Poor anticoagulation control in patients taking warfarin at a tertiary and district-level prothrombin clinic in Cape Town, South Africa

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Background. Warfarin is the most commonly used anticoagulant for both primary and secondary prevention of thromboembolism. For anticoagulation efficacy, the international normalised ratio (INR) needs to be within the therapeutic range for at least 65% of time on warfarin.
Objectives. To describe INR control in patients on long-term warfarin and identified predictors of good INR control at two dedicated warfarin follow-up clinics in Cape Town, South Africa (SA).
Methods. We reviewed clinical records of patients in care at the INR clinics at Mitchell's Plain Community Health Centre and Groote Schuur Hospital. We included patients who had been on warfarin therapy for at least 27 months and excluded patients with <6 months of INR monitoring data or a >70-day gap between INR tests in the calculation period, and if >25% of follow-up time was at an alternative site. The time in therapeutic range (TTR) over 180 days using the Rosendaal method was calculated, and we categorised INR control as good if the TTR was ≥65%. We constructed a multivariate logistic regression model to identify associations with good INR control.
Results. We included 363 patients, with a median age of 55 years (interquartile range (IQR) 44 - 64), of whom 65.6% were women. The most common indications for warfarin were valvular heart disease (45.7%) and atrial fibrillation (25.1%). The mean TTR was 47%, with only 91/363 patients having good INR control. In a multivariate model adjusted for age, sex, clinic and target INR, patients aged ≥55 years were more likely to have good INR control than younger patients (adjusted odds ratio 1.69, 95% confidence interval 1.03 - 2.79). Poorly controlled patients had more frequent INR monitoring than those with good INR control, with a median of 8 INRs (IQR 6 - 10) v. 6 INRs (IQR 5 - 8) in the 180-day period ($p<0.0001$).
Conclusions. Only 25.1% of patients in our study achieved good INR control, despite regular INR monitoring. There is an urgent need to improve anticoagulation control of patients receiving warfarin in SA. Validated dosing algorithms are required, and access to lower warfarin dosage formulations may optimise individual dose titration. Advocacy for these formulations is advised.

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Atrial fibrillation (AF) and valvular heart disease (VHD) increase the risk of thrombus-related morbidity and cardioembolic stroke.[1] Stroke is one of the top four causes of death and adult disability in South Africa (SA).[2,3] Appropriately dosed anticoagulation therapy decreases morbidity and mortality due to cardioembolic stroke.[4-6]

Warfarin is the most widely used oral anticoagulant for primary and secondary stroke prevention[7] and is the only vitamin K antagonist (VKA) available in SA.[8] Alternative oral anticoagulants are not routinely available in public sector healthcare facilities owing to their high cost.[9] Aspirin is a poor alternative in patients with AF, as it is much less effective at preventing cardioembolic events.[7,10] Warfarin has unpredictable pharmacokinetics and dynamics, and requires individualised dosing to achieve optimal anticoagulation. Warfarin has a narrow therapeutic range, placing patients at risk of bleeding if the target is exceeded and at risk of thromboembolic complications if subtherapeutic.[5,10] Warfarin is a leading cause of adverse drug reaction (ADR)-related medical admissions in SA.[11]

Time in the therapeutic range (TTR) is a calculation that reflects the duration of time in which a patient's international normalised ratio (INR) values were within the desired range and is used to evaluate the effectiveness of warfarin therapy. For effective anticoagulation, patients on warfarin should achieve an INR in the therapeutic range for ≥65% of the follow-up time.[10] Patients with TTR <65% have reduced warfarin efficacy.[10] Low TTR is also associated with an increased risk of both bleeding and thrombo-embolic complications.[10] Two multinational multicentre clinical trials (ACTIVE W and RE-LY) that included patients from SA found poor INR control in SA patients receiving warfarin.[10,12]

Objectives

We quantified anticoagulation control over a 6-month period for patients on long-term warfarin managed at two dedicated INR clinics in Cape Town, SA. Specific objectives were to determine the proportion of patients achieving a TTR ≥65%, and to identify predictors of adequate control (TTR ≥65%).

Methods

We reviewed folders of patients attending the warfarin anticoagulation monitoring clinics at Mitchell's Plain Community Health Centre (MPC) and Groote Schuur Hospital (GSH) in Cape Town. These

outpatient clinics assess the INR at patient visits and adjust the warfarin dose in response to the INR result. At GSH, INR results are available within hours and dose modification occurs immediately. At MPC, INR results are available the next day and dose adjustment instructions are given to patients telephonically. Both facilities use the same, unvalidated dosing algorithm to guide dose adjustments.

We identified patients who were on long-term warfarin therapy, which we defined as at least 2 years on warfarin, after an initial 3-month dose-stabilisation period to achieve the required INR. The INR monitoring results were reviewed, and we excluded patients with <6 months of consecutive INR data and those who visited both or other sites and had >25% of follow-up visits at an alternative site. We also excluded patients who had >70 days between INR quantification.[13] Patient follow-up at clinics occurs at least every 2 months (56 days) and we allowed for patients to be 14 days late for routine follow-up. We excluded patients with larger gaps between INRs as this may affect the accuracy of TTR quantification and under- or overestimate the TTR.[13]

We powered the study to detect a 15% difference in the mean TTR between the two sites (with α=0.05 and 80% power) and calculated that we would need 173 patients from each site for a total sample size of 346.

We calculated the TTR using the widely accepted Rosendaal method.[13] The calculation assumes a linear relationship (increase or decrease) between consecutive INR values to determine the proportion of time within the therapeutic range.[13] We calculated TTR over 6 months (180 days) and excluded the first 90 days of regular INR monitoring data from the TTR calculation, to allow patients newly initiated on warfarin to achieve stability. TTR was therefore calculated starting from the first INR result after the 90-day window. The target INR range for patients taking warfarin for AF and most other indications is 2.0 - 3.0. The target INR range for VHD is 2.5 - 3.5.[14] The therapeutic range for the patient's clinical condition was used as the target for that patient in the TTR calculation. In patients with an unknown indication for warfarin therapy, we assumed a target INR range of 2.0 - 3.0. We defined poor control as TTR <65% over the 180-day period, and good control as TTR ≥65%.[10]

Statistical analysis

We summarised continuous variables as means (standard deviation (SD)) if normally distributed and as medians with interquartile ranges (IQRs) if abnormally distributed, and used the Wilcoxon rank-sum test for between-group comparisons of continuous variables. Univariate associations between categorical variables were explored using the χ^2 test. We constructed a multivariate logistic regression model of associations with good anticoagulation (TTR ≥65%), and included age, sex, site and target INR in the model based on an *a priori* decision. Age was split into two groups at the median and included in the model as a binary variable. A *p*-value <0.05 was considered statistically significant. Stata SE 13.1 (StataCorp, USA) was used for the analyses.

Ethical considerations

The study was approved by the Human Research Ethics Committee at the University of Cape Town (ref. no. 658/2014) and the Western Cape Health Research Committee (ref. no. WC_2015RP8_111). Permission to conduct the research was given by hospital management of MPC and GSH. The study was conducted in accordance with the Declaration of Helsinki (last updated 2013)[15] and the Guideline for Good Clinical Practice.[16]

Results

We screened the clinical records of 949 patients, of whom 586 were excluded and 363 were included in the analysis (Fig. 1). Screening took place in September 2014. INR data were reviewed between 2009 and 2014, and all participants with more than 27 months of INR data were included in the study.

Patient characteristics are set out in Table 1. The most common indications for warfarin therapy were AF (25.1%) and VHD (45.7%). Other indications were pulmonary embolus, venous thromboembolism, systemic lupus erythematosus, hypercoagulable states and atrial flutter. An indication was not documented in 10.5% of patients.

The mean (SD) TTR was 47.0% (24.0%) and did not differ significantly between sites (Fig. 2). In 272/363 patients (74.9%) the TTR was <65%. Poorly controlled patients had more frequent INR monitoring than those with good control, with a median of 8 readings (IQR 6 - 10) and 6 readings (IQR 5.0 - 8.0) over the 6-month period, respectively (rank-sum $p<0.0001$). Patients aged <55 years had a mean TTR of 43% (95% confidence interval (CI) 40 - 47) compared with a mean of 50% for those aged ≥55 years (95% CI 46 - 53) ($p=0.0105$). In the multivariate analysis, age ≥55 years was associated with better INR control (Table 2).

Discussion

The majority of patients in our study had poor INR control – only 25.1% had a TTR ≥65%. Older age was associated with better control, but even in patients aged ≥55 years, only 30.6% achieved a TTR of ≥65% (Table 2). This is a concerning finding. Despite regular follow-up, most patients did not achieve adequate INR control for efficacy and are at risk of warfarin adverse effects.

Even under clinical trial conditions, anticoagulation control of South Africans taking warfarin was poor. SA partici-

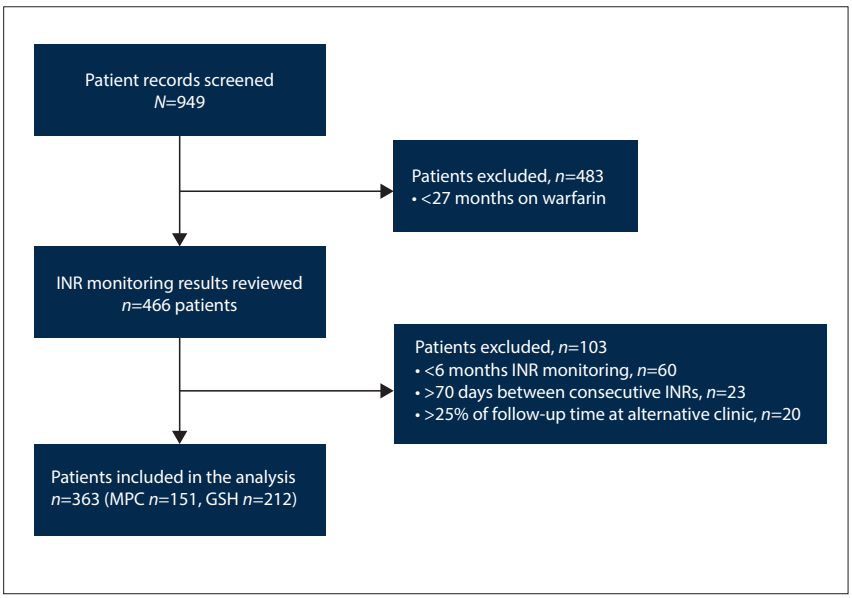

Fig. 1. Selection of patients included in the analysis. (INR = international normalised ratio; MPC = Mitchell's Plain Community Health Centre; GSH = Groote Schuur Hospital.)

Table 1. Characteristics of included patients (*N*=363)

	MPC	GSH
Patients, *n* (%)	151 (41.3)	212 (58.4)
Female sex	100 (66.2)	138 (65.1)
Age (years), median (IQR)	57 (48 - 66)	53 (41 - 62)
Target INR range, *n* (%)		
2.0 - 3.0*	121 (80.1)	76 (35.9)
2.5 - 3.5†	30 (19.9)	136 (64.2)

MPC = Mitchell's Plain Community Health Centre; GSH = Groote Schuur Hospital; IQR = interquartile range; INR = international normalised ratio.
*Target INR range of 2.0 - 3.0 for patients anticoagulated with warfarin because of atrial fibrillation, pulmonary embolus, venous thromboembolism, systemic lupus erythematosus, hypercoagulable states, atrial flutter or undocumented indication.
†Target INR range of 2.5 - 3.5 for patients anticoagulated with warfarin because they had valvular heart disease.

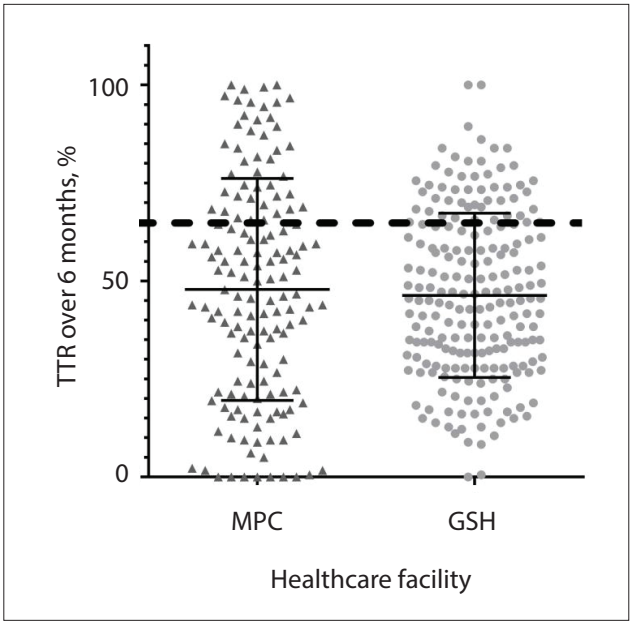

Fig. 2. Scatter plot of the percentage of time the INR was in the therapeutic range over 6 months of warfarin therapy. Solid bars represent means and standard deviations. The dotted line is at the TTR target (INR in therapeutic range for 65% of the time). TTR below the target indicates inadequate INR control. (INR = international normalised ratio; TTR = time in therapeutic range; MPC = Mitchell's Plain Community Health Centre; GSH = Groote Schuur Hospital.)

pants with AF randomised to warfarin in the international multicentre ACTIVE-W trial (dual antiplatelet therapy v. warfarin anticoagulation) had a mean TTR of 46%.[10] In the RELY trial (randomised evaluation of long-term anticoagulation therapy), which randomised participants with AF to dabigatran or warfarin, the mean TTR of SA participants was 58%.[12]

In keeping with our findings, in an earlier study[17] only 50% of patients in Cape Town receiving warfarin for rheumatic heart disease had good anticoagulation control as measured by TTR calculated by the Rosendaal method, but only three INR readings were used in this study. A cross-sectional study at Victoria Hospital in Cape Town found that only 49% of patients had a therapeutic INR.[18] There are few African studies outside SA. In an Ethiopian cross-sectional study, only 30.3% of patients had a therapeutic INR.[19] These cross-sectional studies are limited in their design by the fact that they only provide a snapshot of INR control at a single time point. The association between older age and improved control that we observed is in keeping with findings from other studies.[18,20] The Victoria Hospital study in Cape Town found that patients aged ≥60 years were more likely than younger patients to have a therapeutic INR. A Swedish study also found a correlation between improved TTR and older age.[18,20] We found no association between INR control and sex, similar to the study at Victoria Hospital.[18] INR control did not differ between the two clinics in our study.

Patients with poor anticoagulation control (TTR <65%) had more frequent INR monitoring than those with good control, but despite regular monitoring to guide dose adjustments, INR control was poor in these patients. This may reflect flaws in the unvalidated algorithm used to guide warfarin dose adjustment at our study sites.

Poor INR control may result in serious clinical consequences. A recent SA survey found that warfarin was the fourth most commonly implicated drug in ADR-related admissions and the most commonly implicated drug in preventable ADR-related admissions.[11] A median

Table 2. Multivariate logistic regression model of associations with good anticoagulation control (TTR ≥65%) over 6 months (363 patients included in the model)

			Univariate analysis		Multivariate analysis	
Variable	**Category**	**TTR ≥65%, *n* (%)**	**OR (95% CI)**	**Wald test *p*-value**	**Adjusted OR (95% CI)**	**Wald test *p*-value**
Age	<55 years	34/177 (19.2)	ref	-	ref	-
	≥55 years	57/186 (30.6)	1.86 (1.14 - 3.02)	0.013	1.69 (1.03 - 2.79)	0.039
Sex	Female	56/238 (23.5)	ref	-	ref	-
	Male	35/125 (28.0)	1.26 (0.77 - 2.07)	0.351	1.21 (0.73 - 1.99)	0.451
Site	MPC	44/151 (29.1)	ref	-	ref	-
	GSH	47/212 (22.2)	0.69 (0.43 - 1.12)	0.132	0.85 (0.50 - 1.46)	0.560
INR target	2 - 3*	57/197 (28.9)	ref	-	ref	-
	2.5 - 3.5†	34/166 (20.5)	0.63 (0.39 - 1.03)	0.065	0.75 (0.43 - 1.30)	0.312

TTR = time in therapeutic range; INR = international normalised ratio; OR = odds ratio; CI = confidence interval; MPC = Mitchell's Plain Community Health Centre; GSH = Groote Schuur Hospital.
*INR target 2 - 3: atrial fibrillation, pulmonary embolus, venous thromboembolism, systemic lupus erythematosus, hypercoagulable states, atrial flutter.
†INR target 2.5 - 3.5: valvular heart disease.

hospital stay of 6 days (IQR 4 - 8.5) for all bleeds related to warfarin and non-steroidal anti-inflammatory drugs was recorded.[11] In an American study, INR instability was associated with higher healthcare utilisation, driven by increased length of hospital stay.[21]

Direct oral anticoagulants (DOACs) are an alternative to warfarin. DOACs have a number of advantages, but are expensive when the direct cost is considered and therefore currently not routinely available in the SA public sector. DOACs have more rapid onset than warfarin, do not require heparin bridging, have fixed doses, are less susceptible to food and drug-drug interactions and do not require routine anticoagulation monitoring.[9,22-24] A meta-analysis of stroke prevention in AF patients comparing three DOACs (rivaroxaban, dabigatran and apixaban) with VKAs, published in 2017, found a significantly lower risk of intracranial haemorrhage with DOACs, with similar efficacy to that of DOACs.[25] However, warfarin therapy is likely to remain an important anticoagulant option in our setting, as DOACs are currently not easily accessed in the public healthcare sector. In addition, poor TTR control may be compounded by suboptimal warfarin dose adjustment practice. In SA, healthcare workers may prescribe half-tablet dosages in order to achieve a warfarin dose less than the only available 5 mg strength. A study comparing warfarin measured half-tablet drug content against target drug content found that a third of half-tablets fell outside of the proxy *United States Pharmacopeia* specification.[26] These findings suggest that warfarin may not always be uniformly distributed within the tablets, which may contribute to the variability and difficulty in achieving effective warfarin dose titration. Individualised small incremental dose adjustments may therefore not always be possible.

Study limitations

Our study has several limitations. We did not have data on some covariates such as concomitant comorbid disease, including hepatic or cardiac dysfunction, interacting medications and diet, which could affect anticoagulation control. Data on warfarin adherence, dosing recommendations or adherence to dose adjustment recommendations were not available. Patients with >70-day gaps between INRs were excluded, in line with recommendations for the Rosendaal method.[13] This may bias towards inclusion of more adherent patients, as patients missing clinic visits would be excluded. Despite this potential for bias, TTR was low in our included patients. Patients with <27 months of follow-up were not included, and this exclusion may also have introduced some bias, as patients with an indication for long-term anticoagulation who died before 27 months were not eligible for inclusion. For patients with 'unknown indication' we assumed a lower INR target level. This may have biased TTR control positively if the higher target (INR 2.5 - 3.5) was required. Although our total sample from the two sites exceeded the 346 patients required based on our power calculation, we were only able to include 152 patients who were eligible for inclusion from the MPC site. We therefore did not meet the power requirement to detect a 15% TTR difference between the two sites. The Rosendaal method to calculate TTR, which is the widely recommended method for describing anticoagulation control, also has certain limitations, particularly when individual INR values are far outside the recommended therapeutic range, as it assumes that the change in INR over time is linear between each time-point, which may not always be true. Our TTR target of ≥65% is derived from studies in AF, and may be too conservative for patients with VHD.

Despite these limitations, this study provides good evidence in clinical practice of inadequate anticoagulation control in patients attending two high-volume INR clinics located in an urban SA community healthcare centre and at a tertiary academic hospital.

Conclusions

We found poor levels of anticoagulation control in our longitudinal study at two large urban dedicated SA INR clinics. Poor INR control places patients at risk of complications due to toxicity or lack of efficacy of therapy. Further research identifying predictors of poor control is required. The impact of poor anticoagulation control on clinical outcomes and healthcare costs in SA patients requires quantification. Warfarin therapy is likely to remain an important anticoagulant option in our setting, until the affordability and hence accessibility of alternative agents in SA conditions have been formally assessed. Evidence-based, locally validated algorithms to guide warfarin dose adjustment are urgently needed. The only warfarin formulation currently available in the public sector is the 5 mg tablet. Lower warfarin dosage formulations may optimise individual dose titration, and advocacy for these formulations is advised.

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