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International normalised ratio control in a non-metropolitan setting in Western Cape Province, South Africa

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Background. The quality of international normalised ratio (INR) control determines the effectiveness and safety of warfarin therapy. Data on INR control in non-metropolitan settings of South Africa (SA) are sparse.
Objectives. To examine the time in therapeutic range (TTR) and its potential predictors in a sample of Garden Route District Municipality primary healthcare clinics (PHCs).
Methods. INR records from eight PHCs were reviewed. The TTR and percentage of patients with a TTR >65% were determined. A host of variables were analysed for association with TTR.
Results. The median (interquartile range (IQR)) age of the cohort (N=191) was 56 (44 - 69) years. The median (IQR) TTR was 37.2% (20.2 - 58.8); only 17.8% of patients had a TTR ≥65%. Compared with patients aged >50 years, those aged <50 had worse INR control (median (IQR) TTR 26.6% (16.1 - 53.0) v. 43.5% (23.5 - 60.1); p=0.01). Patients hospitalised for any reason during the study period had worse INR control than patients not hospitalised (median (IQR) TTR 26.2% (16.2 - 50.2) v. 42.9% (23.5 - 62.0); p=0.02). On multivariable regression analysis, participants on warfarin for atrial fibrillation/flutter had better INR control than those with other indications for warfarin (odds ratio 2.21; 95% confidence interval 1.02 - 4.77; p=0.04), but the control was still very poor.
Conclusions. INR control, as determined by TTR and proportion of TTR ≥65%, in these non-metropolitan clinics was poor. Age and hospitalisation as a marker of illness predicted poor control. There was a difference in control between groups, depending on the indication for warfarin. Evidence-based measures to improve the quality of INR control in patients on warfarin therapy need to be instituted as a matter of urgency.

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Warfarin is the most commonly used anticoagulant worldwide. The effectiveness of warfarin therapy in reducing morbidity and mortality related to thromboembolic disease is well established.[1] The degree of anticoagulation effected by warfarin is determined by measuring the prothrombin time and is reported as the international normalised ratio (INR).[1] The INR is influenced by a variety of factors that contribute to the complexity of warfarin therapy.[1] Warfarin has a narrow therapeutic index; in order to maximise the benefit from warfarin therapy while avoiding the risk of bleeding, the INR needs to be maintained within a target range for a period above a minimum amount of time.[2,3] This is known as the time in therapeutic range (TTR). A minimum TTR of 65% is required for warfarin therapy to be regarded as effective. Below this value, warfarin is unlikely to prevent thromboembolic disease effectively, and the risk of bleeding complications increases.[4,5] The TTR is a useful, albeit imperfect, parameter by which the quality of anticoagulation is estimated.[6]

Warfarin is the only readily available oral anticoagulant in the public health sector in South Africa (SA). There is a paucity of data regarding the quality of INR control, as well as the complications associated with poor INR control, in non-metropolitan and rural SA settings. Previous studies conducted in metropolitan areas in SA and in the wider sub-Saharan Africa region have shown INR control to be poor.[4,7-14] The quality of INR control in non-metropolitan and rural primary healthcare clinic (PHC) settings in SA is largely unknown. This lack of data is particularly important in light of the relative scarcity of resources and facilities and limited ability to manage complications related to poor INR control such as bleeding, stroke, peripheral emboli and valve thromboses in these settings.

The Garden Route District Municipality is situated in the south-eastern part of Western Cape Province, SA. There are no dedicated anticoagulation clinics in the district, and patients requiring anticoagulation therapy are referred to their nearest PHC for initiation and/or continuation of warfarin therapy. INR testing is offered 24 hours a day at George Regional Hospital by the National Health Laboratory Service (NHLS). There are no standardised manual or computer-based algorithms regulating dosage adjustments or follow-up. Point-of-care (PoC) testing and self-testing are not currently available in the district. Samples are transported daily from distant PHC facilities and satellite clinics to George Regional Hospital for analysis, with some clinics >90 km away from the laboratory. The resultant delay in processing of samples often leads to delayed adjustment of warfarin dosage, as well as questionable results in some instances. Patients are often required to return to their local clinics on another day to obtain their results and have adjustments made to their therapy.

Objectives

To examine the quality of INR control in PHC clinics in a non-metropolitan/rural setting in SA and assess the relationship between INR control and specific demographic and clinical factors over a 12-month period. The specific objectives were to calculate the TTR and the proportion of patients with a TTR ≥65%; to analyse INR control stratified by age (≥50 years), gender, employment status, government support grant status and indication for warfarin; and to determine the influence of all-cause hospital admissions during the study period on INR control. Furthermore, the association between TTR and the frequency of INR testing and early follow-up of out-of-range results with repeat testing was assessed. No outcomes of INR control were assessed in this study.

Methods

Study design

The study was a retrospective review of the records and available results of patients who underwent INR testing for the purpose of monitoring warfarin therapy at PHCs in the Garden Route District Municipality between July 2016 and June 2017.

Participating clinics

In order to represent different non-metropolitan and rural settings in the Garden Route District Municipality, eight PHCs were non-randomly selected. Four clinics from small town centres, two clinics situated in townships and two rural satellite clinics were included.

Ethical considerations

Ethical approval for the study was granted by the University of Cape Town Human Research Ethics Committee (ref. no. 785/2017). Permission was obtained before data were made available from the NHLS. Permission for research and data collection in the PHCs was obtained from the Western Cape provincial government (ref. no. WC_201711_028). As this was a retrospective review with no patient interaction, informed consent was not obtained.

Patient population

All patients aged ≥18 years who were on warfarin therapy and had INR testing performed during the study period were eligible. Those with an unknown indication for warfarin and/or <2 INRs performed during the study period were excluded.

Data collection

INR values were obtained from the NHLS database. Patient files were extracted at the relevant healthcare facilities to obtain the age, gender, employment status, indication for warfarin therapy, and whether the patient required hospital admission during the study period. The TTR was calculated using the Rosendaal method of linear interpolation, which assumes linear increases and decreases of the INR between successive INR values over time. From this assumption, the time period during which the INR falls within the predetermined therapeutic range can be calculated and can be converted to a percentage of total time.[6,15] For mechanical valve replacement an INR of 2.5 - 3.5 was regarded as therapeutic, and for all other indications a range of 2 - 3 was regarded as therapeutic.[16]

Statistical analysis

Statistical analysis was performed using Stata version 14.2 (StataCorp, USA). Descriptive statistics were used to summarise data. Continuous variables were summarised as means with standard deviations for parametric data or medians with interquartile ranges (IQRs) for non-parametric data. Categorical variables were expressed as frequencies and percentages. Variables evaluated for association with INR control are shown in Table 1.

For age and TTR, categorical variables were created (age <50 years, TTR ≥65%). Continuous variables (i.e. TTR) were compared for age <50, gender and hospital admission during study period, using either Student's *t*-test for parametric data or the Wilcoxon rank-sum test for non-parametric data. Categorical variables (i.e. TTR ≥65%) were compared for age <50, gender and hospital admission during the study period using χ^2 and Fisher's exact tests. Univariable regression analysis was performed using the following variables: age <50, gender, employment status, indication for anticoagulation therapy, and hospital admission during the study period. Variables significantly associated with a TTR ≥65% ($p<0.05$) were used for the multivariable regression model. A fit of the model was assessed using the Hosmer-Lemeshow goodness-of-fit test. The association between TTR and the number of INRs per patient, the time interval between tests and the percentage of out-of-range INRs that were followed up within 7 days with a repeat test was measured with a Spearman rank test. An r^2 value approaching 1 showed high levels of correlation between TTR and the number of INR tests, time interval between tests and percentage of out-of-range tests followed up within 7 days with a repeat test. A *p*-value <0.05 was considered statistically significant.

Results

Study population

Of the 287 eligible participants, 191 met all the stipulated inclusion and exclusion criteria (Fig. 1). The median (IQR) age of the study population was 56 (44 - 69) years, and the majority of the participants (56.5%) were unemployed women on government support grants. In descending order, the three most common indications

Table 1. Variables compared for assessment of association with improved or worse INR control

Demographic variables
Age
Gender
Employment status (employed, unemployed, government support grant)
Clinical variables
Indication for warfarin therapy (atrial fibrillation/flutter, venous thromboembolism, mechanical prosthetic valve, antiphospholipid syndrome, left ventricular thrombus)
Hospital admission during study period for any indication
Total number of INR tests per patient
Average time interval between tests (days)
Percentage of out-of-range INRs followed up within 7 days with repeat test

INR = international normalised ratio.

for warfarin therapy were atrial fibrillation/flutter (42.4%), venous thromboembolism (VTE) (28.8%) and mechanical prosthetic heart valves (24.1%) (Table 2).

Over the study period, a total of 2 635 INR tests were available for analysis. The median (IQR) TTR was 37.2% (20.2 - 58.8). Only 17.8% of patients had a TTR ≥65%.

Table 3 outlines the TTR and percentage TTR ≥65% stratified by age (above and below 50 years), gender, employment status, grant status, indication for warfarin, and all-cause hospital admission during the study period.

Regarding the TTR for different indications for warfarin, patients with atrial fibrillation and flutter had a median (IQR) TTR of 44.5% (25.3 - 62.3), patients with VTE a median of 26.7% (9.6 - 53.0), patients with a mechanical valve replacement a median of 38.3% (20.0 - 58.7), patients with antiphospholipid syndrome a median of 34.9 (6.3 - 50.1) and those with a left ventricular thrombus a median of 48.2% (11.5 - 71.7). Patients who were employed had a median (IQR) TTR of 28.8% (15.4 - 51.9), unemployed patients a median of 29.3% (16.2 - 59.1) and those receiving a government support grant a median of 46.8% (27.1 - 62.0). The results of the univariable and multivariable regression analysis for demographic and clinical factors associated with a TTR ≥65% are summarised in Table 4.

The multivariable regression analysis showed better INR control for patients with atrial fibrillation or flutter compared with other indications (odds ratio (OR) 2.21; 95% confidence interval (CI) 1.02 - 4.77; p=0.04). Patients who were hospitalised during the study period had worse INR control than those who were not hospitalised (OR 0.39; 95% CI 0.15 - 0.98; p=0.05). However, this did not remain significant in the multivariable model (OR 0.39; 95% CI 0.15 - 1.03; p=0.06). As shown in Table 5, no significant associations were found between TTR and total INR tests, INR testing frequency, or percentage of repeat testing for out-of-range values within 7 days.

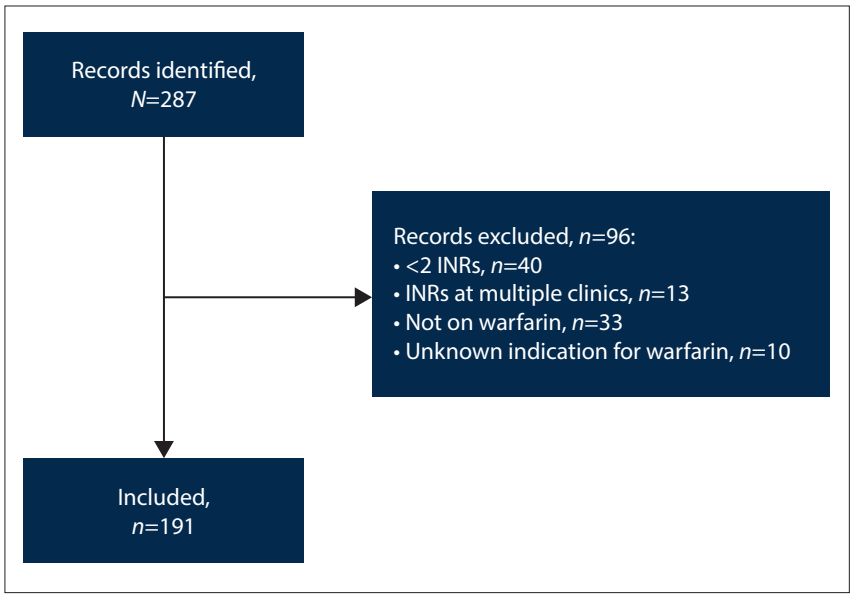

Fig. 1. Study participants selection diagram. (INR = international normalised ratio.)

Discussion

This is the first comprehensive study to assess the quality of INR control in a non-metropolitan PHC setting in SA. There were two major findings. First, the quality of INR

Table 2. Baseline characteristics of the study population (*N*=191)

Age (years), median (IQR)	56 (44 - 69)
Female, median (IQR)	108 (56.5)
Employment status, *n* (%)	
Employed	32 (16.8)
Unemployed	59 (30.9)
Government support grant	60 (31.4)
Unknown employment status	40 (20.9)
Indication for warfarin, *n* (%)	
Atrial flutter/fibrillation	81 (42.4)
Venous thromboembolism	55 (28.8)
Mechanical valve replacement	46 (24.1)
Antiphospholipid syndrome	6 (3.1)
Left ventricular thrombus	3 (1.6)
All-cause hospital admission during study period, *n* (%)	62 (32.5)
INR tests per patient, median (IQR)	13 (7 - 19)
Duration of INR testing (months), median (IQR)	10.1 (6.6 - 11.4)
Time interval between INR tests (days), median (IQR)	21.4 (14.3 - 31.6)
INR tests in range (%), median (IQR)	33.3 (16.7 - 47.4)
Out-of-range tests above range (%), median (IQR)	33.3 (14.8 - 50)
Out-of-range tests below range (%), median (IQR)	66.7 (50.0 - 85.2)
Out-of-range INRs followed up within 7 days with repeat INR (%), median (IQR)	22.2 (0 - 45.5)
TTR (%), median (IQR)	37.2 (20.2 - 58.8)
Percentage TTR ≥65%, *n* (%)	34 (17.8)

IQR = interquartile range; INR = international normalised ratio; TTR = time in therapeutic range.

Table 3. Patient-related variables and TTR

	TTR (%), median (IQR)	*p*-value	TTR ≥65%, *n*/*N* (%)	*p*-value
Age (years)				
<50	26.7 (16.1 - 53.0)	0.01	9/71 (12.7)	0.15
≥50	43.5 (23.5 - 60.1)		25/120 (20.8)	
Gender				
Female	32.0 (19.1 - 55.4)	0.1	14/108 (13.0)	0.06
Male	46.6 (20.7 – 63.0)		20/83 (21.1)	
All-cause admission during study period				
Admitted	26.2 (16.2 - 50.2)	0.02	6/62 (9.7)	0.04
Not admitted	43.0 (23.5 – 62.0)		28/129 (21.7)	

TTR = time in therapeutic range; IQR = interquartile range.

Table 4. Univariable and multivariable regression analysis of demographic and clinical factors associated with a TTR ≥65%*

	Univariable regression analysis			Multivariable regression analysis		
Variables	Unadjusted OR	95% CI	*p*-value	Adjusted OR	95% CI	*p*-value
Age <50 years	0.55	0.24 - 1.26	0.16			
Female	0.47	0.22 - 1	0.05	0.48	0.22 - 1.03	0.06
Employed	0.43	0.12 - 1.49	0.18			
Unemployed	0.77	0.34 - 1.77	0.54			
Government support grant	1.44	0.67 - 3.13	0.35			
Atrial fibrillation/flutter	2.24	1.05 - 4.78	0.04	2.21	1.02 - 4.77	0.04
Mechanical valve replacement	0.63	0.24 - 1.62	0.34			
VTE	0.47	0.18 - 1.21	0.12			
APS	0.92	0.1 - 8.14	0.94			
Hospital admission	0.4	0.15 - 0.99	0.05	0.4	0.15 - 1.03	0.06

TTR = time in therapeutic range; OR = odds ratio; CI = confidence interval; VTE = venous thromboembolism; APS = antiphospholipid syndrome.
*Demographic and clinical variables that were considered for the regression analysis included age <50 years, female gender, employment status, government support grant, atrial fibrillation/flutter, mechanical valve replacement, VTE, APS, and hospital admission during the study period. Variables that were significantly associated with a TTR ≥65% ($p<0.05$) were retained in the multivariable model.

Table 5. Association between TTR and total INR tests, INR testing frequency and repeat testing for out-of-range values and TTR

	r^2	*p*-value
Total number of INR tests during study period	0.01	0.16
Time between INR tests (days)	0.04	0.01
Percentage of out-of-range tests followed up within 7 days with repeat test	0.02	0.08

TTR = time in therapeutic range; INR = international normalised ratio; r^2 = square of the Spearman rho value.

monitoring in the eight broadly representative PHCs included was poor, as evidenced by a median TTR of 37.2% and a TTR ≥65% of 17.8%. Second, we found that the only clinical, demographic or social predictors of poor INR control were age and the need for hospitalisation. Patients with atrial fibrillation/flutter had better INR control than those with other indications for warfarin, but the TTR was well below acceptable effective levels. There was lack of a significant association between TTR and all other variables included in our models.

We did not assess patient outcomes in the study. However, given the well-established relationships between poor INR control and major adverse events, the finding that 82.2% of our patients were unlikely to derive any significant benefit from warfarin therapy, and were at increased risk of developing thrombotic and thromboembolic (as well as haemorrhagic) complications, is concerning.

Our findings correlate with a limited number of previous studies in SA and confirm that INR control in the public health sector in SA, and particularly in rural settings, is poor.[7-9] Importantly, our findings suggest that compared with INR control in urban and peri-urban anticoagulation clinics, INR control outside these settings is worse. In the Cape Town metropolitan area, Barth *et al.*[7] demonstrated a mean TTR of 42% in patients with rheumatic heart disease without previous mitral valve replacement surgery, and 67% in patients who had had a previous mitral valve replacement. However, the study sample was small and only 334 INRs were analysed. Sonuga *et al.*[9] demonstrated, in a cross-section-of-files review at a secondary-level hospital INR clinic in Cape Town, that 48.5% of INRs were outside the target range. Only 136 INR values were included in the analysis. Ebrahim *et al.*[8] compared the TTR at two INR clinics in the Cape Town metropolitan area and calculated a mean TTR of 47%, with only 25.1% of patients having a TTR ≥65%.[8]

Data from large multicentre international trials also give some insight into the quality of INR control for atrial fibrillation in SA. Three large international multicentre trials, namely the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF), the Randomised Evaluation of Long-Term Anticoagulation Therapy trial (RE-LY), and the Clopidogrel Trial

with Irbesartan for prevention of Vascular Events (ACTIVE W), all demonstrated mean TTRs <60% for patients in the SA cohorts. In all three trials there was little difference in INR control between SA public and private sites.[4,12,13]

The data from studies performed in developed countries, metropolitan settings or dedicated INR clinics cannot be assumed to apply to non-metropolitan or rural settings where dedicated INR clinics are lacking and a unique set of challenges exist. Many patients in rural settings live more remotely from PHCs than their counterparts in metropolitan areas, and readily available transport to and from clinics is not guaranteed. Public infrastructure, such as roads, and public transport in many of these areas in SA are less well developed, posing a further challenge to regular easy access to healthcare, particularly for ill and frail patients who require care most. Many rural areas are serviced by satellite or mobile clinics for their health needs on an interval basis only. Community service medical officers and nurses play a vital role in staffing the rural and remote health facilities across SA. These staff members are required to practise in more remote areas with less clinical experience and supervision, and regular turnover of staff is commonplace.[17] Access to laboratory services and INR testing is a further challenge in rural areas. Samples need to be transported to distant laboratories, exposing the samples to degradation, and results are not always timeously available. Patients may need to return for results on different days in order for adjustments to be made to warfarin dosages. Cellphone and internet signal is not always available in rural areas for telephonic dose adjustments to be facilitated. These factors make our findings particularly relevant in the broader SA context. The vast majority of South Africans are dependent on government facilities for their healthcare. Furthermore, the healthcare needs of the majority of South Africans are serviced by PHCs, many of which are under-resourced, under-staffed and located far from the nearest regional or tertiary facility.[18]

Previous studies have looked at the association between various demographic and clinical factors and TTR. Factors found to be associated with poor INR control included younger age, patients from poorer communities, alcohol abuse, smoking and substance abuse.[19] Concurrent medication use, medical comorbidities (cancer, chronic liver or kidney disease) and increased hospitalisation were also associated with poor INR control, with increased hospitalisation in this context being an indirect measure of sicker patients with more drug interactions and comorbidities as opposed to an outcome variable related to poor INR control.[19,20] Our study confirms the finding of worse INR control in younger patients and patients hospitalised for any reason during the study period.

In our study, only 22.2% of out-of-range tests were followed up with a repeat test within 7 days. There is limited evidence guiding the optimal frequency of INR testing. The frequency of testing is influenced by the stability of the INR over time, the INR response to dose adjustment, and whether a patient is admitted or managed as an outpatient.[21] After initiation of therapy or dose adjustments as an outpatient, the American College of Chest Physicians (ACCP) recommends more frequent INR testing until the INR is stable and then at least every 4 weeks.[22] The ACCP furthermore recommends a monitoring frequency of up to once every 12 weeks in patients with stable INRs who have required no dose adjustments for a period of 3 months.[16] It has been shown that shorter intervals between INR tests are associated with better INR control.[22] In our study, no association could be shown between more frequent INR testing and TTR. A larger sample size would be required to further investigate the association between the frequency of INR testing and TTR, as well as clinical outcomes.

Standardised protocols recommending algorithm-based dosage adjustments of warfarin therapy, instead of adjustments based on clinical experience, have been associated with improvements in TTR.[13,23] Algorithm-based computer programs recommending dose adjustments and scheduling follow-up testing have also been shown to improve TTR.[24,25] In the Garden Route District Municipality, standardised algorithms and protocols are not used to guide decision-making regarding warfarin therapy, and dose adjustments are made at the discretion of the treating clinician.

Self-testing and self-monitoring of the INR in appropriately selected patients using PoC devices has been associated with improved patient satisfaction and TTR, and a reduction in clinical thromboembolic events with no increase in adverse events.[16,26-28] PoC testing is an appealing alternative to the routine laboratory measurement of the INR, particularly in rural resource-limited settings. In settings similar to the Garden Route District Municipality, specimens often need to be transported long distances for analysis. Furthermore, patients often need to come back to the facility on a different day to get their INR result for dosage adjustments to be made. A number of PoC devices are on the market. There have been concerns about the reliability of PoC INR results across different devices and compared with laboratory measurements. However, PoC testing is accepted as a reliable option for INR monitoring, with specific advantages over routine laboratory testing.[29] It is important to note that PoC INR values that are out of range, particularly above range, do become discrepant from laboratory values and need confirmation with laboratory testing.[30] PoC testing may play an important role in improving the effectiveness of warfarin therapy in SA.

Finally, a number of non-vitamin K oral anticoagulants (NOACs) are available in SA (rivaroxaban, dabigatran, apixaban). As a class, these agents have been shown to be non-inferior or superior to warfarin therapy in patients with non-valvular atrial fibrillation, with significantly better safety profiles, and are the preferred agents for the treatment of VTE.[31-34] Patients with valve lesions were excluded from these pivotal trials. The advantages of the use of these agents instead of warfarin include a much quicker onset of therapeutic levels of anticoagulation, a fixed drug dose with predictable levels of anticoagulation, fewer food and drug interactions, and absence of the need for regular monitoring of the INR. These agents should not be used in patients with prosthetic heart valves or valvular atrial fibrillation, or in pregnant patients, and caution needs to be exercised in patients with renal failure.[34,35]

Study strengths and limitations

Our study has several limitations. It was a retrospective observational study, and limited conclusions can be drawn regarding cause and effect. Many variables known to influence warfarin therapy and TTR were not analysed, including co-administration of medications, alcohol and drug use, smoking, dietary factors and comorbidities. The sample size was small, and bigger studies are needed to confirm the findings. Although the clinics were selected to represent patients from varying demographic settings in the Garden Route District Municipality, the findings are not generalisable throughout the diverse society of SA. Patient compliance with therapy was not accounted for in the study. The contribution of patients defaulting follow-up and not taking their treatment undoubtedly plays a role in the quality of INR control. Outcomes of INR control were not assessed.

The method used to assess the quality of anticoagulation has limitations. Because of the assumption of a linear increase or decrease in INR between consecutive tests in the Rosendaal method, large time gaps between tests (>60 days) can give an incorrect representation of

the TTR. However, the percentage of tests in range was also assessed and is not influenced by this assumption. Although care was taken to exclude patients having INRs tested at different facilities, patients moving around between different clinics and districts or between the private and public sectors for INR monitoring could not be fully accounted for. Whether patients were already established on warfarin therapy or newly initiated was not taken into account. Newly initiated patients will require time for the INR to stabilise in the therapeutic range.

Conclusions

This study is the first to give insight into the current status of warfarin therapy in a non-metropolitan PHC setting in SA, which included rural clinics. We showed that the quality of INR control in this setting is poor and that very few patients are likely to derive any benefit from warfarin therapy, with younger and hospitalised patients having the highest likelihood of poor INR control. Despite the unique challenges regarding anticoagulation therapy in rural areas, there are clear gaps in warfarin management that can be addressed by instituting basic interventions. The adoption of dose adjustment protocols and training of staff in their use may improve INR control. Investment in computer-based algorithms and required infrastructure could also be beneficial, with the cost weighed against the cost of poor INR control. PoC testing will improve the turnaround time of INR tests and negate the need for patients to return to PHCs on different days, and will further avoid the need for telephonic dose adjustments. On a societal level, access to healthcare can be improved by ensuring adequate roads, public transport and infrastructure in rural areas. The expanded use of NOACs may prove to be uniquely beneficial in settings where challenges with INR testing abound that were not accounted for in the non-inferiority trials comparing these agents with warfarin. While the cost of NOACs, compared with effective warfarin therapy, is seen as prohibitive for their expanded use, the cost of ineffective warfarin therapy is largely unaccounted for. At the very least, increasing the availability of NOACs in the public sector for selected patients (e.g. those with non-valvular atrial fibrillation/flutter and VTE) in whom INR control is proving to be a problem despite good adherence, needs to be considered.

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