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Evaluation of time in therapeutic range in patients receiving warfarin therapy in Zagazig University Hospital

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ABSTRACT

Objectives: To assess the quality of INR control in Egyptian patients who are on warfarin therapy through calculating the TTR and study different variables affecting INR control in those patients. Methods: A Retrospective cohort study conducted in Cardiology Department, Zagazig University Hospitals, from December 2018 to August 2019. It included 250 patients who were prescribed Warfarin therapy for different indications. Results: After calculating 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 62% had poor control with TTR less than 50% and 17.20% had Intermediate control with TTR 50-70%. Patients with good TTR control represented 20.8%. 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. Male gender and employment were significant predictors for good INR control.

Key words: Warfarin, INR control, Anticoagulation

Introduction:

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 [1]. 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.

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) ISI, 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 [2] [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].

The Rosendaal interpolation method assumes that a linear relationship exists between two INR values with either increasing or decreasing trends in between and allows us to determine a specific INR value to each day for each patient. Also, the INR-specific incidence rates of events, either thromboembolic or hemorrhagic, are calculated. The numerator of the incidence rate is based on data on the INR at the time of the event and the denominator consisting of the person-time during which the INR measurements were taken during follow up [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

This study was a retrospective cohort study conducted in Cardiology Department, Zagazig University Hospitals, from December 2018 to August 2019. It included 250 patients who were prescribed Warfarin therapy for different indications.

This study included all patients receiving Warfarin therapy for more than one month.

Exclusion criteria was the following: all patients who are 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 were also excluded.

Data were collected as follows**:** Age, sex, Socio-economic status like employment and educational degree, History of comorbid conditions (Detailed past medical history including Diabetes, Hypertension, Ischemic Heart disease, Valvular heart disease, Renal or liver impairment)

- Warfarin was indicated to be used in these conditions: 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 and others like severe coronary slow flow and coronary ectasia.

Medications with known interactions with warfarin included: Aspirin, Clopidogrel, digoxin, Amiodaron, Loop and potassium sparing diuretics, NSAIDS, Antibiotics, statins, ACEI, ARBS, H2 blockers and proton pump inhibitors.

Past INR measurements over 3 month's 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.

Each patient's TTR was calculated using the Rosendaal method.

The Rosendaal linear interpolation methodology 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.

Calculation of Time in therapeutic range using Rosendaal method was done by 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 % and Poor control : TTR <50%

The studied cohort of patients was categorized according to their targeted INR values into 2 groups: Group A: patients with target INR 2-3 and Group B : Patients With Target INR 2.5-3.5

Ethical consideration:

Consent was obtained from every patient after explanation of the procedure. Medical research and ethics committee 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, while categorical variables were expressed as numbers and percentages. Comparison of continuous variables among groups was made using the student's t-test. Associations between two categorical variables were tested using the appropriate. Statistical correlation between continuous variables was tested using -moment coefficient of correlation (r). All tests of significance were two tailed and a p- considered statistically significant.

Result:

Female patients represented 50.4% and male patients 49.6%. Mean age was 46.12+10.8 and the median age was 46 years. 29.2% of patients reported to be employed while 70.8% were currently unemployed. Percentage of patients who held a university degree is 10% and those who only completed school education was 33.6% while the rest of population who were illiterate was 56.4% **(Table 1)**

Current smokers percentage was 13.6% while ex-smokers counted 22.4%, rest of patients were non-smokers with 64%. 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. Patients with PE and DVT represented 3.6% and 4.8% respectively. Patients who received warfarin for sole indication of AF counted 24 cases9.6% (**Figure 1)**.The relative frequencies of past medical history and concomitant disorders show that 30.8% of patients have hypertension, 76 cases 30.4% had HF. 9.2 % of patients were diabetic, 47 patients 18.8% had IHD and 8 cases 3.2 had PVD. 3.2 % of patients had renal impairment while 26 patients 10.4% had liver impairment. about 42 patients 16.8%had documented cerebrovascular events. 3.2% of patients had hypothyroidism (**Table 2)**.

Regarding number of co-administered medications. 181 patients 72.4% received less than 3 medications while 69 cases 27.2% received 3 or more medications.

Majority of patients 62% had poor control with TTR less than 50% and 17.20% had Intermediate control with TTR 50-70%. Patients with good TTR control represented 20.8% (**Figure 2)**.

There was no statistically significant relation between age and degree of TTR f=0.46 and P>0.05. Male patients had better TTR control in relation to females around 20.6% had good and intermediate TTR control while males with same degree of TTR control represented 55.6% F=32.77 P<0.001. 37% and 27.4% of employed patients had good and intermediate TTR control respectively while 27% of unemployed patients had same degree of anticoagulation control cumulatively F=30.7 P<.001.

Regarding smoking, it was found that smoking history was associated with poorer anticoagulation compared with non-smokers and ex-smokers F=13.8, p>0.05.

In higher education level, were more likely to have intermediate and good INR control compared with illiterate or patients with only school education.12/ 25 highly educated cases (48%) had poor anticoagulation control, 6 patients (24%) had Intermediate control while 7 patients (28%) had good control with TTR>70%.

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 *F=15.09, p<0.05*.

Regarding degree of anticoagulation control, 12% and 18.5% of patients with MVR has good and intermediate TTR control respectively while 36% and 22.2 % of patients with AVR had the same degree of TTR control ***X=7.41, p<0.05***. Regarding patients with DVR, 26.2 % and 19.7 % had good and intermediate TTR control (***$X^{=}$1.13, p>0.05***). 12.5% of AF patients had good TTR control *$X^{=}$11.52, p<0.05.*

Patients with pulmonary embolism and deep venous thrombosis were more to be allocated in the Poor TTR control, all patients with DVT had their TTR< 50 (***X =7.72, p<0.05***). Around 66.7% of Patients who were diagnosed with PE had poor Anticoagulation control with TTR<50% (*X=0.24, p<0.05*).

Table 1 showing demographic data distribution among the studied group

		Age	
Mean± SD (years)		**46.12±10.8**	
Median (Range)		**46.0 (24-73)**	
		N	**%**
Gender	**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**
Smoking	**No**	**160**	**64.0**
	Ex	**56**	**22.4**
	Smoker	**34**	**13.6**
	Total	**250**	**100.0**

Table 2 The different percentage of patients with varying indications for warfarin therapy

	N	**%**
MVR	108	43.2
AVR	36	14.4
MVR & AVR	61	24.4
PE	9	3.6
DVT	12	4.8
AF	24	9.6
Total	250	100.0

Table 3: Showing numbers and relative frequencies of associated medical disorders.

Medical disorder		N	%
Diabetes Mellitus	No	227	90.8
	Yes	23	9.2
Hypertension	No	173	69.2
	Yes	77	30.8
Ischemic heart disease	No	203	81.2
	Yes	47	18.8
Peripheral vascular disease	No	242	96.8
	Yes	8	3.2
Heart failure	No	174	69.6
	Yes	76	30.4
Renal impairment	No	242	96.8
	Yes	8	3.2
Liver impairment	No	224	89.6
	Yes	26	10.4
Cerebro-vascular events	No	208	83.2
	Yes	42	16.8
Endocrine	No	242	96.8
	Yes	8	3.2
	Total	250	100.0

Table 4: Showing the different percentages of patients according to the number of co-medications besides warfarin.

Polypharmacy		N	%
Drugs	Less than three medications	181	72.4
	More than three medications	69	27.6
	Total	250	100.0

Table 5: showing the percentage of each group of patients according to their TTR values.

		N	%
TTR	Poor control	155	62.0
	Intermediate	43	17.2
	Good	52	20.8
	Total	250	100.0

Table 6: Comparison of different socio-demographic items according to degree of TTR.

			TTR CONTROL			F/X^2	P
			Bad	Moderate	Good		
Age	Mean ±SD		46.02±10.6	47.44±10.4	45.3±11.9	0.46	0.63
Gender	Female	N	100	13	13	32.77	<0.001
		%	79.4%	10.3%	10.3%		
	Male	N	55	30	39		
		%	44.4%	24.2%	31.5%		
Employment	No	N	129	23	25	30.7	<0.001

		%	72.9%	13.0%	14.1%		
	Yes	N	26	20	27		
		%	35.6%	27.4%	37.0%		
Education	Illiterate	N	102	19	20	15.09	<0.05
		%	72.3%	13.5%	14.2%		
	School	N	41	18	25		
		%	48.8%	21.4%	29.8%		
	High	N	12	6	7		
		%	48.0%	24.0%	28.0%		
Smoking	No	N	109	27	24	13.8	<0.05
		%	68.1%	16.9%	15.0%		
	EX	N	30	12	14		
		%	53.6%	21.4%	25.0%		
	Smoker	N	16	4	14		
		%	47.1%	11.8%	41.2%		
Total		N	155	43	52		
		%	62.0%	17.2%	20.8%		

Table 7: Different values of TTR control according to different indications for warfarin therapy

			TTR			X^2	P
			Bad	Moderate	Good		
Diagnosis	AVR	N	15	8	13	7.41	<0.05
		%	41.7%	22.2%	36.1%		
	MVR	N	75	20	13	8.18	<0.05
		%	69.4%	18.5%	12.0%		
	DVR	N	33	12	16	1.13	>0.05
		%	54.1%	19.7%	26.2%		
	AF	N	21	0	3	11.52	<0.05
		%	87.5%	0.0%	12.5%		
	PE	N	6	1	2	0.24	<0.05
		%	66.7%	11.1%	22.2%		
	DVT	N	12	0	0	7.72	<0.05
		%	100.0%	0.0%	0.0%		
Total		N	155	43	52		
		%	100.0%	100.0%	100.0%		

Table 8: Multivariate logistic regression Analysis.

	Wald	P	OR	95% C.I.	
				Lower	Upper
Male Gender	12.18	<0.001	0.33	0.173	0.611
Employment	5.92	<0.05	4.39	1.187	12.835
Smoking	2.15	>0.05	1.25	0.524	5.254
HIGH Education	0.25	>0.05	1.13	0.700	1.824
AVR	0.005	>0.05	0.99	0.800	1.231

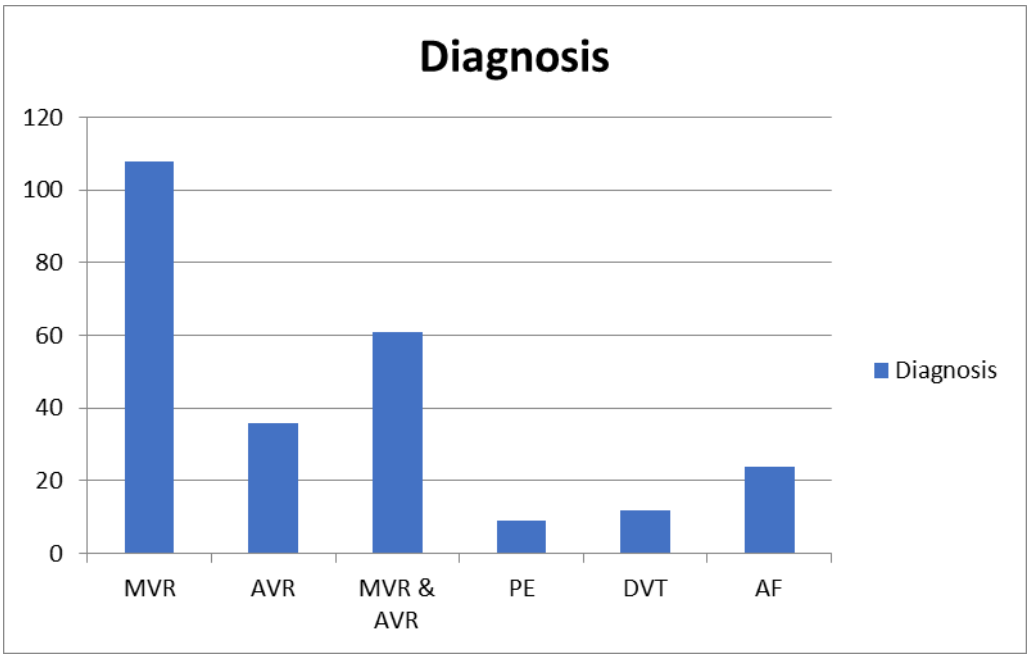

Figure. (1): A bar chart showing the relative cause distribution of the selected cohort.

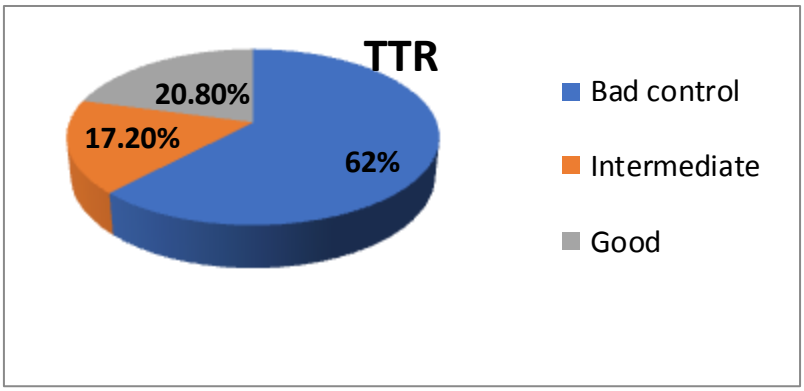

Figure (2): A Pie chart showing the relative distributions of TTR Control groups

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 shabaan et al 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 [8].

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_2R_2 that identifies women as population at risk for inadequate anticoagulation with 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 are 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.

Regarding co-medication and polypharmacy**,** 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 [15]. The association between lower TTR readings with increased numbers of medications co-administered raises the need for closer monitoring of patients with polypharmacy.

In our study, there was no significant relation between number of medication and TTR. Mean TTR in different groups of patients categorized according to their Number of medications besides Warfarin didn't differ significantly.

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.

Different factors could be attribute to the relative difference in the distribution of control groups. In our study Patients with AVR were associated with higher TTR values amongst different indication categories in our study, the mean TTR in those patients was 63.83% while those with DVR had mean TTR of 57.79% followed by Patients with MVR with TTR mean 47.1430%. So, patients with AVR were significantly associated with higher TTR followed by patients with DVR and MVR.

On the other hand, patients with DVT were associated with lower TTR value with a mean TTR of 23.9%

This is in contrast to a study conducted on a sample of Portuguese patients that showed no significant differences in average TTR between the different indications for VKA treatment [11].

In another study conducted in Turkey, the main reasons for warfarin usage in the Turkish population were mechanical valve (42.6%) and non-valvular AF (38.4%). Although the patients with mechanical valves had more awareness than the non-valvular AF patients, this situation did not reflect on the TTR rates [16].

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 also; it is a single center study, with a small number of patient subgroups.

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