ORIGINAL ARTICLE

Anticoagulation control among patients with nonvalvular atrial fibrillation: A single tertiary cardiac center experience

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ABSTRACT

There is a limited knowledge about the predictors of anticoagulation control in patients with nonvalvular atrial fibrillation (NVAF). Furthermore, few reports addressed the role of time in therapeutic range (TTR) that could reflect the safety and efficacy of anticoagulation therapy. We aimed to assess factors that affect the quality of anticoagulation therapy utilizing TTR in patients with NVAF. A retrospective observational study was conducted for patients with NVAF who were maintained on warfarin >6 months at a tertiary cardiac care hospital. Patients were categorized according to the TTR status (≥65% vs. <65%). A total of 241 eligible patients were identified. A high-quality anticoagulation based on TTR values ≥65% was found in 157 (65.1%) patients; the remaining (34.9%) patients represented the low-quality anticoagulation group (TTR <65%). Demographics and clinical characteristics were comparable in the two TTR groups. Both groups were comparable in terms of warfarin dose and medications use. When compared to patients with high-quality anticoagulation, patients in the low-quality anticoagulation group were more likely to seek outpatient warfarin clinic visits more frequently (22.3 ± 5.5 vs. 18 ± 4.4, $P = 0.001$) and to have higher rate of polypharmacy (57.1% vs. 42%, $P = 0.03$). Of note, patients in both groups had similar major bleeding events ($P = 0.41$). After adjusting for age and sex, polypharmacy use was a predictor of poor coagulation control (odds ratio = 1.89, 95% confidence interval: 1.03–3.33; $P = 0.03$). In NVAF patients, TTR is generally high in our cohort. Patients with polypharmacy and frequent clinic visits have lower TTR. High-quality oral anticoagulation could be achieved through optimizing TTR without a significant risk of major bleeding.

Key words: Anticoagulation, atrial fibrillation, polypharmacy, time in therapeutic range, warfarin

INTRODUCTION

Vitamin K antagonists like warfarin are indicated for treatment and prevention of thrombus formation with a proven reduction in morbidity and mortality.[1] Given the narrow therapeutic index and multiple food and drug interactions, the efficacy and safety of warfarin are not readily achieved. To attain this goal, the international normalized ratio (INR) should lie within the therapeutic range most of the patient follow-up time to minimize the likelihood of bleeding or thromboembolic complications associated with supra- or sub-therapeutic INR.[2-5]

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Time in therapeutic range (TTR) could reflect the quality of anticoagulation therapy as TTR inversely correlates with poor outcomes such as thrombosis or bleeding. Several studies have demonstrated that through maintaining a therapeutic INR and attaining a percentage of time spent in the TTR, fewer negative consequences could be anticipated with anticoagulant therapy, with a TTR cutoff of about 65%.[6-11] However, subtherapeutic levels of anticoagulation control are still commonly reported with warfarin therapy.[4,5,12]

Several factors can contribute to this out-of-range INR values including genetic predisposition, drug and diet interactions, cognitive impairment, poor adherence, and polypharmacy.[13-17] Therefore, it is important to evaluate the modifiable factors that can contribute to suboptimal warfarin therapy.

Up to the best of our knowledge, these factors that influence TTR in patients treated with warfarin are not evaluated in our region before. The goal of this analysis is to assess the predictors of quality of anticoagulation control in terms of TTR in nonvalvular atrial fibrillation (NVAF) patients.

METHODS

A retrospective observational study was conducted at the Heart Hospital in the state of Qatar for patients who were maintained on warfarin therapy (>6 months) at the outpatient warfarin clinic (OWC) between 2012 and 2013. Patients included in this study were those who diagnosed with NVAF and had Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke/Transient Ischemic Attack (CHADS2) scores of ≥1. Patients' demographics and clinical data were retrieved by reviewing the electronic records while INRs were measured on days 3, 5, and 10 of starting warfarin and then at least once a month thereafter to attain stable INR readings. We excluded results obtained during the first 6 months of therapy. The quality of anticoagulation management was assessed by calculating TTR based on INR range of 2.0–3.0 and using the longitudinal extrapolation method of Rosendaal *et al*.[18] Patients were categorized into two groups based on their TTR values (≥65% or high-quality anticoagulation group vs. <65% or low-quality anticoagulation group). The definition of major bleeding was based on the need of transfusing at least two units of packed red blood cells or bleeding associated with severe outcomes including profound hypotension.

The extracted data included age, sex, race, body mass index (BMI), comorbidities (hypertension, acute coronary syndrome, diabetes mellitus, chronic kidney disease, dyslipidemia, heart failure, depression, thyroid disorders), CHADS2 score, bleeding events, use of other medications (antiplatelet agents, antiarrhythmic medications, beta blockers, calcium blockers, angiotensin converting enzyme inhibitors/angiotensin receptor blockers, statins, furosemide, digoxin, antibiotics, oral hypoglycemic agents, insulin, thyroxin, phenytoin, proton pump inhibitors, ranitidine, antidepressants), basic laboratory results (creatinine, liver enzymes, bilirubin, and INR), number of warfarin clinic visits, doses of warfarin, and bridging with low-molecular-weight heparins (LMWHs). Polypharmacy defined as the use of ≥6 medications. As the data were collected retrospectively with confidentiality to protect patients' data, a waiver of consent was granted, and Ethical approval was obtained from the Medical Research Center (IRB #13208/13) at Hamad Medical Corporation, Doha, Qatar.

Statistical analysis

Data were expressed as proportions, mean ± standard deviation or percentages as appropriate. Data were analyzed and compared using Student's *t*-test for continuous variables. Categorical variables were presented as percentages and analyzed by Chi-square test. A significant difference was considered when a two-tailed $P < 0.05$. Multivariate analysis after adjusting for age and sex were performed to look for the predictors of poor coagulation control. Data analysis was carried out using the Statistical Package for Social Sciences version 18 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 241 patients with NVAF were identified; of them, 157 (65.1%) patients had TTR ≥65% while 84 (34.9%) patients showed TTR of <65%. Demographics and clinical characteristics of the study cohort are presented in Table 1. Overall patients median TTR was 70% (range 19–100). Mean TTR was relatively higher in Arabs in comparison to Asian patients (71% ±15% vs. 67% ±17%, $P = 0.15$). The two groups were comparable for age, race, gender, BMI, comorbidities, and medications used. Similarly, there was no difference between both groups in bridging with LMWHs, basic laboratory results, and CHADS2 score. Table 2 shows medications used based on the TTR.

The potential impact on INR control was statistically significant with better TTR readings in patients with nonpolypharmacy use compared to their counterparts (42% vs. 57.1%, $P = 0.03$) and patients with less frequent warfarin clinic visits (18 ± 4.8 vs. 22.3 ± 5.5, $P = 0.001$). Figure 1 shows the association between polypharmacy and TTR. During follow-up, major bleeding occurred in four cases only, and no stroke cases were reported. Patients in both groups had similar major bleeding rates ($P = 0.14$). After adjusting for age and sex, multivariate analysis showed that polypharmacy use (odds ratio = 1.89, 95% confidence interval: 1.03–3.33; $P = 0.03$) was predicting poor coagulation

Table 1: Patient demographics, risk factors, medications, and outcomes

Variable	TTR		*P*
	≥65% (*n*=157)	<65% (*n*=84)	
Age (mean±SD)	63.5±12	63.5±13	0.0.95
Gender, *n* (%)			
Male	83 (53.2)	39 (46.4)	0.32
Race			
Arab	129 (82.2)	62 (73.8)	0.06
Asian	28 (17.8)	22 (26.2)	for all
Warfarin dose	4.7±1.8	4.3±2.0	0.16
Number of clinic visits	18±4.8	22.3±5.5	0.001
BMI (mean±SD)	31.6±7.3	30±8.2	0.27
CHADS2 (mean±SD)	2.2±0.7	2.1±0.6	0.72
Alanine transaminase (mean±SD)	21±12.5	21±11	0.98
Serum creatinine (mean±SD)	95.5±77	107±91	0.32
Diabetes mellitus, *n* (%)	63 (40.1)	28 (33.3)	0.33
Chronic kidney disease, *n* (%)	16 (10.2)	16 (19.0)	0.05
Heart failure, *n* (%)	64 (40.8)	33 (39.3)	0.82
Acute coronary syndrome, *n* (%)	25 (15.9)	10 (11.9)	0.4
Hypertension, *n* (%)	114 (72.6)	63 (75.0)	0.69
Hyperlipidemia, *n* (%)	88 (56.1)	40 (47.6)	0.21
Depression, *n* (%)	5 (3.2)	0	0.10
Major bleeding, *n* (%)	4 (2.5)	0	0.14

CHADS2: Congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus, scores 1 point each, and prior history of stroke/transient ischemic attack scores 2 points. Inhibitors/angiotensin receptor blockers. BMI: Body mass index, TTR: Time in therapeutic range, SD: Standard deviation

Table 2: Medications used based on the time in therapeutic range

Variable	TTR		*P*
	≥65% (*n*=157)	<65% (*n*=84)	
Aspirin, *n* (%)	48 (30.6)	24 (28.6)	0.75
Clopidogrel, *n* (%)	14 (8.9)	4 (4.8)	0.24
Digoxin, *n* (%)	39 (24.8)	19 (22.6)	0.7
Calcium channel blockers, *n* (%)	47 (29.9)	27 (32.1)	0.72
ACEIs/ARBs, *n* (%)	105 (66.9)	51 (60.7)	0.34
Statins, *n* (%)	88 (56.1)	40 (47.6)	0.21
Antiarrhythmic medications, *n* (%)	11 (7.0)	6 (7.1)	0.97
Bridging with LMWH, *n* (%)	44 (28)	32 (38.1)	0.11
Levothyroxine, *n* (%)	17 (10.8)	10 (11.9)	0.8
Furosemide, *n* (%)	64 (40.8)	33 (39.3)	0.82
Anti-depressants, *n* (%)	5 (3.2)	0 (0.0)	0.10
Phenytoin, *n* (%)	1 (0.6)	1 (1.2)	0.65
PPIs, *n* (%)	55 (35)	36 (42.9)	0.23
Ranitidine, *n* (%)	17 (10.8)	9 (10.7)	0.98
Insulin, *n* (%)	14 (8.9)	9 (10.7)	0.65
Oral hypoglycemic agents, *n* (%)	55 (35.0)	25 (29.8)	0.41

ARBs: Angiotensin receptor blockers, ACEIs: Angiotensin-converting enzyme inhibitors, LMWHs: Low-molecular-weight heparins, PPIs: Proton pump inhibitors, TTR: Time in therapeutic range

control. Figure 2 shows multivariate analysis for predictors of TTR.

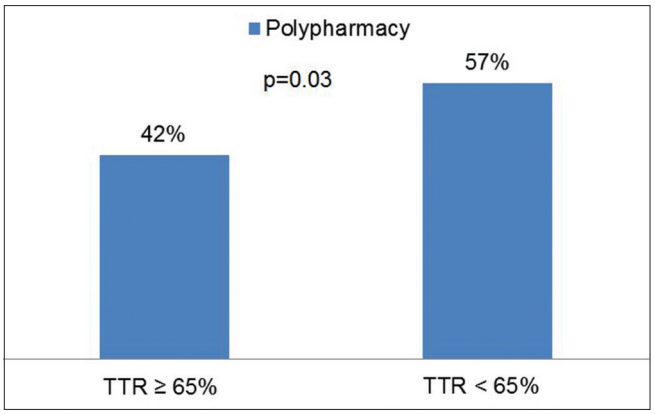

Figure 1: The association between polypharmacy and time in therapeutic range

DISCUSSION

The current study is unique from our Arab Middle Eastern region that assesses the quality of anticoagulant therapy (TTR) using the method of Rosendaal *et al*.[18] Our study identified factors associated with low-quality of anticoagulation control in patients with NVAF treated with warfarin. To assess the quality of warfarin therapy, TTR value of 65% was used to assess the efficiency anticoagulation control. After adjusting for age and sex, polypharmacy use was significantly predicting poor coagulation control in our cohort.

A *post hoc* analysis of the active W trial showed no treatment benefit with warfarin compared with the combined aspirin and clopidogrel therapy in patients with a TTR below the median value of 65%, while there was a major reduction in vascular events in patients with a TTR ≥65%.[7] In the present study, patients with nonpolypharmacy had their target INR range maintained for a longer time resulting in higher TTR (≥65%) than their counterparts at equivalent warfarin doses. It is generally accepted that taking multiple medications is linked with increased risk of drug interactions, cognitive impairment, reduced functional capacity, and nonadherence that can lead to sub-optimal INR readings.[19] Due to the fact that we did not assess socioeconomic, language barriers and educational factors especially with the multicultural population in Qatar, one can argue that nonadherence may be a major contributing factor for lower TTR readings in our patients with polypharmacy use. However, several initiatives that promote cultural competencies are integrated throughout our organization to provide culturally appropriate patient care. Ensuring access to interpreters, a private counseling room and the use of advanced technology by the pharmacy department in counseling patients and dispensing of medications are major contributors for better adherence. Therefore, we do believe that patients at our institution are receiving appropriate counseling regarding the importance of drug adherence

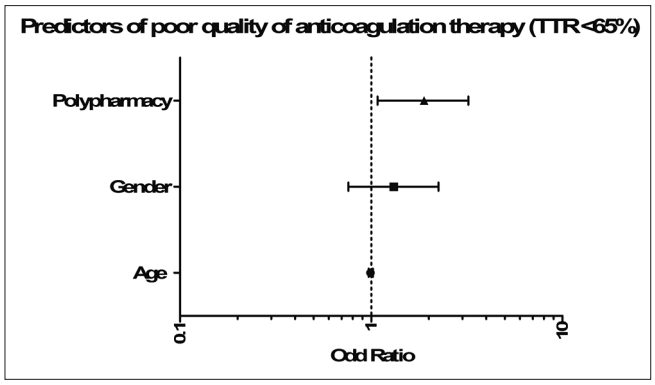

Figure 2: Multivariate analysis for predictors of time in therapeutic range

to maximize safety and efficacy of prescribed medications with a special focus on warfarin. Our analysis also revealed that the impact of polypharmacy on TTR readings may not be due to significant drug interactions as both groups were comparable in terms of antiarrhythmic medications and phenytoin use that may interact with warfarin through altering the drug-metabolizing enzyme system.

Interestingly, poor quality of anticoagulation was associated with frequent OWC visits. Of note, guidelines are not consistent in terms of the optimal time between INR tests due to a paucity of evidence. In this context, our results were similar to those shown in a study that was conducted by Rose *et al*.[20] which examined the impact of length of time of follow-up between clinic visits and TTR values at 100 centers in 104,451 people receiving warfarin. In that study, about 65% of the entire cohort had atrial fibrillation with a target INR of 2.0–3.0. Results revealed that TTR increased as the number of days between INR checks increased.

Our results have shown that in comparison to the high-quality TTR cohort, similar proportions of NVAF patients in the low-quality warfarin TTR cohort had comorbidities. This is in contrast to the findings of other large real-world studies which have shown that certain comorbidities such as heart failure, diabetes, and cancer, are predictive of low warfarin TTR.[21-23]

In the present study, there was no association between age and the quality of anticoagulation control despite conflicting results on its effect on TTR in the literature. Two studies found no differences in age among groups categorized based on TTR values.[1,6] However, Melamed *et al*. found poor quality control of anticoagulant therapy in patients >70 years old[24] while another study revealed that age more than 50 years predicted a good quality of anticoagulation with higher TTR.[25] Similarly, despite the fact that female gender was associated with low TTR in several studies,[21,26] our study has shown inconsistent findings with no difference observed between both groups.

We also found that race was comparable between the two groups indicating a minor impact of race on the anticoagulation control.

Another interesting finding is that despite having an average CHADS2 score of around 2 suggesting an overall low risk of thrombosis, a good percentage of patients in both groups received bridging with LMWHs. Hence, the practice of routine bridging when the anticoagulation interruption is indicated needs to be revised.

Our results revealed that the adverse effect of major bleeding was similar between both groups. Of note, our present study analyzed an intermediate outcome (TTR) and not the clinical outcomes of thromboembolic complications and mortality.

The overall quality of anticoagulation control was satisfactory in our cohort with a comparable or even higher TTR reported in previous studies. One systematic review[27] reported a TTR of 61% (ranging from 48.6% to 76.7%) and most of the included studies were conducted in developed countries in North America and Europe. Our report revealed a better quality control than that in Asians with an average TTR of 55% suggesting low quality of anticoagulant therapy in this population.[28]

The present study highlights the issue of potential interaction between polypharmacy and the frequency of warfarin clinic visits on the quality of anticoagulation control. The association between lower TTR readings with increased numbers of medications coadministered raises the need for closer monitoring of patients with polypharmacy. Thus, it is important to minimize as possible the number of medications prescribed to patients. Utilizing fixed-dose combination pills and removing drugs with no clear indication could help better control. Furthermore, patients in the low-quality group had suboptimal TTR readings despite frequent OWC visits may warrant shifting to the new oral anticoagulant drugs, such as dabigatran, apixaban, and rivaroxaban, which will thus negate INR monitoring. However, the risk of bleeding should be of consideration.

Limitations

The retrospective nature of this analysis may influence our findings. Information about educational and socioeconomic status was not explored as well. Our study did not assess the clinical impact of TTR variation. We were also unable to fully account drug and food interactions and the inherent impact on INR values.

CONCLUSIONS

In NVAF patients, TTR is generally high in our cohort with no significant influence of age, gender, race,

and comorbidities. Patients with polypharmacy and frequent clinic visits have lower TTR. High-quality of oral anticoagulation could be achieved through optimizing TTR without a risk of bleeding. Patients may need closer monitoring and intervention to minimize polypharmacy as possible.

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Conflicts of interest
There are no conflicts of interest.

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