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Warfarin prophylaxis for arterial thromboembolism: Age is the prime dose determinant and atrial fibrillation is the main indication in an Afro-Arab Ethinic community

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Keywords

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Introduction

Arterial Thromboembolism (TE), is due to a heterogeneous group of disorders that associate with faulty hemostasis with consequent vascular thrombosis and embolism [1], the sequel of the latter are sometimes lethal. The arterial TE disorders including prosthetic valves, are predominantly presented by atrial fibrillation (AF) and strokes [2]. Though, the management of the primary disorder is a target, warfarin therapy is a lifesaving management and prophylaxis. Warfarin, works by inhibiting synthesis of vitamin-K dependent clotting factors II, VII, IX, X and proteins C and S [3]. It is transported bounded to protein, extensively metabolized by the liver microsomal enzymes, cytochromes P450s, to warfarin alcohols [3], thus, drug-drug interactions could occur with drugs that share the same metabolic pathway. About 85% of warfarin is excreted in urine as metabolites [3].

The optimum warfarin dose determination is a major challenge in clinical practice as warfarin is characterized by a narrow therapeutic index, pronounced inter-individual dose variability and fatal consequences of under and over dosing [4]. Therefore, it worth to define the warfarin indications, and dose determinants anywhere, and to monitor the warfarin dose using the international normalized ratio –INR. This study aimed to define the arterial TE disorders that necessitate warfarin therapy and to explore the reasons behind the variation in warfarin dose in a multiethnic society in central Sudan. Undeniably, the patient genetic makeup and ethnicity are important players in dose variability, in addition to age, sex, diet, smoking, alcohol, and pathological indication for warfarin treatment and co-morbidities [5].

Methods

A cross sectional study was conducted between Nov 2019 and Jan 2020, in Ahmed Gasim Cardiac Centre, one of the main reference hospitals for cardiology in Khartoum. The main inclusion criteria were; adult male or female patient on warfarin therapy, while patients with any organ failure or on drug/s known to have a major interaction with warfarin, and severely ill patients as judged by clinical practitioners (e.g. hospitalized patients, debilitated patients, cancer patients), were excluded. All patients attended the anti-coagulant clinic were included. The study was approved by the ethical committee of Sudan Medical Speciation Board (SMSB). Informed consent was obtained from all patients. Data was collected using a questionnaire, which included personal, demographic and life style data, past medical and drug history, in addition to the clinical examination and investigations.

Patient at high risk of TE were prescribed warfarin tablets. An initial empirical dose of 5 mg/day for 4 consecutive days or 10 mg/day for day 1 & 2 and 5 mg for day 3, then the INR was measured on day 5 or day 4, respectively. Accordingly the warfarin dose was adjusted to keep the INR between 2.3 to 3.5. The data was analyzed through software program Sigma Stat.

Results and Discussion

As seen in (Table 1), 175 participants were included in this study, with comparable male to female ration (92 vs. 83), and age (median, 25%-75%, 51.0, 33.0-60.0 vs. 40.0, 31.0-59.8, respectively, P = 0.226, Mann-Whitney Rank Sum Test (MW), with a mean (± SD - standard deviation) age of 45.9 ± 15.1 yrs. The patients were categorized into 7 groups based on the disorder/s for which warfarin was prescribed; atrial fibrillation -AF (30.9%), stroke (8%), valve replacement -VR (6.3%), idiopathic thromboembolism –TE (5.1%), AF+VR (40%), double pathology (d-Path - combination of any 2 of the previous 4 disorders) (4.6%), and triple pathology -t-Path (4.6%). However, the commonest indication for warfarin was AF, whether in patients underwent VR or primary AF, which accounted for about 71% (Table 1). Noticeably, there was marked variation in age between the groups (Figure1-i A).

The average Pt-INR-adjusted warfarin dose was 5.0, 3.0-6.0 mg/day, with broad range of 1.0 to 9.5 mg/day. Males and females required comparable doses of warfarin; 5.0, 3.0 - 6.0 *vs.* 5.0, 3.0 - 6.0, P = 0.536, MW, i.e., the warfarin dose was not influenced by sex in the present study as reported elsewhere [6], although women were shown before to require lower doses than men [7]. However, there was significant variations in the adjusted warfarin dose for the different disorders (Figure 1-i B), ranked as follows; VR (5.0, 4.3-7.0 mg/day), VR/AF (5.0, 4.0-6.0), d-Path disorders (5.0, 3.0-6.5), t-Path (4.0, 3.0-5.0), AF and stroke (3.0, 3.0-5.0, each) and TE (3.0, 3.0-5.5), P<0.001, Kruskal-Wallis One Way Analysis of Variance on Ranks (KW). However, there was also marked variations in age between the 7 groups, ranked from oldest (60.0, 55.0-65.0 yrs.) to youngest (34.0, 30.3-38.8) as follow; stroke, TE, AF, t-Path, d-Path, AF/VR and VR, P <0.001, KW (Table 1 & Figure 1-i A). The interpretation of the combined observations was that the differences in the doses were basically due to differences in ages only. Adjusting for age by stratification and grouping of the conditions associated with low warfarin dose (TE, stroke and AF) *vs.* high warfarin dose (VR, VR/AF and d-Path), the required warfarin dose was turned to be comparable, 5.0, 3.0-6.0 *vs.* 5.0, 3.0-

6.0 mg/day, respectively, P = 0.648, MW, contrasting other studies [8]. Moreover, the warfarin dose was strongly negatively correlated with age, CC -0.723, P <0.001, Pearson Product Moment Correlation (Figure 1.ii upper). Furthermore, the warfarin doses for all patients aged <40 yrs., (6.0, 5.0-7.0 mg/day), 40 to 60 yrs., (3.0, 3.0-5.0) and >60yrs., (3.0, 2.0-3.0), respectively, were different, P <0.001, MW.

Most participants (78.9%) were within the normal BMI, 18.2% were overweight and 2.9% were underweight. However, there was significant BMI variation between the disorders, P = 0.001, T-test, with mean (± SD) BMI 22.7 ± 2.6 kg/m^2 (Table 1). Worth noting, the warfarin dose was not correlated with the BMI, CC -0.081, P = 0.285, Pearson Product Moment Correlation (Fig. 1-ii mid), and it was comparable between the underweight (6.0, 4.25-7.0, mg/day), normal weight (5.0, 3.0-6.0) and overweight patients (3.0, 3.0-5.0), P = 0.109, MW. Though were not significant the differences in warfarin dose can be explained by the difference in age; 20.0, 20.0 - 23.3, 43.5, 31.0 - 60.0, and 55.0, 38.0 - 60.0, respectively, P<0.001, MW. In contrast, one study reported a positive strong correlation between warfarin dose and BMI [9].

Only 12.6% of the study subjects were smokers, while only 1.1% were alcohol consumers. Unexpectedly, smokers required lower warfarin dose than non-smokers, 3.0, 3.0 - 5.0 *vs.* 5.0, 3.0 - 6.0, P = 0.008, MW, and were achieved lower Pt-INR score, P = 0.064, MW. However, the smoker were older than the non-smokers, P<0.001, MW, and more obese, P = 0.041, MW. After correction for age by stratification, the warfarin dose was found to be comparable between the two groups, 3.0, 3.0 - 5.0 vs. 3.0, 3.0 - 4.0, P = 0.299, MW. Increased warfarin dose was previously shown to be associated with smoking [5].

The comorbidities associated with warfarin-treated disorders, were diabetes mellitus (DM) 23.4%, DM plus hypertension - DM/HTN (8.6%), and HTN alone (2.3%) (Table 1). Patients with DM or HTN compared to non-diabetic, or non-hypertensive patients, were received significantly lower warfarin dose, P <0.001, MW. However, the former were markedly older than the latter, P <0.001, MW, thus, both comorbidities were not determinants for warfarin dose after correction for age (Table 1 supplementary). The HTN was previously shown to influence the warfarin dose [10]. In contrast, patients with and without liver diseases (LD) were received comparable doses of warfarin, P = 0.581, MW. Similarly, the patients with and without renal disease (RD), had comparable doses, P = 0.408, MW (Table 1 supplementary). However, the number of patients were relatively small, and the liver and kidney function were not tested. The implications of the liver and renal diseases were more relevant in relation to the warfarin dose rather than the TE per se. since the liver is the main site for warfarin metabolism and the kidney is the main route for excretion [3].

The mean INR for all patients was 2.4 ± 0.4, with range between 1.3 and 3.5. The Pt-INR values were significantly different between the different disorders, P <0.001, KW (Figure 1-i C), even after correction for age, P <0.001, KW, but still within the normal range for all groups, 2.3 – 3.5. The highest median Pt-INR was of the VR (2.5, 2.35-2.75) and VR+AF patients, followed by the t-Path and d-Path, then the AF, while the lowest Pt-INR was of stroke and the TE (2.1, 1.98-2.13). Finally, the warfarin dose was not correlated with the Pt-INR, CC 0.070, P = 0.355, Pearson Product Moment Correlation (Figure 1-ii lower). Taking all the above results together, age was proved to be the only determinant for the warfarin dose, which was

inversely correlated with the dose (Figure 1-ii upper). Interestingly, patients younger than 40 yrs., their adjusted warfarin dose was double that of the patients >40 yrs. The reduced warfarin dose with aging was consistently noticed worldwide [6].

Table 1: Characteristics and distribution of the study participants according to warfarin indications (disorders).

Diagnosis	Number	Sex (M/F)	Age (Years)	BMI Kg/m^2	Co-morbidity		
					DM	HTN	DM/HTN
Atrial fibrillation (AF)	30.9% (54)	33:21	55.0, 35.0-65.0	22.7 ± 2.0	19	0	3
Stroke	08% (14)	11:03	60.0, 55.0-65.0	24.2 ± 3.0	1	0	11
Valve replacement (VR)	6.3% (11)	05:06	34.0, 30.3-38.8	20.9 ± 2.8	0	0	0
Thromboembolism (TE)	5.1% (9)	05:04	58.0, 45.5-65.0	24.7 ± 2.0	0	2	1
AF+VR	40% (70)	36:34	35.0, 31.0-53.0	22.6 ± 2.4	17	2	0
Double pathology (d-Path)	4.6% (8)	00:08	36.5, 31.5-53.5	22.8 ± 2.4	2	0	0
Triple pathology (t-Path)	4.6% (8)	02:06	48.0, 33.0-56.5	20.6 ± 4.4	2	0	0
P			<0.001	0.001			
Other	0.6 (1)	00:01	33	23.7			
Total	175	92:83 1.1:1	Mean (45.9 ± 15.1) Range (18.0-81.0)	22.7 ± 2.6	41 (23.4%)	4 (2.3%)	15 (8.6%)

M/F, male/female; BMI, body mass index; DM, diabetes mellitus; HTN, hypertension

Sup Table 1: Comparisons between study subjects based on co-morbidity grouping: daily warfarin dose, age and Pt-INR.

Disease	Warfarin dose / age		*p*	Pt-INR		*p*
	Co-morbidity			Co-morbidity		
	Yes	No		Yes	No	
Liver disease Warfarin (mg) Age (yrs.)	(8) 4.0, 3.0 - 5.5 57.5, 43.0 - 62.5	(167) 5.0, 3.0 - 6.0 45.0, 31.25 - 60.0	0.581 0.151	2.3, 2.1 - 2.5	2.3, 2.1 - 2.6	0.689
Renal disease Warfarin (mg) Age (yrs.)	(20) 3.5, 3.0 - 6.0 54.0, 31.0 - 62.5	(155) 5.0, 3.0 - 6.0 45.0, 32.0 - 60.0	0.408 0.597	2.35, 2.15 - 2.5	2.3, 2.1 - 2.6	0.674
Diabetes mellitus Warfarin (mg) Age (yrs.)	(56) 3.0, 3.0 - 5.0 59.5, 50.5 - 65.0	(119) 5.0, 3.25 - 6.0 35.0, 31.0 - 55.0	<0.001 <0.001	2.2, 2.1 - 2.5	2.3, 2.2 - 2.6	0.008
Hypertension Warfarin (mg) Age (yrs.)	(19) 3.0, 3.0 - 3.0 60.0, 60.0 - 66.5	(156) 5.0, 3.0 - 6.0 40.0, 31.0 - 58.0	<0.001 <0.001	2.1, 2.1 - 2.2	2.3, 2.2 - 2.6	0.038

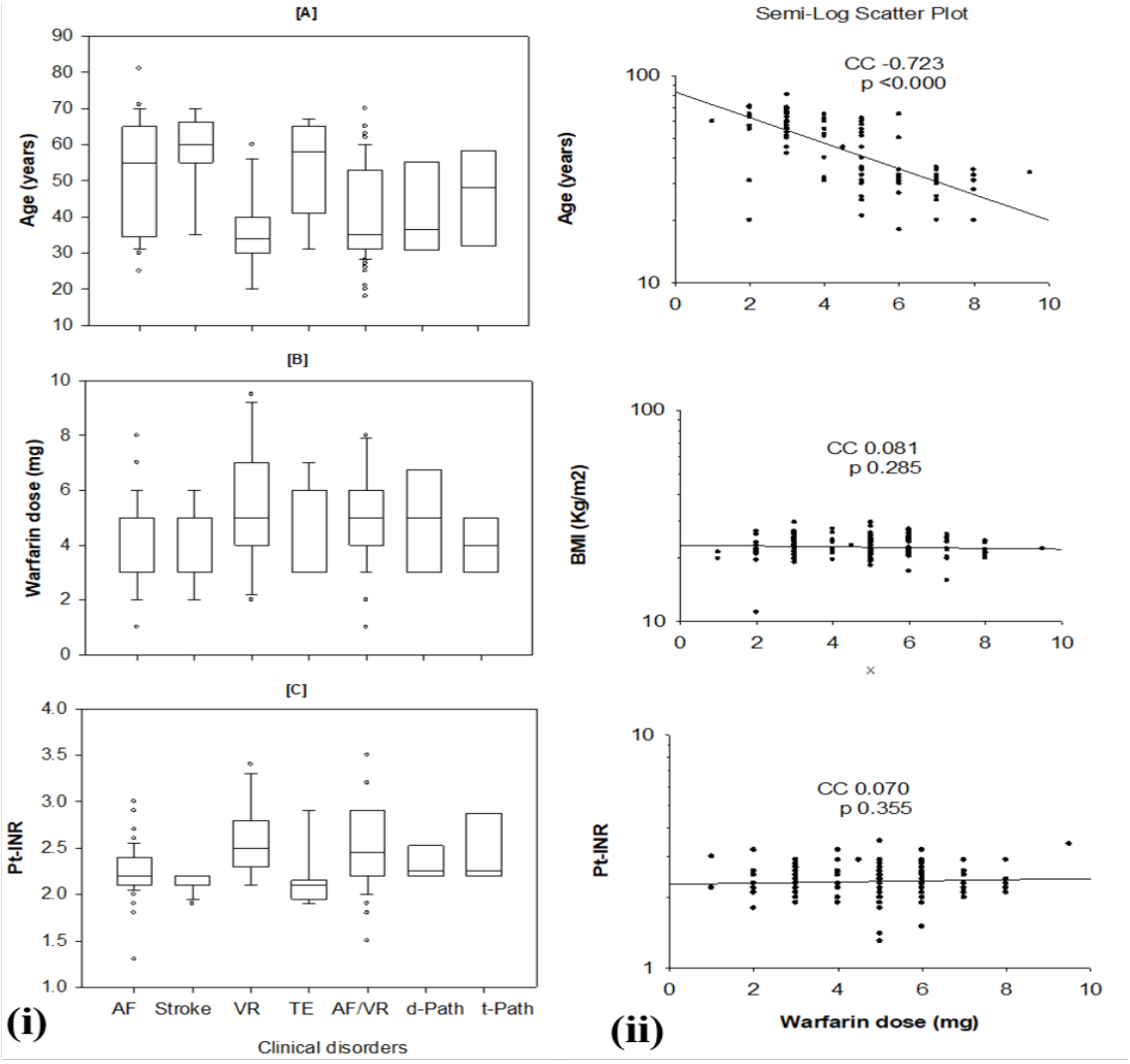

Figure 1: **i.** The median warfarin dose **(A)** and Pt-INR levels **(B)** for the different warfarin-treated clinical disorders, and the median age of the subjects in each disorder group **(C)**, the differences between the clinical disorders in the 3 figures were significant, p <0.001, KW. In **(A)**, disorders that required the lowest warfarin dose, had the lowest Pt-INR (B), and associated with the oldest age groups **(C)** [AF, stroke, and TE], and the disorders that required highest warfarin dose were, [VR, VR/AF and d-Path], while the t-Path group had intermediate age and required intermediate dose. In all figures, the bars bottoms and tops are the 25% and 75% percentiles, respectively, with the horizontal line in between is the median, the upper and bottom caps of the vertical lines are the 95% and 5% percentile and the individual circles are outliers.
ii. Correlation of the warfarin dose with patients' age, BMI and Pt-INR. The semi-log scatter plot and scatter plot (upper) shows strong negative correlation between the warfarin dose and age for all study subjects, CC (correlation coefficient) -0.723, p <0.001, while there was no correlation for the warfarin dose with BMI, CC-0.0812, *p* 0.285 (middle) or Pt-INR CC 0.0703, p 0.355 (lower).

Conclusion

In conclusion, the arterial TE indications for warfarin therapy in a multiethnic community were; AF stroke, VR, idiopathic TE, AF+VR, and their combination, however, AF and VR alone and in combination with other disorders were accounted for 85.7% of the warfarin indications. The median daily warfarin requirement was 5.0, 3.0-6.0 mg. On initial analysis, we found no influence for sex, BMI, liver or renal disease on the warfarin dose. Though, significantly low warfarin doses were associated with AF, stroke and idiopathic TE disorders, and DM and HTN comorbidities and smoking, after correction for cofounders, only age

remained as warfarin dose determinant, and it was inversely correlated with the dose. Interestingly, after the age of 40 yrs., the warfarin dose was cut to the half. Finally, it remains to know the molecular role played by age.

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