Original Research

Quality of Anticoagulation with Warfarin Across Kuwait

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Introduction: Warfarin is widely used in patients with non-valvular atrial fibrillation (AF) because it is effective in reducing thromboembolic complications. However, it has a narrow safe therapeutic window. We aimed to examine the frequency of maintaining this therapeutic window in daily practice.

Methods: We enrolled consecutive patients with non-valvular AF presenting to five busy general hospitals in Kuwait for regular international normalised ratio (INR) testing. Patients were required to be on warfarin for more than 3 months and to have had at least 5 INR measurements. We recorded up to 20 INR measurements per patient. Time in therapeutic range (TTR) was assessed by the Rosendaal method and the percentage of INR measurements in the therapeutic range was recorded.

Results: A total of 369 patients with non-valvular AF underwent 4392 INR measurements. (mean age 62.89 ± 11 years, 56% women, 78% had hypertension and 58% had diabetes). Mean duration of warfarin use was 13 ± 9.1 months. Of all INR measurements, 47% were in the therapeutic range of 2–3 and TTR by Rosendaal method was 52.6%.

Conclusions: The quality of anticoagulation with warfarin in non-selected daily practice in Kuwait is poor. This could have serious implications for patients' outcomes.

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Several randomized trials in the 1990s showed oral anticoagulation (OAC) therapy with warfarin to be substantially more efficacious than aspirin in reducing stroke in patients with atrial fibrillation (AF).[1] Based on this evidence, guidelines for the management of AF published in the United States and Europe[2-3] recommend chronic OAC for patients with non-valvular AF who have risk factors for ischemic stroke and systemic thromboembolism. The gold standard agent used for OAC is warfarin. Physicians have to titrate its doses according to measurements of individual and serial international normalised ratio (INR). Obtaining strict and consistent INR levels results in the desired benefit and safety of warfarin.[4] This consistency of INR control is translated into a time in therapeutic range (TTR) of 58% or higher and leads to a more than twofold reduction in vascular events.[5]

Assessing TTR in physicians' daily practice allows physicians to measure the success and complications of warfarin therapy. Achieving a TTR of 58% is central to this success; however, it is considered to be a challenge even in tightly controlled randomised trials, let alone real-world practice.[6] Therefore, we planned to assess the quality of chronic OAC in daily clinical practice in 5 hospitals across Kuwait.

Methods

This retrospective multicenter study was conducted in 5 hospitals in Kuwait during July 2011. The study protocol was approved by a central joint committee for the protection of human subjects in research. Written informed consent was obtained from all patients.

Study patients

Patients with non-valvular AF were enrolled if they were aged 21 years or older, had been taking warfarin for more than 3 months, and had a minimum of 5 INR measurements available. We collected baseline data and up to a maximum of 20 previous INR measurements from a review of the patients' charts or their INR record booklet.

Determining TTR

TTR was determined using the following methods:

1. Traditional method (proportion of INR readings in therapeutic range). This method counts the number of INR values in the therapeutic range and divides them by the total number of measurements obtained.
2. Rosendaal method (percentage of days in therapeutic range). This method assumes that there is a linear relationship between two INR values and allows one to allocate a specific INR value to each day for each patient.[7]

Statistical analysis

The patients' clinical characteristics and the distribution of INR and TTR were described using standard descriptive and comparative statistics. Continuous variables are presented as mean ± standard deviation, while categorical variables are presented as frequencies and percentages. The chi-square (χ^2) test or likelihood ratio was used for comparison between the distributions of two categorical variables. One-way ANOVA (F-test) was used for comparison between means of more than two samples. We examined the quality of OAC based on the length of time the patient had been taking warfarin and divided the duration into three different time periods: 3 to <6 months, 6-12 months and >12 months. In multiple logistic regression analysis, the association between exposure (age, gender, duration, history of antihypertensive therapy, history of antidiabetic therapy) and outcome (inadequate anticoagulation) was expressed in terms of odds ratio (OR) and 95% confidence interval (95% CI). All explanatory variables included in the logistic model were categorized into two or more levels. A p-value <0.05 was considered statistically significant. All data analysis was carried out using the Statistical Package for Social Sciences version 19 (SPSS Inc, Chicago, IL).

Results

Patients' clinical characteristics

We enrolled 369 patients with non-valvular AF who were receiving chronic warfarin therapy. The total number of INR measurements was 4392. The mean age of the study population was 62.9 ± 11 years and 207 (55.5%) were women. Diabetes mellitus and hypertension were present in 215 (57.6%) and 291 (78%) of patients, respectively. The mean duration of anticoagulation at the time of enrolment was 13 ± 9.1 months (range 0.97–64.4 months) and 301 (80.7%) had been on warfarin for more than 1 year. The majority, 358 (95.9%), had more than 5 INR measurements. The mean number of INR measurements per person per month was 1.2 ± 0.71.

Adequacy of OAC

Using the traditional method, 47% of all INR values were found to be in the therapeutic range of 2–3. Using the Rosendaal method, TTR was 52.6% and a TTR of more than 58% was achieved in 166 (44.5%) patients.

For the three different durations of warfarin consumption: 3 to <6 months, 6-12 months and >12 months, TTR using the traditional method was 39.4%, 41.1%, and 47.9%, respectively (Table 1). TTR >58% (Rosendaal method), was 36.8%, 50%, and 44.8% in the three time durations, respectively.

Table 2 shows that among patients with non-valvular AF on warfarin, females (OR=1.9, 95% CI: 1.2–3.0, p<0.001) and patients with no history of hypertension (OR=2.0, 95% CI: 1.2–3.6, p<0.001) were more likely to have poor anticoagulation (expressed as Rosendaal <58%).

Discussion

Patients taking warfarin for non-valvular AF in the uncontrolled environment of daily practice in Kuwait

Table 1. Distribution of INR and TTR in the three time durations of warfarin consumption.

	OAC > 1 year n=301	OAC 6–12 months n=30	OAC 3–6 months n=38	p
Fractions of INR in range:				
INR < 2 n (%)	1429 (38)	120 (39)	130 (47)	0.001
INR 2-3 n (%)	1808 (48)	125 (41)	108 (39)	NS
INR >3 n (%)	533 (14)	59 (19)	36 (13)	NS
The Rosendaal TTR method:				
Overall TTR (%)	53	52	48	NS
TTR > 58% n (%)	135 (45)	15 (50)	14 (37)	NS
TTR>50% n(%)	178 (59)	16 (53)	15 (39)	NS

INR – international normalised ratio; OAC – oral anticoagulation; NS – non-significant; TTR – time in therapeutic range.

Table 2. Multiple logistic regression analysis showing the factors associated with inadequate anticoagulation (Rosendaal TTR<58%).

Factors	OR (95% CI)	p
Female gender	1.9 (1.2–3.0)	<0.01
No history of hypertension	2.03 (1.2–3.6)	<0.01

TTR – time in therapeutic range; OR – odds ratio; CI – confidence interval.

achieved a TTR of 52.6% and only 47% of their INRs fell in the therapeutic range of 2 to 3. As a result, patients were spending most of the time outside the recommended therapeutic range. The quality of anticoagulation was poorer in women and patients with no history of hypertension.

Epidemiological studies have shown that AF increases the risk of stroke by four- to fivefold[8] and the risk of death from AF-related stroke is doubled.[9,10] Randomised controlled trials in patients with non-valvular AF have established the efficacy of OAC with warfarin for reduction of thromboembolism.[11-13] However in order to achieve this reduction, two important conditions are required. First, a certain level of anticoagulation should be achieved, corresponding to an INR of 2–3.[11-13] Second, this optimal INR level should be persistent and consistent throughout the duration of treatment.[1] The consistency of maintaining an effective INR is reflected by TTR, which is a measure of the duration of time that the patient spends within an optimal INR range. It has been demonstrated that a TTR of 58% indicates adequacy of anticoagulation and results in more than a twofold reduction of vascular events.[4,14,15] Analysis of outcomes of patients randomized to warfarin therapy in the SPORTIF III and V studies indicated that the risks of death, myocardial infarction, and stroke or systemic embolic event were lower in patients with TTR ≥60% compared to those with TTR <60%.[16] A *post-hoc* analysis of the ACTIVE W study showed that for hospitals, a target threshold TTR exists (estimated between 58% and 65%) below which there appears to be little benefit of OAC over antiplatelet therapy.[17] It is alarming that our hospitals were found to have a TTR below this target threshold.

Warfarin has been shown in clinical trials to significantly reduce the risk of stroke in AF patients by 64% (absolute risk reduction of 2.7% for primary prevention and 8.4% for secondary prevention) versus controls.[18] However, these rates of efficacy have not been duplicated in daily practice outside controlled trials. An analysis of Medicare beneficiaries with AF showed a disappointing 35% reduction in ischemic strokes among patients exposed to warfarin versus those who did not receive warfarin, revealing a discrepancy between effectiveness in clinical trials and actual clinical practice.[19] This discrepancy is probably due to the fact that physicians achieve a lower quality of anticoagulation (translated into lower TTR) in daily practice compared to controlled trials. Possible reasons for a lower achieved TTR in daily practice include less patient compliance, less strict monitoring of INR, the absence of a normogram that is followed by all treating physicians, multiple physicians providing instructions for changes in warfarin dose, and uncontrolled interruption and resumption of warfarin before and after surgical and dental procedures. Our study was undertaken in 5 large hospitals across Kuwait and confirms the poor quality of anticoagulation in daily practice, with patients being in the therapeutic range only about 50% of the time. It is disappointing to see that this poor INR control was present even in patients who had been consuming warfarin for more than 12 months. The finding that

women achieved a lower TTR than men has been observed by others.[20] However, it is not clear why that is the case.

Clinical implications

The quality of chronic OAC with warfarin in daily clinical practice in Kuwait is poor. This can have serious implications, as it is expected to adversely affect patient outcomes. It will be extremely useful to study the influence of this inadequacy of anticoagulation on stroke and mortality outcomes in the patient population of Kuwait, taking in consideration that our AF patient population has different baseline characteristics compared to those reported in the literature from Europe and North America.[21] In addition, the reasons behind the poor control need to be explored. This will guide educational programs directed at patients and physicians, which are urgently needed to improve the quality of OAC therapy in Kuwait. Finally, whether the availability of new oral anticoagulants, which do not require frequent monitoring, would prove to be safer and more effective than warfarin in daily practice, needs to be examined.

Limitations

The study did not collect data regarding factors that could possibly affect INR values. These factors include types of food consumed, antibiotic use, and possible disruption and resumption of warfarin use by patients before and after anticipated surgical and dental procedures. In addition, although it was not the purpose of the study, we did not collect data that might correlate TTR and systemic thromboembolic events.

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