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Factors Associated with Time in Therapeutic Range among Patients on Oral Anticoagulation Therapy in a Tertiary Teaching and Referral Hospital in Kenya

S.W. KARURI[1]*, D.G. NYAMU[1], S.A. OPANGA[1] AND T.B. MENGE[2]

[1]*Department of Pharmaceutics and Pharmacy Practice, School of Pharmacy, College of Health Sciences, University of Nairobi, P.O. Box 19676-00202 Nairobi, Kenya.*
[2]*Kenyatta National Hospital, P.O. Box 20273-00202, Nairobi, Kenya.*

Oral anticoagulation with warfarin is challenging owing to the drug's narrow therapeutic index. Achievement of therapeutic range ensures safety and efficacy of warfarin therapy. A retrospective study of four hundred and six patients on warfarin anticoagulation was conducted at Kenyatta National Hospital, Kenya for the period between January 2014 and June 2016. The percentage of follow-up time spent in therapeutic international normalized ratio range was computed by Rosendaal linear interpolation method. Factors associated with this time were also explored. The mean age of the participants was 42.7±16.9 years and the ratio of females to males was 3:1. The mean percentage of time spent in therapeutic international normalized ratio range was 31.1%. Poor anticoagulation control was associated with congestive heart failure (p=0.047) and the independent predictor of time in therapeutic range was renal dysfunction (β= -13.3, 95% CI: -25.9, -0.8, p=0.038) suggesting that management of these patients needs to be intensified.

Key words: Warfarin, time in therapeutic range, oral anticoagulation.

INTRODUCTION

Warfarin is the most widely prescribed anticoagulant used in the management of thromboembolic disorders [1]. It is efficacious and cost effective for most patients [2] although its use is associated with bleeding and thrombotic complications as it has a narrow therapeutic window. Consequently, patients on warfarin therapy require regular monitoring to allow adjustments on the dose to ensure they stabilize in therapeutic international normalized ratio (INR) values of 2.0-3.0 for most indications and 2.5 to 3.5 for patients with prosthetic or mechanical valves [3,4].

Duration of time spent within therapeutic INR is a strong indicator of clinical outcomes and is used as measure of the quality of anticoagulation control [5,6]. The benchmark average duration in therapeutic INR for patients on warfarin therapy is approximately 60% [7,8]. Below this, the benefits of warfarin therapy are not optimized, and risk of complications is increased. Although resource-rich countries such as Sweden and Japan have attained this threshold and provide quality anticoagulation services [9,10], studies in Africa have shown that anticoagulation control is a challenge and warfarin therapy is under-utilized [1,11–13]. Patients are mostly under-anticoagulated possibly due to safety concerns [6]. For instance, in

*Author to whom correspondence may be addressed. Email: sal.karuri@gmail.com

Kenya, bleeding is the major adverse effect associated with warfarin use occurring in about 35% of patients [14,15].

Anticoagulation control is affected by both patient and clinical factors, including age, female gender, short duration on anticoagulants, comorbidities, concurrent use of other medicines known to interact with warfarin, diet and genetics, among others [16–18]. There is scant literature on this in our setting, hence this study sought to identify factors associated with time in therapeutic INR range among patients on warfarin therapy on follow up at the largest teaching and referral hospital in Kenya.

METHODS

This was a retrospective study that reviewed data from files of patients treated with warfarin and on follow-up at Kenyatta National Hospital (KNH), Kenya between January 2014 and June 2016. The hospital is the largest teaching and referral hospital in the country, managing approximately 200 out-patients on warfarin every month in the cardiac, hemato-oncology and cardiothoracic clinics. A list of patients requiring anticoagulation with warfarin was generated from the KNH health records database. Universal sampling method of patient files that could be retrieved and met the inclusion criteria was done. The study included all files of patients on warfarin for various indications with at least two INR readings during the study period but excluded those who had been on warfarin for less than one month for better assessment of anticoagulation control. A total of 406 patient files were included in the study.

Structured data collection forms were used to collect information from patient files on demographics, indication for anticoagulation, duration of warfarin therapy, date of INR test and corresponding INR results recorded during the study period. In addition, comorbidities and drugs concomitantly prescribed with warfarin were also extracted. The average percentage of time the INR was in the therapeutic range (TTR) was determined using the Rosendaal linear interpolation method [19], whereby the change between two consecutive INRs was assumed to be linear over that specific time interval. Time in sub-therapeutic and supra-therapeutic INR was calculated in the same way. Patients were stratified per TTR values of 50% and above ($\geq$50%) and below 50% (<50%) and the proportion of patients with TTR below 50% were considered to have poor anticoagulation control.

Statistical analysis was performed using IBM SPSS version 22 software. The factors associated with percentage time in the therapeutic INR range were analyzed in multilinear regression models to determine independent predictors of the outcome. Results with p-value <0.05 were statistically significant. Ethical approval was granted by the KNH/UON Ethics and Research Committee vide reference KNH-ERC/A/123.

RESULTS

One thousand and nine patient files were retrieved for the study. However, data were analyzed from 406 files as the rest did not meet the inclusion criteria. The mean age of the participants was 42.7 years (16.9) and majority of them were female (74.1%). Most of the patients

required anticoagulation due to venous thromboembolism (VTE) arising from deep venous thrombosis (72.4%) and pulmonary embolism (10.1%), whereas patients with prosthetic valves (7.6%), atrial fibrillation (6.9%) and valvular heart disease (6.9%) were less common. The mean duration on warfarin therapy was about 9 months (± 12.7 months) and about 80% of the patients had used warfarin for less than a year.

Figure 1 shows that approximately 40% of the patients had comorbidities that may influence INR. HIV was the commonest (15.5%) followed by hypertension (14.3%) and cancer (10.3).

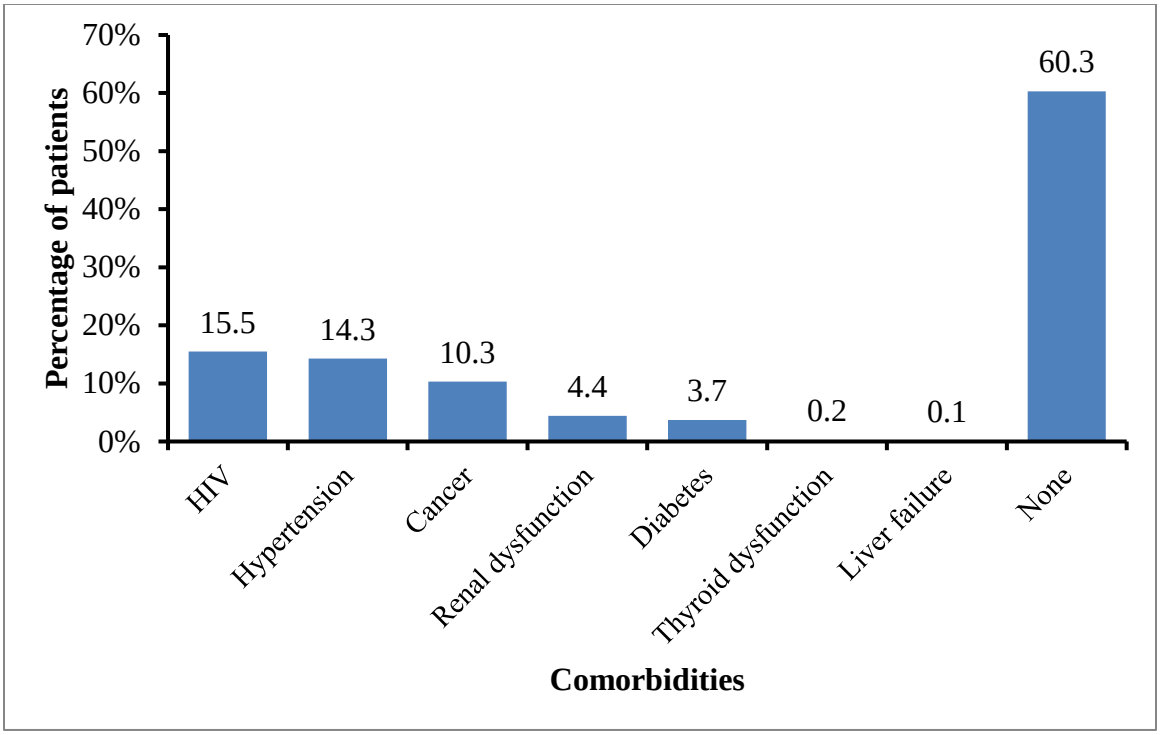

Figure 1: Comorbidities that may influence anticoagulation control.

Table 1 shows that majority (95%) of the patients were on concurrent medicines known to interact with warfarin. Antithrombotics were the most commonly used (78.3%) followed by antimicrobials (39.2%) and analgesics (35.2%). The mean percentage of follow up time patients were in therapeutic INR was 31.1% (±26.7) and as shown in Figure 2, almost half of the follow-up time was spent in sub-therapeutic INR.

About a quarter of the patients were in therapeutic range for 0-10% of follow-up time and only a fifth of them were in therapeutic range 50% or more of their follow up time (Figure 3). Analysis showed that congestive heart failure was the only significant factor associated with poor anticoagulation control of TTR less than 50% (p= 0.047) (Table 2).

Table 1: Concurrent drugs interacting with warfarin used by study participants

Group	Group frequency n (%)	Class	Class Frequency n (%)
Antimicrobials	159 (39.2)	Antibacterial	152 (37.4)
		Antifungal	10 (2.5)
		Antiviral	51 (12.6)
Analgesics	143 (35.2)	NSAIDS	49 (12.1)
		Opioids	113 (27.8)
		Paracetamol	2 (0.5)
CNS drugs	11 (2.7)	Anticonvulsants	11 (2.7)
		Antidepressant	1 (0.2)
Cardiovascular drugs	83 (20.4)	Antiarrhythmics	69 (17.0)
		Statins	20 (4.9
Antithrombotics	318 (78.3)	Anticoagulants	317 (78.1)
		Antiplatelets	14 (3.4)
Immunosuppressant	17 (4.2)	Corticosteroids	17 (4.2)
Gastrointestinal	103 (25.4)	Proton pump inhibitors	103 (25.4)

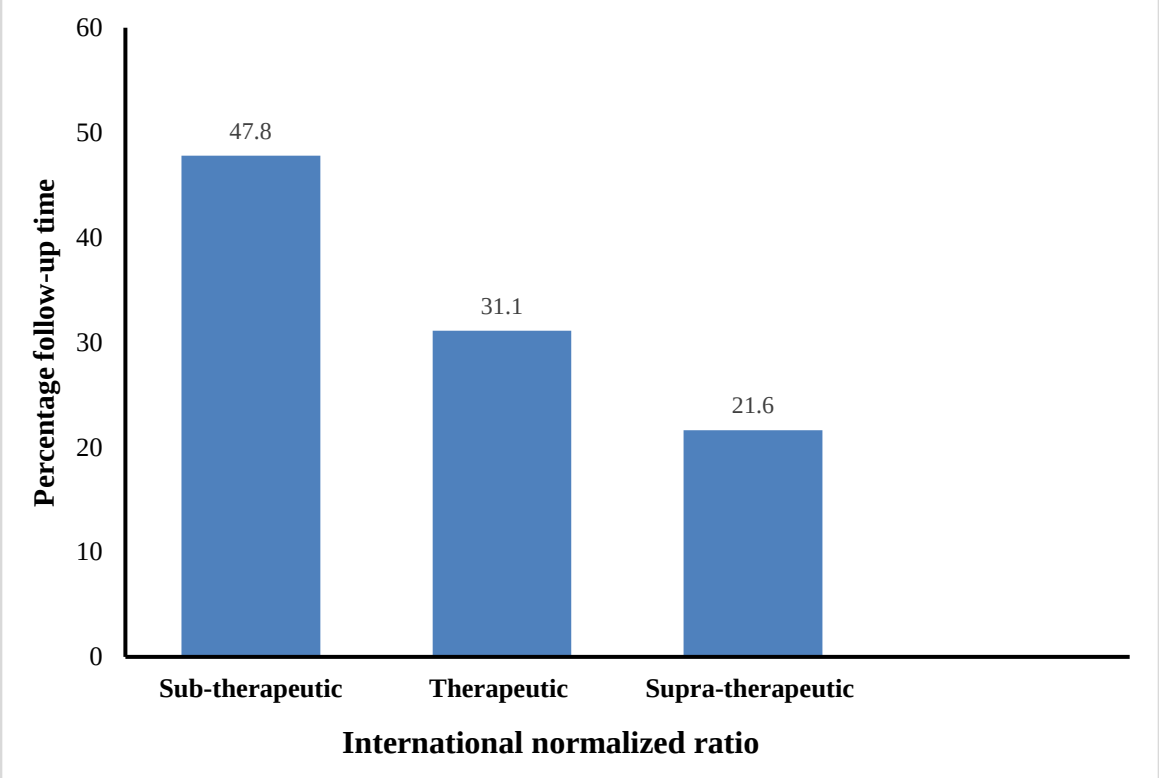

Figure 2: Percentage follow-up in therapeutic range for study participants

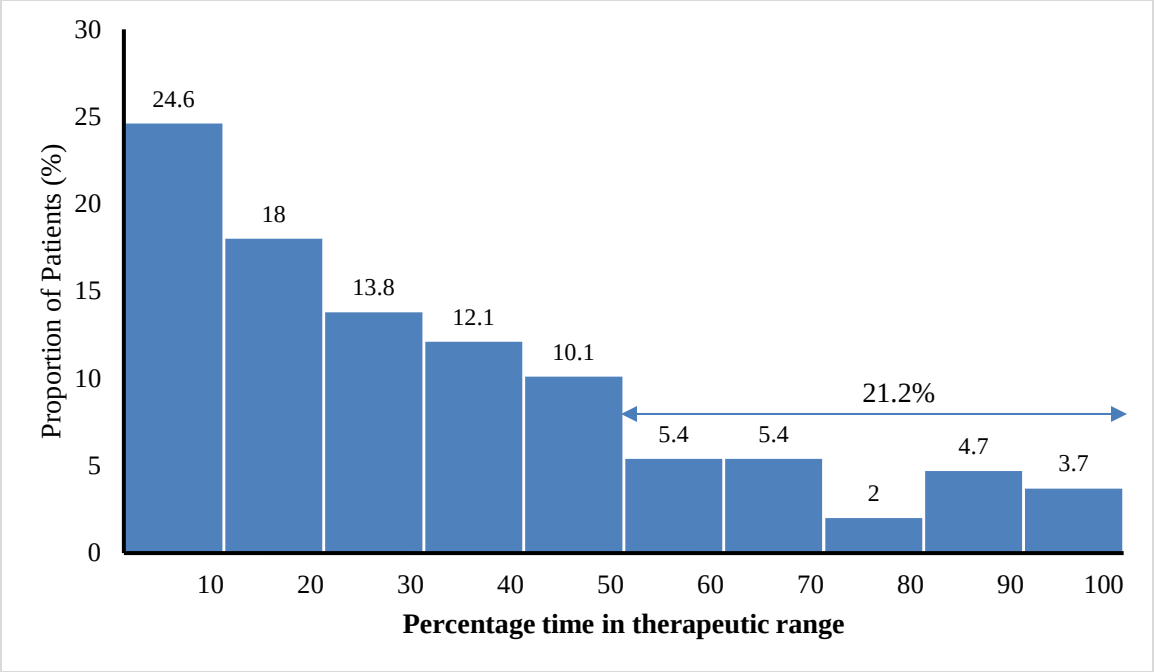

Figure 3: Percentage time in therapeutic INR versus proportion of patients.

Table 2: Factors associated with spending less than 50% of follow up time in therapeutic INR

	Patient proportion			
Variable	**TTR<50% of time n (%)**	**TTR≥50% of time n (%)**	**OR (95% CI)**	**p-value**
Age (years)				
0-18	20 (74.1)	7 (25.9)	0.9 (0.3-28)	0.836
19-35	96 (80.0)	24 (20.0)	1.2 (0.5-3.0)	0.627
36-65	174 (78.7)	47 (21.3)	1.2 (0.5-2.6)	0.738
>65	29 (76.3)	9 (23.7)	1.0	
Gender Male	84 (80.0)	21 (20.0)	1.1 (0.6-2.0	0.679
Marital status Married	178 (77.7)	51 (22.3)	0.9 (0.6-1.4)	0.891
Employment status Employed	210 (76.9)	63 (23.1)	0.7 (0.4-1.2)	0.247
Religion Christian	311 (78.5)	85 (21.5)	0.9 (0.2-4.4)	0.911
Educational level Primary and below	173 (81.6)	39 (18.4)	1.5 (0.9-2.4)	0.114
Alcohol consumption	35 (77.8)	10 (22.2)	1.0 (0.5-2.0)	0.891
DVT	232 (78.9)	62 (21. 1)	1.1 (0.7-1.9)	0.721

PE	29 (70.7)	12 (29.3)	0.6 (0.3-1.3)	0.197
Valvular heart disease	19 (67.9)	9 (32.1)	0.5 (0.2-1.3)	0.230
Atrial fibrillation	21 (75.0)	7 (25.0)	0.8 (0.3-2.0)	0.633
Congestive heart failure	14 (100.0)	0	-	**0.047**
Thrombophilia	3 (100.0)	0	-	1.000
Prosthetic valves	27 (87.1)	4 (12.9)	1.9 (0.6-5.6)	0.229
Stroke	1 (50.0)	1 (50.0)	0.3 (0-4.4)	0.383
Duration of OAC use				
1-3 months	147 (78.6)	40 (21.4)	1.1 (0.6-2.0)	0.840
4-12 months	110 (78.1)	29 (20.9)	1.1 (0.6-2.1)	0.776
>12 months	62 (77.5)	18 (22.5)	1.0	
Frequency of monitoring				
<7 Days	57 (93.4)	4 (6.6)	2.4 (0.2-24.8)	0.470
7-14 days	78 (75.0)	26 (25.0)	0.5 (0.1-4.3)	0.530
15-30 Days	87 (73.7)	31 (26.3)	0.5 (0.1-4.0)	0.490
31-90 Days	91 (78.4)	25 (21.6)	0.6 (0.1-5.3)	0.651
91-180 Days	6 (85.7)	1 (14.3)	1.0	
Comorbidities				
Diabetes	5 (33.3)	10 (66.7)	1.9 (0.6-5.7)	0.331
Hypertension	13 (22.4)	45 (77.6)	1.1 (0.6-2.1)	0.863
Thyroid dysfunction	0	1 (100.0)	-	1.000
Liver failure	0	1 (100.0)	-	1.000
Renal dysfunction	1 (5.6)	17 (94.4)	0.2 (0-1.6)	0.139
Cancer	8 (19.0)	34 (81.0)	0.9 (0.4-1.9)	0.843
HIV	16 (25.4)	47 (74.6)	1.3 (0.7-2.4)	0.406
Others	1 (16.7)	5 (83.3)	0.7 (0.1-6.3)	1.000
Concurrent medicines				
Antibacterial	35 (23.0)	117 (77.0)	1.2 (0.7-1.9)	0.544
Antifungal	2 (20.0)	8 (80.0)	0.9 (0.2-4.4)	0.911
Antiviral	12 (23.5)	39 (76.5)	1.2 (0.6-2.3)	0.696
NSAIDS	7 (14.3)	42 (85.7)	0.6 (0.3-1.3)	0.194
Opioids	23 (20.4)	90 (79.6)	0.9 (0.5-1.6)	0.743
Paracetamol	0	2 (100.0)	-	0.459

Anticonvulsants	1 (9.1)	10 (90.9)	0.4 (0.1-2.9)	0.312
Antidepressants	0	1 (100.0)	-	1.000
Antiarrhythmics	13 (18.8)	56 (81.2)	0.8 (0.4-1.6)	0.565
Statins	3 (15.0)	17 (85.0)	0.6 (0.2-2.2)	0.472
Anticoagulants	73 (23.0)	244 (77.0)	1.6 (0.9-3.0)	0.138
Antiplatelets	2 (14.3)	12 (85.7)	0.6 (0.1-2.7)	0.743

As shown in Table 3, patients with pulmonary embolism spent a higher percentage of follow-up time in therapeutic range than those without pulmonary embolism (p=0.038). On the other hand, patients with renal dysfunction spent significantly lower percentage of follow up time (17.5%) in therapeutic range compared their counterparts (31.7%, p=0.027).

Table 3: TTR versus clinical characteristics of study participants

Variable		**Time in the therapeutic range**		
		n (%)	**Mean (%)**	**p-value**
DVT	Yes	294(72.4)	29.7	0.079
	No	112 (27.6)	35.0	
Pulmonary embolism	Yes	41(10.1)	39.3	**0.038**
	No	365(89.9)	30.2	
Valvular heart disease	Yes	28(6.9)	39.8	0.074
	No	376(93.1)	30.5	
Atrial fibrillation	Yes	28(6.9)	31.6	0.923
	No	376(93.1)	31.1	
CHF	Yes	14(3.4)	25.1	0.389
	No	392(96.6)	31.4	
Prosthetic valves	Yes	31(7.6)	28.8	0.613
	No	375(92.4)	31.4	
Duration on OAC	1-3	187(46.1)	30.2	
(months)	4-12	139(34.2)	29.9	0.294
	>12	80(19.7)	35.3	
Comorbidities				
Diabetes	No	391(96.3)	31.1	0.912
	Yes	15(3.7)	31.7	
Hypertension	No	348(85.7)	30.8	0.642
	Yes	58(14.3)	32.6	
Renal dysfunction	No	388(95.6)	31.7	**0.027**
	Yes	18(4.4)	17.5	
Cancer	No	364(89.7)	31.4	0.447
	Yes	42(10.3)	28.1	
HIV	No	343(84.5)	31.5	0.521
	Yes	63(15.5)	29.1	

Key: DVT: deep vein thrombosis, CHF: congestive heart failure, OAC: oral anticoagulation, HIV: human immunodeficiency virus, PE: pulmonary embolism.

On multilinear regression analysis using backward stepwise method to determine the independent predictors of TTR (Table 4), presence of renal dysfunction was the only significant factor that reduced time in therapeutic range (β= -13.3%, p= 0.038).

Table 4: Predictors of percentage follow up time in TTR among study participants

Variable	β co-efficient	95% CI	p-value
Pulmonary embolism	8.4	0.2, 17.1	0.054
Renal dysfunction	-13.3	-25.9, -0.8	**0.038**

DISCUSSION

The study comprised mostly of married adults with a mean age of 43 years where majority of them were females (74%). These findings are consistent with other studies done in KNH [11,20]. This female predominance is comparable to studies done elsewhere [12,18,21]. Conversely, several other studies have recorded a male majority [6,9,10]. Patients maintained therapeutic INR levels only a third of the follow-up time indicating that they are at increased risk of complication since TTR has been used as a surrogate measure of outcomes [6,9]. This suboptimal level of anticoagulation is consistent with studies in Nigeria and South Africa [12].

One recent study in KNH that used the cross-section-of-files method of TTR determination recorded a slightly higher TTR of about 44% [20]. Our study however, used the Rosendaal interpolation method which considers the follow-up time. In contrast, patients followed up at Eldoret, Kenya attained better anticoagulation control comparable to many resource-rich countries with TTR levels of about 65% [22]. This difference could be attributed to the dedicated anticoagulation clinic managed by pharmacists hence better patient care as compared to usual physician follow-up clinics in our setting. Studies done in similar follow-up clinics have comparable results [23,24]. In these anticoagulation clinics, patients are followed up more intensely, taken through detailed patient education counselling and standardized management protocols availed for dosage adjustment [22,23].

Similar to many studies [10,11,25], we found that patients were more under-anticoagulated than over-anticoagulated when outside the therapeutic range. This could be because clinicians are more concerned about the safety of warfarin [6]. In contrast, one study done in Ethiopia found that more than half of the patients were over-anticoagulated while only about 13% had sub-therapeutic INR [21]. However, the methodological differences could account for this disparity. The nearest INR values at the time of screening for drug interactions or bleeding were used to determine these proportions whereas the Rosendaal interpolation method was used in our study. The poor level of anticoagulation control in our setting illustrates the need for closer monitoring, better dosage adjustment and more intense patient education so that there is maximum benefit from anticoagulation with

minimal risk of thromboembolic and bleeding complications.

Only a fifth of the patients maintained an adequate anticoagulation level for 50% or more of their follow up time indicating poor anticoagulation control for the majority. Higher patient proportions were recorded elsewhere [6,26]. Similar to a study by Apostolakis *et al*. [27], we found that congestive heart failure was significantly associated with poor anticoagulation control. In addition to the potential drug interaction between warfarin and medicines used to treat CHF, congestive heart failure is a risk factor for over-anticoagulation as it interferes with the plasma distribution of warfarin [28,29]. Additionally, it activates the coagulation cascade and causes endothelial dysfunction by activating the neuroendocrine system [30].

We did not find any association between poor anticoagulation and age, female gender, interacting medicines and duration on anticoagulants contrary to several other studies [16,18,27,31]. We however found that renal dysfunction was an independent predictor of reduced TTR (β= -13.3, p=0.038). This finding is consistent with the Veterans Affairs Study To Improve Anticoagulation (VARIA) [16]. Since patients with kidney disease are more likely to be outside therapeutic range because renal dysfunction interferes with systemic clearance of warfarin [32], closer monitoring and appropriate dosage adjustment in these patients is important to minimize risk of bleeding. Different studies have shown a variation in the comorbidities that affect anticoagulation including COPD, heart failure, cancer [31] liver dysfunction, diarrhea, fever [29] and HIV [22]. Therefore, due to this variation there is need for closer follow-up of any patient with comorbidities to ensure they remain within therapeutic range.

CONCLUSION

TTR in patients on anticoagulation follow-up at KNH is sub-optimal with majority of them being under-anticoagulated for most of the time. Renal dysfunction and congestive heart failure were associated with poor anticoagulation control hence need for better management of these patients. Further research to show the effect of TTR and outcome of therapy should be investigated.

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