF), valvular prostheses, and venous or pulmonary embolism venous thromboembolism (VTE).[1,2] The vitamin K antagonist warfarin is widely used compared to non-vitamin K antagonist oral anticoagulant (NOAC) agents, especially for elders and patients with comorbidities.[3] A major problem of warfarin therapy is the narrow therapeutic index that requires close monitoring of the international normalized ratio (INR). Maintaining INR values within a narrow target range (INR: 2.0-3.0) requires frequent blood tests to ensure the safety and efficacy of warfarin used.[4] Maximizing the time in the therapeutic range (TTR) within the optimal INR range provides the greatest benefit for the prevention of embolic or thrombotic events and avoidance of severe side effects.[5,6] The TTR is a good indicator of anticoagulation control and the best predictor for patients' quality outcomes.[6]

The target TTR in clinical trials may be different than the target TTR achieved in community practice. The Thrombosis Canada Guidelines State that good INR control is defined arbitrarily as a TTR >60%.[5] Low TTRs reflect poor anticoagulation control and are associated with thromboembolic or bleeding events. High TTRs provide a better quality of life and health outcomes with fewer adverse events.[7]

Few studies have examined the quality of anticoagulation clinics in high-load centers in our region. We conducted this study to evaluate the quality of an anticoagulation clinic in a tertiary hospital and identify factors affecting the TTR and its relation to different complications.

Methods. This was a single-center, retrospective cohort study conducted at Prince Sultan Military Medical City, Riyadh, Kingdom of Saudi Arabia (KSA) from March 2015 to June 2016. We included patients who were followed up for warfarin therapy at the outpatients' clinic (n=1914). The patients were divided into 4 groups according to the indication of warfarin: non-valvular AF (n=403), valvular AF (n=227), prosthetic valves (n=700), and venous or pulmonary embolism (n=584). All patients who presented to the outpatient clinic during the study period were included. Patients who had INR control for a procedure or during the hospitalization were excluded.

Anticoagulation monitoring. Patients were followed in the outpatient clinic by the cardiologists, cardiac surgeons and internists. Follow-up visits were scheduled routinely each 2-3 months and patients with uncontrolled INR required more follow-up visits. International normalized ratio testing was carried out for all patients in the clinic laboratory during the outpatient visit.

We obtained 31547 INR readings with an average of 16 readings per patient during the study period. The therapeutic ranges were calculated using the Rosendaal method (taking the number of INRs within the target range divided by the total number of INRs during the selected time interval).[6] The INR was tested using the CoaguChek® XS system (Roche, Indianapolis, IN, USA).

Data collection and study outcomes. We extracted the patients' data from the hospital electronic medical records. Baseline data included age, gender, associated comorbidities, and baseline laboratory investigations reported at the initial visit at the time of enrollment. Echocardiographic data, including the ejection fraction, were recorded. All concomitant medications at the time of study enrollment were reported with an emphasis on the medications with interactions with warfarin. We followed the patients longitudinally for adverse effects that occurred during warfarin therapy, such as bleeding and stroke. The study outcomes were the quality of anticoagulation control and influencing factors.

Ethical considerations. The study was approved by the local Institutional Review Board, and they waived the need for consent to participate in the study (reference number: R17004). The study was conducted according to principles of Helsinki Declaration.

Statistical analysis. Continuous variables were presented as 25th, 50th (median) and 75th percentiles, and categorical data was reported as frequencies and percentages. The normality distribution of the quantitative data was assessed using the Shapiro-Wilk test. Comparisons between multiple groups were performed using one-way analysis of variance with Tukey's post-hoc test for normally distributed continuous variables and the Kruskal-Wallis test with Dunn's test for skewed data. Pearson's chi-squared test or Fisher's exact test was utilized to compare categorical variables as appropriate. Fractional regression analysis was used to identify predictors of poor TTR control. Logistic regression was used to study the associations among the TTR and different complications. The statistical analysis was conducted using the Statistical Package for Social Sciences (SPSS), version 25 (IBM Corp., Armonk, NY, USA).

Results. Among the 1914 patients receiving anticoagulants included in this study, 74% were living

within Riyadh. Their median age was 56 (25th, 75th percentiles: 45, 67) years, 20.7% were 70 years of age or older, and the age varied significantly among the groups; the patients with prosthetic valves and valvular AF were significantly younger than those with non-valvular AF (p<0.001). Serum creatinine levels were within the normal range in all the groups but were significantly lower in the nonvalvular AF group (p<0.001). The other laboratory data was within normal ranges with slight variations without significant differences. The baseline characteristics are presented in Table 1. The post-hoc test results for significant continuous variables are presented in Table 2.

Factors affecting the TTR. The median TTR in our study was 0.52 (0.28-0.76). The TTR was not affected by the patients' residence area, age, or gender. Medications such as antiplatelet agents, amiodarone, digoxin, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers, diuretics, and statins did not affect the TTR. In contrast, low hemoglobin (p=0.007) and high alkaline phosphatase (ALP), (p=0.020) levels negatively affected the TTR (Table 3). Venous thromboembolism was associated with a lower TTR.

Adverse events. Bleeding was classified according to the International Society of Thrombosis and Hemostasis into 3 categories; minor bleeding, clinically relevant minor bleeding (CRMB) and major bleeding. Minor bleeding was reported in 64 patients (3.35%), CRMB (1.57%), and intracranial bleeding in one patient in the VTE group. Ischemic stroke was reported in 40 patients (2.1%). Low TTR was not associated with minor bleeding (odds ratio [OR]: 0.49; p=0.09), CRMB (OR: 1.06; p=0.73), or stroke (OR: 1.21; p=0.23). There was no difference among the groups in bleeding (minor bleeding and CRMB). The incidence of stroke was higher among patients with VTE, did not reach statistical significance (Table 4).

Discussion. The TTR has become the most widely accepted and validated method to measure the quality of anticoagulation control and predict adverse events.[8] The Thrombosis Canada Guidelines (2017) state that good INR control is defined arbitrarily as a TTR >60%.[5] The updated chest guidelines and expert panel report (2018) recommend a target TTR ≥70% when adjusting the dose of warfarin to achieve the highest quality of anticoagulation control, and TTRs <65% require therapeutic intervention.[7] This study showed that patients receiving warfarin for different indications had TTRs below the recommended level for optimal anticoagulation control, with a median TTR of 52%. The TTR in this study was comparable to that found in other studies that showed low TTRs including the global anticoagulation registry in the FIELD-AF registry (31.1%) and other studies conducted in developing countries.[3,6,9-16] A higher mean TTR of 65±20 was reported in the ORBIT-AF registry in the United States of America (USA), as well as a TTR of ≥60% found in a study in Japanese patients.[17,18] The difference between our studies and others is that our patient population included a wider range of warfarin indications that were not only limited to AF. This, in turn, led to the ability to assess the TTR in a different range of indications.

Our hospital is a tertiary-care governmental institution that has a large load of patients visiting the anticoagulation clinic daily. This high patient number may affect TTR findings in several ways. Anticoagulation clinic appointments are limited in relation to patients' numbers; therefore, close follow-up may not be feasible for all patients. Additionally, several patients reside in remote areas, and these patients may skip their anticoagulation appointments if they are not scheduled with their other clinic visits.

As warfarin has a wide variety of interactions, it is crucial to advise patients about the potential drug interactions to avoid potential harm. Despite the numerous interactions of warfarin, other concomitant drugs do not seem to affect the TTR. The unique inherited culture of our community concerning the use of herbal remedies, especially those with evidence-based reports like ginger, chamomile, garlic, green tea, curcuma, and fenugreek, may place patients at a high risk of warfarin- and herbal remedy-associated interactions, thus affecting both efficacy and safety.[19] Although this variable was not documented, physicians at our hospital remain committed to providing routine counseling against herbal remedy consumption.

We evaluated factors affecting the TTR. Low hemoglobin levels, high ALP levels, and the use of warfarin for a VTE indication were found to be associated with poor TTR control. Poor TTR in previous studies was affected by different factors: age, gender, socioeconomic status, medical comorbidities, and polypharmacy.[5] Results from the VARIA study indicate that advanced age is a predictor of a low TTR.[20] Heart failure has been shown previously to be an important factor that affects the quality of warfarin therapy.[21,22] Nelson et al,[23] showed that diabetes, heart failure, and previous stroke are associated with low TTRs. In a study performed in Kuwait, the female gender was associated with poor TTRs; another study in Kingdom of Saudi

Arabia showed poor anticoagulation control in patients with AF and higher CHADS2 scores.[9,10]

The TTR, which reflects the anticoagulation quality control, is affected by different patient characteristics. In this study, we found that age did not affect the TTR, which can be explained by good compliance of patients receiving warfarin. Our findings suggested that patients with low hemoglobin levels will have less effective anticoagulation management, which indicates that patients receiving warfarin therapy should maintain strict control of their hemoglobin levels.

Patients in the VTE group were found to have the lowest TTRs, and this may be explained by more

Table 1 - Demographic and clinical characteristics of patients according to the indication (N=1914).

Variables	Total	N-valvular (n=403)	Valvular (n=227)	Metallic (n=700)	VTE (n=584)	P-value
Age, (years)	56 (45, 67)	68 (58, 76)	61 (51, 70)	53 (44, 60)	50 (37, 62)	<0.001
Weight, (Kg)	77 (66, 89)	77 (66, 90)	75 (65, 87)	76 (66, 88)	77 (68, 90)	0.269
Patient residence						
Inside Riyadh	1417 (74.0)	299 (74.2)	173 (76.2)	492 (70.3)	453 (77.6)	0.024
Outside Riyadh	497 (26.0)	104 (25.8)	54 (23.8)	208 (29.7)	131 (22.4)	
Female	990 (51.7)	187 (46.4)	162 (71.4)	338 (48.3)	303 (51.9)	<0.001
Comorbidities						
Hypertension	1137 (59.4)	333 (82.6)	156 (68.7)	367 (52.4)	281 (48.1)	<0.001
Uncontrolled HTN	115 (6.0)	49 (12.2)	7 (3.1)	30 (4.3)	29 (5.0)	
CAD	388 (20.3)	141 (35.0)	38 (16.7)	80 (11.4)	129 (22.1)	
Diabetes	740 (38.7)	242 (60.0)	102 (44.9)	191 (27.3)	205 (35.1)	
CHF	145 (7.6)	51 (12.7)	21 (9.3)	36 (5.1)	37 (6.3)	
Dyslipidemia	516 (27.0)	149 (37.0)	61 (26.9)	133 (19.0)	173 (29.6)	
Laboratory values						
Baseline INR (n=1907)	2.4 (1.9, 3)	2.2 (1.7, 2.7)	2.2 (1.8, 3)	2.8 (2.3, 3.3)	2.2 (1.8, 2.7)	<0.001
Hemoglobin (n=1564)	12.6 (11.1, 14.1)	12.6 (11.2, 14.1)	12.5 (10.9, 13.4)	12.6 (11.3, 14.1)	12.6 (10.9, 14.1)	0.227
Hematocrit (n=1560)	0.387±0.06	0.391±0.06	0.380±0.06	14.1	0.387±0.06	0.252
ALT (n=1504)	18 (13, 26)	17 (12, 24)	18 (13, 25)	0.387±0.06	19 (13, 28)	0.038
ALP (n=1522)	81 (64, 104)	82 (64, 105)	82 (66, 105)	19 (14, 27)	79 (63, 102)	0.635
Serum creatinine (n=1573)	76 (60, 99)	88.5 (68, 117)	73 (60, 91.5)	83 (64.3, 105)	71 (55, 94)	<0.001
Creatinine clearance (n=1554)	95 (67.8, 127.2)	76 (51, 101)	85.5 (67, 110)	75 (61, 91) 102 (73, 131.3)	106.5 (76, 144)	<0.001
Echocardiography						
EF (n=1736)	55 (45, 55)	55 (45,55)	55 (50,55)	55 (50,55)	55 (35,55)	<0.001
Apical aneurysm (n=1735)	28 (1.5)	4 (1.0)	0	1 (0.1)	23 (3.9)	
LV clot (n=1734)	84 (4.4)	3 (0.7)	2 (0.9)	3 (0.4)	76 (13.0)	
Medications						
ACE inhibitors	517 (27.0)	149 (37.0)	53 (23.3)	178 (25.4)	137 (23.5)	<0.001
Amiodarone	58 (3.0)	22 (5.5)	13 (5.7)	10 (1.4)	13 (2.2)	
Anti-platelets	862 (45.0)	198 (49.1)	89 (39.2)	359 (51.3)	216 (37.0)	
ARB	347 (18.1)	115 (28.5)	55 (24.2)	106 (15.1)	71 (12.2)	
Beta blockers	1168 (61.0)	311 (77.2)	182 (80.2)	465 (66.4)	210 (36.0)	
Digoxin	309 (16.1)	83 (20.6)	85 (37.4)	122 (17.4)	19 (3.3)	
Diuretics	783 (40.9)	221 (54.8)	140 (61.7)	272 (38.9)	150 (25.7)	
Statin	975 (50.9)	277 (68.7)	129 (56.8)	293 (41.9)	276 (47.3)	
PPI	935 (48.9)	242 (60.0)	128 (56.4)	303 (43.3)	262 (44.9)	

Values are presented as number and percentage (%). HTN: hypertension, CAD: coronary artery disease, CHF: congestive heart failure, INR: international normalized ratio, ALT: alanine aminotransferase, ALP: alkaline phosphatase, EF: ejection fraction, LV: left ventricle, ACE: angiotensin-converting enzyme, ARB: angiotensin II receptor blockers, PPI: proton pump inhibitors. Continuous data are presented as median (25th- 75th percentiles) and categorical data as number and percent.

Table 2 - Pairwise multiple comparison post-hoc test results for non-normally distributed continuous variables.

Variable	G1	G2	G3	G4
Age	G1-G2 = 0.001 G1-G3 = <0.001	G2-G3 = <0.001 G2-G4 = <0.001	G3-G4 = 0.960	G4-G1= <0.001
INR at enrollment	G1-G2 = 0.287 G1-G3 = <0.001	G2-G3 = <0.001 G2-G4 = >0.999	G3-G4 = <0.001	G4-G1 = >0.999
Alanine transaminase	G1-G2 = >0.999 G1-G3 = 0.028	G2-G3 = >0.999 G2-G4 = >0.999	G3-G4 = >0.999	G4-G1 = 0.259
Creatinine	G1-G2 = <0.001 G1-G3 = <0.001	G2-G3 = >0.999 G2-G4 = >0.999	G3-G4 = >0.999	G4-G1 = <0.001
Creatinine clearance	G1-G2 = <0.023 G1-G3 = <0.001	G2-G3 = <0.001 G2-G4 = <0.001	G3-G4 = 0.630	G4-G1 = <0.001
LV EF	G1-G2 = 0.003 G1-G3 = <0.001	G2-G3 = >0.999 G2-G4 = 0.015	G3-G4 = <0.001	G4-G1 = >0.999
TTR	G1-G2 = 0.120 G1-G3 = >0.999	G2-G3 = 0.585 G2-G4 = >0.999	G3-G4 = 0.049	G4-G1 = 0.005

G1: non-valvular AF group, G2: valvular AF group, G3: metallic valve group, G4: venous thromboembolism group, EF: ejection fraction, EDD: end diastolic dysfunction, ESD: end systolic dysfunction, LV: left ventricle, PASP: pulmonary artery systolic pressure, TTR: time in therapeutic range

Table 3 - The factors affecting the time in therapeutic range (TTR).

TTR	Coef. (95% CI)	*P*-value
Weight	-0.001 (-0.003- 0.001)	0.495
Inside Riyadh	-0.044 (-0.136- 0.048)	0.353
Hemoglobin	0.027 (0.007- 0.046)	0.007
ALP	-0.001 (-0.002- -0.0001)	0.020
Creatinine	-0.0001 (-0.001- 0.0001)	0.743
Gender	0.060 (-0.033- 0.153)	0.207
Age	-0.001 (-0.004- 0.002)	0.576
Valvular AF	-0.115 (-0.252- 0.023)	0.102
Prosthetic valve	-0.058 (-0.168- 0.052)	0.302
VTE	-0.156 (-0.275- -0.038)	0.010
Uncontrolled hypertension	-0.014 (-0.171- 0.142)	0.858
CAD	-0.005 (-0.12- 0.111)	0.937
Diabetes mellitus	0.037 (-0.05- 0.124)	0.402
CHF	-0.066 (-0.221- 0.089)	0.402
Ejection fraction	0.001 (-0.004- 0.005)	0.810
Apical aneurysm	-0.302 (-0.63- 0.026)	0.071
Amiodarone	-0.116 (-0.34- 0.107)	0.307
Digoxin	-0.053 (-0.17- 0.064)	0.372
ACE inhibitors	0.040 (-0.58- 0.138)	0.424
ARBS	-0.037 (-0.144- 0.070)	0.502
Beta blockers	-0.014 (-0.112- 0.084)	0.778
Diuretics	0.002 (-0.092- 0.097)	0.967
Statins	0.035 (-0.06- 0.131)	0.470
PPI	-0.073 (-0.158- 0.013)	0.096
Antiplatelet	0.033 (-0.054- 0.12)	0.453

CI - confidence interval, ALP - alkaline phosphatase, CAD - coronary artery disease, ACE - angiotensin enzyme, CHF - congestive heart failure, ARB - angiotensin receptor blockers, PPI - proton pump inhibitors, VTE - venous thromboembolism.

acute events in this group that may be affecting their compliance. The significant association between ALP levels and the TTR may be attributed to hepatic insufficiency, which needs further investigation.

Although there are interactions between some drugs such as amiodarone and digoxin with warfarin, these do not show a significant effect on the TTR. This might be attributed to the awareness of such interactions and protocols to manage such combinations by physicians in the anticoagulation clinic.

Regarding bleeding events, we found no association between the low TTR target and bleeding events. This might be attributed to the low number of events found in our study. Poor TTRs can be explained by the lack of implementation of warfarin dosing protocols in our institution, including clinical pharmacist clinics, which were used later.[2] These results are of concern because they have a significant economic impact, and previous studies have shown that warfarin is associated with a higher annual outpatient cost in comparison to that of NOAC agents.[24]

Poor TTRs may negatively affect the cost of the treatment, even with no increase in the complication rate. Our study suggests that strict hemoglobin control is essential for patients receiving warfarin therapy, and patients with VTE may benefit from frequent follow-up visits. Further studies are required to confirm our findings.

Table 4 - Adverse events of warfarin therapy in different indications.

Adverse events	Total	Non-valvular AF	Valvular AF	Prosthetic valve	VTE	*P*-value
Minor bleeding	64 (3.4)	12 (3.0)	8 (3.5)	29 (4.2)	15 (2.6)	0.449
CRMB	30 (1.6)	3 (0.7)	7 (3.1)	12 (1.7)	8 (1.4)	0.156
Stroke	40 (2.1)	8 (2.0)	4 (1.8)	9 (1.3)	19 (3.3)	0.109

Values are expressed as number and percentage (%).
AF: atrial fibrillation, CRMB: clinically relevant clinical bleeding, VTE: venous thromboembolism

Study limitations. Our study was a single-tertiary-center study with a retrospective design that had inherent biases. Several factors that might affect the TTR were not recorded, such as the use of herbal remedies and education level of the patients. Additionally, the lack of time and resources for patient counseling may have also affected the TTR outcomes. As a drawback of the retrospective design, patients' compliance could not be assessed.

In conclusion, our study represents a real-life experience of anticoagulation control. Our patients spend less than half the TTR within the INR. The low target TTR mandates the need to improve the quality of the service and control factors affecting the TTR, such as hemoglobin levels and close follow-up for patients with VTE. Poor TTR control suggests the shifting of eligible patients to direct oral anticoagulants if possible.

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