

Time in therapeutic range values of patients using warfarin and factors that influence time in therapeutic range

Varfarin kullanan hastalarda terapötik aralıkta geçen zaman ve terapötik aralıkta geçen zamanı etkileyen faktörler

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ABSTRACT

Objective: The time in therapeutic range (TTR) of international normalized ratio (INR) is essential for the safety and efficacy of warfarin treatment. In this study, we aimed to determine TTR and the factors that affect TTR in patients using warfarin.

Methods: Patients taking warfarin for valvular and nonvalvular atrial fibrillation (AF) or prosthetic heart valves who were admitted to our cardiology outpatient clinic were enrolled. TTR was calculated using the linear interpolation method. The patients were analyzed according to warfarin indications and TTR efficiency (TTR \geq 60%). Weekly warfarin dose, the duration of warfarin use, the frequency of INR visits per year, and the awareness of patients regarding target INR were noted.

Results: The TTR of 248 patients (aged 57.21 \pm 12.45 years, 33.1% male) was 55.92 \pm 27.84%, and 48.0% patients exhibited efficient TTR. Clinical and demographic characteristics (age, sex, socioeconomic status, and comorbidities) exerted no effect on TTR and TTR efficiency. The frequency of INR visits per year was 10.02 \pm 3.80. TTR was related to the frequency of annual INR visits ($r=0.131$, $p=0.039$). Only one-third (30.2%) of patients were aware of their target INR. The literacy of the patients and duration of warfarin use exerted a positive effect on awareness ($p=0.011$ and $p=0.024$, respectively).

Conclusion: The findings of our study demonstrated that TTR and TTR efficiency were low and not associated with the characteristics of patients or indications. Unfortunately, in patients with valvular AF and prosthetic valves, warfarin is the sole drug that can be used. Thus, awareness and knowledge regarding target INR are essential to overcome poor anticoagulation monitoring with frequent INR visits.

ÖZET

Amaç: Uluslararası normleştirilmiş oranın (INR) terapötik aralıkta geçen zamanı (Time in therapeutic range - TTR) varfarin tedavisinin etkinliği ve güvenliği için zorunludur. Bu çalışmada, varfarin kullanan hastalarda TTR değerlerini ve TTR'yi etkileyen faktörleri belirlemeyi amaçladık.

Yöntemler: Kardiyoloji polikliniklerine başvuran valvüler-valvüler olmayan AF veya prostetik kalp kapağı için varfarin kullanan hastalar çalışmaya alındı. Terapötik aralıkta geçen süre doğrusal interpolasyon yöntemi ile hesaplandı. Hastalar varfarin endikasyonlarına ve TTR etkinliğine (TTR \geq 60) göre analiz edildi. Haftalık varfarin dozu, varfarin kullanım süresi, yıllık INR kontrol sıklığı ve hastaların hedef INR değeri konusunda farkındalıkları not edildi.

Bulgular: Katılan 248 hastanın (ortalama yaş: 57.21 \pm 12.45 yıl, %33.1'i erkek) TTR değeri %55.92 \pm 27.84 idi ve hastaların % 48.0'i etkin TTR'ye sahipti. Klinik ve demografik özelliklerin (yaş, cinsiyet, sosyoekonomik durum, komorbiditeler) TTR ve TTR etkinliği üzerinde etkisi gösterilemedi. Yıllık INR kontrolü sıklığı 10.02 \pm 3.80 idi. Yıllık INR kontrolü sıklığıyla TTR ilişkili bulundu ($r=0.131$, $p=0.039$). Hastaların sadece 1/3'ü (%30.2) hedef INR değerinin farkındaydı. Hastanın okur-yazarlık durumu ve ilaç kullanım süresi farkındalık üzerinde olumlu etki sağladığı görüldü (sırasıyla $p=0.011$ ve $p=0.024$).

Sonuç: Çalışmamız TTR ve TTR etkinliğinin düşük olduğunu ve bu iki parametrenin hastaların karakteristikleri ve varfarin endikasyonuyla ilişkili olmadığını gösterdi. Maalesef valvüler AF ve protez kapak varlığında kullanılacak tek ilaç varfarindir. Bu nedenle kötü antikoagülasyon izleminin üstesinden gelmek için sık INR kontrolleri ile takip olmak, varfarin hakkında bilgi sahibi olmak ve farkındalık gereklidir.

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Anticoagulation with warfarin in patients with Atrial fibrillation (AF) prevents stroke by 64% compared with placebo; however, there exist ischemic and bleeding risks owing to the fluctuation of the international normalized ratio (INR).^[1] The management of warfarin therapy is rather difficult because of its narrow therapeutic window, drug–drug interactions, inter-individual variability, pharmacogenetic differences, intake of vitamin K with foods, close monitoring requirement, and serious complications owing to warfarin itself that restrict its effective use.

Nowadays, direct oral anticoagulants (DOACs) are being used widely in patients with nonvalvular AF (NVAF). However, patients with valvular AF and prosthetic mechanical heart valves have no choice other than warfarin. Thus, warfarin is the only option for preventing thromboembolic events in these patients; however, it necessitates lifetime monitoring. The most important parameter that determines the efficiency of the therapy in patients using warfarin is the time in therapeutic range (TTR). As the TTR value decreases, the therapeutic effect of warfarin diminishes. Warfarin efficiency could not be demonstrated when TTR was less than 58%.^[2,3] Unfortunately, studies conducted in Turkey revealed that the mean TTR of patients using warfarin was lower than the target range.^[4-6] Warfarin itself is a complex drug, and it is difficult to predict its response. Various individual factors and the duration of warfarin treatment affect TTR.^[7]

In the history of warfarin, the focus has always been on the difficulty in monitoring it and its complications. This study aimed to determine the mean TTR values of patients using warfarin and to describe the factors affecting the mean TTR values and TTR efficiency.

METHODS

Study design

Between June and December 2012, patients who were 18 years of age or older and admitted to our hospital for INR control with indications of NVAF, valvular AF, and mechanical heart valves were enrolled in the study. The valvular AF group was composed of only patients with moderate-to-severe mitral stenosis, excluding those with mild stenosis or any degree of mitral regurgitation and aortic valve pathological condi-

tions. Patients with a follow-up duration of more than 6 months and those who had registered at least 4 INR values in the hospital database in the pre-

vious 6 months of enrollment were included. Patients with a history of stroke, malignancy, or hospitalization in the previous 6 months; warfarin interruption for any reason, active infection, active hepatitis, or chronic liver disease and those who were not regularly admitted to INR visits and had less than 6 total INR controls until the inclusion period was over were excluded. The enrolled patients were assigned to 3 groups according to warfarin indications as follows: valvular AF (33 patients), NVAF (56 patients), and prosthetic heart valves (159 patients). Socioeconomic status, clinical history, frequency of INR visits, awareness regarding target INR values, and previous hemorrhagic and embolic complications during warfarin treatment were noted. Written informed consent was obtained from all participants.

The study was conducted in accordance with the ethical standards stated in the Declaration of Helsinki and was approved by the Ethics Committee of Turkey Yüksek İhtisas Hospital (registration number: EPKK-619-00370).

Data collection

Clinical history, cardiovascular risk factors, medications including antiplatelets (acetylsalicylic acid, clopidogrel, and dipyridamole), non-steroidal anti-inflammatory drugs that affect warfarin and can cause warfarin-associated complications, frequency of INR visits, presence of warfarin interruption, and previous bleeding and thromboembolic events were interrogated and recorded. At the index visit, 12-lead electrocardiography was performed (Nihon Kohden Cardiofax ECG-9132K). Transthoracic echocardiographic evaluation was performed using a Vivid 7 (General Electric, Norway) echocardiography device with a 2.5-3.5-MHz transducer. Cardiac chamber quantification was performed as recommended in the guideline.^[8] After a 12-hour fast, venous blood samples were drawn for evaluating plasma glucose, high-density lipoprotein, triglycerides, total cholesterol, INR value, complete blood count, and serum

Abbreviations:

AF	Atrial fibrillation
CAD	Coronary artery disease
CKD	Chronic kidney disease
DOAC	Direct oral anticoagulant
GFR	Glomerular filtration rate
INR	International normalized ratio
NVAF	Nonvalvular atrial fibrillation.
TTR	Time in therapeutic range

creatinine. Physical examination was performed after 10 min of rest. The blood pressure of the patients was measured using an appropriate sphygmomanometer as suggested by the guidelines.^[9]

Definitions

Educational level (illiterate/literate and the last graduated school degree) and monthly income (low: <350 EUR, moderate: 350–750 EUR, and high: >750 EUR) were recorded. The mean monthly income of a family was calculated in Turkish Lira (TRY) and then converted to EUR. Low income is defined as <350 EUR/month and corresponds to the minimum wage. Moderate income is defined as twice the minimum wage (350–750 EUR); high income is defined as three times the minimum wage (>750 EUR). A patient was classified as an active smoker even if they smoked 1 cigarette per day for at least 1 year. Weekly warfarin dose was calculated as the total dose of warfarin during the week before the last visit. The patients were asked about the frequency of hospital admission for INR control in the last 1 year; the awareness regarding INR target was queried with simple yes/no questions, and the answers were noted.

Hypertension was defined as systolic and/or diastolic blood pressures $\geq 140/90$ mmHg or the use of any antihypertensive drug.^[10] Diabetes mellitus was defined according to the criteria of the American Diabetes Association Diabetes Guideline, i.e., fasting blood glucose levels ≥ 126 mg/dL or glycated hemoglobin (HbA1c) ≥ 6.5 or the use of any antidiabetic drug.^[11] Dyslipidemia was diagnosed if the patients' total cholesterol level was more than 200 mg/dL or if the patients were using antihyperlipidemic drugs. Coronary artery disease (CAD) was diagnosed if the patient had a history of previous acute coronary syndrome or revascularization or both or if there was $\geq 50\%$ stenosis in any coronary artery. Chronic kidney disease (CKD) was defined according to the estimated glomerular filtration rate (eGFR) calculated using the modification of diet in renal disease formula.^[12] If the eGFR value was <60 mL/min/1.73m², the patients were diagnosed with CKD. Heart failure was diagnosed if the patients' left ventricular ejection fraction was $\leq 40\%$ and the signs and symptoms of heart failure were present.

Target INR ranges were defined according to recent guidelines.^[13] The mean TTR value was calculated

using the Rosendaal linear interpolation method.^[14] The patients' INR values in the hospital database were recorded with their dates (day/month/year), and target INR and INR ranges were entered into an electronic program called INR Desk 2.0.^[15]

At the index visit, the patients were asked about the complications associated with warfarin. They provided information regarding their history of complications. Such complications were classified as clinically relevant non-major bleeding (bleeding that does not meet the criteria for major bleeding and that does not require any medical or surgical intervention, e.g., gingival bleeding, hematuria, epistaxis, etc.), major bleeding (bleeding with a decline in hemoglobin level >2 g/dL, with the transfusion of ≥ 2 units of erythrocyte or whole blood, that occurs in a critical location such as intracranial, intraocular, or retroperitoneal areas, or that causes death),^[16] and peripheral and cerebral embolic events.

Statistical analysis

Statistical analysis in this study was performed using the SPSS 13.0 statistical package program (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov normality test and the Levene test were performed to check the distribution of normality of the variables. Descriptive statistics of continuous variables were shown as mean \pm standard deviation, and categorical variables were shown as the percentage (%) of patients within the category. Continuous variables were compared across the groups using independent samples t-test or Mann-Whitney U test according to the distribution of variables. One-way ANOVA and post-hoc Bonferroni tests were used for comparing continuous variables between more than 2 groups. The categorical variables were compared using the chi-square test. The Pearson and Spearman correlation tests were used for correlation analysis according to the state of the variables. A p value less than 0.05 was considered statistically significant.

RESULTS

A total of 274 patients were included in this study. Of the 274 patients, 26 patients were excluded owing to irregular INR control or warfarin interruption or insufficient registered INR values in the hospital database (<6 INR values). The remaining 248 patients were analyzed. The mean age of the study

population was 57.21 ± 12.45 years, and 33.1% were men. The socioeconomic status and comorbidities of the participants are listed in Table 1. The mean TTR value of the patients was $55.92 \pm 27.84\%$, and TTR efficiency (TTR $>60\%$) was found in 48.0% of the patients. Among the patients, 49.6% had a history of thromboembolic and bleeding complications (31.5% had clinically relevant non-major bleeding, 11.7% had major bleeding, 2.4% had cerebral emboli, and 4.0% had peripheral emboli). Only 30.2% of the patients (75 patients) were aware of their INR target values. The average weekly warfarin dose of the patients was 33.33 ± 15.38 mg, and the duration of warfarin use was 7.48 ± 6.18 years (8 months-35 years) (Table 1).

Characteristics of the patients according to warfarin indications

The study patients were divided into 3 groups according to warfarin indications (159 patients had prosthetic heart valves, 33 patients had valvular AF, and 56 patients had NVAf). There existed no statistically significant difference between the groups in terms of education level, monthly income, and smoking status (Table 1). The mean TTR value and TTR efficiency (TTR $\geq 60\%$) of the patients were also similar in the 3 groups ($p=0.668$ and $p=0.901$, respectively).

Patients in the NVAf group were significantly older, and the prevalence of men, hypertension, and CAD was higher in this group than in the other groups ($p<0.001$, $p<0.001$, $p<0.001$, $p=0.004$, respectively). The total weekly warfarin dose was lower in the NVAf group than in the other 2 groups ($p=0.004$). In addition, weekly warfarin dose was negatively correlated with age ($r=-0.277$, $p<0.001$).

In the prosthetic heart valve group, the presence of a history of warfarin-associated complications was significantly higher than that in the other 2 groups ($p=0.027$). The duration of warfarin use was longer and weekly warfarin dose was significantly higher than that in the other groups ($p<0.001$, $p=0.004$, respectively). The ratio of patients who were aware of target INR values was higher in the prosthetic heart valve group ($p<0.001$).

Factors that affect the mean TTR value and TTR efficiency

No significant difference was observed in the

mean TTR values ($55.20 \pm 26.73\%$ in women and $57.38 \pm 30.07\%$ in men) and TTR efficiency in terms of sex ($p=0.564$ and $p=0.209$, respectively) (Table 2). No significant relationship was found between the education level and monthly income level of the patients and the mean TTR value ($p=0.718$ and $p=0.168$, respectively) and TTR efficiency ($p=0.494$ and $p=0.125$, respectively) (Table 2 and Table 3). No statistically significant relationship was observed between the mean TTR value, TTR efficiency, and the presence of comorbidities such as diabetes, hypertension, hyperlipidemia, CAD, smoking status, CKD, and heart failure ($p>0.05$ for all, Table 3). No statistically significant difference was observed between the weekly warfarin low-dose (<15 mg/week) users and high-dose (≥ 15 mg/week) users in terms of mean TTR ($p=0.711$) and TTR efficiency ($p=0.623$). The mean TTR value was positively correlated with the frequency of INR visits per year ($r=0.131$ and $p=0.039$) (Figure 1).

Presence of a history of hemorrhagic and embolic complications

Among the patients, 49.6% had a history of hemorrhagic or embolic complications. Of these, 31.5% had clinically relevant non-major bleeding, 11.7% had major bleeding, 2.4% had cerebral emboli, and 4.0% had peripheral emboli.

Awareness of INR target value

Although the mean TTR value of the patients who were aware of the target INR value was

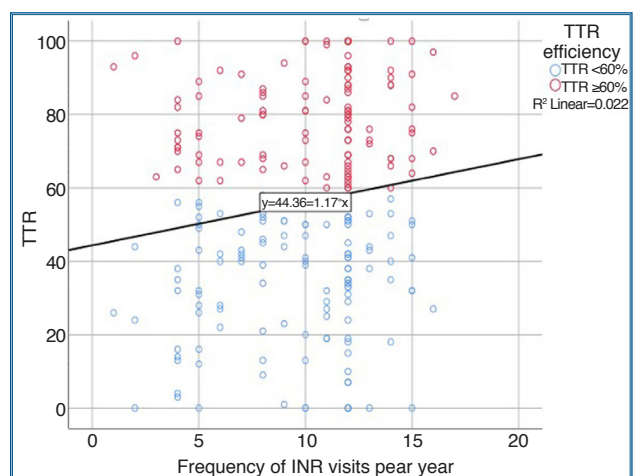


Figure 1. Relation between mean TTR, TTR efficiency and the frequency of INR visits per year. TTR: time in therapeutic range; INR: international normalized ratio.

Table 1. Characteristics of the patients according to warfarin indications

Characteristics	All patients (n=248)	Prosthetic heart valve (n=159)	Valvular AF (n=33)	Nonvalvular AF (n=56)	p
Age (year±SD)	57.21±12.45	52.96±11.24	57.97±11.96	68.82±7.77	0.013
Male sex, n (%)	82 (33.1)	56 (35.2)	1 (3.0)	25 (44.6)	<0.001
Educational level					
Illiterate, n (%)	58 (22.2)	34 (21.4)	7 (21.2)	14 (25.0)	0.225
Elementary school, n (%)	133 (53.6)	78 (49.1)	23 (69.7)	32 (57.1)	
Secondary school, n (%)	24 (9.7)	18 (11.3)	3 (9.1)	3 (5.4)	
High school, n (%)	26 (10.5)	21 (13.2)	0 (0.0)	5 (8.9)	
University, n (%)	10 (4.0)	8 (5.0)	0 (0.0)	2 (3.6)	
Monthly income					
Low, n (%)	110 (44.4)	62 (39.0)	15 (45.5)	33 (58.9)	0.082
Moderate, n (%)	108 (43.5)	73 (45.9)	15 (45.5)	20 (35.7)	
High, n (%)	30 (12.1)	24 (15.1)	3 (9.1)	3 (5.4)	
SBP (mmHg±SD)	123.93±18.56	122.56±18.21	124.24±18.03	127.64±19.63	0.906
DBP (mmHg±SD)	78.08±10.59	76.95±9.77	79.70±11.24	80.32±12.07	0.610
Hypertension, n (%)	127 (51.2)	64 (40.3)	15 (45.5)	48(85.7)	<0.001
Dyslipidemia, n (%)	77 (31.0)	44 (27.7)	12 (36.4)	21(37.5)	0.306
Diabetes, n (%)	31 (16.9)	19 (11.9)	9 (27.3)	3 (25.0)	0.019
Smoking					
None, n (%)	152 (61.3)	95 (59.7)	25 (75.8)	32 (57.1)	0.167
Quit smoking, n (%)	75 (29.0)	45 (28.3)	6 (18.2)	21 (37.5)	
Active smoker, n (%)	24 (9.7)	19 (11.9)	2 (6.1)	3 (5.4)	
Coronary artery disease, n (%)	58 (23.4)	32 (20.1)	4 (12.1)	22 (39.3)	0.004
Heart failure, n (%)	18 (7.3)	8 (0.05)	1 (3.0)	9 (16.1)	0.014
Chronic kidney disease, n (%)	48 (19.4)	28 (17.6)	5 (15.2)	15 (26.8)	0.483
Creatinine clearance*	79.61±23.02	82.90±23.97	74.55±19.12	73.23±20.68	0.010
Weekly warfarin dose (mg)	33.33±15.38	35.58±16.90	31.68±11.05	27.92±11.18	0.004
The duration of warfarin use (year)	7.48±6.18	9.49±6.58	3.82±2.47	3.91±3.31	<0.001
Complication history (%)	123 (49.6)	89 (56.0)	13 (39.4)	21 (37.5)	0.027
Awareness of target INR value (%)	75 (30.2)	64 (40.39)	4 (12.1)	7 (12.5)	<0.001
Frequency of INR visits per year	10.02±3.80	9.99±3.94	10.52±4.10	9.82±3.19	0.558
The mean TTR (%±SD)	55.92±27.84	55.24±28.53	61.48±25.90	54.59±27.01	0.668
Efficient TTR (TTR ≥60%), n (%)	119 (48.0)	75 (47.2)	17 (51.5)	27 (48.2)	0.901

*(mL/min/1.73m²).
AF: atrial fibrillation; SD: standard deviation; SBP: systolic blood pressure; DBP: diastolic blood pressure; INR: international normalized ratio; TTR: time in therapeutic range.

60.31±28.11%, the mean TTR value of the patients who were not aware of the target INR value was 54.02±27.58%. No statistically significant difference was observed between these 2 groups (p=0.103). The ratio of the patients who were aware

of the target INR value was higher in the literate group (p=0.011) (Figure 2). A statistically significant relationship was found between the duration of warfarin use and the awareness of the target INR value (p=0.024) (Figure 3).

Table 2. The mean TTR value of the patients according to their characteristics

		Patient n, (%)	Mean TTR (mean±SD)	p
Sex	Male	82 (33.5)	57.38±30.07	0.564
	Female	166 (66.5)	55.20±26.73	
Educational level	Illiterate	55 (22.2)	53.62±27.85	0.718
	Elementary school	133 (53.6)	55.39±26.81	
	Secondary school	24 (9.7)	56.17±32.35	
	High school	26 (10.5)	59.50±32.01	
	University	10 (4.0)	65.80±19.08	
Monthly income	Low	110 (44.4)	53.07±26.45	0.168
	Moderate	108 (43.5)	59.72±28.59	
	High	30 (12.1)	52.70±29.30	
Smoking status	None	152 (61.3)	55.34±26.26	0.698
	Quit smoking	72 (29.0)	55.64±32.14	
	Active smoker	24 (9.7)	60.50±24.14	
Diabetes	Absent	206 (83.1)	56.13±28.22	0.795
	Present	42 (16.9)	54.90±26.16	
Hypertension	Absent	121 (48.8)	54.60±26.80	0.464
	Present	127 (51.2)	57.19±28.84	
Dyslipidemia	Absent	171 (69.0)	54.58±27.51	0.260
	Present	77 (31.0)	58.90±28.50	
Coronary artery disease	Absent	190 (76.6)	56.99±27.74	0.276
	Present	58 (23.4)	52.43±28.09	
Chronic kidney disease	Absent	200 (80.6)	57.15±27.37	0.157
	Present	48 (19.4)	50.81±29.43	
Heart failure	Absent	230 (92.7)	56.18±27.68	0.646
	Present	18 (7.3)	52.67±30.36	

SD: standard deviation; TTR: time in therapeutic range.

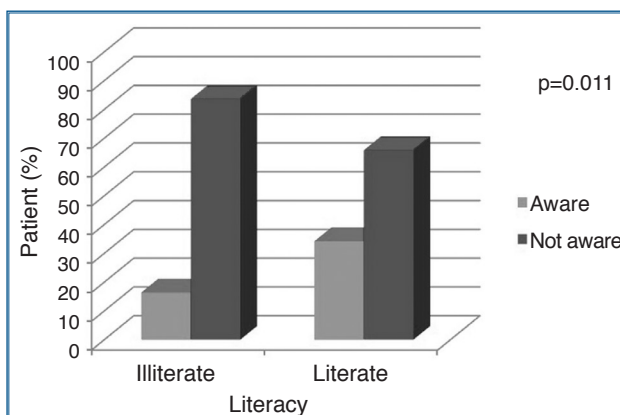
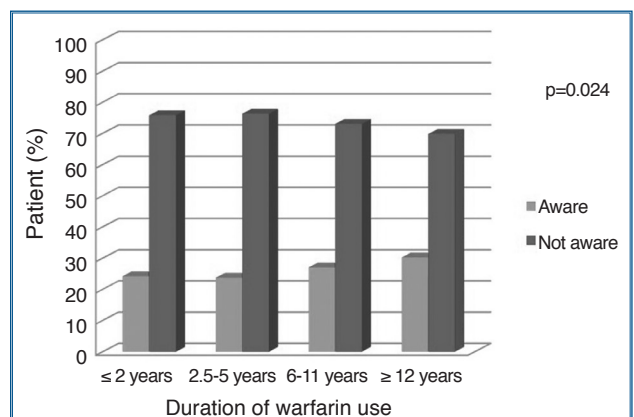
**Figure 2.** Awareness of the target INR value according to literacy.
INR: international normalized ratio.**Figure 3.** Awareness of the target INR value according to the duration of warfarin use.
INR: international normalized ratio.

Table 3. The efficient TTR distribution according to patients' characteristics

Characteristics	TTR <60% (n=129)	TTR ≥60% (n=119)	p
Age (year±SD)	57.91±12.85	56.45±12.01	0.360
Male sex, n (%)	38 (29.5)	44 (37.0)	0.209
Educational level			
Illiterate, n (%)	32 (24.8)	23 (19.3)	0.494
Elementary school, n (%)	70 (54.3)	63 (52.9)	
Secondary school, n (%)	13 (10.1)	11 (9.2)	
High school, n (%)	10 (7.8)	16 (13.4)	
University, n (%)	4 (3.1)	6 (5.0)	
Monthly income			
Low, n (%)	65 (50.4)	45 (37.8)	0.125
Moderate, n (%)	49 (38.0)	59 (49.6)	
High, n (%)	15(11.6)	15(12.6)	
SBP (mmHg±SD)	123.53±17.03	124.37±20.16	0.349
DBP (mmHg±SD)	77.82±10.01	78.35±11.22	0.306
Hypertension, n (%)	64 (49.6)	63(52.9)	0.600
Dyslipidemia, n (%)	36 (27.9)	41(34.5)	0.256
Diabetes, n (%)	25 (19.4)	17(14.3)	0.285
Smoking			
None, n (%)	84 (65.1)	68 (57.1)	0.367
Quit smoking, n (%)	35 (27.1)	37 (31.1)	
Active smoker, n (%)	10 (7.8)	14 (11.8)	
Coronary artery disease, n (%)	33 (25.6)	25 (21.0)	0.395
Heart failure, n (%)	9 (7.0)	9 (7.6)	0.872
Chronic kidney disease, n (%)	27 (20.9)	20 (16.8)	0.436
Creatinine clearance (mL/mn/1.73m ² ±SD)	77.88±22.07	81.48±23.96	0.965
Weekly warfarin dose (mg)	32.39±12.95	34.36±17.65	0.314
The duration of warfarin use (year)	7.77±6.34	7.17±6.02	0.448
Complication history, n (%)	63 (48.8)	60 (50.4)	0.886
Awareness of target INR value, n (%)	36 (27.9)	39 (32.8)	0.411
Frequency of INR visits per year	9.60±3.75	10.48±3.81	0.070

TTR: time in therapeutic range; SD: standard deviation; SBP: systolic blood pressure; DBP: diastolic blood pressure; INR: international normalized ratio.

DISCUSSION

The mean TTR value of the patients admitted to our cardiology outpatient clinic was 55.92±27.84%. Efficient TTR (TTR ≥60%) was present in 48.0% patients. Only 30.2% patients were aware of their target INR values. Contrary to previous studies, comorbidities (CAD, hypertension, congestive heart failure [CHF], and smoking status), sex and socioeconomic level exhibited no effect on TTR and TTR efficiency.

The frequency of annual visits for INR control was 10.02±3.80 and was lower than that in other studies.^[17-19] A weak relationship was found between TTR and the frequency of INR visits per year.

Since the prevalence of CAD, hypertension, and CHF increased with age, the rate of these diseases and the mean age of the NVAf group were higher than those in the other 2 groups. The mean age of NVAf patients in our study was significantly lower

than that in other similar studies. Owing to the low socioeconomic level and poor living conditions of the elderly population in our study, medication might not have been initiated for patients with advanced age in the NVAF group. In the atrial fibrillation in Turkey: epidemiologic registry (AFTER) study conducted in Turkey, the ratio of physicians who refrained from warfarin therapy in elderly patients was 30.6%.^[20] Both the physicians and patients avoid the use of warfarin at an advanced age owing to decreased cognitive capacity with aging, increased risk of bleeding, and difficulty in follow-up. Advanced age is an important predictor of warfarin dose.^[21,22] In our study, the total weekly warfarin dose was lower in the NVAF group than in the other two groups. This may be associated with decreasing vitamin K stores and the slowing of warfarin metabolism with advanced age.

In many studies, it has been demonstrated that average TTR increases with age.^[21,23-25] On the contrary, in this study, no difference was observed in TTR efficiency and mean TTR between decades of age because the elderly patient group contributed only a small part of the included patients and warfarin indications in our study were not limited to NVAF, unlike in other studies.^[24]

The mean TTR of patients who were admitted to our hospital's outpatient clinic was $55.92 \pm 27.84\%$. Although this value was lower than that in many studies,^[26] it was found to be similar to that in some studies.^[27] Most studies consisted only of NVAF patients with advanced age.^[21,23] Since these patients have a more stable warfarin metabolism, they have a lower target INR value and lower weekly warfarin dose requirements. Our study included the prosthetic valve group with younger patients, higher target INR values, and higher weekly warfarin dose requirements. As a result, our mean TTR value might have been lower than that in other studies.^[21,23] However, the mean TTR value of this study was higher than that in the WARFARIN-TR study ($49.52 \pm 22.93\%$) that analyzed the TTR value of patients from across Turkey with various indications such as valvular AF, NVAF, deep vein thrombosis, and prosthetic heart valves.^[6] The mean TTR value of patients with AF (valvular AF [61.48 ± 25.90] and NVAF [54.59 ± 27.01]) in our study was higher than that in the WATER (Warfarin in Therapeutic Range) registry (42.3 ± 18.4) from our country.^[4] The ratio of patients with efficient TTR

was higher in our study (48%) than that in the WARFARIN-TR study (24.6%)^[6] and the AFTER study (37%) from Turkey.^[20] In these 2 nationwide studies, the participants were included from all geographical regions of Turkey. Furthermore, various factors such as ethnicity, genetic variants, and different geographical locations of the participants could affect the results. In another single-center study conducted in Turkey that included 155 patients with AF, NVAF, prosthetic heart valves, and deep vein thrombosis, the mean TTR value ($57.2 \pm 22.5\%$) and the ratio of the patients with efficient TTR (TTR $\geq 60\%$ in 45.8% of the study group) were found to be similar to those in this study.^[28]

In the ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) registry, TTR of patients followed at anticoagulation clinics was found to be higher than that of patients not followed at anticoagulation clinics (69% versus 66%, respectively, $p < 0.0001$).^[29] In specialized INR clinics with experienced pharmacists, nurses, and physicians, the mean TTR value was found to be higher than that in other outpatient clinics.^[19,30] Kilic et al.^[19] studied the effects of specialized INR clinics and general outpatient cardiology clinics on the efficacy and safety of warfarin in a single center from the Aegean region of Turkey. They found that the mean TTR value of all patients was $62.10 \pm 20.73\%$ and was better in specialized INR clinics than that in general outpatient cardiology clinics (68.80 ± 15.88 versus 51.60 ± 23.04 respectively), and the patients visited for INR control more frequently than they did in our study (14.1 ± 3.67 versus 10.2 ± 3.8 , respectively). In the subgroup analysis of WARFARIN-TR study that analyzed the mean TTR value in patients from different geographic regions of Turkey, it was found that patients from the Aegean region had the second highest TTR (54.65 ± 24.21) (patients from the Marmara region had the highest TTR of $54.99 \pm 20.91\%$), whereas the mean TTR value of patients from Central Anatolia, Turkey, was $45.47 \pm 19.97\%$.^[25] Our study was conducted at a single tertiary center in Central Anatolia; however, the mean TTR value of our study was higher than that of the WARFARIN-TR subgroup. Participants of studies that analyze TTR exhibit different characteristics, ethnicity, drug usage, nutritional habitus, warfarin indications, warfarin monitoring technique, and frequencies of INR control. Therefore, when comparing the TTR value of

studies, we should consider whole characteristics of the study population. To overcome poor anticoagulation, specialized INR clinics should be widely organized to monitor more patients closely. Additionally, knowledge and awareness assessment of the patients should be integrated into INR visits, and dietary vitamin K intake, drug-drug interactions, and warfarin compliance should be queried at each visit.

Young age, female sex, low income, Black race, frequent hospitalization, multi-drug usage, decompensated heart failure, dementia, and CHF were associated with low TTR.^[21,24,29] In our study, no sex difference was observed in terms of mean TTR and TTR efficiency. However, other studies showed that the male sex exhibited a positive effect on TTR efficiency and TTR value.^[21,31,32] The reason for this might be that there were 3 groups of patients and the characteristics of the patients included in the study were non-homogeneous; therefore, a sex bias was not observed.

No difference was found between the smoking status and TTR efficiency and mean TTR. However, studies have shown that smoking has increased warfarin metabolism.^[33,34] Smoking increases warfarin clearance by inducing CYP1A2, shortens the half-life, and decreases the volume of distribution of warfarin. The amount of daily cigarette consumption, the density of tobacco in cigarettes, and the passive smoking status of nonsmokers were not queried. Therefore, there was no significant relationship between the mean TTR value, TTR efficiency, and smoking.

In this study, a relationship between TTR and the frequency of INR visits per year was observed. The linear regression showed that patients should make at least 14 INR visits per year to have efficient TTR (TTR $\geq 60\%$). Frequent visitors (40 patients, $>13/\text{year}$) were further analyzed for evaluating TTR efficiency. Factors such as age, socioeconomic level, smoking, and the presence of comorbid conditions exerted no effect on TTR efficiency. This can be attributed to numerous factors, including genetic factors, drug-drug interactions, changes in diet, and the small sample size of our study. In a study that investigated the factors that affect INR variability, no cause was found in the majority of cases (52.8%); of all the known factors, noncompliance was most commonly noted (19.8%) along with food (13.2%), drugs

(10.0%), alcoholic beverages (3.1%), and herbal supplements (1.1%).^[35]

Awareness of the target INR value was higher in the prosthetic valve group. The duration of warfarin use was found to be longer in patients with prosthetic heart valves. Our study showed that as the duration of drug use increased, the awareness of the INR target value increased. The awareness in the prosthetic heart valve group being higher than that in the other groups could be attributed to the duration of warfarin use being longer than that in the other groups. The patients in the prosthetic valve group had undergone major surgery earlier or had a history of warfarin-associated complications; these important experiences might have increased their awareness. The mean TTR value of the patients who were aware of the target INR value was higher than that of the patients who were unaware of the value ($60.31 \pm 28.11\%$ versus $54.02 \pm 27.58\%$, respectively). The difference could have been statistically significant if the study population were greater.

DOACs are favorable options for patients with NVAF without effective INR control. Current guidelines recommend preferring any DOAC to warfarin with a Class Ia recommendation. Warfarin is the sole drug recommended for patients with valvular AF and prosthetic heart valves. Therefore, close monitoring and patient awareness and knowledge are crucial for this group.

Limitations

The study findings should be interpreted in the light of some limitations. The main limitations include the observational design with a small sample size. Since the study was conducted at a single center, its results may not be generalizable. The linear interpolation method is not the right choice for TTR measurement when INR measurement intervals are more than 56 days. In our study, some intervals of INR controls exceeded this duration. The study population is non-homogeneous in terms of warfarin indication (prosthetic heart valve patients constitute the majority of the participants) and other clinical characteristics.

Conclusion

In this study, anticoagulation control was found to be below the targeted TTR. The relationship between socioeconomic level, clinical-demographical characteristics, and warfarin efficacy could not be demon-

strated. The poor awareness of the patients regarding the target INR values and poor anticoagulation control showed that warfarin follow-up itself was complex and required close monitoring. Particularly, DOACs should be preferred in patients who do not have an effective TTR value with suitable indications. Moreover, in the remaining patient group, the factors that may affect TTR should be reviewed, and necessary arrangements should be made.

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