RESEARCH ARTICLE

Evaluation of quality of warfarin therapy by assessing patient's time in therapeutic range at a tertiary care hospital in Pakistan

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Abstract

Objective: To assess the time in therapeutic range in patients on warfarin anti-coagulation therapy.

Methods: The retrospective chart review was conducted at Aga Khan University Hospital, Karachi, and comprised data of patients having undergone anti-coagulation with warfarin from January 2013 to April 2015. To determine the mean time in therapeutic range, Rosendaal method was used. Association of time in therapeutic range with the composite outcome, bleeding and thromboembolic events was also assessed. Percentage of patients with time in therapeutic range <60% was calculated.

Results: There were 92 patients whose median time in therapeutic range was 34.9% (interquartile range: 20.0-55.7). Overall, 71(77.2%) patients had time in therapeutic range below 60% which had statistically significant correlation with the composite outcome ($p<0.05$). Number of comorbids was significant in predicting time in therapeutic range and patients with time in therapeutic range< 60% ($p<0.05$).

Conclusion: Subjects had poor anti-coagulation quality. It might be prudent to move towards novel oral anticoagulant drugsas the first choice for therapeutic anti-coagulation.

Keywords: Warfarin, Stroke, International normalised ratio, Anticoagulants. (JPMA 68: 1339; 2018)

Introduction

The primary and secondary prevention of various thromboembolic events increasingly entail novel oral anticoagulation agents (NOACs), but warfarin is still the drug of choice for patients with valvuloplasty and especially in developing countries because of its perceived cost-effectiveness. Warfarin's optimal management presents a challenge to physicians because of its narrow therapeutic index, variable dose response, multi-factorial interactions and the need for adequate monitoring.[1] To deal with this challenge, Western countries have devised strategies and recommendations such as dedicated anti-coagulation clinics, patient self-monitoring, computer programmes and using NOACs.[2]

Monitoring of patients on warfarin is usually done by international normalized ratio (INR) of prothrombin time (PT) and the quality of anti-coagulation assessed by a linearly interpolated percent time in therapeutic range (TTR) as an intermediate outcome.[3] A TTR of less than 60% has been found to confer no apparent benefit of warfarin therapy over anti-platelet therapy against thromboembolic events.[4]

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A few multi-centre studies have established meantime in therapeutic range across geographic regions representing mostly Western populations with some Eastern/Asian participation; ranging from 77% in the Swedish population, 64% in the United States population to 49% and 36% in the Indian population.[5,6] Such low TTRs in Asians can be attributed to multiple factors, including ethnicity/genetics,[7] limited resources and poor infrastructure for adequate monitoring of warfarin anti-coagulation.[8]

Limited studies from Pakistan have assessed quality of anti-coagulation using INR within target range as a quality measure for warfarin anti-coagulation.[9,10] However, these studies do not specify the use of one of the most extensively studied methods of determining TTR- the Rosendaal method.[1] The current study was planned to evaluate the quality of warfarinisation of patients employing TTR determination according to the Rosendaal method.[11]

Patients and Methods

This retrospective chart review was conducted at Aga Khan University Hospital (AKUH), Karachi, and comprised data of patients on warfarin anti-coagulation with INR testing for 1st year of treatment related to the period from January 2013 to April 2015. The records were identified through the international classification of diseases version 9 (ICD 9) coding system maintained by the AKUH health information management

department Ethical approval was taken from institutional ethics review committee. Sample size was calculated using Epi tool online software with an assumed population standard deviation of 23.34,[6] confidence interval (CI) of 95% and desired precision of 5. Based on these calculations, we set a sample size of 100. Non-probability convenience sampling was used. Patient characteristics, including demographics, anthropometrics and clinical data, recorded from medical charts. INR values and dates of INR testing were obtained from computer records of the AKUH laboratory only. Patients with less than 2 consecutive INR values after start of warfarin anti-coagulation, INR testing intervals of more than 56 days in the first 3 months of warfarin anti-coagulation, and patients already on warfarin for more than 3 months previously were excluded.

TTR of the subjects was determined and so was the percentage of patients on warfarin anticoagulation with a mean TTR <60%. Also, factors associated with TTR values were determined and mean TTR of patients across all 4 quarters (3 month time periods) for the 1st year after therapy were compared. The association of TTR with composite outcome; defined as all outcomes whether major / minor bleeding and thromboembolic events combined, was also explored. Thromboembolic events were defined as any episode of thrombosis or ischemia in any system. Bleeding events included major and minor bleeding events combined. Major bleeding was defined as any bleeding requiring transfusion and/or symptomatic bleeding in a critical area, including intracranial bleeds, and minor bleeding was defined as any bleeding not covered under the definition of major bleeding.

Descriptive statistics were used to explain demographic and general measures, including measures for central tendency and dispersion. Individual percentage time in therapeutic range (iTTR) was calculated using the Rosendaal method[11] for each patient. This method uses linear interpolation to assign an INR value to each day between successive observed INR values. Gaps of 56 days or more between INR values were not interpolated as it is traditionally understood to indicate a lack of monitoring, and a period across which iTTR is not interpolated. After interpolation, the percentage of time during which the interpolated INR values lie between the specified target range (2.0-3.0 or 2.5-3.5) was calculated. TTR was also calculated for each patient during the4 quarters and compared. Percentage of patients with TTR <60% was calculated as well.

For comparison of TTR between two groups, 2 tailed t-test was used. For comparison of TTR among 3 or more groups, one-way analysis of variance (ANOVA) or Kruskal-Wallis test, as appropriate, was used. For relationship of continuous independent variables with TTR, linear regression analysis was performed. Logistic regression analysis was performed to identify risk factors for TTR <60% and assess relationship of TTR with outcomes. For comparison of TTR between quarters, repeated measures Friedman's ANOVA was used. Threshold of significance was set at $p<0.05$.

Results

Of the 1141 patient files reviewed, 92(8%) were included. Of the 1049 cases excluded, 356(34%) had only 1 INR value, 534(52%) had less than 3 months follow-up, and 159(15%) were already on warfarin for more than 3 months previously.

Most common indication was deep vein thrombosis (DVT) 24(26%).

A Total 1214 INR Tests were performed, with a median of 11 (inter-quartile range [IQR]: 6-17) tests per patient. Median INR tests in range were 31.1% (IQR: 23.1-47.7) and the median time in therapeutic range (TTR) was 34.9% (IQR: 20.0-55.7) while the median extended TTR (INR 1.8 to 3.5) was 60.6% (IQR: 37.8-80.0). Median total time below therapeutic range (TBTR) was 38.9% (IQR: 19.8-67.9) with percentage time below INR 1.5 (increased thrombotic risk) of 5.9% (IQR: 0.1-20.3). Median time above therapeutic range (TATR) was 8.3% (IQR: 0.2-26.9) with median total time above INR 4.5 (increased haemorrhagic risk) of 0.0% (IQR: 0.0-2.9). Overall, 71(77.2%) patients had iTTR below 60% (Table-1).

Observing patient TTR according to INR target range showed that 86(93.5%) patients had target INR between 2.0 and 3.0, with a mean TTR of 40.5±23.6% compared to 6(6.5%) patients in the target INR group between 2.5-3.5who had mechanical prosthetic heart valves with mean TTR of 15.7±14.8% ($p=0.013$). Furthermore, 70(75.6%) patients with target INR range of 2-3 had TTR <60% and all 6(6.5%)patients with target INR range of 2.5-3.5 had TTR <60% ($p=0.330$).

Multiple regression analysis predicted iTTR) with number of co-morbids contributing significantly to the prediction model ($p<0.0005$) (Table-2).

Logistic regression model to ascertain the relationship of predictors with TTR <60% was statistically significant ($p=0.000008$). The model explained 41.2% (Nagelkerke R2) variance in TTR<60% and correctly classified 81.5%

Table-1: Baseline Characteristics of Patients.

	Population N = 92 Median (IQR) or (% within category)	TTR % Median (IQR) or Mean (±SD)	P-value	TTR<60% (% within group)	P-value
Gender			.077‡	33(75.0%)	.634χ2
Male	44 (47.8%)	43.5%(±24.2)		38(79.2%)	
Female	48 (52.2%)	34.6% (±23.1)			
Age(years)	56 (36-71)				
<35	18(19.6%)	30.7% (14.7-55.9)	.274*	14(77.8%)	.447**
35-65	42 (45.7%)	45.3% (27.3-61.2)		30(71.4%)	
>65	32 (34.8%)	31.7% (19.7-41.8)		27(84.4%)	
BMI	26.7 (23.4-31.0)		.711*	3(60.0%)	.843**
Underweight (<Below 18.5)	5(5.4%)	48.3% (16.5-63.4)		21(80.8%)	
Normal (18.5 – 24.9)	26(28.3%)	31.9% (15.5 – 50.9)		27(77.1%)	
Overweight (25.0 – 29.9)	35(38.0%)	39.4% (27.5-55.8)		20(76.9%)	
Obese (≥30.0)	26(28.3%)	32.6% (22.3 – 55.4)			
Co-Morbids		N/A	N/A	N/A	N/A
Hypertension	45(48.9%)				
Diabetes Mellitus	31 (33.7%)				
Ischaemic Heart Disease	18(19.6%)				
Dyslipidaemia	5 (5.4%)				
Cancer	7 (7.6%)				
Chronic Kidney Disease	4(4.3%)				
Psychiatric Illnesses	2(2.2%)				
Others	20(21.7%)				
Indication			.135~		.159**
Deep Venous Thrombosis	24(26.1%)	44.4%(±27.6)		16(66.7%)	
Atrial Fibrillation (non-valvular)	22(23.9%)	33.9%(±16.8)		19(86.4%)	
Atrial Fibrillation (valvular)	3(3.3%)	32.1(±37.7)		2(66.7%)	
Mechanical Prosthetic Heart Valves	9(9.8%)	32.4%(±29.3)		7(77.8%)	
Pulmonary Embolism	8(8.7%)	37.2%(±14.8)		7(87.5%)	
Hypercoagulable States	9(9.8%)	63.5%(±22.2)		4(44.4%)	
Mesenteric Thrombosis	6(6.5%)	33.1%(±19.8)		5(83.3%)	
Cerebral Venous Sinus	3(3.3%)	20.1(±19.7)		3(100%)	
Thrombosis	8(8.7%)	31.1(±15.8)		8(100%)	
Others					
Specialty Monitoring Anticoagulation					
Anticoagulation Clinic	36	41.4%(±27.6)	.425‡	27(75.0%)	.159χ2
Others	56	37.2%(±21.3)		44(88.6%)	

‡ - Independent T-test, χ2 - Pearson Chi-square, * -Kruskal-Wallis Test, ** -Fisher's Exact Test,
~ - Welch ANOVA. All p values < 0.05 are significant.
BMI: Body mass index.
TTR: Time in therapeutic range.

cases. Sensitivity was 52.4% and specificity was 90.1% with positive predictive value (PPV) of 61.1% and negative predictive value (NPV) of 86.5%. Of all the predictors, only the number of co-morbids was statistically significant (p<0.05).

TTR<60% was statistically significant with composite outcome (p<0.05). Increasing TTR was associated with a reduction in likelihood of composite outcome, and TATR significant with an increase in likelihood of composite outcome and bleeding events (p<0.05).

Comparison between the four quarters was done after excluding 24(26%) DVT cases as they had a median follow-up time of 125 (IQR: 83.25-174.5). There was no significant difference across all 4 quarters for TTR or percentage of patients with TTR <60% (p>0.05). Furthermore, 50% (34) patients were lost to follow-up by the start of the 4th quarter which further increased to 48(70.6%) by the end of the year (Table-4).

Table-2: Summary of Multiple regression analysis of predictors for iTTR.

	Population N = 92 Median (IQR) or (% within category)	TTR % Median (IQR) or Mean (±SD)	P-value	B	S.E.	Beta
Intercept			< 0.0005	54.762	5.854	
Number of Co-Morbids						
No Co-Morbids			< 0.0005	-11.882	1.899	-0.568
1	26(28.3%)	55.0%(±25.8)				
2	20(21.7%)	44.8%(±21.9)				
3	24(26.1%)	31.4%(±18.7)				
	22(23.9%)	22.4%(±12.8)				
Length of Follow-Up	198 (108-329) days	-	0.122	0.034	0.022	0.162
Interval of INR Testing	18.7(10.0-28.1) days	-	0.303	-0.194	0.187	-0.123
Number of Invalid Intervals				-2.273	4.036	-0.073
0	43(46.7%)	38.5%(±3.5)	0.575			
1	36(39.1%)	41.1%(±4.5)				
2	11(12.0%)	33.0%(±5.6)				
3	2(2.2%)	39.5%(±5.2)				

B=unstandardized regression coefficient, SE = standard error of the coefficient, Beta= standardized coefficient.
All p values < 0.05 are significant.
TTR: Time in therapeutic range. iTTR: Individual percentage time in therapeutic range.

Table-3: Correlation of Outcomes with TTR, TTR<60%, TATR and TBTR.

	No Outcome	Composite Outcome	Thromboembolic Events	Bleeding Events	Major Bleeding	Minor Bleeding
Population (N=92)	77(83.7%)	15(16.3%)	4(4.3%)	9(9.8%)	5(5.4%)	4(4.3%)
TTR<60% (N=71)	56(78.9%)	15(21.1%)* a	4(5.6%)*	9(12.7%)*	5(7.0%)*	4(5.6%)*
TTR¤	39.40%	27.5%¤	14.60%	31.20%	17.50%	32.80%
	(21.8-61.2)	(12.8-32.1)	(12.3-24.7)	(13.9-43.4)	(10.3-43.5)	(31.2-48.3)
Time Below Therapeutic Range¤	18.90%	18.90%	61.30%	11.80%	6.40%	17.20%
	(6.4-65.7)	(6.4-65.7)	(47.9-77.0)	(3.2-22.6)	(0-50.4)	(10.8-24.5)
Time Above Therapeutic Range	42.70%	42.7%¤	24.90%	49.0%¤	57.00%	45.90%
	(22.2-57.0)	(22.2-57.0)	(7.6-29.6)	(40.2-66.6)	(22.4-83.0)	(38.9-50.4)

* - Fischer's Exact Test, significant at p=.019
¤Logistic Regression analysis revealed-
-TTR significant with composite outcome ($\chi 2$ (1) =5.498, p=0.019).
-Time above therapeutic range significant with composite outcome ($\chi 2$ (1) =16.514, p=0.000048).
-Time above therapeutic range significant with Bleeding Events ($\chi 2$ (1) =16.809, p=0.000041).
All p values < 0.05 are significant.
TTR: Time in therapeutic range
TATR: Time above therapeutic range. TBTR: Time below therapeutic range.

Table-4: Comparison of TTR and TTR<65% across the 4 quarters.

Quarters	Population (N = 68)	Median TTR¤ %(IQR)	TTR<60% (N=20§)
1st quarter	68(100%)	27.8(12.5-51.8)	18(90.0%)
2nd quarter	44(64.7%)	38.8(14.5-67.6)	12(60.0%)
3rd quarter	34(50.0%)	37.9(17.6-60.3)	14(70.0%)
4th quarter	23(33.8%)	46.7(19.5-80.3)	13(65.0%)

µ - Friedmann test was not significant, p value = .056
§ - Cochran's Q Test was not significant, Exact P value = 0.134
All p values < 0.05 are significant.
TTR: Time in therapeutic range. IQR: Interquartile range.

Discussion

Our cohort of patients on warfarin therapy had aTTR of 34.9% according to Roosendaal method which is among the lowest reported TTR in literature even for Southeast Asia.[6] Furthermore, 77.2% of our patients had a TTR of less than 60% denoting no benefit of warfarin therapy over anti-platelets.[4]

The number of co-morbids was the only factor that statistically explained poor anti-coagulation. In contrast to other studies, neither patient level factors such as gender, age and BMI had any association with TTR in our cohort nor did any treatment level characteristics. Our results showed a median of 11 INR tests per patient and 18-day interval between consecutive tests with an IQR of 6-17 and 10-28 days respectively. These IQRs have more variation compared to vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET-AF) results which showed IQR of 18-34 for INR tests per patient and IQR of 19-25 days for interval between 2 consecutive INR tests, which might be contributing to our poorer TTR, although this was not proven statistically in our cohort.[6]

Even though 53.3% patients had at least 1 invalid interval, number of invalid intervals had no association with TTR which is again in contrast with literature.[12] This could be attributed to small sample size and the overall poor TTR in our sample. There was no statistically significant difference in TTR between anti-coagulation monitoring and other clinics contrary to the experience of European countries.[2]

Patients mostly remained below therapeutic range 38.9% of the time and above therapeutic range only 8.3% of the time which is similar to the trend seen in ROCKET-AF.[6] However, 4.3% of patients experienced thromboembolic events while 9.3% experienced bleeding events, suggesting our population was not only at a higher risk of developing adverse outcomes, but also at a higher risk of bleeding events with even below therapeutic range TTR on warfarin. These results expose the unique challenges in achieving adequate warfarinisation in Asian populations which go beyond infrastructure constraints and affordability issues. The traditional preference for adopting multitude of herbal remedies along with contemporary treatment may pose a significant but particularly difficult-to-account-for challenge for the treating physician in terms of unexpected drug-drug interactions.[13] The varied dietary patterns and thus fluctuations in dietary vitamin K intake also make dose prediction uncertain.[13,14]

Furthermore, genetics / ethnicity along with geographical location independently determine the level of warfarinisation being achieved.[7,14] Due to the unavailability of routine genetic testing in our setup, the effect of pharmacogenetics on our results could not be taken into account.

TTR and TATR had significant association with outcomes in our study as established in literature.[3] All 15 patients with adverse outcomes had TTR less than 60%.No significant difference between different quarters was found in our patients unlike other studies which showed an improving TTR over time for patients on warfarin therapy.[6,15]

Our study had a significant dropout rate which not only contributed to poor TTR but also skewed our results. We could not assess the factors behind this loss of follow-up due to our study design. Hence, further studies need to be done to evaluate these factors and strategies need to be devised to improve regular follow-up in our setup. Although definite conclusion cannot be drawn due to relatively small sample size, the data of this cohort does show that patients have very poor anti-coagulation with warfarin and that strategies such as anti-coagulation clinics do not improve these outcomes even in a tertiary care hospital setup in Pakistan. Therefore, an alternative option could be to encourage the use of NOACs which do not require regular monitoring, have lesser interactions compared to warfarin, and provide equivalent protection to warfarin even with lower levels of compliance.[16] The barrier to NOACs in our country is the cost which needs to be addressed by cost-effective local manufacturing of these newer anti-coagulation agents as suggested in literature.[17]

Conclusion

The average TTR of patients on anti-coagulation with warfarin was poor which corroborates with the trend seen in literature. Considering the myriad of factors at play in the background, ranging from cost and infrastructure constraints to pharmacology of warfarin, it might be prudent to look at NOACs as first choice for anti-coagulation in the developing world.

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