RESEARCH ARTICLE

Factors affecting target INR levels in homebound and ambulatory patients who use warfarin

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Abstract

Objective: To investigate the rates of reaching target international normalised ratio levels and the factors affecting these rates in patients undergoing warfarin therapy.

Method: The prospective cross-sectional study was conducted between 16.08.2023 and 16.11.2023 at Izmir Bozyaka Training and Research Hospital and comprised patients of either gender who had been reciving warfarin therapy for at least 6 months. Those who were under the care of Home Health Services were in group A, while those being followed up at the cardiology outpatient clinic were in group B. All the patients had been receiving regular monitoring for international normalised ratio. Data was collected using a self-designed 41-item questionnaire. Data was analysed using SPSS 27.

Results: Of the 200 patients, 100(50%) were in each of the 2 groups. The overall mean age of the sample was 69.54±12.70 years. There were 131(65.5%) females, 108(54%) had international normalised ratio level within the target range, 101(50.5%) stated they had received education about warfarin, 120(60%) were aware of the side effects, and 81(40.5%) indicated they experienced complications while using warfarin. Group A patients received more education/information about warfarin, and warfarin-related complications were few in such patients ($p<0.05$).

Conclusion: International normalised ratio monitoring among patients under the care of Home Healthcare Service was more reliably and effective compared to cardiology inpatients.

Key Words: Warfarin therapy, Anticoagulants, Patients' education.

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Introduction

Warfarin is a vitamin K antagonist used as an anticoagulant for treating and preventing various coagulopathic and thromboembolic disorders.[1] Despite its proven effectiveness and long history as the golden standard of anticoagulant therapy, the narrow therapeutic window of warfarin creates some clinical challenges.[2] Severe adverse effects of warfarin include intracranial haemorrhage, gastrointestinal bleeding, hematemesis, intraocular bleeding and haemarthrosis.[3] Patients treated with warfarin should be closely monitored to ensure the safety and efficacy of the drug. Periodic blood tests are recommended to assess the patient's prothrombin time (PT) and international normalised ratio (INR).[4] For patients treated with warfarin, the therapeutic target INR depends on the indication, but may vary depending on the patient's clinical status. The target INR for patients using warfarin due to deep vein thrombosis (DVT), pulmonary embolism (PE), ischaemic stroke and atrial fibrillation (AF) is 2.0-3.0. However, specific indications, such as mechanical prosthetic valves, require a higher target INR. For example, it can be 2.5-3.5 in mitral prosthetic valves, or up to 4 in case of additional risk factors.[5] Regular medication use is essential in such chronic diseases, which should be closely monitored in terms of drug side effects and complications.

Education of patients before starting warfarin treatment, which has a high drug and food interaction, and during follow-up is essential in terms of reaching the target dose. Doctors in outpatient clinics may not provide adequate and practical education during short interactions. In contrast, the Home Health Service (HHS) policy is to provide more effective teaching to the patients with educational brochures in the home environment. Implementing structured and patient-centred education practices is necessary to effectively increase the level of knowledge of patients and thus improve the quality and safety of warfarin treatment.[6] Patients should be educated about easy bleeding or bruising that are common side effects. Patients should also be counselled on correctly managing cuts, bruises and epistaxis.[3]

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HHS deals with bedridden or semi-dependent, homebound patients, and all patients aged >80 years at their respective homes, in the actual environment they live in.[7] HHS patients needing warfarin regularly are visited at their homes and examined along with blood analyses and INR monitoring. HHS regulates medication dosage according to the target INR values and the medication intake scheme of the patients. When necessary, it provides service with the support of the relevant specialty department. It ensures that patients are referred to the emergency service when necessary, such as dangerously high INR values and bleeding that may occur during warfarin use.

The current study was planned to evaluate and compare factors affecting INR levels in homebound patients under HHS care and ambulatory patients using warfarin.

Patients and Methods

The prospective cross-sectional study was conducted between 16.08.2023 and 16.11.2023 at Izmir Bozyaka Training and Research Hospital. After committee approval from the local clinical research ethics committee with decision no:2023/119, the sample size was calculated with a finite population using the formula: $n = [DEFF*Np(1-p)]/[(d^2/Z^2_{1-\alpha/2}*(N-1)+p*(1-p)]$ with the help of OpenEpi[8] v.3.01 calculated with 95% confidence interval, design effect (DEFF) 1, population size (N) 3,500, precision (d) 5%, hypothesized frequency of outcome factor in the population (p) 14.5%+/-5%. The population size 3,500 reflected the total number of patients under HHS care, while hypothesised frequency of outcome factor in the population 14.5% indicated the rate of anticoagulant use in HHS records. The study followed a general survey model, and the sample was raised using convenience sampling within the scope of non-probability sampling techniques.[9,10]

Within the aim to reach this patient group, two people refused to participate in the study and two people were excluded because they had just started warfarin treatment. Those included were patients of either gender who had been reciving warfarin therapy for at least 6 months, had regular INR monitoring, and were being followed up by the same doctor. Informed consent was obtained from all the subjects. Those who refused to participate and those who did not meet the inclusion criteria were excluded. These HHS patients were placed in group A. As many patients were enrolled from the cardiology outpatient clinic who were subjected to the same inclusion criteria. They were placed in group B. Power analysis evaluation was performed for all parameters and comparisons, and, according to Cohen methodology, the power of the study was >80%.[11]

Data was collected using the Computer Assisted Face-to-Face Interview (CAPI) and Paper and Pencil Personal Interview (PAPI) techniques.[12] All the particpints were subjected to a 41-item self-designed questionnaire. In the first section, socio-demographic and clinical characteristics of the patients, incluing age, gender, marital status, educational status, chronic diseases, and physical activity status, were noted. In the second section, the reason for starting the treatment, information about the treatment, complications of the treatment, history of drug-related bleeding, interaction with food/other medicine, and weekly warfarin dose were asked. The third section explored the target INR level, whether it was within the target range in 2 of the preceding 3 visits, and, if not, the reasons for not reaching the target. Patients with at least 2 of the preceding 3 INR measurements in hospital records within the target range were considered to have a controlled INR value. These 3 sections of the questionnaire were answered by all the subjects in both the groups, while the final section was only meant for group A patients who were asked about their HHS experience.

Data was analysed using SPSS 27. Descriptive data was expressed as frequencies and percentages, mean ± standard deviation, or median with interquartile range (IQR), as appropriate. Chi-square test was used to assess the relationship of and INR control with the place of follow-up and sociodemographic characteristics. Student t test was used to assess the relationship involving the duration of warfarin use and doses, information questions and the place of follow-up. $P<0.05$ was considered significant for all analyses, and the relationships were evaluated with 95% confidence interval (CI).

Results

Of the 200 patients, 100(50%) were in each of the 2 groups. The overall mean age of the sample was 69.54±12.70 years. There were 131(65.5%) females, and 131(65.5%) had primary school education or below. The most common chronic diseases were heart disease 115(57.5%), hypertension (HT) 116(53%), and diabetes mellitus (DM) 48(24%). There were 31(15.5%) patients completely bedridden. In terms of INR target, 78(39%) patients stated that the INR level was within the target range in 2 of the preceding 3 measurement, but hospital records indicated that the INR level of 108(54%) patients was within the target range; 60(55.6%) in group A (HHS patients) and 48(44.4%) in group B (cardiology outpatients). Patients in group B were found to be using warfarin for longer periods(142,83±111,10 months vs

Table-1: Warfarin-related characteristics of the patients (n=200).

Questions	n	%
Do you know the reason for the use of the drug?		
Yes	194	97.0
No	6	3.0
What is your reason for treatment with warfarin?		
AF	60	30.0
DVT	21	10.5
Greft Thrombosis	1	0.5
Heart valve prosthesis	104	52.0
Peripheral vascular diseases	3	1.5
Pulmonary embolism	11	5.5
What was the localisation of your warfarin-induced bleeding?		
Brain	11	5.5
Bruising of the skin	13	6.5
Gums	18	9.0
Epistaxis	23	11.5
GIS	9	4.5
Haematuria	3	1.5
Conjunctival haemorrhage	1	0.5
Have you received training/information about warfarin?		
Yes	101	50.5
No	99	49.5
Do you know the side effects of warfarin?		
Yes	120	60.0
No	80	40.0
Have you been informed about what to do if your INR value is abnormal?		
Yes	154	77.0
No	46	23.0
What is the side effect when warfarin is taken underdosed?		
I don't know	76	38.0
Haemorrhage	2	1.0
Thrombosis (clotting)	122	61.0
What is the side effect when warfarin is taken overdosed?		
I don't know	53	26.5
Haemorrhage	141	70.5
Thrombosis (clotting)	6	3.0
Is it difficult for you to split the pill?		
Yes	22	11.0
No	178	88.0
How often do you have blood test for INR monitoring?		
Once a week	20	20.0
Every 2 weeks	25	25.0
Every 3 weeks	15	15.0
Once a month	40	40.0
Have you ever been to the emergency department because of an abnormal INR level?		
Yes	58	29.0
No	142	71.0
Do you have a history of warfarin-related complications?		
Yes	81	40.5
No	119	59.5
Do you think warfarin can interact with food?		
Yes	150	75.0
No	50	25.0
Do you think warfarin can interact with other medicines?		
Yes	78	39.0
No	122	61.0
How often do you consume green leafy vegetables?		
Every other day	42	21.0
Once a month	26	13.0
Once a week	64	32.0
Twice a week	26	13.0
Every day	15	7.5
Never	27	13.5

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GIS: Gastrointestinal system.

85,98±91,25 months) and at higher doses(30,02±12,71 mg/week vs 24,27±9,45 mg/week) than group A patients. There was no association between the controlled INR level and the duration and dose of warfarin use (p>0.05).

Overall, 101(50.5%) patients stated they had received education about warfarin, 120(60%) were aware of the side effects, and 81 (40.5%) indicated they experienced complications while using warfarin (Table 1).

Patients in group A were generally single, older, and had higher rates of chronic disease, while all patients with PE and the majority of patients with DVT and peripheral vascular disease were in group A. There was a significant difference related to the reasons for starting warfarin between the groups (p<0.05) (Table 2).

Patients who did not receive education/information about warfarin, who were not informed about what to do in case of an abnormal INR value, who did not think that foods consumed with warfarin could interact and who did not know the target INR level range correctly had higher rates of uncontrolled INR levels compared to the controlled group (Table 3).

The rate of receiving education or information about warfarin was significantly higher in group A patients, and the history of warfarin-related complications was significantly higher in group B patients (Table 4). There was no significant difference between groups A and B in terms of correlation with the rate of knowing the target INR range correctly (p=0.476). There was no significant correlation between the INR value in the target range in hospital records and group A and B (p=0.089).

Discussion

The current study investigated the basic characteristics of the patients using warfarin who were being followed up in the cardiology outpatient clinic or by the HHS. In the study, 54% patients were found to have a target INR level. In previous studies, it was observed that the average rate of reaching the target INR ranged 32-53%.[13-16] This rate

Table-2: Intergroup comparison of sociodemographic characteristics and indications for warfarin use

Sociodemographic and clinical characteristics	Subgroups of sociodemographic and clinical characteristics	Follow-up clinic		p
		Group A (HHS) (n=100)	Group B (Cardiology) (n=100)	
Age (years)		76.13±10.11	62.95±11.59	<0.001
Gender				
	Male	35 (50.7)	34 (49.3)	0.882
	Female	65 (49.6)	66 (50.4)	
Marital status				
	Single	47 (59.5)	32 (40.5)	0.030
	Married	53 (43.8)	68 (56.2)	
Education status				
	Primary school and below	72 (55.0)	59 (45.0)	0.053
	Secondary school and above	28 (40.6)	41 (59.4)	
Chronic illness				
	Heart diseases	70 (60.9)	45 (39.1)	<0.001
HT	56 (52.8)	50 (47.2)	0.395	
	DM	21 (43.8)	27 (56.3)	0.321
	CVA	24 (68.6)	11 (31.4)	0.016
	Thyroid diseases	9 (34.6)	17 (65.4)	0.093
	COPD/asthma	13 (76.5)	4 (23.5)	0.022
	Kidney diseases	8 (53.3)	7 (46.7)	0.788
	Muscle and joint diseases	9 (81.8)	2 (18.2)	0.030
Reason for starting warfarin				
	AF	36 (60.0)	24 (40.0)	0,064
	DVT+peripheral vascular disease	22 (91.7)	2 (8.3)	<0.001
	Graft thrombosis+ heart valve prosthesis	31 (29.5)	74 (70.5)	<0.001
	Pulmonary embolism	11 (100.0)	0 (0.0)	<0.001

HHS: Home Healthcare Service, INR: International normalised ratio, HT: Gypertension, DM: Dibetes mellitus, CVA: Cerebrovascular accident, COPD: Chronic obstructive pulmonary disease, DVT: Deep vein thrombosis.

can be increased to much higher levels after appropriate interventions regarding education and awareness. It was found that HHS patients received more training/information about warfarin and had fewer warfarin-related complications than cardiology outpatients. Although there was no significant difference, the rate of reaching the target INR was higher in HHS patients. However, the rate of knowing the target INR level range, warfarin side effects and interaction rates with other drugs and foods was lower in both groups. No significant difference was found between the groups. Most HHS patients were very satisfied with the services they received, and thus their compliance with treatment increased.

The most common reasons for warfarin use in the current study were the presence of heart valve prosthesis and AF. Heart valve prosthesis was more frequent in cardiology outpatients, and AF was more frequent in HHS patients. There was a significant association between the reasons for warfarin initiation and follow-up clinic between the groups. In earlier studies on warfarin, the most common reason for warfarin use was operated valve (42-57%), followed by AF (20-30%).[17] Since AF is a common rhythm disorder and the frequency of valve operations is increasing, the need for anticoagulant therapies is increasing by the day. Warfarin is the most commonly used anticoagulant agent in the treatment and prevention of thromboembolic events.[15] The most common reason for warfarin use in AF is to prevent cerebral thromboebolism and stroke. New oral anticoagulants which may be an alternative to warfarin have been recommended in European and American guidelines, especially in the prevention of stroke in non-valvular AF. These include the direct thrombin inhibitor fabigatran, and the factor Xa inhibitors rivaroxaban, apixaban and edoxaban. Although these therapies are advantageous compared to warfarin since INR monitoring is not required, bleeding complications, limited antidotes and being expensive are the most important disadvantages.[18]

Compliance of patients to warfarin treatment is very difficult due to the narrow therapeutic range of the drug, drug-drug interactions, interpersonal variability, pharmacokinetic differences, intake of vitamin K with food, and the risk of serious complications.[19] Patients using warfarin should be under strict INR monitoring to assess whether the appropriate dose is being taken.[20] Patients who do not have regular INR monitoring are likely to experience worse clinical outcomes (increased bleeding, thromboembolic events, mortality) because of the expected duration in the lower therapeutic range.[21] The risk of thromboembolic events is considerably increased, especially in patients with prosthetic valves, moderate to advanced mitral stenosis, low left ventricular systolic function, previous cerebrovascular diseases (CVDs) and AF, and intensive and effective anticoagulation is very important in these patients.[22]

Table-4: Relationship between follow-up clinic and warfarin knowledge.

	Follow-up Clinic		
	Group A (HHS)	Group B (Cardiology)	P
Have you received training/information about warfarin?			
Yes	61 (60,4)	40 (39,6)	0,003
No	39 (39,4)	60 (60,6)	
Do you know the side effects of warfarin?			
Yes	66 (55,5)	53 (44,5)	0,073
No	34 (42,5)	46(57,5)	
Have you been informed about what to do if your INR value is abnormal?			
Yes	79 (51,3)	75 (48,7)	0,502
No	21 (45,7)	25 (54,3)	
Have you ever been to the emergency department because of an abnormal INR level?			
Yes	30 (51,7)	28 (48,3)	0,755
No	70 (49,3)	72 (50,7)	
Do you have a history of warfarin-related complications?			
Yes	33 (40,7)	48 (59,3)	0,030
No	66 (56,4)	51 (43,6)	
Do you think warfarin can interact with food?			
Yes	75 (50,0)	75 (50,0)	1,000
No	25 (50,0)	25 (50,0)	
Do you think warfarin can interact with other medicines?			
Yes	38 (48,7)	40 (51,3)	0,772
No	62 (50,8)	60 (49,2)	
What is the side effect when Warfarin is taken underdosed?			
I don't know	38 (50,0)	38 (50,0)	1,000
Haemorrhage	1 (50,0)	1 (50,0)	
Thrombosis (clotting)	61 (50,0)	61 (50,0)	
What is the side effect when Warfarin is taken overdosed?			
I don't know	27 (50,9)	26 (49,1)	0,707
Haemorrhage 71 (50,4)	70 (49,6)		
Thrombosis (clotting) 2 (33,3)	4 (66,7)		

HHS: Home Healthcare Service.

The biggest limitations in INR monitoring are transportation, taking time off during working hours, and being home or bedridden.[23] Home INR monitoring is especially important in terms of patient satisfaction and improvement in quality of life. Matchar et al. reported that quality of life and patient satisfaction showed significant improvement in patients with home INR monitoring.[24] Unfortunately, INR measurement at home is very limited in Turkey due to the cost of both the devices and the kits used, and the difficulty of access. In addition, even if these devices are available, most patients may have physical and cognitive difficulties in dose calculation. This is more evident in patients with advanced age and those with a history of stroke and cognitive impairment.[25] On the other hand, most of the INR measurements performed at home in Turkey are performed by the HHS. It is performed by analysing in hospital the blood sample taken at home. Most of these patients are those who are unable to receive healthcare services outside the home due to the surgery they have undergone or chronic diseases they have. In the current study, it was observed that most patients' compliance with treatment increased under HHS care, and they were very satisfied with these services.

The current study showed that approximately 50% patients did not receive education and information about warfarin. In addition, 40% of the patients were not informed about the side effects of the drug. While 75% of the patients were informed about the interaction with food, 39% were informed about drug interaction. In a study, 43.3% patients had information about the interaction of warfarin with food, and 44.2% had information about drug interaction.[26] In a study of patients admitted to the emergency department, <20% of patients were informed about the interaction of warfarin with other drugs and foods. Since this population was admitted to the emergency department with warfarin complications, the level of knowledge may have been found to be lower. [27]

It was observed that HHS patients received more education and information about warfarin and experienced fewer complications than cardiology outpatients. Since HHS patients are older, these findings are very valuable. The low complication rate in HHS patients may be attributed to the joint role between the homebound patients and their relatives in the treatment process and regular follow-up. Considering the presence of comorbidities and other medications used by the elderly, age-related changes in their metabolism, difficulties in compliance with their treatment and difficulties in remembering information, it is necessary to be more careful in terms of dose adjustment and complications of warfarin in such individuals.[28]

The most common and most important side effect of warfarin, which is mainly used to prevent thromboembolic events, is bleeding. The incidence of bleeding complications related to oral anticoagulant use varies between 0.8% and 3.5%.[29] In the current study, it was found that 40% of the patients experienced warfarin-related complications; the most common bleeding complication was epistaxis, followed by gingival bleeding.

It is an obvious finding that those who do not receive training/information about warfarin, who are not informed about the requirements in case of an abnormal INR value, who do not think that foods consumed with warfarin may interact, and who do not know the target INR level range correctly are more uncontrolled in INR follow-up compared to the others. In a study conducted in China, a significant correlation was found between

patients' level of knowledge about warfarin and controlled INR levels.[30] Due to the limited time allocated to the patient in cardiology outpatient clinics, adequate information may not be provided from the physician to the patient, which explains the decrease in uncontrolled INR and TTR (time in therapeutic range) values in those visiting cardiology outpatient clinics. In particular, the primary physician should inform the patient about the interaction of warfarin and the foods consumed. In addition, the frequency of INR measurement should be increased if temporary or permanent changes have been made in other medications used by the patient.

Another important current finding was that 11% of the patients had difficulty in dividing the warfarin. The lack of doses <5mg in Turkey (1mg and 2mg) has led to the necessity to split the pill for small-dose users. This will increase the margin of error in drug use. If this issue can be corrected in Turkey, patient drug compliance will increase and the risk of complications will definitely decrease.

The current study has limitations. Firstly, the sample size is relatively small, but the study still has the power to provide clinically significant results. It is obvious that the cost decreases significantly with Home Health Service(HHS) due to fewer complications, but a clear financial calculation of this factor has not been made by the current study.

In the light of the current findings, it is clear that performing INR monitoring at home, which requires close medical attention, resulted in a more successful treatment and follow-up process. HHS can play an important and active role in connecting patients and cardiologists who may use NOACs (new oral anticoagulants) as an alternative to warfarin.

Conclusion

Patients under HHS care were more likely to have received education or information about warfarin. The rate of reaching target INR was higher, and complication rates were significantly lower in HHS patients.

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