



## Original Research

# Determining INR Awareness of the Patients who Use Warfarin and Rates of Achieving the Target Dosage

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### Abstract

**Objectives:** Warfarin is the most frequently used therapy as an oral anticoagulant medication for reducing the risk of thromboembolic complications. However, poor adherence to therapy may cause ineffective INR levels with increased complication risk. In our study, we aimed to show the rates of INR awareness of patients with atrial fibrillation (AF) using warfarin and whether they achieved the targeted INR values.

**Methods:** In this study, 300 male (60%, n=180) and female (40%, n=120) patients over 18 years of age who applied to warfarin polyclinic and were receiving warfarin treatment due to AF were included. The levels of INR between 2-3 were estimated as effective. Same questionnaire was applied to all patients.

**Results:** Our study showed that 57% of the patients who used warfarin were not in the therapeutic range. We also determined that INR awareness was extremely low in the majority of the patients. In this study, 72.2% of the patients who used warfarin did not know the definition of INR, 68% of the patients did not know the side effects of the medicine, 75.7% of the patients did not know the precautions needed to be taken in daily life and 83.7% of the patients did not know the foods rich in vitamin K. Patients who knew the meaning of INR were more likely have INR levels in the effective range, but these rates were not statistically significant. There was no statistically significant relationship between the educational level, marital status, and INR control frequency of the patients with the achievement of targeted INR levels.

**Conclusion:** At the beginning of the warfarin treatment, advantages and disadvantages should be balanced by the doctor. The patient and patient's relatives should be informed directly and comprehensibly about the effects and side effects of the medicine, as well as the interactions, pursuance and precautions need to be taken in daily life. Various modern methods should be enabled for surveillance and the patients who are not in the therapeutic range should be followed closer.

**Keywords:** Drug compliance; INR; warfarin.

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Atrial fibrillation (AF) is a rhythm disorder characterized by rapid and disorganized atrial electrical activations and impaired coordination of atrial contractions.<sup>[1]</sup> Typical symptoms include palpitations, anxiety, chest pain, shortness of breath and weakness. For the early diagnosis of AF, the opportunity of examination of every patient aged  $\geq 65$  should be taken and pulse and ECG control should be done.<sup>[2, 3]</sup> Stroke, thromboembolism, heart failure, decreased quality of life and impaired cognitive functions are the most important causes of morbidity and mortality. The main topics in the treatment are the pulse rate and rhythm control, long-term therapy, upstream therapy to prevent remodeling and antithrombotic therapy. Anticoagulation has a major role in the prevention of stroke and thromboembolism, which are the most important complications among these.

Although great progress has been made with newly developed oral agents in anticoagulant therapy, warfarin is still the molecule with no alternative in many cases. Difficulties in warfarin use, complications that may develop, the requirement of high patient compliance, having a narrow therapeutic index, etc. may cause some hesitations in patients and physicians. It is a drug with a high risk of developing complications due to non-compliance with treatment. Warfarin has been reported among 10 drugs with serious side effects by the FDA (Food and Drug Administration) between 1990 and 2000. A 'black box' warning, including risk factors that increase the bleeding side effect, has been added to its package insert.

Commercially available warfarin is a racemic mixture of S and R enantiomers. S form, which is a five times more potent anticoagulant, is primarily metabolised by the CYP2C9 microsomal enzyme system in the liver. R isomer is metabolised by CYP 1A2 and CYP 3A4. This enzyme system can be both induced by many drugs and have many genetic variants, both of which can alter the in vivo activity of warfarin. Warfarin binds strongly to plasma proteins, primarily albumin, and only its free form remains biologically active. Any other agent that can bind to albumin can release warfarin from where it is attached. This increases the biological effect of warfarin. Warfarin is a drug that should be used with caution concerning its interaction with foods and drugs. Foods, such as cabbage, spinach, chard, parsley, purslane, curly, lettuce, roasted chickpea, green tea, contain high amounts of vitamin K and should be consumed with caution, and necessary information should be given to patients at the beginning of treatment. There are many interacting drugs that exist and their number is increasing day by day. Mechanisms that may be related to interactions:

- Altered platelet function (e.g., aspirin, clopidogrel)

- Gastrointestinal (GI) injury (e.g., non-steroid anti-inflammatory drugs-NSAID)
- Altered synthesis of vitamin K in the GI tract (e.g., antibiotics)
- Altered metabolism of warfarin (e.g., amiodarone, rifampin, simvastatin)
- Inhibition of vitamin K metabolism (eg., acetaminophen)

The use of antibiotics, such as amoxicillin, clarithromycin, norfloxacin, trimethoprim- sulfamethoxazole, after the first three days has increased risk of anticoagulation. There is an increased risk of anticoagulation when used with proton pump inhibitors, lansoprazole and esomeprazole. Again, the simultaneous use of antiplatelet agents, such as aspirin and clopidogrel/dicumarol, increases the risk of bleeding.

TTR (time in the therapeutic range) used in the follow-up of patients receiving warfarin is used to determine the time the patients spend and the rates of the patients in the therapeutic range. Since our study was cross-sectional and a single INR value was used during the survey, no TTR evaluation was performed.

In this clinical study, we aimed to determine INR awareness and the rate of achievement of goals in AF patients using warfarin.

## Methods

Approval was obtained from Şişli Etfal Training and Research Hospital Ethics Committee for our study (11/09/2012-No:169).

In this study, 300 patients, including men and women over the age of 18, who admitted to Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital specific outpatient clinic between January 2013 and June 2013, who received warfarin treatment due to AF, were included. INR values between 2-3 were evaluated as effective. Patients under the age of 18, patients who used warfarin for another reason, patients who had discontinued warfarin for a short period of time (e.g., due to tooth extraction and operation preparation) during the interview, patients who did not want to participate in this study were excluded from this study.

The patients' awareness about the warfarin was evaluated with the questionnaire we prepared and the INR values at the time of control were examined. The questionnaire was applied to all patients by the same physician, and all interviews were conducted face to face. At the end of the meeting, all participants were given information about warfarin treatment and an information form about the interactions and the things to be considered were shared. The data eval-

uated in our questionnaire were age, sex, marital status, education, number of missed doses of warfarin, number of overdose use of warfarin, diet change, alcohol use, drug therapy (NSAIDs, herbal, antibiotics, amiodarone, drugs that are started/discontinued), whether the foods containing vitamin K are known or not, whether the meaning of INR is known or not, whether the side effects of warfarin are known or not, when the INR level was last checked, whether the precautions to be taken in daily life are known or not, the frequency of INR level checking, the patient's ability to perform their own activities, whether the patient is living alone or not and INR level.

Blood samples obtained from the antecubital vein at least eight hours after fasting were used to determine the INR levels of all patients included in the study. 2 cc of blood was taken into the citrated tube, and the optical method was used to examine the blood in the Trinity Biotech MDA 2 (Ireland) device.

### Statistical Analysis

SPSS (Statistical Package for the Social Sciences) 20 program was used for statistical analysis while evaluating the findings obtained in this study. While evaluating the study data, besides descriptive statistical methods (mean, standard deviation, frequency), an independent sample t-test was used to compare quantitative data, and the Chi-Square test was used to compare qualitative data. Results were evaluated at 95% confidence interval and significance was evaluated at the level of  $p < 0.05$ .

### Results

Of the 300 patients, 40.0% were female ( $n=120$ ) and 60.0% were male ( $n=180$ ). Frequency distribution characteristics of the participants' age, education, marital status and INR level are summarized in Table 1.

When evaluated concerning INR values, it was seen that the lowest INR level was 1.100 and the highest INR level was 7.300. The mean INR value was  $2.213 \pm 0.820$ . When the INR levels were examined, it was that 46.0% of them were below 2 ( $n=138$ ), 43.0% of them were between 2-3, which was the effective level ( $n=129$ ), 11.0% of them were above 3 ( $n=33$ ).

It was seen that 118 of the participants were at the age of 64 and below and 182 were at the age of 65 and over. While the INR level of 41.5% of the participants aged 64 and under was at effective level, this rate was 44.0% for participants aged 65 and over.

While 86 of the participants were in the illiterate group, the remaining 214 participants had at least elementary school education. While the INR of 34.9% of illiterate participants

**Table 1.** Age, education and marital status frequency distributions

	n	%
Age (years)		
54 and below	42	14.0
between 55-64	76	25.3
between 65-74	112	37.3
between 75-84	59	19.7
85 and above	11	3.7
Education		
No education	86	28.7
Elementary school	172	57.3
Middle high school	22	7.3
High school and above	20	6.7
Marital status		
Married	227	75.7
Single	6	2.0
Widow	67	22.3
INR* level		
<2	138	46.0
2-3	129	43.0
>3	33	11.0

\*INR: International normalized ratio.

was at an effective level, 46.3% of the participants who had elementary school or higher education level had INR at effective level. There was no statistically significant difference in the level of INR effectiveness between illiterate participants and participants with at least elementary school education ( $p=0.07$ ).

While 227 of the participants were married, the remaining 73 were single or widow. While the INR of 44.1% of the married participants was at an effective level, 39.7% of the single or widow participants were at effective level. There was no statistically significant difference between the married and single/widow participants in terms of INR effectiveness ( $p=0.516$ ).

According to the results of the warfarin compliance questionnaire, dose non-compliance was found as 22% and diet non-compliance as 67.7%. The antibiotic use rate was 18.7%. Other results are summarized in Table 2.

Patients' rate of knowing foods containing vitamin K was 16.3% ( $n=49$ ), and the rate of knowing the meaning of INR was found as 28.8% ( $n=84$ ) (Table 3). The rate of patients who know the meaning of INR was found to be higher than those who did not know the effective INR range (50%, 40.3%, respectively), but the difference of these rates were not statistically significant ( $p=127$ ) (Table 4).

The question of when was the most recent INR measurement performed was answered as follows: one week ago

**Table 2.** Frequency distributions of warfarin compliance evaluation survey

	n	%
Missed dose		
Absent	249	83.0
1 dose	36	12.0
2 doses	12	4.0
3 doses	3	1.0
Additional dose		
Absent	285	95.0
1 dose	13	4.3
2 doses	2	0.7
Same	97	32.3
In the last 1 week		
K vit.* positive food cons.		
1-2 portion more	54	18.0
3-4 portion more	32	10.7
4 portion more	15	5.0
In the last 1 week		
1-2 portion less	67	22.3
K vit. negative food cons.		
3-4 portion less	27	9.0
Less than 4 portion	8	2.7
Alcohol		
Absent	298	3
Present	2	0.7
Antibiotic		
Absent	244	81.3
Present	56	18.7
Herbal		
Absent	289	96.3
Present	11	3.7
Aspirin		
Absent	186	62.0
Present	114	38.0
Amiodarone		
Absent	291	97.0
Present	9	3.0

\*K vit: K vitamin; cons.: consumption.

(n=55) in 18.3%, two weeks ago (n=68) in 22.7%, three weeks ago (n=47) in 15.7%, four weeks ago (n=118) in 39.3% and five weeks and later (n=12) in 4.0%. The rate of patients who had their INR value measured once a week was 11%, who had it measured every two weeks was 22%, every three weeks it was 14.3% and the monthly measurement rate was 51.3% (Table 3). While the mean last time for the participants with an effective INR level to have an INR measurement in the last few weeks was 2.97 weeks, this was 2.81 weeks for participants with non-effective INR levels. According to the results of Independent Sample t-test

**Table 3.** INR properties frequency distribution

	n	%
*Does they know the meaning of the INR?		
No	216	72.2
Yes	84	28.8
Time when the most recent INR measurement was taken		
1 week ago	55	18.3
2 weeks ago	68	22.7
3 weeks ago	47	15.7
4 weeks ago	118	39.3
5 weeks and later	12	4.0
How often did they take an INR measurement		
Once every week	33	11.0
Every 2 weeks	66	22.0
Every 3 weeks	43	14.3
Every 4 weeks	154	51.3
Every 5 weeks and longer	4	1.3

\*INR: International normalized ratio.

**Table 4.** The relationship between knowing the meaning of INR and INR effectiveness

Variable	INR EFFECTIVITY		
	Effective n (%)	Not Effective n (%)	Total n (%)
Do you know the meaning of INR?			
No	87 (40.3)	129 (59.7)	216 (100)
Yes	42 (50.0)	42 (50.0)	84 (100)
Total	29 (43.0)	171 (57.0)	300 (100)

Chi Square: 2.332df:1p=0.127.

analysis, there was no significant difference concerning the frequency of INR measurement between the participants whose INR was at effective level and the participants with a non-effective INR level (p=0.261) (Table 5).

32.0% of the participants stated that they knew the side effects of the drug (n=96), 24.3% stated they took precautions, 97.7% stated that they were able to perform their own activities and 70.3% stated that they were not living alone (Table 6).

### Discussion

The most important result we found in this study was that 57% of patients using warfarin did not reach the targeted, effective INR levels. Again, the majority of patients were found to have low awareness of INR. 72.2% of the patients

**Table 5.** Independent sample t-test analysis results to determine whether the frequency of INR measurement of the participants differentiates according to the INR effectiveness variable

Score	Effectivity Status	n	X	SD	t	df	P
INR Level	Effective	129	3.16	1.071	.749	298	0.455
	Not Effective	171	3.06	1.131			

$p > 0.05$ .

**Table 6.** Frequency distribution properties of other treatment variables

	n	%
Do they know the side effects of the drug?		
Yes	96	32.0
No	204	68.0
Do they know the precautions to be taken in daily life?		
Yes	73	24.3
No	227	75.7
Can they perform their daily activities?		
Yes	290	97.7
No	10	2.3
Do they live alone?		
Yes	29	70.3
No	271	29.7

who used warfarin did not know the definition of INR, 68% of the patients did not know the side effects of the medicine, 75.7% of the patients did not know the precautions needed to be taken in daily life and 83.7% of the patients did not know the foods rich in vitamin K.

Millions of people are at risk of severe complications, such as bleeding, ischemic or hemorrhagic stroke, due to the suboptimal warfarin compliance each year. This mostly preventable situation also puts an extra burden on health expenses. The drug that is most associated with emergency hospitalizations in patients aged 65 years and older (due to noticeable side effects) is warfarin in America, and warfarin non-compliance rates are reported as 22-32%.<sup>[4]</sup>

Patients using warfarin still spend most of their time outside the desired INR range. In a meta-analysis involving 67 studies, the findings showed that 57155 patients spent only 64% of the follow-up time in the therapeutic INR range.<sup>[5]</sup>

In our study, only 129 (43%) of 300 patients were determined to be in the desired effective INR range, and because our study was a cross-sectional study, the time spent in the therapeutic INR range was not evaluated because only a single INR level was measured. The rates of patients in the effective INR range who know the meaning of INR were higher than those who did not (50%; 40.3%, respectively), but these rates were not statistically significant.

Drug non-compliance can be defined as the failure to take the prescribed drug or not to have it re-prescribed it after it is finished, discontinuation of the drug before the end of treatment, taking more or less than the prescribed dose and taking the drug at the wrong hours.

The first year tolerability of warfarin treatment in patients aged 80 years or older was evaluated in the USA, and the major bleeding rate was found as 19.5% in patients with a CHADS2 score of 3 and as 32.6% in patients who discontinued the treatment.<sup>[6]</sup> In the same study, the major bleeding rate was 23.4% in patients with a CHADS2 score of 4 and above, while the rate of patients who discontinued the treatment was 35.1%.<sup>[6]</sup>

While 17% of the cases included in our study stated that they missed the warfarin dose by mistake, 5% stated that they received an additional dose by mistake. Many of the patients who used warfarin were at an older age, which increased the risk. 60.7% of the patients who participated in our study consisted of patients aged 65 and over. While the INR of 41.5% of participants aged 64 and under was at effective level, this rate was 44% among participants aged 65 and over.

Drug and food interactions are among the important issues to be considered in warfarin use, especially in elderly patients at high risk of polypharmacy. In a randomized study, an average of 27% increase in INR values was observed after one week in patients who received a diet containing 80% lower vitamin K.<sup>[7]</sup> In a similar study, when the vitamin K content in the diet was increased by 100 mcg/day, a decrease of 0.2 in the INR level was observed within an average of 4 days.<sup>[8]</sup> While 32.3% of the participants in our study stated that they consumed the same amount of food that contains vitamin K in the last week, 33.7% of them consumed more food that contain vitamin K compared to their normal diet and 34% consumed less food containing vitamin K compared to their normal diet. Thus, almost three out of every five patients did not pay attention to their diet. In a series of patients with coagulopathy induced by ciprofloxacin and warfarin use, the average number of drugs taken per patient was 6.5 and the median INR was 10.0.<sup>[9]</sup> When our patients were evaluated in terms of other risk factors, 56 of them started or discontinued antibiotics, 11 herbal products, 114 aspirin, and nine of them started or discontinued amiodarone, and two of them were drinking alcohol regularly.

When starting warfarin treatment, training the patients and their relatives on issues, such as the effects and side effects, interactions of the drug are essential for good compliance. It was observed that pharmacists being more active in this process caused positive results on negative issues.<sup>[10]</sup> 72.2%

of the patients who used warfarin did not know the definition of INR, 68% of the patients did not know the side effects of the medicine, 75.7% of the patients did not know the precautions needed to be taken in daily life and 83.7% of the patients did not know the foods rich in vitamin K.

In a study conducted by Orensky et al., marital status, living conditions, and drug regimen were shown to play a prominent role in the non-compliance with treatment.<sup>[11]</sup> In addition, being divorced or never married was associated with less compliance. In another study, it was shown that in patients with psychiatric disorders, such as schizophrenia, major depressive disorder, and bipolar disorder, 36% increased ischemic stroke risk, 46% increased intracranial hemorrhage risk and 19% increased GIS bleeding risk was detected.<sup>[12]</sup> According to the same study, the risk of intracranial hemorrhage in substance addicts is increased by 135% compared to those who do not use any substance, and social risk factors, such as living alone and homelessness, are associated with an increased risk of gastrointestinal system (GIS) bleeding by 28%.<sup>[12, 13]</sup>

Two hundred twenty-seven of the participants in our study were married, the remaining 73 were single or widow; 271 of them stayed with their family, 29 of them lived alone; 290 could perform their own activities, while 10 needed help. While the INR of 44.1% of the married participants was at an effective level, 39.7% of the single or widow participants were at effective level. However, the difference was not statistically significant. Due to the frequency distribution of the variables of living alone and performing their own activities, their relationship with the INR effectiveness could not be evaluated. While most of the patients were able to perform their own activities, many of them were not living alone because of the Turkish family structure. That the psychiatric diseases and substance addiction of the patients participating in our study were not questioned is one of the limitations of our study.

An inverse relationship between education level and treatment compliance was shown in the IN-RANGE (Results From the International Normalized Ratio Adherence and Genetics Study) study and in another study.<sup>[14, 15]</sup> Although it cannot be attributed to a definitive reason, this situation has been tried to be explained by the daily struggle that can prevent taking the drug in people who are actively working. This situation is tried to be explained in those with higher education level, with patients having better ability to make independent decisions and having less confidence in clinicians (compared to less knowledgeable people).

In our study, 86 of the participants were not literate. One hundred seventy-two of them were elementary school graduates, 22 were middle-high school graduates, and

20 were high school and above graduates. While the INR of 34.9% of illiterate participants was at an effective level, 46.3% of those who have elementary school or higher education level had INR at effective level. However, since the sample did not show a homogeneous distribution, the INR awareness difference between the high school and above graduates and others could not be compared.

When the frequency of how often and when the patient had INR controls was evaluated, 51.3% had it checked every four weeks, 1.3% had once every five weeks or longer, 11% had it once a week, 22% had it once every two weeks and 14.3% of them had it checked every three weeks. 39.3% of them had their INR level checked one month ago for the last time. No significant difference was found between the participants whose INR was in the effective range and the participants whose INR level was not in the effective range, concerning the frequency of INR measurement.

Warfarin is the leading drug among the treatments where drug compliance is the most important issue. Patient compliance or the inability of the patient to come for follow up for any reason is a treatment contraindication in itself. In a study performed with new oral anticoagulant treatments that did not require monitoring, which seemed like a good alternative, compliance has been shown to be lower than warfarin.<sup>[16]</sup>

Unpredictable anticoagulant effect, frequent dose adjustment, monitorization requirement, drug/food/herbal product, etc. interaction, high patient compliance requirement, narrow therapeutic range, and potentially life-threatening side effects are currently the problems that have not been overcome with warfarin. As a result of our study, it was thought that the effective INR levels could not be reached in the majority of the patients who were started warfarin treatment and the underlying cause of patient non-compliance was not having sufficient information about this treatment and its side effects. We believe that taking necessary precautions in this regard and informing the patients well, calling to the controls at regular intervals or ensuring easy access by phone, providing detailed information about the side effects, drug and food interactions, using the follow-up forms that prioritize the visuality if necessary, registering the patients and calling them for control by phone when necessary will minimize such non-compliance.

#### Disclosures

**Ethics Committee Approval:** Approval was obtained from Şişli Etfal Training and Research Hospital Ethics Committee for our study (11/09/2012No:169).

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

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