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Venessa Mogashoa; Dineo Mpanya; Nqoba Tsabedze

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Anticoagulation control for nonvalvular atrial fibrillation in a tertiary academic centre in Johannesburg

Vanessa Mogashoa[1], Dineo Mpanya[1†] and Nqoba Tsabedze[1*†]

Abstract

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

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

Results The study population comprised 177 patients diagnosed with NVAF. The mean age 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% (optimal anticoagulation control). 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 available 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 optimal anticoagulation control, was found in only 35.6% of patients with NVAF on warfarin.

Keywords Atrial fibrillation, Anticoagulation, Warfarin, International normalised ratios

†Joint senior authorship: These authors contributed equally to this work.

*Correspondence:
Nqoba Tsabedze
Nqoba.Tsabedze@wits.ac.za

[1]Division of Cardiology, Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, 17 Jubilee Road, Johannesburg 2193, Gauteng Province, South Africa

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Background

Optimal anticoagulation is one of the pillars of atrial fibrillation (AF) management. This is required to mitigate the associated high risk of mortality, stroke, and impaired quality of life [1, 2]. Atrial fibrillation carries a five-fold increased risk of stroke. Atrial fibrillation-related strokes are associated with significant disability and mortality compared to non-AF-related strokes [3, 4]. Optimal anticoagulation control remains challenging, particularly in low-and middle-income countries (LMIC). The efficacy of direct oral anticoagulants (DOACs) has led to their increasing use and incentivised ongoing research into their safety profile. As such, DOACs are progressively being considered for nonvalvular atrial fibrillation (NVAF), even in previously neglected high-risk populations such as those with chronic kidney disease and frail patients [5, 6].

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% [7]. In rural South Africa, the crude incidence rate for non-AF-related stroke is 244 per 100,000 person-years [8].

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 2024 European Association of Cardiology guidelines for the management of AF, developed in collaboration with the European Association for Cardiothoracic Surgery, recommends switching patients from vitamin K antagonists to DOACs if the TTR is below 70% as a class I indication [1, 9]. There are limited data describing anticoagulation control in patients with NVAF in LMICs. Therefore, this study aimed to determine the level of oral anticoagulation control in patients with NVAF treated with warfarin 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 warfarin, an oral vitamin K antagonist, and had outpatient international normalised ratios (INR) measured for a minimum of six months as outpatients were included in the analysis. This rationale 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 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 and 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 score which incorporates variables such as congestive heart failure/left ventricular ejection fraction < 40%, hypertension, age > 75 years, diabetes mellitus, stroke/transient ischemic attack (TIA)/thromboembolism history, vascular disease, age 65–75 years, and female sex. The HAS-BLED score, which incorporates hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (age > 65), and drugs/alcohol use, was also estimated for each of the study participants [1]. Laboratory parameters such as the estimated glomerular filtration rate (eGFR) and the INR were obtained from the National Health Laboratory Services website.

Following the latest AF guidelines for an INR target between 2 and 3 for all patients with NVAF on warfarin, we calculated the TTR using the Rosendaal method [1, 10, 11]. Furthermore, patients with NVAF were stratified according to the TTR (TTR < 70% and TTR ≥ 70%). The TTR estimates the percentage of time a patient's INR is within the therapeutic treatment range or goal, with a higher TTR directly correlated with a reduction in thromboembolic complications [11]. 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 or transient ischaemic attacks. Haemorrhagic events included warfarin toxicity, defined as bleeding in a patient with an INR above four that necessitates hospital admission or blood transfusion. Permission to conduct the study was obtained from the University of the Witwatersrand Human Research Ethics Committee (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 18.5 (StataCorp. 2019. College Station, TX: StataCorp LLC). Categorical variables are expressed as frequencies and percentages. Continuous variables are expressed as the mean and standard deviation when normally

distributed and as the median with interquartile ranges (IQR) when the distribution is non-normal. 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 (Fig. 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 only three (1.7%) people living with human immunodeficiency virus (PLWH). Among all patients with NVAF, 125 (70.6%) were pensioners. The rest of the baseline demographic and clinical characteristics are depicted in Table 1.

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 only 63 (35.6%) patients (Fig. 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 and optimal anticoagulation control ($p = 0.4932$). Among the 175 patients with available 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% ($p < 0.001$).

The baseline or first median 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 (Fig. 3).

Complications

Warfarin toxicity was documented in 13 (7.3%) patients, and 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, and ischaemic strokes were documented in 6 (3.4%) patients.

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 (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, calcium channel blockers, and digoxin) and duration on warfarin. None of the variables were associated with poor anticoagulation control (Table 2).

Discussion

We retrospectively reviewed the 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 [12]. 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 other regions [12]. 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) [4]. 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 associated with warfarin use. Furthermore, a study conducted in Kwa-Zulu Natal, South Africa, found that only ten (10.4%) patients with NVAF maintained a TTR above

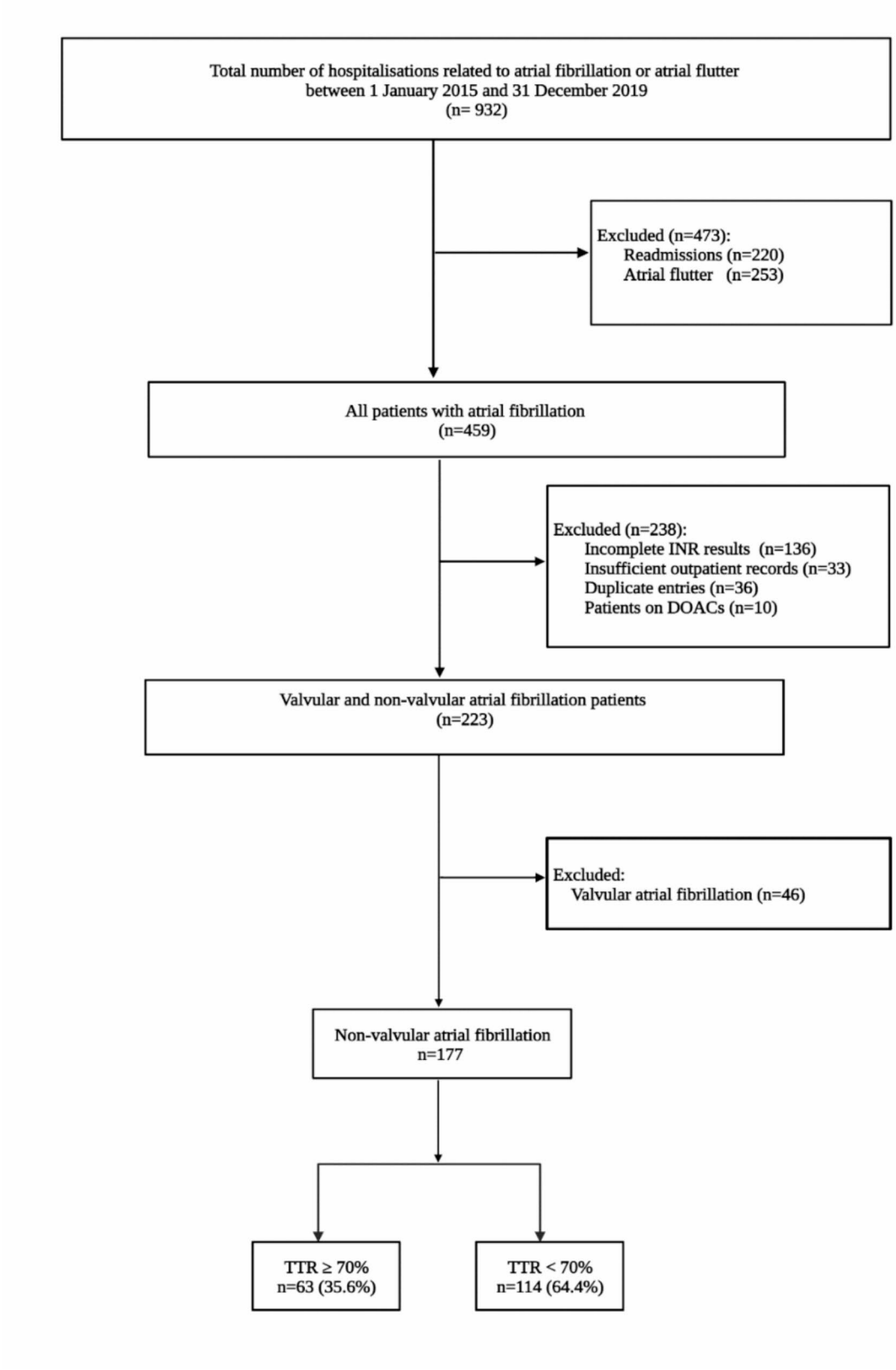

Fig. 1 Flow chart showing the selection of patients included in the study. DOACs: direct oral anticoagulants, INR: international normalised ratio, TTR: time in the therapeutic range

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*

	All patients (*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
Sex				0.9570
Male	96 (54.2)	62 (54.4)	34 (54.0)	
Female	81 (45.8)	52 (45.6)	29 (46.0)	
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

Categorical variables are represented as frequencies and percentages. Continuous variables with a normal distribution are represented as the mean and standard deviation (SD). The median and interquartile ranges (p25-p75) were used to summarize continuous variables with a non-normal distribution. 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 variables. A Wilcoxon rank sum test was used to compare medians for continuous variables with a non-normal distribution. ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; BP: blood pressure; LVEF: left ventricular ejection fraction; MI: myocardial infarction. * Time in therapeutic range estimates the percentage of time a patient's INR is within the therapeutic treatment range or goal, with a higher TTR directly correlated with a reduction in thromboembolic complications

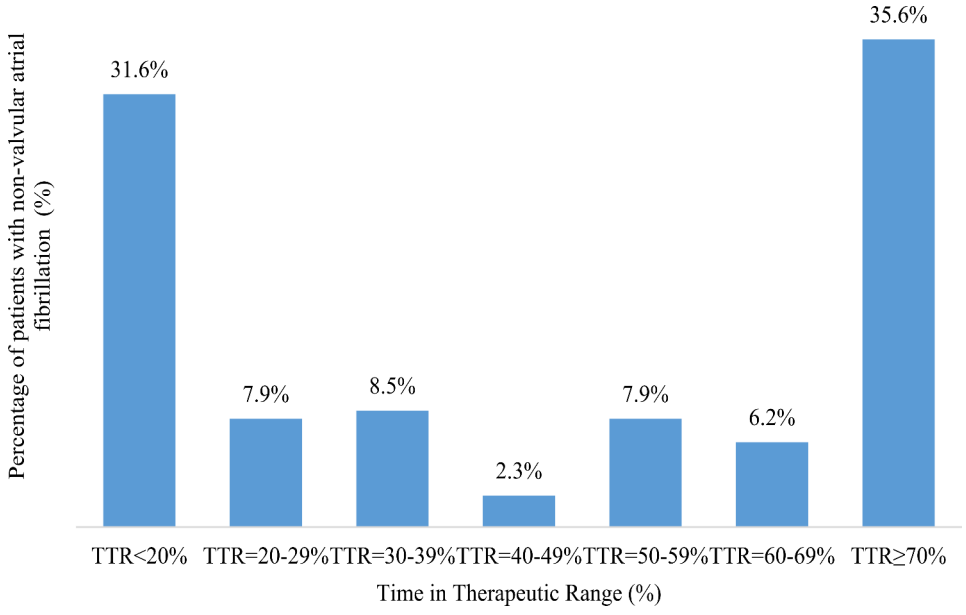

Fig. 2 Time in therapeutic range in nonvalvular atrial fibrillation patients on warfarin

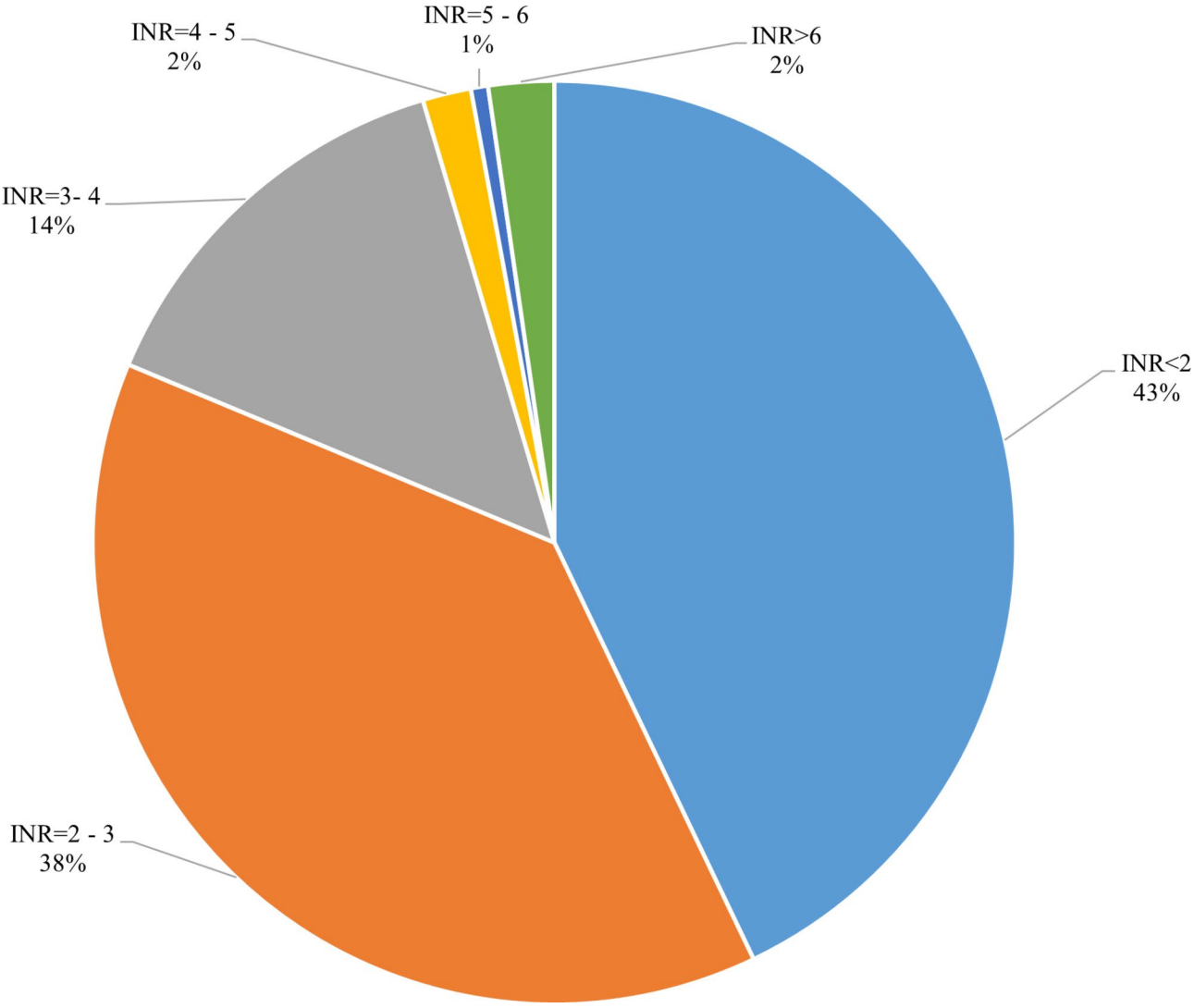

Fig. 3 Distribution of baseline or first international normalised ratio (INR) measurements in non-valvular atrial fibrillation patients on warfarin

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

	Odds ratio	*p*-value	95% CI
ACE inhibitors 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 blockers; CI: confidence interval

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 [13].

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 [14]. It has been shown that even with correction for cardiovascular risk factors, a CD4 count of less than 200 and a viral load exceeding 100,000 copies/ml had a 1.4-2.0-fold and 1.7-fold increased risk of AF, respectively [15]. 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 [14].

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) [16]. 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 [16]. 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% [17].

The occurrence of thromboembolic and bleeding complications in AF patients with poor anticoagulation control is well described [18–21]. 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 true 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 one of the common complications, 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; $p=0.03$) [22]. In our study, none of the clinical variables predicted poor anticoagulation control. Other predictors of a low TTR reported in the literature are advanced heart failure, frailty, and prior valve surgery [23]. Additionally, a study by Rose et al. on 124 619 patients receiving warfarin identified cancer, liver disease, chronic kidney disease, and diabetes as predictors of a lower TTR [24]. Routine care of patients on anticoagulation at a specialised INR clinic has also been associated with a higher TTR [25].

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 show that the use of warfarin therapy in 64.4% of our patient group is inefficient and potentially harmful. Suboptimal warfarin use is not innocuous, as patients are at a greater risk for increased bleeding and strokes [26]. Healthcare systems in LMICs need to evaluate whether the cost of newer oral anticoagulation may be offset by regular INR monitoring, frequent outpatient visits, and a reduction in the expenses of 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.

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 mellitus, stroke/transient ischemic attack/thromboembolism 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

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None.

Author contributions

VM collected the study data, prepared all figures, 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.

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Data availability
Datasets used in the study are available from the corresponding author on reasonable request.

Declarations

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.

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

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