Patient Associated Factors that Affect Adherence to Warfarin Therapy in a Tertiary Referral Hospital in Kenya

K. MARIITA[1], D. G. NYAMU*[1], C. K. MAINA[1], P. N. KARIMI[1], G. A. MUGENDI[1] AND T. B. MENGE[2]

[1]*Department of Pharmaceutics and Pharmacy Practice, School of Pharmacy, University of Nairobi, P.O. Box 19676-00202, Nairobi, Kenya. Corresponding author: dgitonga@uonbi.ac.ke.*
[2]*Kenyatta National Hospital, P.O. Box 20273-00202, Nairobi, Kenya.*

Warfarin is the most widely used oral anticoagulant but non-adherence to its therapy contributes significantly to sub-optimal anticoagulation control. A cross-sectional study was carried out among 147 adult outpatients at Kenyatta National Hospital to determine the level of adherence and explore the associated factors. Adherence was associated with age, gender heart valve surgery, alcohol consumption, and cost of treatment. On multivariate analysis, the independent variables associated with adequate adherence were age (OR = 0.429, 95% CI = 0.228-0.808; p = 0.009), gender (OR = 0.299, 95% CI = 0.123-0.728; p = 0.008) and the type of thromboembolic disease (OR = 0.385, 95% CI = 0.214-0.690; p = 0.001). Adherence was better among females, older age groups and patients who had undergone heart valve surgery. Adherence was poorer among males, younger participants and patients with venous thromboembolism. We suggest that medication adherence counseling to warfarin therapy should be emphasized in poor-adherent patient populations.

Key words: Warfarin, adherence, patient factors, Kenya

INTRODUCTION

Poor adherence to medicines can limit the benefits of treatment leading to decreased efficacy, greater adverse effect potential, disease relapse, increased medical expenditure, and decreased quality of life [1]. Adherence to treatment is important especially in the management of long term diseases such as thromboembolic disorders. Warfarin is the most widely used oral anticoagulant in the prophylaxis and treatment of venous thromboembolism and atrial fibrillation because of low cost and ease of administration [2]. Dosing of warfarin is complicated by the fact that it has a narrow therapeutic index and therefore non-adherence makes patients vulnerable to serious adverse effects such as bleeding or recurrent thrombosis.

Poor adherence to warfarin has been found to be a major contributor to sub-optimal anticoagulation among patients attending anticoagulation clinics where adherence is emphasized [3]. Adherence has also been significantly associated with achievement of stable warfarin dose and time taken to achieve therapeutic international normalized ratio (INR), with poor adherers taking longer [4]. This has economic implications as patients who are yet to achieve stability on anticoagulation require more frequent clinic visits for monitoring of the INRs and adjustment of warfarin dose. Similarly, adherence to oral anticoagulants is associated with a significant reduction in

*Author to whom correspondence may be addressed.

hospital admissions and total health care cost in some settings, implying that improving adherence to oral anticoagulation is important to attaining the clinical and economic benefits of therapy [5].

Non-adherence is associated with poor anticoagulation control [6-8]. The International Normalized Ratio Adherence and Genetics (IN-RANGE) study demonstrated that poor adherence was potentially a major source of poor anticoagulation control [3]. Adequate adherence was significantly associated with good anticoagulation control in other studies in the United States [9, 10].

Published epidemiological data on the prevalence of atrial fibrillation, thromboembolism and other conditions that require anticoagulation is limited in Africa. One report estimates that there are 1.1 cases of venous thromboembolism (VTE) per 1,000 population in low and middle-income countries [11]. In these countries, VTE associated with hospitalization was the leading cause of disability adjusted life-years (DALYs). Prevalence of atrial fibrillation has been reported to be low at 0.70% in Kenya and 0.67% in Tanzania [12]. The incidence of thrombosis increases rapidly with advancing age [11]. This coupled with lifestyle changes such as physical inactivity, refined diets, alcohol use and smoking are major cause of morbidity and the use of warfarin therapy is likely to increase [13].

Factors associated with adherence to medication are broadly categorized into patient-related, socio-economic, and health system related [14]. Patient related factors include family income and psychosocial factors, among others. At Kenyatta National Hospital (KNH), anticoagulation control is poor [15] and patients associated factors

contributing to this have not been explored. This study sought to determine the level of adherence of patients to warfarin in KNH and explore the associated factors in order to provide a basis for designing strategies to improve it.

METHODS

A cross-sectional study was conducted among 147 adult patients on warfarin attending three out-patient anticoagulation clinics at KNH between March and April 2015. Each clinic operates once a week on separate days. The cardiac clinic serves patients with cardiovascular disorders such as rheumatic heart disease and those with atrial fibrillation. The hemato-oncology clinic serves patients on treatment for VTE and those at high risk of developing thrombosis such as patients with cancer. The cardiothoracic clinic serves patients who have undergone heart valve surgery and are therefore on prophylactic anticoagulation therapy.

Consecutive sampling was used to recruit the patients during the 8 week study period. All eligible patients were invited to participate. The inclusion criteria for the study subjects were patients 18 years and above, taking warfarin, who voluntarily consented to be participate. Patients that were too sick and unable to communicate were excluded from the study. The study was approved by the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee under a reference number KNH-ERC/A/34. Participants' confidentiality was ensured throughout the study.

Data collection

Data was collected using a pre-tested investigator administered questionnaire in a

face to face interview with the patients. The questionnaire was translated to the national language (Kiswahili) and back-translated to English to ensure that the information was consistent. Data recorded included socio-demographics and patient factors that could influence adherence such as family/social support, relationship with prescribers, life style habits, financial implications of treatment, as well as their beliefs, perceptions and attitudes towards anticoagulation therapy.

Adherence was measured using patients' self-report using the 8-point modified Morisky Medication Adherence Scale (MMAS-8) [16]. This was an indirect method of measuring adherence to medication that has been widely used and has a high degree of concordance with pharmacy fill data or electronic monitoring devices [17]. The scale consists of 8 questions designed to describe the medication-taking behaviour of patients.

The first two questions assess unintentional non-adherence due to forgetfulness and carelessness. The next two questions measure intentional non-adherence: stopping medication when feeling better or worse. The last four questions try to identify and address circumstances or situations related to adherence behavior. The addition of this third dimension makes the MMAS-8 scale superior to the original four point scale [17]. The first 7 questions require yes/no responses while the last question is a five item Likert scale question. Adherence favoring responses were allocated a score of zero. Therefore, a score of 0 represented high adherence, 1-2 represented medium adherence, and a score of 3 and above represent low adherence.

Data analysis

The data was entered in a Microsoft Excel spreadsheet version 2010 and then exported to SPSS version 20 software for descriptive and inferential analysis. Patients with high adherence were considered to have adequate adherence. The prevalence of adequate adherence was then computed as the proportion of patients who had high adherence. Bivariate analysis was done to determine associations between the independent variables and adherence. Chi-square tests and Fischer's exact tests were adopted to determine the associations. Variables with p value ≤0.05 were considered significant and therefore, subjected to multivariate analysis. Stepwise backward logistic regression was done to adjust for potential confounders and determine the independent patient factors related to adherence.

RESULTS

Characteristics of the study participants

As captured in Table 1, a majority of the participants were female at 74.1%. Patients who had visited the anticoagulation clinic in the previous one month were 37.4%. More than two thirds of the respondents had been on warfarin for over one year. Warfarin was mainly used for management of VTE (48.6%).

Adherence to warfarin therapy

The patients' self-reported adherence was fairly good as 77 (52.4%) scored high on the MMAS-8 scale. Over a third reported medium adherence while only 17 (11.6%) reported low adherence (Figure 1).

Table 1: Characteristics of the study participants

Characteristic	n (%)
Age group (years)	
18-37	51 (35.4)
38-57	81 (56.3)
> 57	12 (8.3)
Sex	
Female	109 (74.1)
Male	38 (25.9)
Indication for warfarin	
Heart disease/atrial fibrillation	26 (17.8)
VTE	71 (48.6)
Heart valve replacement	50 (33.6)
Duration of warfarin use	
< 3 months	12 (8.2)
3 months – 1 year	33 (22.4)
> 1 year	102 (69.4)
Duration since last visit to anticoagulation clinic	
In the last 1 month	55 (37.4)
Between 1 and 2 months ago	24 (16.3)
> 2 months ago	68 (46.3)

*VTE = venous thromboembolism; N=147.

Patient factors associated with adherence to warfarin

Table 2 shows that adequate adherence to warfarin therapy was significantly associated with patients' age, gender, indication of warfarin anticoagulation, non-alcohol consumption and low cost of treatment. Elderly patients reported higher adherence than younger patients while female patients were more adherent to treatment than their male counterparts. Similarly, those using warfarin as prophylaxis against thromboembolism after heart valve replacement had higher adherence levels than those using warfarin for other indications. Alcohol consumption had a great impact on adherence as non-alcoholics were shown to be highly adherent. The general costs of therapy also influenced adherence to warfarin with high costs having a negative impact. Patients who were financially better had higher adherence compared to those that were adversely affected by these costs.
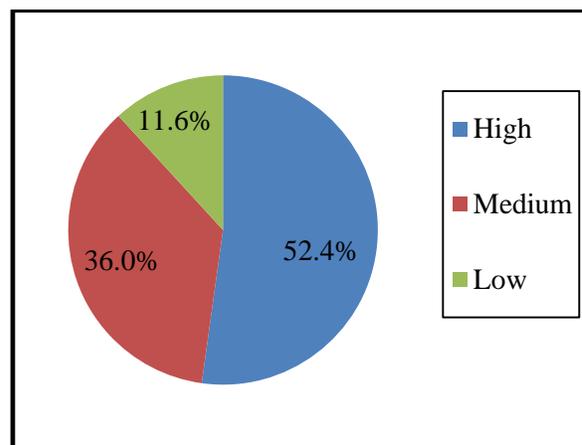

Figure 1. Level of adherence to warfarin therapy.

On multivariate analysis however, independent patient factors associated with adherence were patients' age, gender, and the type of thromboembolic disease as shown in Table 3.

Table 2: Association of patient factors with levels of adherence to warfarin

Variable		Adherence		P-value
		High n (%)	Medium/Low n (%)	
Age group (years)	18-37	20 (13.9)	32 (21.5)	
	38-57	47 (31.9)	36 (24.3)	0.050
	> 57	9 (6.3)	3 (2.1)	
Gender	Male	13 (8.8)	25 (17.0)	0.015
	Female	64 (43.5)	45 (30.6)	
Indication of warfarin	Heart disease	5 (3.4)	21 (14.3)	
	VTE	39 (26.5)	32 (21.8)	0.002
	Valves replacement	32 (21.8)	18 (12.2)	
Alcohol consumption status	Yes	0 (0)	8 (5.4)	
	No	77 (52.4)	62 (42.2)	0.005
Participant's buddies	Alone	12 (8.2)	10 (6.8)	
	Family	69 (46.9)	53 (36.1)	0.776
	Others	1 (0.7)	2 (1.4)	
Patient support from family members	Supported	67 (45.6)	55 (37.4)	
	Not supported	17 (11.6)	8 (5.4)	0.814
Participant's perception on usefulness of treatment	Useful	76 (51.7)	62 (42.2)	
	Not useful	4 (2.7)	5 (3.4)	0.628
Alternative remedies (herbs)	Using	10 (6.8)	6 (4.1)	0.522
	Not using	68 (46.3)	63 (42.9)	
Regularity of adhering to clinic appointments	Regular	15 (10.2)	19 (12.9)	
	Irregular	61 (41.5)	52 (35.4)	0.396
Participant's convenience of coming to clinic	Convenient	49 (33.3)	38 (25.9)	
	Slightly inconvenient	21 (14.3)	18 (12.2)	0.281
	Significantly inconvenient	8 (5.4)	13 (8.8)	
Financial perceptions of anticoagulation therapy	Not costly	13 (8.8)	3 (2.0)	
	Somehow manageable	35 (23.8)	34 (23.1)	0.006
	Very costly	30 (20.4)	32 (21.8)	
Frequency of prescribers counseling on disease state	Always	60 (40.8)	49 (33.3)	
	Sometimes	13 (8.8)	17 (11.6)	0.610
	Never	4 (2.7)	4 (2.7)	

VTE = venous thromboembolism; (N=147).

Table 3: Independent patient factors associated with adherence to warfarin

Variable	Coefficient	S.E. of coefficient	P value	OR	95% C.I. for OR	
					Lower	Upper
Age (years)	-0.847	0.323	0.009	0.429	0.228	0.808
Gender	-1.206	0.453	0.008	0.299	0.123	0.728
Indication of warfarin use	-0.956	0.298	0.001	0.385	0.214	0.690

C.I. = confidence interval; OR = odds ratio; S.E. = standard error.

DISCUSSION

This study found an association between adherence to warfarin and older age, female gender, use of warfarin after heart valve surgery, alcohol non-consumption and affordability of the cost of treatment. Almost half (52.4%) of the patients reported adequate adherence which is consistent with a study conducted in patients attending specialized anticoagulation clinics in New York City that reported 50% adequate adherence to warfarin [9]. Similar findings were demonstrated in Canada and Saudi Arabia. Adherence among patients taking vitamin K antagonists in a Canadian hospital was found to be 52.2% [18] while 46.4% of patients attending anticoagulation clinics in a Saudi Arabia hospital reported high adherence to warfarin [7].

Studies that have shown conflicting findings employed different techniques of adherence assessment. For instance, warfarin non-adherence occurred in 22% of total patient days observed in a study conducted by Cruess *et al.* [19] who used the electronic medication event monitoring system of adherence that captured the date and time of every instance patients opened their medication container. Another study utilized the measurement of treatment adherence (MTA) method and reported 97.2% adherence to warfarin but the authors admitted weak psychometric properties when that tool was adapted to individuals using anticoagulants [20]. Comparatively, the study that has reported the least adherence to warfarin was one done among Korean patients where only 27.5% were reported to be adherent. The definition of adherence in the latter case was much more stringent as patients were assessed on a variety of aspects including following instructions on frequency, dosage, time and precautions of taking warfarin [6].

Younger age has been found to be a predictor of inadequate adherence in multiple studies. In one case control study, non-compliant patients were found to be younger than compliant controls [21]. This was replicated in another study where adequate adherence was significantly associated with older age [9]. Elsewhere, age was similarly found to be a predictor of adherence to both vitamin K antagonists and direct oral anticoagulants [18]. In yet another study, patients below 50 years of age were twice as likely as those above 50 years to have low adherence [7]. Probably younger patients, due to their better physical well-being, have less fear and are less cautious about their health. Alternatively, the younger persons could be busy struggling for financial and social stability in their lives until they forget to adhere to their treatment.

Male gender has been identified as a risk factor of low adherence [18]. In another study, non-compliant cases had 3.5 times the

odds of compliant controls of having been male [21]. A systematic review in the year 2010 also identified studies that reported poor adherence to be associated with male gender [22].

There is limited information regarding psychosocial determinants and adherence to warfarin. A review identified alcohol and drug abuse, lack of family support and psychiatric disease as being inversely related to warfarin use [22]. It was found that those who took alcohol were less adherent probably due to a possible fear of the interaction between warfarin and alcohol or just forgetfulness by patients.

The study also found that patients who could afford treatment had higher adherence which is consistent with a study in Brazil that identified drug cost as a factor influencing adherence [8]. In Brazil, patients who reported adequate adherence spent less on the drug compared to those who reported low adherence. The cost of drugs prescribed to non-adherent patients was on average twice as high as the cost of drugs prescribed to patients who adhered to the treatment. Similarly, adherence was better in patients with higher annual incomes, implying that these patients could afford the treatment [9].

Study Limitations

As common with cross-sectional studies involving face to face interviews, participants could have under reported or over reported their experiences. Some patients especially those over 70 years found it difficult to comprehend the questions. This necessitated further elaboration of the questions and this could have led to distortion of information.

A limited number of variables were measured that may affect adherence. The unmeasured variables such as concomitant drugs may also have an effect on adherence which could not be assessed using MMAS.

CONCLUSION

Adherence to warfarin therapy at this Kenyatta National Hospital is inadequate. Younger age, male sex, non-surgical indications of warfarin anticoagulation, alcohol consumption and high cost of treatment were directly associated with poor adherence. Counseling of patients on warfarin should be emphasized especially to males, young patients, and those on anticoagulation due to non-surgical conditions.

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