Anticoagulation For Nonvalvular Atrial Fibrillation In South Africa

Dr Vanessa Mogashoa, MBBCh (Wits), FCP (SA)

Student number: 371296

Supervisors:

Prof Nqoba Tsabedze, MBBCh (Wits), FCP (SA), Cert Cardio (SA), MMed (Wits), FESC

Dr Dineo Mpanya, MBChB (UCT), FCNP (SA), MMed (Wits), PhD (Wits)

Research Report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Medicine (Internal Medicine)

April 2024

Declaration by the student

I, Vanessa Mogashoa, student number 371296, declare that this research report (submissible article and protocol with comprehensive literature review) is my unaided work. It is being submitted for the Degree of Master of Medicine at the University of the Witwatersrand. It has not been previously submitted for any other degree or examination at this or any other University.

Signature: 

Date: 2024/04/28

Declaration by supervisors

I, Nqoba Tsabedze, the primary supervisor declare that the student, Vanessa Mogashoa reviewed the literature, analysed the data, and worked independently. She also wrote the first draft of the manuscript appearing in this research report.

Name of Primary Supervisor: Professor Nqoba Tsabedze

Signature of Primary Supervisor ……...

Date: 2024/04/28

I, Dineo Mpanya, the co-supervisor declare that the student, Vanessa Mogashoa reviewed the literature, analysed the data, and worked independently. She also wrote the first draft of the manuscript appearing research report.

Name of Co-Supervisor: Dr Dineo Mpanya

Signature of Co-Supervisor ……..……..

Date: 2024/04/28

Co- authors agreement

By signing this declaration, the co-authors listed below agree to the use of the article by the student as part of her research report. The co-authors confirm that their contribution entailed supervision, addressing technical queries and reviewing the manuscript.

Authors	**Name**	**Signature**	**Date**
1st author	Vanessa Mogashoa		2024/04/28
2nd author	Dineo Mpanya		2024/04/28
3rd author	Nqoba Tsabedze		2024/04/28

Dedications

To my family for their ongoing love and support.

Acknowledgements

To my supervisors Prof Tsabedze and Dr Mpanya for their tireless contributions to this manuscript whilst being beacons of excellence and inspiration.

Table of Contents

Authors Guidelines – BMC Cardiovascular Disorders

Preparing your manuscript

The information below details the section headings that you should include in your manuscript and what information should be within each section.
Please note that your manuscript must include a 'Declarations' section including all of the subheadings (please see below for more information).

Title page

The title page should:

- present a title that includes, if appropriate, the study design e.g.:
  - "A versus B in the treatment of C: a randomised controlled trial", "X is a risk factor for Y: a case control study", "What is the impact of factor X on subject Y: A systematic review"
  - or for non-clinical or non-research studies a description of what the article reports
- list the full names and institutional addresses for all authors
  - if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the "Acknowledgements" section in accordance with the instructions below
  - Large Language Models (LLMs), such as ChatGPT, do not currently satisfy our authorship criteria. Notably an attribution of authorship carries with it accountability for the work, which cannot be effectively applied to LLMs. Use of an LLM should be properly documented in the Methods section (and if a Methods section is not available, in a suitable alternative part) of the manuscript.
- Indicate the corresponding author

Abstract

The Abstract should not exceed 350 words. Please minimise the use of abbreviations and do not cite references in the abstract. Reports of randomised controlled trials should follow the CONSORT extension for abstracts. The abstract must include the following separate sections:

- Background: the context and purpose of the study
- Methods: how the study was performed and statistical tests used
- Results: the main findings
- Conclusions: brief summary and potential implications
- Trial registration: If your article reports the results of a health care intervention on human participants, it must be registered in an appropriate registry and the registration number and date of registration should be stated in this section. If it was not registered prospectively (before enrollment of the first participant), you should include the words 'retrospectively registered'. See our editorial policies for more information on trial registration

Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

Methods

The methods section should include:

- the aim, design and setting of the study
- the characteristics of participants or description of materials
- a clear description of all processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses
- the type of statistical analysis used, including a power calculation if appropriate

Results

This should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

Discussion

This section should discuss the implications of the findings in context of existing research and highlight limitations of the study.

Conclusions

This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations should be provided.

Research report - Submissible format

Anticoagulation For Nonvalvular Atrial Fibrillation In South Africa

Authors

Vanessa Mogashoa, Dineo Mpanya, Nqoba Tsabedze*

Division of Cardiology, Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

***Corresponding Author**

Professor Nqoba Tsabedze

Division of Cardiology, Charlotte Maxeke Johannesburg Academic Hospital

17 Jubilee Road, Parktown, 2193, Johannesburg, Gauteng Province, South Africa

Telephone: +27 11 488 3611

Fax: 27 11 642 9041

Email address: Nqoba.Tsabedze@wits.ac.za

Abstract

Background: Nonvalvular Atrial fibrillation (NVAF) is a growing epidemic in Africa. Anticoagulation, considered the backbone of NVAF management, is limited to warfarin as the mainstay of available anticoagulation therapy in most low-and-middle-income countries (LMICs). The optimal time in the therapeutic range (TTR) while on warfarin is crucial to avoid bleeding and thromboembolic complications. This study aimed to assess anticoagulation control in patients with NVAF on warfarin in Johannesburg, South Africa.

Methods: We conducted a cross-sectional retrospective study on consecutive patients with NVAF managed between the 1st of January 2015 and the 31st of December 2019 at a tertiary-level academic centre in Johannesburg, South Africa. Anticoagulation control for patients with NVAF was assessed by calculating the time in therapeutic range using the Rosendaal method.

Results: The study population comprised of 177 patients diagnosed with NVAF. The mean age in the study population was 65.0 ± 13.1 years. The median TTR among patients with NVAF was 46% [interquartile range (IQR): 8.7 – 86.0], and 63 (35.6%) patients with NVAF had a TTR ≥ 70%. Patients with poor anticoagulation control (TTR<70%) were on warfarin for a shorter duration compared with those with optimal anticoagulation control [56 days (IQR: 43 – 84) vs 70 days (IQR: 56 – 140), p=0.0013]. The mean CHA_2DS_2-VASc score was 4 ± 1.5, and it did not differ between patients with poor or optimal anticoagulation control. Among the 175 patients with calculable HAS-BLED scores, 21 (12.0%), 112 (64.0%) and 42 (24.0%) were at a low, moderate, and high risk for bleeding, respectively. Of the 21 patients in the HAS BLED low risk category, only 4 (19.0%) had a TTR<70% (p<0.001). Warfarin toxicity was documented in 13 (7.3%) patients.

Conclusion: In our study, a TTR ≥ 70%, suggesting poor anticoagulation control was found in 35.6% of NVAF patients on warfarin. Larger multicentre trials comparing the occurrence of bleeding, thromboembolic events, as well as the total cost to the healthcare system in patients treated with warfarin compared to direct oral anticoagulation therapy are required to guide oral anticoagulation strategies in Africa.

Keywords: atrial fibrillation; anticoagulation; warfarin; time in therapeutic range; direct oral anticoagulants; international normalised ratio

Background

The bedrock of nonvalvular atrial fibrillation (NVAF) management is optimal anticoagulation. This is required to mitigate the associated high risk of mortality, stroke, and impaired quality of life. [1]. Atrial fibrillation (AF) carries a five-fold increased risk of complicating with a stroke. Atrial fibrillation-related strokes are associated with significant disability and mortality compared to non-AF-related strokes [2, 3]. Optimal anticoagulation control remains challenging, particularly in low-and-middle-income countries (LMICs). The efficacy of direct oral anticoagulants (DOACs) has led to increasing use in NVAF and incentivised ongoing research into their safety profile. As such, DOACs are progressively being considered for NVAF, even in previously neglected high-risk populations such as those with kidney disease and frail patients [4, 5].

In LMICs, the introduction of DOACs in the management plan of patients with NVAF is currently not perceived as cost-effective despite a higher incidence of NVAF-related complications such as stroke. In a prospective cross-sectional observational AF registry of 29 medical institutions in urban South Africa involving 302 patients with a mean age of 67 years, the prevalence of AF-related strokes was 8.3% [6]. In rural South Africa, the crude incidence rate for non-AF-related stroke is 244 per 100,000 person-years [7].

The high stroke burden associated with AF necessitates maintaining an optimal time in the therapeutic range (TTR) to prevent thromboembolic events and curtail the bleeding effects of poor warfarin control. The 2020 European Association of Cardiology guidelines for the diagnosis and management of NVAF, developed in collaboration with the European Association of Cardiothoracic Surgery, recommends switching patients from vitamin K antagonists to direct oral anticoagulants (DOACs) if the TTR is below 70% as a class I indication [1]. There is limited data describing anticoagulation control in patients with NVAF in LMICs. Therefore, the study aimed to determine the level of oral anticoagulation control in patients with NVAF treated with vitamin K oral anticoagulation in a tertiary academic centre in Johannesburg, South Africa.

Methods

We conducted a cross-sectional retrospective study in the Division of Cardiology at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) on patients with NVAF diagnosed between 1 January 2015 and 31 December 2019. Patients 18 years of age and older with the International Classification of Disease (ICD-10) code for AF who were treated with oral vitamin K anticoagulation (warfarin) and had outpatient international normalised ratios (INR) measured for a minimum of six months were included in the analysis. The rationale for this was to mitigate the effects of warfarin initiation titration dosing. We excluded records of patients who had valvular atrial fibrillation, as evidenced by echocardiographic features of mitral stenosis or a previous history of valve surgery for organic valvular heart disease. Patients who were not prescribed oral anticoagulation therapy and those on DOACs were also excluded.

Study data was collected from an electronic health record system that captures admission data for all patients hospitalised in the cardiology wards as well as from outpatient medical records at the CMJAH. The following variables were collected and analysed as part of the study: demographic data, comorbidities, oral medication, heart rate, systolic and diastolic blood pressure, the left ventricular ejection fraction, the CHA_2DS_2-VASc (Congestive heart failure/left ventricular ejection fraction <40%, hypertension, age >75 years, diabetes mellitis , stroke/transient ischemic attack/thromboemobolism history, vascular disease , age 65-75 years , female sex) score as well as the HAS-BLED (Hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalised ratio, elderly [age>65], drugs/alcohol concomitantly) score [1]. Laboratory parameters such as the estimated glomerular filtration rate (eGFR) and the INR were obtained from the National Health Laboratory Services website.

In accordance with the latest AF guidelines for an INR target between 2 - 3 for all patients with NVAF on warfarin, we calculated the TTR using the Rosendaal method for patients with NVAF [1, 8-10]. Furthermore, patients with NVAF were stratified according to the TTR (TTR<70% and TTR ≥70%).

We also took note of documented thromboembolic and haemorrhagic events that occurred within the study period. Thromboembolic events were defined as an occurrence of a cerebrovascular event, transient ischaemic attacks, pulmonary embolism, or deep vein

thrombosis. Haemorrhagic events included warfarin toxicity defined as: bleeding in a patient with an INR above 4 that necessitates hospital admission or blood transfusion.

Permission to conduct the study was obtained from the University of the Witwatersrand Human Research Ethics Committee, Medical (certificate number: 201091) and relevant hospital authorities. Individual patient consent was waived since the study entailed a retrospective review of medical records.

Statistical Analysis

Statistical analyses were performed using Stata SE version 17 (StataCorp. 2019. College Station, TX: StataCorp LLC). Data is expressed as the mean and standard deviation when normally distributed and as the median with interquartile ranges (IQR) when the distribution is non-normal. Categorical data is expressed as frequencies and percentages. For continuous variables with a normal distribution, a Student t-test was used to test for intergroup differences (TTR<70% vs. TTR ≥70%), and the Pearson's chi-square test was used to compare categorical data. A Wilcoxon rank sum test was used to compare medians for continuous variables with a non-normal distribution. All variables with a p-value of less than 0.25 after conducting the Pearson's chi-square test, Student's t-test or Wilcoxon rank sum test after testing for intergroup differences (TTR<70% vs TTR≥70%) were selected for further exploration in the univariable logistic regression model. Confidence intervals (CI) were set at 95%, and a p-value of less than 0.05 was considered to represent statistical significance.

Results

Demographic and clinical characteristics

The final study population comprised 177 patients with NVAF (**Figure 1**). There were 96 (54.2%) males, and the mean age in the study population was 65.0 ± 13.1 years. Heart failure was reported in 146 (82.5%) patients. A history of myocardial infarction (MI) was documented in 44 (24.9%) patients, and 17 (9.6%) patients with NVAF had a history of previous cerebrovascular accidents or transient ischaemic attacks (TIA). There were three (1.7%) people living with human immunodeficiency virus (PLHIV). Among all patients with NVAF, 125 (70.6%) were pensioners. The rest of the baseline demographic and clinical characteristics are depicted in Table 1.

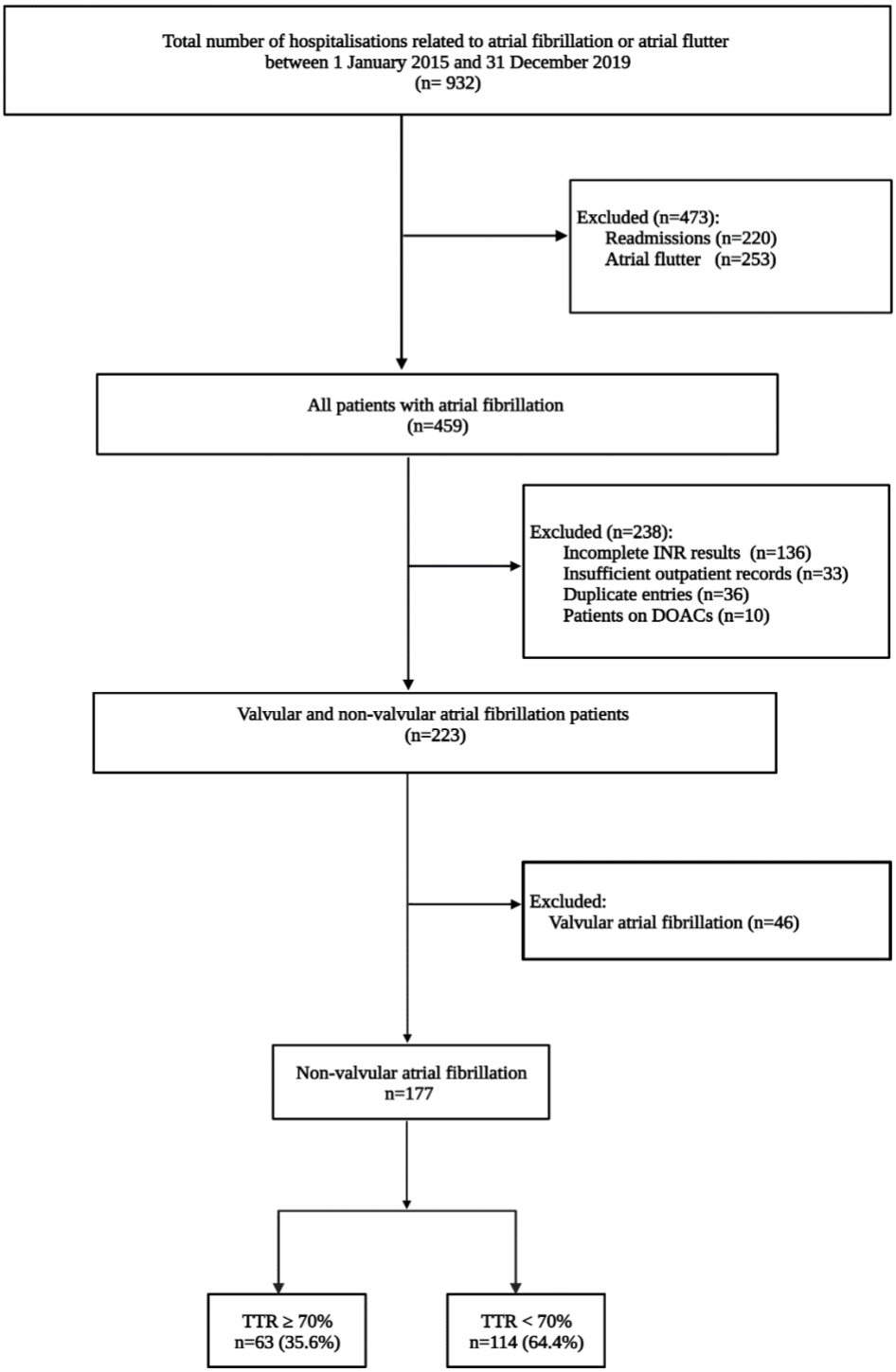

Figure 1 Flow chart showing the selection of patients included in the study. DOACs: direct oral anticoagulants, INR: international normalised ratio, TTR: time in therapeutic range

Table 1 Baseline demographic and clinical characteristics of patients with non-valvular atrial fibrillation on warfarin categorised according to the time in the therapeutic range

Clinical Parameters	All patients with NVAF (n=177)	TTR <70% (n=114) 64.4%	TTR ≥70% (n=63) 35.6%	p-value
Age (years)	65.0 ± 13.1	64.7 ± 12.4	65.7 ± 14.3	0.6225
Male	96 (54.2)	62 (54.4)	34 (54.0)	0.9570
Ethnicity				
African	77(43.7)	52 (45.6)	25 (40.3)	0.4990
Caucasian	75 (42.6)	46 (40.3)	29 (46.8)	0.4100
Indian	11 (6.2)	8 (7.0)	3 (4.8)	0.5680
Mixed Ancestry	13 (7.4)	8 (7.0)	5 (8.1)	0.8000
Comorbidities				
Hypertension	140 (79.1)	90 (78.9)	50 (79.4)	0.9480
Diabetes Mellitus	68 (38.4)	47 (41.2)	21 (33.3)	0.3010
Previous MI	44 (24.9)	28 (24.6)	16 (25.4)	0.9020
Heart Failure	146 (82.5)	95 (83.3)	51 (80.9)	0.6900
Medication				
Beta blockers	142 (80.2)	89 (78.1)	53 (84.1)	0.3330
Calcium channel blockers	23 (13.0)	12 (10.5)	11 (17.5)	0.1890
ACE inhibitor or ARB	97 (54.8)	68 (59.6)	29 (46.0)	0.0810
Digoxin	22 (12.4)	10 (8.8)	12 (19.0)	0.0470
Heart rate, bpm	91 (80 – 109)	88 (78 – 107)	97 (82 – 115)	0.2699
Systolic BP, mmHg	128 ± 21.8	130 ± 23.0	125 ± 19.1	0.1488
Diastolic BP, mmHg	82 ± 16.6	84 ± 17.5	80 ± 14.4	0.1070
LVEF, %	44 ± 17.1	44 ± 17.8	43 ± 16.1	0.6565

Data are represented as the mean and standard deviation (SD) for continuous variables with a normal distribution and the median and interquartile ranges (p25-p75) when the distribution is non-normal. Categorical data are represented as frequencies and percentages. ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; BP: blood pressure; LVEF: left ventricular ejection fraction; MI: myocardial infarction

Anticoagulation control in patients with nonvalvular atrial fibrillation

The median TTR among patients with NVAF was 46.0% (IQR: 8.7 – 86.0), and the TTR was greater than or equal to 70% in 63 (35.6%) patients (**Figure 2)**. The weekly median warfarin dose did not differ significantly between patients with poor (TTR<70%) or optimal (TTR≥70%) anticoagulation control [35.0 mg (IQR: 25.0 – 35.0) vs 35.0 mg (17.5 – 35.0), p= 0.8232]. Patients with poor anticoagulation control (TTR<70%) were on warfarin for a shorter duration compared with those with optimal anticoagulation control [56 days (IQR: 43 – 84) vs 70 days (IQR: 56 – 140), p=0.0013]. The eGFR did not differ significantly between patients with a TTR<70% and those with a TTR ≥70%, [54.5 ml/min/1.73m^2 (IQR: 42 – 74) vs 58 ml/min/1.73m^2 (IQR: 42 – 79), p=0.7119]. The mean CHA_2DS_2-VASc score was 4 ± 1.5, and it did not differ significantly between patients with poor or optimal anticoagulation control (p=0.4932). Among the 175 patients with calculable HAS-BLED scores, 21 (12.0%), 112 (64.0%) and 42 (24.0%) were at a low, moderate, and high risk for bleeding, respectively. Of the 21 patients in the HAS BLED low risk category, only 4 (19.0%) had a TTR<70% (p<0.001).

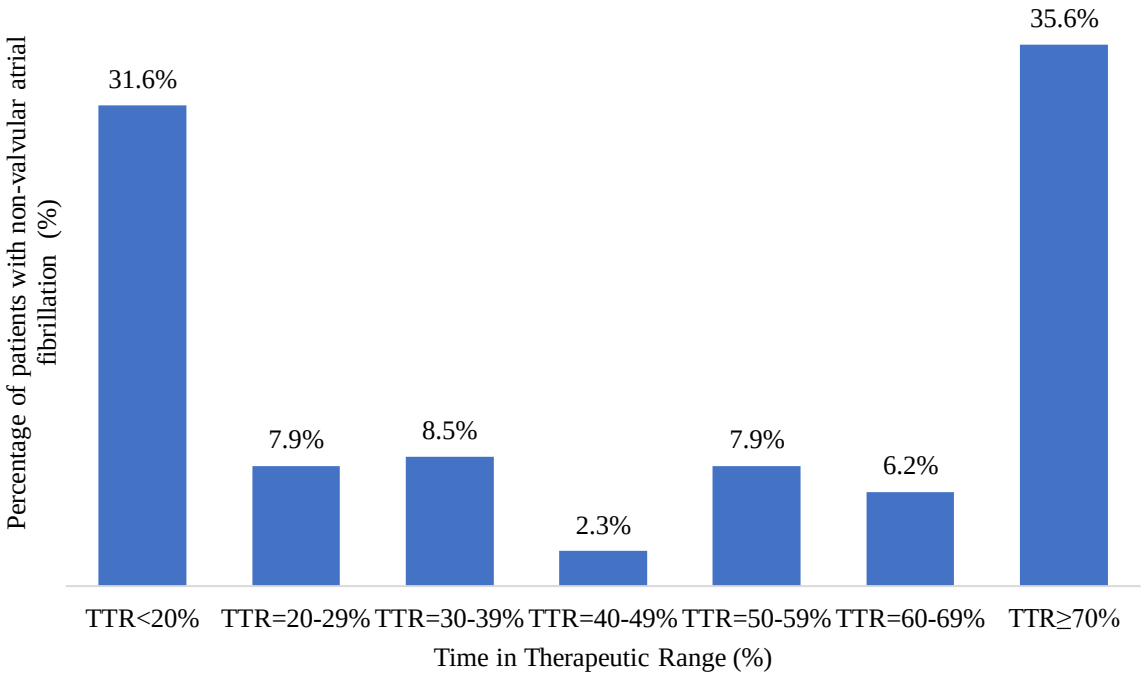

Figure 2 Time in therapeutic range in nonvalvular atrial fibrillation patients on warfarin

The median baseline or first INR measured was 2.1 (IQR: 1.5 – 2.8), and the median duration between the baseline or first INR and the third INR measurement was 62 days (IQR: 49 – 97). There were 68 (38.4%) patients with a baseline INR between 2.0 and 3.0 (**Figure 3)**.

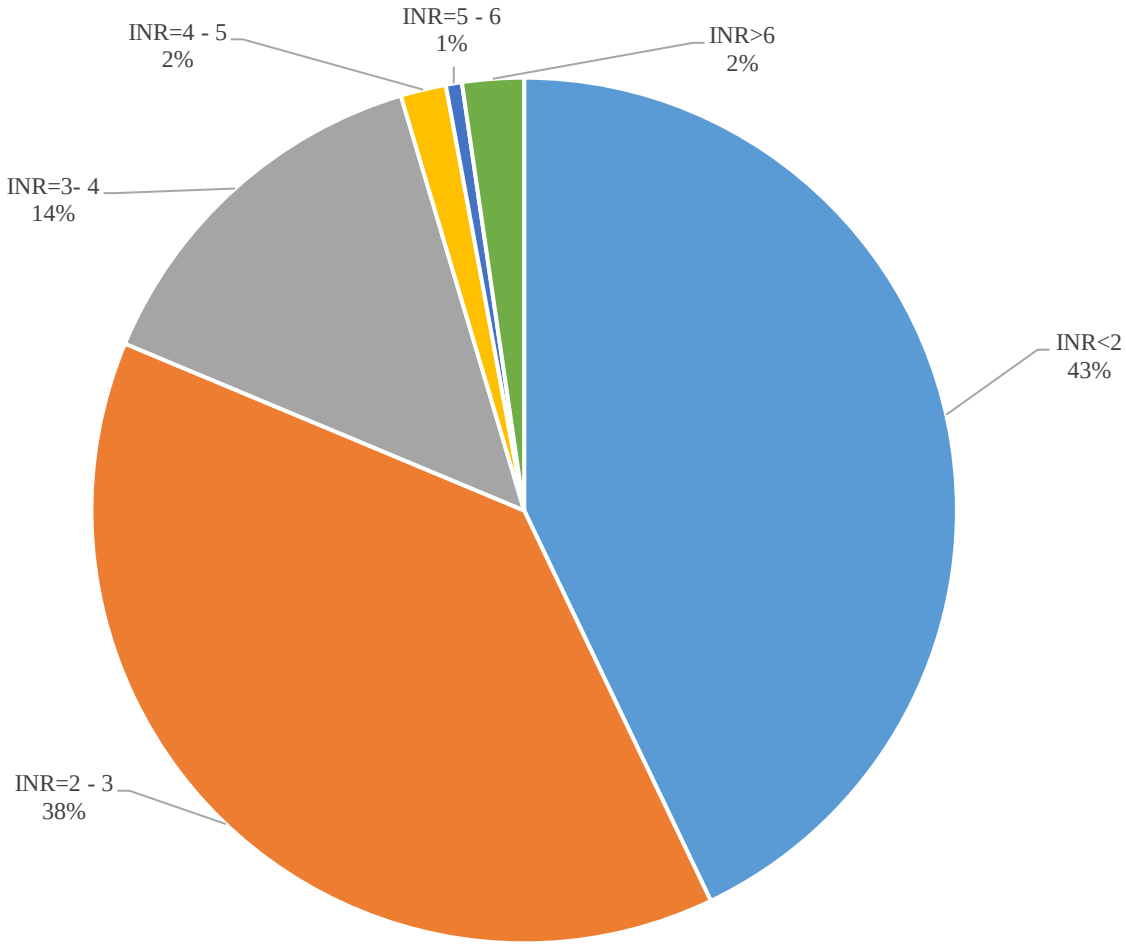

Figure 3 Distribution of baseline or first international normalised ratio (INR) measurements in non-valvular atrial fibrillation patients on warfarin

Complications

Warfarin toxicity was documented in 13 (7.3%) patients where gastrointestinal bleeding was reported in one (0.6%) patient .The median duration between the diagnosis of NVAF and the occurrence of warfarin toxicity was 129 days (IQR: 24 – 783). Major bleeding requiring a blood transfusion was documented in one (0.6%) patient.

Thromboembolic complications were only documented in a few patients, with ischaemic strokes documented in 6 (3.4%) patients, acute pulmonary embolism in one (0.6%) patient and lower limb deep vein thrombosis in one (0.6%) patient.

Predictors of poor anticoagulation control

To assess for predictors of poor anticoagulation control (TTR< 70%) among patients with NVAF, the following variables were included for further exploration in the univariable logistic regression model: systolic and diastolic blood pressure, medications (ACE or ARB, calcium channel blockers, and digoxin) and duration on warfarin. The HAS-BLED score was not included in the univariable logistic regression model since it incorporates INR. This was done to avoid collinearity between the HAS-BLED score and the TTR. None of the variables were associated with poor anticoagulation control.

Table 2: Univariable regression analysis of variables associated with poor anticoagulation control (TTR <70%) in nonvalvular atrial fibrillation patients on warfarin

Clinical Parameter	Odds ratio	p-value	95% CI
ACE inhibitor or ARB	1.733	0.083	0.931-3.224
Digoxin	0.408	0.052	0.165-1.009
Calcium channel blocker	0.556	0.193	0.229-1.356
Systolic blood pressure	1.011	0.149	0.996-1.025
Diastolic blood pressure	1.016	0.109	0.997-1.036
Duration on warfarin (days)	0.997	0.079	0.993-1.000

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; BP: blood pressure; CI: confidence interval.

Discussion

We retrospectively reviewed medical records of 177 patients with NVAF treated at the CMJAH, a tertiary state-owned academic hospital in Johannesburg, South Africa. Our study demonstrated that anticoagulation control in patients with NVAF is suboptimal, with only 35.6% of our patients achieving a TTR above the recommended 70%. The median TTR was 46.0% (IQR: 8.7 – 86.0) and was higher than that reported by the Randomized Evaluation of Long-Term Anticoagulation Therapy (RELY) Atrial fibrillation Registry, a multicentre global trial which included 20 sites from Africa [11]. In the RELY trial, the mean TTR among 1137 patients recruited from Africa was 33%, and patients from Africa with NVAF had the lowest TTR compared to their counterparts in high-income countries and other LMICs [11]. Also, a study by Semakula and colleagues evaluating the TTR in outpatients requiring INR monitoring services in Uganda and South Africa showed that, despite regular INR monitoring at least once per month, the median TTR was 41% (IQR: 14 - 69) [3]. Although this study by Semakula et al. included all patients on warfarin irrespective of the clinical indication for warfarin, it highlighted some of the shared difficulties we also found in our study associated with warfarin use. Furthermore, a study conducted in Kwa-Zulu Natal, South Africa, found that only ten patients (10.4%) with NVAF maintained a TTR above 70%. In their study, the mean TTR estimated using the Rosendaal method among 96 patients with NVAF was 44% ± 18.5, comparable to the TTR obtained in our study [12].

Frailty is a biological syndrome with multiple cumulative physiological declines and a reduced ability to employ homeostatic resilience and reserve to recover from stressors [13]. Atrial fibrillation increases frailty by four-fold and may be a marker of frailty [13, 14]. In our study, NVAF patients had a mean age of 65 years, comparable to other studies [3, 15]. Although frailty was not assessed in our patients, frailty remains relevant in AF management. Frail patients are less likely to receive anticoagulation due to warranted concern about adverse outcomes such as bleeding. The clinical tendency to not anticoagulate this inherently high-risk stroke population group is likely further exacerbated by polypharmacy interactions and the impact of multiple comorbidities. Evidence supports a net clinical benefit of anticoagulation in frail AF patients [16].

Heart failure and AF have a synergistic effect in increasing the risk of thromboembolism and all-cause mortality [17]. In a study involving Framingham Heart Study participants with AF,

the hazard ratio (HR) for the occurrence of heart failure with preserved ejection fraction was 2.34 (95% CI: 1.48 – 3.70, p=0.0003). Participants with heart failure were 2.18 times more likely to be diagnosed with AF (HR: 2.18, 95% CI: 1.26 – 3.76, p=0.005) [18]. Yuyun et al. evaluated the spectrum of cardiac arrhythmias in sub-Saharan Africa (SSA) and reported that hypertension was the most common risk factor associated with AF, reported in 50-87% of patients, followed by heart failure in 32-64% of all patients with AF [19]. In our study, heart failure and hypertension were the most common comorbidities, with a prevalence of 82.5% and 79.1%, respectively. In addition, The Heart of Soweto Study, involving patients residing in the urban part of South Africa, showed that hypertension is one of the most common and undertreated significant modifiable risk factor for cardiovascular disease in patients with and without AF. In their study, 56% of all patients had hypertension, highlighting the need to screen vigorously, optimally monitor and treat all patients with hypertension using guideline-directed management [20].

The safety and efficacy of anticoagulation therapy in patients with AF and concomitant chronic kidney disease (CKD) have unique clinical implications. There is an increased AF prevalence of up to 10-25% with deteriorating renal function [5]. Furthermore, CKD patients are at a high risk of thromboembolic events and major bleeding, independent of oral anticoagulation [5]. Studies show a baseline increased cerebral haemorrhage potential up to 10 times higher in CKD patients than those with normal renal function [21]. Warfarin is currently the mainstay of anticoagulation in AF patients with CKD [21]. Our study did not show an association between renal dysfunction and poor TTR. Patients with a TTR less than 70%, had an eGFR of 54.5 ml/min/1.73m^2 (IQR: 42 – 74) compared to 58 ml/min/1.73m^2 (IQR: 42 – 79) in the group with a TTR≥70%. This is potentially related to a healthcare provider treatment bias and hesitance that may exist to prescribe anticoagulation to AF patients with declining renal function because of the concern of bleeding. Insights from ongoing randomised control trials such as the Oral Anticoagulation in Haemodialysis Patients (AVKDIAL) and The Danish Warfarin Dialysis Study - Safety and Efficacy of Warfarin in Patients with Atrial Fibrillation on Dialysis (DANWARD) will hopefully have a positive impact on prescriber confidence in the management of AF patients with CKD [22, 23].

The advent of combination antiretroviral therapy has dramatically improved the life expectancy of PLHIV [24]. Consequently, AF has emerged as a significant contributor to high cardiovascular risk and mortality in the ageing population of PLHIV, with a prevalence

of 2-3% [23, 25]. However, it is unclear whether contemporary anticoagulation guidelines for AF can be safely applied to PLHIV [25]. This is particularly relevant in SSA, where the National Institute of Health estimates that there are 7.9 million PLHIV in South Africa [24]. In our study, there were only three PLHIV, possibly due to underreporting.

Traditional risk calculators such as the CHA_2DS_2-VASc score and the HAS-BLED score help estimate the risk of strokes and major bleeds in patients with AF. However, they might not be well calibrated to accurately assess the true risk of stroke in patients with AF and in PLHIV [25]. It has been shown that even with correction for cardiovascular risk factors, a CD4 count of less than 200 and a viral load exceeding 100000 copies/ml had a 1.4-2.0-fold and 1.7-fold increased risk of AF, respectively [24]. This and other human immunodeficiency virus-specific factors like interactions with ARVs, the role of hyperhomocysteinemia and comorbid opportunistic infections are largely neglected in anticoagulation efficacy and safety research [25].

The C-statistic of the CHA_2DS_2-VASc model for one-year risk of ischaemic stroke or TIA among patients with AF was 0.679 (95% CI: 0.670 – 0.686) [26]. Despite correcting for ethnic differences, the C-statistic, which measures the ability of a model to discriminate between positive and negative cases, did not improve, suggesting that the model may have modest predictive powers [26]. In our study, the mean CHA_2DS_2-VASc score was 4, and it did not differ between patients with poor and optimal anticoagulation control (p=0.4932). Therefore this infers that the overall risk of ischemic strokes, systemic embolisms and TIA in our study cohort with NVAF could be between 4.8% and 6.7% [27].

The occurrence of thromboembolic and bleeding complications in AF patients with poor anticoagulation control is well described [28-31]. In our study, warfarin toxicity was documented in 7.3% of all patients, despite INR monitoring. Furthermore, our study also demonstrated that the rate of thromboembolic complications was low. This is likely not representative of the actual burden of thromboembolic complications since most hospitalised patients with AF-related strokes and thromboembolic complications are primarily managed in general medical or surgical wards and not in cardiology wards. Ischaemic strokes were the most common complication, documented in 3.4% of all patients with NVAF. One of the common predictors of poor anticoagulation control reported in the literature is polypharmacy, where NVAF patients on six or more oral medications were at risk of poor anticoagulation

control (TTR<65%), (Odds Ratio:1.89, 95% CI: 1.03–3.33; $p = 0.03$) [32]. In our study, none of the clinical variables predicted poor anticoagulation control.

In most LMICs, the most feasible approach for managing AF patients on vitamin K antagonists is patient counselling, education, and frequent INR monitoring. Recent guidelines suggest that in patients who fail to maintain a TTR above 70%, DOACs should be considered [1]. The findings from our study have shown that the use of warfarin therapy in 64.4% of our patient group is inefficacious and potentially harmful. Suboptimal warfarin use is not innocuous, as patients are at a greater risk for increased bleeding and strokes [33]. Healthcare systems in LMICs need to evaluate whether the cost of newer oral anticoagulation may be offset by the cost of regular INR monitoring, frequent outpatient visits and a reduction in costs immanent in managing warfarin-related complications.

The study's retrospective nature and the relatively smaller sample size are the main limitations. Although we could demonstrate a low TTR in patients with NVAF, we could not accurately showcase the complications associated with such poor control. This is related to a selection bias in our study, where only patients with cardiac-specific complications would have been admitted to the cardiology department. In addition, since the study was conducted at a single-centre, academic tertiary hospital, it excluded patients who would have presented to their local hospitals with AF and its related complications. Incomplete record keeping was a significant challenge, particularly when mining the electronic health record system. Despite these limitations, our study has demonstrated the need to consider introducing DOACs to high-risk individuals with a TTR persistently below 70% after adequate counselling and patient education.

Conclusions

Our study found suboptimal anticoagulation control in 64.4% of patients with NVAF. There is an urgent need to improve access to DOACs to ensure these patients are adequately protected from AF-related morbidity and mortality. Cost-effectivity analysis studies are required in LMICs to determine which therapeutic strategy would be effective and cost-saving to the entire healthcare system, considering all direct and indirect costs involved in managing patients with AF.

List of abbreviations

ACE: angiotensin-converting enzyme

AF: atrial fibrillation

ARB: angiotensin receptor blockers

BP: blood pressure

CI: confidence interval

CKD: chronic kidney disease

CMJAH: Charlotte Maxeke Johannesburg Academic Hospital

DOACs: direct oral anticoagulants

CHA_2DS_2-VASc: Congestive heart failure/left ventricular ejection fraction <40%, hypertension, age >75 years, diabetes mellitis , stroke/transient ischemic attack/thromboemobolism history, vascular disease , age 65-75 years , female sex)

HAS-BLED: Hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalised ratio, elderly (age>65), drugs/alcohol concomitantly

eGFR: estimated glomerular filtration rate

HR: hazard ratio

INR: international normalised ratio

IQR: interquartile range

LMICs: low-and-middle-income countries

LVEF: left ventricular ejection fraction

MI: myocardial infarction

NVAF: non-valvular atrial fibrillation

TIA: transient ischaemic attack

TTR: time in therapeutic range

Ethics approval

Permission to conduct the study was obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical), clearance certificate no. M201091.

Consent for publication

Not applicable

Competing interests

NT is a cardiologist and has received consultation fees from Pfizer, Novartis Pharmaceuticals, Novo Nordisk, Boston Scientific, Servier, Phillips, Takeda, AstraZeneca, Acino Health Care Group, Sanofi and Merck. NT has also received educational and research grants from Medtronic, Biotronik, Boston Scientific and Vertice Health Care Group. VM and DM do not have any competing interests.

Funding

The research study was funded by Pfizer. The funders were not involved in the study design, data collection, data analysis and review and editing of all versions of the manuscript.

Authors' contributions

VM collected the study data, wrote the first draft and edited the final version of the manuscript. NT and DM supervised the research project, conducted the statistical analysis and edited the manuscript. All authors read and approved the final version of the manuscript.

Acknowledgements

None

References

1. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021;42(5):373-498.10.1093/eurheartj/ehaa612
2. Lee E, Choi EK, Han KD, Lee H, Choe WS, Lee SR, et al. Mortality and causes of death in patients with atrial fibrillation: A nationwide population-based study. PLoS One. 2018;13(12):1-14.10.1371/journal.pone.0209687

3. Semakula JR, Mouton JP, Jorgensen A, Hutchinson C, Allie S, Semakula L, et al. A cross-sectional evaluation of five warfarin anticoagulation services in Uganda and South Africa. PloS one. 2020;15(1):1-9.10.1371/journal.pone.0227458
4. Kim D, Yang PS, Sung JH, Jang E, Yu HT, Kim TH, et al. Effectiveness and Safety of Anticoagulation Therapy in Frail Patients With Atrial Fibrillation. Stroke. 2022;53(6):1873-82.10.1161/STROKEAHA.121.036757
5. Parker K, Hartemink J, Saha A, Mitra R, Lewis P, Power A, et al. A systematic review of the efficacy and safety of anticoagulants in advanced chronic kidney disease. J Nephrol. 2022;35(8):2015-33.10.1007/s40620-022-01413-x
6. Jardine MRF, J; Obel I.W.P. A survey on the treatment of atrial fibrillation in South Africa. S Afr Med J. 2014;104(9):623-7.10.7196/SAMJ.8111
7. Maredza M, Bertram MY, Tollman SM. Disease burden of stroke in rural South Africa: an estimate of incidence, mortality and disability adjusted life years. BMC Neurol. 2015;15:1-12.10.1186/s12883-015-0311-7
8. Zhu X, Xiao X, Wang S, Chen X, Lu G, Li X. Rosendaal linear interpolation method appraising of time in therapeutic range in patients with 12-week follow-up interval after mechanical heart valve replacement. Front Cardiovasc Med. 2022;9:925571.10.3389/fcvm.2022.925571
9. Caldeira D, Cruz I, Morgado G, Stuart B, Gomes AC, Martins C, et al. Is the time in therapeutic range using the ratio of tests equivalent to the Rosendaal method? Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis. 2015;26(8):972-6.10.1097/MBC.0000000000000312
10. Pro INR. Helping manage anticoagulation patients for over 18 years 2013. Available from: www.inrpro.com. Accessed on 13 February 2023.
11. Oldgren J, Healey JS, Ezekowitz M, Commerford P, Avezum A, Pais P, et al. Variations in cause and management of atrial fibrillation in a prospective registry of 15,400 emergency department patients in 46 countries: the RE-LY Atrial Fibrillation Registry. Circulation. 2014;129(15):1568-76.10.1161/circulationaha.113.005451
12. Sadhabiriss DSLB, S.L. 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. SA Heart. 2021;18(1):28-38
13. Villacampa-Fernandez P, Navarro-Pardo E, Tarin JJ, Cano A. Frailty and multimorbidity: Two related yet different concepts. Maturitas. 2017;95:31-5.10.1016/j.maturitas.2016.10.008

14. Fumagalli S, Tarantini F, Guarducci L, Pozzi C, Pepe G, Boncinelli L, et al. Atrial fibrillation is a possible marker of frailty in hospitalised patients: results of the GIFA Study. Aging Clin Exp Res. 2010;22(2):129-33.10.1007/BF03324785
15. Sadhabiriss D, Brown SL. Warfarin: time in therapeutic range, a single centre study on patients using warfarin for stroke prevention in non-valvular atrial ifbrillation and prosthetic heart valves. SA Heart. 2021;18(1):28-38.doi:10.10520/ejc-saheart-v18-n1-a7
16. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383(9921):955-62.10.1016/S0140-6736(13)62343-0
17. Brown LAE, Boos CJ. Atrial fibrillation and heart failure: Factors influencing the choice of oral anticoagulant. Int J Cardiol. 2017;227:8638.10.1016/j.ijcard.2016.09.086
18. Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA, et al. Atrial Fibrillation Begets Heart Failure and Vice Versa: Temporal Associations and Differences in Preserved Versus Reduced Ejection Fraction. Circulation. 2016;133(5):484-92.10.1161/CIRCULATIONAHA.115.018614
19. Yuyun MF, Bonny A, Ng GA, Sliwa K, Kengne AP, Chin A, et al. A Systematic Review of the Spectrum of Cardiac Arrhythmias in Sub-Saharan Africa. Glob Heart. 2020;15(1):1-30.10.5334/gh.808
20. Sliwa K, Wilkinson D, Hansen C, Ntyintyane L, Tibazarwa K, Becker A, et al. Spectrum of heart disease and risk factors in a black urban population in South Africa (the Heart of Soweto Study): a cohort study. Lancet. 2008;371(9616):915-22.10.1016/S0140-6736(08)60417-1
21. Tsagalis G, Bakirtzi N, Manios E, Chouliaras I, Papagiannidou P, Stamellou E, et al. Atrial fibrillation in chronic hemodialysis patients: prevalence, types, predictors, and treatment practices in Greece. Artif Organs. 2011;35(10):916-22.10.1111/j.1525-1594.2011.01229.x
22. Elfar S, Elzeiny SM, Ismail H, Makkeyah Y, Ibrahim M. Direct Oral Anticoagulants vs. Warfarin in Hemodialysis Patients With Atrial Fibrillation: A Systematic Review and Meta-Analysis. Front Cardiovasc Med. 2022;9:1-12.10.3389/fcvm.2022.847286
23. Liu G, Long M, Hu X, Hu CH, Liao XX, Du ZM, et al. Effectiveness and Safety of Warfarin in Dialysis Patients With Atrial Fibrillation: A Meta-Analysis of

Observational Studies. Medicine (Baltimore). 2015;94(50):1-9.10.1097/MD.0000000000002233

24. Zuma K, Simbayi L, Zungu N, Moyo S, Marinda E, Jooste S, et al. The HIV Epidemic in South Africa: Key Findings from 2017 National Population-Based Survey. Int J Environ Res Public Health. 2022;19(13).10.3390/ijerph19138125
25. Vizcarra P, Guillemi S, Eyawo O, Hogg RS, Montaner JS, Bennett M. Stroke and Systemic Thromboembolism Prevention in People Living With Human Immunodeficiency Virus With Atrial Fibrillation: A Review of Its Implications for Clinical Practice. CJC Open. 2019;1(5):245-55.10.1016/j.cjco.2019.06.002
26. Chen LY, Norby FL, Chamberlain AM, MacLehose RF, Bengtson LGS, Lutsey PL, et al. CHA(2)DS(2)-VASc Score and Stroke Prediction in Atrial Fibrillation in Whites, Blacks, and Hispanics. Stroke. 2019;50(1):2833.10.1161/STROKEAHA.118.021453
27. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur Heart J. 2012;33(12):1500-10.10.1093/eurheartj/ehr488
28. Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, et al. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalised ratio control achieved by centers and countries as measured by time in therapeutic range. Circulation. 2008;118(20):2029-37.10.1161/CIRCULATIONAHA.107.750000
29. Senoo K, Lip GY. Relationship of Age With Stroke and Death in Anticoagulated Patients With Nonvalvular Atrial Fibrillation: AMADEUS Trial. Stroke. 2015;46(11):3202-7.10.1161/STROKEAHA.115.010614
30. Van Den Ham HA, Klungel OH, Leufkens HG, Van Staa TP. The patterns of anticoagulation control and the risk of stroke, bleeding and mortality in patients with non-valvular atrial fibrillation. J Thromb Haemost. 2013;11(1):107-15.10.1111/jth.12041
31. Wan Y, Heneghan C, Perera R, Roberts N, Hollowell J, Glasziou P, et al. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. Circ Cardiovasc Qual Outcomes. 2008;1(2):84-91.10.1161/CIRCOUTCOMES.108.796185

32. Mohammed S, Aljundi AH, Kasem M, Alhashemi M, El-Menyar A. Anticoagulation control among patients with nonvalvular atrial fibrillation: A single tertiary cardiac center experience. J Adv Pharm Technol Res. 2017;8(1):14-8.10.4103/2231-4040.197370
33. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007;146(12):857-67.10.7326/0003-4819-146-12-200706190-00007

Appendices

Ethics approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Dr V Mogashoa

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M201091

NAME: (Principal Investigator)	Dr V Mogashoa
DEPARTMENT:	School of Clinical Medicine Department of Medicine Division of Internal Medicine - Cardiology Medical School University
PROJECT TITLE:	Anticoagulation in non-valvular atrial fibrillation in South Africa
DATE CONSIDERED:	2020/10/30
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr D Mpanya and Professor N Tsabedze
APPROVED BY:	Dr N Naran, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	2021/01/05

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **October** and therefore reports and re-certification will be due in the month of **October** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

2021/07/21
Date

Protocol approval letter

2020/10/02
Person Number: 371296
PAG

Dr V Mogashoa

99 Belugo Estate Ormonde Street
Bryanston
Johannesburg
2191

Dear Dr Vanessa Mogashoa

Master of Medicine – Internal Medicine: Approval of Proposal

We have pleasure in advising you that your proposal has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Title: *Anticoagulation for non-valvular atrial fibrillation in South Africa*

Yours sincerely

Ms Kgomotso Tlala
On behalf of Mrs Sandra
Benn Faculty Registrar

Faculty: Postgraduate – Faculty of Health Sciences
Tel: +27 (0)11 717 2125; Email: Kgomotso.Tlala@wits.ac.za
Room 212, 2nd Floor, Phillip V Tobias Building, 29 Princess of Wales Terrace, Parktown, Johannesburg, 2193, SOUTH AFRICA

Protocol

Anticoagulation for non-valvular atrial fibrillation in South Africa

Candidate: Dr Vanessa Mogashoa
MBChB (Wits)
Department of Internal Medicine, University of the Witwatersrand
Student number: 371296

Supervisors: Prof Nqoba Tsabedze

MBBCh (Wits), FCP (SA), Cert. Cardiology (SA), MMed (Int. Med) (Wits)

Academic & Clinical Head: Division of Cardiology
Charlotte Maxeke Johannesburg Academic Hospital
University of the Witwatersrand

Dr Dineo Mpanya
MBChB (UCT), FCNP (SA), MMed (Nucl. Med) (Wits),
PhD (Wits)
Specialist Nuclear Physician, PhD Clinical Research Fellow
Charlotte Maxeke Johannesburg Academic Hospital
University of the Witwatersrand

1.1 INTRODUCTION

Atrial fibrillation (AF) is a growing epidemic affecting 1-2% of the population globally (1). A rising prevalence of AF, attributed to an increase in the burden of non-communicable diseases in an ageing society, has been observed in rural and urban sub-Saharan Africa (SSA) (2). In SSA, atrial fibrillation also occurs in a population almost a decade younger compared to economically developed countries due to the added burden of infectious diseases (3). Furthermore, limited access to healthcare facilities restricting the detection, management and follow-up of patients with AF has led to most patients presenting with established thromboembolic events or haemorrhagic complications (4).

1.2 LITERATURE REVIEW /BACKGROUND

Individuals with AF have a five-fold increased risk of cerebrovascular accidents or strokes (4). In 2010, strokes were the leading cause of mortality in females above the age of 60 years in South Africa (2). Also, AF-associated strokes tend to carry a higher risk of death and disability compared to other aetiologies, rendering anticoagulation as the cornerstone in the management of patients with AF (4).

Atrial fibrillation is the most common cardiac arrhythmia. It occurs when disorganised and diffuse electrical activity in the atria disrupts or sometimes even replaces normal sinus rhythm (5). It has a predilection for the elderly, occurring in 8-10% of people above 80 years compared to only 1% in those less than 60 years old (6). Other important risk factors include cardiac diseases such as congestive cardiac failure and valvular heart disease (5). Arrhythmogenic remodeling underlies the basic pathophysiology of atrial fibrillation which can occur as a result of electrical, structural or neural remodeling from a plethora of causes (7). The principles of Virchow's triad, namely stasis, endothelial disruption and coagulation, further potentiate the most critical sequelae of AF, thromboembolism (8). Thrombi formed in the left atrial appendage in particular, are an essential determinant in cerebrovascular accidents related to AF (7, 8).

There are two broad categories of anticoagulants: those targeted at platelet predominant thrombi formed in arteries and those aimed at thrombi in a stasis prone left atrium or venous system (7). A thrombus formed in a vein is made up of an intricate network of fibrin that enclose platelets to form a clot. Thus, some drugs are designed to target specific regions on

thrombi for anticoagulation: unfractionated heparin, low molecular weight heparin, vitamin K antagonists and novel oral anticoagulants (9). Vitamin K antagonists (VKA), such as warfarin have proven to be effective anticoagulants in reducing the risk of thromboembolic events and all-cause mortality associated with AF. Most notably, there is a 64% reduction in strokes and a 24% reduction in all-cause mortality with optimal warfarin use (10). Thus, in most parts of SSA, warfarin is the mainstay for therapy in patients with AF that qualify for anticoagulation based on the CHA_2DS_2-VASc score (11). Although warfarin is affordable, some of the disadvantages of using warfarin include multiple drug and food interactions as well as the requirement for constant monitoring of the international normalised ratios (INR). The monitoring process is a challenge, particularly in resource-limited settings (12).

Worldwide, the advent of Novel Oral Anticoagulants (NOACs) has resulted in the paradigm shift for the management of patients with AF, specifically in non-valvular atrial fibrillation (NVAF) (13). Despite findings from various trials such as the Apixaban for Reduction in Stroke and Other Thromboembolic Events (ARISTOTLE) trial confirming the superiority of apixaban over warfarin in preventing strokes and reducing all-cause mortality, the cost of NOACs is still a barrier to access in SSA (2, 14). Furthermore, a study done in the South African private-health sector showed that the relatively high cost of a NOAC, dabigatran, compared to warfarin is offset by the increased cost related to INR monitoring, transport costs for patients and in-hospital management of warfarin related complications (15). Effective anticoagulation control using warfarin is assessed by the time in the therapeutic range (TTR). The TTR is a quality measuring tool that uses the Rosendaal method to estimate the time a patient's INR is within the desired therapeutic range over a specified period. Intuitively, the higher the TTR, the better the patient outcomes (4, 16). The National Institute for Health and Care Excellence recommends that NOACs should be considered in patients who fail to maintain a TTR > 65% (17). This TTR target has proven to be challenging even in well-resourced countries; hence many health centres in these regions use NOACs for their patients with NVAF (14).

Despite the paucity of current literature available evaluating the anticoagulation in Africa; there are some international and local studies that have alluded that anticoagulation control using warfarin in Africa is poor. The Randomised Evaluation of Long-Term anticoagulation therapy (RE-Ly) study registry reported Africa to have the lowest TTR compared to Europe and North America (18). Furthermore, a randomised prospective trial comparing warfarin

therapy with clopidogrel plus aspirin (ACTIVE W) found that patients from South Africa randomised to warfarin therapy had the lowest TTR, a finding attributed to poor healthcare access (13, 19).

Locally, in 2018, the TTR in outpatients requiring INR monitoring services in Uganda and South Africa revealed that irrespective of regular INR monitoring (at least once monthly), the mean TTR was 41% (20). In Cape Town, South Africa, anticoagulation control was evaluated in an outpatient INR department, which found that the TTR in patients on warfarin was also low at only 44% (21). The drawback of the currently available research data done in Africa is that all patients on warfarin were evaluated- irrespective of the indication for warfarin use. As a result, the TTR in patients with NVAF was not sufficiently represented. In addition, the predictors of poor control in South Africa were not completely identified.

1.3 PROBLEM STATEMENT

In December 2019, the United States of America (USA) Food and Drug Administration (FDA) approved the development of the generic version of Apixaban. The generic version promises increased access to this drug at a lower cost (22). Thus there is a need to start reconsidering the effectiveness of current anticoagulation protocols using warfarin and the potential role of NOACS for NVAF patients in SSA. To our knowledge there is no published data assessing the anticoagulation control in patients with non-valvular atrial fibrillation in South Africa . We hypothesise that the TTR for patients with NVAF on warfarin in the South African public sector is well below the recommended minimum of 65%.

1.4 STUDY AIMS AND OBJECTIVES

1.4.1Aim

The aim of the study is to assess oral anticoagulation control among patients with non-valvular atrial fibrillation on warfarin by calculating the time in therapeutic range (TTR)

1.4.2 Objectives

The primary objective of the study is to describe the demographics and clinical characteristics of patients with atrial fibrillation (valvular and non-valvular AF).

The secondary objective is to estimate the prevalence rate of thromboembolic events (cerebrovascular accidents, transient ischaemic attacks (TIA), pulmonary embolism, deep vein thrombosis) and all-cause mortality in patients with atrial fibrillation.

1.5 RESEARCH METHODOLOGY

1.5.1 Study design and study population

This retrospective study will be conducted in the Division of Cardiology at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). An estimated 90 to100 patients, demarcated with the International classification 10th revision (ICD 10) code for atrial fibrillation, are admitted in this department annually. Therefore, we aim to retrieve data from the last five years (2015-2019) in order to achieve a minimum of 200 patient records to be evaluated for our study. Consecutive patient records will be selected from the database.

1.5.2 Inclusion criteria

All adult patients who are 18 years of age and older diagnosed with atrial fibrillation.
Patients on oral dosages of warfarin for at least six months.
Patients with a minimum of three INR results.

1.5.3 Exclusion criteria

Clinical presence of malignancy
Indications for warfarin other than atrial fibrillation

1.5.4 Data collection

The data collection sheet is shown in Appendix A. Data will be collected from the Electronic Health Record (EHR) system that captures data of all patients admitted in the cardiology wards at the CMJAH. Patients with a primary diagnosis of atrial fibrillation (ICD: I48) will be retrieved from the database. Clinical and demographic information, including documented comorbidities for the first admission, will be obtained from the EHR and used as baseline data. After discharge from the hospital, a minimum of three INR results will be retrieved from the outpatient medical records. Using the Rosendaal method, we will calculate the percentage of time spent in the therapeutic range for patients with non-valvular atrial fibrillation. (5) Calculations will be performed in a dedicated Microsoft excel sheet template freely available that is freely available (Appendix B).(23)

In the calculation, we will presume a linear relationship between INR values, therefore allowing standardisation when calculating the TTR. A TTR level ≥70% will be considered to represent good control, a TTR between 50-70% intermediate control and a TTR < 50% poor control. Study data collected will be captured and stored in the Research Electronic Data Capture (REDCap) tool hosted at the University of the Witwatersrand. The study data will be password protected and only the principal investigator and the supervisors will have access to the data collected. The date of birth as well as the hospital number will be used for verification of biochemical results as well as for removing duplicate entries while cleaning the data. Once the data has been exported for the statistical analysis, both the date of birth and the hospital numbers will be removed.

1.5.5 Data analysis

Statistical analysis will be performed using STATA version 14. Data will be expressed as means and standard deviations when normally distributed and as medians with inter-quartile ranges when non-normally distributed. Data that is categorical will be expressed as numbers and percentages. Analysis of variance (ANOVA) will be used to test for intergroup (TTR<70% and a TTR≥70%) differences with the Chi-square test being used to test for intergroup proportion differences. Univariable and multivariable logistic regression analysis will be used to determine the predictors of a TTR <70%. A p-value of less than 0.05 will be considered representative of statistical significance.

1.6 ETHICAL CONSIDERATIONS

Upon protocol approval, an application for ethics clearance will be submitted to the University of the Witwatersrand Human Research Ethics Committee (Medical). Permission letters from the Head of the Division of Cardiology as well as from relevant hospital authorities at the CMJAH will be obtained before collecting data. Individual patient consent will not be required, as the study will be a retrospective record analysis.

1.7 PROJECT OUTLINE

1.7.1 Time Frame

	2020								2021						
	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul
Literature review															
Protocol preparation															
Protocol assessment															
Ethics application															
Data collection															
Data analysis															
Write up															

1.7.2 Funding

This study is funded by Pfizer.

1.7.3 Potential limitations/problems

Incomplete patient records and unavailability of biochemical results may result in problems during the data collection process.

1.8 REFERENCES

1. Lip GY, Kakar P, Watson T. Atrial fibrillation--the growing epidemic. Heart. 2007;93(5):542-3.

2. Mwita JC, Ocampo C, Molefe-Baikai OJ, Goepamang M, Botsile E, Tshikuka JG. Characteristics and 12-month outcome of patients with atrial fibrillation at a tertiary hospital in Botswana. Cardiovasc J Afr. 2019;30(3):168-73.
3. Mayosi BM, Flisher AJ, Lalloo UG, Sitas F, Tollman SM, Bradshaw D. The burden of non-communicable diseases in South Africa. Lancet. 2009;374(9693):934-47.
4. Merinopoulos I, Venables P, Chalmers I, Vassiliou V. NOAC or Warfarin for Atrial Fibrillation: Does Time in Therapeutic Range Matter? Recent Adv Cardiovasc Drug Discov. 2015;10(1):60-4.
5. Zimetbaum P. Atrial Fibrillation. Ann Intern Med. 2017;166(5):ITC33-ITC48.
6. Kannel WB, Benjamin EJ. Current perceptions of the epidemiology of atrial fibrillation. Cardiol Clin. 2009;27(1):13-24, vii.
7. Iwasaki Y-k, Nishida K, Kato T, Nattel S. Atrial Fibrillation Pathophysiology. Circulation. 2011;124(20):2264-74.
8. Watson T, Shantsila E, Lip GY. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. Lancet. 2009;373(9658):155-66.
9. Neal M. Medical Pharmacology at a Glance. 6th ed: Wiley-Blackwell; 2009.
10. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007;146(12):857-67.
11. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur Heart J. 2012;33(12):1500-10.
12. Laäs DJ, Naidoo M. Oral anticoagulants and atrial fibrillation: A South African perspective. S Afr Med J. 2018;108(8):640-6.
13. Oldgren J, Healey JS, Ezekowitz M, Commerford P, Avezum A, Pais P, et al. Variations in cause and management of atrial fibrillation in a prospective registry of 15,400 emergency department patients in 46 countries: the RE-LY Atrial Fibrillation Registry. Circulation. 2014;129(15):1568-76.
14. Easton JD, Lopes RD, Bahit MC, Wojdyla DM, Granger CB, Wallentin L, et al. Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of the ARISTOTLE trial. Lancet Neurol. 2012;11(6):503-11.
15. Laäs DJ, Naidoo M. An evaluation of warfarin use at an urban district-level hospital in KwaZulu-Natal Province, South Africa2018.

16. Secretariat M. Point-of-Care International Normalized Ratio (INR) Monitoring Devices for Patients on Long-term Oral Anticoagulation Therapy: An Evidence-Based Analysis. Ont Health Technol Assess Ser. 2009;9(12):1-114.
17. Lip GYH, Keshishian A, Li X, Hamilton M, Masseria C, Gupta K, et al. Effectiveness and Safety of Oral Anticoagulants Among Nonvalvular Atrial Fibrillation Patients. Stroke. 2018;49(12):2933-44.
18. Camm AJ. The RE-LY study: Randomised Evaluation of Long-term anticoagulant therapY: dabigatran vs. warfarin. European Heart Journal. 2009;30(21):2554-5.
19. Ezekowitz MD, Connolly S, Parekh A, Reilly PA, Varrone J, Wang S, et al. Rationale and design of RE-LY: randomised evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. Am Heart J. 2009;157(5):805-10, 10.e1-2.
20. Semakula JR, Mouton JP, Jorgensen A, Hutchinson C, Allie S, Semakula L, et al. A cross-sectional evaluation of five warfarin anticoagulation services in Uganda and South Africa. PloS one. 2020;15(1):e0227458-e.
21. Ebrahim I, Bryer A, Cohen K, Mouton JP, Msemburi W, Blockman M. Poor anticoagulation control in patients taking warfarin at a tertiary and district-level prothrombin clinic in Cape Town, South Africa. S Afr Med J. 2018;108(6):490-4.
22. Administration FaD. FDA approves first generics of Eliquis 2019. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-first-generics-eliquis. Accessed on 7 September 2020.
23. System IPR. INR charts graphs and statistical analysis from your patient management system 2020. Available from: http://inrpro.com/data_upload/home.asp. Accessed on 7 September 2020.

Data collection sheet

Baseline Data

Study ID	_____
Atrial fibrillation	◯ Valvular ◯ Non-valvular
Heart rate	_____
Systolic BP	_____
Diastolic BP	_____
Medication	☐ Aspirin ☐ Amiodarone ☐ Heparin
Total daily warfarin dose (mg)	_____
Comorbidities	☐ Cardiac failure (current/ previous) ☐ Hypertension ☐ Diabetes ☐ HIV ☐ Previous myocardial infarction ☐ Peripheral vascular disease ☐ Other
If other comorbidity, specify	_____
Left ventricular ejection fraction (%)	_____
eGFR (MDRD)	_____
Renal disease (Transplant, Dialysis, CR>2.26mg/dL or 200micromol/L)	◯ Yes ◯ No
Liver disease (Cirrhosis or bilirubin >2X normal plus AST/ALTALP > 3 X normal)	◯ Yes ◯ No
CHADS2Vasc2 SCORE	_____
HAS-BLED SCORE	_____

Complications	☐ Ischaemic stroke ☐ Haemorrhagic stroke ☐ Transient ischaemic attack (TIA) ☐ Gastrointestinal bleeding ☐ Other major bleeds requiring blood transfusion ☐ Deep vein thrombosis ☐ Acute pulmonary embolism ☐ Over- warfarinized ☐ Other
If other complication, specify	_____
Number of hospital admissions	_____
Is compliance an issue in this patient?	○ Yes ○ No ○ Not documented

INR tests

First INR date	----------
First INR result	----------
Second INR date	----------
Second INR result	----------
Duration between first and third INR (days)	----------
Third INR date	----------
Third INR result	----------
Total Days (on therapy)	----------
Number of days within the therapeutic range	----------

Rosendaal method Example Excel spreadsheet

Test Date	INR	Days Since the Last Test	INR Diff	Previous INR Within Range?	Current INR Within Range?	INR Diff Above Range	INR Diff Within Range	INR Diff Below Range	Days within Range since the Last Test	% Days within Range since the Last Test

Low Range	2
High Range	3

Rosendaal Method

Days Within range	**0,0**
Total Days	**0,0**
% Days Within Range	**#DIV/0!**

% in range

Total Number of Tests	**0,0**
Number of Tests in Range	**0,0**
% of Tests in Range	**#DIV/0!**

Turnitin Report

NVAF Turnitin-4.docx

by Vanessa Mogashoa

Submission date: 31-Jul-2023 03:57PM (UTC+0200)

Submission ID: 2139531463

File name: NVAF_Turnitin.docx (65.4K)

Word count: 3570

Character count: 19853

Anticoagulation control for nonvalvular atrial fibrillation in South Africa

Authors

Vanessa Mogashoa, Dineo Mpanya, Nqoba Tsabedze*

Abstract

Background: In an ageing society, atrial fibrillation (AF) is a growing epidemic in Africa. Anticoagulation, considered the backbone of AF management, is limited to warfarin as the mainstay of available anticoagulation therapy for non-valvular atrial fibrillation (NVAF) in most low-and-middle-income countries (LMICs). Thus, necessitating an optimal time in therapeutic range (TTR) to avoid bleeding and thromboembolic complications. This study aimed to assess warfarin anticoagulation control among patients with NVAF in a tertiary academic centre in Johannesburg, South Africa.

Methods: We conducted a retrospective study of consecutive patients with atrial fibrillation managed at a tertiary-level academic centre in Johannesburg, South Africa. Anticoagulation control was assessed by calculating the time in therapeutic range (TTR) using the Rosendaal method for patients with NVAF.

Results: The study population comprised 223 patients with AF and a mean age of 62.3 ± 14.3 years. Non-valvular atrial fibrillation was diagnosed in 177 (79.3%) patients. Among the 223 patients with atrial fibrillation, a pre-existing history of cerebrovascular accidents and transient ischaemic attacks was documented in 20 (9.0%) patients. A history of heart failure symptoms was reported in 186 (83.4%) patients, and 146 (78.5%) heart failure patients had NVAF. The median TTR among patients with NVAF was 46% [interquartile range (IQR): 8.7 – 86], and the TTR was greater than 70% in 114 (35.6%) patients with NVAF. The mean CHA_2DS_2-VASc Score was 4 ± 1.5, and it did not differ between patients with poor and optimal anticoagulation control. Warfarin toxicity was documented in 18 (8.1%) of the 223 patients, and among the 18 patients with warfarin toxicity, 13 (83.3%) had NVAF.

Conclusion: In our study, a TTR greater than 70% was found in 35.6% of NVAF patients on warfarin. This is despite a mean CHADS-VASc Score of 4, indicating a high annual stroke risk. Multiple bio psycho-ecological factors contribute to poor TTR in LMICs. Larger multicentre trials comparing the occurrence of bleeding, thromboembolic events, as well as the total cost to the healthcare system in patients treated with warfarin compared to direct oral anticoagulation therapy are required to guide oral anticoagulation strategies in Africa.

Keywords: atrial fibrillation; anticoagulation; warfarin; time in therapeutic range; direct oral anticoagulants; international normalised ratio

Background

The bedrock of atrial fibrillation (AF) management is optimal anticoagulation. This is required to mitigate the associated high risk of mortality, stroke, and impaired quality of life in patients with AF [1]. Atrial fibrillation carries a five-fold increased risk of complicating with a stroke. AF-related strokes are associated with significant disability and mortality compared to non-AF-related strokes [2,3]. However, optimal anticoagulation control remains challenging, particularly in low-and-middle-income countries (LMICs). The efficacy of direct oral anticoagulants (DOACs) has led to increasing use in AF and incentivised ongoing research into their safety profile. As such, DOACs are progressively being considered for non valvular atrial fibrillation (NVAF), even in previously neglected high-risk populations such as those with kidney disease and frail patients [4, 5].

In LMICs, the introduction of DOACs in the management plan of patients with AF is currently not perceived as cost-effective, despite a higher incidence of AF-related complications such as stroke. In a prospective cross-sectional observational AF registry of 29 medical institutions in urban South Africa involving 302 patients with a mean age of 67 years, the prevalence of AF-related strokes was 8.3% [9]. In rural South Africa, the crude incidence rate for non-AF-related stroke has been reported to be 244 per 100,000 person-years [6].

The high stroke burden associated with AF necessitates an optimal time in the therapeutic range (TTR) is maintained to prevent thromboembolic events and curtail the bleeding effects of poor warfarin control. The 2020 European Association of Cardiology guidelines for the diagnosis and management of NVAF, developed in collaboration with the European Association of Cardiothoracic Surgery, recommends switching patients from vitamin K antagonists to direct oral anticoagulants (DOACs) if the time in therapeutic range is below 70% as a class I indication [7,9]. Therefore, the

study aimed to determine the level of oral anticoagulation control in patients with NVAF treated with vitamin K oral anticoagulation in a tertiary academic centre in Johannesburg, South Africa.

Methods

We conducted a retrospective study in the Division of Cardiology at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) in Johannesburg, South Africa. Patient data was collected from an electronic health record system housing admission data for all patients hospitalised in the cardiology wards at the CMJAH. All patients 18 years of age and older with the International Classification of Disease (ICD-10) code for atrial fibrillation were included in the study. Patients on oral vitamin K anticoagulation (warfarin) with outpatient international normalised ratio (INR) results for at least six months before the study period were included in the analysis. The rationale for this was to mitigate the effects of warfarin initiation titration dosing.

Data was additionally collected from outpatient records at the arrhythmia clinic for those with an electrocardiogram (ECG) diagnosis of AF between 1 January 2015 to 31 December 2019. We excluded records of patients that were not prescribed oral anticoagulation therapy and those on DOACs. We then categorised the patient data according to the type of AF, NVAF and valvular atrial fibrillation (VAF). Patients were placed in the VAF category if they had echocardiographic features of mitral stenosis or were previously subjected to valve surgery for organic valvular heart disease.

In accordance with the latest AF guidelines for an INR target between 2 - 3 for all patients with NVAF on warfarin, we calculated the TTR using the Rosendaal method for patients with NVAF [10-13]. We also documented thromboembolic and haemorrhagic events that occurred within the study period. Thromboembolic events were defined as an occurrence of a cerebrovascular event, transient ischaemic attacks, pulmonary embolism, or deep vein thrombosis. Haemorrhagic events

included warfarin toxicity, defined as bleeding in a patient with an INR above 4, necessitating hospital admission and or a blood transfusion. Permission to conduct the study was obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical) and relevant hospital authorities. Individual patient consent was waived since the study entailed a retrospective review of medical records.

Statistical Analysis

Statistical analyses were performed using Stata SE version 17 (StataCorp. 2019. College Station, TX: StataCorp LLC). Data is expressed as means and standard deviations when normally distributed and as medians with interquartile ranges when the distribution is skewed. Categorical data is expressed as numbers and percentages. For continuous variables with a normal distribution, a student t-test was used to test for intergroup (TTR<70% and TTR>70%) differences, and the chi-square test was used to compare categorical data. A Wilcoxon rank sum test was used to compare medians for continuous variables with a skewed distribution. Univariable and multivariable logistic regression analyses were performed to determine the predictors of a TTR <70%. Confidence intervals (CI) were set at 95%, and a p-value less than 0.05 was considered to represent statistical significance.

Results

Demographic and clinical characteristics

The final study population comprised 223 patients with AF, of which 177 (79.3%) had NVAF. The mean age in the entire study population was 62.3 ± 14.3 years, and patients with NVAF were older, with a mean age of 65.0 ± 13.1 years (95% CI: 63.1 – 67.0, p<0.0001). There were 119 (53.4%) females, with 81 (68.1%) diagnosed with NVAF. More than half (50.45%) of the study population were of black African ancestry, and 77 (68.7%) had NVAF.

Hypertension was reported in 157 (70.4%) patients, and 72 (32.3%) had diabetes mellitus. Forty-seven (21.1%) patients had a history of myocardial infarction (MI), and 44 (93.4%) of these patients with a history of MI had NVAF. A pre-existing history of cerebrovascular accidents and transient ischaemic attacks was found in 20 (9.0%) patients, and 186 (83.4%) of patients had heart failure symptoms, of which 146 (78.5%) had NVAF. In total, 193 (92.3%) patients were unemployed, and 143 (68.4%) were pensioners.

The weekly median warfarin dose was 35 mg (IQR: 17.5 – 35), and it did not differ significantly between patients with VAF and NVAF [35 mg (IQR: 17.5 – 35) vs 35 mg (IQR: 25.0 – 35.0), p=0.5169]. There were 179 (80.3%) patients on oral beta beta-blocker therapy, 27 (12.1%) on calcium channel blockers, and 120 (53.8%) on oral angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). The rest of the baseline demographic and clinical characteristics of patients with NVAF are reported.

Anticoagulation control in patients with non-valvular atrial fibrillation

The median TTR among patients with NVAF was 46% (IQR: 8.7 – 86), and the TTR was greater than 70% in 114 (35.6%) patients with NVAF. The weekly median warfarin dose did not differ significantly between patients with poor (TTR<70%) and optimal (TTR>70%) anticoagulation control [35 mg (IQR: 25 – 35) vs 35 mg (17.5 – 35), p= 0.8232]. The baseline median INR was 2.1 (IQR: 1.5 – 2.8), and the median duration between the baseline or first INR and the third INR measurement was 62 days (IQR: 49 – 97). Fifty-six (31.6%) patients with NVAF had a baseline INR range between 2.0 and 3.0. Patients with NVAF and poor (TTR<70%) anticoagulation control were on warfarin for a shorter duration compared with those with optimal anticoagulation control [56 days (IQR: 43 – 84) vs 70 days (IQR: 56 – 140), p=0.0013]. On the univariable analysis, this relationship was not statistically significant [Odds ratio (OR): 0.99, 95% CI: 0.993 – 1.00, p=0.079). The estimated glomerular filtration rate did not differ between patients with a TTR less

than and above 70%, respectively [54.5 ml/min (IQR: 42 – 74) vs 58 ml/min (IQR: 42 – 79), p=0.7119].

The mean CHA_2DS_2-VASc Score was 4 ± 1.5, and it did not differ between patients with poor and optimal anticoagulation control (p=0.4932). On the univariate logistic regression analysis, patients on oral dosages of ACE inhibitors or ARBs were 1.7 times more likely to have a TTR<70% (95% CI: 0.93 – 3.22, p=0.083), and those on digoxin were less likely to have poor anticoagulation control (OR: 0.4; 95% C: 0.16 – 1.00, p=0.052). None of the study variables were independent predictors of poor anticoagulation control in patients with NVAF.

Risk of bleeding and study outcomes in all patients with atrial fibrillation

The median duration of hospitalisation for all patients with atrial fibrillation was five days (IQR: 3 – 9) days, and it did not differ significantly in patients with VAF and NVAF, as well as in those with NVAF and a TTR above and below 70%. The median frequency of hospitalisations at the CMJAH was two admission episodes (IQR: 1 – 3). Warfarin toxicity was documented in 18 (8.1%) patients, and 13 (83.3%) of these patients had NVAF. The median duration between the diagnosis of atrial fibrillation and occurrence of warfarin toxicity was 129 days (IQR: 24 – 783). Based on the HAS BLED score, 144 (65.2%), 47 (21.3%) and 30 (13.6%) of all atrial fibrillation patients were at a low, moderate, and high risk for bleeding, respectively. Thromboembolic complications were only documented in a few patients, with ischaemic strokes documented in 10 (4.5%), haemorrhaging stroke in one patient (0.4%), a transient ischaemic attack in two (0.9%) patients, and lower limb deep vein thrombosis in one patient. Major bleeding requiring a blood transfusion was documented in two (0.9%) patients.

Discussion

We conducted a retrospective chart review of 223 patients with AF treated at CMJAH, a tertiary state-owned academic hospital in Johannesburg, South Africa. Among the 223 patients with atrial fibrillation, 177 (79.3%) had NVAF. Our study demonstrated that anticoagulation control in patients with NVAF is suboptimal, with only 36% of our cohort achieving a TTR above the recommended 70%. The median TTR was 46% (IQR: 8.7 – 86) and was slightly higher than that reported by the Randomized Evaluation of Long-Term Anticoagulation Therapy (RELY) Atrial fibrillation Registry, a multicentre global trial which included 20 sites from Africa [14]. In the RELY trial, the mean TTR among 1137 patients recruited from Africa was 33%, and patients from Africa with NVAF had the lowest TTR compared to their counterparts in high-income countries and other LMICs [14]. Also, a study by Semakula and colleagues evaluating the TTR in outpatients requiring INR monitoring services in Uganda and South Africa showed that, despite regular INR monitoring at least once per month, the median TTR was 41% (IQR: 14 - 69) [3]. Although this study by Semakula et al. included patients on warfarin irrespective of the clinical indication for warfarin, it highlighted some of the shared difficulties we also found in our study associated with warfarin use. Furthermore, a study conducted in Kwa-Zulu Natal, South Africa, found that only 10 patients (10.4%) with NVAF maintained a TTR above 70%. The mean TTR estimated using the Rosendaal method among 96 patients with NVAF was 44% ± 18.5%, comparable to the TTR obtained in our study [15].

Frailty is a biological syndrome with multiple cumulative physiological declines and a reduced ability to employ homeostatic resilience and reserve to recover from stressors [33]. Atrial fibrillation increases frailty by four-fold and may be a marker of frailty [33,34]. In our study, NVAF patients had a mean age of 65 years, comparable to other studies in the region [3,15]. Although frailty was not assessed in our patients, frailty remains relevant in AF management. Frail patients are less likely to receive anticoagulation due to warranted concern of adverse outcomes such as bleeds. The clinical tendency to not anticoagulate this inherently high-risk stroke

population group is further exacerbated by polypharmacy interactions and the impact of multiple comorbidities [35]. Evidence supports a net clinical benefit with the use of anticoagulation in frail AF patients [36].

Heart failure and AF have a synergistic effect in increasing the risk of thromboembolism and all-cause mortality [37]. In a study involving Framingham Heart Study participants with AF, the hazard ratio (HR) for the occurrence of heart failure with preserved ejection fraction was 2.34 (95% CI: 1.48 – 3.70, p=0.0003). Participants with heart failure were 2.18 times likely to be diagnosed with AF (HR: 2.18, 95% CI: 1.26 – 3.76, p=0.005) [16]. Yuyun et al. evaluated the spectrum of cardiac arrhythmias in sub Saharan Africa (SSA), and reported that hypertension was the most common risk factor associated with AF reported in 50-87% of patients, followed by heart failure in 32-64% of all patients with AF [17]. In our study, heart failure and hypertension were the most common comorbidities in all patients with AF, with a prevalence of 83.4% and 70.4%, respectively. Also, The Heart of Soweto Study, involving patients residing in the urban part of South Africa, showed that hypertension is one of the most common and under treated significant modifiable risk factors in patients with and without AF. The authors reported that in the patients studied 56% had hypertension, highlighting the need to screen vigorously, optimally monitor and treat all patients with hypertension using guideline-directed management [18].

The safety and efficacy of anticoagulation therapy in patients with AF and concomitant chronic kidney disease (CKD) have unique clinical implications. There is an increased AF prevalence of up to 10-25% with deteriorating renal function [5]. Furthermore, CKD patients are at a high risk of thromboembolic events and major bleeding independent of oral anticoagulation [5]. Studies show a baseline increased cerebral haemorrhage potential up to 10 times higher in CKD patients than those with normal renal function [5, 38]. Warfarin is currently the mainstay of anticoagulation in AF patients with CKD. Our study did not show an association between renal dysfunction and poor

TTR. Patients with a TTR less than 70%, had an estimated glomerular filtration rate of 54.5 ml/min (IQR: 42 – 74) compared to 58 ml/min (IQR: 42 – 79) in the group with TTR's above 70% (p=0.7119). This is potentially related to a healthcare provider treatment bias and hesitance that may exist to prescribe anticoagulation to AF patients with declining renal function because of the concern of bleeding risk. Insights from ongoing randomised control trials such as the Oral anticoagulation in haemodialysis patients (AVKDIAL) and The Danish warfarin dialysis study safety and efficacy of warfarin in patients with atrial fibrillation on dialysis (DANWARDD) will hopefully have a positive impact on prescriber confidence in the management of CKD AF patients [39,40].

The advent of combination antiretroviral therapy (cART) has dramatically improved the life expectancy of people with Human immunodeficiency virus (HIV) [42]. Consequently, AF has emerged as a significant contributor to high cardiovascular risk and mortality in the aging HIV population, with a prevalence of 2-3% [40,41]. However, it is unclear whether contemporary anticoagulation guidelines for AF can be safely applied to patients with HIV [41]. This is particularly relevant in SSA where the National Institute of Health estimates that 7.9 million people live with HIV in South Africa [42]. In our study only four patients in our cohort had documented HIV which may be due to the persisting stigma that is attached to a HIV diagnosis in SSA.

Traditional risk calculators such as the CHA_2DS_2-VASc score, and the HAS-BLED score are useful for estimating the risk of strokes and major bleeds in patients with AF. However, they may not be well calibrated to accurately assess the true risk of stroke in the AF HIV population [41]. It's been shown that even with correction for cardiovascular risk factors: a CD4 count of less 200 and a viral load of >100000 copies/ml had a 1.4-2-fold and 1.7-fold increased risk of AF respectively [41]. This, as well as other HIV specific factors like interactions with ARV's, the role of hyperhomocysteinemia and comorbid opportunistic infections are largely neglected in anticoagulation efficacy and safety research. [41]

241

242 The C-statistic of the CHA_2DS_2-VASc model for one-year risk of ischaemic stroke or transient
243 ischaemic attacks (TIA) among patients with atrial fibrillation was 0.679 (95% CI: 0.670 –
244 0.686)[19]. Despite correcting for ethnic differences, the C-statistic, which measures the ability of
245 the model to discriminate between positive and negative cases, did not improve, suggesting that the
246 model may have modest predictive powers [19]. In our study, the mean CHA_2DS_2-VASc score was
247 4, and it did not differ between patients with poor and optimal anticoagulation control (p=0.4932),
248 thus inferring that the overall risk of ischemic strokes, systemic embolisms and TIA in our study
249 cohort with AF could be between 4.8% and 6.7% [20]. In contrast, the HAS-BLED score,
250 classified 144 (65.2%), 47 (21.3%) and 30 (13.6%) atrial fibrillation patients in our study to be at a
251 low, moderate, and high risk for bleeding, respectively.
252
253 The occurrence of thromboembolic and bleeding complications in AF patients with poor
254 anticoagulation control is well described [23-26]. In our study, warfarin toxicity was documented in
255 8.1% of all AF patients, despite INR monitoring, and was common in patients with NVAF.
256 Furthermore, our study also demonstrated that the rate of thromboembolic complications was low.
257 This is likely not representative because most patients who are hospitalised, in this medical
258 institution, with AF related strokes and thromboembolic complications are mostly managed in
259 general medical or surgical wards - not in cardiology wards. Ischaemic strokes were the most
260 common complication, documented in 4.5% of all patients with AF. One of the common predictors
261 of poor anticoagulation control reported in the literature is polypharmacy, where NVAF patients on
262 six or more oral medications were at risk of poor anticoagulation control (TTR ≥65%). (OR:1.89,
263 95% CI 1.03–3.33; $p = 0.03$) [27]. In our study, none of the clinical variables were independent
264 predictors of poor anticoagulation control.
265

In most LMICs, the most feasible approach for managing AF patients on vitamin K antagonists is patient counselling, education, and frequent INR monitoring. Recent guidelines suggest that in patients who fail to maintain a TTR >70%, DOACs should be considered [1]. The findings from our study have shown that the use of warfarin therapy in 64% of our patient group is inefficacious and potentially harmful. Suboptimal warfarin use is not innocuous, as patients are at a greater risk for both increased bleeds and strokes [28]. Health care systems in LMICs need to evaluate whether the cost of newer oral anticoagulation may be offset by the cost of regular INR monitoring, frequent outpatient visits and a reduction in costs immanent in managing warfarin-related complications.

The study's retrospective nature and the relatively smaller sample size are the study's main limitations. Although we could demonstrate a low TTR in patients with NVAF, we could not accurately showcase the complications associated with such poor control. This is related to a selection bias in our study, where only patients with cardiac-specific complications would have been admitted to the cardiology department. In addition, since the study was conducted at a single-centre, academic tertiary hospital, it excluded patients that would have presented to their local hospitals with AF and its related complications. Incomplete record keeping was a significant challenge, particularly when mining the electronic health record system. Despite these limitations, our study has demonstrated the need to consider introducing DOACs to high-risk individuals with a TTR persistently below 70% after adequate counselling and patient education.

Conclusions

Our study found suboptimal anticoagulation control in 64% of patients with NVAF. There is an urgent need to improve access to DOACs to ensure these patients are adequately protected from AF-related morbidity and mortality. Cost-effectivity analysis studies are required in LMICs to determine which therapeutic strategy would be effective and cost-saving to the entire healthcare system, considering all direct and indirect costs involved in managing patients with AF.

Acknowledgements

I would like to thank my supervisors Dr Mpanya and Prof Tsabedze for their tireless contributions to this manuscript whilst being beacons of excellence and inspiration.

ORIGINALITY REPORT

14%	9%	11%	2%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	"Monday, 29 August 2011", European Heart Journal, 08/02/2011 Publication	1%
2	deepblue.lib.umich.edu Internet Source	1%
3	www.scienceopen.com Internet Source	1%
4	amersa.org Internet Source	1%
5	www.science.gov Internet Source	1%

		1%
6	Nqoba Tsabedze, Dineo Mpanya, Claude Bailly, Samantha Nel et al. "Clinical characteristics and one-year all-cause mortality outcomes in Africans with dilated cardiomyopathy", International Journal of Cardiology, 2023 Publication	
7	www.frontiersin.org Internet Source	1%
8	Agnieszka Kotalczyk, Wern Yew Ding, Christopher F. Wong, Anirudh Rao, Dhiraj Gupta, Gregory Y.H. Lip. "Atrial Fibrillation in Patients with Chronic Kidney Disease", Cardiology Clinics, 2021 Publication	1%
9	Laila Mahmoud Ali Matalqah. "Knowledge, Adherence, and Quality of Life among Warfarin Therapy Users", IntechOpen, 2019 Publication	<1%
10	hdl.handle.net Internet Source	<1%

	<1%
Oliver Königsbrügge, Hannah Meisel, Aljoscha Beyer, Sabine Schmaldienst et al. "Anticoagulation use and the risk of stroke and major bleeding in patients on hemodialysis: From the VIVALDI, a population-based prospective cohort study", Journal of Thrombosis and Haemostasis, 2021 Publication	11
escholarship.mcgill.ca Internet Source	12 <1%
files.covid19treatmentguidelines.nih.gov Internet Source	13 <1%
www.researchsquare.com Internet Source	14 <1%
cyberleninka.org Internet Source	15 <1%
www.researchgate.net Internet Source	16 <1%
macsphere.mcmaster.ca Internet Source	17 <1%
onlinelibrary.wiley.com Internet Source	18 <1%

19	eje.bioscientifica.com Internet Source	<1%
20	Submitted to University of Greenwich Student Paper	<1%
21	www.doctorsforafghanistan.com Internet Source	<1%
22	iono.fm Internet Source	<1%
23	www.uhcprovider.com Internet Source	<1%
24	docksci.com Internet Source	<1%
25	Kathrine Parker, John Hartemink, AnanyaSaha, Roshni Mitra et al. "A systematic review of the efficacy and safety of anticoagulants in advanced chronic kidney disease", Journal of Nephrology, 2022 Publication	<1%
26	www.omicsdi.org Internet Source	<1%

		<1%
27	Andrea Buono, Riccardo Gorla, Alfonso Ielasi, Giuliano Costa et al. "Transcatheter Aortic Valve Replacement With Self-Expanding ACURATE neo2", JACC: Cardiovascular Interventions, 2022 Publication	
		<1%
28	Macedo, Ana Filipa, James Bell, Ciaran McCarron, Rachel Conroy, James Richardson, Anna Scowcroft, Tom Sunderland, and Naj Rotheram. "Determinants of oral anticoagulation control in new warfarin patients: analysis using data from Clinical Practice Research Datalink", Thrombosis Research, 2015. Publication	
29	worldwidescience.org Internet Source	<1%
		<1%
30	Michael D. Ezekowitz, Rangadham Nagarakanti. "Dabigatran in atrial fibrillation: pharmacology and clinical trials", Journal of Interventional Cardiac Electrophysiology, 2011 Publication	

	Sumesh Padayachee, Ahmed Adam, June	<1%
31	Fabian. "The impact of diabetes and hypertension on renal allograft survival- A single centre study", Current Urology, 2022 Publication	
	open.uct.ac.za	
32	Internet Source	<1%
		<1%
33	García-Fernández, Amaya, Francisco Marín, Vanessa Roldán, Emilio Galcerá-Jornet, Juan Gabriel Martínez-Martínez, Mariano Valdés, Francisco Sogorb, and Gregory Y.H. Lip. "The HAS-BLED score predicts long-term major bleeding and death in anticoagulated nonvalvular atrial fibrillation patients undergoing electrical cardioversion", International Journal of Cardiology, 2016. Publication	
		<1%
	Sylvie Perreault, Payman Shahabi, Robert	
34	Côté, Stéphanie Dumas et al. "Rationale, design, and preliminary results of the Quebec Warfarin Cohort Study", Clinical Cardiology, 2018 Publication	

	<1%
"15th Congress of the International Pediatric Nephrology Association", Pediatric Nephrology, 2010 Publication	35

Exclude quotes	On	Exclude matches	< 6 words
Exclude bibliography	On		