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

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A research report submitted to the Faculty of Health Sciences, University of Witwatersrand, for the fulfilment of requirements for the Degree of Master of Medicine

DECLARATION

I, Priya Parbhoo, declare that this research report is my own work. It is submitted for the degree of Master of Medicine (in the submissible format with my protocol and an extended literature review) in the branch of Internal Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this, or any other university.

……

……day of ……2018

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To my closest friends Anisah Mamoojee and Sheetal Chiba, your loyalty and persistent motivation has helped me through the various stages of my registrar training, and allowed me to grow, both as a doctor and a person. Thank you for everything.

Last but not least, I would like to extend my gratitude to my supervisor Professor Jacobson. You always gave me your time and undivided attention. Your vast knowledge and guidance throughout this process provided me with the necessary tools to complete this research. Thank you.

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 to evaluate TTR (time in therapeutic range) has traditionally been used in clinical trials to assess quality of anticoagulation but it's utility in clinical practice is increasingly being questioned due to its tedious method of calculation and inability to account for the duration spent in an out-of-range INR. Frequency in range (FIR) is being reassessed as to its value in view of it being easier to calculate.

Aim

We aimed to compare FIR and TTR (using the Rosendaal method) as a measure to assess the quality of anticoagulation with warfarin in patients with valvular and non-valvular AF at a tertiary South African hospital.

Objectives

Secondary objectives were to assess the predictive ability of FIR to categorize patients with a TTR≥65% as well as to compare the CHA^2DS^2-VASc and HASBLED scores to TTR and FIR.

Methods

We retrospectively analysed the INR values for a cohort of 102 patients over a two year period and calculated both individual and overall mean TTR and FIR. Paired samples t-test was used to compare the two parameters and the Bland-Altman method comparison plot to assess the agreement between them.

Results

The mean overall TTR was 58.1%±SD 16% and the mean FIR was 50.8%±SD 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 ($r= 0.93$, 95% CI 0.90-0.95; $p<0.001$). However the Bland-Altman method plot indicated a 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 (s) = 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.

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ABBREVIATIONS

AF	Atrial Fibrillation
AUC	Area Under the Curve
ECG	Electrocardiograph
ESC	European Society of Cardiology
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
COPD	Chronic Obstructive Pulmonary Disease
FIR	Frequency in Range
INR	International Normalised Ratio
LA	Left Atrium
LAA	Left Atrial Appendage
QALY	Quality Adjusted Life Years
NICE	National Institute for Health and Care Excellence
NOAC	Novel Oral Anticoagulants
NVAF	Non-valvular Atrial Fibrillation
SSEE	Stroke/systemic embolic events
TTR	Time in Therapeutic Range
VHD	Valvular Heart Disease
VKA	Vitamin K Antagonist
vWF	von Willebrand Factor

CHAPTER 1: PROTOCOL WITH EXTENDED LITERATURE REVIEW

1.1 Introduction

Atrial fibrillation (AF) is a supraventricular rhythm abnormality that is frequently encountered in clinical practice. Uncoordinated atrial activity leads to an irregular ventricular rate, at times with haemodynamic instability. Atrial fibrillation is strongly associated with structural heart disease, however many patients may also have no evidence of cardiac disease. In an electrocardiograph (ECG), absent P waves and irregular RR intervals point to the presence of AF. Due to asynchronous atrial contraction, and subsequently ventricular contraction, one experiences symptoms related to a decrease in cardiac output. These include effort intolerance, fatigue, dyspnoea and/or palpitations. Atrial fibrillation occurrence increases with older age. About 5% of persons aged 65 and older develop this condition and this increases to 10% in those older than 75 years of age. Permanent AF, if left untreated, is associated with a deterioration in ventricular systolic function and independently elevates the possibility of systemic thromboembolic events. In those with AF, the risk of developing a stroke is 5 to 6 times higher in comparison to persons of the same age in normal sinus rhythm. This occurs at a rate of approximately 5% per annum.[1]

1.2 Epidemiology

According to the Global Burden of Disease 2010 study, which used evidence from 184 different publications, it was concluded that approximately 33.5 million individuals worldwide had AF. Additionally, almost 5 million new cases were reported on an annual basis. Over the past 20 years, the incidence and prevalence have increased considerably. The study also reiterated previous findings that a direct relationship between older age and AF burden exists. The rates of AF in the ≥35 year old population was observed to be more than twice the overall prevalence. Men were also more frequently affected than women.[2,3]

In 2010, the prevalence of AF (age- adjusted, per 100,000 population) for males and females in Sub-Saharan Africa was 659.8 and 438.1 respectively. Sub Saharan Africa had a lower incidence and prevalence compared to that of North America. Eastern Sub

Saharan Africa showed the least change with regard to median change in prevalence (3.4%), while in North America, this amounted to 40.1%. [2,3] Owing to the superior standard and level of healthcare provided in first world nations such as North America, more patients are perhaps diagnosed much earlier and this may account for the discrepancy noted above. Estimates of global AF prevalence are currently unknown and possibly underestimated due to the high prevalence of asymptomatic AF.[29]

1.3 Classification

The antiquated terms "acute" and "chronic" AF were used to describe the progressive natural course of AF. However in 2014, the American Heart Association/ American College of Cardiology/ Heart Rhythm Society guidelines on AF management provided a classification scheme (Table 1) to replace those terms.[4]

Table 1. Classification scheme as per AHA/ American College of Cardiology [4]

TERM	DEFINITION
Paroxysmal AF	AF that is self-terminating, usually within 48 hours
Persistent AF	Continuous AF that is sustained >7 days.
Long-standing persistent AF	Continuous AF >12 months in duration
Permanent AF	The term "permanent AF" is used when the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm. Acceptance of AF represents a therapeutic attitude on the part of the patient and clinician rather than an inherent pathophysiological attribute of AF. Acceptance of AF may change as symptoms, efficacy of therapeutic interventions, and patient and clinician preferences evolve
Non-valvular AF	AF in the absence of rheumatic mitral stenosis, a mechanical or bio prosthetic heart valve, or mitral valve repair

In patients who had paroxysmal, persistent or permanent AF in the absence of structural heart disease, the term “lone AF” was used.[5]

According to the current AF guidelines[4], one is classified as having lone AF if they are younger than 60 years of age without a history or electrocardiographic features of concurrent cardiovascular or pulmonary conditions, and the absence of an acute trigger (i.e. diabetes mellitus, hypertension, hyperthyroidism etc.). However, these guidelines do not specify which concomitant conditions need to be excluded to classify AF as lone AF, therefore, the utility of this term is now questioned.[5]

1.4 Risk Factors

There are multiple clinical risk factors associated with AF, some of which include: pulmonary thromboembolic disease, increasing age, hypertension, diabetes mellitus, myocardial infarction, valvular heart disease, heart failure, obesity, obstructive sleep apnea, cardiothoracic surgery, smoking, alcohol use, hyperthyroidism, congenital heart disease, chronic obstructive pulmonary disease (COPD), chronic kidney disease, European ancestry and family history. Left ventricular hypertrophy and left atrial enlargement (including causes thereof) also are associated with an increased risk of AF.[4]

1.5 Mechanisms of Thrombogenesis in Atrial Fibrillation

The pathogenesis of thrombus formation in AF is incompletely understood. It is multifaceted, complex and is not only due to fibrillating atria with blood stasis. Virchow’s triad is fulfilled in atrial fibrillation, resulting in the development of thrombi. The triad includes: unusual changes in blood flow, arterial wall abnormalities (endothelial or endocardial injury or dysfunction), and blood constituents (abnormal haemostasis, platelets, and fibrinolysis). This clarifies the hypercoagulable state in this disorder and the need for anticoagulation therapy.[6]

1.5.1 Anatomical Considerations

The left atrial appendage (LAA) is a long and narrow blind-ended passage attached to the left atrium (LA) that predisposes to blood stasis. Changes in the diameters of the LAA and LA has correlated with an increased risk of thromboembolism.[6]

Endocardial wrinkling (resulting from oedema and fibrinous infiltration), endothelial denudation, thrombotic clustering and myocyte hypertrophy or necrosis are changes seen even in patients without valvular heart disease. The preservation of the structural and geometric integrity of the heart is obtained through the extracellular matrix, which provides a supporting framework to the cardiac cells. Disruption of this matrix will lead to conduction abnormalities, as well as infiltration and fibrosis of the endocardium, ultimately promoting further thrombogenesis.[6]

1.5.2 Abnormal Blood Stasis

Blood stasis within non-contractile atria together with the presence of non-valvular AF promotes progressive dilatation of the LA. This increased chamber diameter leads to added stasis and an increased susceptibility to thrombosis. In patients with valvular AF however, the degree to which the LA diameter contributes to clot formation has not been ascertained and agreed upon in studies.[6]

1.5.3 Abnormal Blood Constituents

Serum concentrations of prothrombotic factors like prothrombin fragments 1 and 2, thrombin-antithrombin III complexes, fibrinopeptide A, and D Dimer are raised in AF patients who are complicated by strokes, compared to those with sinus rhythm. D dimer values has been found to remain within the same range over time in chronic AF. It therefore could be used to evaluate the level of hypercoagulability, regardless of age.[6]

Known to be an important indicator of endothelial destruction and dysfunction, von Willebrand Factor can predict the presence of LAA thrombus in AF. It is however non-specific for cardiogenic thromboembolic disease. In patients with a history of AF and cardiogenic emboli, both vWF and tissue factor have been found to be overexpressed.[6]

Platelet activation is increased in AF, however more evidence is required to demonstrate that platelets directly contribute to thrombogenesis. Beta-thromboglobulin is a protein specific to platelets and is suggestive of platelet activation. Compared with controls in sinus rhythm, raised levels has been found in patients with non-valvular and valvular AF. [6]

1.6 Rationale for Anticoagulation in Atrial Fibrillation

Analyses of the Framingham Heart Study has described the association between atrial fibrillation, stroke and thromboembolism. The risk of developing a stroke from valvular AF (AF from rheumatic origin) is 17 times higher, whilst non-rheumatic (non-valvular) AF is linked to a 5-fold increased risk.[7,8]

Despite concomitant conventional risk factors for atherosclerotic cerebrovascular disease (i.e. hypercholesterolaemia, diabetes, and hypertension) in certain patients, the most credible reason for anticoagulation in AF is due to the high prevalence of LAA thrombus formation. As mentioned earlier, stasis within the fibrillating LA and fluctuating LAA flow velocities are the basis of flow abnormalities in AF. Emboli arising from the LAA occurs in more than 90% of cases in non-valvular AF. Endocardial abnormalities arise from gradual and ongoing atrial dilatation, endocardial stripping, and fibro-elastic infiltration of the extracellular matrix. Atrial fibrillation related strokes are mostly due to cardiac thromboembolism, and therefore these patients are also at risk for systemic emboli (to the lungs, kidneys etc.).[7,8,9]

As already stated, the relationship between AF caused by rheumatic heart disease and an increased risk for stroke is well established. Further risk stratification in these patients is therefore unhelpful, irrespective of risk factors.[8]

In contrast, the risk of stroke in non-valvular AF changes with the presence of stroke risk factors, and for this reason, various risk stratification scores such as the $CHADS^2$ and CHA^2DS^2-VASc score (Table 2)[10] have been formulated to allow identification of higher versus lower risk groups in an attempt to improve outcomes of estimated event rates [8,10] by maximizing the benefit to risk ratio.

1.6.1 Risk Stratification Groups

The $CHADS^2$ score allocates a point each for congestive heart failure, hypertension, age over 75 years and diabetes mellitus. Two points are allocated for a history of stroke or transient ischaemic attack. Numerous studies have substantiated the $CHADS^2$ score as it strongly identifies patients who are at a higher risk for stroke. The CHA^2DS^2-VASc score (Table 2)[10], which includes 3 additional risk factors, was developed to allow for

better risk stratification in seemingly lower risk groups. This scoring system places patients into a low risk (i.e. those with lone AF, or those with a CHA^2DS^2-VASc score of 0), moderate (score of 1) or high risk (score of ≥2) category. Oral anticoagulation is recommended for the high risk category. In a patient with a score of 1, guidelines suggest that either antiplatelet therapy (i.e. aspirin) may be used, or oral anticoagulation. Oral anticoagulation is not recommended in patients with a score of 0.[10] In several studies, the CHA^2DS^2–VASc score was determined to predict a better stroke risk among patients with low baseline $CHADS_2$ scores (0 to 1). The utility of the CHA^2DS^2–VASc score in the native African community remains uncertain as it has not been validated in this setting.[15]

The risk of bleeding while on anticoagulation is assessed using the HAS-BLED score (Table 3)[10]. In clinical practice, calculation of these scores may be difficult due to missing or unavailable data points. A lack of evidence from prospective studies also does not support withholding anticoagulation on the basis of a high bleeding score.[8]

Table 2. The CHA^2DS^2-VASc score

Letter	Risk Factor	Score
C	Congestive Heart Failue/ Left Ventricular Dysfunction	1
H	Hypertension	1
A	Age ≥ 75 years	2
D	Diabetes Mellitus	1
S	Stroke/ Transient Ischaemic attack/ thrombo-embolism	2
V	Vascular disease	1
A	Age 65-74 years	1
Sc	Sex category (i.e. female)	1

Max. score = 9

Table 3. The HAS-BLED score

Letter	Risk Factor	Score
H	Hypertension	1
A	Abnormal renal and/or Liver function	1 or 2*
S	Stroke	1
B	Bleeding	1
L	Labile International Normalised Ratio's	1
E	Elderly (age > 65)	1
D	Drugs and/or alcohol	1 or 2*

Max score = 9, *1 point each

1.7 Available Anticoagulation Agents

For more than a decade, vitamin K antagonists (VKA's) or coumarins (of which warfarin is one of them) have been shown to be better than antiplatelet drugs (i.e.

aspirin) in preventing stroke and embolic events in patients with non-valvular AF. Warfarin reduces stroke risk by 68%.[10]

Warfarin works by interfering with the conversion of Vitamin K and its 2,3 epoxide (vitamin K epoxide). The glutamate residues on the N-terminal sections of factors II, VII, IX and X (vitamin K-dependent factors) cannot undergo γ-carboxylation and are therefore inhibited from exerting their pro-coagulant outcome. Carboxylation allows calcium to bind, which then facilitates binding on the phospholipid surfaces. Treatment with a VKA causes the liver to produce partly carboxylated and decarboxylated proteins with minimized coagulant activity.[11]

The International Normalized Ratio (INR) is a measure of blood's coagulability. By using the World Health Organization's international reference reagent, a standardized ratio is obtained which allows for the bleeding risk in patients receiving VKA's to be monitored. The ratio is of a person's prothrombin time to the usual average prothrombin time. The normal INR value is 1. Maintaining the INR within a therapeutic range of 2-3 is required for atrial fibrillation (excluding AF secondary to mechanical heart valves where an INR range of 2.5-3.5 is generally used, depending on the position of the valve and type of valve inserted). Lower values (less than 2) are linked with higher risks of thromboembolic events, and higher values (above 3.5-4) with bleeding.[12,13,23]

Vitamin K antagonist use is problematic in practice due to several factors. Apart from a narrow therapeutic window, there is also substantial inconsistency in dose response among patients, cross interaction with many foods and drugs and standardization of laboratory control is difficult. These limitations contribute to poor patient adherence and underuse by clinicians.[11]

For the above-mentioned reasons, numerous novel oral anticoagulants (NOACs) have arisen that offer numerous advantages over warfarin i.e. fewer interactions with both food and drugs, a rapid onset of action as well as shorter half-life. These NOACs may either dose-dependently inhibit thrombin (dabigatran) or activated factor X (rivaroxaban, apixaban, and edoxaban). The anticoagulation effects of these NOACs are predictable and allows for fixed doses to be given in the absence of repeated INR testing.[13]

To date, there have been four important phase 3 randomized trials comparing the use of NOACs to warfarin in patients with non-valvular AF. It is important to note that all 4 trials were non-inferiority trials i.e. the primary outcome was not to test if NOACs were better than warfarin.

These trials are: Randomized Evaluation of Long Term Anticoagulation Therapy (RE-LY; dabigatran), Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF), Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE), and the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation- TIMI 48 study (ENGAGE AF-TIMI 48).[13]

A meta-analysis of the above trials, looking at all 71 683 patients, was presented in The Lancet by Ruff and colleagues.[24] The conclusions that may be drawn from this meta-analysis are that NOACs are at best as effective as warfarin in preventing ischaemic stroke and intracranial bleeding. In general, the NOACs had an assuring profile in comparison with warfarin in respect of safety. However, they (except Apixaban) were associated with a higher risk of gastrointestinal bleeding.[13] A substantial limitation of all these NOAC trials is that a large proportion of patients were European, meaning that the number of black subjects or patients from Africa were extremely low. Additionally, the number of patients afflicted with valvular-AF is also thought to be higher in Africa. Thus, the use of NOACs in those from the African continent is not well-justified.[13,15]

The major drawbacks of such a meta-analysis, is that it assumes that all NOAC drugs are the same (in terms of class-effect), and that the randomized trials are uniform (comparing the same outcome using the same drugs), which in both instances, is not the case. As a result, it remains doubtful as to which NOAC is the best in terms of safety and efficacy. Although auxiliary assessments between NOACs have been discrepant, these comparisons indicate that, ultimately, the drug could be suited to the patient, or the patient suited to the drug. This is dependent on safety, efficacy, and other patient factors like drug compliance and renal function.[13]

1.8 The Cost-Effectiveness of NOACs versus Warfarin

Despite the fact that NOACs are capable of saving on medical costs due to fewer adverse events and lack of INR monitoring, the direct incremental drug cost does however increase the total medical cost over the lifetime of a patient.[14] However, many studies also concur that life expectancy and QALYs (quality-adjusted life years) are higher in patients treated with NOAC's compared to warfarin. Even though the expected lifespan of patients taking NOACs is higher, the decreased severity of stroke and number of events result in lower in-patient hospital and follow-up costs.[14]

Anticoagulation drug costs, INR monitoring and the treatment of drug-related adverse events are all the costs considered with AF. Cost-effectiveness studies comparing NOACs with warfarin are limited. In South Africa, a study conducted at a private hospital has shown that dabigatran, used as first-line treatment in AF patients, was economical in reducing the risk of stroke. Estimated costs of Dabigatran versus warfarin was higher (R60 365 (Rands) and R24 243 respectively). This amounts to a significant difference (R36 122) in costs per year, reflecting dabigatran's potential unaffordability in the South African state sector. However, adverse events and follow-up costs with Dabigatran were lower than anticipated when compared to warfarin [R23 246 vs R24 888 and R236 496 vs R252 229 respectively].[15]

From the above, it is clear that that the cost-effective management of AF in the African population is of paramount importance given the scarcity of resources available.[14]

1.9 Measuring the Quality of Anticoagulation with Warfarin

As mentioned before, the anticoagulation effect of warfarin is measured by the INR (international normalized ratio), where a target therapeutic range of 2-3 is recommended for most indications, including atrial fibrillation. The extent of time spent in the therapeutic range (TTR – time in therapeutic range) has been closely linked with adverse outcomes, i.e. stroke, haemorrhage and mortality[16], and as such, has been used in many studies as a surrogate marker of warfarin control.[17]

TTR can be measured in several ways: 1) the frequency of INR's in range (FIR) – this is calculated by using the total number of INR's that fall within the therapeutic range and dividing it by the total number of INR tests performed for all patients during a certain time period. 2) the cross-section-of-the-files methodology uses the INR that is closest to the midpoint of the therapeutic range divided by the total number of INR tests for everyone and 3) Rosendaal linear interpolation method, which allows one to assign a specific INR value daily for each patient as a linear relationship between 2 INR measurements is assumed.[17]

The calculation of TTR using the Rosendaal method has been used in almost all the studies comparing warfarin to NOACs. However, the calculation remains a tedious process for everyday clinical practice and requires computer software.[17,23] As an alternative, FIR can be more easily and manually calculated.[23] One of the main differences between the two methods is that time between INR measurements is taken into account when calculating the TTR using the Rosendaal method. This curtails the unpredictable effect of short-term repeated INR testing. This is expected to provide a better correlation with adverse clinical events.[19]

The best way to understand how the Rosendaal method works, is through example. A patient requiring a therapeutic INR range of 2 to 3 has an INR of 2.4 on 1st November and 3.9 on 17th November. The Rosendaal method assumes that a patient gradually moves to a reading of 3.9 over the 16 day period.

The total shift = 1.5 (Derived by subtracting 2.4 from 3.9)

The amount of the shift that is within the therapeutic range = 0.6 (i.e. 3 – 2.4)

Percent of the total shift that is within range = 0.6/1.5 = 40%

Therefore, 40% of the 16 days were within range = 6.4 days, while 9.6 days were out-of-range.

Another way of understanding it is through the graph (*figure 1*) below.

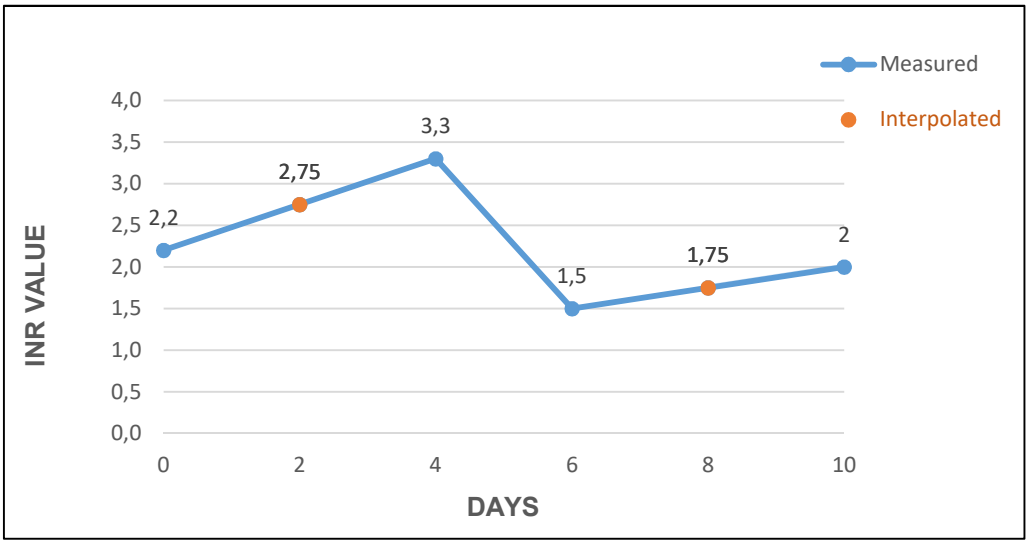

Figure 1. An Example of the Rosendaal Linear Interpolation Method

The orange (interpolated) dots indicate the assumed INR values based on the postulation that changes between serial INR measurements are linear over time. From the above, if an INR increases steadily from 2.2 to 3.3 over a period of 4 days, it increases at a rate of 0.275 per day as per Rosendaal (difference between the two readings divided by the number of days between them). If an INR is <2 or >3, and the time between checks is long, the TTR will be falsely low.[28]

In reality however, if an INR is out-of-range, the warfarin dose is adjusted and within days, the INR will increase. *Figure 2* below highlights the duration spent in an out-of-range INR soon after the warfarin dose is increased, compared to *figure 3* which depicts the Rosendaal method.[28]

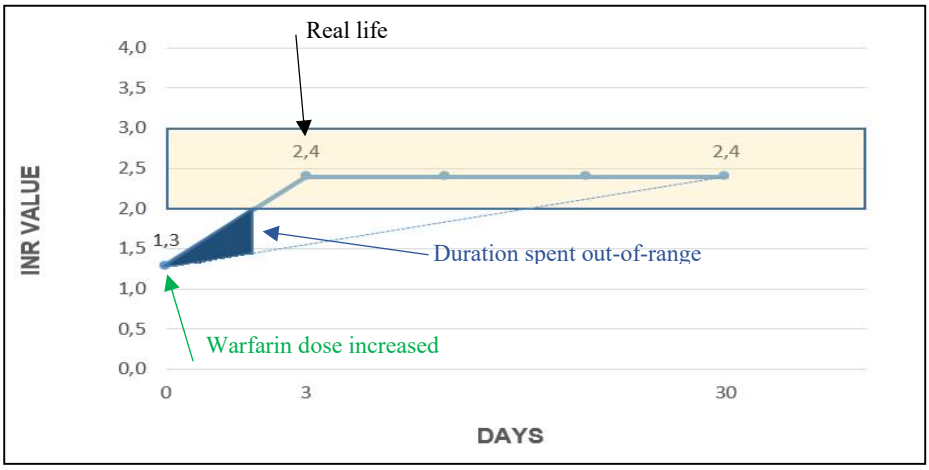

Figure 2. A representation of the time outside therapeutic range in real-life

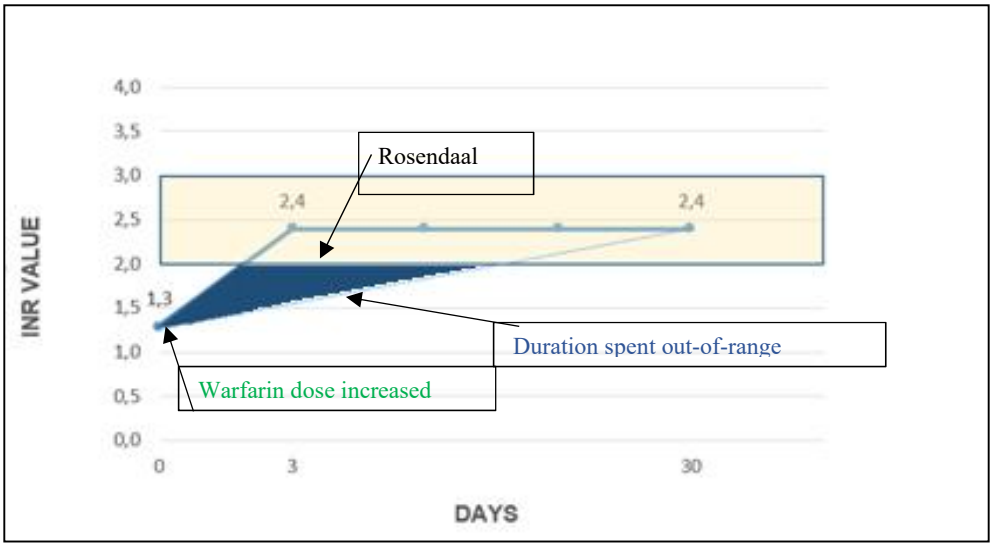

Figure 3. A representation of the time outside therapeutic range using the Rosendaal method

From the above, we can see that if the warfarin dose is changed for an INR <2, the Rosendaal TTR will be lower as a result of a longer duration spent out of the therapeutic range. Rosendaal TTR also does not capture periods characterized by extreme deviations in INR.[16] If INR testing frequency soon after warfarin dose change differs, Rosendaal's TTR cannot be uniformly compared across trials.[28]

The advantages and disadvantages of the three methodologies have been discussed in the literature and are summarized below in Table 4.[17]

Table 4. Advantages and Disadvantages of Methods to Obtain Time-in Therapeutic Range [17]

Methodology	Advantage	Disadvantage
Fraction of INR's	• Simple to calculate • Requires only one INR value per patient in clinic population • Not influenced by extent of INR out-of-range	• More frequent testing in unstable patients may bias overall results (will under-estimate TTR of group) • Does not take into account actual days within target range • Does not consider individual patients
Cross-section-of-the-files	• Simple to calculate • Considers individual patients • Not influenced by extent of INR out-of-range	• Does not take into account actual days within target range • Only considers one point in time
Rosendaal linear interpolation	• Takes into account actual days in target range • Allows one to calculate INR specific incidence rates of adverse events	• Calculation more difficult • Makes assumptions about INR between actual tests • Does not consider individual patients • Extreme out-of-range INR values may bias overall results

Reprinted by permission from: Copyright Clearance Centre Right's Link. [Springer Nature. Journal of Thrombosis and Thrombolysis. Quality Assessment of Anticoagulation Dose Management: Comparative Evaluation of Measures of Time-in-Therapeutic Range. L. Schmitt, J. Speckman, J. Ansel. 2003

The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE W) trial was a randomized trial of oral anticoagulants versus clopidogrel plus aspirin in patients with documented AF. The mean TTR for the 526 centers throughout fifteen countries were calculated by using individual TTRs (calculated using the Rosendaal method). The study found that a threshold TTR exists and indicated a critical value (to be of benefit) for TTR of 65%. Based on the population average, a minimum TTR threshold of ~58% was suggested. From the same study, South Africa's mean TTR was 46.3%, which was below the median of 65% that defined the minimum TTR required to show benefit from oral anticoagulation.[18]

From the above, it is suggestive that South Africa may not achieve the usual benefit from warfarin use due to poor delivery of anticoagulation, and this may even be associated with a higher risk of hemorrhage and/or thrombosis.[10]

The 2014 National Institute for Health and Care Excellence (NICE) guidelines recommend a validated tool such as the Rosendaal method if computers and the necessary software is available, while the FIR for manual dosing. A TTR<65% is an adequate gauge of suboptimal anticoagulation control. Other guidelines have suggested different cutoff values for TTR. The European Society of Cardiology (ESC) proposes a target TTR of at least 70% while the Asia Pacific Heart Rhythm Society advocates for a minimum TTR of 60% for optimal VKA control.[10]

There is limited published data on using FIR as a marker for the quality of anticoagulation control. Most publications have described FIR at centre or regional level, making its application for individual patients unreliable.[19] In a 2016 study by Fitzmaurice et al that used data from the Global Anticoagulant Registry in the FIELD–Atrial Fibrillation (GARFIELD-AF), the agreement between FIR and TTR was evaluated. Here, FIR values were lower than TTR values overall. Although the two parameters correlated at the centre level, there was still widespread discrepancy between them at the individual levels. Their analysis concluded that FIR was disproportionate to TTR and cannot be used interchangeably.[23]

A study in Chinese patients with non-valvular AF found that the Pearson correlation coefficient between FIR and TTR was 0.81 (P<0.0001), despite numerical discrepancy between them. They found that a cutoff value of FIR≤56.1% effectively detected

patients with a TTR<65%, with a high sensitivity of 98.3% and a positive predictive value of 91.9%.

With such marked differences in results from studies comparing TTR and FIR, it remains unclear as to whether FIR can be used interchangeably with TTR to assess quality of anticoagulation with VKA's.

1.10 The Challenges with Valvular Heart Disease

Varying definitions for the term "valvular AF" have been used in recent trials. Patients with moderate to severe mitral stenosis or a mechanical prosthetic heart valve have constantly been excluded from the 4 major phase 3 trials (mentioned above) comparing NOACs with warfarin.[25] They have however included patients with alternate forms of valvular heart disease (VHD) like aortic incompetence, mitral incompetence, aortic stenosis and mitral valve prolapse.[27] A phase 2 trial testing Dabigatran in patients with mechanical prosthetic valves was prematurely terminated due to increased stroke rates.[26] In these patients therefore, VKA's are the only suggested anticoagulants for the prevention of stroke or systemic embolic events (SSEE).[25]

The RE-LY, ROCKET AF, ARISTOTLE and ENGAGE AF-TIMI 48 trials all included variable proportions of patients with VHD. Separately, they provided no proof of a disparity between the safety and efficacy of NOAC's compared with warfarin in valvular and non-valvular AF. A meta-analysis that endeavored to gauge the relative safety and effectiveness of NOACs in VHD [25] suggested that:

When comparing NOAC use in those with and without VHD, patients with VHD

- tend to have higher rates of major bleeding and all-cause death
- have a higher $CHADS_2$ score with a greater frequency in sustained AF. A higher prevalence for heart failure and coronary artery disease (CAD) also contribute to the high scores.

Therefore, this meta-analysis concluded that in the 4 major phase III trials above, NOACs' relative safety and efficacy were comparable in patients with or without mitral regurgitation, aortic stenosis, aortic regurgitation, bio-prosthetic valves, or valve repair

surgery. Literature suggests that in patients without mechanical valves or moderate to severe mitral stenosis, NOACs can be safely used.[25]

The decision regarding use of NOACs versus warfarin in AF patients with concomitant VHD can be challenging. Current guidelines only provide recommendations for NOAC use in non-valvular AF. The potential role of NOACs in patients with specific types of VHD has not been directly assessed. Consensus regarding the definitions of non-valvular and valvular AF are needed to standardize future clinical practice and the design of randomized trials.[27]

In conclusion, oral anticoagulation is the most effective treatment in preventing stroke and other adverse vascular events associated with AF.[18] Up until 2009, the only available anticoagulants were VKAs. Now however, physicians have alternatives available since the arrival of NOACs.[13,24] Their safety and efficacy in non-valvular AF is well-established. However, there remain many unanswered questions around their use in VHD as well as concerns relating to direct drug costs. For these reasons, warfarin use will possibly remain the standard of care in South Africa for the near future.[10]

2.0 Study Aims, Objectives and Methods

2.1 Aims

The aim of this study was to compare TTR and FIR as a marker of the quality of anticoagulation with warfarin in patients with non-valvular and valvular atrial fibrillation, who were managed exclusively at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) anticoagulation clinic.

2.2 Objectives

Further objectives were to:

- Assess the predictive ability of FIR to categorize patients as having a TTR above or below 65%
- Compare the CHA^2DS^2-VASc and HASBLED scores of patients with a TTR above and below 65%, and with FIR above and below the cut-point established above.

2.3 Methods

2.3.1 Study Design

This was a retrospective observational study, that aimed to investigate out-patients with atrial fibrillation who were initiated on warfarin for stroke prevention and who presented to the CMJAH anticoagulation clinic for regular International Normalized Ratio (INR) testing.

2.3.2 Methodology

The Charlotte Maxeke Johannesburg Academic Hospital's dedicated anticoagulation clinic serves approximately 1500 patients in the greater Johannesburg area. Of the many patients who require anticoagulation for other reasons, on average, 30 to 40% are anticoagulated for prevention of arterial embolism due to AF. Patients are assessed and monitored by nurses who staff the clinic, as well as doctors from the haematology department, National Health Laboratory Service and the University of the Witwatersrand.

On the day of the patients' appointments, those who met the inclusion criteria as stipulated below, were enrolled and invited to participate in the study. This was done through a participant information sheet (Annexure A). Once the patient expressed willingness to participate, written informed consent was obtained by the researcher (Annexure B).

Files were retrospectively reviewed for INR results over a two year period (explained below), while patients were interviewed immediately so as to obtain the information highlighted in Annexure C. No patients had refused to participate in the study. Files of patients were screened as they arrived, until the desired sample size was achieved. Therefore, not all files belonging to the clinic were looked at.

2.3.3 Inclusion Criteria

- All male and female patients with atrial fibrillation on warfarin who were older than 18 years of age
- Patients were required to have been on warfarin for more than 3 months before 01/12/2014.
- Non-valvular AF
- Valvular AF inclusive of the following:
    - Native valve disease (INR range of 2-3)
    - Bio prosthetic valve, except for the first 3 months postoperatively (INR range 2.5-3.5)
    - Mechanical prosthetic valves (INR range 2.5–3.5)

2.3.4 Exclusion Criteria

- Younger than 18 years of age
- Indication for warfarin other than atrial fibrillation
- < 3 months duration of warfarin before 01/12/2014
- Less than 20 INR measurements in the period between 01/12/2014 and 31/12/2016

2.3.5 Data Sources

All records were retrieved from the patients' files and was audited manually by the researcher for concordance with the above-mentioned criteria. The number and value

of INR determinations were collected for each patient. A minimum of twenty INR measurements between 01/12/2014 and 31/12/2016 were used.

2.3.6 Measurements

Anticoagulation control was assessed by the measurement of each individual's TTR, using the Rosendaal method as well as the frequency of INR's in range (FIR) method. Thereafter, the overall centre TTR and FIR were calculated using the average of all participants' levels.

As mentioned before, an INR range of 2.0 to 3.0 has been defined as therapeutic by AF trials investigating stroke prevention.[18] The CMJAH anticoagulation clinic, as per their Standard Operating Procedure, also used an INR range of 2-3 for permanent non-valvular atrial fibrillation and an INR range of 2.5–3.5 for valvular atrial fibrillation. Hence, these were the defined INR ranges for this study.

The primary endpoint of this study was to determine whether the TTR, calculated using the FIR method, was comparable to the method used in clinical studies worldwide, namely the Rosendaal method.

2.3.7 Sample Size

Sample size estimation was determined by the key research question/s, in this case (1) the comparison of the TTR and FIR methods and (2) the assessment of the predictive ability of FIR in categorizing patients as having TTR above or below 65%.

For (1), Bland-Altman analysis required at least 60 (preferably 100) samples.[20] For (2), based on an anticipated ratio of patients with TTR below/above 65% of 1.5, 80% power, the 5% significance level and an expected Area Under the Curve (AUC) of 0.66 (a conservative estimate of the predictive power of FIR), a sample size of 100 patients was required. Sample size calculations were carried out in R (package pROC).[21] Thus, a minimum sample size of 100 was required for the study.

2.3.8 Data Capture

No personal information was required for this study. The patient's hospital number was used as a means of reference that allowed for accurate data capture. These hospital numbers were coded and kept separately in a password-protected database. A structured

questionnaire was administered, which included the following: age, sex, hypertension, diabetes, heart failure or left ventricular dysfunction, prior stroke or transient ischaemic attack, other forms of vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), hyperthyroidism and history of cigarette smoking. As a result, the CHA^2DS^2-VASc and HASBLED scores were obtained.

The excel spreadsheet (Annexure D) provided by INR Pro, downloaded from the following website, http://www.inrpro.com/article.asp?id=27, calculated TTR using the FIR and Rosendaal methods. Each participant's INR values, date of sampling etc. was recorded on this spreadsheet.

2.4 Data Analysis

Descriptive analysis of the data was carried out as follows: Categorical variables were summarised by frequency and percentage tabulation, and illustrated by means of bar charts. Continuous variables were summarised by the mean, standard deviation, median and interquartile range, and their distribution illustrated by means of histograms. The overall TTR and FIR was compared using the paired samples t-test as well as the Bland-Altman method comparison methodology. The correlation between the two methods was also reported on.

The assessment of predictive ability of FIR to categorize patients as having TTR above/below 65% was carried out by ROC (Receiver Operating Characteristic) curve analysis.

Finally, the CHA^2DS^2-VASc and HASBLED scores of patients with TTR above and below 65%, and with FIR above and below the cut-point established above, was compared.

Data analysis was carried out in SAS (SAS Institute, North Carolina, USA) version 9.4 for Windows. The 5% significance level was used.

2.5 Limitations and Bias of the Study [22]

Retrospective design can be a strength but since data extraction relies on precise and comprehensive medical records and documentation, this limits the accuracy of information gathered.

This study did not allow for acquisition of data regarding clinical outcomes (stroke and bleeding rates). For this reason, TTR, due to its robust association with VKA adverse effects, was chosen as a surrogate indicator for outcome.

Scheduled interruptions of oral anticoagulation (peri-procedural, hospitalization etc.) could not be assessed, and therefore TTR may have been underestimated.

2.6 Ethical Considerations

Although this study involved human subjects, the actual study and data needed was not of a personal nature. No names of patients were used, and all information that was recorded in the data sheet used only coded hospital numbers, which ensured patient confidentiality. As questions were directed to patients regarding their risk factors for stroke etc., written informed consent was obtained (Annexure B).

Permission to conduct the study was requested from hospital management, and approval thereof attached (Annexure E). The study also received clearance from the Human Research Ethics Committee (Reference No. M160775).

2.7 Funding

No funding was required for the purposes of this study. The expected costs were paid for by the researcher.

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CHAPTER 2: SUBMISSIBLE ARTICLE

Title: 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 to evaluate TTR (time in therapeutic range) has traditionally been used in clinical trials to assess quality of anticoagulation but it's utility in clinical practice is increasingly being questioned due to its tedious method of calculation and inability to account for the duration spent in an out-of-range INR. Frequency in range (FIR) is being reassessed as to its value in view of it being easier to calculate.

Aim

We aimed to compare FIR and TTR (using the Rosendaal method) as a measure to assess the quality of anticoagulation with warfarin in patients with valvular and non-valvular AF at a tertiary South African hospital.

Objectives

Secondary objectives were to assess the predictive ability of FIR to categorize patients with a TTR≥65% as well as to compare the CHA^2DS^2-VASc and HASBLED scores to TTR and FIR.

Methods

We retrospectively analysed the INR values for a cohort of 102 patients over a two year period and calculated both individual and overall mean TTR and FIR. Paired samples t-test was used to compare the two parameters and the Bland-Altman method comparison plot to assess the agreement between them.

Results

The mean overall TTR was 58.1%±SD 16% and the mean FIR was 50.8%±SD 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 ($r= 0.93$, 95% CI 0.90-0.95; $p<0.001$). However the Bland-Altman method plot indicated a 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 (s) = 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.

Introduction

Atrial fibrillation (AF) is by far the commonest arrhythmia seen in daily practice. It is rapidly becoming a healthcare burden due to an aging population and improved survival from coexisting cardiovascular and non-cardiovascular diseases. There are close to five million new cases globally per annum. By 2050, the prevalence of AF in Africa is expected to surpass that of any other country. AF is associated with a greater 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 are ten times higher than the developed world, largely due to limited health care access, suboptimal treatment and an impoverished community.[1–5]

For almost fifty years, the mainstay of oral anticoagulation has been vitamin K antagonists (VKA's).[6] This class of drugs, which includes warfarin, have been well-described to lessen the risk of stroke and embolic events in patients with AF. Low-cost generic versions are also now obtainable.[4] However, their use remains challenging due to a slow onset of action, a long half-life, narrow therapeutic window, various food and drug interactions, repeated laboratory monitoring and high risk of bleeding.

The recent phase 3 trials approving the use of the novel oral anticoagulants (NOACs) in non-valvular AF (NVAF) has obviated many of the problems experienced with warfarin.[6] NOACs however have not been shown to be safe and effective in AF secondary to moderate or severe mitral stenosis and cannot be utilised in those with mechanical prosthetic heart valves.[8] They are also unaffordable to most South Africans and therefore warfarin is likely to remain the anticoagulant of choice.[7]

The optimal international normalized ratio (INR) for non-valvular AF and AF secondary to native valve disease 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. Sub-optimal TTR's are

associated with adverse outcomes.[9–10] The Rosendaal Method, the most commonly used method in clinical trials, is cumbersome to calculate. An alternative, the FIR (frequency in range) is easier to calculate and can be done manually.[11–12] Based on the limited published data, conflicting results make it uncertain as to whether FIR can be used interchangeably with TTR to assess anticoagulation control.

In this study, we aimed to correlate FIR with TTR in a cohort of AF patients receiving warfarin therapy at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). Secondary objectives were to assess the predictive ability of FIR to categorize patients as having a TTR above or below 65%, and to compare the CHA^2DS^2-VASc and HASBLED scores with TTR's and FIR's.

Materials and Methods

Study Design

The CMJAH's dedicated anticoagulation clinic serves approximately 1500 patients in the greater Johannesburg area. Of the many patients who require anticoagulation for other reasons, on average, 30 to 40% are anticoagulated for prevention of arterial embolism secondary to AF. Patients are assessed and monitored by nurses who staff the clinic, as well as doctors from the haematology department, National Health Laboratory Service and the University of the Witwatersrand.

We retrospectively reviewed the INR results of 102 patients with atrial fibrillation who received warfarin therapy at the anticoagulation clinic between 1st December 2014 and 31st December 2016. 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 1st December 2014 were also excluded because of more frequent INR testing and great variations in readings during initial warfarin adjustment.[11] Non valvular AF as well as 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 INR's. An INR range of 2-3 was defined for NVAF as well as those with native valve disease, and a range of 2.5-3.5 was defined for bio-prosthetic and mechanical prosthetic heart valves. TTR (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 so that basic demographic data and stroke risk

factors (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 available. The CHA^2DS^2-VASc and HASBLED scores were subsequently only calculated for patients with non-valvular AF, as risk stratification in valvular heart disease is not helpful owing to the increased risk of stroke despite the presence of traditional risk factors.[6]

Permission to conduct the study was acquired from the Chief Executive Officer of Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), and cleared by the WITS University Human Research Ethics Committee (Reference No. M160775).

Statistical Analysis

Descriptive analysis of the data was done with categorical variables summarized as frequency and percentage tabulations. Continuous variables were summarised by the mean, standard deviation, median and interquartile range. The overall TTR and FIR was compared using the paired samples t-test. The TTR and FIR measures were compared using Bland-Altman method comparison methodology. 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 established, were compared using the independent samples t-test. Data analysis was carried out in SAS (SAS Institute, North Carolina, USA) version 9.4 for Windows. The 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±SD 15.6 years and 61.8% were female. *Figure 1* represents the graphical distribution of age. From the non-valvular AF group (n=72), 69.0% of patients were 65 years or older, reiterating previous observations that AF burden increases with advancing age.[2,13] *Table 1* summarizes the basic demographic data of the study population: The mean CHA^2DS^2-VASc and HASBLED scores were 3.6±SD 1.5 and 1.8±SD 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%±SD 16% and 57.4% (interquartile range, 47.0% - 69.9%), respectively. From the cohort of 102 patients, 41 patients (40.2%) had a TTR≥65%, of which 80.5% constituted NVAF. The mean and median FIRs were 50.8%±SD 16.7% and 50.0% (interquartile range, 39.3%-62.5%), respectively. *Figure 2* and *Figure 3* depict the distribution of the mean overall TTR and FIR respectively.

The mean TTR was significantly higher than the mean FIR (paired samples t-test; p<0.0001). *Figure 4* illustrates a scatterplot of FIR vs TTR, in which FIR was positively correlated with TTR in a linear fashion (r= 0.93, 95% CI for r: 0.90-0.95; p<0.001).

According to *Figure 5*, the regression relationship between TTR and FIR shows a negative intercept of -5.9±SD 4.6% (p=0.012) and a positive slope of 0.98±SD 0.08% (p<0.0001). Thus, there is a constant, but not a proportional difference between the methods.

In contrast, *Figure 6 (*The Bland-Altman method comparison plot to compare TTR and FIR), indicates a 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%.

The predictive ability of FIR for TTR was very high [AUC (Area Under the Curve) = 0.981; 95% CI: 0.963-0.999], as indicated by the ROC Curve in *figure 6.* A cut off value of FIR≥53.3% was found to be a good predictor of TTR≥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 CHA^2DS^2-VASc and HASBLED scores with FIR's above and below the established cut off value (*Table 2*), showed no significant difference. *Table* 3 demonstrates that the mean CHA^2DS^2-VASc score for patients with TTR≥65% (3.1; SD 1.1) was significantly lower than that for patients with TTR<65% (4.0; SD 1.6) (independent sample t-test; p=0.010).

Discussion

One of the important findings of this study which looks at a cohort of 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 somewhat 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 (46.3%) was the lowest amongst 15 countries. 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. A TTR<58% grants no benefit over antiplatelet therapy in the prevention of AF-related adverse vascular events, as emphasized by Connolly et al.[14]

The Rosendaal method to calculate TTR has been the most commonly used surrogate marker in clinical trials for warfarin control.[12,15] One of its' main advantages is that it allocates an INR value to each day and allows the linear relationship between two INR values to curtail the unpredictable effect of short-term repeated INR testing.[11,15] At the CMJAH, patients with out-of-range INR's were dose adjusted and retested as early as three 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 INR's formed the minority of the cohort.

From the above, it is clear that South Africa persistently achieves a TTR less than that recommended by international guidelines. However, one needs to consider other variables in comparison to overseas trials as a potential cause for these low results. Singer et al reported a noteworthy influence of patient clinical features and geographic region on the overall TTR. Seemingly, this may be a reflection of varying levels of perseverance in achieving a target INR, different systems in managing warfarin, as well as different regional impediments to frequent INR testing and warfarin dose adjustments.[16] In a setting such as ours, where there is poor overall patient education and insight, language barriers, resource availability and access to health care[4], it is perhaps not unreasonable to assume that the interplay of these factors contributed to poor treatment adherence by patients, lack of understanding for regular follow up and INR testing, which ultimately impacted on and resulted in low individual and centre TTR's, as seen in this cohort.

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 main differences between the two audit parameters is that 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.[11] Also, standard definitions regarding valvular and NVAF 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.

Our outcomes, consistent with findings derived from data in the GARFIELD-AF (Global Anticoagulant Registry in the FIELD–Atrial Fibrillation)[10] and another Portuguese study (Caldeira et al, 2015), showed that although highly correlated ($r= 0.93$, $p<0.001$), there was lack of agreement between FIR and TTR. 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. From the 41 patients with TTR≥65%, only two patients had FIR's of ≤ 53.3% (the calculated predictor of TTR≤65%). This may advocate for using FIR as an ongoing method of surveillance in those who have previously well documented TTR's or to identify new patients with poor control, while the Rosendaal method is still to be employed as the "standard of care" in assessing poor control overall.

Chan and colleagues found an FIR of ≤ 56.1% to be an adequate predictor of TTR<65%.[11] Our lower cut off value of 53.3% seems justified as our mean TTR and FIR was between 15-20% higher than that of the Chinese cohort.

The CHA^2DS^2-VASc score, in comparison to the older $CHADS_2$, includes three additional common stroke risk factors to broaden prognostication in AF.[17] Although not validated for use in the native African community, [4] its' use is supported by the European, American and British (National Institute for Health and Care Excellence- NICE) guidelines.[18–20] Patients with a high risk of stroke (i.e., CHA^2DS^2-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 found that the mean CHA^2DS^2-VASc score for patients with TTR≥65% (3.1; SD 1.1) was significantly lower than that for patients with TTR< 65% (4.0; SD 1.6) (independent sample t-test; $p=0.010$). Although statistically significant, a mean CHA^2DS^2-VASc score of 3.1 is by no means low according to guidelines. The mean HASBLED score was 4.0. Recently, a study involving Australian and Singaporean patients showed that a high HASBLED score of ≥3, in addition to assessing bleeding risk, may also serve as a valuable predictor of poor warfarin control as measured by the TTR, especially in populations achieving poor overall control.[22] Though this may hold true for that population, each centre or country would need to define their acceptable minimum TTR before applying HASBLED as a predictor of warfarin control.

Limitations of the study

We recognize that this study has certain inherent limitations. The retrospective nature of the study made data extraction difficult and to a certain degree (i.e. with the CHA^2DS^2-VASc and HASBLED scores) inaccurate, due to incomplete and incomprehensive documentation. Patients were relied upon to give account of presence or absence of stroke risk factors, as these were not available in the anticoagulation file records. Patients were excluded if they had less than 20 INR measurements over the two year period. This may have falsely elevated the overall mean TTR/FIR as defaulting therapy was not considered.

As only 102 patients at a single centre were looked at, it does not reflect results at a provincial or national level.

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] Many more studies using the Bland-Altman plot for TTR versus FIR would need to be conducted, in order to define the maximum limits of acceptable differences. 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≤65%. Scheduled interruptions of warfarin therapy (i.e. for hospitalization, peri-procedural etc.) was not taken into account. In addition, variability in INR as a result of drug interactions, diet, inter-current infections and warfarin dosing errors by nursing staff was not accounted for. Therefore, TTR may have been overestimated. These factors may possibly be the reason behind the six outliers seen on the Bland-Altman plot.

Way forward

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

Much of the available 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 would 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.

Acknowledgements

Nil

Disclosure statement

The authors have no conflict of interest to declare.

Table 1: Basic Demographic Data

Variable	Category	n	Percentage (%)
Total Cohort (n=102)			
Atrial Fibrillation	Non-valvular	72	70.6
	Valvular	30	29.4
Sex	Female	63	61.8
	Male	39	38.2
Non valvular Atrial Fibrillation (n=72)			
Sex	Female	41	57
	Male	31	43
Risk factors for CHA^2DS^2-VASc score	Hypertension	56	78
	Female	41	57
	Heart Failure	38	53
	Age 65-74y	31	43
	Age ≥ 75y	19	26
	Vascular Disease	15	21
	Diabetes	14	19
	Previous Stroke	13	18
Risk factors for HASBLED score	Hypertension	56	78
	Age > 65y	50	69
	Previous Stroke	13	18
	Abnormal renal/ liver function	2	3
	Bleeding	4	6
	Labile INR's	7	10
	Drugs/ alcohol	7	10
Smoking status	No	56	78
	Yes	8	11
	Ex-Smoker	8	11
Hyperthyroidism	No	70	97
	Yes	1	1
	Ablated	1	1
Valvular Atrial Fibrillation (n=30)			
Sex	Female	22	73
	Male	8	27
Valvular lesion	Native valve disease	7	23
	Prosthetic Heart Valve	23	77

Table 2: Independent Sample's t-test comparing the CHA^2DS^2VASc and HASBLED scores to FIR's above and below 53.3%

Analysis Variable : CHA^2DS^2-VASc score									p-value for between-group test
FIR (%)	N	Mean	Std Dev	Median	Interquartile range		Minimum	Maximum	
<53.3%	35	3.9	1.6	4	3	5	1	8	0.050
≥53.3%	37	3.3	1.3	3	3	4	1	7	

Analysis Variable : HASBLED score									p-value for between-group test
FIR (%)	N	Mean	Std Dev	Median	Interquartile range		Minimum	Maximum	
<53.3%	35	2.0	1.0	2	1	3	0	4	0.14
≥53.3%	37	1.7	1.0	2	1	2	0	4	

SD: standard deviation, IQR: interquartile range

Table 3: Independent Sample's t-test comparing the CHA^2DS^2VASc and HASBLED scores to TTR's above and below 65%

Analysis Variable : CHA^2DS^2-VASc score									p-value for between-group test
TTR (%)	N	Mean	Std Dev	Median	Interquartile range		Minimum	Maximum	
<65%	39	4.0	1.6	4	3	5	1	8	0.010
≥65%	33	3.1	1.1	3	3	4	1	6	

Analysis Variable : HASBLED score									p-value for between-group test
TTR (%)	N	Mean	Std Dev	Median	Interquartile range		Minimum	Maximum	
<65%	39	2.0	1.0	2	1	3	0	4	0.10
≥65%	33	1.6	1.0	2	1	2	0	4	

SD: Standard Deviation, IQR: Interquartile Range

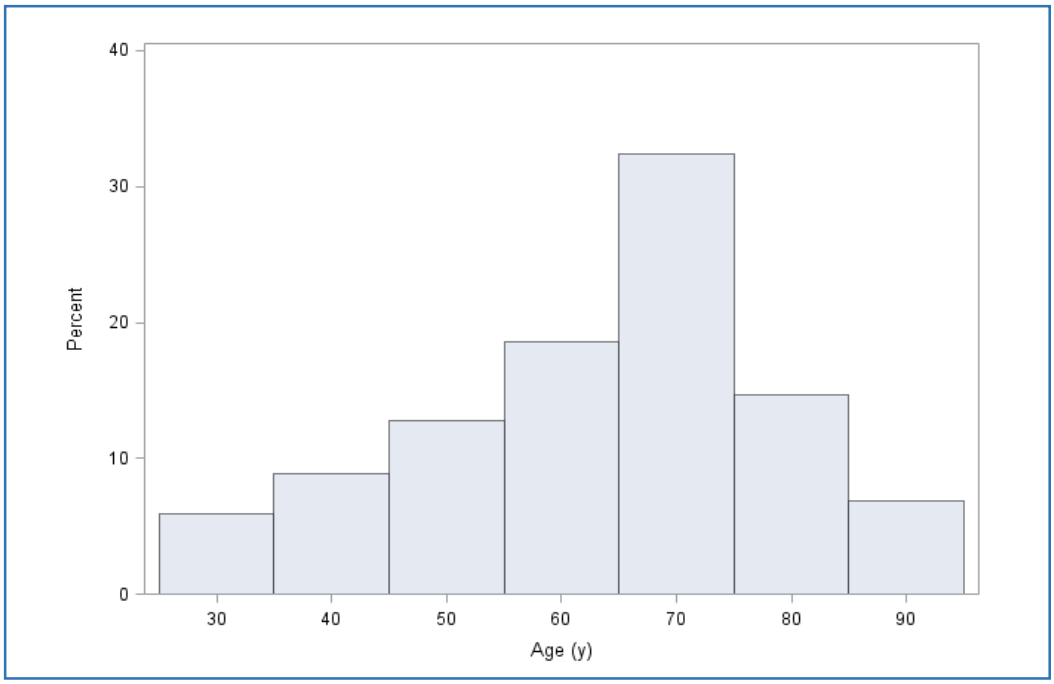

Figure 1: Age Distribution within the Cohort

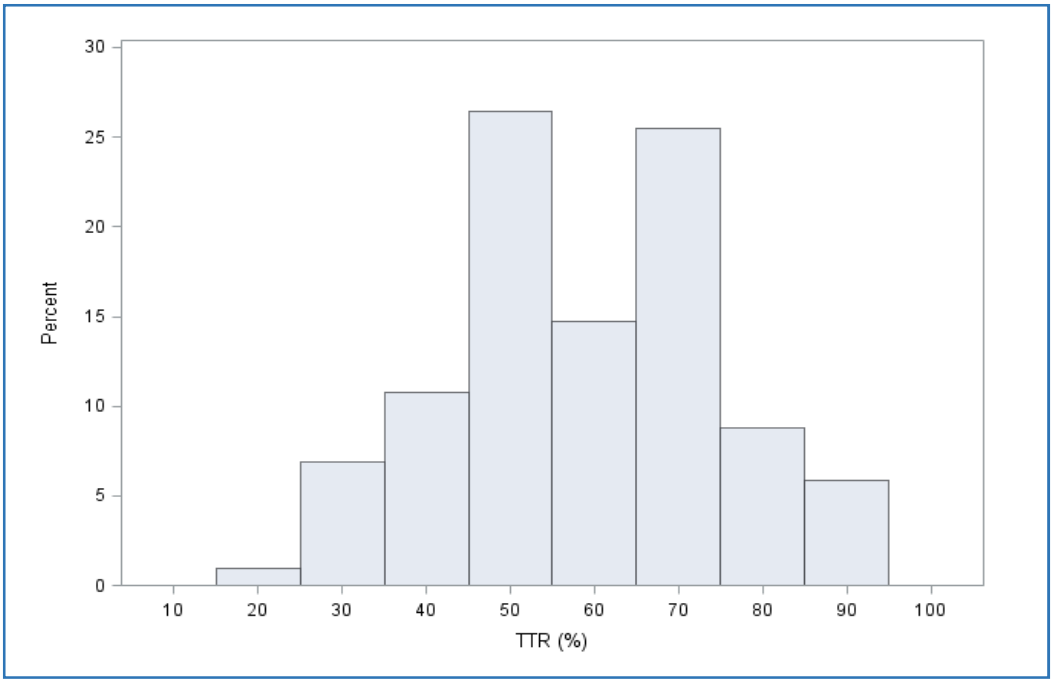

Figure 2: Distribution of TTR within the Cohort

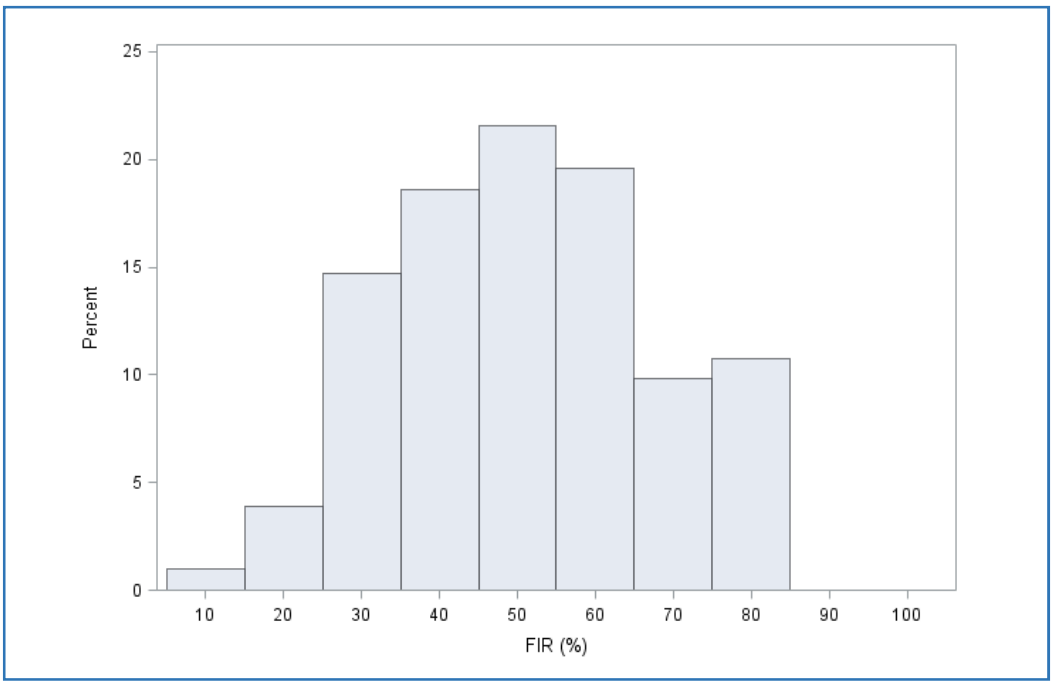

Figure 3: Distribution of FIR within the Cohort

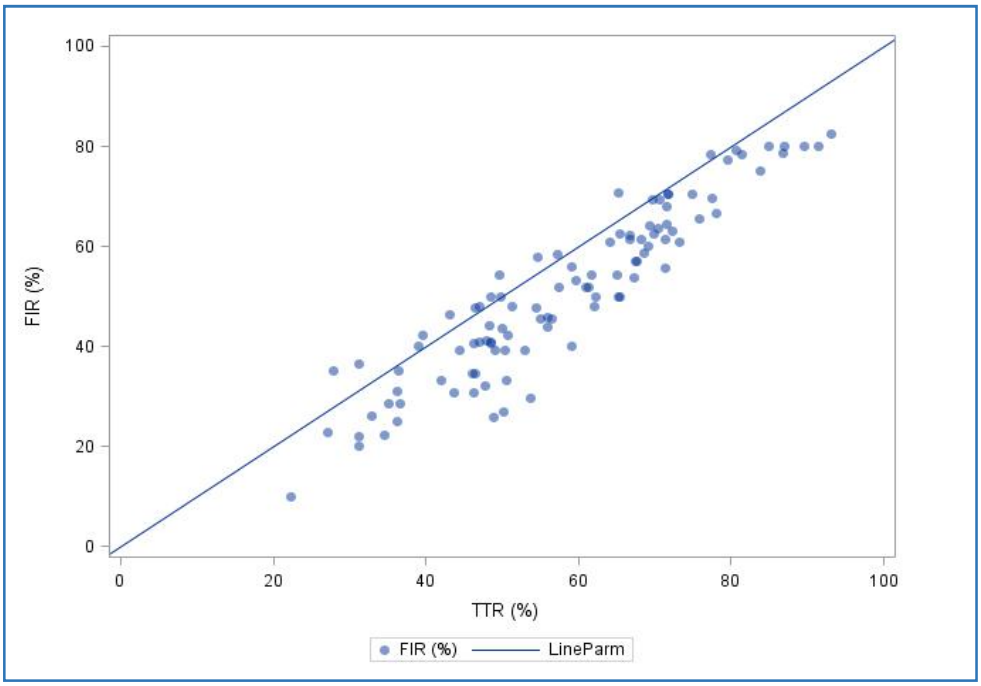

Figure 4: Scatterplot of TTR vs FIR

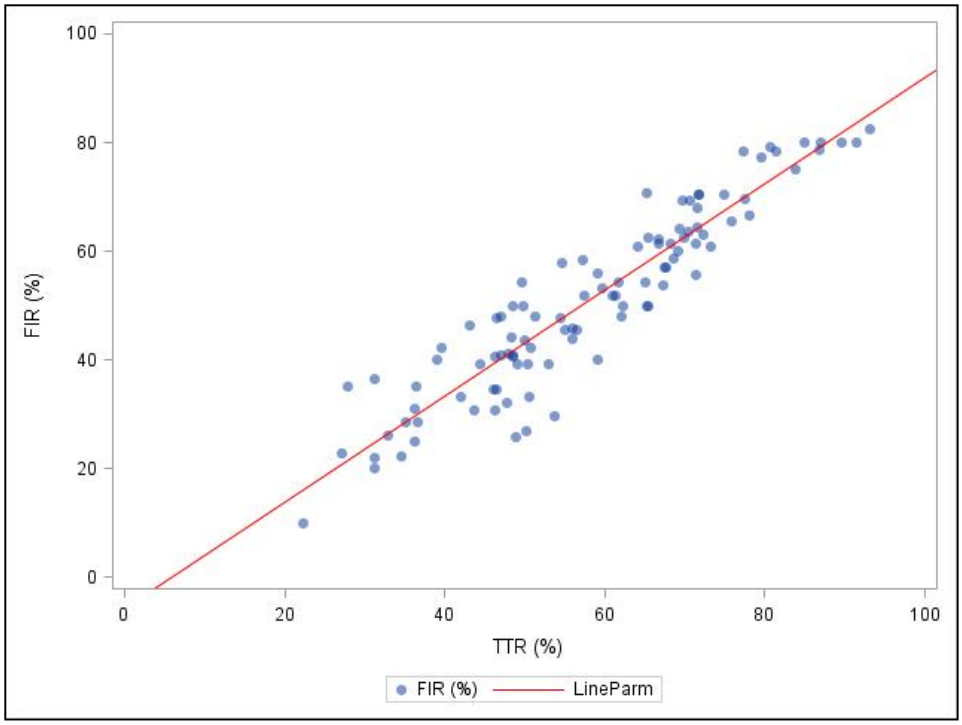

Figure 5: The Regression Analysis between TTR and FIR

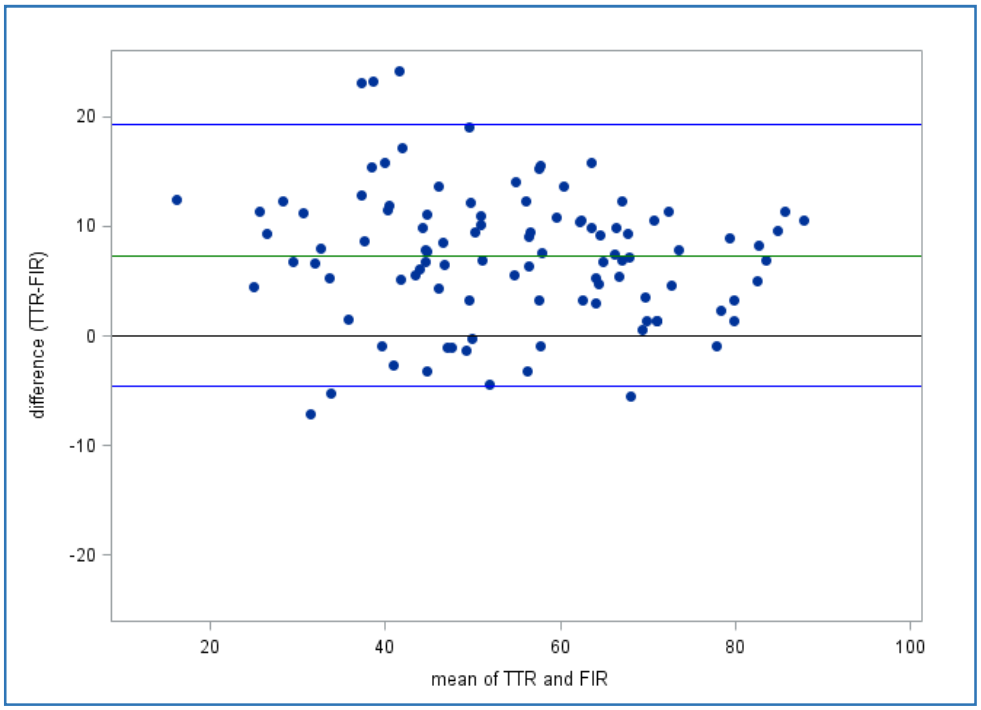

Figure 6: Bland-Altman Plot comparing TTR and FIR

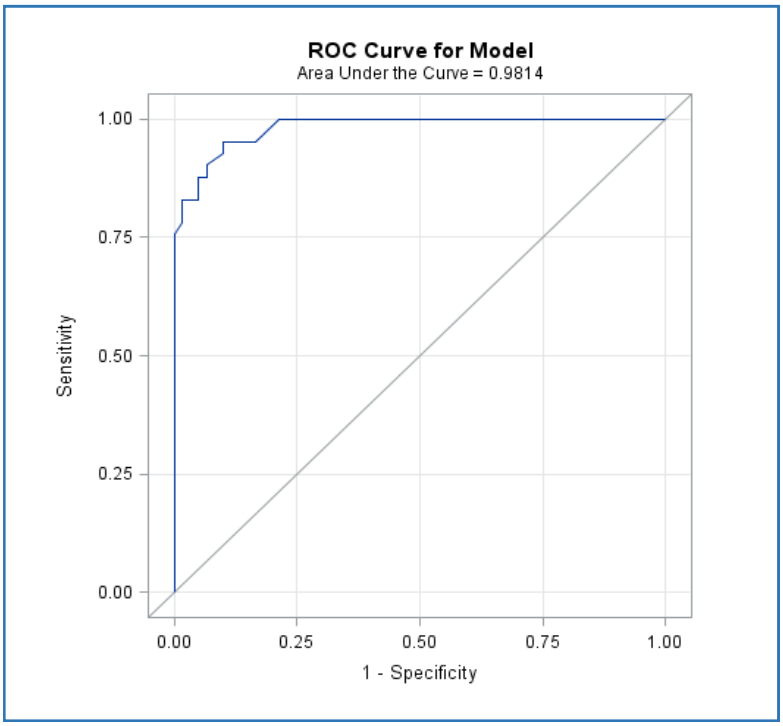

Figure 7: ROC Curve assessing Predictive Ability of FIR for TTR

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Chapter 3: APPENDICES

3.1 Participant Information Document

Study title: A Comparison between TTR and FIR as a measure of the quality of anticoagulation in patients with atrial fibrillation

.

Hello, and thanking you for taking the time to read this document. My name is Dr Priya Parbhoo and I am currently a registrar in the department of Internal Medicine, registered at the University of Witwatersrand. The above-mentioned study is a requirement for the completion of my Master's degree in Medicine.

I therefore invite you to participate in this study.

As you know, atrial fibrillation is a condition that predisposes one to developing thrombi (clots) in the heart, which may increase your risk for developing a stroke. This is why patients with this condition require warfarin. The effectiveness of warfarin therapy is measured by a test called the INR, which is the blood test you come to do every month at the clinic. A range of 2-3 is what we as physicians aim for, or a range of 2.5-3.5 if you have an artificial mechanical valve. If the INR is less than 2, it indicates that the blood is "too thick," putting you at risk for stroke. If the INR is more than 3, this means that the blood is "too thin" and may cause bleeding.

Therefore, the aim of this study is to use two different methods of calculation to assess your overall control of warfarin therapy. If you agree to participate in this study, I will need access to your file at the warfarin clinic as well as ask you a few questions regarding other risk factors you may have to develop a stroke. From your clinic file, I will be using your hospital number, your INR measurements and the date on which the test was done. The measurements used will be taken from the period between 01/12/14 and 31/12/16. These INR values will allow me to measure the TTR (time in therapeutic range) and FIR (frequency of INR's in range), which are numbers that indicates how well your warfarin is working to keep the INR between 2 and 3. There will be no risk to yourself by participating in this study, nor any direct benefit.

The results of the study will be made available to the warfarin clinic as well as the department of internal medicine. Please note that your participation is voluntary and that refusal to participate will not involve any penalty or loss of benefits to which you are otherwise entitled. You may also choose to withdraw your participation from the study, without any penalty or loss of benefits. All personal information that you provide will be kept anonymous and only myself and the study supervisor will have access to all information. Organizations that may inspect and/or copy my research records for quality assurance and data analysis include the Human Research Ethics Committee.

Contact details:
For further information you may contact the following:

Human Research Ethics Committee:
Chairperson: peter.cleaton-jones1@wits.ac.za
Administrators - Ms Zanele Ndlovu/ Mr Rhulani Mkansi/ Mr Lebo Moeng
Tel: (011) 717 2700/2656/1234/1252
Email: HREC-Medical.ResearchOffice@wits.ac.za

Dr Priya Parbhoo (Researcher): 072 697 7631, Professor Barry Jacobson: 011 489 8414

3.2 Written Informed Consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

I have been made aware of the following:

- There is no risk to myself by participating in the research, nor is there any direct benefit or remuneration.
- I will not incur any additional costs by participating
- I may choose to withdraw from the research at any point in time, and will not suffer any consequences
- Any information I provide that is of a personal nature, will be kept anonymous and will only be available to the researcher and study supervisor

Print Name of Participant_____

Signature of Participant _____

Date _____

Day/month/year

3.3 Data Collection Sheet

HOSPITAL NUMBER:

VALVULAR AF	NON-VALVULAR AF

AGE:

SEX: M F

RISK FACTORS FOR STROKE:

Do you have hyperthyroidism? _____

Do you smoke? _____

CHA^2DS^2-VASc Risk Score	Score
Congestive heart failure or LVEF ≤ 40%	1
Hypertension	1
Age ≥ 75 years	2
Diabetes	1
Previous stroke/ TIA/ thromboembolism	2
Vascular disease (prior myocardial infarction; peripheral artery disease; aortic plaque)	1
Age 65-74 years	1
Female gender	1
TOTAL	9

HASBLED Risk Score	Score
Hypertension	1
Abnormal renal and/or liver function	1 or 2
Previous stroke	1
Bleeding	1
Labile INR's	1
Elderly: Age > 65 years	1
Drugs and/or alcohol	1 or 2
TOTAL	9

3.4 Ethics Clearance Certificate

REVISED

R14/49 Dr Priya Parbhoo

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M160775

NAME: (Principal Investigator)	Dr Priya Parbhoo
DEPARTMENT:	School of Clinical Medicine Division of Internal Medicine Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	A comparison between TTR and FIR as a measure of the quality of anticoagulation in patients with atrial fibulation
DATE CONSIDERED:	29/07/2016
DECISION:	Approved unconditionally
CONDITIONS:	Change of project title, supervisor and study site approved on 31 August 2017
SUPERVISOR:	Professor B Jacobson
APPROVED BY:	Professor CB Penny, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	06/09/2017

UNIVERSITY OF THE WITWATERSRAND
PROF CLEMENT PENNY
HREC (MEDICAL) AND REC
- 7 SEP 2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand.
I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. I agree to submit a yearly progress report. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in July and will therefore be due in the month of July each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES