

## Clinical characteristics and overdose risk factors of patients hospitalized due to warfarin overdose

Varfarin doz aşımı nedeniyle kliniğe yatırılan hastaların klinik özellikleri ve doz aşımı ile ilgili risk faktörleri

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### ABSTRACT

**Objectives:** This study aims to investigate the relationship between overdose and patient characteristics by specifying characteristics such as age, gender, comorbidity, laboratory, diet, and treatment in patients hospitalized due to warfarin overdose.

**Materials and methods:** A total of 167 (91 males, 76 females, mean age 77±12 years; range 26 to 94 years) consecutive patients hospitalized at the Göztepe Training and Research Hospital Internal Medicine Clinic between May 2015 and May 2016 with International Normalized Ratio (INR) >3.50 were included in the study. Demographic data, comorbidity states, warfarin indications, thromboembolic risk scoring (CHA<sub>2</sub>DS<sub>2</sub>-VASC), bleeding risk score (HASBLED), laboratory parameters and previous hospitalizations for the same cause, current medications, diet, and bleeding origin of patients were documented.

**Results:** The most common warfarin indication was atrial fibrillation and the most common comorbidity was hypertension. Mean warfarin dosage was 30.8±8.7 mg/week. Mean CHADS<sub>2</sub>-VASC was 4.2±1.2, mean HASBLED was 3.6±0.9, mean INR was 8.0±3.6, and mean Time in Therapeutic Range (TTR) was 28.7±22.6%. The most common drug with warfarin interaction were proton pump inhibitor. A total of 68.9% of patients were found to be using over five medications and %21.6 of patients consuming food with possible warfarin interaction. Rate of rehospitalization due to warfarin overdose was %28.7. Bleeding frequency was %58.1. Mean INR and HASBLED was higher and mean TTR (p=0.04) was lower in patients with bleeding compared to non-bleeding patients (p=0.007, p<0.001). Male gender (p=0.007) and high HASBLED score (p<0.001) were independent risk factors for bleeding.

**Conclusion:** In inpatients hospitalized due to warfarin overdose, medications, and consumption of foods interacting with warfarin were found to be frequent; almost one third of patient were rehospitalized due to warfarin overdose, and high HASBLED score, and low TTR was associated with higher bleeding risk.

**Keywords:** Bleeding, clinical characteristics, risk factors, warfarin overdose.

### ÖZ

**Amaç:** Bu çalışmada varfarin doz aşımı nedeniyle yatan hastaların yaş, cinsiyet, komorbidite, laboratuvar, diyet ve tedavi gibi özellikleri belirlenerek, doz aşımı ile hastaların özellikleri arasındaki ilişki araştırıldı.

**Gereç ve yöntemler:** Çalışmaya Göztepe Eğitim Araştırma Hastanesi İç Hastalıkları Kliniği'ne Mayıs 2015 - Mayıs 2016 tarihleri arasında yatışı olan ve herhangi bir nedenle varfarin kullanıp uluslararası normalleştirilmiş oranı (INR) >3.50 saptanan ardışık 167 hasta (91 erkek, 76 kadın, ort. yaş 77±12 yıl; dağılım, 26-94 yıl) dahil edildi. Hastaların demografik verileri, eşlik eden hastalık durumları, varfarin endikasyonu, tromboemboli risk skoru (CHA<sub>2</sub>DS<sub>2</sub>-VASC), kanama riski skoru (HASBLED), laboratuvar sonuçları, daha önce aynı nedene bağlı yatışları, kullandıkları ilaçlar, mortalite, diyet ve kanama kaynakları kaydedildi.

**Bulgular:** En sık varfarin endikasyonu atriyal fibrilasyon, en sık eşlik eden hastalık hipertansiyon idi. Ortalama varfarin dozu 30.8±8.7 mg/hafta idi. Ortalama CHADS<sub>2</sub>-VASC 4.2±1.2, ortalama HASBLED 3.6±0.9, ortalama INR 8.0±3.6, ortalama terapötik aralıkta olma zamanı (TTR) %28.7±22.6 idi. Varfarinle etkileşebilecek ilaç en sık proton pompa inhibitörü idi. Hastaların %68.9'unun 5'ten fazla ilaç kullandığı, %21.6'sının varfarin ile etkileşime girebilecek riskli olabilecek yiyecek tükettiği görüldü. Varfarin doz aşımı nedeniyle tekrar yatış oranı %28.7 idi. Kanama sıklığı %58.1 idi. Kanaması olan hastalarda INR ve HASBLED ortalamaları kanaması olmayanlara kıyasla yüksek (p=0.007, p<0.001), TTR ortalaması düşük (p=0.04) idi. Erkek cinsiyet (p=0.007) ve HASBLED skoru yüksekliği (p<0.001) kanama için bağımsız risk faktörleri idi.

**Sonuç:** Varfarin doz aşımı nedeniyle yatan hastalarda varfarin ile etkileşebilecek ilaç ve gıda tüketiminin yüksek bulunduğu, yaklaşık her üç hastadan birinde varfarin doz aşımı nedeniyle tekrar yatış gerektiği ve yüksek HASBLED skoru ve düşük TTR kanama riskinin daha yüksek olması ile ilişkili idi.

**Anahtar sözcükler:** Kanama, klinik özellikler, risk faktörleri, Warfarin doz aşımı.

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Warfarin is a drug commonly used in the prevention and treatment of various thromboembolic diseases. It aims to provide anticoagulant effect at a level of preventing thromboembolic events without increasing bleeding risk.<sup>[1]</sup>

Warfarin shows its effects by antagonizing the effects of vitamin K. Oral anticoagulants (OAC) block epoxide reductase enzyme which transforms inactive vitamin K to vitamin K, therefore blocking gamma carboxylation and causing inactive molecules to emerge. Consequently, anticoagulant effect is achieved by reducing blood levels of active factors.<sup>[2]</sup> Warfarin is commonly used in patients with deep vein thrombosis (DVT), pulmonary thromboembolism (PTE), stroke, recurrent infarction, prosthetic heart valve, and atrial fibrillation (AF).<sup>[3,4]</sup>

The increasing use of warfarin in various indications, unfortunately, has increased the prevalence of adverse effects as well as benefits.<sup>[5]</sup> When International normalized ratio (INR), used to evaluate anticoagulant efficacy, is above 3, it has been determined that there is five times increased risk of bleeding. A large majority of bleeding due to warfarin toxicity does not pose a significant threat, however it may rarely cause major or life-threatening bleeding. Studies on major bleeding associated with warfarin report a rate of 3%.<sup>[6-9]</sup>

The most important problem faced during warfarin treatment is thromboembolic event due to failure to achieve target INR value, or bleeding caused by overdose.<sup>[10]</sup> Because of warfarin's narrow therapeutic index, even small changes in daily life can cause fluctuations in anticoagulant treatment control. Many factors such as patient compliance to treatment, age, comorbidities, additional medications, vitamin K content of consumed foods, and unpredictable or patient-specific dose response may affect effective and reliable anticoagulant treatment.<sup>[11]</sup>

Our hospital's internal medicine clinic has frequent hospitalizations due to warfarin overdose. In this study we aimed to investigate the relationship between warfarin overdose and patient characteristics by determining clinical, age, gender, comorbidities, laboratory, diet, and treatment characteristics of patients with warfarin overdose.

## MATERIALS AND METHODS

A total of 167 (91 males, 76 females, mean age 77±12 years; range, 26 to 94 years) patients hospitalized due to warfarin overdose at the Göztepe Training and Research Hospital Internal Medicine Clinic between May 2015 and May 2016 were included in the study. Written consent was obtained from all patients before conducting the study. Appropriate permission for the study was provided by the Istanbul Medeniyet University Göztepe Training and Research Hospital Ethics Committee (Date: 05/12/2015; No. 2015/0047). The study was conducted according to principles of the Helsinki Declaration.

### *Inclusion criteria of the study:*

1. Over age 18
2. Use of warfarin for any reason
3. INR ≥3.50 and hospitalization

### *Exclusion criteria:*

1. Liver cirrhosis
2. Under 18 years of age

Demographic characteristics and laboratory analyses of the patients who met inclusion criteria and agreed to participate in the study were documented from admission records. Comorbidities, previous hospitalizations due to the same cause, current medications, dietary features, and presence of bleeding symptoms were questioned and recorded in forms.

### **Age-comorbidity-indications-laboratory results**

Warfarin indications, age, comorbidities, and laboratory results of the patients were documented from admission folders. Thromboembolic risk scoring (CHA<sub>2</sub>DS<sub>2</sub>-VASC)<sup>[12]</sup> was calculated in all non-valvular atrial fibrillation (AF) patients and bleeding risk score (HASBLED)<sup>[13]</sup> was calculated in all patients.

### **Medications and diet**

Medications and dietary features were learned from patients or their relatives. Use of medications that could interact with or cause overdose of warfarin was considered positive for drug risk.<sup>[14]</sup> Frequency of use of drugs considered positive was calculated. Patients were also grouped according to number of medications they used, as 1-3, 3-5, and over 5.

For diet, consuming of foods within the last week that had high interaction with warfarin (cabbage, spinach, chard, parsley, purslane, romaine, lettuce, chickpeas, liver, green tea, broccoli, Brussel sprouts, turnip, fish oil) was also questioned. Consuming of these foods was considered positive.<sup>[15]</sup>

### Bleeding characteristics

Patients were foremost questioned on whether or not they had bleeding. Patients with bleeding were grouped as major and minor bleeding. The major bleeding group included patients with gastrointestinal, retroperitoneal, cranial, bleeding

requiring intraabdominal or invasive intervention, bleeding causing decrease in hemoglobin of two units, and patients needing more than three units of blood products in transfusion. Patients aside from these criteria were included in the minor bleeding group. Bleeding origins were also documented.

### INR and warfarin dosage

International normalized ratio values of the patients at initial hospitalization was recorded. Patients were grouped as INR of 3.5-4.99, 5-9.99, and  $\geq 10$ . Warfarin dosage was accepted as cumulative dose (mg/week).

**Table 1.** Demographic and clinical characteristics of patients

	n	%	Mean $\pm$ SD
Age (year)			77 $\pm$ 12
Gender			
Male	91		
Female	76		
Frequency of comorbidities			
Hypertension	123	73.7	
Congestive heart failure	97	58.1	
Diabetes mellitus	53	31.7	
Coronary artery disease	51	30.5	
Stroke	40	24.0	
Chronic renal failure	36	21.6	
Chronic obstructive pulmonary disease	28	16.8	
Warfarin indications			
Non-valvular atrial fibrillation	111	66.5	
Valvular heart disease	21	12.6	
Stroke	12	7.2	
Deep vein thrombosis-pulmonary thromboembolism	11	6.6	
Drugs with interaction			
Proton pump inhibitor	64	38.3	
Acetylsalicylic acid	28	16.8	
Cardiac glycosides	18	10.8	
Antibiotics	14	8.4	
Statin	12	7.2	
Steroid	10	6.0	
Other	2	1.2	
Multiple drug use (piece)			
<3	4	2.4	
3-5	48	28.7	
$\geq 5$	115	68.9	
Rate of consumption of risky foods	36	21.6	
Rate of rehospitalization	48	28.7	

SD: Standard deviation.

**Table 2.** Comparison of clinical characteristics according to bleeding presence

	Bleeding			No bleeding			p
	n	%	Mean±SD	n	%	Mean±SD	
International normalized ratio			8.6±3.7			7.1±3.4	0.007
Time in therapeutic range			26.1±22.3			32.6±22.7	0.04
Thromboembolic risk score			4.1±1.2			4.4±1.2	0.22
HASBLED			3.9±0.8			3.1±0.8	<0.001
Warfarin dose (mg/week)			31.3±9.5			30.1±7.6	0.31
Risky food	22	22.7		14	20.0		0.71
Risky drugs	89	91.8		59	84.3		0.14

Thromboembolic risk score: CHA<sub>2</sub>DS<sub>2</sub>-VASc; HASBLED: Bleeding risk score.

### Time in therapeutic range (TTR)

Time in therapeutic range of patients was calculated as percentage using the Rosendaal method.<sup>[16]</sup> Time in therapeutic range ≥60% was considered effective dose range, while <60% was considered outside of effective dose range.

### Statistical analysis

The collected data was analyzed using the IBM SPSS version 21.0 (IBM Corp., Armonk, NY, USA) software program. Descriptive statistics were expressed as mean ± standard deviation. Chi-square test was used to assess categorical variables. In the analysis of continuous variables, according to distribution of data, parametrically distributed data was assessed with Student's t-test for independent samples, and Mann-Whitney U test was used for non-parametric data. For the comparison of three groups, when there was homogeneous variance and normal distribution, ANOVA, post hoc test was used; Tukey test was used for comparisons. Pearson and Spearman's correlation tests were used to evaluate correlation.

In the analyses, p value less than 0.05 was considered significant.

## RESULTS

The most common comorbidity among the patients was hypertension (HT) (73.7%) and the most common indication was non-valvular AF (66.5%). The most common medication with warfarin interaction was proton pump inhibitor (38.3%). According to multiple drug use, 68.9% of patients were using five or more medications. Risky foods were consumed by 21.6% of patients. Medications with risk of warfarin interaction were used by 89% of the patients. The rate of patients with previous hospitalizations due to warfarin overdose was 28.7%. Other demographic and clinical characteristics of the patients is displayed in Table 1.

Sources of bleeding, in order of frequency, were gastrointestinal (36%), hematuria (26%), ecchymosis (23%), epistaxis (12%), other (2%), and intracranial hemorrhage (1%).

**Table 3.** Comparison of clinical characteristics according to major and minor bleeding

	Major bleeding			Minor bleeding			p
	n	%	Mean±SD	n	%	Mean±SD	
International normalized ratio			8.2±3.8			8.9±3.6	0.23
Time in therapeutic range			28.1±22.2			24.8±22.5	0.41
Thromboembolic risk score			4.2±1.4			4.1±1.1	0.61
HASBLED			4.0±0.7			3.9±0.8	0.63
Warfarin dose (mg/week)			32.2±6.9			30.8±10.7	0.23
Risky food	7	19.4		15	24.6		0.62
Risky drugs	34	94.4		55	90.2		0.71

Thromboembolic risk score: CHA<sub>2</sub>DS<sub>2</sub>-VASc; HASBLED: Bleeding risk score.

**Table 4.** Clinical characteristics of the patients according to INR values

	INR (3.5<INR<5)			INR (5<INR<10)			INR (≥10)			p	
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median		Min-Max
Major bleeding	9	23.1				15	19.7				
Minor bleeding	10	25.6				28	36.8				0.37
No bleeding	20	51.3				33	43.4				
Thromboembolic risk score				4	2-7				4	2-7	0.11
HASBLED				3	2-6				4	2-6	0.59
Warfarin dose (mg/week)			27.8±8.4		8.5-35.0			31.3±8.8		10-70	0.02
Risky food	32	82.1				69	90.8				0.33
Risky drugs	8	20.5				15	19.7				0.76

INR: International normalized ratio; SD: Standard deviation; Min: Minimum; Max: Maximum; Thromboembolic risk score: CHA<sub>2</sub>DS<sub>2</sub>-VASc; HASBLED: Bleeding risk score..

Bleeding symptoms were present in 58.1% of patients. Of these patients, while 36.5% of all patients (63% of patients with bleeding symptoms) showed minor bleeding, 21.6% (37% of those with bleeding symptoms) had major bleeding.

According to the clinical characteristics of bleeding states, patients with bleeding symptoms had statistically significantly higher mean INR (8.6±3.7) compared to those who did not (7.1±3.4) (p=0.007). Similarly, mean HASBLED score was also significantly higher in patients with bleeding symptoms (3.9±0.8) compared to those who did not (3.1±0.8). To the contrary, mean TTR was significantly lower in patients with bleeding symptoms (26.1±22.3) compared to those without bleeding symptoms (32.6±22.7). There was no statistically significant difference between patients with and without bleeding symptoms according to CHA<sub>2</sub>DS<sub>2</sub>-VASc score, warfarin dose, consuming risky foods, and use of risky medications (Table 2).

According to clinical characteristics of major and minor bleeding states in patients with bleeding symptoms, there was no difference between the two groups in terms of mean INR, HASBLED score, and TTR. Similarly, there was no difference between patients with major and minor bleeding according to warfarin dose, consuming of risky foods, and use of risky medications (Table 3).

When clinical characteristics of patients were evaluated according to INR levels, patients with elevated INR (3.5-5; 27.8±8.4, 5-10; 31.3±8.8, INR ≥10; 32.2±8.5) were using warfarin dosage that was significantly higher (p=0.02). Presence of major bleeding, minor bleeding, no bleeding, CHA<sub>2</sub>DS<sub>2</sub>-VASc score, HASBLED score, eating risky foods and using risky medications were similar among the groups divided based on INR level (Table 4).

According to risk factors that could predict bleeding state, male gender (p=0.007) and HASBLED score (p<0.001) were observed as statistically independent risk factors (Table 5).

## DISCUSSION

The increasing use of warfarin in various indications and at higher rates has unfortunately

**Table 5.** Factors affecting bleeding

	B	OR (95%CI)	p
Age (year)			
<65	1.932	0.55-6.71	0.29
65-74	0.405	0.09-1.68	0.21
≥75	0.518	0.14-1.79	0.30
Gender			
Male	2.863	1.32-6.18	0.007
International normalized ratio			
3.5-4.9	0.628	0.23-1.71	0.35
5.0-9.9	0.993	0.39-2.47	0.98
≥10	1.593	0.58-4.34	0.36
Warfarin dose (mg/week)	1.022	0.97-1.06	0.31
Risky food	1.829	0.60-5.51	0.28
Risky drugs	1.830	0.71-4.69	0.21
Time in therapeutic range	0.989	0.97-1.01	0.16
HASBLED	3.771	2.27-6.26	<0.001

OR: Odds ratio; CI: Confidence interval; HASBLED: Bleeding risk score

increased the prevalence of adverse effects along with benefits. A large majority of bleeding occurring due to warfarin toxicity does not pose an important threat, however it may rarely cause major or life-threatening bleeding. In our study, bleeding due to warfarin overdose was present in over half of the patients, and it was established that it could be predicted by male gender and increased HASBLED score. Major and minor bleeding was observed to be independent from INR.

Warfarin is used to prevent thrombosis development in diseases such as AF, heart valve replacement, DVT, PTE, ischemic stroke, factor V Leiden mutation, and hyperhomocysteinemia.<sup>[17]</sup> Many studies list AF and stroke as the top indications for warfarin use.<sup>[18]</sup> In our study, while the most common warfarin indication was AF, the second was heart valve replacement, and the third was stroke, differing from the literature.

In a study by Erdogan et al.,<sup>[19]</sup> comorbidities in patients presenting with warfarin overdose found HT as the most common, followed by coronary artery disease, and congestive heart failure. Shireman et al.<sup>[20]</sup> also reported HT as the most common comorbidity. In our study, HT was also the most common comorbidity and consistent with the literature, however, congestive

heart failure was the second most common, and diabetes mellitus was the third.

There is limited information in the literature on the use of drugs and food with warfarin interaction. Baykal et al.<sup>[21]</sup> found the rate of risky drug use as 75%. In our study, 89% of the patients were using at least one drug that could present a risk. The three most common drugs were proton pump inhibitors, acetylsalicylic acid, and cardiac glycosides. In addition, 68.9% of patients were using five or more drugs, and 21.6% consuming risky foods that could increase warfarin interaction and facilitate overdose. All of these may have contributed to the rehospitalization rate (28.7%) due to warfarin overdose.

Bleeding is the most important major complication of warfarin treatment. One of the most important factors to affect bleeding risk is the intensity of anticoagulant treatment. When INR is between the range of 3.0-4.5, bleeding risk is significantly increased; when INR>5.0, it poses a life-threatening bleeding risk.<sup>[21-23]</sup> Minor or major bleeding rate is reported between 7.6-16.5%. Alay et al.<sup>[24]</sup> determined that 45% of patients presenting with warfarin overdose had major bleeding and 55% minor bleeding. According to sources of bleeding due to warfarin overdose, the most common were gastrointestinal, hematuria,

and soft tissue bleeding, while intracranial bleeding was less common.<sup>[25,26]</sup> Two separate studies have found gastrointestinal bleeding as the most common source at rates of 38.5% and 33.3%.<sup>[24,27]</sup> In our study, 58.1% of patients had bleeding symptoms, relatively higher than in the literature, however this could be because the literature evaluated all patients using warfarin, while in our study we only evaluated patients with overdose. Of the patients with bleeding symptoms, 37% were major bleeding, and 63% were minor bleeding, and compared to the literature, major bleeding was less frequent and only one patient had mortality. In our study, the most common bleeding source was gastrointestinal bleeding at 36%, consistent with the literature.

Increased INR is known to increase bleeding.<sup>[28]</sup> Lindh et al.<sup>[29]</sup> found that there was no linear relationship between INR and bleeding, while Landefeld et al.<sup>[30]</sup> found that every 1.0 increase in INR caused 40 times increased risk of bleeding. In a study by Veeger et al.,<sup>[28]</sup> although TTR value was not concisely determined, TTR value below 45% compared to TTR over 65% was associated with increased risk of recurrent venous thromboembolism and bleeding. Many bleeding risk scores have been developed to determine bleeding risk in patients using warfarin. HASBLED bleeding risk score is an easy to use scoring system to determine the patient's risk of bleeding. A score of 3 or more shows high risk of bleeding.<sup>[13]</sup> When clinical characteristics of patients in our study were evaluated according to bleeding status, INR value was significantly higher in patients with bleeding symptoms compared to those without bleeding, which was consistent with the literature. Similarly, HASBLED score was also significantly higher. Considering the components of HASBLED score are risk factors that increase bleeding, these results are not surprising. In contrast to the literature, mean TTR was significantly lower in patients with bleeding symptoms compared to those without bleeding. Since the selected patients were those with warfarin overdose, low TTR was an expected result in patients with bleeding symptoms.

One study reported significantly higher INR in patients with major bleeding compared to those with minor bleeding.<sup>[24]</sup> In our study, when patients with bleeding symptoms were grouped

according to major or minor bleeding, there was statistically significant difference in INR value. But HASBLED score, and mean TTR, they were no significantly different between patients with and without bleeding.

Regardless of overdose in patients using warfarin, it is known that many factors such as elderly age, female gender, comorbid illnesses, previous history of bleeding, eating foods or using drugs with warfarin interactions, TTR, and genetics may affect occurrence of bleeding.<sup>[31]</sup> Studies on these risk factors present conflicting results. Shirman et al.<sup>[20]</sup> reported that female gender and Lindh et al.<sup>[29]</sup> that male gender was an independent risk factor for bleeding, while other studies reported that gender was not significant. In the same way, while there are studies that report that bleeding risk increases with age,<sup>[32]</sup> there are also studies that state that age is an independent risk factor.<sup>[33]</sup> In our study, according to risk factors that could predict bleeding state, male gender and increased HASBLED score were found as statistically independent risk factors.

In conclusion, it was observed that inpatients hospitalized due to warfarin overdose had increased food consumption and use of drugs with warfarin interaction, approximately one out of every three patients required rehospitalization due to warfarin overdose, and that patients with high HASBLED score and low TTR had increased bleeding risk.

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