A Comparison between TTR and FIR As a Measure of the Quality of Anticoagulation in Patients with Atrial Fibrillation

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Abstract

Background: Atrial fibrillation (AF) is a growing concern worldwide. In order to prevent AF-related adverse vascular events, adequate oral anticoagulation with warfarin is essential. The Rosendaal method has long been used to calculate time in therapeutic range (TTR) in clinical trials to assess the quality of anticoagulation but now suffers dwindling popularity due to its tedious method of calculation and inability to account for the duration spent in an out-of-range international normalized ratio (INR). Frequency in range (FIR) is being reassessed as to its value as it is easier to calculate.

Objectives: We aimed to compare FIR and TTR (using the Rosendaal method) as a measure to assess the quality of anticoagulation with warfarin in a cohort of 102 consecutive patients with valvular and non-valvular AF at a tertiary South African hospital. Secondary objectives were to assess the predictive ability of FIR to categorize patients with a TTR ≥ 65% as well as to compare the CHA2DS2-VASc and HASBLED scores with TTRs and FIRs.

Methods: We retrospectively analysed the INR values for all patients over a 2-year period and calculated both individual and overall mean TTR and FIR and assessed the agreement between these parameters.

Results: The mean overall TTR was 58.1% ± 16% and the mean FIR was 50.8% ± 16.7%. The mean TTR was significantly higher than the mean FIR (p < 0.0001). At the individual level, FIR was positively correlated with TTR in a linear fashion (r = 0.93, p < 0.001). However, the Bland–Altman method plot indicated lack of agreement between TTR and FIR, with a bias of 7.4% (95% CI: 6.1%–8.6%) and limits of agreement −4.6% to 19.3%, standard deviation (SD) = 6.1%. A cut-off value of FIR ≥ 53.3% was found to be a good predictor of TTR ≥ 65%.

Conclusion: Our study shows that although TTR and FIR are highly correlated with the individual INR levels, they are not equal. The two methods cannot be used interchangeably to assess warfarin control, and TTR should probably remain the gold standard.

Keywords: Atrial fibrillation, warfarin, INR assessment

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia seen in daily practice. It is rapidly becoming a health-care burden due to an ageing population and improved survival from coexisting cardiovascular and non-cardiovascular diseases. There are close to five million new cases of AF globally per annum. By 2050, the prevalence of AF in Africa is expected to surpass that of any other country. AF is coupled with a heightened risk of cerebrovascular accidents and thromboembolic events. Depending on the setting, stroke prevalence differs throughout Africa. The degree of disability and death as a result of strokes is 10 times higher than the developed world, largely due to limited health-care access, suboptimal treatment and an impoverished community.(1–5)

For almost 50 years, the mainstay of oral anticoagulation has been vitamin K antagonists (VKAs). These VKAs, including warfarin, have been well described to lessen the risk of stroke and thromboembolic events in AF patients. Low-cost generic versions are also now available.(4) However, their use remains challenging due to a slow onset and offset of action, a narrow therapeutic window, numerous food and drug interactions, repeated laboratory monitoring and high risk of bleeding.(6)

The recent phase III trials approving the use of the novel oral anticoagulants (NOACs) in non-valvular AF (NVAF) have obviated many of the problems experienced with warfarin.(7) However, NOACs have not been shown to be safe and effective in AF secondary to moderate or severe mitral stenosis and cannot be utilized in those with mechanical prosthetic heart valves.(8) They are also largely unaffordable to most South Africans and therefore warfarin is likely to remain the anticoagulant of choice.(6)
The optimal international normalized ratio (INR) is 2–3, and 2.5–3.5 for mechanical prosthetic valves. Quality of anticoagulation control, as determined by a TTR (time in therapeutic range) of at least 65%, is of key importance to ensure efficacy and safety of warfarin therapy. Suboptimal TTRs are associated with adverse outcomes.\(^9\,\text{,}^{10}\) The Rosendaal method,\(^11\) which is the most commonly used method in clinical trials,\(^12\) is cumbersome to calculate. As an alternative, the FIR (frequency in range) is easier to calculate and can be done manually.\(^13\,\text{,}^{14}\) Based on limited published data, conflicting results make it uncertain as to whether FIR can be used interchangeably with TTR to assess anticoagulation control.

Thus this study aimed to correlate FIR with TTR in a cohort of AF patients receiving warfarin therapy at a large urban public hospital (Charlotte Maxeke Johannesburg Academic Hospital) in Johannesburg, South Africa. Secondary objectives included the predictive ability of FIR to categorize patients as having a TTR above or below 65% and to compare the CHA\(_{2}\)DS\(_{2}\)VASc and HASBLED scores with TTRs and FIRs.

MATERIALS AND METHODS

Study Design

We retrospectively reviewed the INR results of 102 patients with AF who received warfarin therapy at the anticoagulation clinic between 1 December 2014 and 31 December 2016. The study was approved by the WITS University Human Research Ethics Committee (Reference No. M160775).

Patients were excluded if they were younger than 18 years of age, if warfarin was indicated for conditions other than AF and if there were less than 20 INR measurements over the 2 year period. Patients using warfarin for less than 3 months duration before 1 December 2014 were also excluded because of more frequent INR testing and great variations in readings during initial warfarin adjustment.\(^13\) Both non-valvular and valvular AF patients were included. According to the standard operating procedure of the centre, INR tests were done every 4 weeks or more often for out-of-range INRs. An INR range of 2–3 was defined for NVAF and those with native valve disease, and a range of 2.5–3.5 was defined for bio-prosthetic and mechanical prosthetic heart valves. Time in therapeutic range (using the Rosendaal method) and FIR for each patient was calculated using INR Pro (downloadable from the internet). Informed consent was obtained from all patients and demographic data (age, gender, hypertension, diabetes, heart failure or left ventricular dysfunction, previous stroke or transient ischaemic attack, previous myocardial infarction, peripheral artery disease or aortic plaque, hyperthyroidism and history of cigarette smoking) was collected. The CHA\(_{2}\)DS\(_{2}\)VASc and HASBLED scores were subsequently calculated.

Statistical Analysis

Descriptive analysis of the data was performed with categorical variables summarized as frequency and percentage tabulations. Continuous variables were summarized by the mean, standard deviation, median and interquartile range. The overall TTR and FIR was compared using the paired samples \(t\)-test. Agreement between TTR and FIR measures was assessed using the Bland–Altman method. The ROC (receiver operating characteristic) curve analysis was used to assess the predictive ability of FIR to categorize patients as having TTR above/below 65%. Finally, the risk scores of patients with TTR above and below 65% and with FIR above and below the cut-point were compared using the independent samples \(t\)-test. The data analysis was carried out in SAS (SAS Institute, North Carolina, USA) version 9.4 for Windows. A 5% significance level was used.

RESULTS

A total of 102 patients were included in the final analysis. The mean age of the total cohort was 63.1 \(\pm\) 15.6 years and 61.8% were female. Figure 1 represents the graphical distribution.
of age. The mean age was 68.2 years in the NVAF group \( (n = 72) \), and 69% of patients were 65 years or older. In the valvular AF group \( (n = 30) \), the mean age was 50.8 years.

The basic demographic data of the study population is summarized in Table 1. The mean \( \text{CHA}_{2}\text{DS}_{2}\text{VASc} \) and HASBLED scores were 3.6 \pm 1.5 and 1.8 \pm 1.0, respectively. The most prevalent risk factors were hypertension (78%), diabetes (19%), vascular disease (21%) and previous stroke (18%).

The mean and median TTRs were 58.1% \pm 16% and 57.4% (interquartile range, 47%–69.9%), respectively. In the overall study cohort of 102 patients, only 41 patients (40.2%) had a TTR \( \geq 65% \), of whom 80.5% were from the non-valvular group of patients. The mean and median FIRs were 50.8% \pm 16.7% and 50% (interquartile range, 39.3%–62.5%), respectively. Figures 2 and 3 depict the distribution of the mean overall TTR and FIR, respectively.

The mean TTR was significantly higher than the mean FIR using the paired samples \( t \)-test \( (p < 0.0001) \). The mean difference between the two scores was 7.4% (95% CI: 6.1–8.6%). Figure 4 illustrates a scatterplot of FIR versus TTR, in which FIR was positively correlated with TTR in a linear fashion \( (r = 0.93, p < 0.001) \).

In contrast, the Bland–Altman methodology, Figure 5 indicates a lack of agreement between TTR and FIR, with a bias of 7.4% and limits of agreement −4.6% to 19.3%, standard deviation (SD) = 6.1%.

The predictive ability of FIR for TTR was very high \[ \text{AUC (area under the curve)} = 0.981 \], as indicated by the ROC curve in Figure 6. A cut-off value of FIR \( \geq 53.3\% \) was found to be a good predictor of TTR \( \geq 65\% \), with a sensitivity of 95% (95% CI: 83–99%), specificity of 90% (95% CI: 80–96%) and positive predictive value of 87% (95% CI: 73–95%).

Finally, comparison between the mean \( \text{CHA}_{2}\text{DS}_{2}\text{VASc} \) and HASBLED scores with FIRs above and below the established cut-off value (see Table 2) showed no significant difference. Table 3 demonstrates that the mean \( \text{CHA}_{2}\text{DS}_{2}\text{VASc} \) score for patients with TTR \( \geq 65\% \) (3.1; SD 1.1) was significantly lower than that for patients with TTR <65% (4.0; SD 1.6) \( (p < 0.010) \).

DISCUSSION

One of the important findings of this study in South African patients with AF (both non-valvular and valvular), receiving warfarin therapy, is that anticoagulation control is suboptimal. The mean TTR of 58.1% in this group was much higher than the results obtained from the ACTIVE-W trial (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events), where the mean TTR for South Africa of 46.3% was the lowest amongst 15 countries.(15) This, however, may not have been an accurate representation as there were less than 100 participants from South Africa from a total of 3371 who were randomized to oral anticoagulants. Importantly, it has been emphasized that a TTR <58% grants no benefit over antiplatelet therapy in the prevention of AF-related adverse vascular events.(15)

The Rosendaal method to calculate TTR has been the most commonly used surrogate marker in clinical trials for assessment of warfarin control.(11,14) One of its main...
Fig 2: Distribution of TTR within the cohort

Fig 3: Distribution of FIR within the cohort

Fig 4: Scatterplot of TTR vs. FIR
advantages is that it allocates an INR value to each day and allows the linear relationship between 2 INR values to curtail the unpredictable effect of short-term repeated INR testing. At the clinic, patients with out-of-range INRs were dose adjusted and retested as early as 3 days, depending on the previous result. Frequent INR testing ideally should increase the TTR; however, this was not the case, probably because participants with out-of-range INRs formed the minority of the cohort.

These and other data suggest that in South Africa many patients persistently achieve a TTR less than that recommended by international guidelines. However, compared to studies in developed countries, one needs to consider other variables as a potential cause for low TTR values. Singer et al reported a noteworthy influence of patient clinical features and geographic region on the overall TTR and suggested that this may be a reflection of varying levels of perseverance in achieving a target INR, different systems

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**Fig 5:** Bland–Altman plot comparing TTR and FIR

**Fig 6:** ROC curve assessing predictive ability of FIR for TTR
in managing warfarin, as well as different regional impediments to frequent INR testing and warfarin dose adjustments.(16) In the public health setting in South Africa, there are poor overall patient education levels, resource availability, and access to health care, along with language barriers.(4) It is thus not unreasonable to assume that in this study the interplay of these factors contributed to poor treatment adherence, lack of understanding of regular follow-up and INR testing, resulting in low individual and centre TTRs.

Recent studies have shed some light on the ability of FIR to act as an equal alternative to TTR in patients with NVAF. One of the major differences between the two audit parameters is that the time between INR measurements is not considered when calculating FIR. Theoretically, FIR would correlate well with TTR if the time between INR measurements was kept standard and evenly distributed.(13) Also, standard definitions regarding valvular and non-valvular would be needed to homogenize the population under scrutiny in trials, so as to better compare results. Our study included patients with valvular and NVAF, the definitions of each varying from that used in the major global clinical trials. This makes interpretation of TTR and FIR in valvular versus NVAF groups difficult.

Outcomes from this study are consistent with findings from data in the GARFIELD-AF (Global Anticoagulant Registry in the FIELD–Atrial Fibrillation) study that showed although highly correlated ($r = 0.93$, $p < 0.001$), there was lack of agreement between FIR and TTR.(10) The mean TTR was significantly higher than the mean FIR, and on average, the FIR measured 7.4% (95% CI: 6.1–8.6%) less than the TTR. However, this bias did not increase or decrease with increasing mean TTR or FIR ($p = 0.20$). In general, FIR increased as TTR increased. In this study, the 41 patients with TTR $\geq 65\%$ only 2 patients had FIRs of $\leq 53.3\%$ (the calculated predictor of TTR $\leq 65\%$). These findings may advocate using FIR as an ongoing method of surveillance in those who have well-documented TTRs or to identify new patients with poor control, while the Rosendaal method should be employed as the ‘standard of care’ in assessing poor control overall.

Chan et al found the FIR value of $\leq 56.1\%$ to be an adequate predictor of TTR $<65\%$.(13) Our lower cut-off value of 53.3% seems justified as our mean TTR and

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<th>Analysis variable : CHA$_2$DS$_2$-VASc score</th>
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<tr>
<td><strong>FIR (%)</strong></td>
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**SD**: Standard deviation; **IQR**: interquartile range.

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**SD**: Standard deviation; **IQR**: interquartile range.

### Table 2: Independent sample t-test comparing CHA$_2$DS$_2$VASc and HASBLED scores to FIR values above and below 53.3%.

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### Table 3: Independent sample t-test comparing the CHA$_2$DS$_2$VASc and HASBLED scores to TTR values above and below 65%.
FIR values were 15–20% higher than that of the Chinese cohort.

The CHA\textsubscript{DS-VASc} score, in comparison to the older CHADS\textsubscript{2} score includes three additional common stroke risk factors to broaden prognostication in AF.(17) Although not validated in the native African community,(4) its use is supported by the European, American and British guidelines.(18–20) Patients with a high risk of stroke (CHA\textsubscript{DS-VASc} score >3) also have a high risk of bleeding. This may be partly attributed to the fact that both scores include common risk factors (e.g. age, hypertension and previous stroke).(20,21) In this analysis, we define their acceptable minimum TTR before applying HASBLED as a predictor of warfarin control.

### LIMITATIONS OF THE STUDY

This study has certain inherent limitations due to the retrospective nature of the study. Patients gave account of presence or absence of stroke risk factors, but these were not confirmed on examination. Patients were excluded if they had less than 20 INR measurements over the 2-year period. This may have falsely elevated the overall mean TTR/FIR as defaulting therapy was not considered.

With regard to method comparison, the Bland–Altman method plot only defines limits of agreement. It cannot indicate whether the agreement is sufficient to recommend use of one method in preference to the other.(23) Furthermore, a small sample size may be unreliable to determine larger population parameters.

This study also did not assess clinical outcomes associated with a TTR \(\leq 65\%\) and scheduled interruptions of warfarin therapy (i.e. for hospitalization, peri-procedural etc.) were not taken into account. Therefore, TTR may have been underestimated.

### CONCLUSION

This study shows that TTR and FIR are incongruent. Overall TTR values are higher than FIR values. In a financially and resource constrained setting such as South Africa, FIR assessment may assist in identifying those with poor warfarin control. However, the Rosendaal method should still be used to optimally assess and manage these patients.

Much of the available published data surrounding TTR, FIR, risk stratification scores and clinical guidelines pertain to first world countries. Large prospective studies in sub-Saharan Africa, evaluating the validity of these international parameters in an African population, need to be carried out. Globally, an agreement needs to be reached regarding definitions of valvular and NVAF to allow for equal inter-trial comparisons.

### REFERENCES

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