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# Factors Affecting Quality of Anticoagulation Achieved with Warfarin as Thromboprophylaxis for Stroke Prevention in Non-valvular Atrial Fibrillation

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***Authors' contributions***

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## ABSTRACT

**Background:** Atrial fibrillation is one of the common indications of oral anticoagulation. Warfarin continues to be the most commonly used oral anticoagulant, particularly in developing countries. However, its use is limited by many factors, the most important of which is monitoring its therapeutic effect.
**Objective:** The objective of our study was to assess the anticoagulation quality in patients with atrial fibrillation receiving warfarin for thromboprophylaxis and the impact of various factors on the anticoagulation quality.
**Materials and Methods:** A total of 79 cases with non-valvular atrial fibrillation with or without a history of ischemic stroke attending the neurology clinic from September 2019 to March 2020 were studied. INR readings were taken from the outpatient record register which was converted to TTR (Time in Therapeutic Range) using the Rosendaal method. Cases that had received warfarin for less than 1 year were excluded. TTR value > 70% was considered as good anticoagulation control, TTR 60-70% as intermediate control and TTR < 60% as poor control.

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**Statistical Analysis:** Descriptive statistics and Pearson chi-square analysis using SPSS-20.
**Results and Conclusion:** The mean TTR in our study was 59.72. Only 21.5% of cases in our study achieved a good anticoagulation control (TTR > 70%) while as 55.69% had a poor anticoagulation control (TTR < 60%). Males were reported to have a higher mean TTR value as compared to females (64.24 vs 55.54). High $CHA_2DS_2VASc$ score and HAS-BLED score proved to have a strong predictive value for TTR less than 60. Individually, alcoholism, diabetes mellitus, hypertension and chronic kidney disease were found to be predictors of poor anticoagulation control i,e. TTR < 60. The presence of Transient ischemic attack or ischemic stroke was found to have a positive correlation with TTR > 70. A high number of adverse events (thromboembolic and bleeding) were reported in patients with TTR less than 60. The observations reflect the poor quality of anticoagulation in non-valvular atrial fibrillation patients on warfarin in the studied population.

*Keywords: Ischemic stroke; atrial fibrillation; TTR; anticoagulation control.*

## 1. INTRODUCTION

Atrial fibrillation, a major risk factor for ischemic stroke represents a growing clinical and public health problem. The incidence of atrial fibrillation has significantly increased over the last 20 years and is projected to increase further in the future [1].

Data has shown that the incidence of thromboembolic events increases up to five-fold with non-valvular atrial fibrillation whereas it may increase up to seventeen-fold in those with rheumatic valvular disease and AF [2-7]. Therefore, detection of AF in a patient necessitates the assessment of thromboembolic risk and initiation of oral anticoagulation in appropriate cases.

Warfarin continues to be used as the most common oral anticoagulant as it is the most well-researched molecule and is reported to result in 64% reduction in ischemic strokes in Non-valvular AF patients [8,9]. Other advantages include its inexpensiveness and accessibility of antidotes in case of bleeding events. However, factors like drug and dietary interactions, a narrow therapeutic range and the influence of genetic polymorphism on the pharmacodynamics complicate the use of warfarin [10,11]. These factors necessitate ongoing monitoring of INR with the recommended INR range of 2-3 having the optimum benefit to risk ratio.

Time in therapeutic range TTR has become a well-established measure to monitor the outcome of anticoagulation on warfarin. Several studies have shown a direct relationship between TTR and lower rates of stroke and systemic embolism in patients with AF, while the relationship to bleeding risk has been more variable [12,13]. TTR can be calculated by the fraction of INR in range or cross-sectional study of files or Rosendaal method. However, most studies have used the Rosendaal method for the calculation of TTR [14,15]. The recommended TTR values for a good anticoagulation outcome is 60% or more with a score of less than 60% being considered as a poor anticoagulation outcome [16,17].

Data from several randomized controlled trials has shown that patients on warfarin spend only 60% of their time within the TTR range [18]. Results from observational studies conducted on different AF populations have reported these values to be approximately 50%. This suggests that a significant number of patients on warfarin do not achieve the recommended anticoagulation outcome [19,20,21]. This is also important because those who have TTR<60% are at increased risk of thromboembolic and bleeding events [22].

$CHA_2DS_2VASc$ score score and HAS-BLED score have been found to correlate with the stroke and bleeding risks in patients on warfarin. A gradient increase in bleeding has been reported with an increase in any of these scores [23].

Although novel oral anticoagulants are being used increasingly in developed countries, in developing countries like India, warfarin continues to be the main agent for oral anticoagulation. Due to the paucity of data, however, not much is known about the anticoagulation outcome in patients taking warfarin. Our study aimed to assess this problem in patients attending a tertiary care center.

## 2. MATERIALS AND METHODS

This study was a descriptive study carried out at CNMCH Hospital. Patients with non-valvular

atrial fibrillation receiving warfarin as primary or secondary prophylaxis for the prevention of thromboembolic cerebrovascular events were recruited from the neurology clinic. A total of 79 cases were recruited over 6 months from September 2019 to March 2020. INR testing of all cases had been carried out at the Central Laboratory of CNMCH, Kolkata. Four or more INR recordings were obtained from the OPD register and the Rosendaal method was used to calculate the time in therapeutic range (TTR) from the record of INR values. TTR was defined as the percentage of time international normalized ratio (INR) measurements were between 2.0 and 3.0. Anticoagulation quality control was defined as poor for TTR less than 60%, intermediate for 60–70%, and good for TTR more than 70%. Valvular AF cases were excluded. Cases that had been on warfarin for less than 1 year were also excluded considering the lower TTR values usually observed in the first 6-12 months of anticoagulation. Different parameters such as age, sex, comorbidities, social habits, type of atrial fibrillation, and adverse events including both thromboembolic and bleeding episodes were recorded. Statistical analysis was done using descriptive analysis and Pearson chi-square analysis utilizing SPSS 20 software.

## 3. RESULTS

A total of 79 cases were recruited in this study. 41(51.9%) were females and 38(48.1%) were males. Age ranged from 43 to 94 years with a mean of 70.19 (standard deviation = 8.76). Age distribution showed that most of the warfarin users were in the age group of 60 to 70(49.4%) and 70 to 80(32.9). Table 1 shows the descriptive statistics of various nominal parameters in our study.

In our study, TTR ranged from 36 to 85 with a mean of 59.72(S.D.=2.535). Mean TTR in males was 64.24(S.D.=12.02) which was higher than 55.54(S.D.=11.63) in females. However, the results were statistically insignificant (p-value 0.151).

The results from our study showed that 55.69% of cases had a poor anticoagulation control (TTR below 60%), 25.31% had intermediate control (TTR 60-70) and 18.98% had good anticoagulation control (TTR >70).

10.12% of cases (n = 8) had history of alcoholism. Smoking history was present in 49.36% (39 cases). HTN was the most common comorbidity found in 62%, followed by DM in 57% and CAD in 36.7%. Other comorbidities included CKD, Congestive heart failure, ILD, COPD, bronchial asthma, peripheral vascular disease. Table 2 shows the prevalence of various comorbidities in the study population.

35 cases had suffered a TIA or ischemic stroke before the start of anticoagulation whereas warfarin was started as primary prophylaxis in 44 cases. $CHA_2DS_2$ VASc score score ranged from 2 to 6.

The impact of various baseline characteristics on anticoagulation quality control was studied using Pearson chi-square analysis. Alcoholism, HTN, DM, and CKD proved to be significant predictors of TTR < 60. $CHA_2DS_2$ VASc score score and HAS-BLED score were also found to have a negative correlation with TTR < 60. The presence of TIA or ischemic stroke was found to have a positive correlation with TTR > 70.

A total of 16 adverse events were reported with 6 bleeding events, 6 ischemic strokes, and 4 episodes of TIA. Intracranial bleeding was noted in one, gastrointestinal bleeding in 2, and hematuria in 3 cases. The mean TTR of patients witnessing adverse events was 52.50 (S.D = 8.21) as compared to 61.56 (S.D = 13.09) in those with no event.

**Table 1. Descriptive statistics of various nominal parameters**

| | Minimum | Maximum | Mean | Std. Deviation |
|---|---|---|---|---|
| HAS-BLED Score | 1 | 7 | 3.44 | 1.366 |
| $CHA_2DS_2$ VASc score | 2 | 6 | 4.09 | 1.168 |
| TTR % | 36 | 85 | 59.72 | 12.535 |
| Age | 43 | 94 | 70.19 | 8.763 |
| Duration(months) on anticoagulation | 13 | 156 | 46.91 | 28.651 |

**Table 2. Prevalence of various comorbidities in the study population**

| Comorbidity | Prevalence (%) |
|---|---|
| Diabetes mellitus | 57 |
| Hypertension | 62 |
| Coronary artery disease | 36.7 |
| Chronic kidney disease | 11.4 |
| Congestive cardiac failure | 10.1 |
| Bronchial Asthma | 5.06 |
| Interstitial lung disease | 5.06 |
| Chronic obstructive pulmonary disease | 3.79 |
| Peripheral vascular disease | 3.79 |
| Rheumatoid arthritis | 2.53 |

## 4. DISCUSSION

The study highlights the poor anticoagulation outcome in our study population with a mean TTR of 59.72 and 55.69% of patients having a poor anticoagulation control i,e TTR < 60%. These values are better than the mean TTR values (30.8%) reported from African countries like Ethiopia [24]; but certainly, reflect a poor outcome when compared to the observations from developed countries like Italy where it was reported by Poli et al to be 71% [25] and from Australia where it was reported to be 81% by Bernaitis et al. [26]. The study also depicted that most of the patients who had out of range TTR had subtherapeutic INR (83.54%) rather than supratherapeutic INR (16.46%). Similar findings were observed by O Sonuga et al from a study in the South African population and Arbring et al. from a study in the South African population [27,28].

Age distribution of our cases showed that most of the patients were in the age groups of 60-70 and 70-80 which is consistent with the growing incidence of non-valvular AF with age. In our study, we did not find any significant relationship between age and anticoagulation outcome. Some studies, however, have reported a correlation between higher TTR values and increasing age although these studies incorporated non-AF anticoagulation subgroups as well [27,29].

Although the mean TTR in females was found to be lower than males, the gender did not prove to have a statistical significance. However, some studies have reported female gender to be predictive of a poor anticoagulation outcome [27,28].

The most common comorbidity in our study group was HTN with a prevalence of 62%. AF is increasingly associated with HTN as the incidence of both diseases increases with age.

The incidence of adverse events including both thromboembolic and bleeding events was significantly related to TTR value. 13 out of total 16 adverse events occurred in the group having TTR less than 60 whereas only 2 events occurred in those with TTR more than 70 (p-value 0.02). Table 3 shows the relation of TTR with the incidence of adverse events using Pearson chi-square analysis.

We studied different factors for predicting the bad or good anticoagulation outcome using the Pearson chi-square test. Table 4 shows the relationship of different baseline characteristics with the anticoagulation outcome.

Alcoholism was observed to increase the probability of having TTR < 60 (p-value 0.05). The results were just borderline significant possibly because of a small sample. Analyzing separately, HTN, DM, and CKD proved to be predictors of poor anticoagulation outcome. Fredrik et al in their large study in the Swedish population demonstrated many factors to be predictive of poor anticoagulation outcome which included alcoholism, CKD, COPD, dementia, anemia, HTN, diabetes mellitus, and others, though most of these factors increased the risk marginally [30].

HAS-BLED score and $CHA_2DS_2$ VASc score were studied with TTR using Pearson chi-square test. Both the scores proved to have a significant negative correlation with TTR with higher HAS-BLED and $CHA_2DS_2$ VASc score group having more chance of having TTR < 60. These results match well with the conclusions from various large international studies. Jessica et al found both $CHA_2DS_2$ VASc and HAS-BLED scores to be associated with lower TTR values [31]. Turk

et al in their study found a negative correlation between $CHA_2DS_2$ VASc score and TTR as well [32]. Although these scores prove to have a negative correlation with the anticoagulation outcome, the net clinical benefit of anticoagulation has been reported to be higher in patients with a high $CHA_2DS_2$ VASc and HAS-BLED score [33].

While analyzing our data, we observed that the presence of TIA or stroke was associated with an increased probability of having TTR > 70 as demonstrated in Table 5. One plausible explanation may be better compliance and INR monitoring by the patients who observed a thromboembolic event at least once as compared to those who did not have such an event. A similar observation was made by Fredrik et al in their study in the Swedish population [30].

Our study may be limited by the small number of cases. The relation of increased frequency of testing with anticoagulation control could not be studied because a majority of the cases had infrequent INR testing.

**Table 3. Statistical relation of TTR category with adverse events**

| TTR Category | Adverse Events | | p value |
|---|---|---|---|
| | No adverse event | Adverse event | |
| TTR > 70 | 13 | 2 | |
| TTR < 60 | 29 | 13 | 0.021 |

**Table 4. Statistical relation of patient characteristics with anticoagulation control**

| | | TTR>70 | TTR<60 | p-value |
|---|---|---|---|---|
| $CHA_2DS_2$VASc score | score 2-3 | 6 | 8 | |
| | score > 3 | 9 | 36 | 0.032 |
| HAS-BLED score | score 1-3 | 12 | 21 | |
| | score > 3 | 3 | 23 | 0.008 |
| Age Group | Less than 60 | 2 | 4 | |
| | 60-80 | 7 | 22 | |
| | More than 80 | 6 | 18 | 0.853 |
| Female sex | No | 8 | 18 | |
| | Yes | 7 | 26 | 0.151 |
| Alcoholism | no | 14 | 37 | |
| | yes | 1 | 7 | 0.056 |
| Smoking history | No | 9 | 19 | |
| | yes | 6 | 25 | 0.137 |
| DM | Absent | 10 | 12 | |
| | Present | 5 | 32 | 0.002 |
| HTN | Absent | 8 | 12 | |
| | Present | 7 | 32 | 0.028 |
| CKD | Absent | 14 | 36 | |
| | Present | 1 | 8 | 0.033 |
| CCF | Absent | 14 | 39 | |
| | Present | 1 | 5 | 0.668 |
| CAD | Absent | 10 | 25 | |
| | Present | 5 | 19 | 0.181 |
| Duration category | Less than 6 months | 3 | 15 | |
| | 6-12 months | 9 | 22 | |
| | More than 1 year | 3 | 7 | 0.37 |
| Bleeding | Bleeding | 1 | 7 | |
| | No bleeding | 14 | 37 | 0.157 |

**Table 5. Statistical relation of TIA/Stroke with observed anticoagulation control**

| | | TTR < 60 | TTR > 70 | p value |
|---|---|---|---|---|
| TIA/Stroke before anticoagulation | No | 30 | 6 | |
| | Yes | 14 | 9 | 0.012 |

## 5. CONCLUSION

A significant number of patients with atrial fibrillation in the study population did not achieve the recommended TTR on warfarin. A significant association was noted between TTR < 60 and increased incidence of adverse events. Increased HAS-BLED and $CHA_2DS2VASc$ score, alcoholism, HTN, DM, and CKD were shown to be predictors of poor anticoagulation control. Patients with a history of TIA or stroke showed a better anticoagulation control compared to their counterparts. The results from our study reflect poor anticoagulation quality on warfarin in patients with atrial fibrillation. However, larger multicenter studies need to be carried out to reflect the exact status of quality of anticoagulation on warfarin in this particular group of patients.

## CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the authors.

## ETHICAL APPROVAL

Approval for the study was taken from the ethical committee of CNMCH hospital.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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