Indications for warfarin use and determinants of adequate control in patients using warfarin in Central Sudan

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Abstract

Arterial thromboembolism (TE) is associated with several disorders that necessitate warfarin therapy as a lifesaving management and prophylaxis; however, warfarin is characterized by a narrow therapeutic index and wide dose variability. Accordingly, warfarin indications and doses need to be defined in each locality. A total population, cross sectional, hospital based study was conducted in central Sudan (2019/2020). All patients (n=175) were under warfarin treatment, 44.6% of them were <40 years (mean age 45.9±15.0), with comparable sex distribution. The warfarin doses were adjusted to maintain a Pt-INR of 2.0-3.5. The indications for warfarin were; atrial fibrillation -AF (30.9%), previous stroke (8%), valve-replacement -VR (6.3%), idiopathic TE (5.1%), AF/VR (40%), and their combination (9.2%), however, AF and VR were accounted for 85.7%. Patients with AF, TE, and stroke required significantly lower warfarin doses compared to others, $p<0.001$. Moreover, diabetes mellitus and hypertension comorbidities were associated with low warfarin doses, $p<0.001$, unlike renal and liver disease comorbidities. Furthermore, there was significant inverse correlation of

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warfarin dose with age, CC -0.723, p<0.001, but not with Pt-INR or BMI. Finally there was significant association between low warfarin dose and smoking, p 0.008, but not with sex, p 0.536, or overweight, p 0.109. Importantly, after correction for cofounders only age remained a determinant for warfarin dose, p<0.001. On conclusion; AF and VR were the main indications for warfarin therapy and age was the principal dose determinant in contradiction to other studies. Finally, it remains to know the molecular role played by age.

Keywords: Warfarin; Thromboembolism; Age; Pt-INR, Atrial fibrillation; Valve replacement

Introduction

Thromboembolism (TE), is due to a heterogeneous group of disorders that associate with faulty hemostasis with consequent vascular (arterial and venous) thrombosis and embolism [1]. The sequel of the latter are sometimes lethal, thus prevention is the whole mark of management. The thromboembolic disorders can be grouped into cardiovascular, hematological, immunological and metabolic diseases, although idiopathic TE is still not uncommon [2]. The arterial cardiovascular thromboembolic disorders are predominantly presented with atrial fibrillation (AF) and stroke [3] and are mostly associated with atherosclerosis in old people or people with dyslipidemia [1]. As for most complex disorders, genetic and environmental factors are principal contributors to the primary causes of TE [4], as well as drugs and toxins [5]. Although, management of the primary disorder is the target, warfarin is an important therapeutic option for prevention of thromboembolic events in a variety of clinical conditions [3]. Warfarin works by inhibiting the synthesis of vitamin-K dependent clotting factors II, VII, IX, and X [6] and other anticoagulant factors e.g. proteins C and S [7], hence identified as vitamin K antagonist (VKA).

Warfarin, is a 4-hydroxycoumarin-derived molecule, taken orally as a mixture of R and S enantiomers, where the latter exhibits 2–5 times greater anticoagulant potency than the former [8]. It

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is rapidly and almost completely absorbed and about 98% is transported as a protein bound molecule. The peak plasma level is achieved within 2–8 h. The plasma half-life is usually 36–44 h but varies widely from person to person from 10 to 80 h; however, the duration of the clinical effects can exceed the half-life of the drug [9]. Also the peak of the warfarin activity can be delayed due to the relatively long half-lives of the clotting factors, hence, if immediate anticoagulation is needed, other drugs like heparin are used [8]. Warfarin is extensively metabolized in the liver by phase I hepatic microsomal oxidizing enzymes to 6- and 7-hydroxy warfarin, and to warfarin alcohols by reduction [9]. The S and R enantiomers are differentially metabolized by cytochromes P450s, thus, drug-drug interactions could occur with drugs that are metabolized by P450s [10]. About 85% of warfarin is excreted in urine as metabolites, and small fractions are excreted in stool [9]. Accordingly, both liver and renal function need to be assessed in patients on warfarin.

The optimum warfarin dose determination is a major challenge in clinical practice for several reasons including the narrow therapeutic index, fatal consequences of under and over dosing [11], drug side effects, drug-drug interactions [12], and the individual variation of the therapeutic dose. Undeniably, the patient genetic makeup and ethnicity are important players in the pronounced inter-individual variability in dose requirements [13], in addition to age, sex, diet, smoking, alcohol abuse, and pathological disorders/risk factors as indication for warfarin treatment or as co-morbidities [12, 14]. The above mentioned limitations necessitate close monitoring of the warfarin dose using the international normalized ratio -INR [15].

In the present study setting in Sudan, despite achieving fair anticoagulation control, elderly patients had a higher risk of major hemorrhagic events. As populations are ageing and use of warfarin as oral

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anticoagulation is increasing, strategies that mitigate the elevated risk of hemorrhage need to be identified precisely.

Materials and Methods

Study design

This was a cross sectional hospital based study conducted between Nov 2019 and Jan 2020, in the Cardiac Centre of Ahmed Gasim Teaching Hospital in Khartoum, Sudan. This hospital is one of the main reference hospitals for cardiology, which provides services for patients from all over the country.

Study population

The main inclusion criteria were; patient on warfarin therapy, male or female and adults of any age. However, the exclusion criteria included; patients on drug/s known to have a major interaction with warfarin, severely ill patients and any organ failure. All 175 patients, whom were attending the anticoagulant clinic in the study period, were included in the study. Worth noting the study subjects were of different, multiple and broad ethnic backgrounds. The general population of Sudan are mostly of Afro-Arab origins, however, detailed ethnicity of the individual subjects are difficult to define and categorize. Data was collected using a comprehensive interview questionnaire, which included personal, demographic and life style data, past medical and drug history, in addition to the clinical examination, the basic and special laboratory and radiological investigations.

International Normalized Ratio (INR)

The INR, obtained from prothrombin time (PT), is a ratio of the patient's PT relative to a control PT standardized for the potency of the thromboplastin reagent developed by the WHO. It is calculated as follows: INR = Patient PT / Control PT. The PT is the time in seconds taken by plasma to form a

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clot in presence of sufficient calcium and tissue thromboplastin, via the extrinsic pathway of coagulation [16]. The reference values for INR, take in account related variations of device and type of reagents used in measurement of PT, and sensitivity differences in the TF activator. The INR score is a ratio with no unit (normal range 2.0 to 3.0).

Pt-INR-adjusted warfarin dose

Patients 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 was given, then the INR was measured on day 5 or day 4, respectively. Accordingly the warfarin dose was adjusted to keep the INR between 2.0 to 3.5.

Statistical analysis

The data was analyzed through software program Sigma Stat. The analysis included descriptive statistic and frequency count, while comparisons between two or more groups were executed by T-test or Mann-Whitney Rank Sum Test (MW), and by One Way Analysis of Variance or Kruskal-Wallis One Way Analysis of Variance on Ranks (KW). The correlation was tested using Pearson Product Moment Correlation. A $p<0.05$ was considered significant.

Ethical consideration

The study was approved by the ethical committee of the Sudanese medical specialization board (no reference number). Permission was obtained from the hospital administration and no interference with management protocols. Informed consent was obtained from all patients and the data was confidentially maintained.

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Results

Demographic, clinical and social characteristics of the study subjects

As seen in (Tables 1 and 2), 175 participants were included in this study, with comparable male to female ratio (92 vs. 83), 44.6% of the patients were younger than 40 years, with mean age of 45.9 ± 15.1 yrs. The patients were grouped into 7 groups based on the disorder/risk factor for which warfarin was prescribed, 4 groups of solitary disorders/risk factor and 3 groups of combination of previous ones. The most common single indication was atrial fibrillation -AF (30.9%), followed by previous stroke (8%), valve replacement -VR (6.3%), and idiopathic thromboembolism –TE (5.1%). For the combined indications, the most common was AF/VR (40%), followed by other double pathology -d-Path, 4.6% (3 AF/TE, 2 AF/stroke, 2 VR/TE, 1 TE/stroke), and 4.6% triple pathology -t-Path (4 AF/VR/TE, and 4 AF/VR/stroke). However, AF and VR together accounted for 85.7% (150/175).

Most participants (78.9%) were within the normal BMI, while 18.2% were overweight and 2.9% were underweight (Table 3). However, there was significant BMI variation between the groups, *p* 0.001, with mean BMI of 22.7±2.6 kg/m^2 (Table 2). For comorbidities associated with warfarin-treated groups, the most common was diabetes mellitus (DM) 23.4%, followed by DM plus hypertension - DM/HTN (8.6%), and HTN alone (2.3%) (Table 2), with other comorbidities and regrouping of DM and HTN is shown in (Table 6). Finally, 12.6% of the study subjects were smokers (Table 4), while only 1.1% were alcohol consumers (data not shown).

Association of warfarin dose with clinical disorders/risk factors

There were significant variations in the Pt-INR-adjusted warfarin dose for the different groups (Fig.1). The max doses were required for patients with VR (5.0, 4.3-7.0 mg/day; median, 25-75%), VR/AF (5.0, 4.0-6.0) and d-Path disorders (5.0, 3.0-6.5) followed by patients with t-Path (4.0, 3.0-

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5.0), and the lowest doses were prescribed for patients with AF and previous stroke (3.0, 3.0-5.0, each) and TE (3.0, 3.0-5.5), $p<0.001$, KW. However, there was marked variations in age between the 7 groups, ranked from oldest to youngest as follow; previous stroke (60.0, 55.0-65.0 yrs.), TE (58.0, 45.5-65.0), AF (55.0, 35.0-65.0), t-Path (48.0, 33.0-56.5), d-Path (36.5, 31.5-53.5), AF/VR (35.0, 31.0-53.0) and VR (34.0, 30.3-38.8), $p<0.001$, (Table 2). Adjusting for age by stratification and grouping of the conditions associated with low warfarin dose (TE, stroke and AF) *vs.* the conditions that were associated with 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 (Table5). The average warfarin dose for all patients together was; mean 4.6 ± 1.7, with the median being 5.0, 3.0-6.0, and the range 1.0 - 9.5 mg/day (Table 1).

The Pt-INR in the different clinical disorders/risk factors

Though the warfarin dose was adjusted based on target Pt-INR score, the Pt-INR values were significantly different between the different disorders/risk factors, $p<0.001$, KW (Fig. 1C), but still within the normal range for all groups, 2.0 – 3.5. The highest median Pt-INR was of the VR (2.5, 2.35-2.75) and VR/AF patients (2.45, 2.2-2.9), followed by the t-Path (2.25, 2.2-2.85) and d-Path (2.25, 2.2-2.45), then the AF (2.2, 2.1-2.4), while the lowest Pt-INR was that of the TE (2.1, 1.98-2.13) and stroke (2.1, 2.1-2.2). After correction for age as a confounding factor, the Pt-INR was still significantly higher in patients receiving the higher warfarin doses *vs.* the ones who received the lower warfarin doses, $p<0.001$, (Table 5). The mean INR for all patients was 2.4 ± 0.4, with the range between 1.3 and 3.5 (Table 1).

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Associations/correlations of the warfarin dose with age, sex, BMI and INR in all patients together

The warfarin dose was strongly significantly negatively correlated with age, CC -0.723, $p<0.001$, (Fig. 2A), i.e., as age was increased warfarin dose was decreased. Furthermore, the median 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), were significantly different, $p<0.001$ (data not shown).

Furthermore, males and females required comparable doses of warfarin, *p* 0.536, MW, and they achieved similar Pt-INR, *p* 0.544, MW. Although the females (40.0, 31.0-59.8 yrs.) were smaller than males (51.0, 33.0-60.0) the difference was not significant *p* 0.226, MW. Similarly, both sexes had comparable mean BMI, *p* 0.270, T-test (Table 1).

In contrast, the warfarin dose was not correlated with the BMI, CC -0.081, *p* 0.285, (Fig. 2B). Although, the warfarin dose was higher for the underweight (6.0, 4.25-7.0, mg/day) it was comparable with normal weight (5.0, 3.0-6.0) and overweight patients (3.0, 3.0-5.0), *p* 0.109. Similarly, the Pt-INR was comparable between the groups, *p* 0.701. Notably, the age difference between the 3 groups was significant, $p<0.001$, contrasting the warfarin dose (Table 3).

Finally, the warfarin dose was not correlated with the Pt-INR, CC 0.070, *p* 0.355, (Fig 2C).

Association of smoking with the warfarin dose

Unexpectedly, smokers required significantly lower warfarin dose than non-smokers, *p* 0.008, MW, (Table 4), and they achieved lower Pt-INR score, but the difference was not significant, *p* 0.064, However, smokers were significantly older than the non-smokers, $p<0.001$, and more obese, *p* 0.041. After correction for age by stratification, the warfarin dose was found to be comparable between the two groups, *p* 0.299.

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Associations of the warfarin dose with comorbidities

As seen in (Table 6), the most common reported relevant comorbidities were diabetes mellitus –DM (32%), followed by renal disease -RD (11.4%), hypertension –HTN (10.9%), and liver diseases -LD (4.6%). Regardless of the clinical indication for warfarin, patients with and without LD, received comparable doses of warfarin, *p* 0.581. Similarly, the patients with and without RD, had comparable doses, *p* 0.408. In both groups, the Pt-INR was not significantly different, *p* 0.689 and *p* 0.674, respectively. In contrast, patients with DM compared to non-diabetic ones, received significantly lower warfarin dose, $p<0.001$, and scored significantly lower Pt-INR, *p* 0.008. However, the former were markedly older than the latter, $p<0.001$. Similarly, patients with HTN had received significantly lower warfarin doses compared with patients without HTN, $p<0.001$, and were attended significantly lower Pt-INR, *p* 0.038, but also they were significantly older in age, $p<0.001$.

Discussion

This study aimed to define the disorders and risk factors that are associated with arterial thromboembolism and necessitate warfarin therapy/prophylaxis and also to explain the variation in warfarin dose in a multiethnic society in central Sudan. The results revealed that the commonest indication for warfarin was AF in patients who underwent VR, followed by primary AF, which together accounted for about 71%, while previous stroke, VR and idiopathic TE, as solitary disorders/risk factors or in combinations (d-Path and t-Path) accounted for the remaining 29% (Table 2). The same disorders/risk factors are approved as clinical uses of warfarin for prophylaxis and treatment of thromboembolic complications by the FDA [17]. The Pt-INR was measured as an ideal laboratory test for adjustment of warfarin therapy [15].

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In this study, the average adjusted warfarin dose was 5.0, 3.0-6.0 mg/day, with a broad range of doses, 1.0 to 9.5 mg/day. The primary determinant for the warfarin dose was found to be the age, which was inversely correlated with the dose (Fig. 2A). Interestingly, patients younger than 40 yrs, had their adjusted warfarin dose to be double the dose for the patients above 40 yrs. The reduced warfarin dose with aging was consistently noticed in most similar studies worldwide [18, 19, 20].

In contrast the warfarin dose was not influenced by sex in the present study (Table 1) as reported elsewhere [20]. However, several other studies reported that sex is a determinant for warfarin dose; and showed that women require lower doses than men [21, 22].

Furthermore, there was marked significant variation in the warfarin doses between the study groups p <0.001 (Fig. 1B), ranking from the lowest to the highest dose as follows; AF, previous stroke, idiopathic TE, t-Path (combinations of 3 disorders/pathologies), d-Path (2 disorders), VR/AF and VR. However, there was equally marked variation in the ages between the same groups, but ranking opposite to the warfarin dose (Fig. 1A). The interpretation of the combined observations was that the differences in the doses were basically due to differences in ages, and suggest that the disorders/risk factors were not major determinants for the warfarin dose. Furthermore, after correction for confounding variables by stratification, the low warfarin dose users (TE, previous stroke and AF) were found to have a comparable warfarin dose as the high dose warfarin users (VR, AF/VR and d-Path), p 0.648 (Table 5). However, other studies showed the influence of the clinical disorders that require warfarin therapy on the warfarin dose [23].

Although, DM and HTN were not direct indications for warfarin treatment, both conditions were frequently associated with the cardiovascular disorders associated with TE [24] and necessitated warfarin treatment. It remains to know whether or not both comorbidities affect the warfarin dose. In

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the current study, patients with DM or HTN required significantly smaller warfarin doses but they were also significantly older compared to their counterparts, thus, both comorbidities were not key determinants for warfarin dose after correction for age (Table 6). The HTN was previously shown to influence the warfarin dose [25]. Noticeably, there was low prevalence of HTN as a comorbidity in this study. However, DM as the commonest comorbidity is one of the risk factors for development of atrial fibrillation (AF), thus, patients with DM were sometimes recommended for prophylactic warfarin [26].

On the other hand, the implications of the liver and renal diseases were more relevant to the warfarin than the TE per se. since the liver is the main site for warfarin metabolism and the kidney is the main route for excretion [9]. In this current study patient with and without LD or RD had comparable warfarin doses (Table 6), however the number of patients were relatively small, and the liver and kidney functions were not tested. It had been suggested that the increased sensitivity to warfarin with aging is attributed to decreased serum proteins, metabolic activities, and renal excretion [27]. These alterations lead to differences in the pharmacokinetics of a drug that increases the persistence of the drug in the body, and consequently, increased sensitivity to the drug is observed among the elderly [27].

In the present study, there was no correlation between the warfarin dose and the BMI (Fig. 2B). Although the overweight patients required the lowest warfarin dose followed by the normal and then the underweight patients. The difference was not significant, however, this trend can be explained by the difference in age as the overweight patients were significantly older in age (Table 3). At least one study rejected the impact of BMI on warfarin dose [22]. On contrary, in USA, morbid obesity was shown to be associated with increased warfarin dose compared with underweight patients [28], while

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another study reported a positive strong correlation between warfarin dose and BMI [29]. Interestingly, in the setting of this current study, there was no single obese patient and the vast majority (79%) had normal BMI (Table 3).

Though smokers were shown to require significantly less warfarin dose, after correction for age as a confounding variable, smoking was proved not to be a major warfarin dose determinant and both smokers and non-smokers required comparable doses (Table 4). Increased warfarin dose was previously shown to be associated with smoking [14].

Of the limitations of this study is the incomplete information about the liver and renal functions, the relatively small number of study subjects and the lack of their ethnic details, as the latter was shown to influence the warfarin dose significantly [21, 30]. Thus, study of a larger sample size from different sites, that include the above mentioned missed data and the genetic profile of the study subjects, is needed for conclusive and reliable recommendations about the warfarin uses and doses in this and similar settings.

In conclusion, approx. 85% of the patients given warfarin as treatment/prophylaxis against arterial thromboembolism (TE) had atrial fibrillation (AF), of whom 71% had AF alone or with valve replacement and the remainders had either previous stroke or idiopathic TE or their combinations. The median daily warfarin requirement was 5.0, 3.0-6.0 mg (range 1 – 9.5 mg). We found no influence for sex, BMI, liver or renal disease on the warfarin dose. Though, significantly low warfarin doses were associated with AF, previous stroke and idiopathic TE, and with diabetes mellitus and hypertension comorbidities and smoking, upon initial analysis, after correction for cofounders, the prime determinant for warfarin dose was found to be age, which was inversely correlated with the dose. Moreover, after the age of 40 yrs., the warfarin dose was cut to the half. Finally, by defining

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age as the principal dose determinants, it remains to identify the undisclosed effects of age at molecular level.

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Table 1. Description of the total study subjects and comparisons between males and females participants: age, BMI, warfarin dose and Pt-INR.

	Mean (SD)	Median (25% - 75%)	Range	Sex distribution		
				Male	Female	p
No				92 (52.6%)	83 (=47.4%)	
Age	45.9 ± 15.0	45.0, 32.0 - 60.0	18.0 - 81.0	51.0, 33.0-60.0	40.0, 31.0-59.8	0.226
BMI	22.7 ± 2.6	22.6, 21.0 - 24.3	11.0 - 29.4	22.9 ± 2.8	22.4 ± 2.2	0.270
Warfarin dose	4.6 ± 1.7	5.0, 3.0 - 6.0	1.0 - 9.5	5.0, 3.0 - 6.0	5.0, 3.0 - 6.0	0.536
Pt-INR	2.4 ± 0.4	2.3, 2.1 - 2.6	1.3 - 3.5	2.3, 2.1 - 2.5	2.3, 2.1 - 2.7	0.544

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Table 2. 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 replace (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	Mean (45.9±15.1)		41	4	15 (8.6%)
		1.1:1	Range (18.0-81.0)		(23.4%)	(2.3%)	

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

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Table 3. Comparisons between underweight, normal and overweight BMI groups of all study subjects: frequency, age, warfarin dose and Pt-INR

Parameters	**Underweight** **< 18.5 (kg/m^2)**	**Normal weight** **18.5 - 24.9**	**Overweight** **25 - 29.9**	*p*
Frequency	2.9% (5)	78.9% (138)	18.2% (32)	
Age (yrs.)	20.0, 20.0 - 23.3	43.5, 31.0 - 60.0	55.0, 38.0 - 60.0	<0.001
Warfarin (mg/day)	6.0, 4.25-7.0	5.0, 3.0 - 6.0	3.0, 3.0 - 5.0	0.109
Pt-INR	2.3, 2.28 - 2.6	2.3, 2.2 - 2.5	2.25, 2.1 - 2.65	0.701

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Table 4. Comparisons between smokers and non- smokers before and after adjustment for age by stratification: sex, BMI and warfarin dose (mg/day) and Pt-INR

Parameters	Smokers (22)	Non-smokers (All=153) (Stratified =66)	p
Number	22 (12.6%)	153 (87.4%)	
Sex (male/female)	21:01	71:82	
Age – All (yrs.)	60.0, 51.0 - 65.0 (22)	40.0, 31.0 - 60.0 (153)	<0.001
Stratified	60.0, 51.0 - 65.0	60.0, 55.0 - 63.0	0.973
BMI (kg/m^2)	23.5, 22.6 - 24.9	22.0, 20.8 - 24.3	0.041
Warfarin dose – All	3.0, 3.0 - 5.0	5.0, 3.0 - 6.0	0.008
Stratified	3.0, 3.0 - 5.0	3.0, 3.0 - 4.0	0.299
Pt-INR – All	2.2, 2.1 - 2.3	2.3, 2.1 - 2.6	0.064
Stratified	2.2, 2.1 - 2.3	2.2, 2.1 - 2.6	0.290

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Table 5. Comparison between groups of high and low warfarin doses' disorders after adjusting for age by stratification: BMI, daily warfarin dose and Pt-INR.

Parameters	Low-dose warfarin users [TE, stroke, AF]	High-dose warfarin users [VR, VR/AF, d-Path]	*p*
Number	40	40	
Age (stratified)	42.5, 32.5 - 60.0	42.5, 32.5 - 60.0	0.996
Warfarin dose	5.0, 3.0 - 6.0	5.0, 3.0 - 6.0	0.648
Pt-INR	2.15, 2.1 - 2.25	2.5, 2.15 - 2.8	<0.001

BMI: body mass index; Pt-INR: prothrombin time- international normalization ratio;

TE: thromboembolism; AF: atrial fibrillation; VR: valve replacement; d-Path: double pathology

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Table 6. 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)	(8) 4.0, 3.0 - 5.5	(167) 5.0, 3.0 - 6.0	0.581	2.3, 2.1 - 2.5	2.3, 2.1 - 2.6	0.689
Age (yrs.)	57.5, 43.0 - 62.5	45.0, 31.25 - 60.0	0.151			
Renal disease						
Warfarin (mg)	(20) 3.5, 3.0 - 6.0	(155) 5.0, 3.0 - 6.0	0.408	2.35, 2.15 - 2.5	2.3, 2.1 - 2.6	0.674
Age (yrs.)	54.0, 31.0 - 62.5	45.0, 32.0 - 60.0	0.597			
Diabetes mellitus						
Warfarin (mg)	(56) 3.0, 3.0 - 5.0	(119) 5.0, 3.25 - 6.0	<0.001	2.2, 2.1 - 2.5	2.3, 2.2 - 2.6	0.008
Age (yrs.)	59.5, 50.5 - 65.0	35.0, 31.0 - 55.0	<0.001			
Hypertension						
Warfarin (mg)	(19) 3.0, 3.0 - 3.0	(156) 5.0, 3.0 - 6.0	<0.001	2.1, 2.1 - 2.2	2.3, 2.2 - 2.6	0.038
Age (yrs.)	60.0, 60.0 - 66.5	40.0, 31.0 - 58.0	<0.001			

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Figures legends

Figure 1. 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), were AF (atrial fibrillation), stroke, and TE (idiopathic thromboembolism), and the disorders that required highest warfarin dose were, VR (valve replacement), VR/AF and d-Path (double pathology, minor groups of different combinations), while the t-Path (triple pathology - combinations of 3 disorders) 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.

Figure 2. Correlation of the warfarin dose with patients' age, BMI and Pt-INR. The semi-log scatter plot and scatter plot (A) 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 (B) or Pt-INR CC 0.0703, p 0.355 (C).

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Figure 1.

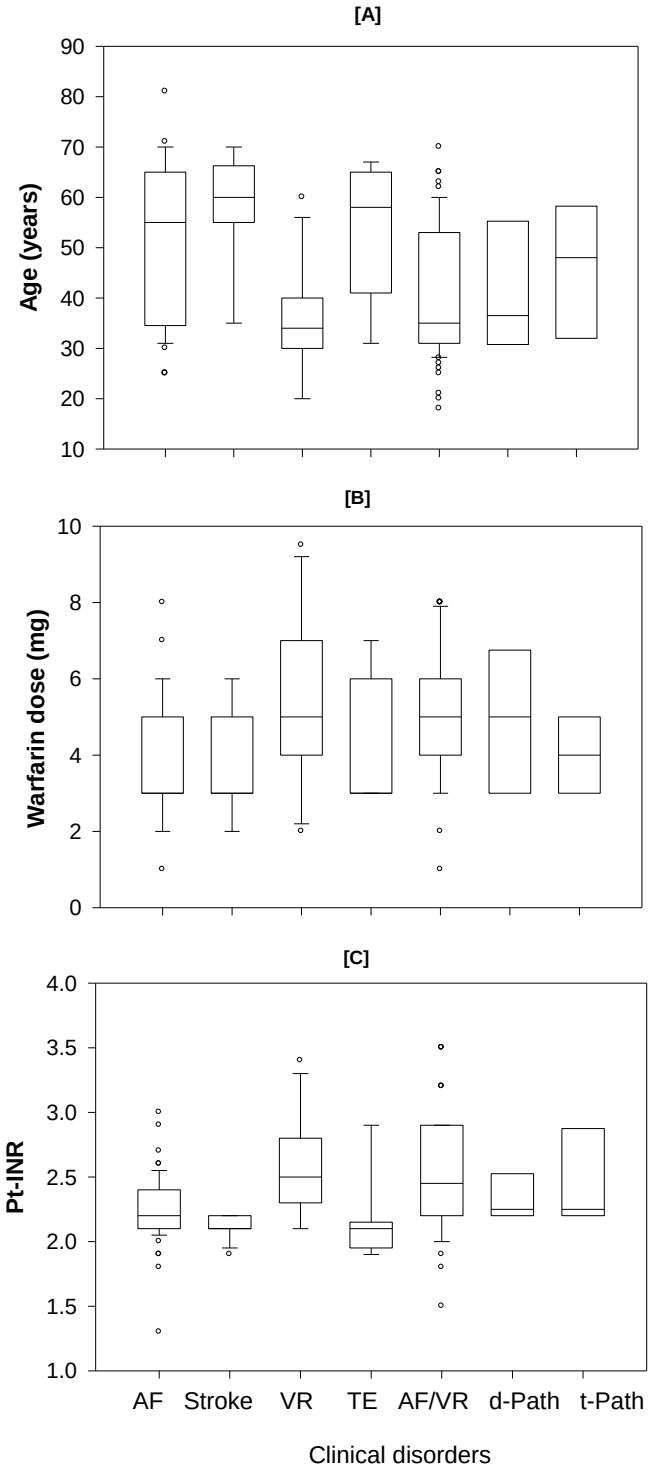

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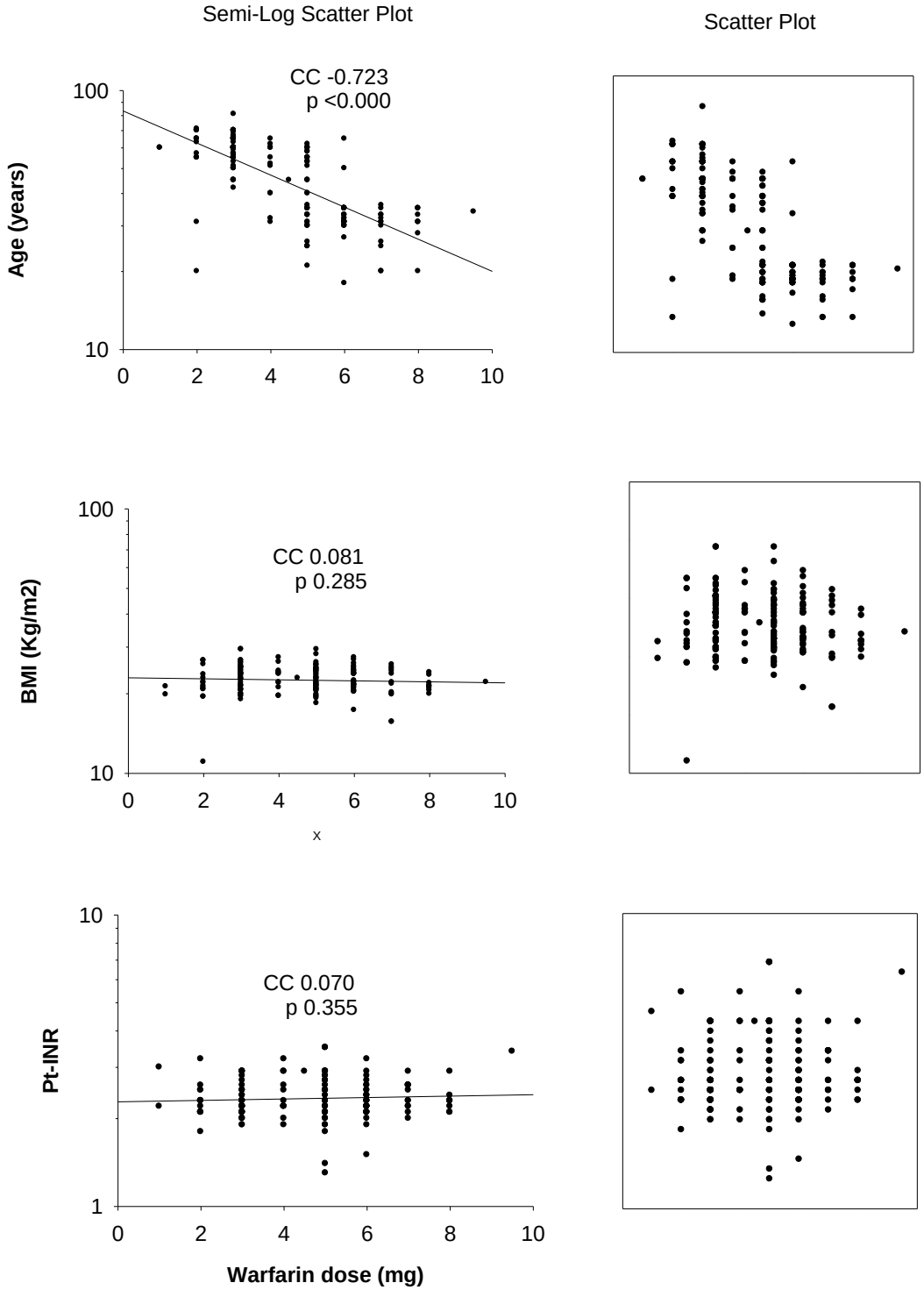
Figure 2.



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