Original Article

Evaluation of Time in Therapeutic Range (TTR) in Patients with Non-Valvular Atrial Fibrillation Receiving Treatment with Warfarin in Tehran, Iran: A Cross-Sectional Study

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ABSTRACT

Introduction: Anticoagulant control is assessed by Time in Therapeutic Range (TTR). For a given patient, TTR is defined as the duration of time in which the patient's International Normalized Ratio (INR) values were within a desired range.

Aim: To assess TTR in patients receiving treatment with warfarin for non-valvular atrial fibrillation at a referral center for cardiovascular diseases in Tehran, Iran.

Materials and Method: Over 6 months, we enrolled eligible patients presenting to Shaheed Rajaie Hospital in Tehran for regular INR testing. Demographic data, medical history, and current medications were determined for all participants. TTR was assessed by the Rosendaal method.

Results: A total of 470 patients (mean age 58.0±14.2 years, 60.2% women) underwent 1450 INR measurements. The mean TTR was calculated as 54.9±11.9%. Of the sample patients, 37.3% were in the good control category (TTR > 70%), 24.6% were in the intermediate category (50% < TTR < 70%), and 38.1% were in the poor control category (TTR < 50%). The number of current medications above four was a significant predictor of poor control (OR = 2.06; 95% CI, 1.87, 2.23). The mean TTR of the studied patients (54.9%) was below the good control range.

Conclusion: The quality of anticoagulant therapy with warfarin in Iranian patients was poorer than that reported in European countries. Based on these results, research considering the causes of poor TTR among Iranian patients is recommended.

Keywords: Anticoagulant, Iranian patients, International Normalized Ratio

INTRODUCTION

Warfarin is now the most widely-used anticoagulant in the world. In the United Kingdon (UK), it has been estimated that at least 1% of the whole population is taking warfarin [1]. Although new oral anticoagulants are available, warfarin remains a viable oral anticoagulant for many patients because of its availability and cost [2]. The risk of warfarin-induced bleeding complications is well-known and is typically managed with vitamin K, which restores the production of vitamin K–dependent coagulation factors within 12–24 hour [3]. The therapeutic range for warfarin therapy is defined in terms of the International Normalized Ratio (INR). The INR is calculated as the prothrombin time ratio (patient prothrombin time/mean of normal prothrombin time for laboratory)^{ISI}, which uses the International Sensitivity Index (ISI) for an exponent, and is dependent on the specific reagents and instruments used in the measurement. For most reagent and instrument combinations in current use, the ISI is close to 1, making the INR roughly the ratio of the patient prothrombin time to the mean normal prothrombin time [4]. Obtaining exact and consistent INR levels maximizes the desired benefits and safety of warfarin [5]. The Time in Therapeutic Range (TTR) estimates the percentage of time a patient's INR is within the desired treatment range or goal and is widely-used as an indicator of anticoagulation control. TTR is commonly used to evaluate the quality of warfarin therapy and is an important tool for assessing the risks versus benefits of warfarin therapy [6]. There are 3 methods for assessing TTR in patients taking warfarin: 1) Calculating the fraction of INRs that are in range, which is the conventional method; 2) Evaluating a cross-section of the patient's files; and 3) using the Rosendaal method [7,8]. Assessing TTR allow physicians to estimate the success of warfarin therapy in patients, because it is a major determinant of warfarin's efficacy and safety, with the maximum benefits evident when TTR is >70% [6,9]. The aim of the present study was to evaluate TTR in patients with non-valvular atrial fibrillation who were receiving warfarin therapy at a referral hospital for cardiovascular diseases in Tehran, Iran.

MATERIALS AND METHODS

This cross-sectional study was done during six months (between September 2014 to March 2015) at outpatient anticoagulant clinic of Shaheed Rajaie Hospital, Tehran, Iran. This is a well-known center for the treatment of cardiovascular diseases in Iran. Patients diagnosed with non-valvular atrial fibrillation were included in the study if they were between 30-85-years-old and had been taking warfarin for >3 months. Patients who did not want to participate in the study were excluded. All study participants signed consent forms after the study procedures were explained. Demographic data such as age, sex, educational level, medical history and current medications were determined for all participants. The INRs of patients were collected during their referral to the clinic where every patient had at least 3 INR measurements taken in total. Each patient's TTR was calculated using the Rosendaal method. The Rosendaal linear interpolation methodology is based on the INR-DAY software program (Dr. F.R. Rosendaal, Leiden, The Netherlands) that assumes a linear relationship exists between two INR values and allows the researcher to allocate a specific INR value to each day for each patient [8].

STATISTICAL ANALYSIS

Results are reported as mean ± SD. Data were analysed using the Statistical Package for the Social Sciences version 20 (SPSS-20), and p-values less than 0.05 were considered statistically significant. The continuous data obtained in this study were analysed using Chi-square test. Significant univariate predictors were subsequently assessed in the multivariate logistic regression

model to determine their independent effect, expressed as Odds Ratio (OR) and 95% Confidence Interval (CI). The p <.05 was considered significant.

RESULTS

This study involved 470 patients receiving warfarin who participated for 6 months. The total number of INR measurements was 1450. The mean (±SD) TTR for 470 patients was 54.9 ± 11.9%. The stratification of patients according to TTR levels was conducted as follows: a TTR level of >70% was considered to represent good control, a TTR level between 50% and 70% was considered to represent intermediate control, and a TTR level of <50% was considered to represent poor control. The good control group contained 175 patients (37.3%), 116 patients (24.6%) were in the intermediate control group, and 179 patients (38.1%) were in the poor control group. The mean age of the sampled patients was 58.0 ± 14.2 years and 283 (60.2%) were women. The patient demographics have been shown in [Table/Fig-1]. As seen in [Table/Fig-1], there is no significant difference across the three TTR categories in terms of age, sex, educational level, or marital status (p = 0.42, 0.38, 0.43, and 0.87, respectively). The TTRs for patients with medical histories such as hypertension, deep vein thrombosis, pulmonary embolism, heart failure, diabetes mellitus, and coronary heart disease were determined. [Table/Fig-2] shows the distribution of sampled patients with medical histories in each category. Analysis showed that there were not any differences between the TTR categories and medical histories. [Table/Fig-3] shows the number of current medications taken in each category of studied patients. The rate of good control is >85% in patients who receive less than 4 medications, but in patients with ≥5 medications, the rate decreases to <20%. Analysis showed that there is a significant difference between TTR categories and number of current medications in the evaluated patients, where, by the number of poor control patients have increased as the number of medications taken increases. To evaluate the independent effects of each variable (including demographic parameters, medical histories, and number of current medications) as a predictor of poor control, we performed a multivariate logistic regression. We identified only numbers of medication >4 as significant predictors of poor control (OR = 2.06; 95% CI, 1.87, 2.23).

		Total	Good control	Intermediate Control	Poor control	p-value
Age	< 75	414	152 (36.7%)	103 (24.9%)	159 (38.4%)	0.42
	≥ 75	56	23 (35.7%)	13 (23.2%)	20 (35.7%)	
Sex	Male	187	74 (36.9%)	40 (21.4%)	73 (39.0%)	0.38
	Female	283	101(35.7%)	76 (26.9%)	106 (37.5%)	
Educational level	Illiterate	75	27 (36.0%)	17 (22.7%)	31 (41.3%)	0.43
	Under Diploma	198	79 (39.9%)	45 (22.7%)	74 (34.7%)	
	Diploma	124	43 (36.3%)	36 (29%)	43 (34.7%)	
	BS	42	12 (28.6%)	10 (23.8%)	20 (47.6%)	
	MS	27	10 (37.0%)	7 (25.9%)	10 (37.0%)	
	Doctorate and above	3	2 (66.7)	0(0%)	1 (33.3%)	
Marital status	Single	145	43 (29.6%)	57 (39.3%)	45 (31.1%)	0.87
	Married	325	101(31.1%)	139 (42.8%)	85 (26.1%)	

[Table/Fig-1]: Demographic parameters of studied patients.

		Total	Good control	Intermediate Control	Poor control	p-value
Hypertension	Yes	142	58 (40.8%)	30 (21.2%)	54 (38%)	0.41
	No	328	117 (35.7%)	86 (26.2%)	125 (38.1%)	
DVT	Yes	8	1 (12.5%)	1 (12.5%)	6 (75%)	0.11
	No	462	174 (37.7%)	115 (24.9%)	173 (37.4%)	
Pulmonary Embolism	Yes	6	2 (33.3%)	2 (33.3%)	2 (33.3%)	0.77
	No	464	173 (37.3%)	114 (24.6%)	177(38.1%)	
Heart Failure	Yes	6	3 (50%)	2 (33.3%)	1(16.7%)	0.58
	No	464	172 (37.1%)	114 (24.6%)	178 (38.4%)	
Diabetes Mellitus	Yes	104	39 (37.5%)	19 (18.3%)	46 (44.2%)	0.16
	No	366	136 (37.2%)	97 (26.5%)	133 (36.3%)	
Coronary Heart Disease	Yes	142	58 (40.8%)	30 (21.1%)	54 (38.0%)	0.41
	No	328	117 (35.7%)	86 (26.2%)	125 (38.1%)	

[Table/Fig-2]: TTR of studied patients based on medical history.

Number of medications	Total	Good Control	Intermediate Control	Poor Control	p
1	8	7 (87.5%)	0 (0%)	1 (12.5%)	0.01
2	33	29 (87.8%)	2 (6.1%)	2 (6.1%)	
3	44	38 (86.3%)	4 (9.1%)	2 (4.6%)	
4	68	58 (85.3%)	6 (8.8%)	4 (5.9%)	
5	128	25 (19.5%)	96 (75.1%)	7 (5.4%)	
>6	189	34 (18%)	145 (76.7%)	10 (5.3%)	

[Table/Fig-3]: Number of current medications in studied patients.

DISCUSSION

Vitamin k antagonists have been shown to be effective in the treatment and prevention of thromboembolic events; however they possess many drug- drug and drug-food interactions, as well as a narrow therapeutic window [10]. The efficacy and safety of oral vitamin K antagonists such as warfarin depend strongly on the percentage of TTR, with the maximum benefits being evident when the TTR is >70% [11,12]. It is well-known that poor control of anticoagulant intensity increases the risks of thrombotic and haemorrhagic events [9]. The consistency of an effective INR is reflected by the TTR, which is a measure of the period in which the patient was in an optimal INR range. Cotte et al., evaluated the TTRs of 6250 patients in four European countries (France, Germany, Italy, and United Kingdom) with atrial fibrillation who had been prescribed vitamin K antagonists. They concluded that 47.8%, 44.2%, 46.1%, and 65.4% of the evaluated patients had TTRs >70% in France, Germany, Italy, and the United Kingdom, respectively [13]. Our results showed that the percentage of good control patients (37.3%) was less than that of each European country as discussed by Cotte et al., [13].

Mark et al., [14] recently analysed data from 272 patients with non-valvular atrial fibrillation in a hospital in Hungary. They did not classify their patients into different TTR categories and only reported the mean TTR, which was found to be 64%. The mean TTR in our study (54.9%) was lower than that reported by Mark et al. It seems that Iranian patients have poorer control of warfarin dosing compared to the patients in European studies [14]. Our results were similar to those from recent research by Zubaid et al., in Kuwait. They evaluated the quality of warfarin therapy for 369 patients with non-valvular atrial fibrillation and estimated TTRs by the Rosendaal method. They reported a mean TTR of 52.6% in their sample, which is close to the mean TTR determined in the present study (54.9%) [15]. Pharmacogenetic and dietary regimens are two important factors to be considered in relation to warfarin [16-18]. Iran and Kuwait are located in western Asia and have similar dietary regimens, cultures and genetic patterns, which may provide reasons for why our results and those in Zubaid's study are similar. Zubaid et al., had concluded that females and patients with no history of hypertension were more likely to have poor anticoagulation (expressed as Rosendaal TTR < 58%).

Unlike Zubaid et al., we did not see any tendencies of poor control among females or patients without hypertension. Melamed et al., [19] studied TTR in 906 patients diagnosed with atrial fibrillation in the United States who were treated with warfarin for at least 6 months. They concluded that poor control (TTR < 60% in their study) was significantly associated with females, advanced age (>75 years), and heart failure [19]. However, in our study, there were no significant differences in TTR between male and females (p = 0.38), patients <75 years, those >75 years (p = 0.42), and patients with and without heart failure (p = 0.58). Previous studies have not referred to the relationship between TTR and the number of patient's medications. In the present study, a significant decrease in good control rates had been observed when the patients were prescribed more than 4 medications. It seems that the number of prescribed medications may be an important factor influencing patient adherence to warfarin therapy that can affect TTR indirectly. Zulling et al., evaluated adherence barriers among patients with cardiovascular risk factors. The most commonly reported medication barrier was having too many medications to take (31%), in their study [20].

CONCLUSION

There are no reports in the literature regarding TTR values in Iranian patients and this is the first study that evaluates TTR in the Iranian population. We found a mean TTR of 54.9% in Iranian patients diagnosed with non-valvular atrial fibrillation who were receiving warfarin therapy. Only one factor was significantly related to poor control among patients: increase in the number of medications administered by the patients. In the future, we recommend evaluating factors that could possibly affect INR values and TTR rates, such as drug-warfarin interactions, food-warfarin interactions and patients' treatment adherence.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Jun 11, 2016**
Date of Peer Review: **Jul 05, 2016**
Date of Acceptance: **Jul 14, 2016**
Date of Publishing: **Sep 01, 2016**