TMJ
Original research
Published by OJS
Doi: 10.4314/tmj.v31i3.367.g244
OPEN ACCESS JOURNAL

Clinical and Anticoagulation Profile of Patients on Warfarin Anticoagulation at Muhimbili National Hospital in Dar es Salaam Tanzania: A Cross-Sectional Study

Omary Minzi[1]*, Leonard Buganda[1], Pilly Chillo[2], Mbonea Yonazi[3]

[1]Department of Clinical Pharmacy and Pharmacology, School of Pharmacy, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania
[2]Department of Internal Medicine, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania
[3]Department of Hematology and Blood Transfusion, Muhimbili National Hospital, Dar es Salaam, Tanzania

***Corresponding author:**

Prof. Omary Minzi

Muhimbili University of Health and Allied Sciences

P. O. Box 65001

Dar es Salaam, Tanzania

Email: minziobejayesu@gmail.com

TMJ
Original research
Published by OJS
Doi: 10.4314/tmj.v31i3.367.g244
OPEN ACCESS JOURNAL

Abstract

Background
Warfarin is still the most commonly used oral anticoagulant in many developing countries, including Tanzania. Due to narrow therapeutic window, the safety and effectiveness of warfarin depends on maintaining a tightly controlled International Normalization Ratio (INR), as sub-therapeutic and supra-therapeutic INR levels are associated with thromboembolic and bleeding complications, respectively. However, in Tanzania the clinical and anticoagulation profiles of patients on warfarin have not been well documented. We therefore studied the clinical characteristics, anticoagulation profile and adverse outcomes of patients on warfarin therapy attending the anticoagulation clinic at Muhimbili National hospital (MNH) in Dar es Salaam, Tanzania.

Methods
This was a hospital-based cross sectional study in which patients attending warfarin anticoagulation clinic for ≥3 months were enrolled. Questionnaires and case report forms were used to gather patients' socio-demographic and clinical characteristics, warfarin use and their most recent INR value. Blood samples were taken and analyzed for current visit INR, full blood count, serum creatinine and albumin levels. Warfarin related complications were obtained through interviews. Associations between INR control levels and warfarin complications with different variables were assessed, and a p-value of < 0.05 was regarded to indicate a significant association.

Results
In total190 patients fulfilled the inclusion criteria and were enrolled. Their mean ±SD age was 41.3±17.4 years, and 63.2% were females. The most common indication for anticoagulation was mechanical heart valves (71.6%) followed by deep vein thrombosis (18.9%), while atrial fibrillation was an indication in 2.1%. In the total population, INR levels were on-target in only 20.0%, while sub- and supra-therapeutic levels were found in 57.9% and 22.1%, respectively. Bleeding complications were reported in 39 (20.5%) while thromboembolism was present in 6 (3.2%) patients. No significant associations were found between age, gender, renal function, platelet count or serum albumin with INR target levels or presence of warfarin complications.

Conclusion
Occurrence of complications in about a quarter of this population indicates that the level of warfarin anticoagulation is sub-optimal. Interventions targeting patients, physicians, clinical pharmacists as well as our health systems are needed to optimize warfarin anticoagulation control and reduce complications.

Key words: *Warfarin, INR, Anticoagulation, Thromboembolic Events, Hemorrhage.*

Published by OJS
Doi: 10.4314/tmj.v31i3.367.g244

Introduction

Despite having many adverse effects, warfarin is still a commonly used oral anticoagulant worldwide.(1) This is because warfarin is less costly and can easily be administered, as it is taken orally. Moreover, the drug is the recommended oral anticoagulant in patients with mechanical heart valves,(2) which makes it the most commonly prescribed anticoagulant in areas where rheumatic heart disease is still rampant, as is the case in many sub Saharan African countries.(3,4) Furthermore, although the newer oral anticoagulants (such as the direct factor X inhibitors) offer better alternatives to warfarin in other anticoagulation indications, the availability of these drugs is hindered by their high cost which is un-affordable to many people in the sub Saharan Africa.(5)

Warfarin works by inhibiting vitamin K epoxide reductase (VKOR), an enzyme that reduces vitamin K epoxide to vitamin K thus interfering with hepatic synthesis of vitamin K dependent clotting factors II, VII, IX, and X.(6) Inhibition of VKOR results into a decreased effective concentration of vitamin K and consequently impairs the synthesis of clotting factors.(7) Following an oral administration, peak absorption of warfarin occurs in 1 to 2 hours and the drug has low volume of distribution due to its extensive (99%) binding to plasma proteins.(7) This also makes warfarin to have a long half-life of up to 60 hours after oral administration.

The primary laboratory test for monitoring of warfarin therapy is prothrombin time (PT) and is expressed as International Normalized Ratio (INR).(8) The safety and effectiveness of warfarin therapy depends on maintaining INR values within the recommended therapeutic range for the underlying condition. For prevention of thrombosis in patients with mechanical heart valves, the target INR should range between 2.5 to 3.5 as recommended by guidelines.(9) While the target INR for other indications including prophylaxis against deep venous thrombosis, pulmonary embolism and stroke the recommended target INR is between 2.0 – 3.0.(8)

Previous studies have indicated that outpatients with supra-therapeutic INRs e.g. >5 face a significant risk of major hemorrhage and require discontinuation of the therapy.(10,11) On the other hand, giving low doses of warfarin decreases risk of hemorrhage but lowers INR values and increase the risk of new thrombus formation.(12) Hemorrhagic conditions caused by warfarin can range from minor petechiae to overt hemorrhage including hemorrhage in joints, muscles or the life threatening intracranial hemorrhage.(12,13) Thromboembolic events are mainly related to inadequate anticoagulation and may manifest as minor events like pain in calf

muscles(14) or severe complications including pulmonary embolism or stroke.(15) Clinically, the determination of warfarin related adverse events and complications is somewhat tricky especially for minor complications, but clinicians normally rely on the patient's reported adverse events. Previous literature has found several factors to associate with lack of target INR control including age, diet, co-morbid conditions, concomitant use of drugs that interact with warfarin, as well as the dose and quality of warfarin taken.(11,16-18) However, in Tanzania both the clinical and anticoagulation profile have not been well studied, and there is limited documented literature in this area. This study describes the clinical and anticoagulation profile of patients on warfarin therapy attending a tertiary referral hospital in Tanzania.

Methods

Study design, area and duration

This was a hospital-based cross sectional study. The study was conducted at the anticoagulation clinic of the Department of Hematology and Blood Transfusion of the MNH in Dar es Salaam, Tanzania. The study duration was from March to June, 2018.

Study population

All adult patients on regular warfarin therapy for a period of at least three months who were attending the anticoagulation clinic at MNH were invited to participate in the study. Patients were excluded if they did not give consent, if they did not have adequate recorded data in their files or if they missed their warfarin doses for two or more consecutive days before the day of the clinic visit.

Sample size and Sampling method

The sample size was calculated by using the formula $n = z^2P(1-P)/\varepsilon^2$ whereby prevalence (P) was taken as 16.5%, level of confidence of the study (z) =1.96 and the margin of error(ε) of 5%. A sample of 190 patients was therefore sufficient to determine the prevalence of warfarin complications among patients on warfarin therapy. Patients were recruited consecutively as they attended the clinic, until the required sample size was reached.

Data collection

The study was explained to the patients and those who consented and fulfilled the inclusion criteria were enrolled. For children, their parents or guardians were interviewed. A pre-tested

structured questionnaire was used to record the required information. Socio-demographic data as well as clinical history was obtained through interviews. Socio-demographic data included history of alcohol consumption, history of use of green vegetables and other variables. Details on the indication for anticoagulation were obtained from the patient' files and their anticoagulation booklets. The dose of warfarin taken by the patient was obtained from the patient's anticoagulation booklet, and this was expressed as weekly warfarin dose in milligram.
Weight and height were measured by using a weighing scale and a standard height board respectively, with patients on bare feet. Weight in kilograms and height in meter square were used to determine the body mass index (BMI) of the study participants. Obesity was considered present when BMI was equal or exceeded 30kg/m^2.

For all patients, blood samples were collected by a phlebotomist at MNH outpatient department laboratory and tested for INR, full blood count, serum albumin and serum creatinine levels. INR, which is the ratio of the patient's prothrombin time (PT) to that of a normal control, was measured using standardized techniques.(8) The PT was measured by adding calcium and tissue thromboplastin to a sample of plasma of a patient, and the time to clot formation was detected by automated light-scattering techniques that measure optical density, according to the laboratory's standard protocols. All tests were done at the MNH Central Pathology Laboratory (CPL), which is the National's reference laboratory. Previous INR data were obtained from patients' anticoagulation booklets and from records of the hospital's Health Information Management System (HMIS).

Determination of warfarin-induced complications was done through interviewing patients on relevant history. Patients were asked if they experienced any of the symptoms of bleeding and/or thromboembolism during the previous 4 weeks before returning to the clinic. For bleeding, the following were asked: nasal bleeding (epistaxis), gum bleeding, blood in urine, heavy(more that one's usual) menstrual bleeding, increased tendency to bruise (ecchymosis), bright red blood in the stool (hematochezia), black or tarry stool (melena), or coughing up of blood (hemoptysis). For thromboembolic events the following were asked: soreness of the calf muscles, chest pain accompanied with shortness of breath, or features of transient ischemic attack or stroke. More information was traced from their records through HMIS, as well as from patients' anticoagulation booklets.

Reference INR values

The reference value for target INR was 2.5 – 3.5 for patients who had mechanical heart valves and 2.0 – 3.0 for other indications including prevention of deep venous thrombosis, stroke prevention, etc.(8,9) For all patients, the preceding INR value was recorded and the average of the preceding and the current visit INR was taken as the patient's average INR for the past 2 months.

Data analysis

Data collected were coded and analyzed by the Statistical Package for Social Sciences (SPSS) version 22 computer software. Tables, bar charts and scatter plots were used to summarize the data. Data is presented as mean ±SD for continuous variables and as number (percentage) for categorical variables. Categorical variables were compared using χ^2 test or Fisher's exact test as appropriate. Comparison between group means was done using one-way Analysis of Variance (ANOVA) test, with Scheffe's post hoc analysis. Bivariate correlations were assessed using Pearson's correlation coefficient (r). All tests were two-sided and a p-value of < 0.05 was regarded as a significant association.

Ethical approval

Ethical clearance was sought from Muhimbili University of Health and Allied Sciences, Research and Publications Committee. The directorate responsible for research at MNH gave permission to conduct the study. Eligible study participants were given a description of the study and they gave written informed consent before they were recruited. For minors, assent was obtained from them and their parents or guardians gave consent to participate in the study. Patients were given identity numbers which ensured confidentiality of their information.

Results

The study included 190 patients, of whom 120 (63.2%) were females. The mean ±SD age of the total studied population was 41.3 ±17.4 years, ranging 6 – 84 years. Majority of the participants were in the age group 18 – 59 years. The most common indication for anticoagulation was post mechanical heart valve replacement surgery (71.6%), followed by prophylaxis against deep venous thrombosis (18.9%), **Table 1**.

Table 1: Socio-demographic and clinical characteristics of study participants (N = 190)

Characteristic	n (%) or mean±SD
Mean ±SD Age (years)	41.3±17.4
Age groups (years), n (%)	
<18	12 (6.3)
18-59	146 (76.8)
≥60	32 (16.8)
Gender, n (%)	
Male	70 (36.8)
Female	120 (63.2)
Mean±SD Body Mass Index (kg/m^2)	24.0±4.5
Overweight status, n (%)	
Underweight	5 (2.6)
Normal weight	126 (66.3)
Overweight	41 (21.6)
Obese	18 (9.5)
Alcohol use, n (%)	6 (3.2)
Green leafy vegetables in the past week, n (%)	
Did not take	127 (66.8)
Once per week	26 (13.7)
Twice per week	57 (30.0)
Thrice per week	19 (10.0)
>3 times per week	22 (11.6)
Indication for anticoagulation	
Post valvular heart surgery	136 (71.6)
Deep Venous Thrombosis	36 (18.9)
Atrial Fibrillation	4 (2.1)
Pulmonary Embolism	7 (3.7)
Others	7 (3.7)

In the total population, the mean weekly dose of warfarin per patient was 33.6mg, (range 17.5 – 87.5mg), and majority of patients were receiving warfarin dose ranging between 35 – 52.5mg per week; equivalent to approximately 5 – 7.5mg daily dose. In the total population, the mean

±SD INR was 2.48 ±1.07, and it ranged between 0.90 – 7.18. INR values were on-target in 20.0%, while about a half (57.9%) of the patients had sub-therapeutic and 22.1% had supra-therapeutic INR levels, **Table 2**.

Table 2: Warfarin prescription patterns, INR and laboratory findings (N = 190)

Variable/characteristic	n (%), or mean ±SD
Mean weekly warfarin dose (mg)	33.62±10.37
Warfarin dose, n (%)	
≤21mg/week	26 (13.7)
21.1 – 34.9mg/week	33 (17.4)
35 – 52.5mg/week	128 (67.4)
>52.5mg/week	3 (1.6)
Mean ±SD INR	2.48±1.07
Target INR findings, n (%)	
On-target	38 (20.0)
Supra-therapeutic	42 (22.1)
Sub-therapeutic	110(57.9)
Renal function, n (%)	
Normal	181 (95.3)
Renal dysfunction	9 (4.7)
Mean ±SD Platelet count (x10^9/L)	267 ± 80
Proportion with low platelet count, n (%)	5 (2.6)
Mean ±SD Serum Albumin level (g/L)	40.49 ± 5.58
Proportion with low albumin level, n (%)	7 (3.7)

INR = International Normalization Ratio

Patients were further subdivided into those with Mechanical heart valve replacement (MHVR) whose INR normal range is 2.5-3.5 and were further categorized into therapeutic, sub therapeutic and supra-therapeutic values. The non-MHVR had normal INR range 2.0-3.0 and were also were categorized as those with INR values that were therapeutic, sub therapeutic and supra-therapeutic value, **Table 3.**

Table 3: Therapeutic, Supra – therapeutic and Sub- therapeutic INR patterns per anticoagulation indication (N = 190)

	INR status				
Variable	**Therapeutic INR**	**Supra-therapeutic INR**	**Sub–therapeutic INR**	***Total***	***P value***
MHVR	26 (19.1%)	29 (21.3%)	81(59.6%)	136 (71.6%)	
Non - MHVR	12 (22.2%)	13 (24.1%)	29 (53.7%)	54 (28.4%)	0.432.
Total	38 (20.0%)	42 (22.1%)	110(57.9%)	190 (100%)	

MHVR – Mechanical Heart Valve Replacement

Table 4 describes correlation between weekly mean warfarin dose, INR and selected variables. Neither the mean weekly warfarin dose nor the mean INR correlated with any of the variables age, BMI, platelet count or serum albumin levels. The mean weekly warfarin dose did not show any correlation with the mean INR levels. However, there was a positive and significant correlation between the individual patient's last visit INR and current visit INR (r = 0.31, p <0.001), **Figure 1.**

Table 4: Correlation between weekly mean warfarin dose, INR and selected variables

Variable	**Mean warfarin dose per week (mg)**		**Mean INR**	
	r	***p-value***	**r**	***p-value***
Age (years)	0.37	0.615	0.052	0.476
Body Mass Index (kg/m^2)	0.025	0.730	-0.091	0.211
Platelet count (x10^9/L)	-0.007	0.919	0.003	0.964
Serum albumin(g/L)	-0.112	0.123	0.051	0.481
Mean weekly warfarin dose (mg)	-	-	0.008	0.911
Mean INR	0.008	0.911	-	-

INR = International Normalization Ratio

Published by OJS
Doi: 10.4314/tmj.v31i3.367.g244

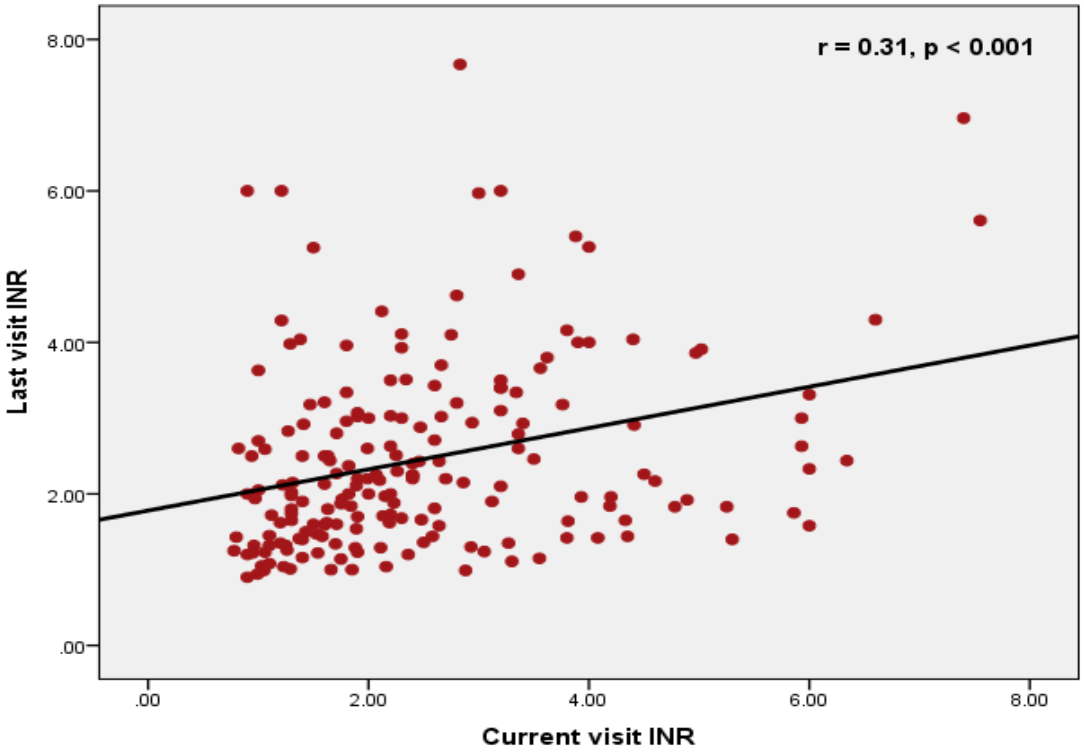

Figure 1: Correlation between last- and current-visit INR values

Comparison of patients without complication and those with bleeding or thromboembolic complications did not find significant differences in terms of gender distribution, age, mean platelet count, mean serum albumin, or history of alcohol and green leafy vegetables consumption (**Table 5**). However, patients who had bleeding complications were more likely to be obese when compared to other group, p = 0.033. Of note, mean weekly warfarin dose did not differ between patients who experienced complications and those who did not, p >0.05.

Patients who achieved therapeutic INR did not significantly differ with those who had sub- and supra-therapeutic INR values in terms of gender distribution, age, BMI, mean warfarin dose as well as other variables as seen in Table 5, all p >0.05. As expected, the mean INR values differed significantly between and within groups, p < 0.001.

In the total population 39 (26 females and 13 males) patients reported to have had at least one bleeding complication during the reported period, while 6 (4 females and 2 males) reported history of a thromboembolic event, **Figure 2.** The rest 145 (76.3%) of the patients did not report any warfarin complication.

Published by OJS
Doi: 10.4314/tmj.v31i3.367.g244

Table 5: Comparison of patients with therapeutic, supra-therapeutic and sub-therapeutic INR values in the total population (N =190)

Variable	Therapeutic (n = 38)	Supra-therapeutic (n = 42)	Sub-therapeutic (n = 110)	p-value
Female gender	27(14.2)	24(12.6)	69(36.3)	0.432
Mean age	42.8 ± 17.1	44.5 ± 17.8	39.2 ± 17.5	0.240
Mean BMI	24.0 ± 4.3	23.2 ± 4.4	24.3 ± 4.7	0.532
Obese individuals	6 (9.4)	1 (3.2)	11 (11.6)	0.893
Mean platelet count	276 ± 88	255 ± 63	265 ± 80	0.464
Mean serum albumin	40.1 ± 4.7	40.9 ± 5.3	40.6 ± 4.3	0.691
Mean INR	2.78 ± 0.42	4.29 ± 0.88	1.69 ± 0.40	<0.001
Mean warfarin dose	33.8 ± 12.2	33.6 ± 7.9	33.5 ± 9.9	0.989
Taking green leafy vegetables	44 (68.8)	22 (71.0)	61 (64.2)	0.726

BMI = Body Mass Index; INR = International Normalization Ratio

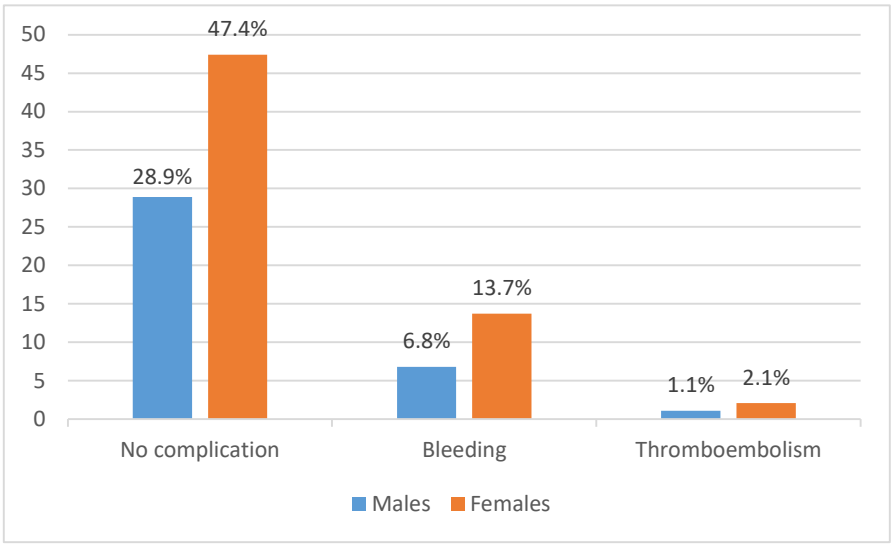

Figure 2: Prevalence of warfarin complications among men and women

Published by OJS
Doi: 10.4314/tmj.v31i3.367.g244

Discussion

This study documents the clinical characteristics, anticoagulation profile and complications encountered by patients on warfarin therapy attending care at a tertiary hospital in Tanzania. The study has found several interesting observations that are worth discussed. Firstly, only 20% of patients on anticoagulation therapy attained the intended target INR; secondly, the dose of warfarin prescribed to this population did not correlate with any of the variables normally used to guide dose adjustment in patients taking warfarin; and thirdly, around a quarter (23.7%) of patients on warfarin therapy experienced adverse events, mainly bleeding events.

The finding that only 20.0 % of the studied population attained target INR is consistent with previous reports from sub Saharan African countries, where anticoagulation control rates have generally been low.(17,18,20) Previous researchers have attributed the unfavorable control rate to a number of factors, including alcohol use, cigarette smoking, poor adherence caused by distance to health facilities, diet, frequent warfarin stock-outs, and possibly other factors related to differences in genetic makeup among people of black origin.(17,20-23) However, none of the studied factors was related to the level of INR control in our study. In this study, we found virtually more than a half of the patients had sub-therapeutic INR levels while 22.1% had supra-therapeutic levels, rendering patients to an increased risk of thromboembolism and bleeding, respectively. Fenta et al reported a similar picture where the proportion of patients on sub-therapeutic, therapeutic and supra-therapeutic was 52.2%, 29.0% and 18.8% respectively in a retrospective analysis of 360 patients receiving warfarin in Addis Ababa.(18) The low level of target INR calls for measures to strengthen warfarin anticoagulation control in the region.

We found the weekly dose of warfarin not to correlate with any of the known factors that need to be considered when calculating and adjusting warfarin dose.(8) Previous studies have found age and weight to correlate with dose of warfarin needed by patients.(24,25) Furthermore, we found neither the anticoagulation indication nor renal function of the patient showing any association with the mean weekly warfarin dose prescribed to the patient. In practice, these are supposed to inform the warfarin dosage. This observation is clinically very relevant as it might be related to lack to follow up of warfarin dosing algorithms, which give details of how and when to adjust the patient's dose.(26) It is therefore possible that the lack of INR control found in this study is partly due to "inactive" dose adjustment practices in our clinical practice. In fact, majority of the patients in this study who were not on-target INR levels, had sub-therapeutic

levels, most likely due to under-dosing. More studies are needed to establish the factors related to poor INR in our local setting; taking into consideration all factors including physicians', patients' as well as health system's factors.

Complications among patients on warfarin therapy is a common encounter and is associated with an increased morbidity and mortality.(13,16) In this study, a quarter of the population reported to have had either bleeding or a thromboembolic event. As expected, bleeding was the most common complication seen in 20.5% of this population. This finding is similar to the frequency of warfarin complications reported elsewhere.(23,27) In the study by Sonuga, et al(23) thrombotic events and bleeding events were seen in 2.2% and in 14% respectively among patients attending a warfarin clinic in Western Cape Province in South Africa, showing a similar pattern of complications as reported in the current study. The mentioned complications were obtained through taking patient history without necessarily conducting additional clinical investigations that could identify those who were at risk. It is known that some of the bleeding complications could take place in joints or soft tissues without the awareness of the patient. Taking thorough clinical investigations to all patients on warfarin would reduce the risk of complications and signal timely intervention.

Our finding that obesity was associated with increased likelihood of bleeding is an interesting one. People who are obese were likely to be under-dosed and we would expect thromboembolism to be the associated risk. However, this association could as well be confounded by other factors, and more rightly-powered research need to be done to confirm this finding.

Lastly, the demographic characteristics and indications of patients on warfarin therapy seen in this study is similar to previous studies from sub Saharan Africa.(18,20) The mean age of 41 years and the female predominance (62.3%) seen in the current study population is remarkably similar to that reported by Mwita, et al in Botswana,(20) indicating the relatively young and predominantly female population of patients on warfarin anticoagulation therapy in sub Saharan Africa. This is mainly due to high proportion of rheumatic heart disease patients in our settings, as opposed to predominantly older population as a result of atrial fibrillation being the main indication for anticoagulation in Western countries.(15) Furthermore, the indications for warfarin therapy in this study were also similar to those in Botswana(20) and Ethiopia,(18) showing mechanical heart valve replacement as the predominant indication for warfarin anticoagulation.

Conclusion

Based on the data we obtained from this study, it can be concluded that occurrence of complications in about a quarter of this population indicates that the level of warfarin anticoagulation is sub-optimal. Interventions targeting patients, physicians, clinical pharmacists as well as our health systems are needed to optimize warfarin anticoagulation control and reduce complications.

Limitations of the study

Being a cross sectional study and with limited sample size, it might have contributed to a failure to establish a true cause and effect relationship between the studied risk factors, poor INR control and the complications encountered by patients. In addition, some of the information that we had expected to obtain from patient records were missing and other factors that influence INR such as co-morbidity, distance to the clinic, ability to purchase medicines, were not systematically collected and therefore could not be assessed as possible risk factors.

Acknowledgements

This study would not have been successful without participation of study patients, clinicians, nurses, laboratory technician at the hematology unit and phlebotomist. They are all acknowledged. We thank the MNH management for giving permission to conduct the study at the site. This study was partially funded by postgraduate grants received from the Ministry of Health, Community Development, Gender, Elderly and Children.

Authors' contribution

OM, PC and BL conceived the study. BL and MY participated in data collection. BL, PC and OM participated in data analysis and manuscripts development.

Conflict of interest

The authors declare no conflict of interest.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on request.

References

1. Hsu JC, Maddox TM, Kennedy KF, Katz DF, Marzec LN, Lubitz SA, et al. **Oral Anticoagulant Therapy Prescription in Patients With Atrial Fibrillation Across the Spectrum of Stroke Risk: Insights From the NCDR PINNACLE Registry.** JAMA cardiology. 2016 Apr 1;1(1):55-62.
2. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, et al. **2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.** The Journal of thoracic and cardiovascular surgery. 2014 Jul;148(1):e1-e132.
3. Zuhlke L, Karthikeyan G, Engel ME, Rangarajan S, Mackie P, Cupido-Katya Mauff B, et al. **Clinical Outcomes in 3343 Children and Adults With Rheumatic Heart Disease From 14 Low- and Middle-Income Countries: Two-Year Follow-Up of the Global Rheumatic Heart Disease Registry (the REMEDY Study).** Circulation. 2016 Nov 8;134(19):1456-66.
4. Carapetis JR, Beaton A, Cunningham MW, Guilherme L, Karthikeyan G, Mayosi BM, et al. **Acute rheumatic fever and rheumatic heart disease.** Nature reviews Disease primers. 2016 Jan 14;2:15084.
5. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. **Dabigatran versus warfarin in patients with atrial fibrillation.** The New England journal of medicine. 2009 Sep 17;361(12):1139-51.
6. Whitlon DS, Sadowski JA, Suttie JW. **Mechanism of coumarin action: significance of vitamin K epoxide reductase inhibition.** Biochemistry. 1978 Apr 18;17(8):1371-7.
7. Takahashi H, Echizen H. **Pharmacogenetics of warfarin elimination and its clinical implications.** Clinical pharmacokinetics. 2001;40(8):587-603.
8. Hirsh J, Fuster V, Ansell J, Halperin JL, American Heart Association/American College of Cardiology F. **American Heart Association/American College of Cardiology Foundation guide to warfarin therapy.** Journal of the American College of Cardiology. 2003 May 7;41(9):1633-52.
9. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, et al. **Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery**

(EACTS). European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2012 Oct;42(4):S1-44.

10. Abadi U, Ellis MH. **[International Normalized Ratio Values and Hemorrhage in Hospitalized Patients Starting Warfarin Therpy: An Observational Study]**. Harefuah. 2015 Aug;154(8):490-3, 541-2.
11. Hylek EM, Chang YC, Skates SJ, Hughes RA, Singer DE. **Prospective study of the outcomes of ambulatory patients with excessive warfarin anticoagulation.** Archives of internal medicine. 2000 Jun 12;160(11):1612-7.
12. Morgan CL, McEwan P, Tukiendorf A, Robinson PA, Clemens A, Plumb JM. **Warfarin treatment in patients with atrial fibrillation: observing outcomes associated with varying levels of INR control.** Thrombosis research. 2009 May;124(1):37-41.
13. Ozturk M, Ipekci A, Kiyak SK, Akdeniz YS, Aydin Y, Ikizceli I, et al. **Bleeding Complications in Warfarin-Treated Patients Admitted to the Emergency Department.** Journal of clinical medicine research. 2019 Feb;11(2):106-13.
14. Binymin KA, Nasher M, Patel D. **Warfarin-induced deep vein thrombosis.** International medical case reports journal. 2014;7:123-5.
15. Haas S, Ten Cate H, Accetta G, Angchaisuksiri P, Bassand JP, Camm AJ, et al. **Quality of Vitamin K Antagonist Control and 1-Year Outcomes in Patients with Atrial Fibrillation: A Global Perspective from the GARFIELD-AF Registry.** PloS one. 2016;11(10):e0164076.
16. Kamuren Z, Kigen G, Keter A, Maritim A. **Characteristics of patients with thromboembolic disorders on warfarin therapy in resource limited settings.** BMC health services research. 2018 Sep 19;18(1):723.
17. Chalachew T, Yadeta D, Tefera E. **Factors associated with sub-optimal control of anticoagulation in patients with prosthetic heart valves taking oral anticoagulants in a sub-Saharan African setting.** Cardiovascular journal of Africa. 2019 May 24;30:1-5.
18. Fenta TG, Assefa T, Alemayehu B. **Quality of anticoagulation management with warfarin among outpatients in a tertiary hospital in Addis Ababa, Ethiopia: a retrospective cross-sectional study.** BMC health services research. 2017 Jun 6;17(1):389.
19. Teklay G, Shiferaw N, Legesse B, Bekele ML. **Drug-drug interactions and risk of bleeding among inpatients on warfarin therapy: a prospective observational study.** Thrombosis journal. 2014;12:20.

20. Mwita JC, Francis JM, Oyekunle AA, Gaenamong M, Goepamang M, Magafu M. **Quality of Anticoagulation With Warfarin at a Tertiary Hospital in Botswana.** Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis. 2018 May;24(4):596-601.
21. Semakula JR, Mouton JP, Jorgensen A, Hutchinson C, Allie S, Semakula L, et al. **A cross-sectional evaluation of five warfarin anticoagulation services in Uganda and South Africa.** PloS one. 2020;15(1):e0227458.
22. Ndadza A, Thomford NE, Mukanganyama S, Wonkam A, Ntsekhe M, Dandara C. **The Genetics of Warfarin Dose-Response Variability in Africans: An Expert Perspective on Past, Present, and Future.** Omics : a journal of integrative biology. 2019 Mar;23(3):152-66.
23. Sonuga BO, Hellenberg DA, Cupido CS, Jaeger C. **Profile and anticoagulation outcomes of patients on warfarin therapy in an urban hospital in Cape Town, South Africa.** African journal of primary health care & family medicine. 2016 May 31;8(1):e1-8.
24. Tellor KB, Nguyen SN, Bultas AC, Armbruster AL, Greenwald NA, Yancey AM. **Evaluation of the impact of body mass index on warfarin requirements in hospitalized patients.** Therapeutic advances in cardiovascular disease. 2018 Aug;12(8):207-16.
25. Khoury G, Sheikh-Taha M. **Effect of age and sex on warfarin dosing.** Clinical pharmacology : advances and applications. 2014;6:103-6.
26. Wilson SE, Costantini L, Crowther MA. **Paper-based dosing algorithms for maintenance of warfarin anticoagulation.** Journal of thrombosis and thrombolysis. 2007 Jun;23(3):195-8.
27. Wysowski DK, Nourjah P, Swartz L. **Bleeding complications with warfarin use: a prevalent adverse effect resulting in regulatory action.** Archives of internal medicine. 2007 Jul 9;167(13):1414-9. PubMed PMID: 17620536.