The adequacy and safety of anticoagulation therapy with warfarin at the medical outpatient clinic of an academic hospital

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Abstract

Introduction: Warfarin remains the mainstay long-term oral anticoagulant in the public sector; newer agents are available only in special situations such as in cases of warfarin allergy. Regular monitoring of the international normalised ratio (INR) is the gold standard for assessing the adequacy of treatment with warfarin. INR determinations are inconvenient and expensive for patients in resource-limited settings as they involve frequent travel. Our hospital serves predominantly indigent communities who might find it hard to adhere to these regular checks, placing them at risk for the complications of over-or-under anticoagulation.

Objective: The primary purpose of the study was to determine the adequacy of anticoagulation among patients on warfarin for the prevention or treatment of various thrombo-embolic phenomena.

Study setting: The INR clinic of Dr George Mukhari Academic Hospital (DGMAH).

Study design: The study was cross-sectional and informed consent was obtained from all participants. The study consisted of both record reviews and face-to-face interviews. The Rosendaal linear interpolation method was used to determe the adequacy of anticoagulation.

Results: A total of 167 patients were studied. The mean age of the study population was 59.2 ± 15.30. The most common indication for anticoagulation was venous thrombo-embolism. In total, only 54 patients (32.4%) were adequately anticoagulated at the time of this assessment (TTR > 60%). The rate of thrombo-embolic events was 2.96 per 100 patient-years, while the rate of bleeding was 6.95 per 100 patient-years.

Conclusion: Most patients were sub-optimally anticoagulated. A few suffered complications related to both inadequate anticoagulation and over-anticoagulation. Additional studies of this nature are required as they may help inform the discussions between healthcare providers and funders about the necessity of access to alternative anticoagulants for appropriate patient groups.

Keywords: anticoagulation therapy, medical outpatient clinic

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Introduction

Anticoagulant therapy has significant clinical benefits when the indication is appropriate and therapy is carefully managed.[1,2] When poorly managed, death and/or significant disability can result from embolic as well as bleeding complications.[3]

Warfarin has been widely used for outpatient anticoagulation therapy.[4] It remains the most commonly used oral anticoagulant for both primary and secondary prevention of thromboembolism in South Africa.[5] Its effectiveness in preventing thrombo-embolic episodes is well established.[6] It remains an important anticoagulant, especially in resource-limited settings.

However, warfarin is challenging for both patients and healthcare providers to manage. It requires frequent monitoring and dosing adjustments so that it remains in the therapeutic range to prevent thrombosis from subtherapeutic INR or haemorrhagic complications from supratherapeutic INR. In addition, it has multiple drug–drug, drug–food, and drug–disease state interactions that patients and clinicians may not be familiar with.[7]

Warfarin has delayed anticoagulant effect, often necessitating bridging therapy. It has a narrow therapeutic index.[8,9]

The problems encountered with the use of warfarin have led to the development of easy-to-manage and safer agents. These newer oral anticoagulants, e.g. thrombin and factor Xa inhibitors, have been compared to warfarin and have been found to have a better risk–benefit ratio.[6,10,11] In addition, they have predictable pharmacokinetics, eliminating the need for monitoring. The exception remains their use in patients with prosthetic heart valves, where they are currently contraindicated, and their role in valvular atrial fibrillation (AF) remains unclear.[12,13] Approriate dose adjustment is necessary in patients with chronic kidney disease (CKD), when the estimated glomerular filtration rate (eGFR) is less than 30mℓ/min.[14]

Aim

To determine the adequacy and safety of anticoagulant therapy with warfarin at the medical outpatient clinic of Dr George Mukhari

Academic Hospital (DGMAH).

Objectives

1. To determine the time spent in therapeutic range (TTR) using the Rosendaal interpolation method. Patient who spent 60% or more of the time in the 2–3 INR range were considered adequately anticoagulated.
2. To determine the presence and frequency of thrombotic and/or bleeding episodes while on treatment through both record reviews and interviews.

Methodology

Study setting

The INR clinic of DGMAH.

Study design and population

This study was cross-sectional and consisted of appropriate patients (≥ 18 years) who were agreeable to being interviewed for the study. The study included both face-to-face interviews and record reviews. Informed consent was obtained. Participants had to have had at least three consecutive INR measurements and only the latest three INR measurements were considered. The number of INR values in the range 2 to 3 (both values included) were counted for each individual patient and expressed as a percentage of 3. Patients with concomittant uncontrolled congestive heart failure (CHF), liver disease (transaminases more than five times upper limit of normal) and those with severe thrombocytopaenia were excluded. These patients were excluded as these disease states increase the risk of bleeding which would confound the interpretation of bleeding as a complication of warfarin therapy. In addition, hepatic congestion from CHF and liver disease can render the INR abnormal.

Sample size

Based on findings from a published study conducted in Israel, the anticipated percentage of warfarin-treated patients reaching the therapeutic INR range was projected to be 43.0%. The study was powered at 85% and with a two-sided alpha error limit of 0.05, the statistically derived sample size was 167 patients.

Data collection

The following data were obtained from all patients: demographics; comorbidities; primary indication for warfarin therapy; duration of warfarin treatment at the time of the interview; and current or previous bleeding events/thrombo-embolic episodes while on treatment. The bleeding episodes were classified as major if they were intracranial or required transfusion. The information relating to the estimation of the TTR, which required at least three INR measurements, was obtained from the patients' records.

Data analysis

The statistical analysis was descriptive and all the procedures were performed on SAS (SAS Institute Inc, Cary, NC, USA), release 9.4. Categorical variables were summed up using percentages and non-categorical variables summarised as means and standard deviations. TTR was determined using Rosendaal's method of linear interpolation (Rosendaal et al, 1993), with a target therapeutic range of 2 to 3.

Ethical considerations

Permission to conduct the study was requested and obtained from the research and ethics committee of Sefako Makgatho Health Sciences University and DGMAH authorities prior to commencement of the study (SMREC/M/244/202:PG). Informed consent to participate in the study was obtained from all patients. The data collection tool was used without patients' identifying details and kept safe by the researchers. Data captured onto the researcher's personal computer was password protected. Patient interviews were confidential and undertaken in a private room.

Results

A total of 167 patients were studied. The mean age of the group was 59.2 ± 15.30. The age distribution was slightly negatively skewed, with 55.0% of the patients 60 years of age or older (see Figure 1).

Comorbidities

Hypertension was the most common comorbidity, constituting 74% (n = 124) of the study population. Other comorbidities included diabetes mellitus (16%; n = 27), controlled congestive cardiac failure 15.5% (n = 26), dyslipidaemia 0.03% (n = 5), CKD 0.2% (n = 3), hypothyroidism 0.05% (n = 1), hyperthyroidism 0.01% (n = 2), HIV 0.13% (n = 21), underlying malignancy 0.04% (n = 6: 1 cervical, 1 breast, 1 colon and 3 prostate), protein C and S deficiency 0.017% (n = 3) and anti-phopholipid syndrome 0.012% (n = 2). Some patients had multiple comorbidities.

Several patients (38.3%; n = *64*)) were taking medication that could potentialy interact with warfarin, such as statins (n = 50), aspirin (n = 3), Epilim (n = 1), rifampicin (n = 1), diclofenac (n = 1), β-blockers (n = 37), carbamazepine (n = 1), carbimazole (n = 1), spironolactone (n = 42) and antiretroviral therapy (ARV) (n = 21).

Indications for treatment

Pulmonary embolism was the most common indication for warfarin therapy in this cohort, making up 50.9% (n = 89) of the

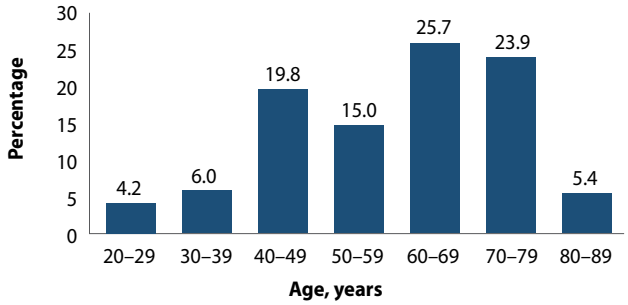

Figure 1: Age distribution
Most (121; 72.5%) of the patients were females

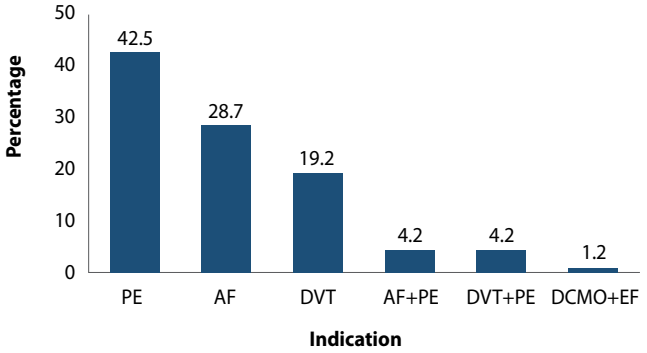

Figure 2: Indications for anticoagulation: PE = pulmonary embolism, AF = atrial fibrillation, DVT = deep vein thrombosis, DCMO = dilated cardiomyopathy.

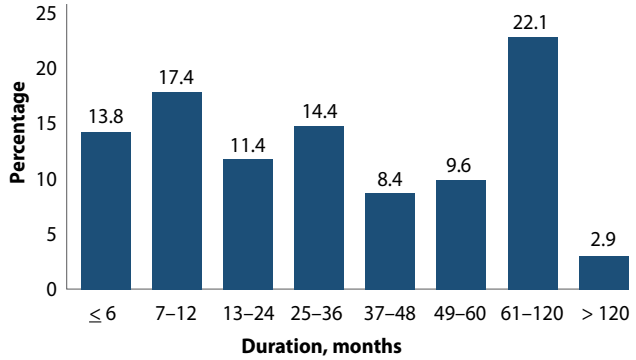

Figure 3: Duration of warfarin therapy

indications. Figure 2 is a summary of the other conditions.

Point-of-care INR testing was the method used to determine the INR in all the cases and evaluations were carried out monthly for all patients.

Twenty-five per cent of the patients had been on warfarin for more than five years. Figure 3 depicts a summary of the length of time that the patients had been on warfarin therapy.

Complications

In total, 40 (24.0%) of the patients experienced a bleeding complication, giving a rate of bleeding of 6.95 per 100 patient-years. In 28 (16.8%) patients, the bleeding was classified as minor.

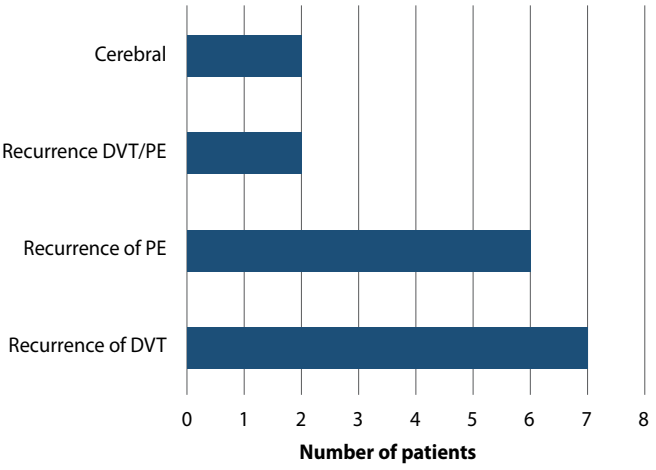

Figure 4: Thrombo-embolic events

Major bleeding occurred in 12 patients (7.2%).

Seventeen (10.2%) patients experienced a thrombo-embolic event. The rate of thrombo-embolic events was 2.96 per 100 patient-years. Figure 4 provides a summary of the thrombo-embolic events encountered within the study population.

A total of 501 INRs were performed. The number of INR values < 2.0 (subtherapeutic) during the study period was 222 (44.3%) and those > 3.0 (supratherapeutic) was 99 (19.8%). A summary of the performance across all patients in the study is reflected in Table I.

Table I: Time in the therapeutic range (TTR)

TTR	Number (%) of patients
0	51 (30.5)
33.3	62 (37.1)
67.7	44 (26.4)
100	10 (6.0)
Total	167 (100)

In total, 44 + 10 = 54 (32.4%) of the patients in the study were adequately anticoagulated with a TTR > 60% during the study period.

A comparison of the proportion of patients who spent TTR by age and gender was performed. The distribution of TTR outcomes for males and females did not differ significantly ($p = 0.522$, Fisher 's Exact test). The distribution of TTR outcomes for patients in the age categories < 50 years vs ≥ 50 yeas did not differ significantly ($p = 0.993$, Fisher's Exact test).

Discussion

The study supports previous findings indicating poor attainment of therapeutic INR among patients on warfarin in a real-world situation.[15,16] The proportion of patients in therapeutic range during the study period, defined as the TTR ≥ 60%, was 32.4%. A meta-analysis of studies looking at anticoagulation control, outcomes and related factors among long-term care patients on warfarin in Africa revealed that 10.4% and 32,3% of patients maintained their TTR within the therapeutic range. Of the studies reviewed, the highest percentage of patients in TTR was 32.25% in Tunisia and the lowest was 10% in Namibia.[17] Studies done in the Western Cape assessing INR control in patients on warfarin therapy did not show dissimilar results. Prinsloo et al.[18] found only 17.8% of their patients (attendees of eight non-metropolitan clinics) were in TTR, defined as TTR > or equivalent to 65%.The median (IQR) TTR was 37.2% (20.2–58.8).

Another study by Ebrahim et al.[15] in Cape Town, South Africa, which found only 25.1% of their study population achieved good INR control, despite regular INR monitoring, also defined as TTR and proportion of TTR more or equivalent to 65%.In the study by Sonuga and colleagues, the results were slightly better, with

48.5% of their study population able to achieve target therapeutic range.[19]

Complications

Bleeding as a complication occurred in 24.0% of the cases in this study (6.95 per 100 patient-years). Eight out of 50 patients who were on concomitant statins experienced a bleeding complication. Just over 10% (10.2%) of the study participants experienced a form of thrombotic or embolic complication (2.96 per 100 patient-years). Thrombotic events while on warfarin were experienced by only 2.2% of the cases, with haemorrhagic adverse events occurring in 14% of the study population in the study by Sonuga and colleagues.[19] Most of the patients with bleeding events in the latter study were on concurrent other medication with potential drug–drug interactions with warfarin.

A Tunisian study of patients in AF on warfarin found a thrombo-embolic incidence of 2.8%; the incidence of bleeding was 3.9%.[20]

A study in Botswana found rates of major bleeding and thrombo-embolic complications to be 1.5 per 100 person-years and 2.80 per 100 person-years respectively.[21]

Unlike the Western Cape studies in which AF and valvular heart disease were the more common reasons for anticoagulation with warfarin, venous thrombo-embolism was the most common indication in this study.[15,18,19] This difference is to be viewed with caution as this study was restricted to the attendees at the general medical outpatient clinic. Most cases of AF and all those with valvular heart disease are normally looked after at the cardiology outpatient clinic in our institution.

Comorbidities

Much like the study by Sonuga and colleagues, hypertension was the most common comorbidity among these patients.[19] In addition, the age distribution of the study population had a slight negative skew, with more than 55% of the patients above the age of 60 years.

Previous researchers looked at the relationship between various demographic and clinical factors and TTR. Among the factors associated with poor INR control were younger age (< 50 years of age), female gender, poor socioeconomic status, concurrent use of medication with potential for interaction with warfarin, and the presence of significant medical comorbidities (CCF, malignancy, chronic liver or kidney disease).[22]

The mean (SD) age of the study population was 59.2 ± 15.30. Previous studies suggested a bigger proportion of older patients (60 years and above) achieving the target therapeutic range compared to younger patients; defined as below 50 years of age.[18,19] In some studies, this was, unfortunately, accompanied by more bleeding complications.[19] Using 50 years of age as cut off between the young and the old, this study could not detect a statistically significant difference in bleeding risk between the two age groups.

The majority of patients enrolled in this study were female. This is similar to other studies.[15, 21] It remains unexplained why fewer male patients were enrolled in the study.

Previous studies have suggested that males achieve better anticoagulation outcomes compared to females.[18,19] This study was not able to confirm those findings.

Drug–drug interactions

It is a known fact that drug–drug interactions between warfarin and other simultaneously administered medication could adversely affect the level of anticoagulation.[23] This study did not assess the impact of known drug interactions with warfarin but a number of observations were made. Sixteen per cent (8/50) of the patients on a statin developed a bleeding complication. The potential interaction of statins and warfarin has been well described with minimal elevations of the INR of unclear clinical significance.[24,25]

Of the 21 patients on ART, four developed bleeds and three (14%) sustained a thrombo-embolic complication. One of the three patients was also on anti-tuberculosis (TB) treatment. South Africa has the largest antiretroviral therapy (ART) programme in the world and TB is endemic in the country.[26] It is, therefore, worth remembering that ART and anti-TB treatment can be a significant source of potential drug–drug interaction with warfarin.

Conclusion

Warfarin therapy is likely to remain an important anticoagulant option in resource-limited settings. The study provides good evidence of periods of inadequate anticoagulation control among patients on warfarin attending our INR clinic. The findings from this study may help inform the discussions between healthcare providers and funders regarding accessibility to alternative agents but further studies are necessary. A number of direct oral anticoagulants are available in South Africa e.g. rivaroxaban, dabigatran and apixaban. As a class, these agents have been shown to be non-inferior and, in some cases, superior to warfarin therapy in patients requiring anticoagulation, with significantly better safety profiles. Care needs to be taken when prescribing warfarin to patients with comorbidities as warfarin interacts with many other drugs.

Study limitations

Data on diet and supplements that could affect anticoagulation control were not collected. Data on compliance with warfarin usage, dosing recommendations or adherence to dose adjustment recommendations were not collected. Other patient populations, such as cases with prosthetic heart valves and cases of valvular AF who receive care in the specialised cardiology clinic were not studied.

Conflict of interest

The authors have no conflict of interest to declare.

Funding source

No funding sources were involved in the manuscript at all stages.

Ethical approval

Permission to conduct the study was requested and obtained from the research and ethics committee of Sefako Makgatho Health Sciences University and DGMAH authorities prior to commencement of the study (SMREC/M/244/202:PG).

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Supplementary file available online