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**ORIGINAL ARTICLE**

# Frequency of Achieving Target INR in Patient on Warfarin for Atrial Fibrillation

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## ABSTRACT

**Background:** Warfarin has long been established as the oral anticoagulant of choice. The benefits of warfarin depend on maintaining the International Normalized Ratio (INR). It has been shown that the optimal INR target range is 2-3 for AF patients. Very less number of patients had been reported to achieve and remain in that target INR range. The prevalence of AF in the general population is about 1.6% in women and 2.4% in men and is generally lower in Asian countries

**Aim:** To determine the frequency of achieving target INR in patient on warfarin for atrial fibrillation.

**Methodology:** This is cross sectional study conducted at national institute of cardio vascular disease, Karachi from 31st May 2016 30th November 2016.The sample size of the study were 111, and nonprobability convenience sampling technique was used.

**Results:** Among study population 61 (54.9%) were male and 50(45%) female patients. Mean duration of atrial fibrillation was 3.44±0.97 years. The mean duration of warfarin taken was 11.34±3.96 months. INR (2-3) target achieved in 72(64.9%) patients. Significant association of achieved INR target was observed with duration of atrial fibrillation, duration of warfarin, hypertension, stroke, and Left ventricular dysfunction.

**Conclusion:** Target of INR was achieved in 64.9% patients when these patients were given warfarin doses of 5.0 to 7.5 mg/day.

**Keywords:** Achieving Target INR, Warfarin, Atrial Fibrillation.

## INTRODUCTION

Atrial fibrillation is a supraventricular arrhythmia electrocardiographically characterized by the presence of rapid, irregular, fibrillatory atrial waves that vary in size, shape, and timing and an irregularly irregular ventricular rhythm[1].

Atrial fibrillation (AF) is the most common clinically significant sustained cardiac arrhythmia, occurring in 1–2% of the general population. Over 6 million Europeans suffer from AF, and its prevalence is estimated to at least double in the next 50 years as the population ages[2,3].

The prevalence of AF in the general population is about 1.6% in women and 2.4% in men and is generally lower in Asian countries as compared to Caucasian data. Hypertension, advanced age, congestive cardiac failure, aortic and mitral valve disease and left atrial enlargement are independent risk factors for the development of AF[4].

Literature supports that warfarin choice for primary and secondary prevention of ischemic stroke in randomized controlled trials and meta-analysis, reducing the risk by 68% and mortality by 33%. Treatment of AF includes rate control or rhythm control strategy. Anticoagulation is recommended in most patients with AF because of increased risk of systemic arterial thromboembolism leading to acute ischemia of limbs, renal or splanchnic vessels, and most importantly causing ischemic stroke; the annual rate of stroke in AF being 4.5%[5,6].

Warfarin has long been established as the oral anticoagulant of choice for primary and secondary prevention of ischemic stroke in randomized controlled trials and meta-analysis, reducing the risk by 68% and mortality by 33 %[7].

However, the benefits of warfarin depend on maintaining the International Normalized Ratio (INR) within a relatively narrow range. It has been shown that the optimal INR target range is between 2.0 and 3.0 for AF patients[8,9].

It may be difficult to maintain the INR in this therapeutic range. A very less number of patients have been reported to achieve and remain in that target INR range. A recent study has shown that only 63% of patients had achieved target INR. It has been suggested that, in patients with underlying ventricular dysfunction, this increased risk of death is due primarily to heart failure. Hypertension, advanced age, heart failure, aortic and mitral valve disease and left atrial enlargement are independent risk factors for the development of AF[10].

It is essential to know the frequency of achieving target INR in this group of patients. It will also open doors for new researches to look into the causes of such variability in achieving target INR if it exists in our population as well as the need to switch to newer oral anticoagulants that do not require INR monitoring despite warfarin being the cheapest and easily available oral anticoagulant in Pakistan. The results of this study will also be used to guide future recommendations for the importance of achieving target INR and guide treatment strategies in these patients.

The objective of the study was to determine frequency of achieving target INR in patient on warfarin for atrial fibrillation.

**Atrial fibrillation**: diagnosed on 12 lead ECG meeting following criteria:

1. Irregularly irregular rhythm (determined by presence of variable R-R interval)
2. Absence of p waves

**Target INR:** INR level between 2 and 3. Results will be labeled as positive if INR is between 2 and 3 at the time of follow up at least three months after starting warfarin therapy.

**Left ventricular dysfunction:** Ejection fraction< 40% on transthoracic echocardiography

## MATERIAL AND METHODS

This is cross sectional study at the anticoagulation clinic of National institute of cardiovascular disease, Karachi from 31st May 2016 to 30th November 2016 after approval from IRB. Non-probability convenience sampling technique was used. Sample size comes out to be n=111.

**Sample selection:** All patients between 18 years and 75 years of age, diagnosed cases of AF on anticoagulation therapy with warfarin for > 3 months, presenting in anticoagulation clinic.

**Data collection analysis:** The data was collected after the approval from the CPSP. The 111 patients were diagnosed as cases of AF was selected as study criteria. Duration and dose of warfarin were confirmed from prescriptions and asking patients directly by showing them warfarin tablets. Blood pressure was measured, and ECG was done on a standard 12 lead format. The diagnosis of AF was confirmed. Adding, 5ml sample of blood was taken for checking INR on the same day. Outcome variable i.e. target INR was labeled positive if result was between 2 to 3. Results were noted in the preform. The data were analyzed through SPSS version 19. Mean and S.D were calculated for continuous variable, for the categorical variable chi-square test in computed, and p=<0.05 as significant.

## RESULTS

**Distribution of age of the subjects:** In the current study 111 sample size were used. The age group divided into two groups as less than 40 years were 53 (48%), with mean age 35.48 with S.D±3.63, and 58(52%) with mean age 47.67 and S.D±5.68. Over all mean and S. D were 41.30±7.71 (Table 1). Further, there is no any significant association find between the age of the study of the subjects and INR achieved target (p=331) (Table 2).

Table 1: Distribution of Age group of the patient

| Age in Years | Frequency | %age |
|---|---|---|
| Up to 40: Mean: 35.48 S.D: ±3.63 | 53 | 48 |
| Above 40: Mean: 47.67 S.D: ±5.68 | 58 | 52 |
| Total | 111 | 100 |
| Distribution of Gender of Subjects | | |
| Male | 61 | 55 |
| Female | 50 | 45 |
| Total | 11 | 100 |
| Distribution of the marital status of subjects | | |
| Married | 102 | 91.1 |
| Unmarried | 09 | 8.1 |
| Total | 111 | 100 |
| Duration of AF Mean & S.D | | |
| Up to 3 years 3.44 , ± 0.97 years | 59 | 53.1 |
| above 3 years | 52 | 46.8 |
| Total | 111 | 100 |
| Duration of warfarin intake : Mean & S.D | | |
| up to 12 years 11.34 ± 3.96 | 77 | 69.3 |
| above 12 month | 34 | 30.6 |
| Total | 111 | 100 |
| Dose of warfarin prescribed | | |
| 2.5 mg | 11 | 9.9 |
| 5.0mg | 72 | 64.8 |
| 7.5mg | 28 | 25.2 |
| Total | 111 | |
| Frequency distribution of prescribed of warfarin | | |
| 5.0 mg | 76 | 68.5 |
| 7.5mg | 35 | 31.5 |
| Total | 111 | 46.8 |
| History of HTN | | |
| Yes | 52 | 46.8 |
| No | 59 | 53.1 |
| Total | 111 | 100.0 |
| Distribution of diabetic mellitus | | |
| Yes | 11 | 9.9 |
| No | 110 | 91.1 |
| Total | 111 | 100 |
| Distribution of stroke | | |
| yes | 06 | 5.4 |
| No | 105 | 94.6 |
| Total | 111 | 100 |
| Frequency of LV Dysfunction | | |
| Yes | 39 | 35.1 |
| No | 72 | 64.8 |
| Total | 111 | 100.0 |
| Frequency of valvular | | |
| Yes | 81 | 730 |
| No | 30 | 27 |
| Total | 111 | 100 |
| Distribution of achieved INR | | |
| Yes | 72 | 64.9 |
| No | 39 | 35.1 |
| Total | 111 | 100 |

Table 2: Contingency table study variable and Target achieved INR target:

| | Target achieved INR | | | |
|---|---|---|---|---|
| | Yes | No | Total | P =value |
| Male | 42 | 19 | 61 | .331 |
| Female | 30 | 20 | 50 | |
| Total | 72 | 39 | 111 | |
| Contingency table of achieved INR Target according to age group | | | | |
| up to 40 years | 36 | 22 | 58 | |
| above 40 years | 36 | 17 | 53 | |
| Total | 72 | 39 | 111 | .519 |
| Contingency table of achieved INR Target to duration of atrial fibrillation(years) | | | | |
| up to 3 years | 47 | 12 | 59 | |
| above 3 years | 25 | 27 | 52 | |
| Total | 72 | 39 | 111 | .001 |
| Contingency table of achieved INR Target to duration of warfarin (years) | | | | |
| up to 12 month | 56 | 21 | 77 | |
| Above 12 month | 16 | 18 | 34 | |
| Total | 72 | 39 | 111 | .009 |
| Contingency table of achieved INR to prescribed dose of warfarin | | | | |
| 5.0mg | 50 | 26 | | |
| 7.5mg | 22 | 13 | 39 | |
| Total | 72 | 39 | 111 | .746 |

| | | | | |
|---|---|---|---|---|
| Contingency table of achieved INR to prescribed dose of warfarin | | | | |
| 2.5mg | 8 | 3 | 11 | |
| 5.omg | 48 | 24 | 72 | |
| 7.5mg | 16 | 12 | 28 | |
| Total | 72 | 39 | 111 | .647 |
| Contingency table of achieved INR to HTN | | | | |
| Yes | 39 | 13 | 52 | |
| No | 33 | 26 | 59 | |
| Total | 72 | 39 | 111 | .036 |
| Contingency table of achieved INR to DM | | | | |
| Yes | 5 | 6 | 11 | |
| No | 67 | 33 | 100 | |
| Total | 72 | 39 | 111 | .155 |
| Contingency table of INR to Stroke | | | | |
| Yes | 1 | 5 | 6 | |
| No | 71 | 34 | 105 | |
| Total | 72 | 39 | 111 | .002 |
| Contingency table of INR to LV Dysfunction | | | | |
| Yes | 17 | 22 | 39 | |
| No | 55 | 17 | 72 | |
| Total | 72 | 39 | 111 | .001 |
| Contingency table of INR to valular heart disease | | | | |
| Yes | 53 | 28 | 81 | |
| No | 19 | 11 | 39 | |
| Total | 72 | 39 | 111 | .837 |

**Distribution of gender of the subjects:** The description of gender was as 61(55%) were male, and 50(45%) were female patients (Table 1). Further, there is no any significant association find between the gender of the study of the subjects and INR achieved target (p=519) (Table 2).

**Distribution of marital status of subjects:** Marital status results showed that out of 111 subjects most of patients 102(91.9%) were married, and 09(8.1%) were unmarried (Table 1).

**Distribution of Duration of atrial fibrillation of subjects:** Duration of atrial fibrillation were stratified into two group as up to 3 years were 59 (53.1%), and above 3 years were 52 (46.8%) years. The over duration of atrial fibrillation was 3.44 ± 0.97 years (Table 1). Further, there is significant association find between the duration of atrial fibrillation and INR achieved target (p=.001) (Table 2).

**Distribution of Duration of warfarin of subjects:** Duration of warfarin intake are stratified into two group up to 12 months 77(69.3), and above 12 months 34(30.6%). Among 111 study subjects were 2.5mg, 5mg and 7.5mg were as 11(9.9%), 72(64.8%), and 28 (25.2%) (Table 1). Further, there is significant association find between the duration of atrial fibrillation and INR achieved target (p=.009) (Table 2).

**Dose of warfarin prescribed:** Out of 111 study subjects, 28(9.9%) study subjects were taking 2.5 mg warfarin, 72(64.9%) taking 5 mg and rest of 11(25.2%) taking 7.5 mg of warfarin (Table 1). Further, there is no significant association find between the dose of warfarin and INR achieved target (p=.746) (Table 2).

**Prescribed dose of warfarin:** Among 111 study subjects most of patients (68.5%) were prescribed 5mg of warfarin while 7.5 mg were prescribed to 31.5% of study subjects (Table 1). Further, there is no significant association find between the prescribed dose of warfarin and INR achieved target (p=.674) (Table 2)

**Distribution of hypertension of subjects:** Hypertension was found in 52(46.8%), and did not have hypertension were 49(53.1%) (Table 1). Further, there is significant association find between the hypertension and INR achieved target (p=.036) (Table 2).

**Distribution of hypertension of subjects:** Among study subjects, diabetic was 11(9.9%), and remained 100(91.1%) were non-diabetic (Table 1). Further, there is no significant association find between the prescribed the diabetic and INR achieved target (p=.155) (Table 2).

**Distribution of stroke of subjects:** Among study subjects 6(5.4%) and have history of stroke, and slum of the as 105(94.6%) subjects have negative history of stroke (Table 1). Further, there is significant association find between the stroke and INR achieved target (p=.002) (Table 2).

**Distribution of s Left ventricular dysfunction of subjects:** Left ventricular dysfunction in 39(35.1%) of the total study subjects (Table 1). Further, there is significant association find between the left ventricular dysfunction, and INR achieved target (p=.0021) (Table 2)

**Distribution of valvular heart disease of subjects:** Valvular heart disease in 81(73%) study subjects. Left ventricular dysfunction in 39(35.1%) of the total study subjects (Table 1). Further, there is significant association find between the valvular disease and INR achieved target (p=.87) (Table 2).

**12. Distribution of INR target achieved of subjects**: In our study, the final outcome i.e. INR target achieved; was found in 72(64.9%) patients.

## DISCUSSION

This is a cross sectional study conducted at the National institute of cardiovascular disease. The current study revealed that the overall mean age with the S.D of the study subjects were 41.30±7.71, which is compared with multiple studies demonstrated that the importance of maintaining a stable INR value between 2.0 to 3.0 for reducing strokes and mortality in patients with AF, and inadequate anticoagulation is frequent in different age groups[3,5,11].

In current study 64.9% of patients taking warfarin for AF were found to be in target INR range while rest were out of the recommended therapeutic range. This is comparable to other studies where 60-70% patients had achieved target INR[12,13].

The current study revealed significant association of achieving target INR in patients with less duration of AF and warfarin intake as compared to those with more chronic AF and longer duration of warfarin intake. This could possibly be due to the fact that patients with longer duration have decreased the follow up visits with less frequent INR monitoring because of variety of reasons including decreased logistics and need to come from far away areas where healthcare facilities are scarce and INR monitoring cannot be done, while recently diagnosed patients are more concerned about their disease and following up frequently in OPDs.

The current study revealed that patients with history of stroke were less frequently found in target INR range and this may well be the reason that noncompliance or inadequate anticoagulation would have led to this complication[14,15].

The current study investigated that target INR was less frequently achieved in patients with LV dysfunction, this has also been shown in multiple studies[16,17]. Absence of LV dysfunction was an independent predictor of achieving and maintaining a stable target INR[18]. Reason for this is unknown but may probably be due to changes in hepatic metabolism due to decompensated heart failure leading to pharmacokinetic variability of drug metabolism.

As regards to HTN more hypertensive patients were found to have achieved target INR than non-hypertensive patients. Similar association was observed in the study[19].

The current study observed that association of older age with achieving stable INR but the same was not reflected in our study.[20,21] This may be because most of our sample population consisted of younger age group as compared to these studies where this association was seen in patients >70 years of age.

DM, another risk factor for thromboembolism in AF patients, has been shown to be negatively associated with achieving stable target INR in previous studies, although no significant association was seen in our study[16,18].

In previous studies presence of valvular heart disease has been found to be negatively associated with achieving stable target INR. INR of only 30-32% patients was found within target range.[16,22] But our study did not show any significant association between presence of valvular heart disease and the outcome variable. The difference may be because of the fact that we excluded patients with prosthetic heart valves and most of the work done previously is largely focused on this group of patients.

## CONCLUSION

The study concluded that target of INR 2-3 was achieved in 64.9% patients with Atrial Fibrillation when these patients were given warfarin doses of 5.0 to 7.5 mg / day. Furthermore, duration of atrial fibrillation, duration of warfarin intake, hypertension, stroke and Left ventricular dysfunction were significantly associated with target INR achieved.

**Study Limitations**: The main limitations of the present study include a single-center experience, low female representation and nonrandomized study design. It was conducted with small sample size therefore; the results might not be generalizable to larger populations.

**Conflict of interest:** There is no any potential interest seen between the authors.

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**Data availability:** It is available from correspondence author on request as per ethical rules.

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