Quality of anticoagulation control among patients with atrial fibrillation: An experience of a tertiary care center in Saudi Arabia

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Sarah M. Alyousif [a,*], Ahmed A. Alsaileek [b,1]

[a] Pharmaceutical Care Department, King Abdulaziz Cardiac Center, King Abdulaziz Medical City, Ministry of National Guard
[b] King Abdulaziz Cardiac Center, King Abdulaziz Medical City, Ministry of National Guard

[a,b] Saudi Arabia

Background: Atrial fibrillation (AF) is the most common chronic rhythm disorder. Patients with AF are at an increased risk of ischemic stroke. Therefore, optimal anticoagulation is essential to reduce the risk of stroke. The aim of this study was to assess the level of anticoagulation control achieved in patients with nonvalvular AF receiving medical care in a tertiary care hospital.

Methods: This was a retrospective cohort study in ambulatory care clinics at tertiary care hospital in Saudi Arabia. We included 110 nonvalvular AF patients treated with warfarin for at least 3 months at King Abdulaziz Medical City, Riyadh, Saudi Arabia, between May 1, 2012, and July 31, 2012. Thereafter, international normalized ratio results were collected for 1 year. Anticoagulation control was assessed by calculating time within therapeutic range (TTR) as per the Rosendaal method.

Results: The mean age was 64.9 ± 16.5 years; 60.9% were female. The mean TTR was 59%. Almost one third of the patients (32.7%) had poor anticoagulation control; TTR of <50%. Poor anticoagulation control was significantly associated with higher CHADS2 (congestive heart failure, hypertension, age, diabetes, stroke) score ($p = 0.043$). TTR was not significantly different between men and women. Similarly, TTR was not associated with age or duration of anticoagulation. There was no adequate information to assess the effect of other factors such as diet, compliance, and level of education on anticoagulation. Thirty-one patients (28.2%) had a history of prior stroke. The overall quality of anticoagulation was not significantly different between patients with and without stroke, (TTR was 56.3% and 60.1%, respectively; $p = 0.46$).

Conclusion: Quality of anticoagulation in patients with AF receiving medical care in a tertiary care hospital was suboptimal, with nearly 40% of the time spent outside the therapeutic range. Methods to improve anticoagulation control among patients with AF should be implemented.

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* Corresponding author.
E-mail address: alyousifsm@gmail.com (S.M. Alyousif).
[1] Address: Health Affairs, PO BOX 22490, Riyadh 11426, Kingdom of Saudi Arabia.

Saudi Heart Association

P.O. Box 2925 Riyadh – 11461KSA
Tel: +966 1 2520088 ext 40151
Fax: +966 1 2520718
Email: sha@sha.org.sa
URL: www.sha.org.sa

King Saud University

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Introduction

Atrial fibrillation (AF) is the most common cardiac rhythm disorder. It is associated with a 4–5-fold increased risk for ischemic stroke [1]. The use of oral anticoagulants such as warfarin has been shown in the clinical trials to reduce the risk of ischemic stroke [2,3]. Thus, warfarin therapy is widely used in patients with AF with high CHADS2 (congestive heart failure, hypertension, age, diabetes, stroke) score and is recommended by various medical societies including the American College of Chest Physicians, Glenview, IL, USA [4–6]. Nevertheless, in order to achieve maximal protection against stroke and to minimize bleeding complications, warfarin therapy must be tightly controlled and maintained within a narrow therapeutic range of international normalized ratio (INR) values between 2 and 3. This task is not easy to achieve as INR levels are known to be influenced by several factors including patient age, concurrent medications, genetic makeup, herb consumption, and diet [7,8]. As a result, oral anticoagulant therapy requires regular monitoring, which can be inconvenient for patients and healthcare providers. The time spent within the therapeutic range (TTR) is the recommend tool used to assess the quality of the anticoagulation control and has a paramount effect on patient outcome such as stroke events and mortality [5,9]. The literature acknowledges the superior outcomes of anticoagulation clinics over routine medical care in terms of anticoagulation control in the

USA [10]. In this study we describe the quality of anticoagulation control achieved in patients with AF receiving medical care within specialized anticoagulation clinic operated by clinical pharmacist in a tertiary care center in Saudi Arabia. The purpose of this study was to assess the quality of anticoagulation control (expressed as TTR) and to explore specific patient related factors that may have significant impact on the level of anticoagulation.

Material and methods

This was a retrospective cohort study conducted at King Abdulaziz Medical City (KAMC), Riyadh, Saudi Arabia from May 1, 2012 to April 30, 2013. The hospital is a tertiary care center with well-developed infrastructure including the use of electronic medical records. All patients had full medical coverage by the National Guard Health Affairs with pharmacy benefits for prescription medication. A computerized anticoagulation clinic database was used to identify all patients with a diagnosis of AF who were treated with warfarin for at least 3 months prior to the study period. Patients were excluded if they fulfilled any of the following criteria: (1) were younger than 18 years; (2) had an active malignancy; (3) had indication for anticoagulation other than AF; (4) had valvular heart disease; and (5) had fewer than five INR determinations during the study period. All records retrieved from the database were audited manually by a researcher (S.M.A) for concordance with the above-mentioned criteria. A total of 110 patients met the study inclusion criteria and were included in the analysis. The patients were managed by a group of clinical pharmacists during the study period. A computerized database provided demographics (e.g., age, sex, height, and weight), medical diagnoses, and CHADS2 score. In addition, the number and value of INR determinations for each patient were collected for up to 1 year after the enrolment period. Anticoagulation control was assessed by measurement of time spent within the therapeutic range TTR (i.e., time in which patient INR values were between 2 and 3). The therapeutic range was calculated with an Excel sheet (Microsoft Corporation, Redmond,

Abbreviations

AF	atrial fibrillation
CHADS2	congestive heart failure, hypertension, age, diabetes, stroke
INR	international normalized ratio
TTR	time in therapeutic range

Table 1. Baseline characteristics.

Variable	All patients $n = 110$
Age (y)	65.9 ± 16.5
Female	67 (60.9)
Height (cm)	155.6 ± 21.1
Weight (kg)	76.9 ± 16.6
BMI (kg/m^2)	32.8 ± 18.8
CHADS2	2.8 + 1.1
CHADS2 ⩽2	61 (55.5)
CHADS2 2.1–4	36 (33.6)
CHADS2 >4	12 (10.9)
Prior stroke	31 (28.2)
TTR Rosendaal	59.0 ± 24.2
TTR (average%)	55.6 ± 22.3
Follow-up duration	284.4 ± 73.1
INR 2–3	491 (55.6)
INR <2	246 (27.9)
INR >3	146 (16.5)

Data are presented as n (%) or mean ± standard deviation.
BMI = body mass index; CHADS2 = congestive heart failure, hypertension, age, diabetes, stroke; INR = international normalized ratio; TTR = time in therapeutic range.

WA, USA) that utilized a linear interpolation model, as described by Rosendaal et al. [11]. The TTR was then classified as follows: (1) TTR level <50% was considered to represent poor anticoagulation control; (2) TTR level between 50% and 75% was considered to represent good anticoagulation control; and a (3) TTR level >75% was considered to represent excellent anticoagulation control. This stratification allowed characterization of patient subsets associated with the different control levels. All statistical analyses were performed using SPSS, version 20.0 (SPSS Inc., Chicago, IL, USA). Potential predictors of poor control were assessed in univariate models (χ^2 test for categorical variables and analysis of variance for continuous variables). A p value <0.05 was considered significant. The study was approved by the local ethical committee (King Abdullah International Research Centre, IRB) and carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Results

Table 1 summarizes clinical characteristics of study population. The mean age was 64.9 ± 16.5 years; 60.9% were female. Forty-nine patients (45.5%) had more than two risk factors for ischemic stroke (age >75 years, diabetes mellitus, hypertension, heart failure, or prior stroke). None were taking antiarrhythmic medications known to interfere with INR level including amiodarone, flecainide, propafenone, sotalol, dofetilide, quinidine, or dronedaron. The mean duration of anticoagulation was 284.4 ± 73.1 days, during which 883 INR determinations were performed. The average number of INR determinations per patient was 8 ± 1. The mean TTR was 59.0 ± 24.1%. Of 110 patients, 32.7% had poor anticoagulation control (Rosendaal TTR <50%), 40.9% had good control (TTR 50–75%), and only 26.4% had excellent anticoagulation control (TTR >75%). Of 883 INR tests, 55.6% were within,

27.9% above and 16.5% below the therapeutic range. Poor anticoagulation control was not associated with age, female sex, or duration of anticoagulation (Table 2). By contrast, there was significant trend towards worse anticoagulation control in patients with higher CHADS2 score (CHADS2 scores were 3.1 ± 1.2, 2.7 ± 1.0, and 2.5 ± 1.0 in patients with poor, good, and excellent anticoagulation control, respectively; $p = 0.043$). Thirty-one patients (28.2%) had a history of prior stroke. The overall quality of anticoagulation was not significantly different between patients with and without stroke (TTR was 56.3% and 60.1%, respectively; $p = 0.46$).

Discussion

This study showed that patients with nonvalvular AF receiving medical care by clinical pharmacists within a large tertiary care center had suboptimal anticoagulation control with a mean TTR of 59%. Additionally, poor anticoagulation control was observed in patients with higher CHADS2 scores. Our results are consistent with the previous studies that showed better anticoagulation control in dedicated anticoagulation clinic control (TTR, 63%; 95% confidence interval, 58–68%) [12,13] compared to routine medical care on a community-based AF anticoagulation control (TTR, 51%; 95% confidence interval, 47–55%) [14]. We also showed that most of the time spent out of the therapeutic range is due to inadequate anticoagulation rather that over-anticoagulation.

Different patient characteristics are possible reasons for discrepant control levels. Poor control has been reported among populations affected by comorbidities. In our study, we did not analyze individual comorbid condition as reason for poor control. However, we found significant association between the level of anticoagulation and CHADS2 score. Considering that most patients with high CHADS2 score have history of stoke, it is extremely important to keep optimal TTR in these patients. By contrast, patients with stoke may have

Table 2. Patient characteristics associated with poor anticoagulation control.

Variable	TTR <50 $n = 36$	TTR 50–75 $n = 45$	TTR >75 $n = 29$	p
Age (y)	68.6 ± 15.6	63.8 ± 16.6	62.1 ± 16.9	0.24
Female	21 (58.3)	27 (60.0)	19 (65.6)	0.83
Follow-up duration	271.4 ± 80.3	288.7 ± 75.5	294.8 ± 56.7	0.40
CHADS2	3.1 ± 1.2	2.7 ± 1.0	2.5 ± 1.0	0.043*
BMI (kg/m^2)	33.2 ± 26.9	31.1 ± 7.2	34.8 ± 19.0	0.70
Prior stroke	12 (33.3)	11 (24.4)	8 (27.6)	0.67

Data are presented as n (%) or mean ± standard deviation.
BMI = body mass index; CHADS2 = congestive heart failure, hypertension, age, diabetes, stroke; SD = standard deviation; TTR = time in therapeutic range.

considerable physical and mental disabilities and without adequate family support, high quality anticoagulation may not be easily achieved [15]. Our results were similar to those previously reported, which showed no age or sex difference among anticoagulation control groups [16]. It is perceived that longer anticoagulation duration is associated with poor control [15]. A possible explanation for this belief is frequent INR determinations and shorter time between visits in patients recently enrolled in the anticoagulation clinic compared to those at longer follow-up. Our result showed that there is no association between the quality of anticoagulation and follow-up duration. Moreover, TTR was not different between patients who had fewer than five INR tests during the study period compared to those with more frequent testing. A number of studies have addressed the effect of diet on anticoagulation. Mediterranean diet has been recently shown to have no significant effect on quality of anticoagulation [17]. Herbal consumption, however, had a significant effect on anticoagulation [18]. There is no previous study that has addressed specific diet in the Middle East or Gulf region. In our study, it was especially difficult to obtain information about diet in our study cohort. Level of patient education may affect the anticoagulation level. A previous study showed that limited health literacy is associated with poor anticoagulation control for patients on warfarin therapy [19]. Lack of medication understanding may hinder the safe and effective use of this narrow therapeutic index drug. We believe that patient education during clinic visits is an essential part of the management. We found no adequate information related to this aspect. In a busy clinic, time assigned for each patient may hinder patient education. Given the retrospective approach, it was not possible to assess the time spent with patients in our study cohort. Instead we reviewed the administrative data over 3 months and collected information about the number of patients in each clinic and the time spent with each patient during their visit to the anticoagulation clinic; on average each patient spent 8 minutes being assessed. This was relatively short and, given the complexity of the medical care in the current practice, caregivers may have found it impossible to spend adequate time for education.

Since optimal anticoagulation control is desirable on both medical and economic grounds, ways to improve control should be sought. If good anticoagulation control cannot be achieved within the current care setting, a validated alternative option such as handheld patient INR meters may be advisable [20]. In the Japanese population, introduction of point-of-care testing in outpatient clinics was associated with improvement in time in therapeutic range in anticoagulant-treated patients [21]. Despite the above-mentioned efforts, warfarin may not ultimately provide the optimal anticoagulation needed. Therefore, its substitution with newer oral anticoagulant drugs may eventually be inevitable. Such drugs have recently proved their efficacy and may be the anticipated substitute for warfarin [22]. As the newer anticoagulant drugs are associated with substantial cost, a careful cost–benefit analysis should be conducted to determine their feasibility.

Poor anticoagulation is associated with increased risk of stroke and to a lesser extent major bleeding [4]. Significant improvement in time to stroke event has been reported in those patients with INR control of >70% of time in therapeutic range (2.0–3.0) compared with the non-warfarin treatment group. In our study, nearly one third of our patients had a history of prior stroke. The study follow-up duration was short (284.4 ± 73.1 days, range 46–361 days), so it is impossible to obtain adequate data about the impact of anticoagulation on stroke.

Our study has several limitations. First, we were unable to acquire data concerning clinical outcomes such as stroke and bleeding event rates for our study population. For that reason, we elected to use anticoagulation control as a surrogate indicator for outcome, given the strong association between TTR levels and clinical outcomes [5,9]. Second, we could not assess scheduled interruptions of oral anticoagulants (i.e., periprocedural, hospitalization), which may have resulted in underestimation of the TTR levels of the study group; finally, our population had a low burden of comorbidities (55.5% of the patients has CHAD2 score of ⩽2), which may limit the study's generalizability to other settings.

Conclusion

This study provides important information about quality of anticoagulation control of patients with AF who receive medical care within a large tertiary care hospital in Saudi Arabia. Overall, patients with AF had suboptimal control, with nearly 40% of the time spent out of the therapeutic range. Patients with high CHADS2 were more likely to have poor anticoagulation. These patients in particular could benefit from methods aimed at improving control such as using point-of-care INR

test, or shifting to new anticoagulant drugs that do not require blood level monitoring.

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