Determinants of Anticoagulation Control in Patients Receiving Warfarin Therapy

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ABSTRACT

Background: Warfarin, nowadays is considered one of the most prescribed anticoagulant medications. In England for example, there is at least 1% of the whole population being prescribed warfarin. Despite the emergence of new agents of anticoagulants like NOACS, warfarin still prevail in most prescriptions knowing that it can't be substituted in certain indications. **Objectives:** To assess different factors associated with International Normalized Ratio (INR) control in patients who are on warfarin therapy for different indications. **Methods:** A retrospective cohort study conducted in National Heart Institute Outpatient Anticoagulation Clinic over six-month period. It included 250 patients on warfarin therapy for different indications. **Results:** After calculating Time in Therapeutic Range (TTR) of each patient the level of anticoagulation control was determined using the following cut off values: a) Good control: TTR>70%, b) Intermediate control: TTR 50 -70 %, c) Poor control: TTR <50%. Majority of patients in our study 62% had poor control with TTR less than 50%. **Conclusion:** Majority of patients have poor anticoagulation control by means of TTR. Male gender, higher education and employment status are associated with higher mean TTR and better anticoagulation control. Male gender and employment were significant predictors for good INR control.

Keywords: Anticoagulation, INR control, Warfarin

INTRODUCTION

The therapeutic range for warfarin therapy is determined by the International Normalized Ratio (INR) which is calculated as the prothrombin time ratio (patient prothrombin time/mean of normal prothrombin time for laboratory). The International Sensitivity Index (ISI) usually is close to 1, and this makes the INR calculation the ratio of the patient's prothrombin time to the mean normal prothrombin time [1-3].

Determining the degree of anticoagulation in each patient becomes of paramount importance especially for those with mechanical valves in whom not achieving a desirable goal would lead to unavoidable consequences. From here many statistical methods emerged to help in solving this issue. The Time in Therapeutic Range (TTR) is defined as the percentage of time a patient's INR is within the desired treatment range. TTR is not only used in determining the quality of warfarin treatment but also is considered for weighing the risks and benefits of oral anticoagulation. Multiple methods used for calculating TTR involve: 1) Calculating the proportion of INR values that are within range 2) Evaluating a cross-section of the patient's Files and 3) using the Rosendaal method [4].

By using this method we can calculate the percentage of the total patient's time that lies within the target ranges. The TTR will allow us to estimate the success of warfarin therapy, because it is very important in assessing warfarin's effectiveness and safety, with the maximum benefits when TTR is >70% [5].

In our paper we try to evaluate the degree of anticoagulation by warfarin among Egyptian patients by means of TTR calculations and to find different factors associated with each degree of anticoagulation like the effects of other co-morbid conditions, medications and other socioeconomic conditions.

PATIENTS AND METHODS

A retrospective cohort study conducted in National Heart Institute Outpatient Anticoagulation Clinic. It included 250 patients on warfarin therapy for different indications.

Inclusions criteria of the study:
This study includes all patients receiving warfarin therapy for more than one month.

Exclusion criteria of the study:
All patients who were hospitalized at the moment of conducting the study in order to include the most stable INR measurements, which are reached usually after 2 weeks from drug initiation during hospitalization, or if they were participating in a clinical trial.

Patients unwilling or unable to provide written informed consent are also excluded.

Data collection:
The data collection includes:
1– Demographic data:
Age and sex, socio-economic status like employment, educational degree and awareness on anticoagulation.

2 - Indication for warfarin therapy:
- Prosthetic valves in mitral or aortic position.
- Valvular atrial fibrillation
- Non valvular atrial fibrillation in patients at risk of stroke by means of CHA2D2-VASC score
- Prior and after elective cardioversion for patients with AF
- Pulmonary embolism
- Deep venous thrombosis
- Intracardiac thrombi
- Others like severe coronary slow flow and coronary ectasia.

3- INR measurements:
Past INR measurements over 3 months period of time at least were taken with regards to each patient target value. All values were taken from each patient follow-up cards after taking a proper consent.

The INRs of patients were collected during their referral to the clinic where every patient had at least 3 INR measurements taken in total.

4- Calculation of Time in Therapeutic Range using Rosendaal method
By using a simple Excel sheet developed by INR PRO Reporting Systems where patients INR values are entered along with testing dates and the target INR levels and then it calculates the TTR for each patient.

After calculating TTR of each patient the level of anticoagulation control was determined using the following cut off values
- Good control : TTR > 70%
- Intermediate control : TTR 50 -70 %
- Poor control : TTR <50%

Ethical consideration:
Consent was obtained from every patient after explanation of the procedure. **Medical Research and Ethics Committee of Zagazig University approved the study.**

Statistical analysis
We used R language (R-studio Version 0.99.484 © 2009-2015) for data analysis. Continuous variables were expressed as mean and standard deviation, median, and range, while categorical variables were expressed as numbers and percentages. Comparison of continuous variables among groups was made using one-way ANOVA test. Associations between two categorical variables were tested using Chi^2 test. All tests of significance were two tailed and a $P<0.05$ was considered statistically significant.

RESULT
Demographic data are shown in table 1. The number of patients, who have cleared the questions proposing a considerable awareness with the drug and ways of regular monitoring, were 220 out of 250. About 29.2% of patients had excellent awareness on anticoagulation and warfarin drug management including side effects, necessity to run regular INR measurements and effect of co-medication.

12% percent didn't demonstrate appropriate standard regarding general knowledge and awareness on anticoagulation by warfarin.

Table (1): Demographic data distribution among the studied group.

		Age	
Mean± SD		**46.12±10.8**	
Median (Range)		**46.0 (24-73)**	
		N	**%**
Sex	**Female**	**126**	**50.4**
	Male	**124**	**49.6**
Employment	**No**	**177**	**70.8**
	Yes	**73**	**29.2**
Education	**Illiterate**	**141**	**56.4**
	School	**84**	**33.6**
	High	**25**	**10.0**
Awareness	**Poor**	**30**	**12.0**
	Good	**147**	**58.8**
	Excellent	**73**	**29.2**

Regarding indication for oral anticoagulation, 205 patients (82%) had prosthetic valves with 108 having MVR and 36 patients having AVR while the remaining 61 had DVR (Figure 1).
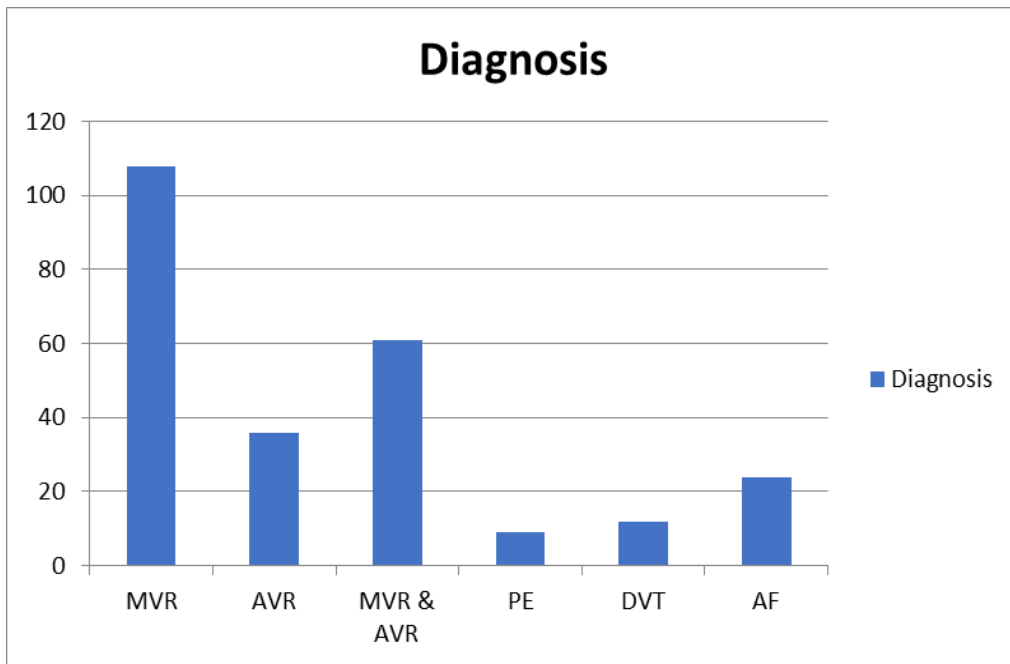
Figure (1): The relative cause distribution of the selected cohort.

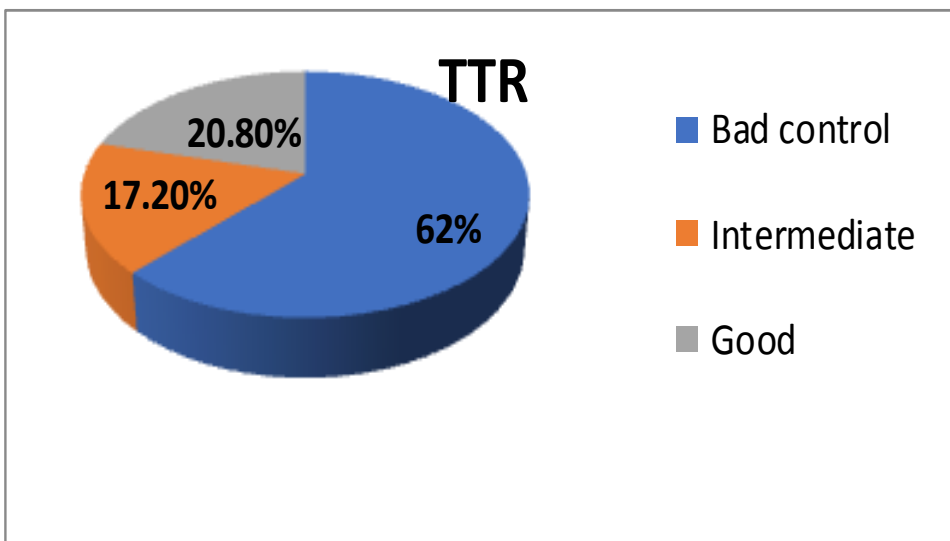Majority of patients 62% had poor control with TTR less than 50% (Figure 2).

Figure (2): The relative distributions of TTR Control groups.

Male patients had better TTR control in than females. 37% and 27.4% of employed patients had good and intermediate TTR control respectively.

In higher education level, it was more likely to have intermediate and good INR control compared with illiterate or patients with only school education.

Out of 141 illiterate cases only 20 patients (14.2%) had TTR>70%, 102 Patients (72.3%) had poor anticoagulation control while 19 patients (13.5%) fell in the intermediate category.

Table (2): Comparison of different socio-demographic items according to degree of TTR.

			TTR CONTROL			F/X^2	P
			Bad N=155	Moderate N=43	Good N=52		
Age	Mean ±SD		46.02±10.6	47.44±10.4	45.3±11.9	0.46	0.63
Sex	Female	N	100	13	13		
		%	79.4%	10.3%	10.3%		
	Male	N	55	30	39	32.77	<0.001**
		%	44.4%	24.2%	31.5%		
Employment	No	N	129	23	25		
		%	72.9%	13.0%	14.1%		
	Yes	N	26	20	27	30.7	<0.001**
		%	35.6%	27.4%	37.0%		
Education	Illiterate	N	102	19	20		
		%	72.3%	13.5%	14.2%		
	School	N	41	18	25	15.09	<0.005*
		%	48.8%	21.4%	29.8%		
	High	N	12	6	7		
		%	48.0%	24.0%	28.0%		
Awareness	Poor	N	15	6	9		
		%	50.0%	20.0%	30.0%		
	Good	N	100	24	23	7.01	0.156
		%	68.0%	16.3%	15.6%		
	Excellent	N	40	13	20		
		%	54.8%	17.8%	27.4%		
Total		N	155	43	52		
		%	62.0%	17.2%	20.8%		

DISCUSSION

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[3].

Current literature suggests that greater TTR correlates with improved patient outcomes for whom treated with warfarin[6]. There is a lack of consensus with regards to an acceptable target for TTR in practice. Different registries have documented TTRs of 55%, 58% and 76% with TTR generally being higher in clinical trials than in community practice[7]. However, maximum benefits were found when TTR level was greater than 70%[5].

Regarding age, in our study we didn't find any statistically significant difference between the three groups. This was in agreement with a study conducted by **Shaban et al.** [8] in Qatar on a group of patients with atrial fibrillation who were prescribed warfarin, it found that there was no difference concerning age and the degree of anticoagulation control despite conflicting results on age effect on TTR in a corresponding literature.

In the SAMe-TT2R2 trial, they concluded that younger patients experienced worse TTR, perhaps as a result of the associated compliance issue. This finding was reinforced by a case control study that showed that patients on warfarin who were non-compliant were more likely to be younger[9,10].

Regarding Gender: in our study we concluded that being male was more associated with higher mean TTR value compared with female contenders. This was in agreement with a Portuguese study that included 377patients, it showed that the female gender was a predictor of low TTR goes in line with the recent SAMe-TT$_2$R$_2$ that identifies women as population at risk for inadequate anticoagulation with vitamin K antagonists (VKA)[11].

The observation that women have lower TTR than men is a common finding in every study that investigated TTR predictors, although the precise reason(s) remain unclear. So, women are known to be at higher risk of AF-related stroke regardless of warfarin use, which may be related to poorer anticoagulation control in women. It has been proposed that the fluctuations of response to warfarin may be contributed to gender difference. Women tend to have a lower mean body mass or hepatic fat content. This may explain the gender difference in the

metabolism of warfarin by cytochrome P450 enzymes, leading to a different pharmacological response and outcomes of warfarin among men and women[12].

It is known that achieving good control with warfarin in women is more difficult, but the precise reasons for this remain unclear. Some studies that have examined the difference in vitamin K intake habits suggest that females ingest more amount of vitamin K daily than males, this might partly explain the poorer anticoagulation in females[13].

Regarding level of education in our study, patients who were highly educated by means of attained university degree represented 10% of total population studied, they had a mean TTR of 63.59% in contrast to those with school degree or illiterate patients with mean TTR of 60.3% and 46.7 % respectively. It was concluded that higher education was significantly associated with higher TTR values. Also, in terms of TTR control group distributions within highly educated patients. Percentage of highly educated patients with poor control represented TTR are 48% in comparison to 72.6 % in illiterate patients.

This was in agreement with a study done in a group of elderly patients with atrial fibrillation which reported that patients with a university degree spent more time in the therapeutic INR range than others[14].

Regarding relation between employment status and anticoagulation control by TTR, in our study patients who were employed exhibited better anticoagulation control by means of higher TTR values. Around 62% of employed patients fell in the category of good or intermediate control, conversely less than 30% of unemployed patients had same level of control. This indicates that current state of employment may reflect better TTR level and anticoagulation control, this might be linked to level of education as most employed personnel are exhibiting sufficient level of education that showed strong association with higher TTR values. However, the association between active employment and poor adherence to warfarin is consistent with the finding of **Palareti** *et al.* [15] who reported active employment as risk factors for INR instability.

Regarding patient awareness and general knowledge on warfarin and anticoagulation, the awareness of warfarin therapy is extremely important to reduce the risk of stroke and bleeding. Because of its narrow therapeutic window, a slim line between bleeding and stroke risk is maintained with respect to warfarin patients [16].

In our study the majority of patients did have an adequate level of awareness regarding the topic of anticoagulation and possible side effects of warfarin. Around 70 % of patients had this level of awareness with only remaining percentage of 30% that exhibited a lack of knowledge regarding the medication administration and ways of monitoring.

Regarding percentage of different TTR control groups in the study, it was found that 75.2 % of patients had TTR value < 60%. Around 20.8% of the studied population fell in the good anticoagulation control group, around 17.20% were in the intermediate control category with TTR values ranging from 50% to 70% and the majority of cases were represented in the poor control section with a percentage of 62%. It is quite obvious that the INR control in Egyptian patients who are taking warfarin is poor which is a little bit consistent with many studies conducted in Asian and middle-eastern countries. This number was quite approximate to mean TTR in a Korean study that calculated TTR of patients with AF and found around 31% of patients had TTR above 60%. The low anticoagulation control in that study was attributed to the physician factor which might also account for the current low TTR rate. Across all INR measurements, 41.7% were INR <2.0 but only 13.7% were >3.0. Therefore, Korean physicians might tend to avoid a high INR level because of bleeding concerns due to Asian populations being at a greater risk of major bleeding with anticoagulation and having a higher incidence rate of primary intracerebral hemorrhage compared to non-Asian populations [17].

CONCLUSION

Majority of Egyptian patients have poor anticoagulation control by means of TTR. Male gender, higher education and employment status are associated with higher mean TTR and better anticoagulation control. The major limitations of our study are that it is an observational non randomized study and also; it is a single center study, with a small number of patient subgroups.

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