



**A REVIEW TO ASSESS THE CURRENT CONUNDRUMS OF
THROMBOPROPHYLAXIS ASSOCIATED WITH WARFARIN THERAPY IN ATRIAL
FIBRILLATION PATIENTS**

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ABSTRACT

Warfarin is a potent vitamin k antagonist that has been widely used for anticoagulation. One of the major indication of warfarin is its prophylaxis use in stroke for atrial fibrillation patients. With the advent of novel oral anticoagulants, thromboprophylaxis treatment for atrial fibrillation has become more intriguing and sophisticated. Due to the narrow therapeutic index of warfarin and a lack of studies associated with newer oral anticoagulants, warfarin still presents a number of predicaments for anticoagulation in Indian atrial fibrillation patients. Our study mainly focuses on these complexities of warfarin therapy from an Indian perspective.

KEYWORDS: Warfarin, Atrial fibrillation, International normalized ratio.

INTRODUCTION

Atrial fibrillation is a common type of arrhythmia, particularly seen in older individuals. It is estimated that its prevalence will be doubled in the next 50 years.^[1] In the year 2050, Asia will have 72 million Atrial fibrillation patients, and 2.9 million among them will suffer from AF-associated stroke.^[2]

Previously, warfarin was the only choice of oral anticoagulant for treating atrial fibrillation patients who were at the risk of developing stroke. With the introduction of newer anticoagulants (dabigatran, rivoroxaban, apixaban and edoxaban) in last few years, there is a wider spectrum of choice in drug therapy for preventing stroke in atrial fibrillation. According to the American college of cardiology, warfarin is recommended for anticoagulation in patients with atrial fibrillation who have mechanical heart valve. For patients who have non valvular atrial fibrillation, with prior stroke, transient ischemic attack (TIA), or a CHA2DS2-VASc score of 2 or greater, oral anticoagulation with warfarin or any of the newer anticoagulants are recommended.

The 4 major randomized control trials, namely, RE-LY, ROCKET, ARISTOTLE and ENGAGE, have already established the noninferiority of novel oral anticoagulants (NOAC) against warfarin.^[3-6] Asian population associated studies have also showed similar results.^[7] However, studies of newer anticoagulants reported on an Indian population is limited. So warfarin still remains as the more reliable drug for Indian

population. Yet warfarin still represents certain dilemmas, when it comes to treatment for non valvular atrial fibrillation.

This review article mainly focuses on the advantages, challenges and future prospects of research for oral warfarin therapy for non valvular atrial fibrillation from an Indian perspective.

WARFARIN

Warfarin is a vitamin k antagonist. It does not directly inhibit the clotting factors instead it inhibits the subunit 1 of vitamin k epoxide reductase complex 1(VKOR1). This will inturn reduce the vitamin k dependent clotting factors II,VII,IX and X.^[8] The major aspect of warfarin therapy, involves the monitoring of International normalized ratio (INR) within the normal range (2.0-3.0). The safety and efficacy of warfarin therapy depends on maintaining the INR within the normal range.

Warfarin vs Aspirin

According to the guidelines recommended by American college of cardiology, for patients with a CHA2DS2-VASc score of 0, it is reasonable to omit antithrombotic therapy and for patients with CHA2DS2-VASc score of 1, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered whereas for patients with non valvular atrial fibrillation, with prior stroke, transient ischemic attack (TIA), or a CHA2DS2-VASc score of 2 or greater, oral anticoagulants are recommended. So aspirin is only recommended for low risk patients (CHA2DS2-VASc score of 1) and

antithrombotic treatment should be initiated in patients with higher stroke risk (CHA2DS2-VASc score of 2 or more). But despite the guideline recommendation, warfarin has been underused in the prophylaxis treatment for high risk atrial fibrillation patients.

Though warfarin is a narrow therapeutic index drug, it has shown to prevent stroke better than aspirin for atrial fibrillation patients. When dose-adjusted warfarin was compared to aspirin, the absolute risk reduction of stroke was 0.6% in warfarinized patients.^[9] In another study by Amar rash et al in 2007 showed the superiority of warfarin against aspirin.^[10] In that particular study, there were significantly more adverse events associated with aspirin than in warfarin. The conclusion of Amar rash et al was that, dose adjusted warfarin therapy was better tolerated with lesser adverse events than aspirin at 300 mg and data regarding lower dose aspirin was not available. However, Hiroshi Sato et al had reported a study in Japanese population showing the ineffectiveness of a much more lower dose of aspirin (150 to 200mg) for atrial fibrillation patients.^[11] Hiroshi et al study was stopped earlier because of the marginally higher risk of bleeding caused by aspirin. Even 75mg aspirin showed poor results against warfarin in the BAFTA randomized trial.^[12] So, these studies shows that warfarin produces more satisfactory outcomes than any dose of aspirin against atrial fibrillation.

In a recent metaanalysis study in 2015 by Jing- Tao et al analysed the safety and efficacy of oral anticoagulants against aspirin in 8 randomized clinical studies.^[13] They found out that, although the risk of stroke is similar in between treatments, patients with non rheumatic atrial fibrillation who were on anticoagulants had lower risk of stroke. Furthermore, their analysis shows that anticoagulants are more effective than aspirin in preventing overall embolism in patients with atrial fibrillation.

So based on the above studies, one can conclude the prominence of warfarin over aspirin despite its narrow therapeutic index and constant need for monitoring of INR. So, effectiveness of warfarin and aspirin on lower risk patients (CHA2DS2-VASc score of 1) has to be

explored, because the current guidelines recommends to use either aspirin or an oral anticoagulants for such patients. This might give a clearer picture on the use of warfarin or aspirin for specific risk patients.

Significance of time in therapeutic range

Time in therapeutic range (TTR) can be said as an indicator that shows the quality of warfarin therapy. The time in therapeutic range is calculated based on the patient's INR values. While on warfarin therapy, the INR of the patient has to be constantly monitored and maintained within the normal range (2.0 – 3.0). The TTR and INR values are correlated with the incidence of adverse events due to warfarin.^[14] So maintaining the TTR and INR values within the normal range can prevent any adverse events and improve the warfarin therapy. Time in therapeutic range shows the amount of time the INR was in normal range. Those patients who achieve more than 70% TTR receives maximum benefit from warfarin therapy. Studies have shown that patients are at a lower risk of any thromboembolic or bleeding event when their TTR values are over 70%.^[15] But the value of TTR reported in studies are varying, suggesting the difficulty in maintaining the TTR above 70%. Bahram-Fariborz Farsad et al study reported a mean TTR of 54.9% and took 50-70% TTR values as the intermediate level of anticoagulation in their Iranian study population.^[16] But Daniel Caldeira et al reported 44.3% of their patients who had a mean TTR <60%, were at an increased risk of thrombotic and hemorrhagic events.^[17] Even the larger randomized trials of newer oral anticoagulants and warfarin in Atrial fibrillation, provided further data about world-wide difficulty in maintaining the TTR level. The mean TTR values of the major large randomized trials (ROCKET-AF trial, ARISTOTLE trial and the RELY trial) were 55.2%, 62.2% and 64%.^[3-5] Figure (1) shows the value of mean TTR obtained in different studies. So there are no standard of accepted range for TTR. The general consensus that we can deduce from these studies is the correlation between increase in TTR values and improvement of the patient outcomes on warfarin therapy.

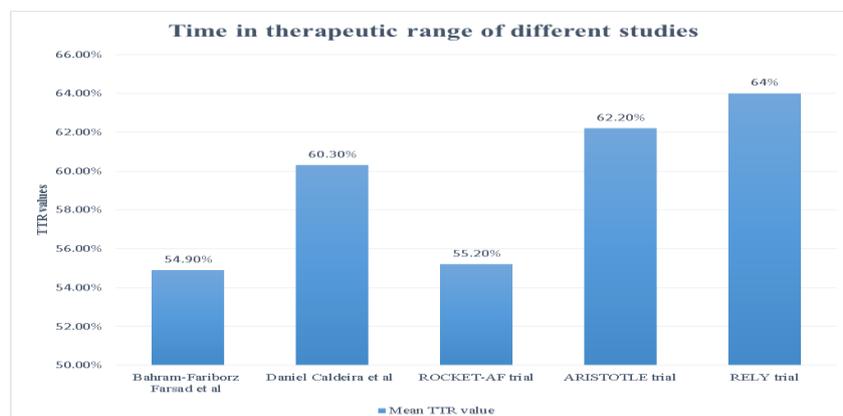


Figure (1): TTR values obtained in various studies.

Risk stratification

Assessment of risk is a major factor in warfarin therapy for atrial fibrillation. Stroke risk and Bleeding risk are the 2 major risk factors that has to be taken into consideration before treating a patient with oral anticoagulants. Previously, CHADS2 score was the scale which was used for determination of stroke risk. But its limitation was highlighted in other studies.^[18] So, in 2010, a much more refined form of stroke prediction scale was proposed by Gregory Y.H. Lip et al (CHA2DS2-VASc score).^[19] The major limitation of CHADS2 scale is that it classifies majority of its patients as intermediate risk group, including patients who are at a lower risk (CHADS2 score 1 or 2). So patients who are at a lower stroke risk are getting anticoagulated unnecessarily. But the CHA2DS2-VASc score refined it by adding some of the most common risk factors such as female gender, vascular disease and age 65 to 74 years into separate risk factor category within the scale which improved its predictive ability. CHA2DS2-VASc score is able to classify patients who are truly at a lower risk (CHA2DS2-VASc score of 0) and does not require any antithrombotic treatment. Subsequently, many studies

validated the better predictive ability of CHA2DS2-VASc score over CHADS2 score in predicting stroke and thromboembolism.^[20-22] It was also validated in Asian population.^[23] However a recent study in 2016 by Tze-Fan Kang-Ling Wang et al, validated a much more modified version of CHA2DS2-VASc score which was specifically meant for Asian population.^[24] The major difference between the CHA2DS2-VASc score and modified version of CHA2DS2-VASc score was the resetting of age threshold for Asian patients (assigning 1 point to patients aged between 50-74 years). This particular resetting was done because of their earlier findings that Asian atrial fibrillation patients had increased risk of ischaemic stroke. So in the present study, Tze-Fan Kang-Ling Wang et al used modified the CHA2DS2-VASc score in order to truly identify the low risk Asian population and it performed better than the CHA2DS2-VASc score for stroke risk stratification in their study. But no other Asian studies have reported the use this modified scale. So further studies are needed to justify the reliability of the modified version [Table (1)].

Table (1): Different stroke risk scores.

Risk factors	CHADS2	CHA2DS2-VASc	mCHA2DS2-VASc
Congestive heart failure	1	1	1
Hypertension: above 140mmHg or treated with antihypertensive medication	1	1	1
Age \geq 75 years	1	2	2
Diabetes mellitus	1	1	1
Prior Stroke or Transient ischaemic attack or Thromboembolism	2	2	2
Age 65-74 y	-	1	-
Age 50-74 y	-	-	1
Sex category (female sex)	-	1	1
Maximum score	6	9	9

Now regarding the bleeding risk assessment, HAS BLED [Table (2)] score has been the one that shows the most accurate results for predicting bleeding. Ron Pisters et al in 2010 first introduced this score and it was correctly able to predict the bleeding of real world patients with atrial fibrillation.^[25] The HAS-BLED score assess annual bleeding risk and its score ranges from 0 to 9, with scores of \geq 3 indicating high risk of bleeding. It has been compared with other risk scores and it has shown better accuracy for predicting bleeding.^[26] In the case of Asian

population, Yu-tao Guo et al in 2016 compared different bleeding risk scores and concluded that HAS BLED has the better predictive ability.^[27] The major advantage of HAS BLED that was found in that particular study was the predictive ability of HAS BLED when it comes to predicting intracranial haemorrhage (ICH). This is significantly important for Asian population because the risk of ICH is more in Asians than in caucasians.^[28]

Table (2): HAS-BLED score.

Risk factor	HAS-BLED
Hypertension (systolic blood pressure >160 mm Hg)	1
Abnormal renal and liver function* (1 point each)	1 or 2
Stroke	1
Bleeding tendency/predisposition	1
Labile INRs (if on warfarin)	1
Elderly (eg, age >65 y)	1
Drugs or alcohol (1 point each)	1 or 2
Maximum score	9

Though these scales are extensively validated in many cohorts, they are not validated in an Indian population. Due to its promising predictive ability on Asian population, it could produce a similar type of outcome on an Indian population.

Medication adherence and INR control

Since warfarin requires constant monitoring of its INR, medication adherence is certainly a major aspect of its therapy. Atrial fibrillation is a disease which mostly occurs at an older age. So this means that adherence to warfarin for such a population would be challenging. Another intriguing factor about adherence associated with warfarin is the INR control. Several studies have already reported the relationship between adherence and INR control.^[29] R. Lakshmi et al study which was done on an Indian population is particularly important in this regard.^[30] In that study, due to the impact of clinical pharmacist, the intervention group had better adherence, better INR control and lesser bleeding than the control group. However, R. Lakshmi et al study had an imbalanced number of atrial fibrillation patients between the control and intervention group. There were only 13 patients on intervention group whereas 32 patients were present on the control group. So, though, patients anticoagulation improved with better adherence on the overall population, the amount of atrial fibrillation patients were less on that study.

Ahmed Y Mayet study in 2016 shows a completely contradictory results from the above mentioned studies. This study did not find any correlation between higher adherence and good INR control.^[31] Another difference between these two studies is that, Ahmed Y Mayet study used Morisky's 8 item adherence scale while R. Lakshmi et al used an internally validated questionnaire. MMAS-8 has been validated in many studies.^[32,33] Similarly Davis et al found significant association between adherence and anticoagulation while Wang et al study did not find any association between them.^[34,35] So, the data regarding the medication adherence and INR control of warfarin in studies are varied. More studies needs to be conducted.

CONCLUSION

Our review mainly encompasses the challenges, advantages and disadvantages of warfarin therapy from an Indian perspective. When comparing warfarin with aspirin at any dose, warfarin has been shown to produce better efficacy and safety. Since Asians have a higher bleeding risk than Caucasians, similar type of results can be expected in an Indian population. Regarding risk stratification, HAS-BLED and CHA2DS2-VASc are the two most reliable scores, though one study used a modified version of CHA2DS2-VASc score to show better accuracy than standard CHA2DS2-VASc score. Yet both of these scores are not validated in an Indian study population.

The importance of TTR has been reported in many studies. Although there is no standard value for TTR

when it comes to good, poor or intermediate anticoagulation, the general conclusion that we can draw from multiple number of studies is the significant association between TTR values and the patients improvement. Another challenge with warfarin therapy is the correlation between medication adherence and INR control. Current studies shows varying results in understanding this correlation. Thus, our review summarises the prospects of future research that has to be conducted on Indian population in order to improve the warfarin therapy for atrial fibrillation.

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