East African Medical Journal Vol. 95 No. 7 July 2018
TRENDS OF ANTICOAGULATION CONTROL AMONG ADULT OUTPATIENTS ON LONG-TERM WARFARIN THERAPY IN A TERTIARY TEACHING AND REFERRAL HOSPITAL IN KENYA

David Gitonga Nyamu, Senior Lecturer of Clinical Pharmacy, Department of Pharmaceutics and Pharmacy Practice, University of Nairobi, P.O. Box 19676-00202 Nairobi. Anastasia Nkatha Guantai, BPharm, MSc, PhD: Professor of Pharmacology & Therapeutics, Department of Pharmacology and Pharmacognosy, University of Nairobi, P.O. Box 19676-00202 Nairobi. George Oyamo Osanjo, BPharm, MSc, PhD: Associate Professor of Pharmacology, Department of Pharmacology and Pharmacognosy, University of Nairobi, P.O. Box 19676-00202 Nairobi. Eleni Aklillu, BPharm, MSc, PhD, Associate Professor & Chief Laboratory Researcher, Division of Clinical Pharmacology, Huddinge University, Karolinska Institute, Sweden.

Corresponding author: David G. Nyamu, BPharm, MPharm, PhD(c), Senior Lecturer of Clinical Pharmacy, Department of Pharmaceutics and Pharmacy Practice, University of Nairobi. Email:dgnyamu@gmail.com.

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D. G. Nyamu, A. N. Guantai, G. O. Osanjo, and E. Aklillu

ABSTRACT

Background: **Anticoagulation control using warfarin therapy has several challenges especially in resource constrained settings.**
Objective: **To describe the trends of anticoagulation control among adult outpatients on warfarin therapy at Kenyatta National Hospital.**
Design: **Cross-sectional study.**
Setting: **Anticoagulation clinics in the hospital.**
Participants: **180 outpatients aged ≥18 years.**
Main outcome measures: **Level of anticoagulation and adverse drug reactions (ADRs).**
Methods: **Participants' sociodemographic characteristics and details of ADRs were acquired through face-to-face interviews. The level of anticoagulation was determined through assessment of international normalized ratios (INRs) for the six clinic attendances with INR of 2-3 being considered therapeutic. Data analysis was conducted onto IBM Statistical Package for Social Sciences version 23. Pearson's Chi square was used to determine the strength of associations between outcome measures and sociodemographics, with statistical significance set at $p \leq 0.05$.**
Results: **Females were majority (76.7%) and the mean age of participants was 43.4 (±13.2) years. Therapeutic anticoagulation was maintained by 35.2-48.4% patients**

across six follow-ups and was better among the males (p=0.0398) especially those suffering from heart diseases. ADRs were experienced by almost 50% of the patients where bleeding (27.8%) mainly occurred at INR>3(80.0%). ADRs were significantly more common among the participants without spouses, who were primarily suffering from heart diseases (p=0.0081).

Conclusions: **Anticoagulation control is poor though patients with cardioembolic disorders have better INRs but more ADRs. Clinical and laboratory monitoring of warfarin therapy should be intensified among females. Future studies should correlate warfarin anticoagulation control with patient, clinician or hospital related factors.**

INTRODUCTION

Warfarin is the agent of choice for the management as well as prevention of thromboembolic events (1) and has been used clinically for almost seventy years (2). Treatment with warfarin has several limitations because of the intra-individual and inter-individual dose variation which necessitate constant monitoring of clinical and laboratory data (3) in order to improve anticoagulation services(4).

The World Health Organization (WHO) introduced international normalized ratio (INR) for standardizing monitoring of warfarin therapy (5), which has remained the most commonly used method over the years (6,7), with an INR of 2-3 being termed therapeutic, except for patients with artificial heart valves where it is between 2.5 and 3.5 (8). Studies have indicated that INR above 3 rises the risk of haemorrhage, while that which is less than 2 increases the chances of thromboembolic events (9).

Regional literature shows that only less than 7% of the patients on warfarin are within the recommended INR ranges for more than half of the follow-up time and suggested better monitoring methods be adopted(10). International studies have recommended clinical monitoring of warfarin therapy through observing adverse effects such as bleeding(11), fractures (12,13) and purple toes (13). Furthermore, studies have indicated that the main side effect of warfarin is haemorrhage (14,15). Meta-analysis of over thirty studies reported serious and fatal bleeding events at the rates of approximately 7.0 and 1.5 per100 patient- years, respectively (14).

Some Kenyan studies on anticoagulation have dwelt on adequacies of anticoagulation control among patients on warfarin therapy (10,16) while others have looked into patients' knowledge(17,18) and adherence(19) on anticoagulation management. The pattern of anticoagulation control among a single patient population with valvular abnormalities has been described in a tertiary teaching and referral hospital (10) but there is scant published local data on the trends of control among patients on long term therapy. This study, therefore, sought to describe the trends of anticoagulation control among adult patients receiving long-term warfarin therapy at Kenyatta National Hospital (KNH).

METHODOLOGY

Study Design and Area: A cross-sectional study was carried out from June –December 2018 among outpatients' aged ≥ 18 years who were undergoing long term warfarin therapy at the anticoagulation clinics of KNH, the

largest teaching and referral hospital in East and Central Africa. The specialized anticoagulation sites included haemato-oncology, cardiac and cardiothoracic clinics, which serve as the focal points and referral centres for all patients undergoing long-term anticoagulation in the hospital.

Study Population: Patients were eligible if they were undergoing follow-up at the study clinics. Patients who were advised not to take warfarin by their primary physician or those who did not adhere to treatment were excluded. Patients suffering from peptic ulcer disease, uncontrolled hypertension or any inherited coagulation disorders were excluded.

Sample Size and Sampling Method: The primary endpoint was the prevalence of any anticoagulation treatment outcomes such as ADRs to warfarin therapy. Previous studies had indicated prevalence of ADRs to warfarin treatment at 13% (20). Using this prevalence and related equation for calculation of sample sizes for such cross-sectional studies(21), a minimum sample of 173 participants was obtained and marked up by 4% to cater for the data losses giving a final sample size of 180. Convenient sampling was employed until the sample size was accomplished.

Study Methods: Study approval was sought and granted by KNH/University of Nairobi-Ethics and Research Committee (KNH/UoN-ERC) reference number KNH-ERC/A/569, Department of Research and Programs at KNH reference MED/25/14 and Heads of Departments governing the study sites. Each of the eligible participants was explained the purpose of the study and taken through detailed consenting process after which consent was requested. A predesigned questionnaire was administered to participants to capture the sociodemographic variables. Participants were also required to state whether they had experienced certain ADRs to warfarin therapy and the INR levels that they occurred. The clinical indications of warfarin therapy were extracted from the participants' medical records. To determine the trend in anticoagulation control, participants were followed-up for the latest six clinic visits noting the INR values, of which levels of 2-3 was classified as within therapeutic range as recommended in international guidelines (2).

Data Entry and Statistical Analysis: Raw data was entered and analyzed onto IBM Statistical Package for Social Sciences version 23. Measures of central tendencies were computed for numerical data and proportions for categorical variables such as ADRs and levels of INRs. INR therapeutic levels were reported as being sub-therapeutic (<2), therapeutic (2-3) or supra-therapeutic (>3). Trend lines were drawn for the levels of anticoagulation at various follow-up dates. Bivariate analysis was conducted to determine associations between the sociodemographic characteristics and the levels of INRs as well as presence or absence of ADRs using Pearson's correlation tests at 95% confidence level.

RESULTS

Table 1 shows the socio demographics characteristics of the respondents.

Table 1

Sociodemographic Characteristics of the Study Participants (N=180)

Variable	Category	Frequency (N=180)	Percentage (%)
Sex	Male	42	23.3
	Female	138	76.7
Age categories(years)	19-30	30	16.7
	31-50	100	55.6
	≥51	50	27.8
Mean Age(±SD) years; Range	*43.4(±13.2; range 19-87years*		
Degree of Obesity	Underweight	11	6.1
	Normal Weight	47	26.1
	Overweight	58	32.2
	Obese	32	17.8
Marital status	Single	39	21.7
	Married	118	65.6
	Divorced/Widowed	23	12.8
Employment status	Unemployed/Student	63	35.0
	Salaried	53	29.4
	Self employed	64	35.6
Highest academic level	College/ University	35	19.0
	Secondary	81	45.0
	Non-formal/ Primary	74	41.0
Denomination	Protestant	86	47.8
	Catholic	84	46.7
	Muslim & other	10	5.6
Tobacco smoking status	No	173	96.1
	Yes	2	1.1
Alcohol use status	No	162	90.0
	Yes	12	6.8

Key: SD-Standard Deviation

The mean age of the study participants was 43.4(±13.2) years. More than half of participants (55.6%) were aged between 31-50 years. Approximately 60% of the study participants had attained at least secondary level of education and had a source of regular income (**Table 1**). The mean levels of INRs obtained across the clinical indications of anticoagulation are shown in **Table 2**.

Table 2

Mean INRs by clinical indications among the study patients

Clinical Indication	INRs			
	Mean	95% C.I.		Median
		Lower	Upper	
Major surgery (n=60)*	2.27	2.00	2.55	2.00
Deep Venous Thrombosis(n=97)	2.25	1.95	2.55	1.90
Pulmonary embolism(n=4)	2.19	0.98	3.40	1.85
Rheumatic heart disease(n=17)	2.38	1.66	3.10	2.15
Atrial fibrillation(n=10)	2.21	1.30	3.12	1.91
Overall	**2.29**	**2.10**	**2.48**	**2.00**

Key: C.I- Confidence interval; INR-International Normalized Ratio

**Major surgeries included aortic, mitral or double valve replacement. Eight patients had more than one clinical indication of anticoagulation.*

The overall mean INR for the study population was 2.29. Participants with rheumatic heart disease had the highest mean INR (2.28), followed by those who had undergone heart valve surgery (2.27) (**Table 2**). Patients were followed up for the six most recent clinic visits while assessing the level of INRs at various follow updates. The results are presented in **Figures 1 and 2**.

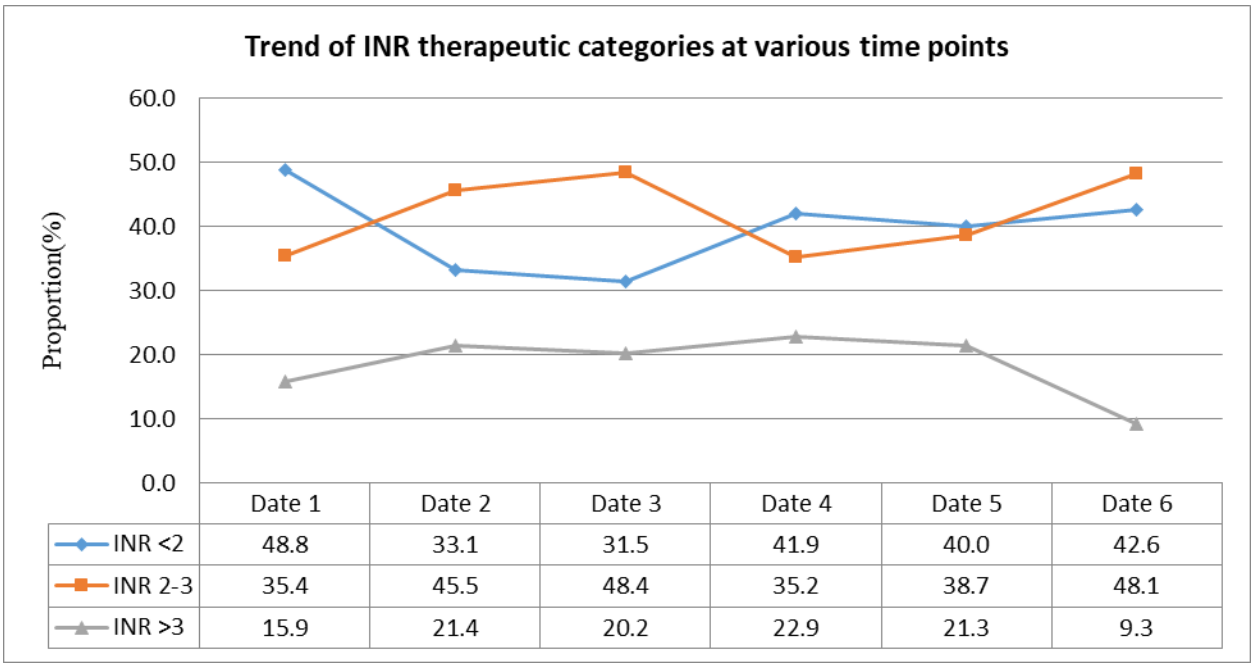

Figure 1: Trend of INR therapeutic categories at various time points

The proportion of patients who were adequately anticoagulated ranged from 35.2 to 48.4% across the follow-up dates. The highest proportion of adequately anticoagulated patients was found during the third and sixth follow-ups (**Figure 1**). For the ease of comparison of the level of anticoagulation control, study participants were grouped into two according to their clinical indications. Participants' suffering from DVT and PE was classified as "VTEs" while those who had heart valve defects were collectively called "heart diseases". **Figure 2** shows comparative results on the level of anticoagulation between the two broad clinical indications.

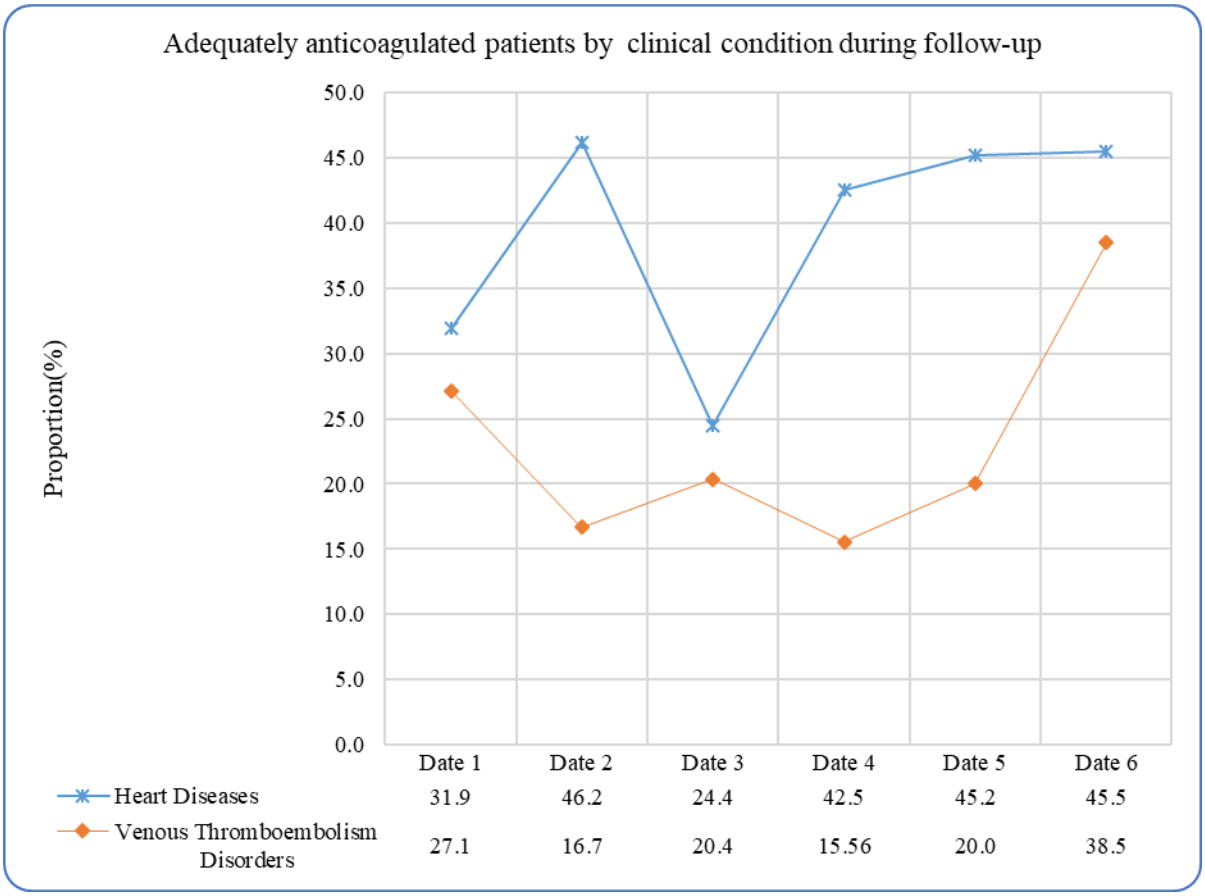

Figure 2: Therapeutic anticoagulation by clinical indications among the study participants during the patients' follow-up

There were larger proportions of therapeutically anticoagulated patients suffering from heart diseases compared to those with venous thromboembolic events during the patients' follow-up (**Figure 2).** The relationships between the sociodemographic characteristics and the level of INRs among the patients are shown in **Table 3**.

Table 3

Association between Participants Sociodemographic Characteristics and Warfarin response as Measured by INRs

Variable	Category	INR Level			Group Differences
		<2 n (%)	2-3 n (%)	>3 n (%)	
Sex	Male	16(41.0)	20(51.3)	3(7.7)	$\chi^2_{(2, 164)}$=6.45; P=0.0398
	Female	64(51.2)	38(30.4)	23(18.4)	
Age	50 and Below years	59(50.0)	41(34.7)	18(15.3)	$\chi^2_{(2, 164)}$=0.27; P=0.8740
	Above 50 Years	21(45.7)	17(37.0)	8(17.4)	
Body mass index	Underweight/Normal	29(58.0)	16(32.0)	5(10.0)	$\chi^2_{(2, 134)}$=4.78; P=0.0917
	Overweight/Obese	33(39.3)	35(41.7)	16(19.0)	
Marital status	Without Spouse	32(53.3)	16(26.7)	12(20.0)	$\chi^2_{(2, 164)}$=3.45; P=0.1779
	With Spouse	48(46.2)	42(40.4)	14(13.5)	
Employment status	Non-Regular Income	55(46.2)	46(38.7)	18(15.1)	$\chi^2_{(2, 164)}$=2.06; P=0.3578
	Regular Income	25(55.6)	12(26.7)	8(17.8)	
Highest academic level	Below Secondary	31(51.7)	19(31.7)	10(16.7)	$\chi^2_{(2, 164)}$=0.57; P=0.7531
	Secondary and Above	49(47.1)	39(37.5)	16(15.4)	
Denomination	Christian	74(48.1)	54(35.1)	26(16.9)	$\chi^2_{(2, 164)}$=2.03; P=0.3628
	Muslim and Others	6(60.0)	4(40.0)	0(0.0)	
Tobacco use	No	78(49.7)	55(35.0)	24(15.3)	$\chi^2_{(2, 159)}$=2.21; P=0.3305
	Yes	1(50.0)	0(0.0)	1(50.0)	
Alcohol Use	No	73(49.7)	50(34.0)	24(16.3)	$\chi^2_{(2, 158)}$=0.76; P=0.6838
	Yes	5(45.5)	5(45.5)	1(9.1)	

Key: INR-International Normalized Ratio

There was a statistically significant difference between gender and the level of anticoagulation) (**Table 3**) with a larger proportion of males recording better anticoagulation than the females (**51.3 % vs 30.4%, P=0.0398)**. Warfarin response was also monitored through documentation of ADRs to therapy. The types of ADRs encountered and their prevalence as well as the levels of INRs at which they occurred are shown (**Figure 3 and 4**). Only fifty two participants (28.9%) had the INRs determined at the time of development of ADRs.

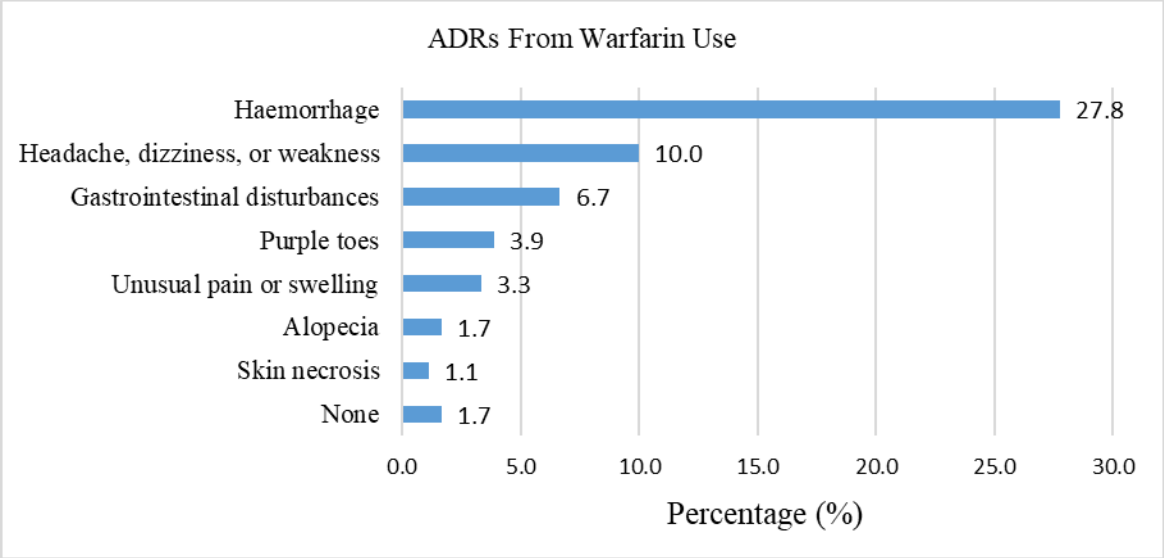

Figure 3: Prevalence of Adverse Drug Reactions of Warfarin among the Study Participants
Key: ADRs-Adverse Drug Reactions

Slightly over half of the participants experienced an ADR with almost 27.8% presenting with bleeding while 10% had headache, dizziness or weakness (**Figure 3**).

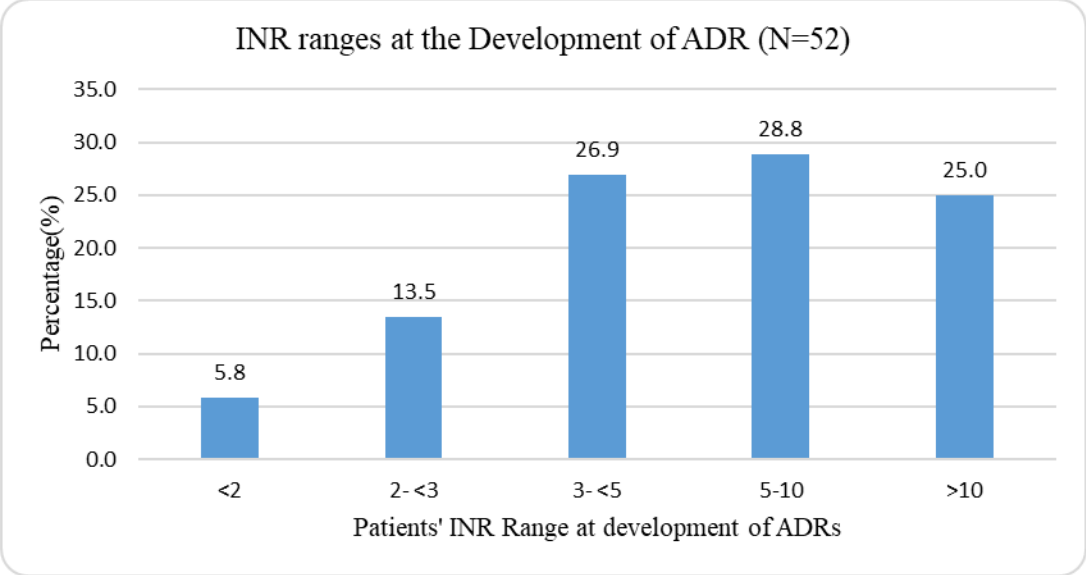

Figure 4: INR ranges at the development of ADRs due to warfarin
Key: INR-International Normalized Ratio

Almost 30% of the ADRs developed at INRs of 5-10. Furthermore, over 80% of the ADRs occurred at INRs above 3 (**Figure 4**). The associations between participants' sociodemographics and presence or absence of ADRs are shown in **Table 4.**

Table 4

Association between participants' sociodemographic and warfarin response as measured by presence or absence of ADRs

Variable	Category	ADRs		Group differences
		No n (%)	Yes n (%)	
Sex	Male	23(54.8)	19(45.2)	$\chi^2_{(1, 180)}$=0.02; P=0.8969
	Female	74(53.6)	64(46.4)	
Age	50 and Below years	66(50.4)	65(49.6)	$\chi^2_{(1, 180)}$=2.38; P=0.1227
	Above 50 Years	31(63.3)	18(36.7)	
Body mass index	Underweight/Normal	30(51.7)	28(48.3)	$\chi^2_{(1, 148)}$=0.11; P=0.7461
	Overweight/Obese	49(54.4)	41(45.6)	
Marital status	Without Spouse	25(40.3)	37(59.7)	$\chi^2_{(1, 180)}$=7.01; P=0.0081
	With Spouse	72(61.0)	46(39.0)	
Employment status	Non-Regular Income	71(55.9)	56(44.1)	$\chi^2_{(1, 180)}$=0.71; P=0.4008
	Regular Income	26(49.1)	27(50.9)	
Highest academic level	Below Secondary	37(57.8)	27(42.2)	$\chi^2_{(1, 180)}$=0.62; P=0.4328
	Secondary and Above	60(51.7)	56(48.3)	
Denomination	Christian	90(52.9)	80(47.1)	$\chi^2_{(1, 180)}$=1.11; P=0.2929
	Muslim and Others	7(70.0)	3(30.0)	
Tobacco use	No	94(54.3)	79(45.7)	$\chi^2_{(1, 175)}$=2.35; P=0.1255
	Yes	0(0.0)	2(100.0)	
Alcohol use	No	88(54.3)	74(45.7)	$\chi^2_{(1, 174)}$=0.72; P=0.3965
	Yes	5(41.7)	7(58.3)	

There was a significant proportion of participants without spouses who developed ADRs compared to those with spouses (**59.7 % vs. 39.0%, P=0.0081**) (**Table 4**).

DISCUSSION

This study documents the general trends in warfarin anticoagulation control among one hundred and eighty patients attending the largest teaching and referral hospital in East and Central Africa. The mean INR was 2.29, ranging 2.19-2.38 across the clinical indications. Ogendo *et al* previously observed a similar mean INR of 2.5±1.18 among patients with valvular abnormalities(10). Patients with rheumatic heart disease showed the highest mean INR at 2.38, which is comparable with 2.32(±1.04) previously obtained for patients with aortic valve replacements(10). The higher INR observed in this group of patients could be as a result of the clinicians trying to achieve recommended target ranges of 2.5-3.5 for patients with valvular abnormalities as suggested in international guidelines(2).

There was poor anticoagulation with only 35.2-48.4% participants reporting therapeutic INR levels during follow up. Previous local studies reported low level of therapeutic anticoagulation at 40.2% among patients with valvular abnormalities(10) and 43.5% on those assessed for adherence (19).Additionally, Karuri *et al* indicated that only 20% of the patients maintained therapeutic anticoagulation for ≥50% of their follow up time, and the overall time they spent in therapeutic INR was approximately 30% (10,15,17). In Tanzania, only 35.5 % patients with mechanical heart valves achieved therapeutic anticoagulation (22). The current findings contrast the revelations from a British population where patients suffering from non-valvular atrial fibrillation were within therapeutic INR for 67.9% of the follow up time time(9). These conflicting reports could be attributable to a number of factors including different patients' population and genetics, study settings and the varying standards of anticoagulation management.

Higher proportions of patients suffering from heart diseases achieved better INRs compared to those with VTEs. Related local studies reported similar observations and attributed it to use of predesigned anticoagulation clinic re-appointment cards (15,17). Possibly adoption of recommendations from previous publications (10,15,17) may also have improved the anticoagulation among patients with valvular abnormalities.

Gender impacted on the level of anticoagulation with the proportion of males who were therapeutically anticoagulated being significantly more than females (51.3% vs. 30.4%; p=0.0398). Related studies have indicated that female gender is a risk factor for poor anticoagulation using warfarin (23,24). In addition, our findings corroborate other regional studies which have shown that significant proportions of females had out-of-therapeutic ranges of INR(17,25). Moreover, previous studies on the outcome of management of cardiovascular diseases among the Western communities have indicated that males have better outcome than females (26). In addition to gender, higher BMI values have been associated with under-anticoagulation (27) while patients' knowledge (17)and adherence(19) have been correlated with better INRs.

The most commonly reported ADR was haemorrhage at 27.8% although related local studies reported lower figures (20.7%) of bleeding episodes among patients with open heart surgery(11). International studies have

reported lower figures of bleeding events such as 15.2 per 100 patient-years in UK(28) and 2.8% in Denmark(29). Other studies have reported that the most common adverse effects of warfarin is bleeding affecting almost 13% of patients(20).

The ADRs to warfarin therapy occurred at therapeutic as well as out-of range INRs as has been revealed in related studies(30). The highest prevalence of ADRs (28.8%) was noted at INR of 3-10 which tallies with other researchers who have indicated that ADRs to warfarin may occur at elevated INRs(31).

There was no gender and age preference in the development of ADRs to warfarin therapy in contrast to some studies that have highlighted that ADRs were more prevalent among the males and patients of older age (32). Similarly, the participants' BMI, employment status, the level of education and tobacco or smoking habits were not significantly associated with development of ADRs to warfarin as has been implicated in associated studies (33).

There was a significant relationship between marital status and ADRs to warfarin, with almost 60.0% of participants without spouses experiencing ADRs (p=0.008). Exploration of our data revealed that majority of participants without spouses were suffering from heart diseases. Related studies indicated that the major adverse effects to warfarin are common in patients with heart valve diseases (11). In addition, some studies have also highlighted that the independent factors for the major adverse effects of warfarin are heart diseases (34). The present study revealed that patients suffering from heart diseases were found to higher INRs suggesting that they were using higher warfarin doses to other participants and as such were likely to experience more ADRs.

Although significant trends in anticoagulation control have been observed in the present study, patients may have overrated or underrated some outcome measures such as the ADRs, which were assessed through face to face interviews. In addition, the study was for a six- months' period and what was occurring at that time may not be reflective of the whole year.

CONCLUSION AND RECOMMENDATIONS

There is need to improve anticoagulation services in Kenyatta National Hospital through monitoring of clinical and laboratory data because less than 50% of the patients are therapeutically anticoagulated and ADRs are prevalent among patients with cardioembolic disorders. Anticoagulation monitoring needs to be intensified among the females and patients with VTEs. Future related studies should correlate anticoagulation control with patient, clinician, or hospital factors impacting on the practice.

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