



**WARFARIN: TIME IN THERAPEUTIC RANGE, A SINGLE CENTRE STUDY ON  
PATIENTS USING WARFARIN FOR STROKE PREVENTION IN NON-  
VALVULAR ATRIAL FIBRILLATION AND PROSTHETIC HEART VALVES**

by

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## Declaration

I, Dr DhirenSadhahiriss declare that

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## Abbreviations

ACC/AHA	The American College of Cardiology/American Heart Association
ACTIVE-W	Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events
AF	Atrial fibrillation (implies non-valvular AF unless otherwise stated)
AFASAK	Copenhagen Atrial fibrillation, Aspirin and Anticoagulation Study
AFFIRM	Atrial Fibrillation Follow-up Investigation of Rhythm Management
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thrombo-embolic Events in Atrial Fibrillation
BAATAF	Boston Area Anticoagulation Trial for Atrial Fibrillation Study
CABG	Coronary artery bypass grafting
CAFA	Canadian Atrial Fibrillation Anticoagulation Study
CT	Computed tomography
EAFT	European Atrial Fibrillation Trial
EDD	End Diastolic diameter
ENGAGE TIMI 48	Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation– Thrombolysis in Myocardial Infarction Study 48
ESD	End Systolic Diameter
HSD	Honestly significant difference
INR	International Normalisation Ratio
ISTH	International Society of Thrombosis and Haemostasis
LV	Left Ventricle
MRI	Magnetic resonance imaging
MS	Mitral stenosis
NICE	National Institute for Health and Care Excellence
NOAC	New oral Anticoagulant
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
NYHA	New York Heart Association
ORBIT –AF	Outcomes Registry for Better Informed Treatment of Atrial Fibrillation
PAS	Pulmonary Artery Stiffness
PT	Prothrombin time
RE-LY	Randomised Evaluation of Long-term anticoagulant therapy: dabigatran vs. warfarin

ROCKET –AF	Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
SPAF	Stroke Prevention in Atrial Fibrillation Study
SPINAF	Veterans Affairs Stroke Prevention in Non-rheumatic Atrial Fibrillation Study
SPORTIF	Stroke Prevention Using an Oral Direct Thrombin Inhibitor in Atrial Fibrillation
STABLE	Self-Testing Analysis Based on Long-term Evaluation
TTR	Time in therapeutic range
THINRS	The Home INR Study
VKA	Vitamin K antagonist
VKOR	Vitamin K 1,2,3-epoxide reductase

## ABSTRACT

**Background:** There are various indications for the use of oral anticoagulants. Two common indications are in patients with atrial fibrillation and prosthetic heart valves. The quality of anticoagulation, determined by the time in therapeutic range, is less often evaluated and has important clinical implications in patient outcomes.

**Objectives:** We sought to identify the indications for anticoagulation and determine the time in therapeutic range and the time out of range at a community-based and district level in patients attending the outpatient department at Mahatma Gandhi Memorial Hospital in KwaZulu Natal, South Africa. Further, we identified factors associated with the quality of anticoagulation and identified prevalence and contributors to thrombo-embolic and haemorrhagic events in anticoagulated patients with atrial fibrillation and prosthetic heart valves.

**Overview of thesis:** Chapter 1 is a review of the literature and identifies the objectives of the study. Chapter 2 describes the study design and methodology. The sample population is described in Chapter 3. Chapter 4 and 5 evaluates the time in therapeutic range and Chapter 6 evaluates for associations thereof. Chapter 7 describes the findings of adverse events and the final chapter summarises the thesis with a general discussion and conclusion.

**Methods:** We conducted a retrospective, descriptive and observational study with chart audits evaluating the anticoagulation control for the preceding one year for each patient. Descriptive statistics included mean and standard deviation for quantitative data and frequencies for categorical data. The variables demonstrated uniformity with linear plots and therefore comparisons of means was conducted by parametric testing. Analysis of variance was conducted for comparisons of variables with post hoc analysis for three groups. Confidence intervals were reported as 95%. Two-tailed  $p$ -values were conducted and any  $p$ -value less than .05 was considered significant.

**Results:** TTR was poor for patients with atrial fibrillation and prosthetic valves (44.5% and 13.7% respectively). We identified older age, less frequent testing and high target ranges as significant factors associated with poorer outcomes. We demonstrated a high prevalence of adverse events (25.4%).

**Conclusion:** Patients in this setting demonstrated poor quality of anticoagulation and had a high prevalence of adverse events.

## **Ethics Approval**

Full ethical approval was obtained from the Biomedical Research Ethics Committee (BREC), University of KwaZulu Natal (UKZN) (BE320/15).

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## CHAPTER 1

### INTRODUCTION AND LITERATURE REVIEW

Warfarin is used as an oral anticoagulant across various conditions in treating and preventing thrombosis and embolism, commonly, for atrial fibrillation (AF), prosthetic heart valves and venous and arterial thrombo-embolism. Due to its complex pharmacodynamics, there is usually no standard dose and therefore requires monitoring to assess its efficacy and reduce the risk of bleeding complications.

#### 1.1 Warfarin as an anticoagulation agent

Warfarin is a vitamin K antagonist (VKA) with excellent bioavailability and is widely prescribed as an oral anticoagulant. VKAs produce their anticoagulant effect by interfering with the cyclic interconversion of vitamin K and its epoxide which, through a complex pathway leads to the depletion of coagulant proteins namely; prothrombin, factor VII, factor IX and factor X. In addition, VKAs impair the regulation of the anticoagulant proteins C and S and therefore impair their function. Warfarin has two isomers namely R and S which are metabolised in the liver by different pathways. The main enzyme involved in the elimination of the S- isomer is the CYP2C9, while the R- isomer of warfarin is eliminated by CYP1A/CYP1A2/CYP3A4<sup>1</sup>. These enzymes may be inhibited or induced by drugs taken by the patient and can have effects on the bioavailability of warfarin and subsequently affect its efficacy or potentiate its effect as an anticoagulant.

The efficacy of warfarin as an anticoagulant is best measured by the prothrombin time (PT) which is reported as an international normalisation ratio (INR), and is a measure of three of the four vitamin K-dependant coagulation factors; factor II, factor VII and factor X. The INR is determined by dividing the PT of a patient with the geometric mean of the PT of at least 20 healthy subjects of both sexes with the same test system. An INR of 1.0 is considered to be normal anticoagulation and an INR of 2.0 means that the clotting time has doubled<sup>1</sup>.

The most important adverse effect of warfarin is the risk of bleeding which is influenced directly by the intensity of anticoagulation therapy and higher INR values confer greater risk. The most notable non-haemorrhagic adverse event associated with warfarin is skin necrosis. This is uncommon and is due to extensive thrombosis of the capillaries and venules in the subcutaneous tissue.

The use of warfarin as a VKA in clinical practice has many indications (Table 1). The most common uses are in the setting of venous or arterial thrombo-embolism or a high risk thereof (as in antiphospholipid antibody syndrome). The different indications have individualised target INR ranges and duration of therapy. Two notable indications for long-term oral anticoagulation are in the setting of non-valvular AF for the prevention of stroke and/or systemic embolisation, and in the presence of prosthetic mechanical heart valves.

**Table 1: Indications for anticoagulation with warfarin and the recommended target INR <sup>2</sup>.**

<b>Indication</b>	<b>Recommended Target INR</b>
<b>Venous thrombo-embolism</b>	
First event	2.5
Recurrence while anticoagulated	3.5
<b>Antiphospholipid antibody syndrome</b>	2.5
<b>Atrial fibrillation</b>	2.5
<b>Elective cardioversion</b>	
At least 3 weeks prior	3.0
Four weeks after	2.5
<b>Valvular heart disease and prosthetic valves</b>	
Mitral stenosis or regurgitation <sup>a</sup>	2.5
Mechanical prosthetic valves	
Low thrombogenicity and no risk factors	2.5
Low thrombogenicity and risk factors	3.0
Medium thrombogenicity and no risk factors	3.0
Medium thrombogenicity and risk factors	3.5
High thrombogenicity regardless of risk factors	3.5
Bioprosthetic heart valves <sup>b</sup>	2.5
<b>Peripheral vascular disease<sup>c</sup></b>	2.5
<b>Myocardial infarction and cardiomyopathy</b>	2.5

a. Patients with mitral stenosis or regurgitation who have atrial fibrillation or a history of systemic embolism or left atrial thrombus or an enlarged left atrium should receive warfarin with an INR target of 2.5

b. Patients with a bioprosthesis in the mitral position should receive 3 months of anticoagulation with warfarin with an INR target of 2.5.

Patients with a bioprosthetic valve and a history of systemic embolism should have at least 3 months of anticoagulation with warfarin with an INR target of 2.5.

Patients with a bioprosthetic valve and left atrial thrombus at surgery should receive warfarin until the clot has resolved with an INR target of 2.5.

Patients with bioprosthetic valves and other prothrombotic risk factors, such as atrial fibrillation and low ventricular ejection fraction, should receive warfarin with an INR target of 2.5.

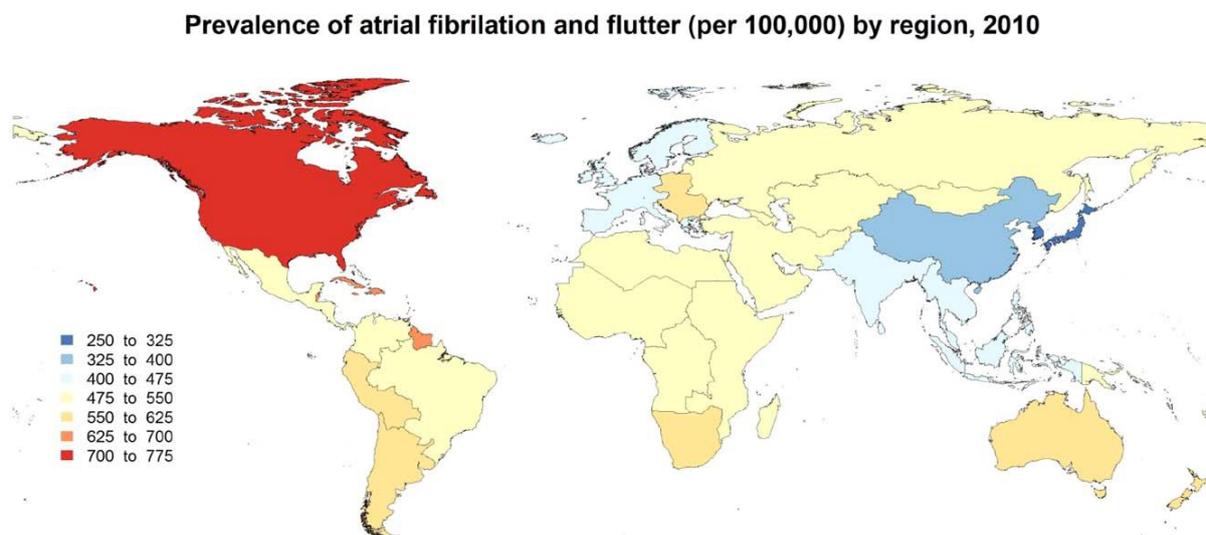
c. Patients with intermittent claudication should not routinely be treated with anticoagulants.

Patients who suffer acute arterial embolism and proceed to embolectomy should be considered for long-term anticoagulation with warfarin with an INR target of 2.5.

## 1.2. Atrial fibrillation

AF is the most common cardiac rhythm abnormality and is associated with significant morbidity, especially heart failure and stroke or thrombo-embolism, as well as mortality. A report in 2010 on the worldwide epidemiology of atrial fibrillation reported the estimated burden of AF and atrial flutter as 33.5 million individuals with increasing trends identified since 1990 (Figure 1). In this report, males were more affected than females<sup>3</sup>.

Although the prevalence of AF is less studied in Africa than in the developed world, global data from the 2010 epidemiology study reports it is as less prevalent but it is expected to increase significantly over the next few decades<sup>3,4</sup>.



**Figure 1: World map showing the age-adjusted prevalence rates (per 100 000 population) of atrial fibrillation in the 21 Global Burden of Disease regions, 2010<sup>3</sup>.**

There are two well accepted categories of AF namely AF associated with valvular heart disease and non-valvular AF. AF associated with valvular heart disease is commonly associated with a prosthetic heart valve, valve repair, or rheumatic valvular heart disease, most commonly stenotic lesions involving the mitral valve. Patients with non-valvular AF have no associated underlying causative heart disease, and are at high risk for stroke, irrespective if classified as paroxysmal, transient or permanent AF<sup>5</sup>. However, findings from the 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) study which randomised 14 264 patients showed that those with permanent AF have a higher risk of thrombo-embolic events and worse survival compared to those with paroxysmal AF<sup>6</sup>.

Forty-five percent of all embolic strokes can be accounted for by AF. In patients in their ninth decade of life, it was found that 36% of these patients had sustained strokes due to AF. Overall, AF increases the risk of stroke five-fold, and when compared to patients with non-AF-related strokes, are associated with higher mortality and greater disability as well as longer hospital stays and poorer

functional outcome<sup>7</sup>. The Framingham study has noted AF as an independent risk factor for stroke<sup>8</sup>. The risk of stroke occurrence in AF is reduced by anticoagulant therapy and all major guidelines emphasise the role of oral anticoagulation use for stroke prevention<sup>5,7,9</sup>.

There are many risk factor tools used in clinical practice to assess the risk of stroke in non-valvular AF and therefore the need for anticoagulation, however the most accepted is the use of a point scoring system called CHA<sub>2</sub>DS<sub>2</sub>-Vascscore (Table 2 and 3) which was initially validated in the Euro-Heart survey cohorts. In a systemic review comprising 122 articles and 92 different studies, it was found that the CHA<sub>2</sub>DS<sub>2</sub>-Vasc score had the best risk factor predictor for stroke in AF and the HASBLED score (discussed further on) the best predictor of bleeding risk<sup>10</sup>. The CHA<sub>2</sub>DS<sub>2</sub>-Vascscore is now the recommended risk score by European, US, and National Institute for Health and Care Excellence (NICE) guidelines.

**Table 2: CHA<sub>2</sub>DS<sub>2</sub>-Vasc scoring tool Table 3: CHA<sub>2</sub>DS<sub>2</sub>-Vasc clinical risk estimation**

CHA <sub>2</sub> DS <sub>2</sub> -Vasc	CHA <sub>2</sub> DS <sub>2</sub> -Vasc score	Adjusted stroke rate(% year)
Congestive heart failure <sup>a</sup>	1	0
Hypertension <sup>b</sup>	1	1.3
Age > 75 years old	2	2.2
Age > 65 years old	1	3.2
Diabetes mellitus <sup>c</sup>	1	4.0
Stroke/TIA/Thrombo-embolism	2	6.7
Vascular disease <sup>d</sup>	1	9.8
Sex -Female	1	7
		9.6
		8
		6.7
		15.2

TIA, Transient ischaemic attack

a-The presence of signs and symptoms of either right or left ventricular failure or both, confirmed by non-invasive or invasive measurements demonstrating objective evidence of cardiac dysfunction. E.g. LVEF < 40% (Left ventricular ejection fraction)

b- A resting blood pressure >140mmHg systolic and/or >90mmHg diastolic on at least two occasions or current antihypertensive pharmacologic treatment c- Fasting plasma glucose level ≥7.0 mmol/L or treatment with an oral hypoglycaemic agent and/or insulin d-Prior myocardial infarction, angina pectoris, percutaneous coronary intervention or coronary artery

bypass surgery. The presence of any the following: intermittent claudication, previous surgery or percutaneous intervention on the abdominal aorta or the lower extremity vessels, abdominal or thoracic surgery, arterial and venous thrombosis

There are multiple studies proving benefit with warfarin in AF for stroke prevention over placebo or an antiplatelet agent<sup>11-15</sup>. The five major studies<sup>11,13,16-18</sup> proving benefit of anticoagulation over placebo or aspirin have demonstrated a 69% risk reduction when data was pooled (Table 4).

**Table 4: Studies evaluating anticoagulation benefit over placebo or antiplatelet therapy in reducing the risk of stroke**

Study/Trial	Number of cases	RRR <sup>a</sup> (%)	Target INR range
AFASAK <sup>b</sup>	1007 (335 on warfarin)	56	2.8 to 4.2
BAATAF <sup>c</sup>	420	86	1.5 to 2.7
SPAF <sup>d</sup>	1330	67	2.0 to 3.5
CAFA <sup>e</sup>	378	37	2.0 to 3.0
SPINAF <sup>f</sup>	571	79	1.4 to 2.8
EAF <sup>g</sup>	1007 (669 on warfarin)	62	2.5 to 4.0
SPAF III	1004	74	2.0 to 3.0

a- Relative Risk Reduction

b- AFASAK, Copenhagen Atrial Fibrillation, Aspirin and Anticoagulation Study

c- BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation Study

d- SPAF, stroke prevention in Atrial Fibrillation Study

e- CAFA, Canadian Atrial Fibrillation Anticoagulation Study

f- SPINAF, Veterans Affairs stroke prevention in Non-rheumatic Atrial Fibrillation Study

g- EAF, European Atrial Fibrillation Trial

### 1.3. Heart valve prosthesis

Since the introduction of valve replacement surgery in the early 1960s, the outcome of patients with valvular heart disease has dramatically changed. The most common indications for a prosthetic heart valve replacement are due to stenotic or regurgitant lesions in the aortic valve or mitral valve. Aortic stenosis (AS) in developed regions is usually the sequel of degenerative change, however, in South Africa and other developing countries, the burden of rheumatic fever with recurrent episodes and subsequent rheumatic heart disease contributes toward the majority of cases of valvular lesions requiring surgical replacement and this remains a concern.

The American College of Cardiology/American Heart Association (ACC/AHA) recommends aortic valve replacement in AS for any symptomatic patient with moderate or severe AS, asymptomatic patients with severe AS undergoing coronary artery bypass grafting (CABG) or surgery on the aorta or other heart valves or for asymptomatic patients with severe AS with left ventricle systolic dysfunction, an abnormal response to exercise, ventricular tachycardia, left ventricle hypertrophy in excess of 15 mm or an aortic valve area of less than 0.6cm<sup>2</sup><sup>19</sup>.

The ACC/AHA recommendations for aortic valve replacement in patients with aortic regurgitation (AR) are for any symptomatic patient with severe AR irrespective of left ventricular systolic function, in asymptomatic patients with chronic and severe AR with left ventricular systolic dysfunction (Ejection fraction less than 50% at rest), in patients with chronic and severe AR or moderate AR undergoing CABG or surgery on the aorta or on other heart valves, or in asymptomatic patients with severe AR with normal left ventricle (LV) function but severe LV dilatation [End Diastolic Diameter (EDD) greater than 75mm or End Systolic Diameter (ESD) more than 55mm] and in asymptomatic patients with severe AR and normal LV function at rest with an EDD more than 70mm or ESD more than 50mm with declining exercise tolerance<sup>19</sup>.

According to ACC/AHA guidelines, mitral valve surgery is indicated in patients with symptomatic [New York Heart Association (NYHA) functional Class III–IV], moderate or severe mitral stenosis

(MS) if percutaneous mitral balloon valvotomy is contraindicated or unavailable or in symptomatic patients with moderate to severe MS who also have moderate to severe mitral regurgitation and in patients with severe MS and severe pulmonary hypertension [Pulmonary Artery Stiffness (PAS) >60mmHg] who have NYHA functional class I-II symptoms<sup>19</sup>.

Patients with prosthetic valves are at risk of thrombo-embolic complications, including systemic embolisation, most commonly cerebral and prosthetic thrombosis causing valve obstruction and/or regurgitation. The risk of thrombo-embolic events is higher with mechanical than with bioprosthetic valves; higher with mitral than with aortic prosthetic valves; and higher in the early (3 months) versus late postoperative phase<sup>20</sup>. The risk is also increased in the presence of concomitant risk factors for thrombo-embolism, including AF, LV dysfunction, left atrial dilation, previous thrombo-embolism, and a hypercoagulable condition<sup>2</sup>.

Prosthetic valve thrombosis is a rare but catastrophic complication with a mortality of approximately 10%<sup>21</sup>. The reported incidence is 0.3 to 1.3% patient-years. Thrombo-embolism is the more common complication reported as 0.7% to 6% patient-years<sup>21</sup>.

Patients with mechanical prostheses require lifelong anticoagulation with warfarin. In the case of an implanted bioprosthesis, anticoagulation with warfarin for 3 months is recommended and some authors recommend warfarin use for a period of 6 months following an aortic valve prosthesis<sup>22</sup>. Lifelong anticoagulation is required in the case of a bioprosthesis implantation if the patient has other indications for anticoagulation like AF<sup>2</sup>.

#### **1.4. INR target range**

INR target ranges vary per indication and per country. The most common usual INR target is a range from 2 to 3 with the midpoint of 2.5 being targeted as optimal (Table 1). The optimal range is determined by defining the risk of thrombo-embolism against the risk of bleeding.

The accepted target INR range in AF is from 2 to 3 and a midpoint of 2.5 targeted as optimal. Many studies have shown reduced incidence of stroke and mortality in patients who are anticoagulated with warfarin and subsequent studies have shown reduced efficacy in stroke prevention with INR values targeted below this range<sup>23</sup>. A record linkage analysis by Oden *et al.*, evaluated the findings from medical literature from 1980 to mid-2004 and concluded that INRs in the interval range of 2.0 to 2.5 give the lowest risk of stroke and death in patients with non-valvular AF<sup>24</sup>.

The risk of haemorrhage remains a concern with any patient being anticoagulated with warfarin and generally accepted as a two-fold risk to the normal population. Gastrointestinal haemorrhage is much more common than intracranial haemorrhage, however intracranial events are usually more devastating. In one study evaluating 13 559 patients being anticoagulated for stroke prevention in non-valvular AF, 76% of patients who had intracranial haemorrhage had severe disability or died compared to 3% of patients with extracranial haemorrhage. Ninety percent of warfarin-associated deaths could be accounted for by intracranial haemorrhage<sup>25</sup>. It should be noted, however, that warfarin use reduced the 30 day mortality from ischaemic stroke<sup>26</sup>. INR levels greater than 4.00 have been associated with increased bleeding risk.

There are many bleeding risk assessment tools used in clinical practice. One such, commonly used in our clinical setting is the HASBLED risk assessment tool (Table 5). This has been validated in multiple studies and a systematic review comprising 122 articles and 92 unique studies noted the HASBLED score as the best predictor of bleeding risk<sup>10</sup>.

**Table 5: HASBLED scoring tool<sup>27</sup>**

HASBLED Scoring tool	
Hypertension <sup>a</sup>	1
Abnormal liver function	1
Abnormal renal function	1
Stroke	1
Bleeding	1
Labile INRs <sup>b</sup>	1
Elderly (Age >65 years old)	1
Drugs <sup>c</sup>	1
Alcohol <sup>d</sup>	1

a- Uncontrolled or systolic blood pressure greater than 160 mmHg

b- With the time in therapeutic range less than 60%

c- Antiplatelet or non-steroidal anti-inflammatory

d- At least eight units per week

The clinical risk estimation of bleeding is 1.13 per 100 patients with a HASBLED score of zero and increases steeply as the score increases. Patients with a score of five have an estimated bleeding risk of 12.5 per 100 patients<sup>27</sup>.

The recommended INR targets for mechanical heart valves depends on the prosthesis thrombogenicity [Low: Carbomedics (aortic position), Medtronic Hall, St Jude Medical (without silzone); Medium: Bjork-Shiley, other bi-leaflet valves; High: Starr-Edwards, Omniscience, Lillehei-Kaster] as well as patient factors which increase the risk of thrombo-embolism (Mitral, tricuspid or pulmonary position; previous arterial thrombo-embolism; AF; left atrium diameter more than 50 mm; MS of any degree; left ventricular ejection fraction of less than 35%; left atrial dense spontaneous echo contrast).

Patients with low prosthetic thrombogenicity and no patient risk factors should have an INR target of 2.5. Those with low prosthesis thrombogenicity and patient risk factors should be optimised at an INR of 3.0. Patients with medium prosthesis thrombogenicity and no patient risk factors have an INR target of 3.0 whereas those with patient risk factors should have INR levels at 3.5. In patients with high prosthesis thrombogenicity, regardless of patient risk factors, an INR of 3.5 should be targeted (Table 6) with some studies suggesting an INR of 4.0 to be considered<sup>2</sup>.

**Table 6: Recommended target INR for mechanical valve prosthesis <sup>2</sup>**

<b>Recommended INR Target</b>		
<u>Thrombogenicity</u>	<u>No Risk Factors</u>	<u>Risk Factors Present</u>
Low	2.5	3.0
Medium	3.0	3.5
High	3.5	3.5

### **1.5. Assessing the quality of anticoagulation**

The clinical benefits of warfarin as an anticoagulant as well as its haemorrhagic risks are related to the proportion of time spent within the target INR range. Anticoagulation with warfarin has a large inter-individual variability and INR monitoring is serially recommended in order to adjust the treatment dose. Patients using warfarin have been well studied for stroke risk reduction and have been used in many clinical trials as an indicator for anticoagulation; however the quality of this anticoagulation is less often measured. The TTR is an acceptable measure of this and confers the quality of anticoagulation control and better defines increased risk of haemorrhage.

There are at least three different generally well accepted methods to measure TTR, each with its own advantages and disadvantages (Table 7):

1. Fraction of INRs in range (taken as the number of INRs in range divided by the total number of INRs for the study interval). This is referred as the Direct method.
2. The cross-section-of-the-files-methodology (takes each patient whose INR is in range at one point in time divided by the total number of INRs done on all patients at that point in time).
3. The Rosendaal Linear Interpolation Methodology (uses a computer software program that assumes a linear relationship exists between two INR values and allows one to calculate a specific INR value to each day for each patient) <sup>28</sup>.

**Table 7: Advantages and disadvantages of the different methods of evaluating time in therapeutic range<sup>29</sup>**

<b>Methodology</b>	<b>Advantages</b>	<b>Disadvantages</b>
Fraction of INRs	Simple to calculate  Requires only one INR value per patient Not influenced by extent of INR outofrange	More frequent testing in unstable patients may bias results Does not take into account actual days within target range Does not consider individual patients
Cross-section-of-files	Simple to calculate  Considers individual patients Not influenced by extent of INR outofrange	Does not take into account actual days within range Only considers one point in time
Rosendaal Linear Interpolation	Takes into account actual days in target range Allows calculation of INR specific incidence rates of adverse events	Calculation is more difficult Makes assumptions about INR between actual tests Does not consider individual patients Extreme out of range results may bias results

TTR is an important and validated quality measure for VKA management<sup>30</sup>. Patients who are under-treated remain at risk of thrombo-embolic events and patients who receive too much anticoagulant therapy are exposed to unnecessary bleeding risk<sup>31</sup>. In the setting of non-valvular AF, patients who have at least one other stroke risk factor are recommended to receive effective stroke prevention therapy, which is essentially an oral anticoagulant (OAC) with well-controlled VKA therapy which implies an INR 2 to 3 and a high TTR percentage of at least 60%<sup>5</sup>. The efficacy of warfarin as an anticoagulant is reliant on the time in therapeutic range. Recent studies comparing the novel anticoagulant dabigatran showed no difference in stroke prevention at higher TTR<sup>32</sup>. Furthermore, a higher TTR percentage, i.e. greater than 70%, conferred better survival for patients with moderate or high risk patients<sup>33</sup>.

In patients with AF, the quality of anticoagulation is therefore accepted as stratified according to the percentage TTR less than 50% conferring bad quality, more than 60% being satisfactory and more than 70% conferring optimal anticoagulation. Patients who are under-anticoagulated are at an increased risk of thrombo-embolic events. The report from a posthoc analysis of the Atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events (ACTIVE-W) indicated that if the TTR was below 58% to 65%, the benefit of warfarin therapy over aspirin was lost<sup>34</sup>.

A high variability of the INR is the strongest independent predictor of reduced survival after mechanical valve replacement. Valve thrombosis is most often encountered in patients with mechanical valves and inadequate antithrombotic therapy<sup>20</sup>. A correlation between treatment quality with warfarin as measured by TTR and serious complications has been shown. It is recommended that best benefit in patients with prosthetic heart valves is achieved when the TTR is at least 83% but a TTR of at least 70% is likely to be sufficient to prevent valve thrombosis<sup>35</sup>.

Further to the efficacy of anticoagulation, improved TTR confers reduced risk of bleeding and mortality. In the SPORTIF III trial (Stroke Prevention using an Oral Direct Thrombin Inhibitor in atrial fibrillation) patients with a TTR of less than 60% had significantly higher ( $p < .01$ ) incidence of major haemorrhage (3.85%) and mortality (4.20%) than patients with TTR beyond 75% (1.58% and 1.69% respectively)<sup>36</sup>.

It is now well accepted and emphasised that the TTR matters and has far reaching implications in both assessing the quality of anticoagulation, determining efficient anticoagulation and reducing the incidence of mortality and major adverse events.

## **1.6. Monitoring of INR**

Maintaining TTR can be a challenging task due to the variability of warfarin effects between individuals and as a result there is no standardised dose when prescribing warfarin. Moreover, dose adjustments are necessary according to INR values. There is evidence to suggest that more frequent testing improves TTR, but this may be impractical in the clinic setting. The Home INR Study (THINRS) sought to evaluate the impact on TTR after one year following the frequency of INR testing on patients being anticoagulated for AF or for prosthetic valves. The results of this study showed TTR increased as testing frequency increased for the groups that underwent testing every four weeks, twice weekly and weekly. The study involved patients who performed self-testing. Furthermore, they found a lower proportion of patients who performed self-monitoring than those who attended clinics in the population with poor anticoagulation control. The study concluded that more frequent INR testing improved TTR and reduced poor patient outcomes<sup>37</sup>. The finding of more frequent testing and improved TTR is consistent in other studies, notably the Self-Testing Analysis Based on Long-term Evaluation (STABLE) trial that evaluated patients who performed home monitoring and concluded a significantly higher TTR ( $p < .001$ ) in patients who tested weekly (74%) than those who tested every 2 to 4 weeks (68.9%) and the superior TTR in more frequent testers was consistent across all indications for anticoagulation<sup>38</sup>.

The setting in which patients have their INR values monitored may also impact the TTR. In a meta-analysis evaluating 11 studies (Three randomised controlled trials and eight cohort studies), patients managed at specialised anticoagulation clinics had superior TTR than patients managed with usual care, however there was no significant differences with regard to mortality, major haemorrhage or thrombo-embolic events<sup>39</sup>. Evaluation from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) found that patients treated at anticoagulation clinics had higher median TTR (69%) than those who were not (66%) ( $p < .0001$ )<sup>40</sup>.

## 1.7. Challenges in maintaining quality anticoagulation

The INR value of patients taking warfarin has substantial inter-individual variability as a result of the drug's complex pharmacokinetics and pharmacodynamics. In addition there are multiple drug and food interactions that have inducing or inhibitory effects on the drug bioavailability, which translates to variability in efficacy and therefore TTR. It is recommended that patients who are starting or stopping any of these drugs, have more frequent INR testing, in order to adjust warfarin doses accordingly. Certain drugs that have no inhibitory or inducing effects on the elimination of warfarin can also influence the INR, most notably the non-steroidal anti-inflammatory drugs like diclofenac, aspirin in high doses and ibuprofen.

Patient compliance with treatment remains an important contributing factor. In one study of patients with out of range INRs, non-compliance was most commonly noted on 214 occasions (19.8%), food interaction on 143 occasions (13.2%), drugs on 109 occasions (10.0%), alcoholic beverage on 34 occasions (3.1%) and herbal remedy on 12 occasions (1.1%). The remaining 52.8% of cases had undetermined causes<sup>41</sup>.

One important factor which is seldom evaluated in community-based practice is warfarin resistance which should be considered when a weekly dose of at least 105mg does not increase the INR to therapeutic range. Warfarin resistance can be acquired (most commonly due to non-compliance with treatment) or hereditary (genetic factors that increase metabolism or reduced sensitivity). Studies in rats and humans have demonstrated abnormalities with increased affinity of vitamin K 1, 2, 3-epoxide reductase (VKOR) for vitamin K and decreased VKOR sensitivity to warfarin.

## 1.8. Alternative therapies to warfarin for anticoagulation

Recently, the introduction of non-warfarin, new oral anticoagulant (NOAC) agents have resulted in exciting studies comparing efficacy for stroke prevention and bleeding complications against warfarin in AF. Three novel drugs (and their respective studies), dabigatran (Re-ly), apixaban (ARISTOTLE) and rivaroxaban (ROCKET-AF) have been studied for efficacy and safety against warfarin and have at least proven non-inferiority. The most recent novel drug studied is edoxaban (ENGAGE-AF-TIMI 48)<sup>30,42-44</sup>.

NOACs are as yet not approved for anticoagulation in patients with prosthetic heart valves and warfarin remains the only option as an oral anticoagulant.

## 1.9. The research objective

It is well accepted that patients with non-valvular AF and patients with prosthetic heart valves require anticoagulation to prevent thrombo-embolic complications. There are many studies proving this benefit<sup>11,13,16-18</sup>. More recently, with the introduction of the NOACs, warfarin has been challenged as the gold standard drug for AF in non-valvular AF. The studies surrounding this evaluation show the efficacy in stroke prevention in AF is comparable to warfarin. The TTR, however, is less often evaluated for patients taking warfarin. Many studies evaluated TTR in a clinical trial setting<sup>30,42,44</sup>. Other studies evaluated the influential factors surrounding these patients<sup>31</sup>, however most studies analyse patients in a controlled trial or in an anticoagulation clinic<sup>39</sup> or those using self-testing or self-monitoring techniques<sup>37,38</sup> that may over-estimate the TTR. In our study, we attempted to evaluate the quality of anticoagulation in a patient population who are not part of a comparative trial, who do not utilise self-monitoring or self-testing devices, who attend a community-based district level hospital and not in the way of a specialised anticoagulation clinic and who do not have access to the NOAC agents.

Our specific objectives:

1. Assessed the overall quality of anticoagulation in patients using warfarin as an oral anticoagulant for prevention of stroke in patients with non-valvular AF and in patients with prosthetic heart valves by determining the TTR.
2. Compared two different methods used to evaluate TTR namely the Direct method (Fraction of INRs in range) and the Rosendaal method (Linear Interpolation of INRs).
3. Determined the overall time out of range i.e. the mean percentage of time being under-coagulated, the percentage of time being over-anticoagulated and the percentage time with an INR value in excess of 4.00 which is associated with a high risk of haemorrhagic complications.
4. Evaluated the indications for anticoagulation with warfarin in this patient population.
5. Evaluated factors that may be associated with TTR or out of range, specifically, gender, age and frequency of monitoring and in the case of patients with prosthetic valves, for different target INR ranges.
6. Evaluated the point prevalence of adverse events, specifically, stroke, haemorrhage, any admission for warfarin toxicity and any cases of prosthetic valve thrombosis in this patient population and determined if there was an association between events and the factors listed above.
7. Evaluated for significant difference between patients who sustained a stroke and those who experienced haemorrhage or warfarin toxicity.

## CHAPTER 2

### METHOD AND STUDY DESIGN

This is a retrospective, descriptive and observational study with chart audits. Review of the literature was done by an online search in Pub Med with the following keywords; atrial fibrillation, time in therapeutic range, warfarin, mechanical valve prosthesis, thrombo-embolic stroke, haemorrhage and the abbreviations or acronyms; INR, TTR, CHAD<sub>2</sub>vasc, HASBLED and AF.

Patients attending the adult medical outpatient department at Mahatma Gandhi Memorial Hospital in KwaZulu Natal, South Africa comprised our patient population. All patients who had INR measurements over a period of four months were initially selected. INR testing in this centre is performed by sampling venous blood in a citrate tube. We determined this with the assistance of the National Health Laboratory Service (NHLS) based at the hospital by providing the phlebotomy log books for this period. We then removed all duplicate cases as well as patients who were not using warfarin to determine the preliminary sample size. Systematic random sampling was utilised and the random number selected was one and therefore we evaluated every case. Patients were then allocated a case number ('n') by true randomness and this was selected by an online internet tool from "Random.org" that uses atmospheric noise rather than algorithmic methods to randomise samples.

We then conducted a comprehensive retrospective chart review for each patient. We thereby determined the indications for anticoagulation in the population. Data collected from chart reviews for each patient included the following:

1. The indication for anticoagulation. Thereafter, all patients treated with warfarin for reasons other than stroke prevention in non-valvular AF or for prosthetic heart valves were excluded from further study which is how the final study population was determined.
2. The age of each patient in completed years.
3. Gender.
4. Date of INR sampling (which was used to determine the days between tests and total days studied for each patient) with the corresponding INR value.
5. Target INR range as per the indication (2.0 to 3.0 for AF and variable for valve prosthesis).
6. The presence or absence of patient risk factors and valve thrombogenicity in cases with prosthetic valves in order to determine the target INR range.
7. The percentage of time below range, above range, with INR values greater than 4.00 and in range using the Direct method (The ratio of INR values in range out of the total number sampled as a percentage).
8. Any adverse event and type of event that was sustained during any period while being anticoagulated and not limited to the data collection period.
9. The data collection tool (Appendix 5) was allocated a case number 'n' to ensure patient anonymity.
10. The TTR using the Rosendaal method. We transcribed this data into the Microsoft<sup>R</sup> Excel program.
11. All INR values and dates of tests were recorded for at least one year or 12 consecutive INR values, whichever was the longer for each individual patient.

All handwritten INR values in files were verified formally by use of the NHLS Labtrack<sup>R</sup> system.

The research period was from November 2015 (Approval date of ethics and gatekeeper permission) to September 2016 (Collection and analysis of data and completion of draft write-up).

The inclusion criterion for participants for both non-valvular AF and valve prosthesis was:

1. Outpatient cases were considered.
2. Patients who were older than 12 years old were evaluated.
3. Patients who were taking warfarin for at least one year were considered.
4. Patients who had mechanical heart valves were considered.

The following exclusion criteria applied to the study:

1. Inpatients and any INR value while an inpatient was not included.
2. Patients who were less than 12 years old were not considered.
3. Patients who were taking warfarin for less than one year were excluded.
4. Patients who had interrupted warfarin use for longer than two months was excluded e.g. pregnant patients.
5. Patients who were being anticoagulated with warfarin for reasons other than non-valvular AF or prosthetic heart valves were not included for further study beyond contributing to the data evaluating the indications for anticoagulation in the study location.

We evaluated the time in therapeutic range by two methods:

1. The Direct method was determined by evaluating the number of INR values in range out of all INR tests for that patient as a percentage. Similarly, the time below range, time above range and time with INR levels greater than 4.00 were determined in this way.
2. The Rosendaal method of determining the time in therapeutic range was determined by analysis with the Microsoft<sup>R</sup> Excel programme.

Time out of range (Time below range, above range and with an INR value greater than 4.00) was determined using only the Direct method.

Data was analysed by the IBM Statistical Package for the Social Sciences (SPSS) for Windows<sup>R</sup>, version 23 (IBM Corp., Armonk, N.Y., USA) software program. Descriptive statistics included mean (M) and standard deviation (SD) for quantitative data and frequencies for categorical data. Variables with means which demonstrated uniformity with linear Q-Q plots and/or P-P plots were conducted by parametric testing using the independent samples T-test and Hartley's statistical test for variance for normally distributed data. Pearson's chi-square test was used for categorical data. Analysis of variance (ANOVA) was conducted for comparisons of variables with post hoc analysis by Tukey honestly significant difference (HSD) for analysis of three or more groups. Homogeneity of variance statistical testing was conducted using Levene's test for quality of variance. Confidence intervals were reported as 95%. Two-tailed p-values were conducted and any p-value less than .05 was considered significant.

#### *Topic Specific methods*

In evaluating TTR, we used the Pearson correlation test to evaluate the Direct and the Rosendaal methods. After determining and analysing the overall TTR for both cohorts, we then categorised patients in the AF cohort into the percentage of patients with TTR less than 60% which was considered as suboptimal anticoagulation and time with increased thrombotic risk, percentage of patients with TTR less than 50% which was considered as a marker of bad anticoagulation and the

percentage of patients with TTR more than 70% which was considered as excellent anticoagulation quality. Patients with TTR more than 60% but less than 70% were considered as having satisfactory anticoagulation. Thereafter, we compared the groups with TTR more than 70% with the TTR less than 60% group according to the results of the Rosendaal method for the conditions of gender, age, average days between tests and the presence of at least one documented adverse event.

We then analysed all patients in the valve prosthesis cohort with regard to TTR and stratified the cohort according to percentage of patients with TTR of at least 70% which was considered satisfactory, the percentage of patients with TTR of at least 83% which was considered as ideal and the percentage of patients with TTR less than 70% which was considered suboptimal.

The frequency of INR testing was categorised into three groups namely; less than 28 days apart; 28 to 32 days apart and more than 32 days apart.

The target INR value for patients with prosthetic heart valves was determined by using the recommendations by Keeling *et al.*, Guidelines on oral anticoagulation with warfarin - fourth edition. Br J Haematology, 2011. 154(3): p. 311-24 (Table 6). This was opted for in view of the laboratory service at this clinical setting adopting the same recommended guideline in their reference for target INR ranges and therefore maintained a consistency between the treating clinician and evaluation in this study. In order to create a target INR range, we accepted the above targets as the minimum acceptable INR value and allowed a 0.5 higher limit to create a range. The target INR range for patients with AF was consistent at 2.0 to 3.0.

We studied all patient population outpatient files to determine the prevalence of any documented adverse event. The study duration in terms of evaluating INR values for each patient spanned only one year, and we therefore sampled any documented adverse event at any time for a particular patient while on anticoagulation. Any event that occurred prior to the patient commencing long-term anticoagulation was not considered. Data capture for any adverse event was reliant on the clinicians' documentation of such as well as any attached discharge note following an inpatient care or any referral note attached to the outpatient file.

Adverse events were categorised as any stroke, which was not defined as ischaemic or haemorrhagic (primarily due to lack of easy access to neuro-imaging at the study location and therefore most patients with a stroke had no documented computed tomography of the brain or magnetic resonance imaging reports) and any event with haemorrhage or warfarin toxicity (Defined as warranting antidote treatment and/or inpatient care). Any episode of minor haemorrhage not requiring admission was discounted. In addition, we assessed for cases of a thrombosed or obstructed prosthetic valve in the context of the patients requiring anticoagulation for prosthetic heart valves.

We determined the point prevalence of these adverse events for the sample population as a whole and then separately for the AF cohort and the valve prosthesis cohort. Analyses include evaluating for associations of adverse events with time in range, time out of range, age, gender, INR testing interval and target INR range (valve prosthesis sub-cohort) using a Poisson regression using Wald chi-square test and a two-tailed *p*-value of less than .05 as significant.

## CHAPTER 3

### DESCRIPTION OF THE SAMPLE POPULATION

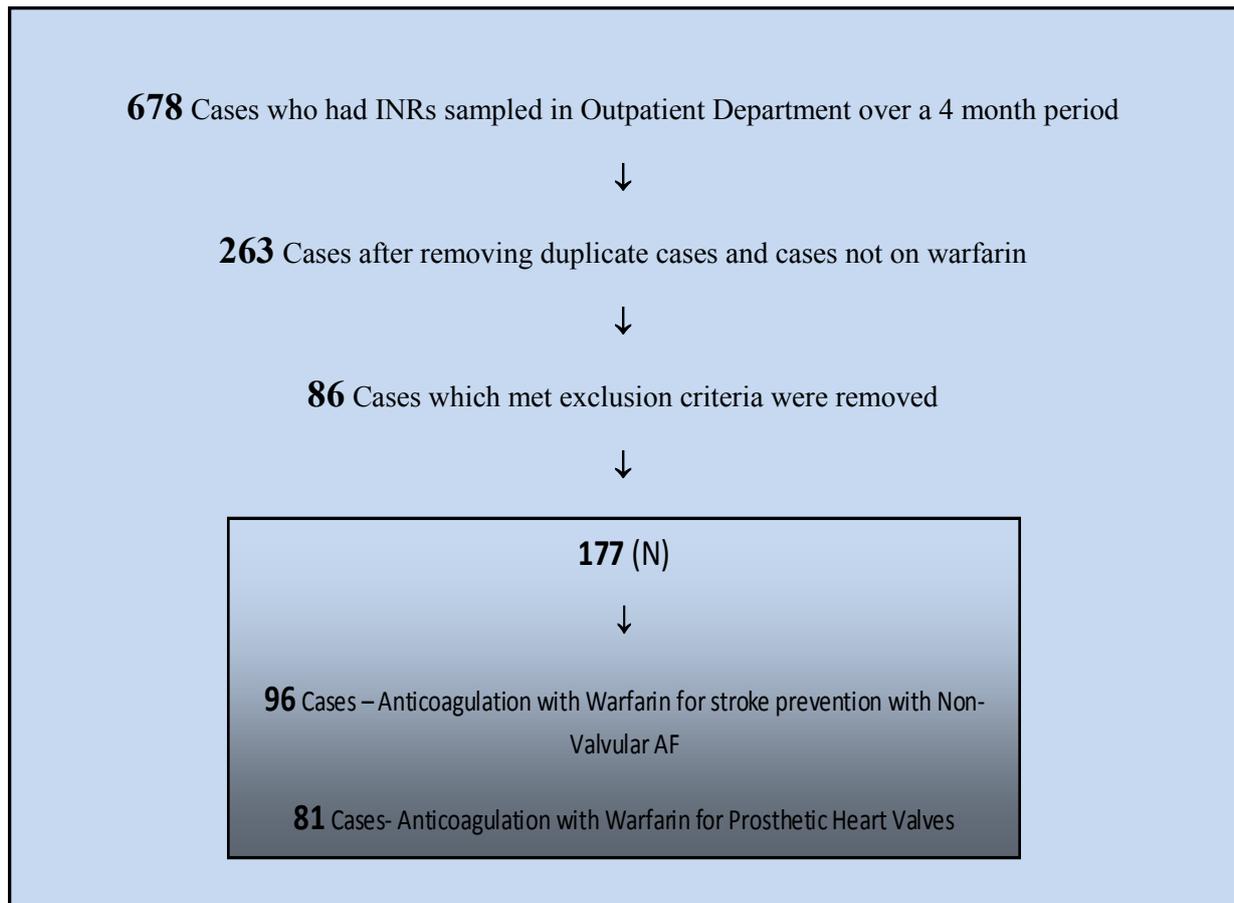
We determined the indication for anticoagulation in a single centre, community-based district level hospital in Phoenix, Durban, KwaZulu Natal, South Africa by performing a comprehensive chart audit on all patients who had INR measurements at the hospital during a four-month period. We observed 678 different INR tests performed over this period (Figure 2). Thereafter, we removed duplicate patients and patients who had INR testing who were not taking warfarin. The remaining 263 individual cases were evaluated according to the indication of anticoagulation at this centre (Table 8). All individual data was collected and collated by review of the patients' hospital outpatient chart.

**Table 8: Indications for anticoagulation**

<b>Indication</b>	<b>n (%)</b>
Non-valvular AF	104 (39.5)
Prosthetic heart valves	94 (35.8)
VTE / DVT / PE	32 (12.2)
Arterial / LV Thrombus	13 (4.9)
Valvular AF	10 (3.8)
CMO with Low EF	1 (0.4)
Files not located/Undetermined	9 (3.4)
<b>Total</b>	<b>263 (100%)</b>

AF- Atrial fibrillation, VTE-Venous thrombo-embolism, DVT- Deep vein thrombosis, PE- pulmonary embolus, LV-Left ventricle, CMO-Cardiomyopathy, EF-Ejection fraction

Patients who were anticoagulated for indications other than for non-valvular AF or for prosthetic heart valves were thereafter excluded from further study (Table 8). A further eight patients from the non-valvular AF subset and 13 patients from the valve prosthesis subset had been anticoagulated with warfarin for less than 12 months and were therefore also excluded.



**Figure 2: Schematic showing how the sample population was determined.**

In order to evaluate the quality of anticoagulation we sampled a total of 177 patients using warfarin for non-valvular AF (n=96) and for prosthetic heart valves (n=81) attending the outpatient department at Mahatma Gandhi Memorial Hospital. The sample population was not part of a specialised anticoagulation clinic.

Descriptive statistics for this sample population included data analyses for gender, age in years and categorised for each subpopulation, total number of days studied per individual patient, the number of INR tests performed per individual patient and the interval days between each test. SD was used to describe the dispersion (Table 9).

The majority of the patients in our sample population were female (68.9% for the entire sample population (n=122), 65.6% (n=63) for AF cohort and 72.8% (n=59) for valve prosthesis cohort).

The mean age of the entire cohort was 54.23 years (SD=17.6), 64.68 years (SD=11.27) for the AF cohort and 41.83 years (SD=15.67) for the valve prosthesis cohort.

We categorised the age of patients in the AF cohort in line with the CHA<sub>2</sub>DS<sub>2</sub>-Vasc scoring system. Patients who were at least 65 years old to less than 75 years old accounted for 35.4% (n=34) of the AF cohort and patients 75 years or older accounted for 17.7% (n=17). The remaining 46.9% (n=45) of patients in the AF cohort were younger than 65 years old.

Patients in the valve prosthesis cohort were categorised into six age categories with the fewest patients (2.5%, n=2) younger than 20 years. The majority of the patients (48.1%, n=39) were from 20 years and less than 40 years old with 17.3 % (n=14) aged at least 60 years old. The remaining 32.1% (n=26) of patients in the valve prosthesis cohort were from 40 years and less than 60 years old.

The total number of days evaluated for the entire cohort was 78975 days or 216.4 years with a mean of 446.2 days (SD=157.1) per patient. The AF cohort was evaluated for a period of 39937 or 109.4 years with a mean of 416 days(SD=111.8) per patient and the valve prosthesis cohort was evaluated for 39038 days or 106.9 years with a mean of 481.9 days (SD=192.4) per patient.

The mean number of days between INR tests for the entire cohort was 33.3 days (SD=12.03); 31.05 days (SD=6.77) for the AF cohort and 35 days (SD=15.82) for the valve prosthesis cohort.

A total of 2382 INR values were analysed for the entire cohort (N=177) with 1285 INR tests studied for the AF cohort and 1097 INR tests studied for the valve prosthesis cohort.

Of the 1285 INR samples of patients studied in the AF cohort, the mean INR value was 2.70 (SD=1.369).

**Table 9: Characteristics of the sample population.**

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<b>Sample Population (N=177)</b>	
Female, n (%)	122 (68.9)
Male, n (%)	55 (31.1)
Mean age (SD)	54.23 (17.6)
Median age (Min, Max)	57 (15,91)
Inter-quartile age range	40-69
Total Days studied (Mean per patient)	78975 (446.2)
Total INRs sampled (Mean per patient)	2382 (13.5)
Mean days between INR tests (SD)	33.3 (12.0)
<i>Less than 28 days apart, n (%)</i>	41(23.2)
<i>28 to 32 days apart, n (%)</i>	75(42.3)
<i>More than 32 days apart, n (%)</i>	61(34.5)
<b>AF Cohort (n=96)</b>	
Female, n (%)	63 (65.6)
Male, n (%)	33 (34.4)
Mean age (SD)	64.7 (11.3)
Median age (Min, Max)	66 (36, 91)
Inter-quartile age range	57-72
<i>Less than 65 years old, n (%)</i>	45(46.9)
<i>65 to less than 75 years old, n (%)</i>	34 (35.4)
<i>75 years or older, n (%)</i>	17(17.7)
Total days studied (Mean per patient)	39937 (416)
Total INRs sampled (Mean per patient)	1285 (13.4)
Mean days between INR tests (SD)	31.1 (6.8)
<i>Less than 28 days apart, n (%)</i>	31(32.3)
<i>28 to 32 days apart, n (%)</i>	36(37.5)
<i>More than 32 days apart, n (%)</i>	29(30.2)
<b>Valve Prosthesis Cohort (n=81)</b>	
Female, n (%)	59 (72.8)
Male, n (%)	22 (27.2)
Mean age (SD)	41.8 (15.7)
Median age (Min,Max)	39 (15, 76)
Inter-quartile age range	30-55
<i>Less than 20 years old, n (%)</i>	2 (2.5)
<i>20 to 29 years old, n (%)</i>	18 (22.2)
<i>30 to 39 years old, n (%)</i>	21 (25.9)
<i>40 to 49 years old, n (%)</i>	14 (17.3)
<i>50 to 59 years old, n (%)</i>	12 (14.8)
<i>60 years or older, n (%)</i>	14 (17.3)
Total Days studied (Mean per patient)	39038 (482)
Total INRs sampled (Mean per patient)	1097 (13.5)
Mean days between tests (SD)	36 (15.8)
<i>Less than 28 days apart, n (%)</i>	10 (12.3)
<i>28 to 32 days apart, n (%)</i>	39 (48.2)
<i>More than 32 days apart, n (%)</i>	32 (39.5)

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## CHAPTER 4

### TIME IN THERAPEUTIC RANGE

#### 4.1. Introduction

Although anticoagulation with warfarin and its' target range for AF and prosthetic valves is well accepted, the quality of this anticoagulation is less often evaluated. The time in therapeutic range is a well validated tool for assessing anticoagulation quality. There are three accepted measures of determining the TTR which has been discussed previously in this work. Each has advantages and disadvantages over the other. The most used methods among the major published works is the Rosendaal interpolation method and the Direct method.

AF, prosthetic valves and the complex pharmacodynamics of warfarin itself preclude to a narrow therapeutic window to prevent thrombosis and to minimise the risk of haemorrhage. The TTR has been evaluated as being an important measure of this balance. The ACTIVE-W trial found the benefit of stroke prevention with warfarin over aspirin and clopidogrel was lost if the TTR was less than 58%<sup>34</sup>. The study by Wan *et al.*, evaluated anticoagulation control and prediction of adverse events in patients with AF by a systematic review of 47 studies. They found that TTR negatively correlated with major haemorrhage ( $r = -0.59$ ;  $p = 0.002$ ) and thrombo-embolic rates ( $r = -0.59$ ;  $p = 0.01$ ). This effect was significant in retrospective studies but not in randomised controlled trials. For retrospective studies, a 6.9% improvement in the TTR significantly reduced major haemorrhage by one event per 100 patient-years of treatment. Furthermore, they concluded that a 12% increase in TTR can reduce the thrombo-embolic rate by one event per 100 patient years<sup>45</sup>. Data from the ROCKET-AF trial, evaluated the relationship between TTR and the comparative treatment effects of rivaroxaban and warfarin and found that patients in the highest quartile of TTR had a lower event rate per 100 person-years than patients in the lowest quartile of TTR (1.3 vs 2.0) when analysing stroke or systemic thrombo-embolism<sup>46</sup>. In a study by Gallagher *et al.*, which evaluated the risk of stroke and mortality with suboptimal anticoagulation in patients with AF found that patients who spent at least 70% of time within therapeutic range had a 79% reduced risk of stroke compared to patients with  $\leq 30\%$  of time in range (adjusted relative rate of 0.21; 95% confidence interval 0.18–0.25). They also reported significantly lower mortality rates with at least 70% of time spent within therapeutic range<sup>47</sup>.

There is considerable variability in TTR within centres and across centres. Analysis of the data from the ARISTOTLE trial by Wallentin *et al.*, which randomised 18201 patients from 1034 centres and 39 countries reported substantial variation in INR control, with median TTR ranging from 49% to 78%. The variability in the time below therapeutic range ranged from 9% to 47%. Time above the therapeutic range (INR greater than 3.0) was more constant with a range from 5% to 15% across countries<sup>44</sup>. A regional variation in TTR was also demonstrated in the RE-LY study<sup>42</sup>.

There are various factors that affect the TTR and therefore the quality of anticoagulation. Apostolakis *et al.*, analysed data from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial and evaluated the following factors as having significant impact on TTR; female sex ( $p < .0001$ ), age less than 50 years ( $p < .0001$ ), age 50 to 60 years ( $p = .02$ ), ethnic minority status ( $p < .0001$ ), smoking ( $p = .03$ ), more than two co-morbidities ( $p < .0001$ ), and being treated with a beta-blocker ( $p = .02$ ), verapamil ( $p = .02$ ), or, inversely, with amiodarone ( $p = .05$ )<sup>31</sup>. Dlottet *et al.*, demonstrated in their study that the significant impact of age on TTR with

younger patients having poorer control and a higher frequency of testing. They also demonstrated an association with income, with patients living in higher median income regions having higher TTR<sup>48</sup>. Another factor that is associated with improved TTR is frequent INR monitoring<sup>38</sup>.

The TTR should be at least 60% in patients with AF to satisfy adequate anticoagulation. A TTR of less than 50% is considered bad anticoagulation and TTR of 70% or more is excellent.

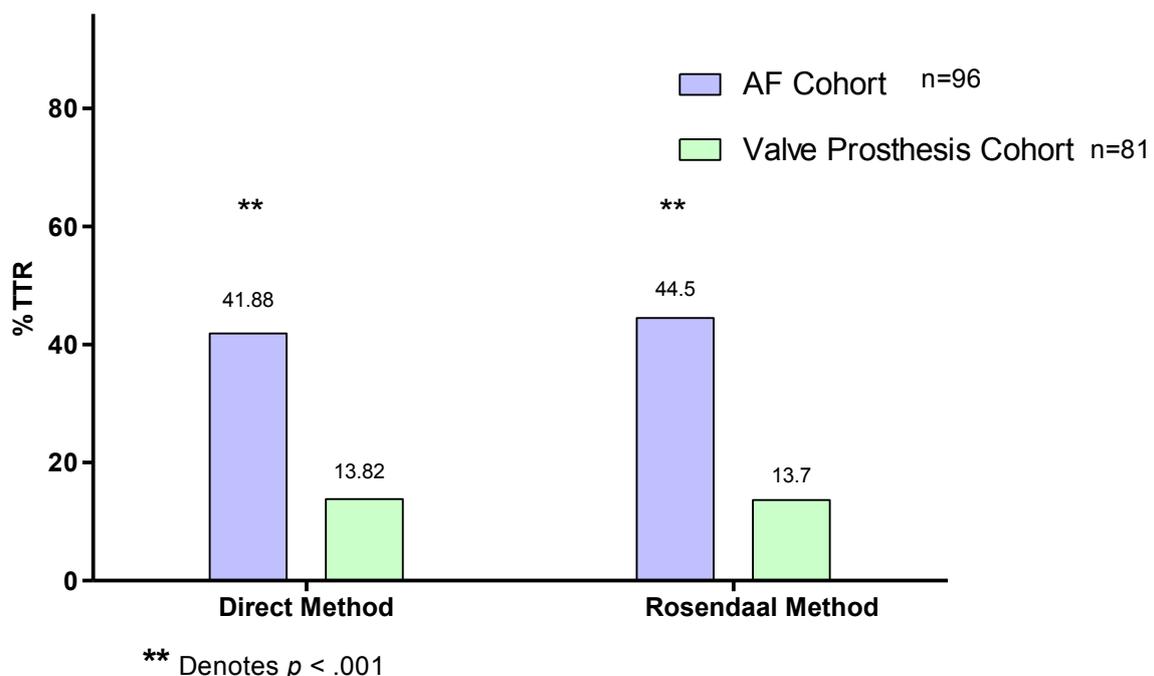
A correlation between treatment quality with warfarin as measured by TTR and serious complications has been shown. It is recommended that best benefit in patients with prosthetic heart valves is when the TTR is at least 83% but a TTR of at least 70% is likely sufficient to prevent valve thrombosis<sup>35</sup>.

Many reports evaluating the TTR have been as a result of clinical trials or in specialised anticoagulation clinics. We sought to determine an unbiased and real-world evaluation of TTR in a community setting in patients not attending a specialised anticoagulation clinic and without access to self-monitoring devices.

## 4.2. Results

Analysis of the mean TTR using the Direct method showed that patients in the AF cohort (M=41.9; SD=19.6) had a significantly higher percentage of TTR than those in the valve prosthesis cohort (M=13.8; SD=12.7),  $t(164) = 11.4, p < .001$  (Figure 3).

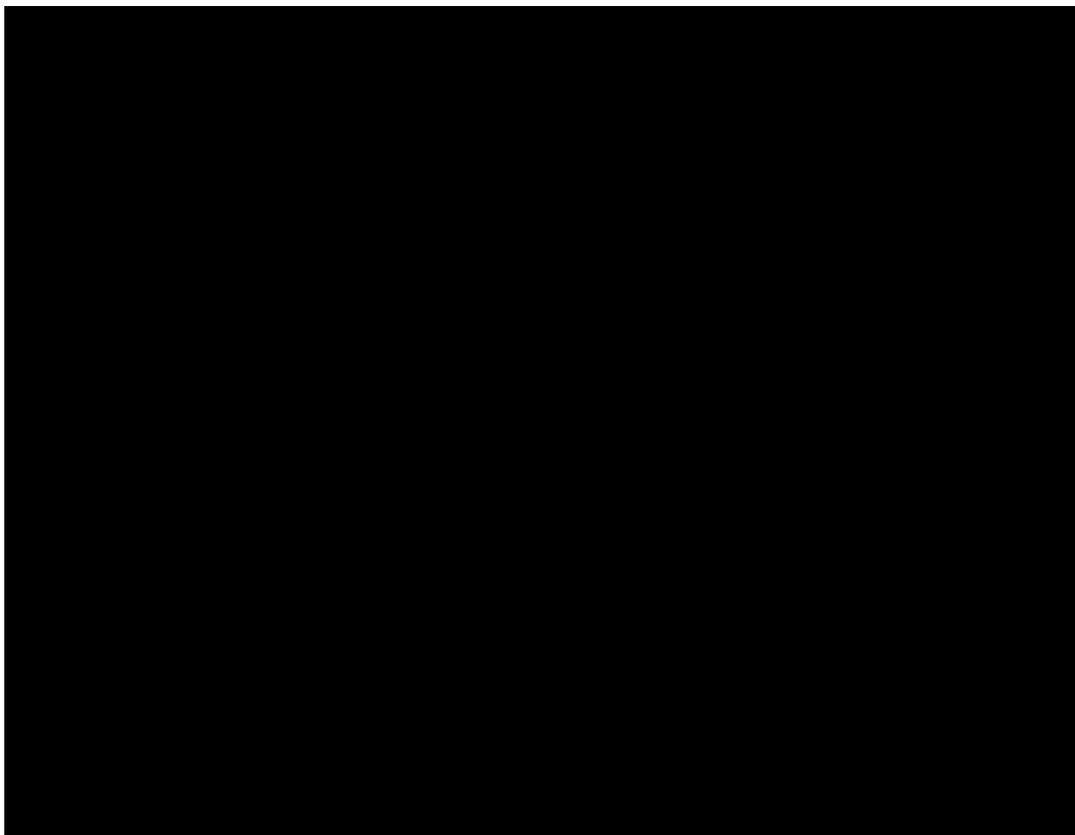
The TTR measured by the Rosendaal interpolation method also showed significantly higher TTR by patients in the AF cohort (M=44.5; SD=18.5) as compared to patients in the valve prosthesis cohort (M=13.7; SD=11.9),  $t(164) = 13.3, p < .001$  (Figure 3).



**Figure 3: Mean percentage of TTR for the AF cohort compared to the valve prosthesis cohort**

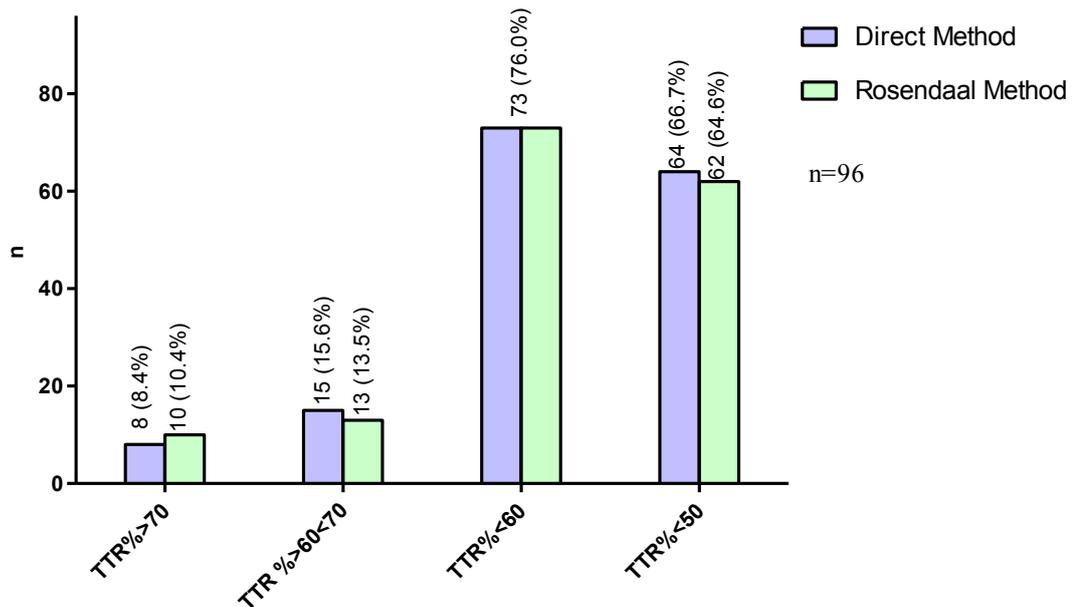
There was no difference in the comparisons of the means between the results from the Direct method and the Rosendaal method for the AF cohort ( $t(190) = -.948, p=.344$ ) or for the valve prosthesis cohort ( $t(160) = .058, p=.953$ ). A Pearson correlation was run between the Direct and Rosendaal methods of determining the TTR. There was a strong and highly significant positive correlation between the results of the two methods ( $r=.823, n=96, p<.001$ ).

We evaluated 1285 INR samples of patients with AF. The mean INR value was 2.70 (SD=1.369). Five hundred and forty-six (42.5%) INR values were within the therapeutic range, 367 (28.6%) INR values were below the therapeutic range and 372 (28.9%) INR values were above the therapeutic range (Figure 4).



***Figure 4: Histogram depicting INR values in patients with AF***

We divided patients from both cohorts into subsets according to the percentage of time in the therapeutic range. Of the 96 patients in the AF cohort, ten patients (10.4%) had INR values in the therapeutic range for more than 70% of the time and considered to have good anticoagulation, 73 (76.1%) patients were in therapeutic range for less than 60% of the time and were therefore, sub-optimally anticoagulated and at increased risk for thrombotic events. Sixty-two patients of the 73 patients who demonstrated suboptimal TTR (84.9% of this subset or 64.6% of the cohort) demonstrated a bad quality of anticoagulation (Figure 5).



**Figure 5: Distribution of patients in the AF cohort (n=96) according to percentage TTR more than 70%, below 60%, below 50% and between 60% and 70%**

We then evaluated for differences in characteristics between the different subgroups (Table 10). The age in years of the patients between the group with TTR more than 70% (M=62.6; SD=12.6) was not statistically significant from the group with TTR less than 60% (M=64.5; SD=10.9) [t (11) = -.463,  $p$ -.652] nor the group with TTR less than 50% (M=66.3; SD=10.0 [t (10.9) = -.882,  $p$ -.397].

Four (40%) of the ten patients with a TTR more than 70% were male. Associations in gender between the groups of patients with TTR more than 70% and those with TTR less than 60% and then less than 50% were also not significant ( $p$ - 1.00 and  $p$ -.429 respectively).

The mean days between tests for the group of patients with TTR more than 70% (M=33.1 days; SD=8.7) was not statistically significant when compared to the group of patients with TTR less than 60% (M=31.1 days; SD=6.8) [t (10.7) = .704,  $p$ -.496] nor for the group of patients with TTR less than 50% [t (10.7) = .829,  $p$ -.425].

Patients considered to have excellent anticoagulation had nine documented adverse events, seven of which, for a documented stroke (undefined) and two for haemorrhage or toxicity requiring admission which results in a 90% point prevalence as compared to the group of patients with TTR less than 60% who had 15 documented adverse events, eight of which were a documented stroke (undefined) and seven for documented haemorrhage or toxicity, which results in a point prevalence of 20.5 %. There is however no statistical significance between the group of patients with TTR >70% and those with TTR <60% for the condition of at least one documented event [Pearson's chi-square test,  $p$ -.490].

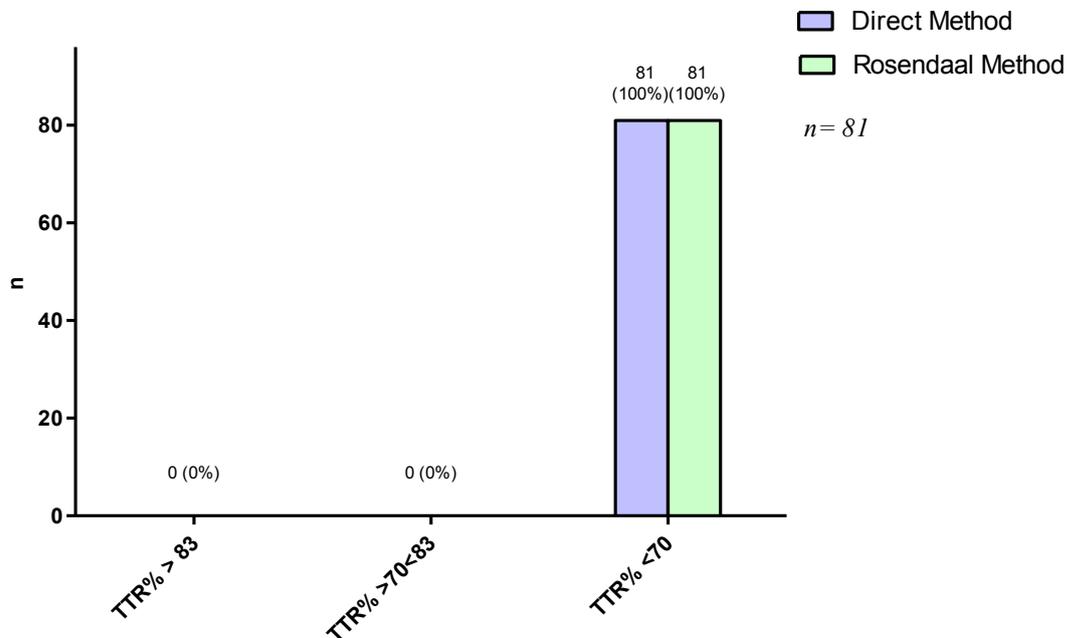
However, the results of Pearson chi-square test, when evaluating the prevalence of adverse events was statistically significantly fewer in patients with TTR > 70% than those with TTR < 50% ( $p$ -.038).

**Table 10: Characteristics of patients with AF (n=96) stratified as TTR by the Rosendaalmethod**

	TTR > 70%	TTR >60<70%	TTR <60 %	TTR <50%
n (%)	10 (10.4)	13 (13.5)	73 (76.1)	62 (64.6)
Male	4 (40)	3 (23.1)	26 (35.6)	22 (35.5)
Female	6 (60)	10 (76.9)	47 (64.4)	40 (64.5%)
Mean age (SD)	62.6	67.1	64.5	66.3
Age < 65 n (%)	4 (40)	5 (38.4)	36 (49.3)	26 (41.9)
Age 65 -<75 n (%)	5 (50)	4 (30.8)	25 (34.2)	24 (38.7)
Age >75 n (%)	1 (10)	4 (30.8)	12 (16.5)	12 (19.4)
Mean days between tests	33.1	29.1	31.1	30.7
Total adverse events (n=28)	9 (32.1%)*	4 (14.3%)	15 (53.6%)	15 (53.6)
Stroke (18 in total)	7 (38.9%)	3 (16.7%)	8 (44.4%)	8 (44.4)
Haemorrhage (10 in total)	2 (20.0%)	1 (10%)	7 (70%)	7 (70)
Time out of range				
Mean time below range	13.1	25.2	32.3	34.2
Mean time above range	14.8	13.3	32.9	33.6
Mean time with INR >4.00	1.5	2.9	11.3	12.9

\*p -.038 using Pearson chi-square test when compared to < 50% TTR subgroup

The mean TTR in 81 patients with prosthetic heart valves was less than 14 %. None of the patients with prosthetic heart valves in our study demonstrated satisfactory quality of anticoagulation and all patients did not achieve the level of 70% TTR (Figure 6).



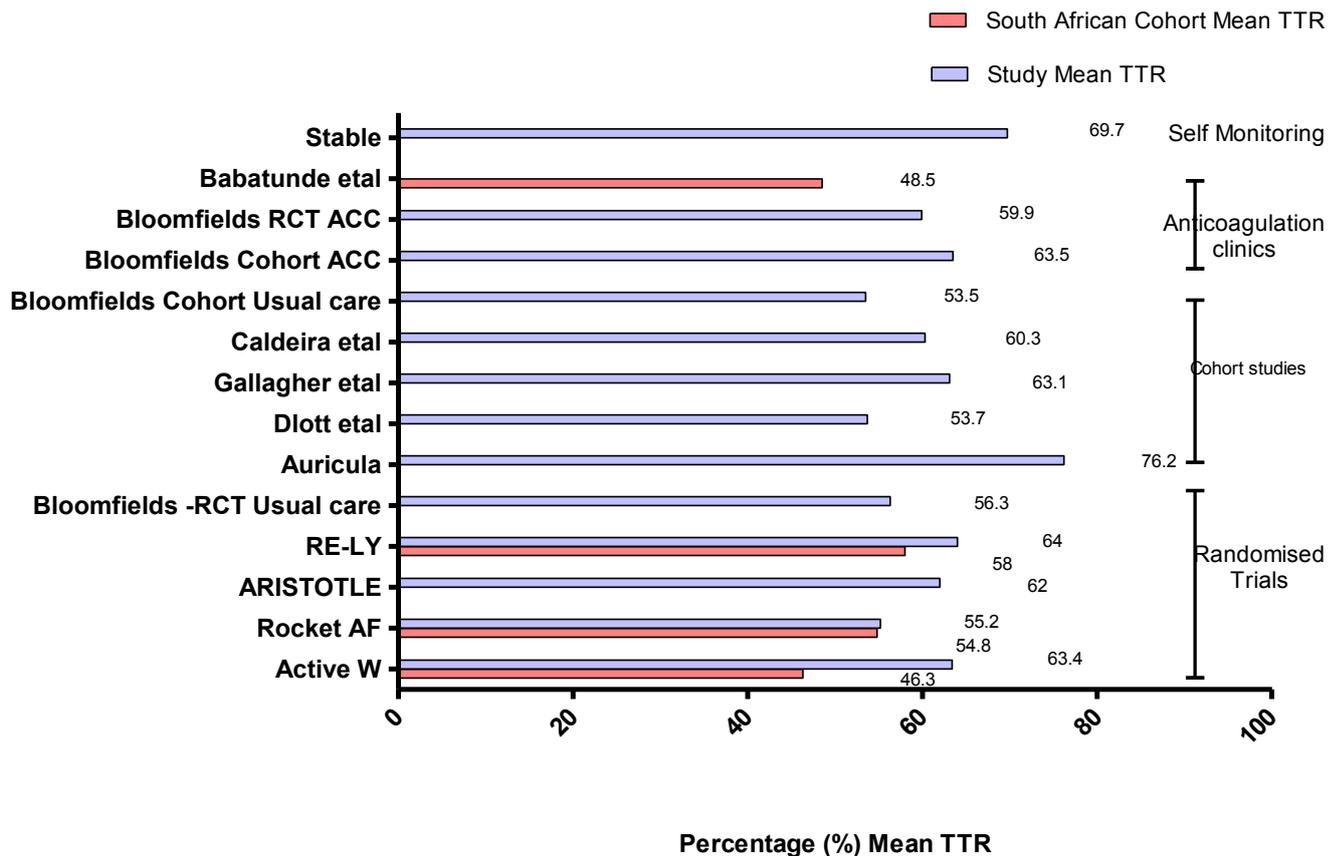
**Figure 6: Percentage of TTR-Valve prosthesis cohort distributed in percentage time >83%, between 70-83% and <70%**

### 4.3. Discussion

Our study demonstrated significant variation in TTR between the two different indications for anticoagulation. Patients with AF had a significantly higher TTR than those with mechanical prosthetic valves ( $p<.001$ ). AuriculA, a Swedish study, was one of a few studies that evaluated TTR across different indications. Patients with AF in that study demonstrated a mean TTR of 76.5% and those with mechanical valves showed a TTR of 79.9%. These findings are in contrast to the findings in our study although some study design differences exist; the participants from AuriculA were not exclusively managed out of specialised anticoagulation clinics and that study utilised only an INR range of 2 to 3<sup>49</sup>.

We found no statistical difference between the Direct method (fraction of INRs in range) and the Rosendaal method. Caldeira *et al.*, in a study of 377 patients that attended an anticoagulation clinic, compared the Rosendaal method to the tests ratio. Similar to the findings in our study, the Rosendaal method and the tests ratio correlated well (Rho Spearman 0.88,  $p<.001$ ), but the Bland-Altman plot evaluation showed a clinically relevant data dispersion [95% confidence interval (95% CI) -12.9 to 23.1] around a mean difference in TTR -5.1% using the tests ratio method. The tests ratio less than 60% had a sensitivity of 91.6%, specificity of 72.3%, positive predictive value of 72.2% and negative predictive value of 91.6%, for the diagnosis of patients inadequately anticoagulated (Rosendaal TTR <60%). Tests ratio underestimated TTR in 5% and was not considered equivalent to Rosendaal TTR due to the high variability between methods, however they concluded it may be a reasonable option to detect inadequate anticoagulation<sup>50</sup>. In the meta-analysis by Wan *et al.*, it was concluded that the fraction of INRs in range was a good proxy to the Rosendaal method and the two methods correlated well<sup>45</sup>. Schmitt performed a comparative evaluation of measures of TTR and demonstrated the fraction of INRs and the cross-section-of-files methods were similar although the linear interpolation method showed shorter TTR at the two, three and six month intervals<sup>29</sup>.

The mean TTR in our study was 44.5% and this varied substantially from the findings in other studies. Most other studies, albeit, under different conditions have demonstrated far superior mean TTR (Figure 7). Various studies have identified a regional variation in TTR<sup>44,46,48</sup>. In a South African study conducted in Cape Town which included analysis of participants from an anticoagulation clinic, the mean TTR was 48.5%. In the major studies that included South African participants, the mean TTR was comparable to findings of our study<sup>34,38,39,44,46-49,51</sup>. Overall, the TTR is poorer in African countries compared to the European and western regions. The difference is likely contributed by the burden of communicable diseases and over-extended health care budgets and challenging socio-economic conditions.



**Figure 7: Comparisons of TTR from different studies.**

The mean age between the subgroups of excellent, satisfactory, poor and bad anticoagulation were not statistically significant. Interestingly, however, the subgroup of patients with the highest TTR had the lowest mean age. This is inconsistent with the findings from Apostolakis *et al.*, and Diott *et al.*,<sup>31,48</sup>. Several studies have shown an association with improved TTR and more frequent testing<sup>37,38</sup>, however, in our study, although not statistically significant, patients with the best TTR had the least frequent testing interval. In a community-based evaluation of TTR by Rose *et al.*, it was demonstrated that longer intervals had significantly better TTR and less INR variability ( $p < .001$ )<sup>9</sup>. The most plausible reason for this finding in our retrospective study is likely due to better controlled patients being evaluated less intensely than the poorer controlled patients. In line with findings of the SPORTIF III trial<sup>36</sup>, patients in the poorest tier of anticoagulation quality as measured by TTR sustained the highest percentage of adverse events for both stroke and haemorrhage.

Overall, patients in our study population have demonstrated modest anticoagulation control compared to studies conducted in Europe and the United States of America. Nonetheless, our findings are comparable to other South African and African studies, at least with regard to patients with AF.

The patients with prosthetic heart valves demonstrated remarkably poor results. All patients from this subgroup were categorised as suboptimal anticoagulation and therefore predisposed to both thrombotic and haemorrhagic events. Patients in this category were on average younger, have higher target INR values and had a higher female representation, all of which are validated factors associated with poor quality of anticoagulation.

## CHAPTER 5

### COMPARISONS OF TTR AND TIME OUT OF RANGE BETWEEN PATIENTS WITH ATRIAL FIBRILLATION AND PROSTHETIC HEART VALVES

#### 5.1. Introduction

There are various indications for anticoagulation (Table 1). Two notable conditions that stress the relevance of quality of anticoagulation as measured by the TTR are in AF and in the presence of prosthetic mechanical heart valves. Both these conditions require long-term anticoagulation and the TTR is vital to achieving adequate anticoagulation as well as imposing the lowest risk of complications. AF is the more studied disease entity with regard to anticoagulation, more so since the introduction of non-VKA drugs. However, the majority of patients with AF are still treated with VKAs. Presently warfarin is the only drug recommended for the management of patients with prosthetic heart valves.

Apostolakis *et al.*, noted that influential factors on TTR included female sex, younger age (less than 60 years old), medical history, interacting drugs, tobacco use and race<sup>31</sup>. The target INR range has also been demonstrated as a factor in contributing to anticoagulation quality<sup>9</sup>. The differing patient characteristics with regard to these established factors between patients with AF and mechanical heart valve prostheses implies a varying degree of quality of anticoagulation. Fewer studies have evaluated the quality of anticoagulation as a comparison between the two conditions.

Our patient population included patients with both conditions and we evaluated for differences in anticoagulation quality between the two indications.

#### 5.2. Results

The mean percentage time in the AF cohort differed significantly from the mean percentage time in the valve prosthesis cohort for all conditions (Table 11). Patients in the AF cohort (M=29.19, SD=19.89) spent significantly less time below range than the patients in the valve prosthesis cohort (M=67.69, SD=20.02). [t (175) = -12.785,  $p < .001$ ] and significantly more time above range (M=28.38, SD=17.21) than the patients in the valve prosthesis cohort (M=18.61, SD=13.88). [t (174.661) = 4.177,  $p < .001$ ].

The mean percentage time with an INR value of greater than 4.0 was significantly lower in the AF cohort (M=9.11, SD=11.04) than the valve prosthesis cohort (M=13.34, SD=10.91). [t (175) = -2.548  $p = .012$ ]

The mean percentage TTR using both the Direct method and Rosendaal method was significantly higher in the AF cohort (M=41.88, SD=19.64 and M=44.49, SD=18.51) than the valve prosthesis cohort (M=13.81, SD=12.76 and M=13.70, SD=11.95). [t (164.8) = 11.431,  $p < .001$  and t (164.3) = 13.3,  $p < .001$  respectively].

**Table 11: Distribution of mean percentage time in range and out of range for the subgroups of AF (n=96) and valve prosthesis (n=81).**

	AF subgroup (n=96)	Valve prosthesis subgroup (n=81)
Mean Age in years	64.7	41.8
Female sex, n (%)	63 (65.6)	59 (72.8)
Time Below range (%)	29.2†	67.7
Time Above range (%)	28.4†	18.6
Time INR >4.00 (%)	9.1*	13.3
TTR- Direct method (%)	41.9†	13.8
TTR-Rosendaal method (%)	44.5†	13.7

†  $p < .001$  when compared to valve prosthesis subgroup using independent samples t-test.

\*  $p < .05$  when compared to valve prosthesis subgroup using independent samples t-test.

### 5.3. Discussion

Our primary objective was to evaluate the quality of anticoagulation by assessing the TTR. Overall, the sample population in our study showed remarkably suboptimal TTR with patients as a whole spending only approximately 30% of the time in therapeutic range. The significantly poorer TTR in patients with a valve prosthesis compared to those with AF may be attributed to higher target INR ranges in these patients and therefore more challenging to the clinician to maintain patients in range. In keeping with the findings from Apostolakis *et al.*, the mean age of patients with valve prosthesis was more than 20 years less than that of patients with AF and the mean age was less than 50 years old which conferred a stronger association ( $p < .001$ ) with poor TTR than patients aged 50-60 years ( $p = .02$ )<sup>31</sup>. Furthermore, the valve prosthesis cohort had a larger percentage of females than the AF subgroup, which is also a significant factor associated with poorer TTR.

The most time spent out of range by patients in both cohorts and therefore in the overall sample population was below range. Patients with valve prosthesis spent a significant percentage of time below range than patients with AF; however patients with AF spent more time above range than those with prosthetic heart valves. The most likely influential factor is the target INR range, where patients with valve prosthesis have higher targeted INR ranges and therefore are more likely to fall short of range than those with AF. Furthermore, there is likely an element of caution applied by clinicians when prescribing warfarin for patients with high target INR ranges so as not to increase the risk of bleeding. The higher target INR ranges in patients with valve prosthesis are likely why these patients in our study spent significantly more time with INR values in excess of 4.00 and are therefore at higher risk of haemorrhagic complications.

The disparity in TTR between the two indications for anticoagulation demonstrated in our study is inconsistent with findings from the study conducted in Sweden by Wieloch *et al.*,<sup>49</sup>. They analysed INR

values from 18 391 patients in 67 different centres and data was evaluated from Auricula (A Swedish national quality registry of patients with atrial fibrillation). In their study, anticoagulation measured as TTR was measured across all indications. AF represented the majority of the patients (64%) and heart valve dysfunction accounted for 13%. The overall mean percentage TTR for the whole population was 76.2% with AF subgroup achieving 76.5% mean TTR and the valve disease cohort specifically the subgroup with mechanical valves demonstrated a mean TTR of 79.9%. These findings are remarkably different from that of our study. However, there are some noteworthy differences between the two studies. In Auricula, patients in the AF subgroup may have included patients with valvular AF. Auricula only included patients with a low target INR of 2.0 to 3.0 and did not include patients managed exclusively out of specialised anticoagulation setting. In addition, the difference in the mean age between the AF subgroup and the mechanical valve subgroup was less than 10 years (73 years and 65 years respectively) and their study had less female representation. Regardless, these findings are impressive and demonstrate that excellent TTR can be achieved.

## CHAPTER 6

### FACTORS ASSOCIATED WITH TIME IN RANGE AND TIME OUT OF RANGE

#### 6.1. Gender association with time in range and time out of range

According to the global burden of AF study<sup>3</sup>, the estimated incidence rates of AF in 2010 were higher in men than in women. This study systematically reviewed population-based studies of AF published from 1980 to 2010 from the 21 Global Burden of Disease regions to estimate global or regional prevalence, incidence, and morbidity and mortality related to AF. The estimated number of individuals with AF globally in 2010 was 33.5 million (20.9 million men [95% uncertainty interval (UI), 19.5–22.2 million] and 12.6 million women [95% UI, 12.0–13.7 million]). Burden associated with AF, measured as disability-adjusted life-years, increased by 18.8% (95% UI, 15.8–19.3) in men and 18.9% (95% UI, 15.8–23.5) in women from 1990 to 2010. The overwhelming majority of studies of patients with AF are in line with a male predominance. The Active-W (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) Trial<sup>34</sup> which evaluated patients with AF in 526 centres and 15 countries had males accounting for more than 67% of their cohort. Similarly, in the ROCKET-AF study (Rivaroxaban Once daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation)<sup>46</sup> which studied 6983 patients taking warfarin for AF across 45 countries, a 61% male predominance was observed.

In AF, females confer higher risk for stroke than male patients. This is validated by the CHA<sub>2</sub>DS<sub>2</sub>-Vascscore (Table 2) where female gender accounts one point in the risk assessment tool.

Females were identified as a significant factor associated with poor quality of anticoagulation (as evaluated by the TTR) in patients with AF. A study evaluating factors affecting quality of anticoagulation control among patients with AF on warfarin (The SAME-TT<sub>2</sub>R<sub>2</sub> Score)<sup>31</sup> which evaluated patients from the AFFIRM trial<sup>52</sup>, found female gender as a significant factor ( $p < .0001$ ) associated with poor quality of anticoagulation.

There is little data on gender association with quality of anticoagulation in patients with prosthetic heart valves.

In our study, we evaluated for a gender association with quality of anticoagulation.

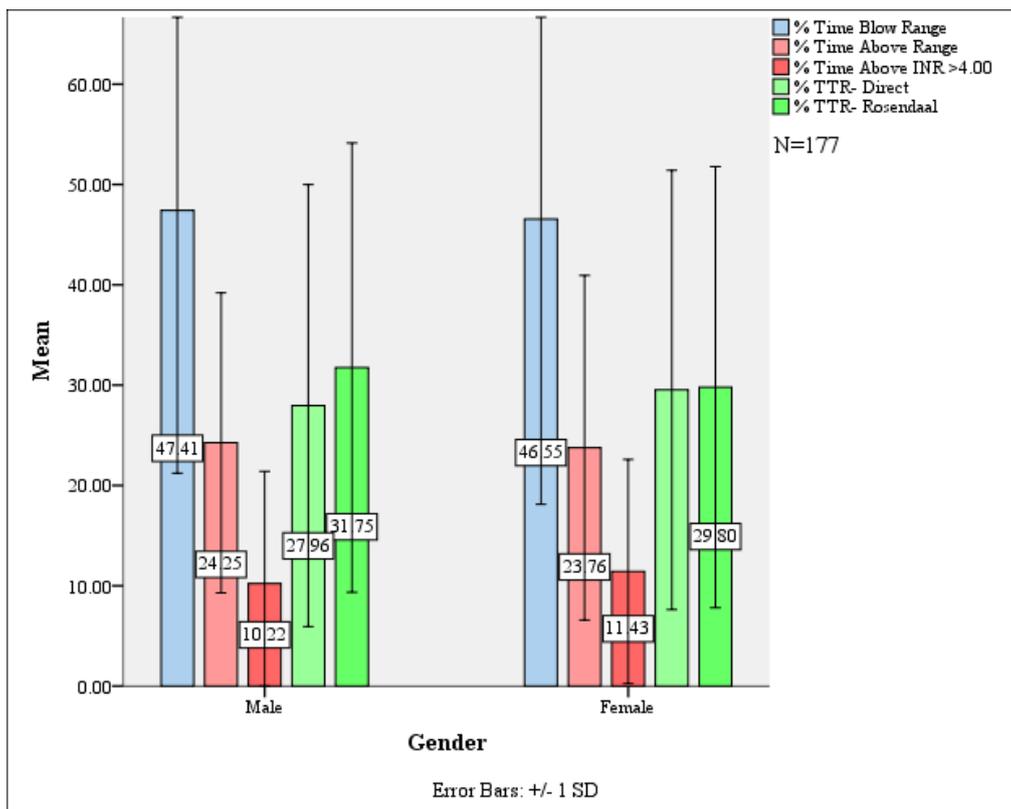
##### 6.1.1 Results

In our study population, of the 177 patients being anticoagulated with warfarin for either non-valvular AF or prosthetic heart valves, the majority were females ( $n = 122, 68.9\%$ ). In the AF subgroup, females accounted for 63 (65.6%) of the 96 patients and in the subgroup of patients with prosthetic heart valves, females accounted for 59 (72.8%) of the 81 patients (Table 12).

**Table 12: Distribution of anticoagulated patients at Mahatma Gandhi Memorial Hospital by gender.**

	Male, n (%)	Female, n (%)
Sample population (N=177)	55 (31.1%)	122 (68.9%)
AF cohort (n=96)	33 (34.4%)	63 (65.6%)
Valve prosthesis (n=81)	22 (27.2%)	59 (72.8%)

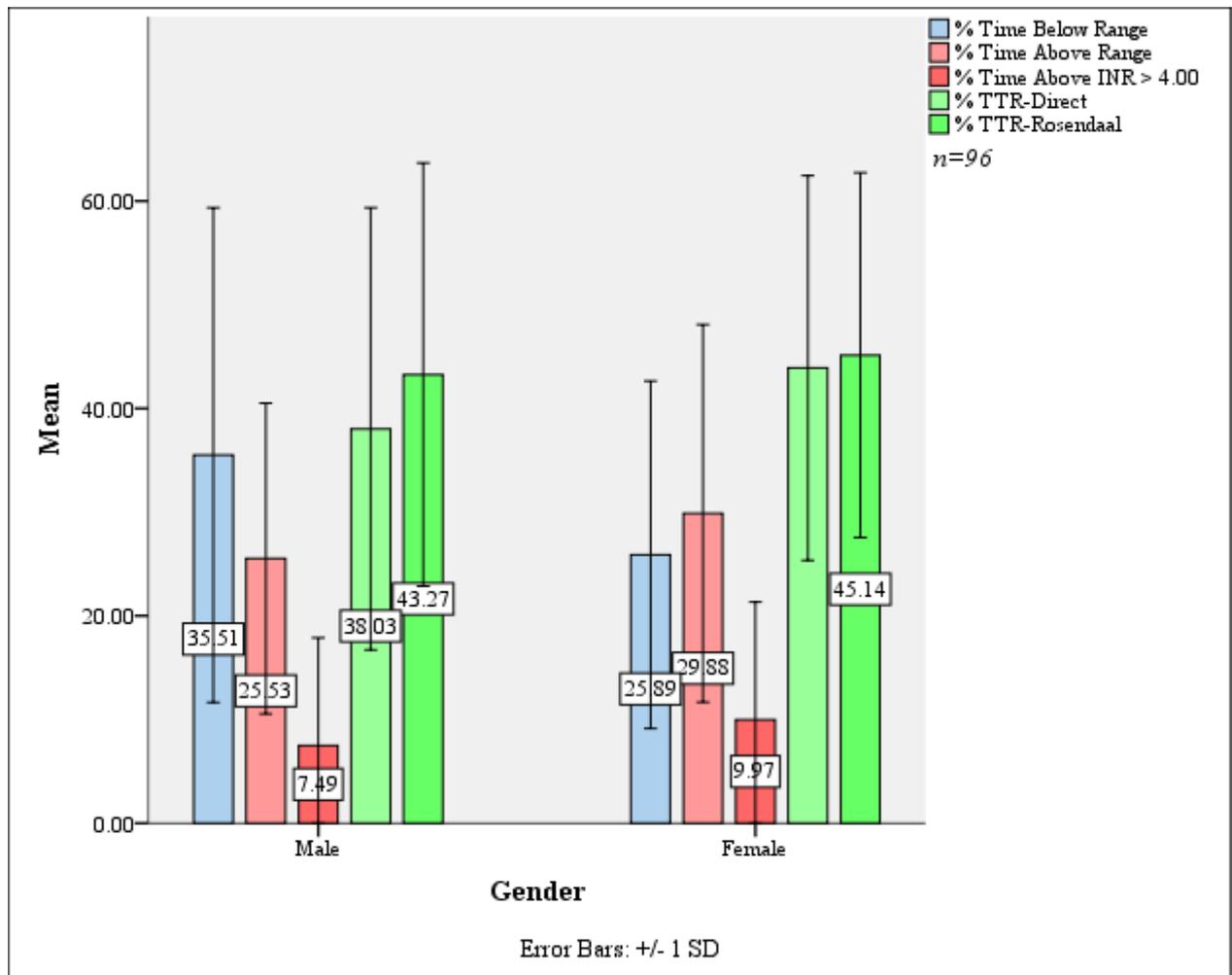
Comparisons between male patients (n=55) and female patients (n=122) in the sample population (Figure 8) showed no significant difference in the mean percentage time below range (M= 47.4; SD=26.1; M=46.5, SD=28.4) [t (175) =.191, p-.849], mean percentage time above range (M=24.2; SD=14.9; M=23.7; SD=17.1) [t (175) =.175, p-.854], mean percentage time with an INR value greater than 4.00 (M=10.2; SD=11.1; M=11.4; SD=11.1) [t (175) = -.665, p-.507], mean percentage TTR using the Direct method (M=27.9; SD=22.0; M=29.5; SD=21.8) [t (175) = -.439, p-.661] and mean percentage TTR using the Rosendaal method (M=31.7; SD=22.3; M=29.8; SD=21.9) [t (175) =.542, p-.542] respectively.



**Figure 8: Distribution by gender within the sample population (N=177) for mean percentage time in range and out of range.**

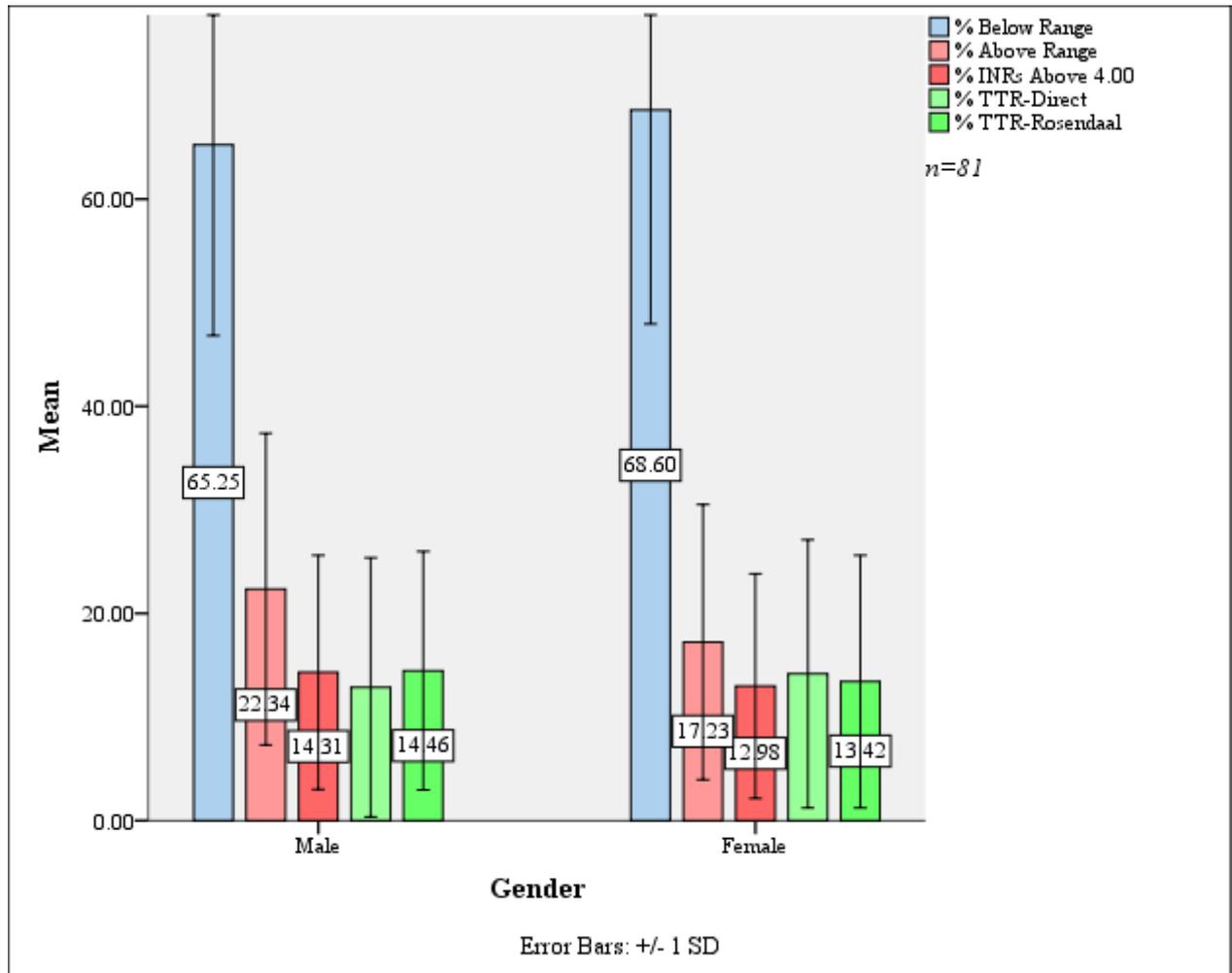
Comparison of means of male patients (n=33) and female patients (n=63) in the AF cohort(Figure 9) showed no significant difference in the mean percentage timeabove range(M=25.5; SD=14.9; M=29.8; SD=18.2) [t(94) = -1.177, p-.242], mean percentage time with anINR value greater than 4.00(M=7.5; SD=10.3; M=9.9; SD=11.3) [t (94) = -1.045, p-.299], mean percentage TTR using the Direct method(M=38.0; SD=21.3; M=43.9; SD=18.5) [t (94) = -1.4,p-.165] and the mean percentage TTR determined by the Rosendaal method (M=43.2; SD=20.4; M=45.1; SD=17.5) [t (94) = -.469,p-.640] respectively.

However, male patients in the AF cohort (M=35.5; SD=23.8) spent significantly more time below range than the female patients in the AF cohort (M=25.5; SD=16.7) [t (94) = 2.064, p-.044].



**Figure 9: Distribution by gender within the AF cohort(n=96) for mean percentage time in range and out of range.**

The comparison of male patients (n= 22) and female patients (n= 59)in the valve prosthesis cohort (Figure 10)showed no significant difference in the mean percentage time below range(M= 65.2; SD=18.4; M=68.6, SD=20.6) [t (79) = -.668, p-.506], mean percentage time above range(M=22.3; SD=15.0; M=17.2; SD=13.3) [t(79) = 1.486,p-.141], mean percentage time with an INR value greater than 4.00 (M=14.3; SD=11.3; M=12.9; SD=10.8) [t (79) =.485,p-.629], mean percentage TTR derived by the Direct method (M=12.8; SD=12.5; M=14.1; SD=12.9) [t (79) =.637, p-.684] and the mean percentage TTR determined by the Rosendaal method (M=14.4; SD=11.5; M=13.4; SD=12.2)[t (79) =.348,p-.729] respectively.



**Figure 10: Distribution by gender within the valve prosthesis cohort (n=81) for mean percentage time in range and out of range.**

### 6.1.2. Discussion

Unlike most other studies of patients on oral anticoagulation, the distribution by gender in our sample population is glaringly different as females represent the majority of this study population. Many of the studies conducted globally have constituted patients largely from out of South Africa. In the ROCKET-AF trial<sup>46</sup>, only 124(2%) of the 6983 patients were from South Africa; 98 patients of the 6706 patients represented South Africa in the ACTIVE-W study<sup>34</sup>. The prevalence and epidemiology of AF in Africa, particularly South Africa is largely understudied as compared to other regions and this most likely accounts for the disparity in gender association. One study in Cape Town, South Africa, which evaluated warfarin utilisation and monitoring records in two hospitals with different patient groups<sup>53</sup>, conducted a chart audit on 111 patients using warfarin. The findings in this local study are similar to that of ours with regard to gender frequency with the majority of the patients being female (62.5% and 80.6% in the two centres respectively). Another local study of patients attending an anticoagulation clinic in Cape Town, evaluated 136 patients on warfarin, of which the majority(56.6%, n=77) were female. One possible reason for the gender distribution disparity in South African populations studied may be explained in the general attendance patterns for medical care, where males have been well shown as having less frequent attendance to medical screening and treatment as compared to females in studies involving a number of other chronic diseases.

Overall, patients in our study population (N=177), had no statistically significant gender bias with regard to time in range and time out of range. The separate cohort of patients being anticoagulated for prosthetic heart valves (n=81) also did not reveal significant differences between males and females. In the AF subgroup (n=96), however, we found male patients spent significantly more time under – anticoagulated than female patients and less TTR than female patients, albeit with no significant difference in TTR. These findings are not in line with the findings of other global studies. In the study by Apostolakis *et al.*, female gender was strongly associated ( $p < .001$ ) with poor anticoagulation<sup>31</sup>. Dlott *et al.*, who identified 138,319 individuals with AF, found females had lower TTR than males (-1.3%, 95% CI: -1.5% to -1.0%)<sup>48</sup>. Similarly Rose *et al.*, in their US study, enrolled 3396 patients from 101 community-based practices in 38 states, found a trend of poorer anticoagulation quality in females. In their study, the group with excellent INR control had the lowest proportion of females (37.9%), followed by the good control group(42.6%), with the highest proportion of females in the poor control group (46.5%;  $p < .001$  for trend)<sup>9</sup>.

The reason for this disparity, in our clinical setting could be explained by the overall socio-economic status of the region, where usually, males are sole bread winners and as a result have a tendency to follow-up less frequently and demonstrate poorer adherence to treatment due to commitment to vocational duties. The implications of these findings in accordance with global study findings suggest that in our region, both males and females have equally high risk for poor anticoagulation when treated for AF.

## 6.2. Age association with time in range and time out of range

The prevalence of AF increases with age. The Global Burden of Disease study in 2010 evaluated the epidemiology of AF by analysing population-based studies of AF published from 1980 to 2010 from the 21 Global Burden of Disease regions. In this study higher rates of AF in older age groups were observed. Men aged 75 to 79 years had double the prevalence rate compared with men who were 65 to 69 years of age and a greater than 5-fold higher prevalence compared with men who were 55 to 59 years of age<sup>3</sup>. Data from the Framingham study<sup>54</sup> and a study by Psaty *et al.*, which evaluated 5201 patients who were at least 65 years old, found the onset of AF to be strongly associated with age. For men who were 65 to 74 and 75 to 84 years old, the incidences were 17.6 and 42.7, respectively, and for women, 10.1 and 21.6 events per 1000 person-years<sup>55</sup>. A cross-sectional study by Go, A.S *et al.*, evaluated 17974 patients with AF and found that prevalence increased from 0.1% among adults younger than 55 years old to 9.0% in persons aged 80 years or older<sup>56</sup>.

An older age is a well validated risk factor for stroke in patients with non-valvular AF. The CHA<sub>2</sub>DS<sub>2</sub>-Vasc scoring tool for risk of stroke uses an age of 65 years or older as a risk predictor with patients 75 years or older inferring even higher risk (Table 2). The Framingham study found that for persons aged 80-89 years, AF was the sole cardiovascular condition to exert an independent effect on stroke incidence ( $p < .001$ ). The study found that the attributable risk of stroke for all cardiovascular contributors decreased with age except for AF, for which the attributable risk increased significantly ( $p < .01$ ), rising from 1.5% for those aged 50-59 years to 23.5% for those aged 80-89 years<sup>8</sup>.

In addition to older age being a risk for AF itself, as well as conferring increased risk for stroke in AF, age has been found to be a factor in affecting the quality of anticoagulation. Unlike the risk of AF or that of stroke, a younger age is associated with a negative quality of anticoagulation.

Apostolakis *et al.*,<sup>31</sup> evaluated clinical factors associated with TTR in patients from the cohort from the AFFIRM trial which conducted a randomised, multicenter comparison of rate versus rhythm treatment strategies in 4060 patients with atrial fibrillation and a high risk of stroke or death. This study showed a negative TTR association with younger patients :age less than 50 years old ( $p < .0001$ ), age 50 to 60 years old ( $p < .02$ ) and included an age less than 60 years old as a significant factor associated with poor TTR or quality of anticoagulation in patients treated for AF<sup>52</sup>.

Rheumatic heart disease as a result of recurrent rheumatic fever is still prevalent in South Africa and other developing countries and accounts for the majority of patients requiring valve replacement surgery as compared to developed regions where age associated and degenerative changes is the common aetiology. A reasonable proportion of patients being anticoagulated for prosthetic heart valves in South Africa are therefore much younger than patients being anticoagulated for AF. There is little data relating to the quality of anticoagulation across different age categories in patients being anticoagulated for prosthetic heart valves.

We evaluated the patients in our study population and the subgroups of AF and valve prosthesis for an association with time in range as determined by the TTR and the time out of range, which was further analysed for time below range, time above range and time with INR greater than 4.00 with age.

### 6.2.1. Results

The mean age of our study population was 54.2 years (SD=17.6). The mean age in the AF sub-cohort (64.7 years, SD=11.3) was higher than in the valve prosthesis cohort (M=41.83 years, SD=15.7). In the AF subgroup, 53.1% (n=51) of the patients were 65 years or older, of which 17 (17.7%) were aged at least 75 years old and therefore predicted higher stroke risk. In the subgroup of patients with prosthetic heart valves, the majority of patients were less than 60 years old (67 patients and 82.7%) (Table 9).

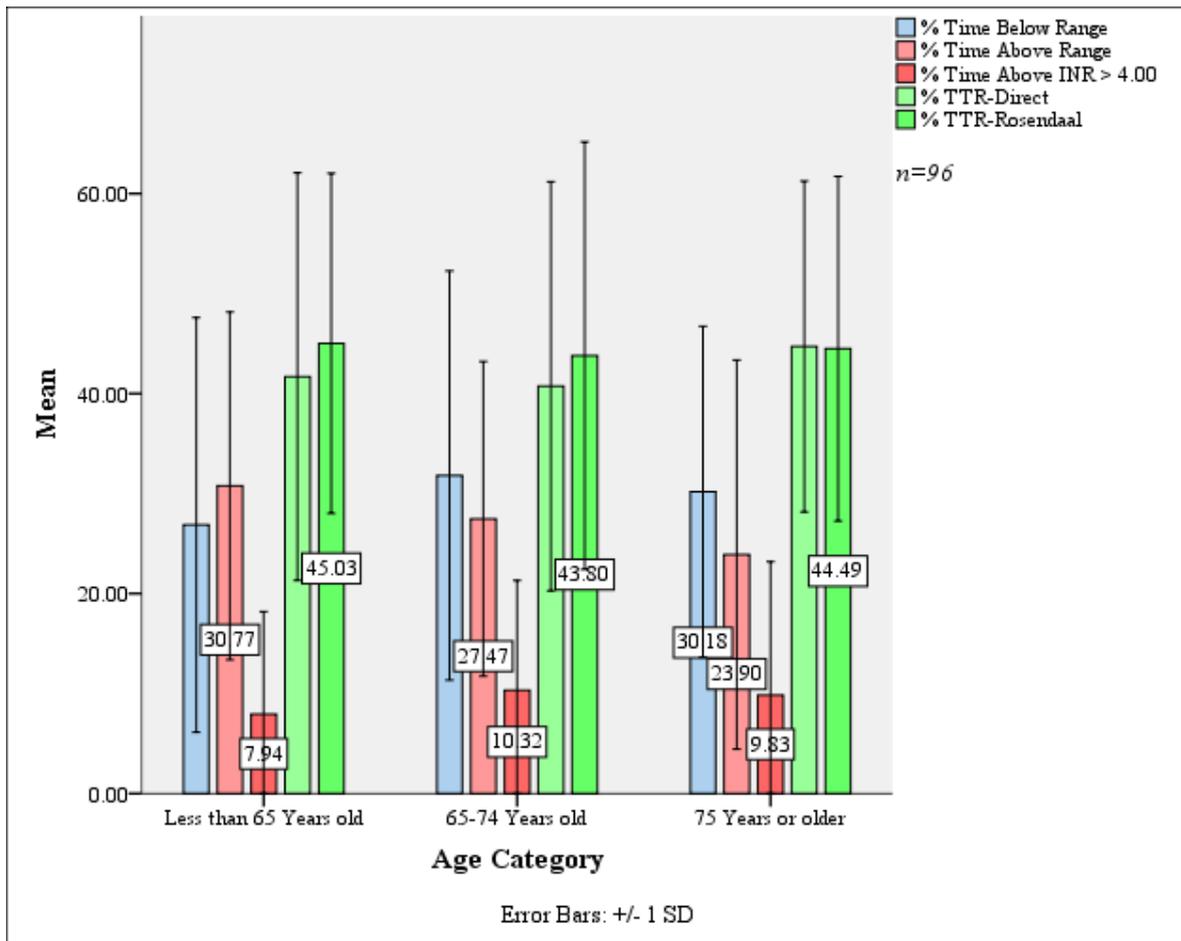
In the AF subgroup of patients (Figure 11), the mean percentage time below range was highest for patients within the 65 years to less than 75 years old age group (M=31.8; SD=20.5) as compared to patients who were 75 years or older (M=30.2; SD=16.5) and patients who were less than 65 years old (M=26.8; SD=20.7) (Figure 11). These differences were however not statistically significant within the three groups [F (2, 93) = .616, *p*-.542].

Patients less than 65 years old spent the most time above range (M=30.7, SD=17.4) compared to the 65 to less than 75 years old group (M= 27.5; SD=15.7) and the 75 years or older group (M=23.9; SD=19.4). The difference in means was not significant [F (2, 93) = 1.056, *p*-.352].

The 65years old to less than 75 years old group had the highest mean time with an INR value in excess of 4.00 (M=10.3; SD=10.9) compared to the 75 years or older group (M=9.8; SD=13.4) and the less than 65 years old group (M=7.9; SD=10.2). Analysis by one way ANOVA showed that the difference was not significant [F (2, 93) = .487, *p*-.616].

The age group with the highest mean percentage TTR using the Direct method was the 75 years or older group (M=44.7; SD=16.5) compared to the less than 65 years old group (M=41.7; SD=20.4) and the 65 to less than 75 years old group (M=40.7; SD=20.4). The difference was not statistically significant [F (2, 93) = .232, *p*-.794].

On analysis of the TTR using the Rosendaal method, the less than 65 years old group had the highest mean TTR (M=45.0; SD=16.9) compared to the 75 years or older group (M=44.5; SD=17.2) and the 65 to less than 75 years old group (M=43.8; SD=21.3), however the difference between the age groups was not of statistical significance [F (2, 93) = .042, *p*-.959].

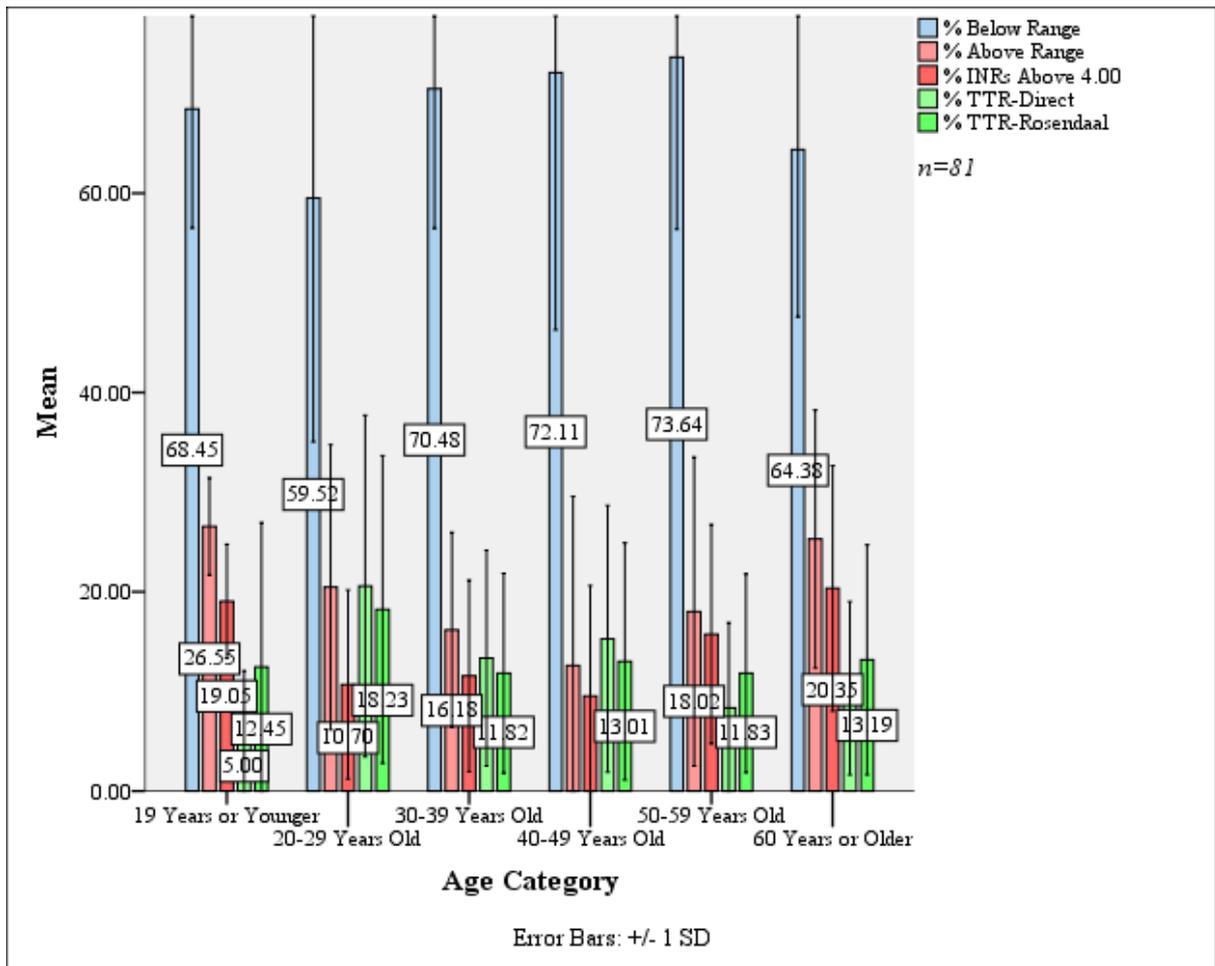


**Figure 11: Distribution by age within the AF cohort (n=96) for mean percentage time in range and out of range.**

Overall, patients in the valve prosthesis cohort (Figure 12) spent the majority percent time below range, however the differences between the age groups was not statistically significant [F (5, 75) = 1.115,  $p$  -.360].

There was no statistically significance difference in means between the age groups for the condition of mean percentage time above range and time with an INR value greater than 4.00. [F (5, 75) = 1.553,  $p$  -.184] and [F (5, 75) = 2.199,  $p$  -.063] respectively.

Similarly, TTR using both the Direct and Rosendaal methods was not significant between the different age groups. [F (5, 75) = 2.013,  $p$  -.086] and [F (5, 75) = .686,  $p$  -.636] respectively.



**Figure 12: Distribution by age within the valve prosthesis cohort for mean percentage time in range and out of range.**

### 6.2.2. Discussion

Our primary objective was to evaluate the TTR and overall, patients in both cohorts i.e. AF and valve prosthesis both demonstrated low mean percentage TTR across all age groups. Patients who were 75 years and older in the AF cohort, showed the best mean percentage TTR using the Direct method, however with analysis by the Rosendaal method, the youngest age category i.e. patients less than 65 years old had the highest mean percentage TTR. This difference was not statistically significant. The findings in our study are different from Dlottet *al.*, who studied anticoagulation control in 138 319 individuals and reported a significantly ( $p < .001$ ) better mean TTR in patients 75 years or older (53.9%) than those who were 45 years or younger (45.5%). However, the study by Dlottet *al.*, reported a mean age of 74 years old and included patients who were being monitored for less than six months<sup>48</sup>. Another study that reported better TTR with older patients was the STABLE study that evaluated quality of anticoagulation in 29457 patients who performed home monitoring. They found that patients aged 65 to less than 75 years old (71.5%) had higher TTR than the younger population of 46 to 64 years (67.0%). Patients who were 75 years or older also achieved relatively high TTR (75-79 years: 70.8%, 80-84 years: 68.9%).<sup>38</sup>

In our study, the AF cohort demonstrated no statistically significant difference age categories and is in line with the findings of Rose *et al.*, who studied 3396 patients across 101 community practices and found similar mean ages for patients with TTR less than 65%, TTR from 65 to 75% and TTR better than 75%<sup>9</sup>. Similarly, Gallagher *et al.*, in a study of 27,458 warfarin-treated patients reported no substantial difference in TTR by age<sup>47</sup>.

We note with concern, however, that patients with higher bleeding risk (patients older than 65 years old) in accordance with the HASBLED predictor of bleeding (Table 5) in the AF cohort demonstrated the most time with an INR value greater than 4.00 which confers an added bleeding risk. This may be attributed to altered pharmacodynamics and altered enzymatic activity in the elderly and possibly due to concomitant drug interactions that the elderly are more likely to be taking. These details were beyond the scope of this study, however, and further evaluation needs to be undertaken.

Our study of patients in the valve prosthesis cohort, demonstrated poor TTR throughout the different age categories and for all conditions studied, the mean percentage time was comparable across the age groups with no significant differences for both TTR and time out of range.

### **6.3. Association of frequency of INR testing with time in range and time out of range**

There is substantial evidence suggesting more frequent INR testing is associated with improved quality of anticoagulation and reduced risk of adverse events. The Home INR Study (THINRS), which evaluated patients being anticoagulated for both AF and prosthetic heart valves found improved TTR in patients tested more frequently<sup>37</sup>. Similarly, the STABLE trial which was a retrospective analysis of 29457 patients with multiple indications for warfarin therapy evaluated patients who were tested more frequently to have a higher percentage TTR<sup>38</sup>. The evidence that more frequent INR monitoring translates to more effective control through dose adjustment is well documented, however, very frequent testing is not feasible in patients who do not have point-of-care devices and rely on clinic or hospital visits. Generally, most clinicians evaluate INR levels at least every 28 days, and this is largely based on expert opinion and clinician experience. However, the study by Rose *et al.*, found that longer INR monitoring intervals were associated with improved INR control<sup>9</sup> and this was in line with studies in England where TTR in excess of 65% with testing frequency as few as 12 weeks<sup>57</sup>. They therefore concluded that a variable follow-up period based on recent INR results should replace fixed testing periods.

In our patient population, we evaluated the impact of frequency of INR testing (if any) on TTR and time out of range (sub-categorised as time below range, time above range and time with an INR level greater than 4.00).

#### **6.3.1. Results**

In the entire cohort of patients (N=177), the mean number of days between INR testing was 33.3 days (SD=12.0). The majority of patients (42.4%, n=75) had INR testing from 28 to 32 days apart. More than one-third (34.5%, n=65) of the patients studied were tested more than 32 days apart and 23.2% (n=41) of the patients had INR monitoring less than 28 days apart (Table 9).

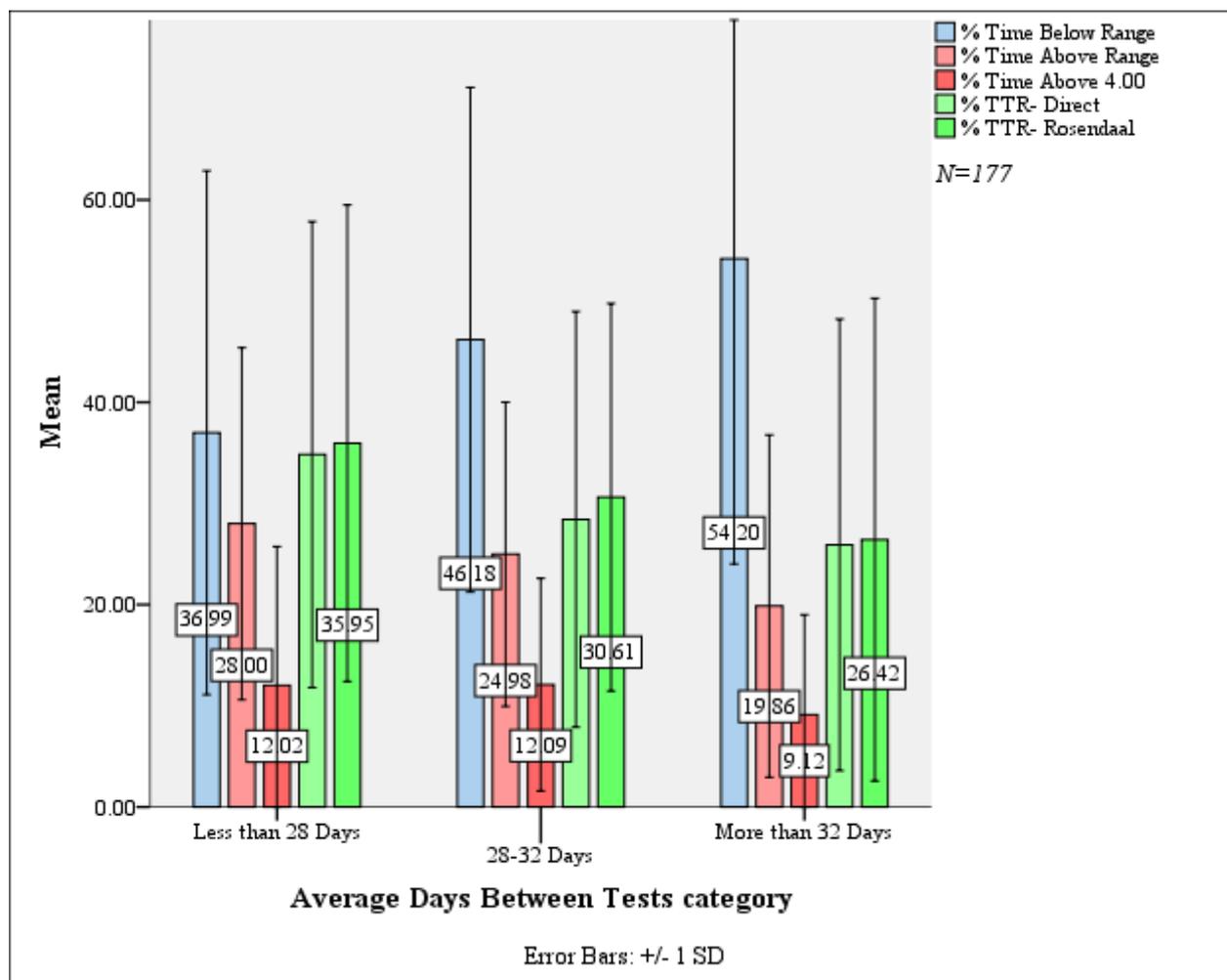
In the AF subgroup, the mean number of days between INR testing was 31 days (SD=6.8) and 36 (37.5%) of the 96 patients had an INR testing frequency of 28 to 32 days apart. Thirty-one (32.3%) of the patients were tested more frequently and the remaining 29 (30.2%) of the patients were tested more than 32 days apart (Table 9).

In the subgroup of patients with prosthetic heart valves, the mean number of days between tests was 36 days (SD=15.8). While the majority (48.1%, n=39) of the patients in this subgroup were tested from 28 to 32 days apart, only 12.3% (n=10) had INR testing less than 28 days apart and almost 40% (n=32) of the patients were tested less frequently (Table 9).

Results for the entire sample (Figure 13) showed that patients who had INR monitoring less than 28 days apart (M=27.9; SD=17.4) spent the most amount of time below range followed by patients who had monitoring from 28 to 32 days apart (M=24.9; SD=15.0). Patients being monitored on average more than 32 days apart (M=19.8; SD=16.9) had the least percentage of time below range. This difference was statistically significant [F (2, 174) = 4.992,  $p$  = .008]. However, post hoc analysis showed differences only between patients who were monitored less than 28 days apart and those monitored more than 32 days apart ( $p$  = .005). Time spent below range between patients monitored less than 28 days apart and those monitored between the 28 days to 32 days apart group were not statistically significant, nor was the time below range between the 28 to 32 days and more than 32 days apart groups ( $p$  = .190 and  $p$  = .202 respectively).

The percentage of time above range was also significantly different between patients depending on frequency of INR testing [F (2, 174) = 3.347,  $p$  = .037]. Post hoc analysis revealed significant differences only between the group monitored less than 28 days apart (M=27.9; SD=17.4) and more than 32 days apart (M=19.8; SD=16.9) ( $p$  = .038). Neither comparisons between the less than 28 day group and 28 to 32 days group (M=24.9; SD=15.0) were significant ( $p$  = .606), nor was the 28 to 32 day group and more than 32 days group ( $p$  = .164).

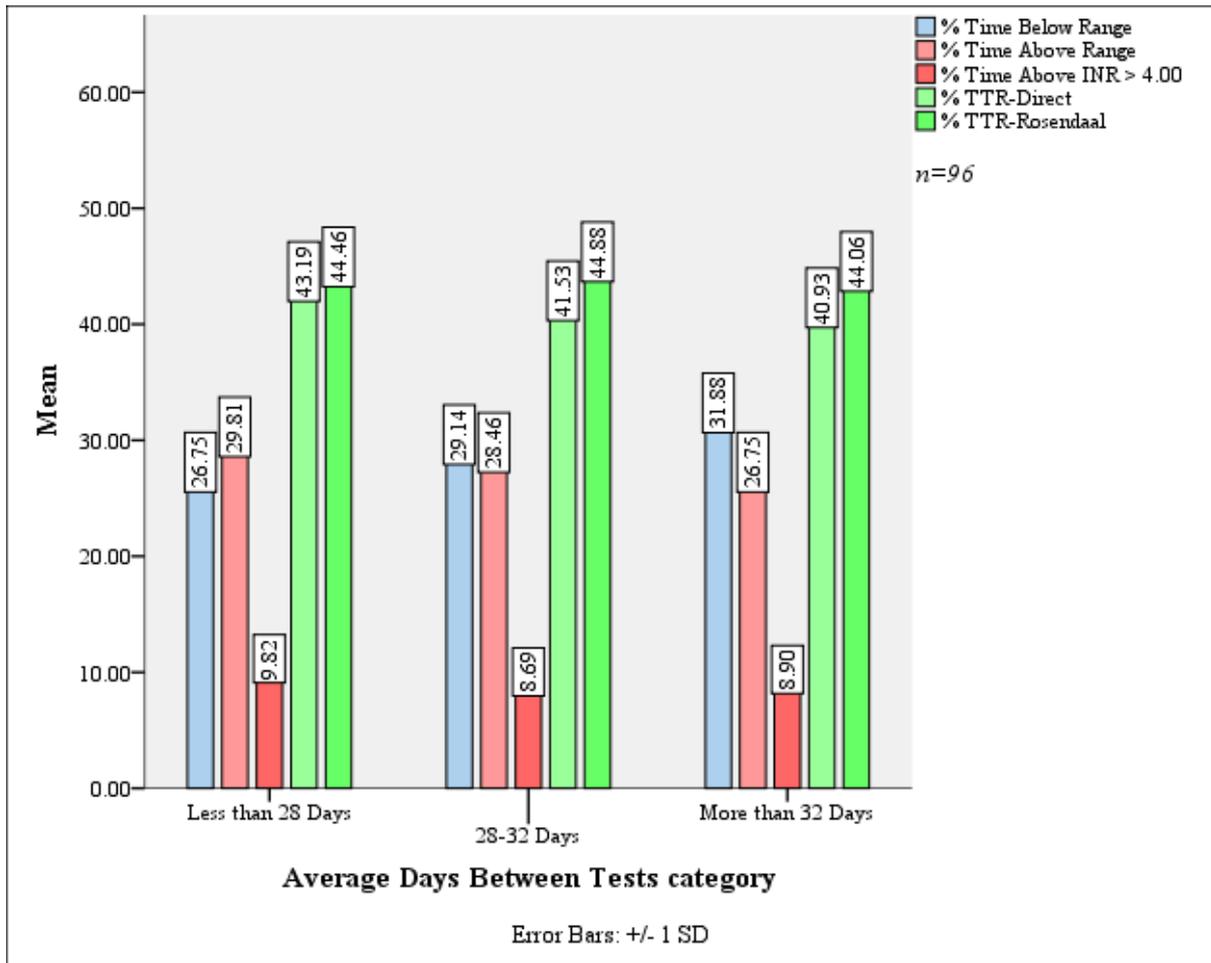
The mean percentage time spent with an INR value greater than 4.00 was not significant [F (2, 174) = 1.405,  $p$  = .248] between the less than 28 days apart group (M=12.0; SD=13.7), the 28 days to 32 days apart group (M=12.1; SD=10.5) and the group being monitored more than 32 days apart (M=9.1; SD=9.8).



**Figure 13: Distribution by frequency of INR testing within the sample population (N=177) for mean percentage time in range and out of range.**

The mean TTR assessed by both the Direct method and the Rosendaal method was inversely related to the frequency of monitoring, with the group of patients being monitored less than 28 days apart (M=34.8; SD=23.0 and M=35.9; SD=23.5) having higher percentages TTR than the group monitored from 28 to 32 days apart and more than 32 days apart (M=28.4; SD=20.5 and M=30.6; SD=19.1) respectively. Similarly the group of patients being monitored from 28 to 32 days apart had higher percentage of TTR than those patients being monitored more than 32 days apart (M= 25.9; SD=22.3 for the Direct method and M=26.4; SD=23.8 for the Rosendaal method). However analysis by one way ANOVA for both the Direct method and the Rosendaal method revealed this difference as not significant. [F (2, 174) = 2.120, *p*-.123] and [F (2, 174) = 2.324, *p*-.101] respectively.

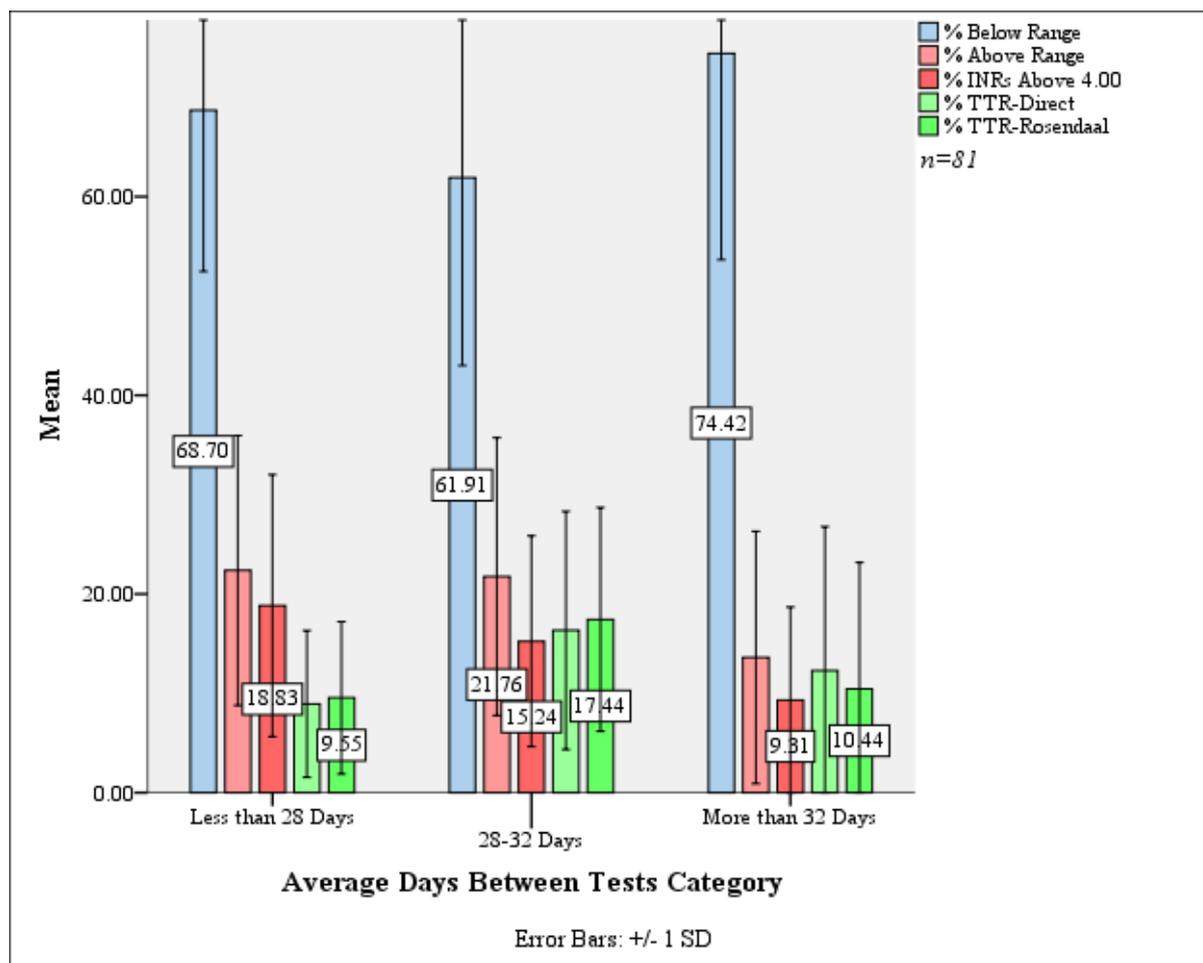
Analysis of the AF cohort (n=96) alone and it was found that there was no statistical significance for the conditions of mean percentage time below range (*p*-.613), above range (*p*-.792), time with an INR value of greater than 4.00 (*p*-.911) and TTR using the results of the Direct (*p*-.899) and the Rosendaal method (*p*-.984) against the mean days between tests (Figure 14).



**Figure 14: Distribution by frequency of INR testing within the AF subgroup (n=96) for mean percentage time in range and out of range.**

Overall in the valve prosthesis cohort (Figure 15), the majority of time was spent below range. When categorised against mean days between INR tests (Figure 15), there was a significant difference between the patients in the different groups [ $F(2, 78) = 3.673, p = .030$ ].

Post hoc analysis using the Tukey HSD statistic test revealed a significance difference ( $p = .023$ ) between patients who had INR monitoring 28 to 32 days apart ( $M = 61.9; SD = 18.9$ ) and patients who were monitored on average more than 32 days apart ( $M = 74.4; SD = 20.7$ ). The difference in time spent below range when comparing the group of patients who are monitored less than 28 days apart ( $M = 68.7; SD = 16.2$ ) and those being monitored from 28 to 32 days apart or patients being monitored more than 32 days apart was not significant ( $p = .587$  and  $p = .695$  respectively).



**Figure 15: Distribution by frequency of INR testing within the valve prosthesis subgroup (n=81) for mean percentage time in range and out of range.**

The mean percentage of time spent above range was significantly different across the different groups [F (2, 78)= 3.6669,  $p$ -.030] with patients monitored less than 28 days apart (M=22.4; SD=13.6) having a higher percentage time above range than those patients being monitored from 28 to 32 days apart (M=21.8; SD=13.9) and the group of patients monitored more than 32 days apart (M=13.6; SD=12.7) having the least percentage time above range. Post hoc analysis revealed asignificant difference only between the group being monitored from 28 to 32 days apart and those patients being monitored more than 32 days apart( $p$ -.035). Comparisons between patients monitored less than 28 days apart and patients monitored from 28 to 32 days apart and more than 32 days apart was not significant. ( $p$ -.991 and  $p$ -.177 respectively)

In line with a significant difference between groups for percentage time spent above range, the mean percentage time spent with an INR value greater than 4.00 was also significant in the valve prosthesis cohort [F (2, 78) = 4.372,  $p$ -.016], between the group of patients with monitoring less than 28 days apart (M=18.8; SD=13.2), patients monitored from 28 to 32 days apart (M=15.2; SD=10.6) and patients monitored more than 32 days apart (M=9.4; SD=9.3). Post hoc analysis revealed significant difference only between patients monitored less than 28 days apart and more than 32 days apart( $p$ -.038). Comparisons between patients monitored less than 28 days apart and those monitored from 28

to 32 days and patients monitored from 28 to 32 days apart and those patients with monitoring more than 32 days apart was not statistically significant ( $p=0.600$  and  $p=0.052$  respectively).

On assessment of the mean percentage TTR by both the Direct and Rosendaal methods the group of patients monitored from 28 to 32 days apart ( $M=16.3$ ;  $SD=11.9$  and  $M=17.4$ ;  $SD=11.2$ ) spent more TTR than the group monitored more than 32 days apart ( $M=12.3$ ;  $SD=14.5$  and  $M=10.4$ ;  $SD=12.7$ ) who in turn had more TTR than patients being monitored less than 28 days apart ( $M=8.9$ ;  $SD=7.4$  and  $M=9.5$ ;  $SD=7.6$ ) respectively. However statistical significance between the Direct method [ $F(2, 78) = 1.755$ ,  $p=0.180$ ] and the Rosendaal method [ $F(2, 78) = 3.975$ ,  $p=0.023$ ] differed. The significance of the condition for TTR by the Rosendaal method only differed between the group tested from 28 to 32 days apart and the group monitored more than 32 days apart ( $p=0.034$ ). The comparison between patients monitored less than 28 days apart with patients monitored less frequently was not statistically significant ( $p=0.137$  against the 28 to 32 days group and  $p=0.975$  when compared to patients monitored more than 32 days apart).

### 6.3.2. Discussion

Overall, more than one-third of our study population had INR testing more than 28 days apart. In our study setting, patients are supplied with a maximum of 28 days of warfarin before the prescription has to be renewed following a clinician review of the patient and the INR value. Therefore, patients who are monitored less frequently have an implied period without anticoagulation. Patients who had recent suboptimal or supratherapeutic INR values are usually followed up prior to 28 days.

This may explain why patients monitored less frequently demonstrated less time above range and less time with an INR value greater than 4.00 compared to those patients monitored less than 28 days apart. Interestingly, however, patients in our study who were monitored less than 28 days apart spent more time below range than patients monitored less frequently. This may be because the group of patients monitored more frequently had been previously identified as having suboptimal anticoagulation which accounts for their more frequent monitoring. This is in line with the findings from Dlott *et al.*, a study of 138319 individuals with AF which found a nonlinear association between INR testing frequency and TTR<sup>48</sup>; INR testing frequency was positively associated with TTR among patients with fewer than 14 INR tests per year, but inversely associated with TTR among those with more frequent testing. This pattern likely reflects increased testing among individuals with poor INR control. The ORBIT (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) trial evaluated 5210 patients with AF on warfarin and treated at 155 sites, concluded similar findings of patients in their study with subtherapeutic or supratherapeutic values having their INR level tested more frequently<sup>40</sup>.

Our primary objective was the TTR, and our study sample demonstrated an improved anticoagulation in patients monitored more frequently than those monitored less frequently which is in line with the findings from the THINRs<sup>37</sup> trial and the STABLE<sup>38</sup> study, both of which concluded more frequent testing was associated with improved TTR. Similarly, results from the ROCKET-AF (Rivaroxaban Once daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) study which evaluated 6983 patients taking warfarin, recruited from 45 countries found that regions with the lowest individual TTR had INR distributions shifted toward lower INR values and had longer inter-INR test intervals<sup>46</sup>. In our study population patients being anticoagulated for AF did not demonstrate significant differences in TTR according to

the frequency of INR testing and therefore likely contributed less to the overall findings than patients with prosthetic valves.

In line with the explanation of drug therapy duration for a maximum of 28 days, patients with prosthetic valves showed significantly less time above range and less time with an INR value greater than 4.00 if they were monitored less frequently. This may also explain the higher mean percentage time spent below range in these patients.

#### 6.4 Association of INR target range and time in range and time out of range

The target therapeutic range for any patient on warfarin is determined by finding the balance of achieving a sufficient anticoagulation effect without substantially increasing the risk of haemorrhage. In AF, several studies have attempted to determine the ideal range (Table 4). Hylek *et al.*, studied a cohort of 13559 patients with non-valvular AF and concluded among these patients that anticoagulation resulting in an INR of 2.0 or greater reduces not only the frequency of ischaemic stroke but also its severity and the risk of death from stroke. Moreover their findings provided further evidence against the use of lower INR target levels in patients with AF and indeed the accepted target range for AF is from 2.0 to 3.0<sup>23</sup>.

The target INR range for patients with prosthetic heart valves are determined by various factors. Two important categories are the degree of valve thrombogenicity (Table 13) and the presence or absence of other patient risk factors for thrombo-embolism. These factors determine the target INR range for any patient being anticoagulated with prosthetic mechanical heart valves (Table 6).

**Table 13: Valve thrombogenicity and types of prosthetic heart valves**

Valve thrombogenicity		
<u>Low</u>	<u>Medium</u>	<u>High</u>
Carbomedics (aortic position)	Bjork-Shiley	Starr-Edwards
Medtronic Hall	Other Bi-leaflet valves	Omniscience
St Jude Medical (without Silizone)		Lillehei-Kaster

There is sufficient evidence of differing quality of anticoagulation with target ranges. Rose *et al.*, studied 3396 patients from 101 community-based practices and concluded TTR is affected by the target INR range<sup>9</sup>. In that study, 127 patients had a target ranges below 2.0 and spent 42.7% of time with an INR below 2.0, compared to 18.8% for patients with the standard target range ( $p < .001$ ). These patients also spent significantly less time than the group with standard target ranges with an INR greater than 3.0 (4.8% vs. 13.6% respectively,  $p < .001$ ). However, patients with the low target range in

their study had a significantly ( $p < .001$ ) lower mean TTR (52.5%) than warfarin users with a normal INR target range (67.5%).

We described the quality of anticoagulation in our population according to the differing target INR ranges and assessed for any association.

#### 6.4.1. Results

All patients in the AF subgroup ( $n=96$ ) had INR target ranges of 2.0 to 3.0. In the subgroup of patients with mechanical heart valve prostheses ( $n=81$ ), target ranges were categorised according to valve thrombogenicity and patient risk factors (Table 13). The three target INR ranges were 2.5 to 3.0 ( $n=14$ , 17.3%), 3.0 to 3.5 ( $n=21$ , 25.9%) and 3.5 to 4.0 ( $n=46$ , 56.8%).

**Table 14: Distribution of patients in the valve prosthesis subgroup according to target INR range.**

	Frequency	Percent
Target INR Range - 2.5-3.0	14	17.3
Target INR Range - 3.0-3.5	21	25.9
Target INR Range - 3.5-4.0	46	56.8
Total	81	100.0

One way ANOVA of the valve prosthesis cohort ( $n=81$ ) showed statistically significant differences for the conditions of mean percentage time below range [ $F(2, 78) = 19.953, p < .001$ ], above range [ $F(2, 78) = 6.609, p = .002$ ] and TTR for both the Direct [ $F(2, 78) = 14.499, p < .001$ ] and Rosendaal [ $F(2, 78) = 26.099, p < .001$ ] methods (Table 15).

Analysis of differences between the target INR ranges and percentage time with an INR value above 4.00 was not statistically significant ( $p = .112$ ) when limited to the valve prosthesis cohort, however when analysed with inclusion of the AF subgroup there was a statistical difference demonstrated ( $p = .014$ ).

A Tukey post hoc test revealed time below range was statistically significant between patients with the target range 2.5 to 3.0 ( $M=42.6$ ;  $SD=20.8$ ) and target range 3.0 to 3.5 ( $M=70.1$ ;  $SD=17.7$ ) ( $p < .001$ ) and target range 2.5 to 3.0 and 3.5 to 4.0 ( $M=74.2$ ;  $SD=14.4$ ) ( $p < .001$ ). The target range 3.0 to 3.5 compared to 3.5 to 4.0 was not statistically significant ( $p = .623$ ).

A TukeyHSD post hoc test showed the most time spent above range was in the group with a target INR range of 2.5 to 3.0 ( $M=29.9$ ;  $SD=15.8$ ) followed by the group with an INR target range of 3.0 to 3.5 ( $M=17.9$ ;  $SD=14.5$ ) and the difference between these groups were statistically significant ( $p = .024$ ). The difference between the groups with a target INR range of 2.5 to 3.0 and 3.5 to 4.0

(M=15.5; SD=11.3) was also statistically significant ( $p<.001$ ). Comparison for the condition time above range for the target INR range 3.0 to 3.5 and 3.5 to 4.0 was not significant ( $p= 1.00$ ).

**Table 15: Distribution by target INR range for time in range and time out of range.**

	INR Target Range:			
	2.0-3.0 (n=96)	2.5-3.0 (n=14)	3.0-3.5 (n=21)	3.5-4.0 (n=46)
Mean % Time below range $p<.001$	29.2*†	42.6†	70.1	74.2
Mean % Time Above range $p<.001$	28.4†	29.9‡	17.9	15.5
Mean % Time INR > 4.00 $p=.014$	9.1‡	9.6	11.1	15.5
Mean % TTR-Direct $p<.001$	41.9*†	28.2†	12	10.3
Mean % TTR-Rosendaal $p<.001$	44.5*†	30†	12.1	9.4

\* $p<.05$  when compared to target groups 2.5-3.0 by Tukey HSD post hoc analysis

†  $p<.05$  when compared to target groups 3.0-3.5 and 3.5-4.0 by Tukey HSD post hoc analysis

‡  $p<.05$  when compared to target group 3.5-4.0 by Tukey HSD post hoc analysis

Patients with a target INR range of 2.5 to 3.0 had the highest TTR for Direct method (M=28.2; SD=14.8) and the Rosendaal method (M=29.9; SD=13.4) followed by the target INR range of 3.0 to 3.5 (M=11.9; SD=13.1 and M=12.1; SD= 9.4 respectively). The group of patients with a target INR of 3.5 to 4.0 had the least TTR when evaluated by both the Direct (M= 10.3; SD=8.5) and Rosendaal (M=9.5; SD=7.8) methods. Post hoc analysis of the differences between groups with a target INR range of 2.5 to 3.0 and 3.0 to 3.5 and 3.5 to 4.0 was statistically significant ( $p<.001$  for both comparisons) for the conditions of TTR using the Direct method as well as the Rosendaal method. Comparison between the target INR range of 3.0 to 3.5 and 3.5 to 4.0 was not significant for either the Direct method ( $p=.836$ ) or the Rosendaal method ( $p=.539$ ).

Patients with AF entirely constituted the group with target INR range of 2.0 to 3.0. This subgroup had performed strongly statistically significantly better than patients with higher target ranges across all conditions and was the only subgroup to show statistical difference for the time with an INR greater than 4.00 ( $p=.007$ ) when compared to patients targeted for the range 3.5 to 4.0.

### 6.4.2. Discussion

In our study population of patients with prosthetic heart valves, significant differences in the quality of anticoagulation when compared by the target INR range was demonstrated. Patients with the lowest target range had a superior TTR than patients with higher targets. This is contrary to the findings from the study by Rose *et al.*,<sup>9</sup> where patients in the low target group had a lower mean percentage TTR

than those with normal INR target range<sup>9</sup>. However, the study by Rose *et al.*, was conducted on patients with AF and not with prosthetic valves and the target INR ranges were lower than for the patients with valve prostheses in this study. Nevertheless we found similarly, that patients in this study with the lowest target range demonstrated the least time below range. However, this subgroup of patients also demonstrated the most time above range which is not in line with the findings by Rose *et al.*

These findings confirm that patients with low target ranges are easier to achieve effective anticoagulation but are also at risk for over-anticoagulation and therefore bleeding as compared to the subgroup of patients with higher INR target ranges. It is noteworthy to mention that patients with the highest targeted range risk imply the presence of risk factors and it is worrying that these patients demonstrated the least efficient anticoagulation.

The group of patients with the lowest target INR (2.0 to 3.0) in our study population was constituted entirely by the AF subgroup and performed statistically better across all conditions versus patients with higher target ranges.

There is extensive literature recommending the target INR ranges and that these should be rigidly adhered to. Indeed, the study by Hyek *et al.*, concluded that their study provided further evidence against the use of lower INR target levels in patients with AF<sup>23</sup>. In patients with prosthetic heart valves, inadequate anticoagulation is a major risk factor for valve obstruction by thrombus. As such, the findings in this study should not be used as motivation for adjusting target ranges in patients requiring anticoagulation. It does however add clinical value in identifying that patients with the highest target ranges have the highest risk of inadequate anticoagulation and may need closer monitoring.

## CHAPTER 7

### ADVERSE EVENTS

#### 7.1. Introduction

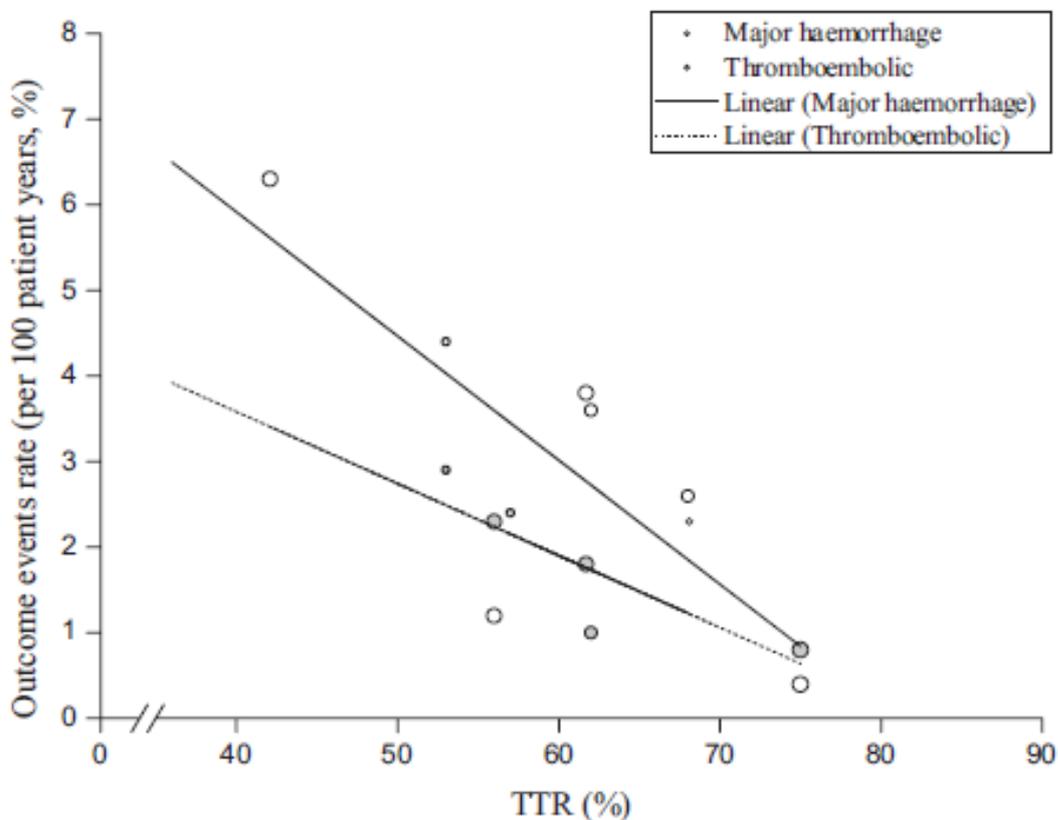
Warfarin, as an anticoagulant is used to prevent thrombo-embolism in patients with AF and mechanical prosthetic valves. One important consequence of anticoagulation is the risk of bleeding. Non-haemorrhagic complications of warfarin include skin necrosis, however this is rare.

AF is a common heart condition and indeed the most common heart rhythm abnormality. According to the 2010 Global Burden of Disease study evaluating the epidemiology of AF, the estimated number of individuals with AF globally has increased.<sup>3</sup>

AF has been evaluated as an independent risk factor for stroke and this risk increases with advancing age.<sup>8</sup> These findings have been discussed in Chapter 1.2 earlier in this work.<sup>7</sup>

There are numerous studies proving risk of stroke reduction with anticoagulation (Table 4). When the findings of the five (AFASAK<sup>11</sup>, BAATAF<sup>16</sup>, SPAF<sup>58</sup>, CAFA<sup>13</sup>, SPINAF<sup>18</sup>) major studies were evaluated in a pooled analysis, it was demonstrated that warfarin attributed a 69% stroke risk reduction (Table 4).

The quality of anticoagulation strongly correlates with the risk of thrombo-embolism or stroke. The ACTIVE-W trial<sup>34</sup> found the benefit of stroke prevention with warfarin over aspirin and clopidogrel was lost if the TTR was less than 58%. The study by Wan *et al.*, evaluated anticoagulation control and prediction of adverse events in patients with AF by a systemic review of 47 studies. They found that TTR negatively correlated with major haemorrhage ( $r = -0.59$ ;  $p = 0.002$ ) and thrombo-embolic rates ( $r = -0.59$ ;  $p = 0.01$ ). This effect was significant in retrospective but not in randomised controlled trials (Figure 16). For retrospective studies, a 6.9% improvement in the TTR significantly reduced major haemorrhage by one event per 100 patient-years of treatment. Furthermore, they concluded that a 12% increase in TTR can reduce the thrombo-embolic rate by one event per 100 patient-years<sup>45</sup>. Data from the ROCKET-AF trial, evaluated the relationship between TTR and the comparative treatment effects of rivaroxaban and warfarin and found that patients in the highest quartile of TTR had a lower event rate per 100 person-years than patients in the lowest quartile of TTR (1.3 vs 2.0) when analysing stroke or systemic thromboembolism<sup>46</sup>.



TTR versus major haemorrhage rate (n=9), correlation:  $r = -0.78$ ;  $P = .006$ ; linear regression:  $Y$  (major haemorrhage rate) =  $11.716 - 0.145X$  (TTR),  $R^2 = 0.61$ ;  $P = .01$ . TTR versus thrombo-embolic rate (n=5), correlation:  $r = -0.88$ ;  $P = .026$ ; linear regression:  $Y$  (thrombo-embolic rate) =  $6.943 - 0.084X$  (TTR),  $R^2 = 0.77$ ;  $P = .05$ .

**Figure 16: TTR versus adverse events for retrospective studies (copied from Wan Y, et al., Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. *Circulation Cardiovascular quality and outcomes*. 2008 Nov;1(2):84-91).**

The risk of haemorrhage has been well described in patients using oral anticoagulation. Since the introduction of the non-vitamin K oral anticoagulants there have been multiple trials assessing the bleeding risks. The International Society of Thrombosis and Haemostasis (ISTH) sought to unify the definition of major bleeding and the committee had agreed upon the following characteristics to fulfil the definition of major bleeding<sup>59</sup>:

1. Fatal bleeding, and/or
2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or
3. Bleeding causing a fall in haemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.

Levine *et al.*, described the haemorrhagic complications of anticoagulant treatment. They noted major determinants of vitamin K antagonist-induced bleeding to be the intensity of the anticoagulant effect, underlying patient characteristics, and the length of therapy<sup>60</sup>.

There have been various studies evaluating bleeding risk in patients being anticoagulated with warfarin which has yielded a number of risk assessment tools. The most accepted bleeding risk tool is the HASBLED score (Table 5). In a meta-analysis by Bloomfield *et al.*, which reviewed 35 studies and 453 918 participants evaluated the risk factors for serious bleeding in patients on oral anticoagulation. They demonstrated the factors most consistently predicting an increased risk of bleeding were age more than 75 years, first months following warfarin initiation, concomitant medication use (particularly aspirin use), co-morbid conditions, history of gastrointestinal bleeding events or diabetes, primary indication for taking warfarin was a valve condition, genetic factors like variation in the CYP2C gene, and bleeding risk indexes<sup>39</sup>.

Since the introduction of the non-vitamin K oral anticoagulants, there have been numerous comparative studies evaluating the adverse events surrounding patients with AF and on VKAs (Table 16). These studies have provided valuable information toward evaluating adverse events in these populations.

**Table 16: Evaluation of stroke or systemic embolism and major bleeding as per comparative studies between warfarin and the non-vitamin K oral anticoagulants.**

Study /Trial		Stroke or systemic embolism	Major bleeding
RE-LY <sup>42</sup> (N=18133)	Warfarin	1.7% per year	3.46% per year
	Dabigatran 110mg	1.55% per year	2.74% per year
	Dabigatran 150mg	1.11% per year	3.22 per year
ROCKET-AF <sup>30</sup> (N=14264) (Events per 100 patient-years)	Warfarin	2.15	3.45
	Rivaroxaban	1.70	3.60
ARISTOTLE <sup>44</sup> (N=18201)	Warfarin	1.60% per year	3.09% per year
	Apixaban	1.27% per year	2.13% per year
ENGAGE-AF-TIMI-48 <sup>43</sup> (N=21105)	Warfarin	1.50% per year	3.43% per year
	Edoxaban 60mg	1.18% per year	2.75% per year
	Edoxaban 30mg	1.61% per year	1.61% per year

Prosthetic valve thrombosis is a rare though devastating complication of prosthetic heart valves. The incidence is higher for mechanical than for biological heart valves, right-sided more common than left-sided and mitral more common than aortic. Valve thrombosis is most often encountered in patients with mechanical valves and inadequate antithrombotic therapy. The incidence of obstructive valve thrombosis varies between 0.3% and 1.3% per patient-year in patients with mechanical valves<sup>21,61</sup>. Serious complications in patients with prosthetic heart valves occur at a rate of 2% to 3% per patient-year<sup>61</sup>. The risk of thrombo-embolism depends not only on prosthesis type but also on valve position and thrombogenicity, patient risk factors and antithrombotic treatment.

## 7.2. Results

### 7.2.1. Descriptive data (Table 17)

For the sample population, 146 patients (82.5%) had no documented adverse event. There were 31 patients with at least one adverse event (17.5%) with ten patients (5.6%) sustaining multiple events and 45 documented adverse events (point prevalence of 25.4%). Stroke (undefined) accounted for 21 of the events (46.7%) and haemorrhage or admission for toxicity the remaining 24 (53.3%) events. There were no documented cases of a thrombosed or obstructed prosthetic valve.

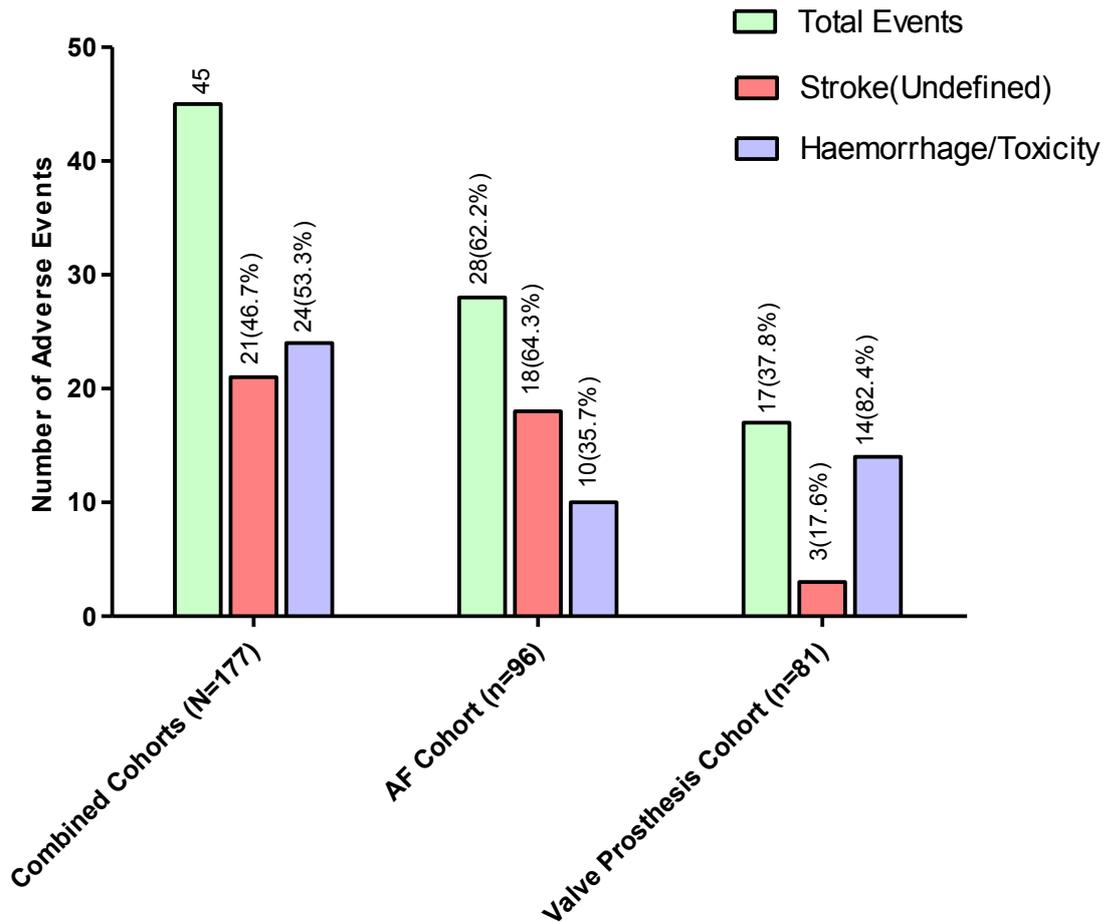
The AF cohort had 19 patients (19.8%) with at least one documented adverse event, seven patients of which sustained multiple events (7.3%) as compared to the valve prosthesis cohort in which 12 patients (14.8%) sustained at least one adverse event and three patients (3.7%) sustaining multiple adverse events.

The AF cohort accounted for 28 (62.2%) of the 45 documented adverse events in the sample population (Figure 17), as compared to the valve prosthesis cohort which accounted for 17 (37.8%) documented events. The majority of the events in the AF cohort was stroke (undefined) which accounted for 18 (64.3%) of the events in the AF cohort compared to the valve prosthesis cohort which had three documented strokes (undefined) and accounted for 17.6% of the events in that cohort. The valve prosthesis cohort had 14 (82.4%) haemorrhagic or toxic events as compared to the AF cohort (10 events or 35.7%).

**Table 17: Characteristics of the sample population, AF and valve prosthesis subgroups and adverse events.**

	No adverse event	Cases with multiple adverse events	Cases with at least one adverse event	Adverse Event sustained	
				Stroke	Toxicity
<b>Whole cohort (N=177)</b>	146 (82.5%)	10 (5.6%)	31 (17.5%)	21 (46.7%)	24 (53.3%)
Male	50 (34.2%)	4 (2.2%)	5 (16.1%)	2 (19%)	8 (33.3%)
Female	96 (65.8%)	6 (3.4%)	26 (83.9%)	14 (81%)	16 (66.7%)
Mean age (years)	54.2	63.6	61.6	54.2	63.6
Mean days between tests	33.6	30.4	31.9	34.2	29.3
Mean time below range	48.3%	28.5%	39.9%	27.7%	49.4%
Mean time above range	23.2%	22.3%	27.1%	29.4%	22.6%
Mean time with INR > 4.00	10.2%	12.3%	14.9%	11.7%	16.7%
Mean TTR	28.2%	49.2%	33.0%	42.9%	28.8%
<b>AF Subgroup (n=96)</b>	77 (80.2%)	7 (7.3%)	19 (19.8%)	18 (85.7%)	10 (41.7%)
Male	30 (39%)	3 (3.1%)	3 (3.1%)	2 (22.2%)	3 (30%)
Female	47 (61%)	4 (4.2%)	16 (16.7%)	13 (77.8%)	7 (70%)
Mean age	64.2	67.8	66.6	63.7*	74.4
Less than 65 years	38 (49.3%)	2 (2.1%)	7 (7.3%)	9 (50%)	0 (0%)
65-<75 years	27 (35.1%)	3 (3.1)	7 (7.3%)	6 (33.3%)	4 (40%)
75 years or more	12 (15.6%)	2 (2.1%)	5 (5.2%)	3 (16.7%)	6 (60%)
Mean days between tests	31.5	31	29.1	30	27.3
Mean time below range	31.2%	17.6%	21.9%	15.6%*	32.4%
Mean time above range	27.5%	19.7%	31.9%	32.7%	24.6%
Mean time with INR > 4.00	8.1%	6.6%	13.4%	10.9%	15.1%
Mean TTR	40.8%	56.0%	46.1%	51.6%	42.9%
<b>Valve subgroup (n=81)</b>	69 (85.2%)	3 (3.7%)	12 (14.8%)	3 (14.3%)	14(58.3%)
Male	20 (29.0%)	1 (33.3%)	2 (16.7%)	0 (0%)	5 (35.7%)
Female	49 (71.0%)	2 (66.7%)	10 (83.3%)	3 (100%)	9 (64.3%)
Mean age	39.8**	53.7	53.6	52.3	54.1
<20 years	2 (2.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
20-29 years	18 (26.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
30-39 years	19 (27.5%)	1 (33.3%)	2 (16.7%)	0 (0%)	3 (21.4%)
40-49 years	11 (15.9%)	0 (0%)	3 (25%)	1 (33.3%)	2 (14.3%)
50-59 years	9 (13.0%)	1 (33.3%)	3 (25%)	1 (33.3%)	3 (21.4%)
>60 years	10 (14.5%)	1 (33.3%)	4 (33.3%)	1 (33.3%)	6 (42.9%)
Mean days between tests	35.9	29	36.3	52	31.1
Mean time below range	67.5%	53.8%	68.5%	80.1%	64.6%
Mean time above range	18.5%	28.2%	19.3%	14.9%	20.8%
Mean time with INR > 4.00	12.6%	25.7%	17.3%	14.9%	18.1%
Mean TTR	14.1%	17.9%	12.2%	4.9%	14.6%
Target INR : 2.5-3.0	14 (20.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Target INR: 3.0-3.5	16 (23.2%)	1 (33.3%)	5 (41.7%)	0 (0%)	6 (42.9%)
Target INR: 3.5-4.0	39 (56.5%)	2 (66.7%)	7 (58.3%)	3 (100%)	8 (57.1%)

\*-  $p < .05$  when compared to patients with haemorrhage or toxicity\*\*- $p = .004$  when compared to patients who sustained at least one adverse event



**Figure 17: Distribution of adverse events between the AF cohort and the valve prosthesis cohort**

### 7.2.2. Multiple events versus single events (Table 17)

Interestingly, patients in our study population with more than one adverse event had spent significantly [ $t(29) = -2.685, p-.012$ ] more time in the therapeutic range ( $M=49.2; SD=26.9$ ) than patients who sustained only one adverse event ( $M=25.2; SD=21.3$ ), albeit overall with a suboptimal TTR. In addition, this subset of patients had a higher mean age ( $M=63.6$  years;  $SD=16.3$  versus  $M=60.7$  years;  $SD=12.6$ ), however this difference was not statistically significant [ $t(29) = -.550, p-.586$ ]. Patients with a single adverse event spent more time below range ( $M=45.4; SD=29.3$ ), above range ( $M=29.3; SD=19.3$ ) and with INR values greater than 4.00 ( $M= 16.2; SD=14.7$ ) than patients with multiple events. ( $M=28.5; SD=21.1, M=22.3; SD=11.1$  and  $M=12.3; SD=13.7$  respectively). The difference for these conditions was not statistically significant [ $t(29) = 1.627, p-.115; t(27.667) = 1.283; p-.210$  and  $t(29) = .698, p-.490$  respectively]. In addition, patients with a single adverse event were monitored less frequently ( $M= 32.7$  days between tests;  $SD=17.0$ ) than patients with multiple events ( $M= 30.4$  days between tests;  $SD=3.3$ ), however this difference was not significant [ $t(22.883) = .596, p-.557$ ].

### 7.2.3. Adverse events in the AF subgroup

#### 7.2.3.1. Adverse event versus no adverse event

In the AF cohort (Table 17), the mean age in years for patients who sustained at least one documented (M=66.6; SD=11.1) was higher than those who did not (M=64.2; SD=11.3), however, this difference was not statistically significant [F (1, 94) = .702, *p*-.404] nor for any of the different age groups [F (1, 94) = 1.460, *p* - .230].

There was no statistically significant gender difference between patients who sustained an adverse event compared to those who did not [F (1, 94) =3.691, *p*-.058].

Patients who sustained an adverse event were monitored more frequently (M=29.1 days apart; SD=5.0) as compared to those who did not have an event adverse event (M=31.5 days apart; SD=7.1). This difference was not significant [F (1, 94) = 1.895, *p*-.172].

The difference in the mean percentage time below range was not significant between the group of patients who did not have at least one adverse event (M=31.0; SD=20.2) and those who did (M=21.9; SD=16.9) [F (1, 94) = 3.267, *p*-.074]. Patients who did not sustain at least one adverse event had a lower mean percentage time than those who did for the conditions of time above range (M=27.5; SD=17.0 and M=31.9; SD=18.1), time with INR values greater than 4.00 (M=8.1; SD=9.8 and M=13.4; SD=14.4) and TTR using the Direct method (M=40.8; SD=18.8 and M=46.1; SD=22.9) respectively. Statistically, these differences were not significant for any of the conditions [F (1, 94) = 1.022, *p*-.074], [F (1, 94) = 3.716, *p*-.057] and [F (1, 94) = 1.117, *p*-.293] respectively.

#### 7.2.3.2. Stroke versus haemorrhage.

In the AF cohort, we compared the population who sustained any stroke (undefined) with the population that sustained any haemorrhage or admission for toxicity (Table 15). There was a significant difference in the mean percentage time below range [t (19) =-2.632, *p*-.016] and for age [t (19) = -2.277, *p*-.035] between the groups. Patients sustaining a stroke spent less mean percentage time below range (M= 15.6; SD=12.8) than those with haemorrhage or toxicity (M= 32.4; SD=16.4) and the mean age of patients was significantly higher for patients with haemorrhage or toxicity (M=74.4 years; SD=6.7) than those with stroke (M=63.7 years; SD=11.9). Patients who sustained a stroke spent more time above range (M=32.7; SD=18.4), in therapeutic range using the Direct method (M=51.6; SD=20.9) and had less frequent monitoring (M=30.0 days apart; SD=4.7) than those who sustained haemorrhagic or toxic events (M=24.6; SD=19.1; M=42.9;SD=26.4 and M=27.3 days apart; SD=4.7 respectively), although these differences were not statistically significant[ t(19) =.974, *p*-.342; t(19) =.835, *p*-.414 and t (19) =1.262, *p*-.222 respectively]. Patients with haemorrhage or toxicity (M=15.1; SD=18.1) had higher mean percentage time with an INR value greater than 4.00 compared to the group with stroke (M=10.9; SD=11.3), though the difference was not significant [t (19) = -.657, *p* -.519].

In patients with AF, a Poisson regression using Wald chi-square test for significance was run to predict the effects of gender, age, days between INR tests, time below range, time above range, time with an INR value greater than 4.00 and TTR on sustaining and adverse event. We found that the only condition which had statistical significance as a predictor was the time with an INR value greater than 4.00, *p*-.035. For every extra percentage time with an INR value greater than 4.00, there would be 1.044 (95% CI, 1.003 to 1.087) times the number of adverse events.

#### 7.2.4. Valve prosthesis cohort:

##### 7.2.4.1. Adverse event versus no adverse event.

In the valve prosthesis cohort (n=81), the only significant difference [F (1, 79) = 8.799,  $p$ -0.004] between patients who sustained an adverse event (M=53.7; SD=14.1) and those who did not (M=39.8; SD=15.1) was for the condition of age in years. There was no significant difference for gender [F (1, 79) = .772,  $p$ -0.382] nor for the condition of target INR range [F (1, 79) = .842,  $p$ -0.362] between the two groups (Table 17).

Patients in the valve prosthesis cohort, who sustained an adverse event spent a higher percentage time below range (M=68.5; SD=13.7), above range (M=19.3; SD=12.9) and time with an INR value greater than 4.00 (M=17.3; SD=14.3) and had less frequent monitoring (M=36.3 days apart; SD=21.5) than those with no documented event (M=67.6; SD=21; M=18.5; SD=14.1; M= 12.6; SD=10.2; M=35.9 days apart; SD=14.8 respectively). These differences were not significant across these conditions [F (1, 79) = .021,  $p$ -0.886; F (1, 79) = .038,  $p$ -0.846; F (1, 79) = 1.881,  $p$ -0.174 and F (1, 79) = .007,  $p$ -0.933 respectively].

Patients who sustained an event in the valve prosthesis cohort spent less time in the therapeutic range (M=12.2; SD=12.1) than those who did not (M=14.1; SD=12.9), however the difference was not statistically significant [F (1, 79) = .226,  $p$ -0.636].

##### 7.2.4.2. Stroke versus haemorrhage.

We then compared patient subsets in the valve prosthesis sub-cohort who sustained a stroke and those with haemorrhage or toxicity (Table 17).

Patients with haemorrhage or admission for toxicity spent more time above range (M=20.8; SD=14.3), with INR values greater than 4.00 (M=18.1; SD=16.2), in therapeutic range using the Direct method (M= 14.6; SD=13.1) than those who sustained a stroke (M=14.9; SD=7.9; M=14.9; SD=7.9 and M=4.9; SD=4.3 respectively). This difference, however, was not statistically significant [t (10) = -.673,  $p$ -0.516; t (10) = -.327,  $p$ -0.751 and t (9.875) = -1.917,  $p$ -0.085 respectively]. In addition, patients with haemorrhage or admission for toxicity had INR monitoring performed more frequently (M=31.1 days apart; SD=6.6) and had a higher mean age (M=54.1; SD=15.5) than patients with a stroke (M=52.0; SD=43.3 and M=52.3; SD=11.2 respectively), although, the difference was also not significant. [T (10) = 1.547,  $p$ -0.153 and t (10) = -.181,  $p$ -0.860 respectively].

Patients with the lowest target INR range (2.5 to 3.0) did not sustain any adverse event and all events categorised as stroke occurred only in patients with the highest target INR range (3.5 to 4.0). Haemorrhage or toxicity was documented for five patients with a target INR range of 3.0 to 3.5 and 4 patients with a target INR range of 3.5 to 4.0.

In patients with mechanical prosthesis valves, a Poisson regression using Wald chi-square test for significance was run to predict the effects of gender, age, days between INR testing, target INR ranges time below range, time above range, time with an INR value greater than 4.00 and TTR on sustaining and adverse event. We found that the conditions which had a strong statistical significance as a predictor were the time below range ( $p$ <.001) and the time above range ( $p$ <0.001). For every extra percentage time below range, there would be 8.335 (95% CI, 7.890 to 8.804) times the number of

adverse events and for every extra percentage time spent above range patients with valve prosthesis would sustain 8.458 (95% CI, 7.267 to 9.843) times the number of adverse events.

### 7.3. Discussion

The prevalence of adverse events in our patient population is worrying. Thirty-one of the 177 patients studied sustained at least one adverse event (17.5%) with ten patients (5.6%) sustaining multiple events. There were 45 documented adverse events with a point prevalence of 25.4% or 1 in 4 patients sustaining an adverse event. The majority of documented adverse events were accounted for by patients with AF (62.2% of events), of which the majority being stroke which accounted for 64.3% of all events and 18 (85.7%) of all strokes sustained. Unfortunately, our study design, did not allow for interpretation of incidence rate or rate per annum or in person-years. However, in comparison to other studies that have described frequency of events, the patients in our population demonstrated much worse prevalence of complications. In the AF cohort, the prevalence of bleeding events was 10.75% and that of thrombotic events was 18.75%. In the Auricula trial, which assessed 4273 patients in two centres for anticoagulation control in Sweden, the frequency of bleeding events was 2.03% and 1.36% for thrombosis for the whole study population. The AF subgroup (n=2491) in that study demonstrated 53 (2.13% of AF subgroup) cases of bleeding and 1.16% of the total AF subgroup accounted for thrombotic events. The subgroup with heart valve dysfunction demonstrated 2.01% of bleeding and 2.35% of thrombosis<sup>49</sup>. The subgroup of patients with prosthetic valves in our study showed 14 bleeding events accounting for 17.28% of this subgroup and three stroke events (3.7%). Connolly *et al.*, evaluated a regional influence using data from the ACTIVE-W trial. That study had 98 South African participants, none of which were in the upper two quartiles of TTR (mean TTR=46.3%) and there were eight documented events (8.1%)<sup>34</sup>. Sonuga, B.O *et al.*, studied 136 patients attending an anticoagulation clinic in Cape Town, South Africa, of which 19 patients (14%) had bleeding events and three patients (2.2%) had thrombotic events<sup>62</sup>. While the high prevalence of adverse events in our study is closer to other South African samples, there are some differences between the studies. The participants in Auricula demonstrated a much higher TTR (mean of 74.9%) than our patients. The AF cohort in Auricula was not exclusively comprised of non-valvular AF and the patients in their valve disease subgroup included participants beyond those with mechanical prosthetic valves. The ACTIVE-W included myocardial infarction and death in their count of events. The study by Sonuga, B.O *et al.*, was conducted on patients exclusively from a specialised anticoagulation clinic.

Patients with AF in our study demonstrated more adverse events than patients with prosthetic heart valves. The most likely association with this finding is the difference in age. The meta-analysis by Bloomfield found older age to be consistently associated with haemorrhage<sup>39</sup>. Indeed, the CHA<sub>2</sub>DS<sub>2</sub>-Vasc score (Table 2) considers an age above 65 years as a major risk factor for stroke in patients with AF as does the HASBLED bleeding risk tool for the risk of haemorrhage. While the mean age of patients with stroke in the AF subgroup was comparable with those who did not have an event (63.7 years vs. 64.2 years), patients in this subgroup with haemorrhage demonstrated a mean age of 74.4 years. Similarly, patients in the valve prosthesis subgroup who did not sustain an event had a mean age less than 40 years whereas those who did had mean ages beyond 50 years. In the AF subgroup we further demonstrated a significant association of older age and haemorrhage. This is consistent with the finding from Auricula which also demonstrated a significant association of older age and bleeding<sup>49</sup>.

In the AF cohort we evaluated for differences between patients with multiple events and single events. Those with multiple events had superior TTR than those with single events and this is likely the effect of sustaining multiple events when both the patient and the clinician likely employed more stringent control. This is supported by the finding of more frequent monitoring in this category of patient. Furthermore, patients with multiple events demonstrated a higher mean age than those who had a single event, although this difference was not significant.

In the valve prosthesis cohort, we again demonstrated an older age to be a significant factor in sustaining an adverse event. Furthermore, we showed the time out of range was an important predictor for an adverse event. This is consistent with various studies emphasising the benefit of high TTR in reducing the risk of adverse events.

Interestingly, despite the majority of patients in the valve prosthesis subgroup having suboptimal anticoagulation as demonstrated by the high percentage time below range, there were no documented events of valve thrombosis. The most likely reason is that valve thrombosis is rare and patients most susceptible to this event are those within the first six months of implantation. In our study, we evaluated patients on warfarin for at least one year and therefore the findings may not be representative of such patients. Furthermore, given the devastating effect of valve thrombosis and high risk of mortality, we may not have included these patients as we enrolled participants on their attendance and would therefore not have included possible mortality cases.

Our study had various limitations in assessing adverse events. Firstly, the documentation of the event was reliant on good note-keeping by the clinician. Secondly, we evaluated only outpatient charts and events requiring admission may have not been stated. Further, we could not differentiate between ischaemic stroke and haemorrhagic stroke, mainly because patients in this study setting do not have easy access to neuro-imaging and the majority of these patients did not have a computed tomography or magnetic resonance imaging of the brain. In addition, because we did not evaluate inpatient folders, we could not strictly adhere to the ISTH guidelines when defining major bleeding and as a result may have overstated haemorrhagic events. Nonetheless, our evaluation of adverse events in this population is in line with the findings that older age confers greater risk of events especially bleeding, time above range and with an INR greater than 4.00 increases the risk of bleeding and time below range that of stroke. We also confirm that lower target INR ranges are associated with fewer events.

## CHAPTER 8

### GENERAL DISCUSSION AND CONCLUSION

#### 8.1. General discussion

We report the results of a single centre, community-based study of patients being anticoagulated for non-valvular AF and mechanical prosthetic heart valves in the setting of usual care and not a specialised anticoagulation clinic. We demonstrated a high variability in quality of anticoagulation among these patients and identified contributing factors. Further, we evaluated the impact of such quality by assessing the adverse outcomes in this population, which is the most important clinical implication.

Interestingly the gender representation in our study population of patients with AF contrasted to reported global epidemiology. The Global Burden of Disease study which evaluated the epidemiology of AF, reported a higher male predominance globally, in developed and developing regions<sup>3</sup>. Females in our population constituted almost twice as many as males (65.6% vs. 34.4%). However the female representation in our study was similar to two South African (both are Cape Town based) studies evaluating patients on warfarin<sup>53,62</sup>. These findings suggest that in South Africa, females constitute at least a higher prevalence of AF than in developed regions, the clinical implications of which are related to mortality, which has a higher association with females than males globally despite a male preponderance<sup>3</sup>.

#### 8.2. Summary of the main results

##### 8.2.1. Variation in TTR.

Overall, the patients in our study demonstrated poor quality of anticoagulation regardless of the indication. The mean TTR achieved in patients with AF was 44.5% which is considerably lower than the recommended minimum of 60%. Most studies conducted in developed regions have reported a superior TTR<sup>34,38,39,46-49,51</sup>. We do note that the findings in our study are closer to the findings of other African studies and the South African participants in global studies<sup>34,42,46,62</sup>. We demonstrated a highly significant difference in TTR by indication. Patients with AF achieved significantly higher ( $p < .001$ ) TTR than those with prosthetic mechanical valves, albeit with both subgroups demonstrating low TTR. Patients with prosthetic heart valves demonstrated a mean TTR of 13.7%.

##### 8.2.2. Variation in quality of anticoagulation by indication

The highest percentage time out of range was below range for both subgroups but this was more significant ( $p < .001$ ) in patients with prosthetic valves (67.7% of the time was below range) than patients treated for AF. This was a consistent findings across all conditions namely time above range ( $p < .001$ ), time with an INR greater than 4.00 ( $p < .05$ ) and indeed TTR ( $p < .001$ ). Although there are few studies comparing TTR across indications, it is reasonable to assume that patients with prosthetic valves are badly anticoagulated in this study population. Wieloch*et al.*, in the Auricula study demonstrated a higher TTR in the subgroup of patients with mechanical valves than those with AF<sup>49</sup>. There are various factors that may account for this disparity in anticoagulation quality between the two groups as compared our study population; in our study the mean age was lower in patients with

prosthetic valves, females had a higher percentage representation in the valve prosthesis subgroup and patients with prosthetic valves had a higher INR target. All these factors have been validated as contributors to poor anticoagulation<sup>31</sup>.

### *8.2.3. Gender association with quality of anticoagulation*

A few studies have consistently associated female gender with poorer anticoagulation quality<sup>9,31,48</sup>. The findings in our study were inconsistent with these and there was no gender association with poor anticoagulation quality demonstrated. This is likely because unlike the global representation of male preponderance in AF, females represented the majority of the patients in our population<sup>3</sup>. Further, we showed males actually had poorer quality of anticoagulation with the time spent under-anticoagulated significant. It has been reported that in South Africa, males tend to seek health care less often than females and this trend could indeed account for this finding.

### *8.2.4. Age association with quality of anticoagulation*

We demonstrated no statistically significant difference between age categories for both the AF subgroup and the valve prosthesis subgroup. In the AF subgroup, the TTR determined by the Rosendaal method in our study showed the best TTR was in patients younger than 65 years old which contrasted with the findings from other studies which reported better TTR in older patients<sup>38,48</sup>. This finding is likely a result of the overall poor TTR across all age groups in our population. Nevertheless, the findings in our study imply a high risk of poor anticoagulation and therefore adverse events even if the patient is younger than 65 years old. It is noteworthy that patients in the AF group who were older than 65 years (which confers a higher risk for haemorrhage according to the HASBLED score) spent more time with an INR value higher than 4.00 which is additive in risk for bleeding. This trend was consistent in the subgroup of patients with prosthetic valves, where those older than 60 years old had the highest mean proportion of time with INR values exceeding 4.00. This is likely due to the altered pharmacodynamics, altered enzymatic activity and concomitant drug use in the elderly but this needs formal validation.

### *8.2.5. Association of frequency of INR testing and quality of anticoagulation*

In patients with AF there was no association that was statistically significant with frequency of INR testing. In patients with prosthetic valves, the time spent below range was significantly higher ( $p=0.023$ ) if INR testing was performed less frequently. Given that patients are prescribed warfarin for a maximum of 28 days before prescription renewal in this setting, it is likely that there is a period for which there is no anticoagulant being taken and this is probably an influential factor for low INR values. This finding was consistent in the AF subgroup but not statistically significant. In line with this explanation, patients monitored more frequently demonstrated more time above range if tested less than 28 days apart than those tested less frequently, however this was only significant in the valve prosthesis cohort ( $p=0.035$ ) for patients tested between 28 to 32 days apart and those tested more than 32 days apart. In keeping with the association of more time above range with frequent testing, patients in the valve prosthesis subgroup showed significantly more time with an INR value higher than 4.00 if tested less than 28 days apart than those with test intervals more than 32 days ( $p=0.016$ ).

Patients monitored between 28 and 32 days apart demonstrated the best TTR for both indications. This was significant in the valve prosthesis cohort for patients tested 28 to 32 days apart and those with test intervals more than 32 days when using the Rosendaal method. ( $p=0.034$ ). Some studies evaluating TTR favour more frequent testing<sup>37,38</sup> while others have shown poorer correlations<sup>9</sup>.

### 8.2.6. Association of target INR range and quality of anticoagulation

The lowest target INR range in our study was entirely constituted by the patients treated for AF and was from 2.0 to 3.0. Patients with this target INR range had the best quality of anticoagulation and significantly better TTR, the least time below and the lowest risk of bleeding by having the lowest percentage of time with INR values in excess of 4.00 ( $p < .05$ ). Within the valve prosthesis subgroup, patients with the lowest target INR range (2.5 to 3.0) demonstrated significantly better TTR, less time below range and above range when compared to the subgroup of patients with the highest target INR range (3.5-4.0) ( $p < .05$ ). These patients also had the lowest proportion of time with INR more than 4.00 within the valve prosthesis cohort but this was not statistically significant ( $p = .112$ ). However, the patients with target ranges from 2.0 to 3.0 and from 2.5 to 3.0 both had significantly higher proportions of time above range. Despite this, they still demonstrated the lowest times with an INR exceeding 4.00 and maintained a lower bleeding risk than those with higher target ranges.

### 8.2.7. Adverse events

Overall, the findings in our study demonstrated poor quality of anticoagulation and therefore suggest that the patients in this study are at higher risks of adverse events and indeed we evaluated a point prevalence of 25.4% across the entire cohort and 17.5% of the patients studied had sustained at least one event, while 5.6% had multiple events. These findings were considerably higher than other studies<sup>34,49</sup>.

The majority of strokes sustained were accounted for by patients with AF (85.7%) while the majority of haemorrhagic events were accounted for by patients from the prosthetic valve subgroup (58.3%). We also demonstrated that the time with an INR above 4.00 is a significant risk factor for an adverse event. In our study sample, there was a highly significant poorer TTR in patients with prosthetic valves compared to those with AF ( $p < .001$ ). Further, patients with mechanical valve prostheses spent a much higher time below range ( $p > .001$ ) than those with AF and even though they had much less time above range ( $p < .001$ ) they recorded higher proportions with INR exceeding 4.00 ( $p < .05$ ). These findings allow us to draw the conclusion that poor TTR is associated with high risk of bleeding and while the time above remains noteworthy, it is the time with INR values exceeding 4.00 that have been shown to significantly be associated with haemorrhagic risk.

## 8.3. Study Limitations

The main limitation of this study was that it was retrospective and single centre based and as a result may not be entirely representative for a region. It is, however, to the best of our knowledge the first study evaluating the quality of anticoagulation in a community-based setting for both AF and prosthetic heart valves in KwaZulu Natal.

Only outpatient folders were analysed and therefore INR values registered in inpatient files or at other facilities may not be represented. The patient population was derived from record keeping of INR sampling and therefore only live cases were analysed. As a result, we were unable to evaluate for associated mortality which remains the most important clinically relevant outcome. Nonetheless, we believe this method of sample recruitment remains the best to achieve the most real-life representation of anticoagulated patients in community practice.

Furthermore, adverse events were entirely reliant on the documentation of such by the attending clinician in the outpatient folder and this may have resulted in under-representation of events. The most important limitations in evaluating events however, was the lack of documented neuro-imaging findings and we were therefore unable to define any stroke as ischaemic or haemorrhagic and the study design precluded us from accurately evaluating for haemorrhage as defined by ISTH guidelines<sup>59</sup> and this may have over-represented the number of bleeding events.

Finally, the data did not include some factors that are known to affect TTR like patient education regarding warfarin use, patient compliance, socio-economic conditions, ethnicity, tobacco use, alcohol use, warfarin resistance and lastly although age was used as factor conferring high risk in AF, a complete CHA<sub>2</sub>DS<sub>2</sub>-Vasc assessment was not performed<sup>29,31,41</sup>.

## 8.4. Conclusion

Non-valvular AF and prosthetic heart valves account for the majority of indications (75.3%) for which patients are being anticoagulated at this study location.

This study confirms poor quality of anticoagulation in this patient population across both indications for anticoagulation namely non-valvular AF and valve prosthesis with the latter subgroup demonstrating poorer quality. The study demonstrates a major gap in quality of anticoagulation compared to developed regions and indeed confirms that the majority of patients (76%) are not achieving the recommended minimum TTR of 60%.

This study confirms that the fraction of INRs is a reasonable method for evaluating TTR and correlates well with the Rosendaal method.

We found no gender or age association with TTR, however INR testing intervals less than 32 days apart and lower target ranges were significant factors favouring better anticoagulation quality.

The majority of time out of range was below target range and this predisposed these patients to thrombo-embolic complications. Patients in this study spent a substantial proportion of time with an INR exceeding 4.0 and this conferred higher risk to haemorrhagic complications. Indeed, a high prevalence of adverse events was demonstrated and older age and proportion of time out of range was a significant factor in sustaining an event.

The findings in this study have remarkable clinical implications. Firstly, further research is required to determine the factors contributing to poor anticoagulation in this population and then proposals based on these findings need to be agreed upon and instituted. These findings also suggest that presently, patients with AF and prosthetic valves are not benefiting from OAC therapy and indeed are at high risk for events. This is important for all stakeholders in health care decision-making to determine if patients in this subpopulation may show improvement if treated in a specialised anticoagulation clinic where an algorithmic approach is utilised or perhaps consider implementing point-of-care devices, adjust frequency of visits or indeed even benefit more from a NOAC than to continue with current conventional VKA therapy.

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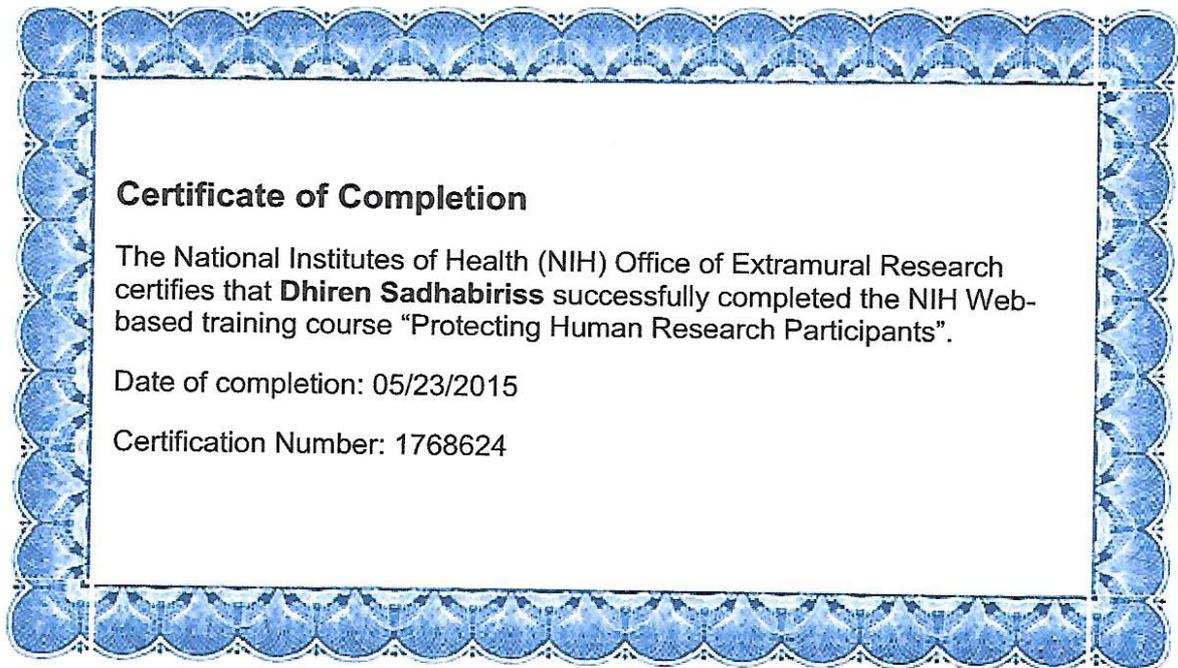
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## Annexures

### Annexure A: ETHICS CERTIFICATE



## Annexure B: BREC APPROVAL LETTER



27 November 2015

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**Protocol:** Warfarin: Time in therapeutic range (TTR), a single centre retrospective study on patients using Warfarin for stroke prevention in non - valvular Atrial Fibrillation or for patients with prosthetic heart valves

**Degree:** MMed

**BREC reference number:** BE320/15

### EXPEDITED APPLICATION

The Biomedical Research Ethics Committee has considered and noted your application received on 13 July 2015.

The study was provisionally approved pending appropriate responses to queries raised. Your responses dated 24 November 2015 to queries raised on 25 August 2015 have been noted and approved by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given **full ethics approval**.

This approval is valid for one year from **27 November 2015**. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at <http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx>.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its meeting taking place on **08 December 2015**.

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

  
Professor J Tsoka-Gwegweni  
Chair: Biomedical Research Ethics Committee

cc supervisor: [postmai@ukzn.ac.za](mailto:postmai@ukzn.ac.za)

cc postgrad: [jantjies@ukzn.ac.za](mailto:jantjies@ukzn.ac.za)

Biomedical Research Ethics Committee

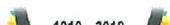
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Annexure C. PERMISSION FROM DEPARTMENT OF HEALTH, KZN



**health**  
Department:  
Health  
PROVINCE OF KWAZULU-NATAL

Physical Address: 330 Langalibalele Street, Pietermaritzburg  
Postal Address: Private Bag X9051  
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782  
Email: [hrkm@kznhealth.gov.za](mailto:hrkm@kznhealth.gov.za)  
[www.kznhealth.gov.za](http://www.kznhealth.gov.za)

**DIRECTORATE:**  
Health Research & Knowledge  
Management

HRKM Ref: 191/16  
NHRD Ref: KZ\_2016RP26\_295

Date: 30 June 2016  
Dear Dr D. Sadhabiriss  
UKZN

**Approval of research**

1. The research proposal titled '**Warfarin: Time in Therapeutic Range (TTR), A single centre retrospective study on patients using Warfarin for stroke prevention in non-valvular Atrial Fibrillation(AF) or for patients with Prosthetic heart valves**' was reviewed by the KwaZulu-Natal Department of Health.

The proposal is hereby **approved** for research to be undertaken at Mahatma Gandhi Memorial Hospital.

2. You are requested to take note of the following:
  - a. Make the necessary arrangement with the identified facility before commencing with your research project.
  - b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.
3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to [hrkm@kznhealth.gov.za](mailto:hrkm@kznhealth.gov.za)

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

**Dr E Lutge**

Chairperson, Health Research Committee

Date: 01/07/16

Fighting Disease, Fighting Poverty, Giving Hope

Annexure D: PERMISSION FROM HOSPITAL MANAGEMENT



**health**  
Department:  
Health  
PROVINCE OF KWAZULU-NATAL

**MAHATMA GANDHI MEMORIAL HOSPITAL**

Physical Address: 100 Phoenix Highway, Phoenix  
Postal Address: Private Bag X13, Mount Edgecombe, 4300  
Tel: 0315021719 ext 2012 Fax: 086 5757 6612 Email: nancy.bridgemohun@kznhealth.gov.za  
[www.kznhealth.gov.za](http://www.kznhealth.gov.za)

Reference: Research

23 November 2015

**DR D.SADHABIRISS**

**RE: PERMISSION TO CONDUCT RESEARCH: WARFARIN: TIME IN THERAPEUTIC RANGE (TTR).**

I wish to inform you that permission is hereby granted for you to conduct the above mentioned research at Mahatma Gandhi Memorial Hospital.

Kindly contact me on 0315021719 make the necessary arrangements.

Yours faithfully,

**DR C. PERSAD**  
**MEDICAL MANAGER**  
**MAHATMA GANDHI MEMORIAL HOSPITAL**

**MMED Protocol Submission**

**Dr D Sadhabiriss**

**UKZN Student number: 200266847**

**Department of Internal Medicine**

**Supervisor: Dr S Brown**

### **Title of the Study:**

Warfarin: Time in Therapeutic Range(TTR), A single centre retrospective study on patients using Warfarin for stroke prevention in non-valvular Atrial Fibrillation(AF) or for patients with Prosthetic heart valves.

### **Aim of the study:**

To assess the quality of anticoagulation of patients on warfarin for stroke prevention in non-valvular Atrial Fibrillation or in the presence of prosthetic heart valves.

### **Specific Objectives:**

1. To assess the Time in Therapeutic Range (TTR) of patients on Warfarin for stroke prevention in non-valvular Atrial Fibrillation or in the presence of prosthetic heart valves.
2. To assess the indication for anticoagulation namely for stroke prevention in Atrial Fibrillation or if in the presence of prosthetic heart valves.
3. To assess the frequency of suboptimal INR levels or toxic levels of INR in relation to Time in Therapeutic Range
4. To assess for any gender association with TTR of patients on Warfarin.
5. To compare findings of the TTR using three different methods.

### **Background and Literature:**

Vitamin K Antagonists (VKA) such as Warfarin are widely prescribed as oral anticoagulants. The efficiency of anticoagulation with Warfarin is measured by the prothrombin time reported as an International Normalisation Ratio (INR) with a different target range for the individual disease condition.

This is done by measuring the Prothrombin Time (PT), International Normalized Ratio (INR), which is a measure of three of the four vitamin K–dependent coagulation factors: II, VII and X. The INR is determined by dividing the PT of a patient with the geometric mean of PT for at least 20 healthy subjects of both sexes with the same test system. An INR of 1.0 is considered to be normal coagulation and an INR of 2.0 means that the clotting time has been doubled [1].

VKA produce their anticoagulant effect by interfering with the cyclic interconversion of vitamin K and its epoxide which through a complex pathway leads to the depletion of coagulant proteins (prothrombin, factor VII, factor IX, and factor X). In addition, the VKA impair the regulation of the anticoagulant proteins (protein C and protein S) and impair their function [1].

Warfarin as an anticoagulant agent has many uses. The two notable indications for long-term oral anticoagulation are in the setting of non– valvular Atrial Fibrillation to prevent stroke and/or systemic embolism and in the presence of a mechanical prosthetic valve. Atrial Fibrillation (AF) increases the

risk of morbidity and mortality because of a substantially increased risk of stroke and systemic thrombo-embolism. Overall, AF increases the stroke risk 5-fold, and when compared with non-AF-related strokes, strokes related to AF are associated with higher mortality, greater disability, longer hospital stays, poorer functional outcome, and lower chance of being discharged home[2]. The Framingham study has noted AF as an independent risk factor for stroke [3].

The risk of stroke in AF is reduced by antithrombotic therapy. Thromboprophylaxis can be obtained with VKA like Warfarin or a non-VKA oral anticoagulant. All the major guidelines emphasize the role of oral anticoagulation (OAC) use for stroke prevention in AF[2, 4, 5].

The introduction of valve replacement surgery in the early 1960s has dramatically improved the outcome of patients with valvular heart disease.

Patients with prosthetic valves are at risk of thrombo-embolic complications, including systemic embolization, most commonly cerebral and prosthetic thrombosis causing valve obstruction and/or regurgitation. The risk of thrombo-embolic events is higher with mechanical than with bioprosthetic valves, higher with mitral than with aortic prosthetic valves, and higher in the early (3 months) versus late postoperative phase [6]. The risk is also increased in the presence of concomitant risk factors for thrombo-embolism, including atrial fibrillation, Left Ventricular (LV) dysfunction, left atrial dilation, previous thrombo-embolism, and a hypercoagulable condition.

Patients with mechanical prostheses require lifelong anticoagulation with Warfarin and for 3 months in the case of an implanted bioprosthesis. Lifelong anticoagulation is required in the case of a bioprosthesis implantation if the patient has other indications for anticoagulation [7].

INR target ranges vary per country and per indication. The most common usual target INR is in the range 2-3[1]. The optimal range is generally determined by defining the risk of thrombo-embolism against the risk for haemorrhage.

Patients with AF who require Warfarin for the prevention of cardio-embolic complication should have an INR target of 2.5[8].

The recommended INR targets for mechanical heart valves depends on the prosthesis thrombogenicity (Low: Carbomedics (aortic position), Medtronic Hall, St Jude Medical (without silzone); Medium: Bjork-Shiley, other bi-leaflet valves; High: Starr-Edwards, Omniscience, Lillehei-Kaster) as well as patient factors which increase the risk of thrombo-embolism (Mitral, tricuspid or pulmonary position; Previous arterial thrombo-embolism; AF; Left atrium diameter >50 mm; Mitral stenosis of any degree; Left ventricular ejection fraction <35%; Left atrial dense spontaneous echo contrast).

Patients with low prosthetic thrombogenicity and no patient risk factors should have an INR target of 2.5. Those with low prosthesis thrombogenicity and patient risk factors should be optimised at an INR of 3.0. Patients with Medium prosthesis thrombogenicity and no patient risk factors have an INR target of 3.0 whereas those with patient risk factors should have INR levels at 3.5. In patients with high prosthesis thrombogenicity, regardless of patient risk factors, an INR of 3.5 should be targeted with some studies suggesting an INR of 4.0 to be considered [8].

The clinical benefits and risks of Warfarin are associated with the proportion of time that INR values are within the target range, meaning the Time in Therapeutic Range (TTR). The quality of anticoagulation control is well accepted as an indicator in many clinical trials, however, it is often not measured. The TTR is a good indicator for the quality of anticoagulation control.

There are at least three different methods to measure TTR: 1. Fraction of INRs in range (taken as the number of INRs in range divided by the total number of INRs for the study interval); 2. The cross-section-of-the-files-methodology (takes each patient whose INR is in range at one point in time divided by the total number of INRs done on all patients at that point in time); 3. The Rosendaal Linear

Interpolation Methodology (uses a computer software program called the INR-DAY programme that assumes a linear relationship exists between two INR values and allows one to calculate a specific INR value to each day for each patient) [9].

TTR is an important and validated quality measure for VKA management [10]. Patients who are under-treated remain at risk of thrombo-embolic events and patients who receive too much anticoagulant therapy are exposed to unnecessary bleeding risk.[11]

In the setting of non-valvular AF, patients who have at least one other stroke risk factor are recommended to receive effective stroke prevention therapy, which is essentially an OAC with either well-controlled VKA therapy (INR 2–3, with a high TTR percentage of, at least 70%) or one of the Novel Oral Anticoagulants (NOAC)[5].

There is a strong correlation between TTR and survival of post AF stroke for moderate or high risk patient under Warfarin treatment, with a much better survival for the patient with TTR >70 % compared to patients at lower TTR. In terms of quality, the “Quality of TTR” was presented as < 50 %= bad quality, > 65 %= best practice in Randomised Controlled Trials, > 80 % = optimal[12]. The report from the ACTIVE-W trial indicated that if the TTR was below 65%, the benefit of Warfarin therapy over aspirin was lost[13, 14].

In the case of non-valvular AF, major bleeding incidence increased with increasing INR. Major bleeding event rates per patient-year were 1.7 for INRs <1.49, 1.8 for INRs between 1.50–1.99, 1.5 for INRs between 2.00–2.49, 3.4 for INRs between 2.50–2.99 and 20.0 for INRs >3.00 [15].

A high variability of the INR is the strongest independent predictor of reduced survival after mechanical valve replacement. Valve thrombosis is most often encountered in patients with mechanical valves and inadequate antithrombotic therapy [6].

A correlation between treatment quality with Warfarin as measured by TTR and serious complications, mainly bleeding but also death has been shown. In order to have the lowest possible risk of complications, the aim of Warfarin therapy in patients with mechanical heart valve prosthesis should therefore be to keep the patient’s TTR within the top quartile, i.e. TTR > 83% [16]. It is plausible that TTR of 70% is already sufficient for prevention of valve thrombosis [16].

The high variability in INR and therefore in TTR poses a difficult challenge to the clinician. The pharmacokinetics, pharmacodynamics and pharmacogenetics of warfarin contribute a major role toward this variability. Warfarin has multiple dietary interactions as well as multiple drug interactions [17].

Vitamin K is the natural antidote to Warfarin. Vitamin K is found in food, and diet therefore imposes variability in Warfarin response. Normal intake of vitamin K is in the range of 60–200 µg/day. Most dark green vegetables such as broccoli, brussels sprouts and spinach contain high levels of vitamin K (>100 µg/2 dl), but also other common foodstuffs contain a fairly large amount of vitamin K. It is estimated that an increase in vitamin K intake of 100 µg per day for 4 consecutive days lowers the INR by 0.2, and Vitamin K intake has therefore been incorporated into some Warfarin dose prediction models [1].

The two Warfarin isomers are metabolised by different pathways. The main enzyme involved in the metabolic elimination of (S)-Warfarin is CYP2C9, while (R)-Warfarin is eliminated by CYP1A1/CYP1A2/CYP3A4. Patients starting or stopping drugs that are known inducers or inhibitors of these enzymes should have extra INR tests, and their dose of Warfarin adjusted accordingly. Examples of drugs that interact with Warfarin are Amiodarone that inhibits the clearance of Warfarin thereby potentiating the anticoagulant effect, and carbamazepine, phenytoin and rifampicin, which induce the metabolism of Warfarin. Drugs that inhibit clotting and increase the risk of bleeding, like aspirin, Diclofenac and Ibuprofen, are also regarded as interacting drugs even though they have no inhibiting or inducing effect on the elimination of Warfarin [1].

In one study of patients with outofrange INRs, non-compliance was most commonly noted in 214 occasions (19.8%), food in 143 occasions (13.2%), drugs in 109 occasions (10.0%), alcoholic beverage in 34 occasions (3.1%) and herbal remedy in 12 occasions (1.1%).The remaining 52.8% was undetermined [18].

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## **Study Design**

### **Study population.**

Patients attending Mahatma Gandhi Memorial Hospital, Adult Medical Outpatients Department for assessment of non valvular Atrial fibrillation or valve prosthesis and treatment with Warfarin.

### **Sampling strategy.**

Systematic Random sampling.

Determined by the following method for each cohort.

N = Total Number of patients in the study population (i.e: total number of patients meeting the inclusion criteria seen in the department during the period from 1<sup>st</sup> October 2015 to 30<sup>th</sup> November 2015 for each cohort)

n = sample size: 150 in the case of Atrial Fibrillation patients and 100 in the case of valve patients

k = Interval size i.e. N/150 in the case of Atrial Fibrillation patients and N/100 in valve prosthesis

A random number will be selected from 1-5 as a starting point and every "k"-th case will be accepted.

The cases in the study population will be randomly ordered and not according to date of visit.

### **Statistical Planning.**

Single centre retrospective observational study on patients attending Mahatma Gandhi Memorial Hospital – Adult Medical Outpatients Department during the period of 1<sup>st</sup> October 2015 to 30<sup>th</sup> November 2015 for assessment of anticoagulation while on Warfarin for either non-valvular Atrial Fibrillation, or in the presence of any valve prosthesis.

The charts of these patients will be retrospectively reviewed for a period of 1 year or 12 visits whichever is the longer time period.

Patients will be sub-categorised into cohorts of patients being anticoagulated for prevention of stroke in non-valvular Atrial Fibrillation (AF), or patients being anticoagulated for valve prosthesis.

The 2 cohorts will be further subdivided into age and gender as a means for comparison.

Chart reviews will include age, gender, indication for anticoagulation, INR levels and the date of sampling, record of any event of haemorrhage or admission for Warfarin toxicity and record of any event of systemic thrombo-embolism while on anticoagulation not limited to the study period.

In addition the chart review will include the average frequency of visits for assessment of anticoagulation. This was included to assist in determining if the frequency of visits for INR sampling while on anticoagulation is influential in the outcome of TTR, and to consider it as a recommendation at the end. These will be subdivided between the AF cohort and the valve prosthesis cohort.

All handwritten INR records will be confirmed *via* the National Health Laboratory Services (NHLS) Labtrack<sup>R</sup> database using the patients' demographics and the patient file number and/or the specimen tracking number.

The indication for anticoagulation, presence or absence of patient risk factors and/or any adverse event will be reliant on the documentation of the attending clinician.

INR sampling in this centre is performed by sampling venous blood in a citrate tube.

The target INR is determined by the recommendations made by Keeling, D., et al., Guidelines on oral anticoagulation with warfarin - fourth edition. Br J Haematol, 2011. **154**(3): p. 311-24. This was opted for in view of the Laboratory Service in use, using the same recommended guideline in their reference to INR results.

Therefore the adopted INR target range for patients in this study with AF will be 2.0-3.0.

Patients with mechanical valve prosthesis will be subdivided as those with low, medium and high valve thrombogenicity in the presence or absence of other risk factors according to the table below.

Recommended INR Target		
Thrombogenicity	No Risk Factors	Risk Factors Present
Low	2.5	3.0
Medium	3.0	3.5
High	3.5	3.5

Time in Therapeutic Range will be determined by using the INR values *via* three methods:

1. The percent of visits in the range (this is the number of visits with INR in range divided by the total number of visits for the study period).
2. The Rosendaal Linear Interpolation Methodology (use of a Microsoft Excel template downloaded from a website called Health Care Systems Solutions which assumes a linear relationship exists between two INR values and allows one to calculate a specific INR value to each day for each patient)
3. Use of an Internet Downloaded software program from Formulae.com called Regulating Anticoagulant Treatment and abbreviated RATi. Input data include the indication for anticoagulation, the target INR, dates of INR results, and the weekly Warfarin dose. The program automatically calculates the percentage of the TTR.

Furthermore a comparison will be done on the results of the three different methods.

Interpretation of the results of the TTR in the cohort of patients with AF will include the following:

1. The primary outcome is to determine the overall TTR.
2. The percentage of patients with TTR <65%, which will be considered suboptimal and “time with increased thrombotic risk”(Lader, Martin et al. 2012).
3. The percentage of patients with TTR <50%, which will be considered as a marker of bad quality of anticoagulation control as well as “time with increased thrombotic risk”(Larsen, T.B. 2012).
4. The percentage of patients with TTR >70% which will be considered as satisfactory.
5. The percent of visits in the range will also be interpreted to include the time in range of increased risk of haemorrhage and accepted as an INR >4.0.

For 2,3,4 and 5 above, the data will be further stratified according to age and gender.

Interpretation of the TTR in the cohort of patients with valve prosthesis will include the following:

1. The primary outcome is to determine the overall TTR.
2. The percentage of patients with TTR >70%, which will be considered satisfactory(Grzymala-Lubanski, Labaf et al. 2014).
3. The percentage of patients with TTR > 83%, which will be considered ideal.(Grzymala-Lubanski, Labaf et al. 2014).
4. The percentage of patients with TTR <70%, which will be considered suboptimal.

For 2,3 and 4 above, the data will be further stratified according to age and gender.

#### **Reliability:**

The nature of testing is consistent throughout i.e. INR values are determined by the same laboratory for all sampled patients. The target INR is also consistent for the Atrial Fibrillation cohort and is in line with the laboratory reference. In the cases of patients with valve prosthesis, the INR reference may differ, in view of the risk factors and thrombogenicity being different, however, the TTR and deviation from target INR will not be compromised, as each case will be interpreted according to that target INR. In the case of any subject having had 2 samplings for INR on the same day the average of the two will be used.

All subjects in both cohorts will have at least 12 INR readings used for interpretation.

The data for TTR will be determined by three different methods, two of which are well published and generally accepted. The third being the RATi software, is based on similar calculation concepts of other previously used software tools used in interpreting TTR.

However, determinants like the indication for anticoagulation, patient risk factors and any adverse event (haemorrhage/Warfarin toxicity/obstructed valve/any systemic thrombo-embolism) is reliant on the documentation of the attending clinician. A full and thorough chart review will be performed in all instances. Should the indication for anticoagulation or patient risk factors in the case of valve prosthesis still not be determined, the data from that chart review will not be used.

#### **Validity:**

The INR measurement is a valid and accepted method of determining the state of anticoagulation. The TTR is determined by interpretation of the INR. The two of the three methods proposed determine the TTR to a daily interpretation, while potential error in the third method, being percentage

of visits in the range (which reviews INR results over a longer interval), is minimised by reviewing the results over 1 year or 12 visits. It has been previously used showing acceptable predictive value.

Bias is minimised by sampling the INR of patients with the same method and using the same laboratory service and the same reference ranges regardless of demographic data. The reference ranges are individualised for the patients on anticoagulation for stroke prevention in Atrial Fibrillation and those with prosthetic valves, however they remain as separate cohorts to each other.

#### **Confounding Factors:**

Concomitant use of other drugs that interact with Warfarin and therefore affect the INR.

#### **Variability:**

Variability in diet between the different patients which may alter Warfarin metabolism and therefore the INR.

#### **Sample Size:**

Patients who attended the Gandhi Memorial Hospital, Adult Medical Outpatients Department from 1<sup>st</sup> October 2015 to 30<sup>th</sup> November 2015 will be randomly selected.

Two cohorts are proposed:

1. 150 Patients with non-valvular Atrial Fibrillation and on oral anticoagulants
2. 100 Patients with valve prosthesis and on oral anticoagulants

#### **Inclusion Criteria**

Patients attending the Mahatma Gandhi Memorial Hospital, Adult Medical Outpatients Department were considered to be enlisted. The sample was determined by retrospectively reviewing the patients' charts of those who attended the unit from 1st October 2015 to 30<sup>th</sup> November 2015.

Only outpatient subjects were considered.

Any patient over the age of 12 years is enlisted if that patient has non-valvular Atrial Fibrillation and is on Warfarin therapy for at least 1 year.

Any patients with any valve prosthesis and who are anticoagulated with Warfarin for at least one year above the age of 12 years old. By inference patients with bioprosthesis were not included.

#### **Exclusion Criteria**

Patients under the age of 12 years old were not considered for this study.

Patients with valvular Atrial fibrillation without a mechanical prosthesis were not considered.

Any patient on anticoagulation for less than one year was not considered.

Inpatients were not considered.

Any patient on oral anticoagulation with an undetermined indication, or not for the purposes of this study eg. Venous Thrombo-embolism was not considered.

Any patient with a valve prosthesis but has an undetermined target INR due to lack of documentation of patient factors.

### **Data collection tools and methods**

Sample selection: Systematically randomised.

Total population (N) - Patients who meet the inclusion criteria for the study period from 1<sup>st</sup> October 2015 to 30<sup>th</sup> November 2015 at Mahatma Gandhi Memorial Hospital, Adult Medical Outpatients Department. These will be randomised to numbers 1 to N.

Sample Size n– 150 patients with non-valvular Atrial Fibrillation and 100 patients with valve prosthesis. Selected using an interval size k as described in Methods of sampling.

Chart Audits: Once the sample cohorts are determined (by indication for anticoagulation), retrospective chart reviews will be undertaken to determine the following parameters for each patient:

1. Age
2. Gender
3. Patient Risk Factors (in the case of valve prosthesis) which is Mitral, tricuspid or pulmonary position; Previous arterial thrombo-embolism; Atrial fibrillation; Left atrium diameter >50 mm; Mitral stenosis of any degree; Left ventricular ejection fraction <35%; Left atrial dense spontaneous echo contrast
4. Prosthetic valve Thrombogenicity ( in the case of valve prostheses patients)
5. INR values for the previous 1 year or least 12 values whichever is the longer time period
6. Number of visits in the period determined in 4.
7. Date of INR values as corresponds with patient visits.
8. Documented adverse event (any period while on anticoagulation) which includes any haemorrhage, any admission for Warfarin toxicity, any systemic embolism, any obstructed valve

This data will then be collected and distributed in table format for each patient as illustrated below:

Patients being anticoagulated for stroke prevention in non-valvular Atrial Fibrillation: **See Figure 1.**

Patients being anticoagulated in the presence of valve prosthesis: **See Figure 2.**

### **Data Analysis Techniques**

For Assessment of TTR, each patient will have an accompanying chart, including the following:

1. Rosendal Method as adapted from Microsoft Excel (**see Figure 3.** for example).
2. The percent of visits in the range (**see Figure 4.** for example)
3. The printout of the spreadsheet from the RATi software program

In addition the Percentage of Visits above the range, Below the Range and above an INR of 4.0 will be recorded. (**See Figure 5, Figure 6 and Figure 7** for example)

For each cohort analysed above, a subdivision of Male and Female gender will be made.

Figure 1. Data Collection Tool in the case of a patient on Warfarin for Stroke prevention with Non-Valvular Atrial Fibrillation

<b>Patient Reference No.</b> ( Corresponds with the number randomly assigned as part of population group N)							
<b>Indication for Anticoagulation:</b> Stroke prevention in non-valvular AF				<b>Age:</b> Number of completed years		<b>Gender:</b> Male or Female	
<b>Adverse events and date of event:</b> 1. _____ 2. _____ 3. _____ 4. _____ 5. _____ 6. _____ 7. _____						<b>Target INR range: 2-3</b>	
Date of visit In reversed chronological order	Days since last visit	Preceding weekly dose of Warfarin	INR Value	INR in Range?	Deviation below Range	Deviation above Range	INR above 4.0?
	<b>Total Days</b>		<b>Total no. of tests</b>	<b>Total INRs in range</b>	<b>Total INRs below Range</b>	<b>Total INRs above Range</b>	<b>Total INRs above 4.0</b>

Figure 2. Data Collection Tool in the case of a patient on Warfarin for valve prosthesis

<b>Patient Reference No.</b> ( Corresponds with the number randomly assigned as part of population group N)							
<b>Indication for Anticoagulation:</b> Valve Prosthesis				<b>Age:</b> Number of completed years		<b>Gender:</b> Male or Female	
<b>Adverse events and date of event:</b> 1. _____ 2. _____ 3. _____ 4. _____				<b>Valve Thrombogenicity:</b> High / Medium / Low	<b>Patient risk Factors:</b> Yes /No	<b>Target INR range:</b>	
<b>Date of visit In reversed chronological order</b>	<b>Days since last visit</b>	<b>Preceding weekly dose of Warfarin</b>	<b>INR Value</b>	<b>INR in Range?</b>	<b>Deviation below Range</b>	<b>Deviation above Range</b>	<b>INR above 4.0?</b>
	<b>Total Days</b>		<b>Total no. Of tests</b>	<b>Total INRs in range</b>	<b>Total INRs below Range</b>	<b>Total INRs above Range</b>	<b>Total INRs above 4.0</b>

Figure 3. Example of Excel spreadsheet with Rosendaal method.

Test Date	INR	Days Since Last Test	INR Diff	Previous INR Within Range?	Current INR Within Range?	Scenario	INR Diff Above Range	INR Diff Within Range	INR Diff Below Range	Days within Range since Last Test	% Days within Range since Last Test
30/05/2006	2.3				In Range						
06/06/2006	3.3	7	1	In Range	Above	Calculate	0.3	0.7	0	4.9	70%
13/06/2006	2.5	7	-0.8	Above	In Range	Calculate	0.3	0.5	0	4.4	63%
20/06/2006	1.8	7	-0.7	In Range	Below	Calculate	0	0.5	0.2	5.0	71%
27/06/2006	2.1	7	0.3	Below	In Range	Calculate	0	0.1	0.2	2.3	33%
04/07/2006	1.5	7	-0.6	In Range	Below	Calculate	0	0.1	0.5	1.2	17%
11/07/2006	1.5	7	0	Below	Below	Below	0	0	0	0.0	0%
18/07/2006	1.8	7	0.3	Below	Below	Below	0	0	0.3	0.0	0%
25/07/2006	3.9	7	2.1	Below	Above	Calculate	0.9	1	0.2	3.3	48%
01/08/2006	3.7	7	-0.2	Above	Above	Above	0.2	0	0	0.0	0%
08/08/2006	3.5	7	-0.2	Above	Above	Above	0.2	0	0	0.0	0%
15/08/2006	1.7	7	-1.8	Above	Below	Calculate	0.5	1	0.3	3.9	56%
22/08/2006	2.4	7	0.7	Below	In Range	Calculate	0	0.4	0.3	4.0	57%
29/08/2006	2.5	7	0.1	In Range	In Range	In Range	0	0.1	0	7.0	100%
05/09/2006	3.2	7	0.7	In Range	Above	Calculate	0.2	0.5	0	5.0	71%
12/09/2006	3	7	-0.2	Above	In Range	Calculate	0.2	0	0	0.0	0%
19/09/2006	2.3	7	-0.7	In Range	In Range	In Range	0	0.7	0	7.0	100%

<b>Low Range</b>	<b>2</b>
<b>High Range</b>	<b>3</b>

Rosendaal Method

<b>Days Within Range</b>	<b>Eg.425.1</b>
<b>Total Days</b>	<b>Eg.701.0</b>
<b>% Days Within Range</b>	<b>60.6%</b>

Percentage in Range (Figure.4)

<b>Total Number of Tests</b>	<b>100.0</b>
<b>Number of Tests in Range</b>	<b>51.0</b>
<b>% of Tests in Range</b>	<b>51.0%</b>

Percentage above Range (Figure.5)

<b>Total Number of Tests</b>	<b>100.0</b>
<b>Number of Tests in Range</b>	<b>14.0</b>
<b>% of Tests in Range</b>	<b>14.0%</b>

Percentage below Range (Figure.6)

<b>Total Number of Tests</b>	<b>100.0</b>
<b>Number of Tests in Range</b>	<b>21.0</b>
<b>% of Tests in Range</b>	<b>42.0%</b>

Percentage above INR >4.

(Figure. 7)

<b>Total Number of Tests</b>	<b>100.0</b>
<b>Number of Tests in Range</b>	<b>11.0</b>
<b>% of Tests in Range</b>	<b>11.0%</b>

### **Statistical Analysis:**

Direct interpretation of the results as a percentage for the following categories for each cohort using the three methods described above:

1. Percentage of time of INR within the therapeutic range
2. Percentage of time of INR within the subtherapeutic range
3. Percentage of time of INR within toxic range.

Arithmetic Mean and Median will be used to characterise the population and directly interpret the findings as a percentage using the 3 methods discussed above.

Standard Deviation will be used to disperse the data

One way ANOVA will be used to evaluate differences across the indications.

This study is predominantly observational and descriptive. Data will be analysed and a p-value <0.05 will be considered significant.

### **Study Location:**

Patients attending Mahatma Gandhi Memorial Hospital, Adult Medical Outpatients Department (Phoenix, KwaZulu Natal, South Africa) for assessment of non valvular Atrial fibrillation or valve prosthesis and treatment with Warfarin.

### **Study Period:**

Patients who attend the Gandhi Memorial Hospital, Adult Medical Outpatients Department from 1<sup>st</sup> October 2015 to 30<sup>th</sup> November 2015 will be randomly selected.

Data will be analysed and interpreted during the period of December 2015 to February 2016.

### **Limitations to the Study:**

The main limitation of this study is that it is based on a retrospective cohort of patients in a single centre.

The data studied here did not reflect any INR levels taken at other hospitals or during hospitalisations.

The study period under review spanned 12 months and this may not necessarily be a long enough period to observe all INR findings.

The size of the population group is limited to 150 and 100 patients for non valvular AF and valve prosthesis respectively and it may not represent the findings of all patients in the study centre.

### **Ethical Considerations:**

Literature reviewed in this study has been referenced using the EndNote system.

The study is a retrospective chart audit which seeks to maintain anonymity of the patients throughout the study.

At no point will any of the patients' charts be removed from the hospital premises nor will any duplication of charts or any part thereof be undertaken. No adjustments or amendments will be performed on any of the charts used. Furthermore patients will be randomised to a study population number and no publication of any patient names, clinician names or hospital or file numbers will take place.

Any chart audit undertaken will be done so after the patient has completed his visit so as to not delay any patients' visit nor disrupt any workings of the department.

At no point will any patient or clinician interviews nor interventions take place.

I will attempt to seek consent from the Department of Health, Kwa Zulu Natal and the Hospital Medical Manager (see Addendum 1) in order to proceed with the proposed study.

This research will attempt at all times to remain impartial, true to findings and independent. There is no conflict of interest by the researcher.

## Addendum1.

In order to ascertain permission for sampling from the proposed site, I have written a formal request addressed to the Medical Manager of the Hospital. (Addendum 1)

Mahatma Gandhi Memorial Hospital

100 Phoenix Highway

Phoenix

To the Medical Manager

Re: Request for permission to conduct a study at your institution

I am currently within the employ of the Department of Health-Kwazulu Natal. In addition I am presently enrolled in a postgraduate registrar training program at the University of Kwazulu Natal.

I wish to conduct a retrospective and observational study on patients who attend the Adult Medical Outpatients Department at Mahatma Gandhi Memorial Hospital for the purposes of an MMED.

The proposed research topic is titled Warfarin: Time in Therapeutic Range (TTR), A single centre retrospective study on patients using Warfarin for stroke prevention in non-valvular Atrial Fibrillation or for patients with Prosthetic heart valves.

The aim of the study is to assess the quality of anticoagulation of patients on Warfarin for stroke prevention in non-valvular Atrial Fibrillation or in the presence of prosthetic heart valves.

The identified study population are patients attending Mahatma Gandhi Memorial Hospital, Adult Outpatients Department for assessment and treatment of non valvular Atrial Fibrillation and valve prosthesis. The study sample and the sample size will include patients who attend during October 2015 and November 2015 and will be randomised into two cohorts of 150 Patients with non-valvular Atrial Fibrillation and on oral anticoagulants and 100 Patients with valve prosthesis and on oral anticoagulants.

Once the sample cohorts are determined (by indication for anticoagulation), retrospective chart reviews will be undertaken to determine the following parameters for each patient:

1. Age
2. Gender
3. Patient Risk Factors (in the case of valve prosthesis) which is Mitral, tricuspid or pulmonary position; Previous arterial thrombo-embolism; Atrial fibrillation; Left atrium diameter >50 mm; Mitral stenosis of any degree; Left ventricular ejection fraction <35%; Left atrial dense spontaneous echo contrast
4. Prosthetic valve Thrombogenicity ( in the case of valve prostheses patients)
5. INR values for the previous 1 year or least 12 values whichever is the longer
6. Number of visits in the period determined
7. Date of INR values as corresponds with patient visits.

8. Documented adverse event (any period while on anticoagulation) which includes any haemorrhage, any admission for Warfarin toxicity, any systemic embolism, any obstructed valve

This data will then be collected and distributed in table format for each patient for the purposes of the study.

I propose access to the study population by using the Medical outpatient department list of patients who are having INRs sampled for the day.

At no point will any of the patients' charts be removed from the hospital premises nor will any duplication of charts or any part thereof be undertaken. No adjustments or amendments will be performed on any of the charts used. Furthermore patients will be randomised to a study population number and no publication of any patient names, clinician names or hospital or file numbers will take place.

Any chart audit undertaken will be done so after the patient has completed his visit so as to not delay any patients' visit nor disrupt any workings of the department.

At no point will any patient or clinician interviews take place.

The perceived outcomes of the study will hold benefit to the patients attending the hospital and may have implications on future best practices. The results of the study will be made available to you upon your request.

I will gladly consent to any signings required for the responsibility of the chart while I am utilising it.

I have applied to seek Ethics approval for this study.

I am at all times being supervised during this study.

In order to continue this study, permission from the institute is required and I therefore request permission to undertake this study for the purposes described at this institution.

Your co-operation in this regard is welcomed.

Kind Regards

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Dr. D Sadhabiriss (MbChB)

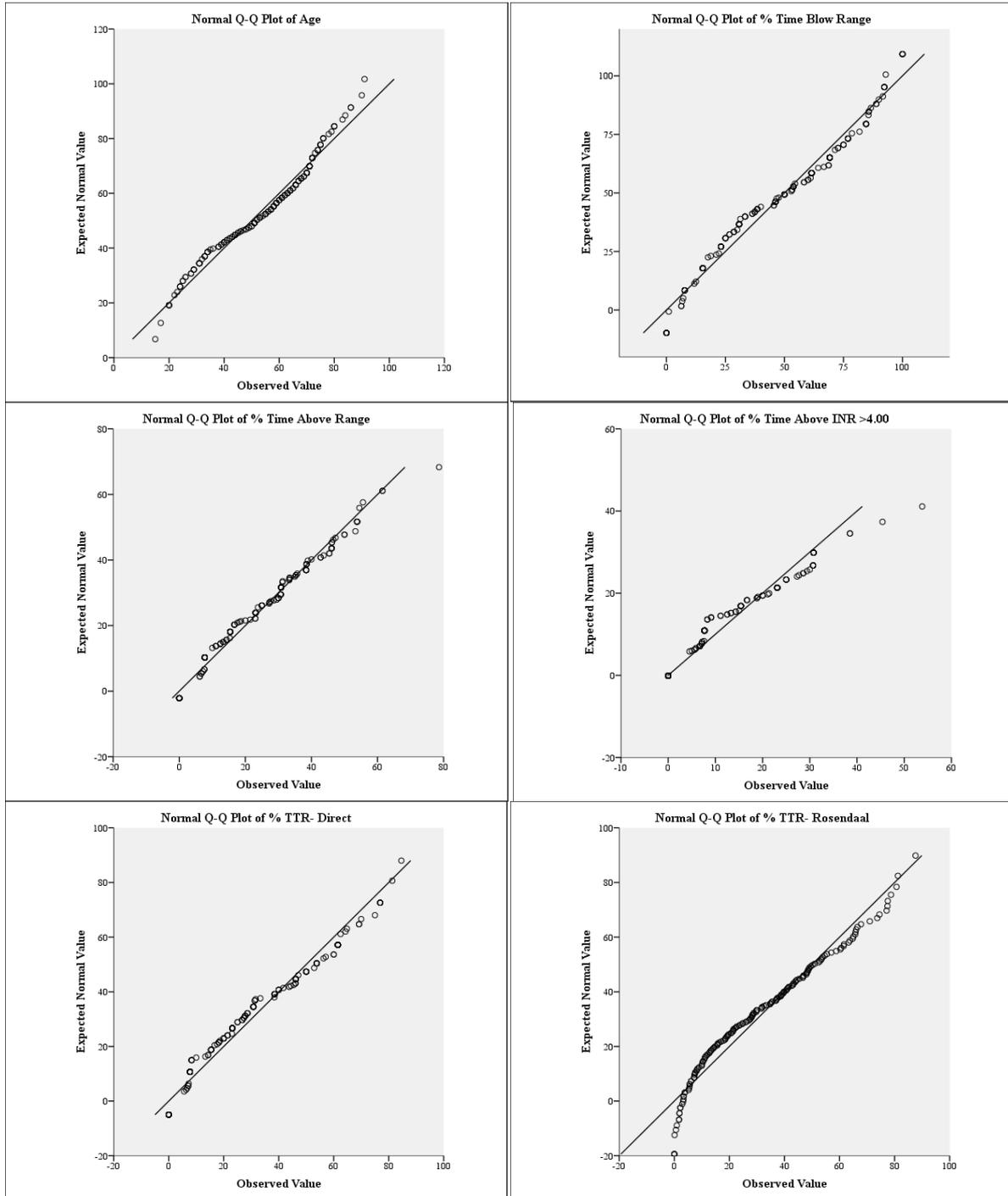
Medical registrar

Tel. 0824417053

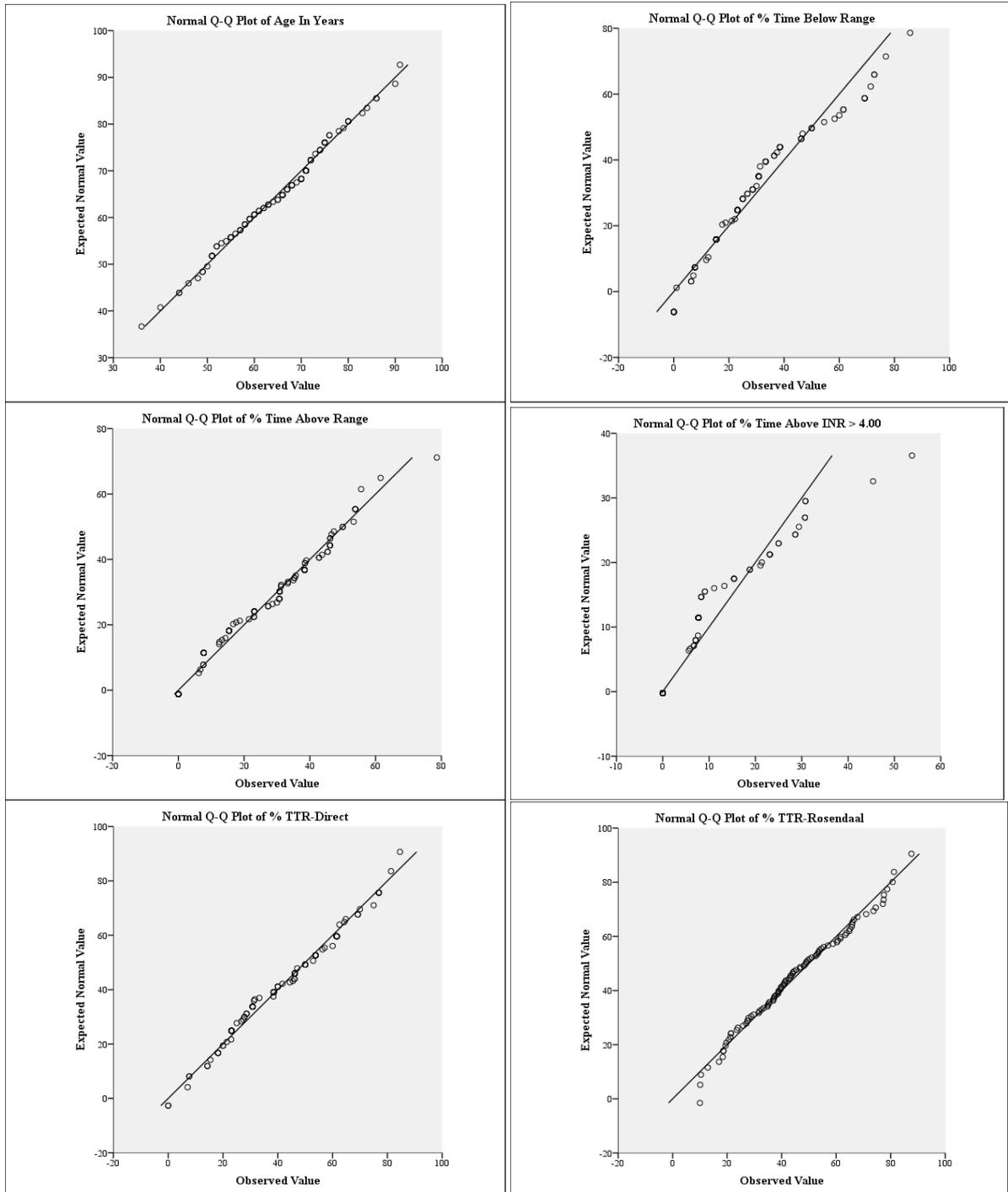
E-mail. dhiren.sadhabiriss@gmail.com

ANNEXURE F: PLOTS OF QUANTITATIVE DATA

Q-Q Plots for N (177) Using Blom's fractional Rank estimation method



Q-Q Plots : AF Cohort (n=96)Using Blom's fractional Rank estimation method



Normal Q-Q Plot : Valve cohort (n=81) Using Blom's fractional Rank estimation method

