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Bleeding Due to Warfarin Treatment: Five Years of Experience

Varfarin Tedavisine Bağlı Kanama: Beş Yıllık Deneyim

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ABSTRACT Objective: The aim of the study was to determine the factors contributing to the development of bleeding and mortality in patients admitted to emergency department with any nontraumatic bleeding (major or minor) complaint while under warfarin therapy. **Material and Methods:** Patients who admitted to the emergency department of a university hospital between 2009 and 2013 due to bleeding complications during warfarin treatment were included in the study which was conducted in a prospective and observational design. The demographic characteristics of the patients, the reasons for using warfarin, the types and localizations of the bleedings, the treatments applied, the duration of hospitalization and mortality data were recorded. The factors that are likely to be effective on bleeding and mortality (age, hemodynamic status on admission, initial INR levels, warfarin dose, etc.) were analyzed comparatively. SPSS version 16.0 program was used for statistical analysis and $p<0.05$ was considered statistically significant. **Results:** A total of 518 patients were enrolled in the study. The mean age of the patients was 64.19±13.28 years, 229 (44.2%) of the patients were male. More than half of the patients were over 65 years of age, the most common indication for warfarin was heart valve disease and atrial fibrillation, and the most mortal bleeding type was gastrointestinal bleeding. There was no correlation between the first INR levels on admission and the bleeding severity and mortality ($p=0.577$, $p=0.788$). The most significant indicator of mortality was hemodynamic instability during admission. Systolic and diastolic arterial blood pressure and haemoglobin levels were significantly lower ($p=0.004$, $p=0.023$, $p=0.001$, respectively) in nonsurvivors, whereas pulse and shock index were significantly higher ($p<0.001$, $p<0.001$). **Conclusion:** Patients under warfarin treatment admit to emergency services with major or minor bleeding independently from INR levels. Especially, patients aged 65 and over are at risk. The most significant indicator of mortality appears to be hemodynamic instability during admission.

Keywords: Warfarin; hemorrhage; drug-related side effects and adverse reactions

ÖZET Amaç: Çalışmanın amacı, varfarin tedavisi altında iken (majör ya da minör) herhangi bir nontravmatik kanama şikayeti ile acil servise başvuran hastalarda, kanama gelişimi ve mortaliteye katkı sağlayan faktörleri belirlemektir. **Gereç ve Yöntemler:** Çalışmaya 2009-2013 yılları arasında bir üniversite hastanesi acil servisine nontravmatik kanama şikayeti ile başvuran ve varfarin kullanmakta olan hastalar dahil edildi. Çalışma prospektif, gözlemsel bir çalışma olarak yürütüldü. Hastaların demografik özellikleri, varfarin kullanma gerekçeleri, kanama tip ve lokalizasyonları, uygulanan tedaviler, yatış süreleri ve mortalite verileri kaydedildi. Kanama ve mortalite üzerine etkili olması muhtemel faktörler (yaş, başvurudaki hemodinamik durum, başlangıç INR düzeyleri, varfarin dozu vb.), karşılaştırmalı olarak analiz edildi. İstatistiksel incelemede SPSS ver. 16.0 programı kullanıldı. $p<0,05$ istatistiksel olarak anlamlı kabul edildi. **Bulgular:** Çalışmaya toplam 518 hasta alındı. Hastaların yaş ortalaması 64,19±13,28, 229'u (%44,2) erkekti. Hastaların yarısından fazlası 65 yaş üzerinde, en sık varfarin kullanım endikasyonu kalp kapak hastalığı ve atrial fibrilasyon, en fazla mortal seyreden kanama şekli gastrointestinal kanama idi. Başvuru sırasındaki ilk INR düzeyleri ile kanama ciddiyeti ve mortalite arasında bir ilişki tespit edilmemiştir ($p=0,577$, $p=0,788$). Mortal seyreden hastalarda sistolik ve diyastolik tansiyon arteryel ve hemoglobin düzeyleri anlamlı olarak ($p=0,004$, $p=0,023$, $p=0,001$, sırasıyla) daha düşük iken, nabız ve şok indeksi anlamlı olarak ($p<0,001$, $p<0,001$) daha yüksek bulunmuştur. **Sonuç:** Varfarin tedavisi altındaki hastalar, INR seviyelerinden bağımsız olarak majör ya da minör kanama şikayetleri ile acil servislere başvurmaktadırlar. Özellikle 65 yaş ve üzerindeki hastalar risk altındadırlar. Mortalitenin en anlamlı göstergesi başvuru esnasındaki hemodinamik kararsızlık olarak görünmektedir.

Anahtar Kelimeler: Varfarin; kanama; ilaç ilişkili yan etkiler ve istenmeyen reaksiyonlar

The use of anticoagulants across the world has increased significantly especially due to the effort to prevent thromboembolic events.[1] This has increased the complications related to these agents. In United States, they are among the drugs that account for the most substantial portion of presentations to emergency units due to drug poisoning.[2] Warfarin is a coumarin derived oral anticoagulant widely used globally. The mechanism of action of warfarin is blocking the gamma carboxylation of vitamin K-dependent coagulation factors (factor 2,7,9,10) and various glutamate residues in prothrombin and protein C and S.[3] Its toxicity is usually related to dose changes, the narrow therapeutic index, the need to constantly adjust the dose based on the International Normalized Ratio (INR) levels, and drug interactions.[4] Although new generation oral anticoagulant (NOACs) agents have been discovered and put into use, warfarin is still important because of its widespread use and it can cause major bleeding. The number of case reports about bleeding complications related to warfarin use or overdose is high in the literature, but the number of studies with extensive case populations is rather limited. Our study discusses the factors that affect the development of bleeding and their clinical results in patients taking warfarin at therapeutic doses, who presented to the emergency units with non-traumatic bleeding complaints.

MATERIAL AND METHODS

The study was conducted as a prospective-cohort study and included patients over 18 years of age who presented to the emergency unit of a university hospital with (non-traumatic) bleeding complaints related to warfarin use between 2009-2013 consecutively. Patients who regularly used warfarin for at least one month were included in the study. Patients exposed to trauma, those who had taken high doses of warfarin with suicidal purposes, those with high INR levels without bleeding and those with hematological malignancies and bleeding-coagulation disorders were excluded from the study. Furthermore, during the study period, the prothrombin complex concentrate (PCC) was not included in the pharmaceutical reimbursement list of the social security institution, and it was not routinely used in any hospital in our country or due to being very expensive. The age, gender, presentation complaint, personal history, weekly warfarin dose (because a substantial portion of the patients did not take the same dose every day), and their vital findings were recorded on the form prepared. The INR and hemoglobin levels of all patients were assessed on presentation. For the measurement of PT (INR), 1.8 cc peripheric venous blood was placed into tubes containing 0.2 cc of 3.2% sodium citrate. Plasma samples obtained once separated by centrifugation were studied by Stago STA-R Evolution® UK's device and clot based method. Additionally, ultrasonography (USG) or computerized tomography (CT) was performed to identify the site of bleeding when necessary. The bleeding types were classified based on the Bleeding Academic Research Consortium Definition for Bleeding (BARC) (Table 1).[5] The treatments delivered to the patients [Packed Red Cell

TABLE 1: The bleeding definitions according to the Bleeding Academic Research Consortium Definition for Bleeding (BARC).

Type 0	is no bleeding
Type 1	is bleeding that "is not actionable" and does not cause the patient to seek medical attention
Type 2	bleeding includes any clinically overt sign of hemorrhage that "is actionable" and requires diagnostic studies, hospitalization, or treatment
Type 3	Type 3 a bleeding includes any transfusion with overt bleeding and overt bleeding plus a hemoglobin drop of ≥3 to <5 g/dL (related to bleeding) Type 3 b bleeding includes overt bleeding plus a hemoglobin drop of ≥5 g/dL, cardiac tamponade, bleeding requiring surgical intervention and intravenous vasoactive drugs Type 3 c bleeding includes intracranial hemorrhage and intraocular bleeding compromising vision
Type 4	bleeding is coronary artery bypass grafting-related (within 48 hours)
Type 5	bleeding is fatal (intracranial, gastrointestinal, retroperitoneal, pulmonary, pericardial, genitourinary, etc)

(PRC), Fresh Frozen Plasma (FFP) and vitamin K amounts and observation results (discharge, referral, death)] were also recorded. The management of these patients was based on the guidelines published by the American Heart Association/American College of Cardiology Foundation in 2003.[6] Patients who meet the inclusion criteria were separated into 3 groups according to their age, INR values and surveys. Age, gender, warfarin dose, INR, hemoglobin (Hb) and platelet levels, vital signs, need for PRC and FFP, duration of hospital stay and mortality of patients were compared to these groups. Our study was approved by the Local Ethical Board of our university ('Hemorrhagic Complications Due to Warfarin Overdose' Name, 29/05/2009 Date and 2009/14 Number). The study was conducted in compliance with the ethical principles of the Helsinki Declaration. Informed consent was taken from the patients themselves or their relatives.

STATISTICAL ANALYSIS

The statistical analysis was performed using the SPSS ver. 16.0 program. Categorical variables were expressed as numbers (percentage) and numeric variables as mean±SD. The normality of the distribution of the variables was assessed using the histogram, the Kolmogorov-Smirnov, and the Shapiro-Wilk tests. The intergroup differences between the categorical data were compared using the chi-square or the Fisher's exact test. The intergroup differences between the normally distributed variables were compared using the Student t test, and the one-way ANOVA Tuker HSD, and the non-normally distributed variables were compared using the Kruskal Wallis and the Mann-Whitney U tests. Multivariate logistic regression analysis was carried out to identify independent risk factors for mortality. Conditions in which the p value was under 0.05 were regarded as statistically significant results.

RESULTS

Among 518 patients included in the study, 229 (44.2%) were male, 289 (55.8%) were female, and the average age was 64.2±13.3 (median 66, maximum-minimum age 18-99). The patients' laboratory values and vital findings on presentation have been displayed in Table 2. The average warfarin dose taken by the patients was identified as 31.9 ± 10.7 mg/week (median 35.0 mg). The average INR level was 9.6±8.6 (median 7.00) and the average hospitalization period was 2.00±1.7 days (1-17 days). During the hospitalization, 435 (83.9%) patients were given an average of 2.4±1.0 U of FFP, 135 (26.0%) were given an average of 2.7±1.3U of PRC, and 125 (24.1%) were given an average of 4.6±3.3 mg vitamin K. Since no oral preparation of vitamin K is available in our country, vitamin K was delivered as intravenous (IV) infusions. Two (0.3%) patients were referred to a different center after having been monitored for a while, and 37 (7.1%) patients lost their lives.

When the patients' complaints on presentation were reviewed, it was identified that gastrointestinal bleeding (21.8%), hematuria (18.1%) and epistaxis (15.4%) were in the first three ranks. The

TABLE 2: Demographic characteristics, hemodynamic values on admission, treatment and mortality data of the patients.

	Value	Range
Gender		
Male, *n (%)*	229 (44.2)	
Female, *n (%)*	289 (55.8)	
Age, *year±SD*	64.2±13.3	(18-99)
Warfarin dose, mg/*wk±SD*	31.9±10.7	(10-75)
INR, *mean±SD*	9.6±8.6	(1.60-60.50)
Hb, *mg/dL±SD*	10.4±2.6	(3.8-16.7)
Platelet, *10^3/μL±SD*	263.4±96.6	(36-650)
SBP, *mmHg±SD*	120.0±23.5	(20-230)
DBP, *mmHg±SD*	73.9±14.4	(0-130)
Pulse, *beat/min±SD*	88.6±18.1	(40-200)
SI, *mean±SD*	0.8±0.4	(0.35-6.50)
MSI, *mean±SD*	1.1±1.0	(0.48-19.50)
FFP, *unit±SD*	2.4±1.0	(1-8)
PRC, *unit±SD*	2.7±1.3	(1-11)
K vit, *mg±SD*	4.6±3.3	(1-20)
Lenght of stay, *day±SD*	2.0±1.7	(1-17)
Mortality, *n (%)*	37 (7.1)	

SD: Standard deviation; INR: International normalized ratio; Hb: Hemoglobin; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; SI: Shock index; MSI: Modified shock index; FFP: Fresh frozen plasma; PRC: packed red cell.

TABLE 3: The localizations and types of bleedings, and mortality causes in patients using warfarin.

Localization	n	%
Gastrointestinal hemorrhage	113	21.8
Hematuria	94	18.1
Epistaxis	80	15.5
Skin/Subcutaneous hemorrhage	74	14.3
Intraabdominal bleeding	39	7.5
Bleeding gums	33	6.4
Intramuscular hemorrhage	31	6.0
Hemoptysis	16	3.1
İntracranial hemorrhage	15	2.9
Lingual haematoma	5	0.9
Intraorbital bleeding	5	0.9
Vaginal bleeding	4	0.8
Intraarticular bleeding	2	0.4
Others	7	1.4
Total	**518**	**100**
Bleeding Type		
1	24	4.6
2	306	59.1
3a	135	26.0
3b	33	6.4
3c	20	3.9
4	-	-
5	28	5.4
Total	*	*
Mortality causes		
Gastrointestinal bleeding	13	35.1
Intracranial hemorrhage	7	18.9
Intraalveolar hemorrhage	5	13.5
Intraabdominal bleeding	3	8.1
Sepsis	5	13.5
CRF+ARF+Hyperkalemia	1	2.7
Pneumonia	1	2.7
CHF	1	2.7
Pulmonary embolism	1	2.7
Total	**37**	**100**

CRF: Chronic renal failure; ARF: acute renal failure; CHF: Congestive heart failure.
*Because some types of bleeding and fatal bleeding were joint, the total number and percentage went up.

patients' bleeding patterns identified on presentation have been presented in Table 3. Based on the classification of bleeding severity, it was noted that nearly 64% of the bleedings were not very severe. Of the patients, 37 (7.1%) lost their lives. However, mortality directly related to bleeding was identified in 28 (5.4%) patients. The causes of death of the patients have also been presented in detail in Table 3.

The assessment of the reasons for using warfarin demonstrated that the most common reason was heart valve replacement (34.2%) followed by atrial fibrillation (29.5%). The other indications have been presented in Table 4 based on the order of frequency.

The comparison performed between patients who survived and those that died did not reveal any statistically significant difference with regard to age, gender, the weekly warfarin dose, or the amount of FFP or PRC administered. However, there was a significant difference between the survivors and non-survivors with respect to the indicators of hemorrhage and hypovolemia, pulse, systolic and diastolic blood pressure, the shock index, and the Hb values (Table 5). The non-survivors had significantly lower hemoglobin levels, systolic and diastolic blood pressures (BP) ($p=0.001$, $p=0.004$, and $p=0.023$, respectively) and higher pulse rates, shock index values, length of stay in hospital ($p<0.001$) and PRC needs ($p=0.004$) than the survivors. On the other hand, the single variant regression analysis carried out to identify the independent risk factors for mortality only showed a significant relationship with hemodynamic parameters (BP, pulse, shock index) ($p<0.001$, $p=0.004$, $p<0.001$, respectively. On the other hand, in the multivariate analysis,

TABLE 4: Rationale of warfarin use.

Indication	n	%
Heart valve replacement	177	34.2
AF	153	29.5
CAD	50	9.7
Stroke	46	8.9
PAD	29	5.6
DVT	17	3.2
PE	16	3.1
Others	30	5.8
Total	**518**	**100**

AF: Atrial fibrillation; CAD: Coronary artery disease; PAD: Peripheral artery disease; DVT: Deep vein thrombosis; PE: Pulmonary embolism.

TABLE 5: Comparison of demographic, clinical and treatment characteristics of survivors and survivors.

	Survivors (n=481)	Nonsurvivors (n=37)	p
Gender			
Male, *n (%)*	212 (44.3)	17 (45.9)	0.842
Female, *n (%)*	267 (55.7)	20 (54.1)	
Age, *year±SD*	64.2±13.2	64.4±14.5	0.675
Warfarin dose, *mg/wk±SD*	32.0±10.9	31.1±7.0	0.883
INR, *mean±SD*	9.7±8.7	9.2±7.4	0.788
Hb, *mg/dL±SD*	10.5±2.6	8.9±2.5	**0.001**
Platelet, *10^3/μL*	264.7±97.2	248.4±87.8	0.745
SBP, *mmHg±SD*	121.4±22.0	103.9±33.6	**0.004**
DBP, *mmHg±SD*	74.7±13.1	64.3±23.2	**0.023**
Pulse, *beat/min±SD*	87.8±17.5	100.7±21.8	**<0.001**
SI, *mean±SD*	0.8±0.2	1.2±1.1	**<0.001**
MSI, *mean±SD*	1.0±0.3	2.2±3.6	**<0.001**
FFP need, *n (%)*			
Yes	401 (83.4)	34 (91.9)	0.170
No	80 (16.6)	3 (8.1)	
FFP, *unit±SD*	2.4±0.9	2.5±1.3	0.592
PRC need, *n (%)*			
Yes	118 (24.6)	17 (45.9)	**0.004**
No	363 (75.4)	20 (54.1)	
ES, *unit±SD*	2.6±0.9	3.5±2.4	0.137
Lenght of stay, *day±SD*	1.9±1.3	4.2±4.0	**<0.001**

SD: Standard deviation; NR: International normalized ratio; Hb: Hemoglobin; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; SI: Shock index; MSI: Modified shock index; FFP: Fresh frozen plasma; PRC: packed red cell.

only the shock index was found to be significant (p=0.008).

When age groups were compared, it was seen that only two age groups differed from the others. The Hb level in the ≥75 years of age group was lower than that in the other groups (p=0.013), and the PRC needs were higher (p<0.001). The pulse, shock index, and modified shock index were found to be higher in the≥75 age group and the<45 age group than in the other groups (p=0.035, p=0.005, p=0.003, respectively). No statistically significant difference was detected between the other parameters (Table 6).

The patients were divided into three groups based on their INR values (≤5.00, 5.01-9.00 and >9.00). No difference was observed concerning age in the inter-group comparison, but it was observed that the INR values of ≤5.00 and >9.00 were more frequent among women. The weekly warfarin dose, pulse rate, shock index values, the number of patients requiring FFP and the amounts delivered were significantly higher in patients with INR values of > 9.00, and the systolic blood pressure (SBP) was found to be lower (p=0.021, p=0.030, p=0.004, p<0.001, p=0.002, respectively). However, no significant relationship was determined between the type of the bleeding and mortality and INR levels (p=0.577 and p=0.344) (Table 7).

DISCUSSION

Warfarin is used for many indications with both prophylactic and therapeutic purposes. Warfarin is an agent with a narrow therapeutic index. It is recommended to keep the INR value between 2-3 to maintain anticoagulation.[7] It has been reported that INR values of ≤2 increase the thromboembolism risk and INR values of ≥5 increase the risk of major bleeding.[8] In a study, it was reported that there were differences with respect to the patient profile, anticoagulant indication, and bleeding foci, and that the risk of warfarin-related bleeding was 1-5% and the risk of fatal bleeding was 0.1-1.1%.[9] It has been stated that advanced age individuals who use warfarin are at higher risk of bleeding complications and major bleeding.[10] In their study, Eroglu and colleagues also stated that age was not an independent risk factor, although 73% of the patients admitted to the intensive care for warfarin overdose were over 65 years of age.[11] In the study conducted with 84 patients, Cruickshank J. et al. reported the average age as 68.8 (29-85).[12] In our study, the average age of the patients was approximately 65 (median 66), and approximately 57% were over 64 years of age. This is consistent with the data that the patient population that uses warfarin usually comprises elderly patients. However, a direct relationship between age and mortality was not identified in our study. On the other hand, the comparison performed based on age groups showed that the Hb levels were lower, the shock index was higher, and the need for ES was higher in patients older than 75 years of age than in the other groups. Therefore, although advanced age is not an inde-

TABLE 6: Demographic, clinical and treatment characteristics of patients according to age groups.

	<45 y (n=37)	45-54 y (n=78)	55-64 y (n=109)	65-74 y (n=155)	≥75 y (n=139)	p
Gender						
Male, *n (%)*	12 (32.4)	30 (38.5)	48 (44.0)	68 (43.9)	71 (51.1)	0.215
Female, *n (%)*	25 (67.6)	48 (61.5)	61 (56.0)	87 (56.1)	68 (48.9)	
Warfarin dose, *mg/wk±SD*	35.5±14.3	32.6±12.5	31.1±9.2	31.1±9.5	31.7±10.1	0.630
INR, *mean±SD*	8.2±4.5	10.5±9.3	7.7±5.9	10.2±9.2	10.3±10.1	0.242
Hb, *mg/dL±SD*	10.3±2.0	11.0±2.5	10.6±2.9	10.5±2.5	9.8±2.6	**0.013**
Platelet, *10^3/µL*	264.1±93.6	263.4±82.6	257.7±74.3	279.9±116.8	248.9±93.4	0.242
SBP, *mmHg±SD*	114.7±22.4	123.4±22.9	120.9±20.7	122.7±24.7	115.8±24.2	0.190
DBP, *mmHg±SD*	70.3±17.1	76.5±11.2	74.5±11.9	75.3±13.7	71.3±16.9	0.142
Pulse, *beat/min±SD*	91.9±16.0	84.0±13.2	88.9±20.8	87.4±16.3	91.4±20.3	**0.035**
SI, *mean±SD*	0.9±0.7	0.7±0.2	0.8±0.3	0.6±0.6	0.9±0.6	**0.005**
MSI, *mean±SD*	1.4±2.1	0.9±0.2	1.0±0.4	1.0±0.3	1.2±1.6	**0.003**
FFP *need, n (%)*						
Yes	32 (86.5)	64 (82.1)	90 (82.6)	129 (83.2)	120 (86.3)	0.880
No	5 (13.5)	14 (17.9)	19 (17.4)	26 (16.8)	19 (13.7)	
FFP, *unit±SD*	2.5±1.2	2.6±1.1	2.2±0.8	2.4±0.9	2.4±1.0	0.269
PRC need, *n (%)*						
Yes	6 (16.2)	11 (14.1)	28 (25.7)	36 (23.2)	54 (38.8)	**<0.001**
No	31 (83.8)	67 (85.9)	81 (74.3)	119 (76.8)	85 (61.2)	
ES, *unit±SD*	3.2±1.5	3.0±1.3	3.0±1.9	2.7±1.1	2.5±0.8	0.553
Lenght of stay, *day±SD*	1.7±1.2	1.7±0.8	2.2±2.4	2.1±2.0	2.0±1.2	0.646
Mortality	5 (13.5)	2 (2.6)	9 (8.3)	10 (6.5)	11 (7.9)	0.271

SD: Standard deviation; INR: International normalized ratio; Hb: Hemoglobin; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; SI: Shock index; MSI: Modified shock index; FFP: Fresh frozen plasma; PRC: packed red cell.

pendent cause of mortality in warfarin related bleedings, it can be concluded that a risk is present, since hemodynamic instability can develop easier in elderly patients. In the study conducted by Koo and colleagues, it was observed that the rate of female patients (46%) was lower than male patients.[13] On the other hand, Eroglu and colleagues claimed that female gender could not be dominant with respect to complications despite the number of female patients being higher.[11] In our study, approximately 56% of the patients were female. Furthermore, a significant portion of the female patients was in the group with INR values of >9 (p=0.020). However, no significant relationship was identified between gender and mortality. Therefore, we do not consider gender to be a factor responsible for bleeding severity and mortality alone.

When the reasons for using warfarin were examined, two conditions drew attention: atrial fibrillation (AF) and valvular heart disease (VHD). While AF is reported as the most common reason is some publications, others report that VHD-related use is more common. Unverir and colleagues reported AF as the most common anticoagulation indication, while Nargis and colleagues reported that warfarin was most often used for VHD.[14,15] In our study, too, the most common indication was heart valve replacement (34.2%) followed by AF (29.5%).

A substantial portion of the bleedings that develop in patients using warfarin is minor bleedings. However, life-threatening and fatal bleedings have also been reported. Intracranial or gastrointestinal system (GIS) bleedings are the leading fatal bleedings.[10,11] In our study, the three most frequent bleedings were GIS bleeding (21.8%), hematuria (18.1%), and epistaxis (15.5%). The rate of intracranial bleeding was lower (2.9%). When we examined the site of bleeding in fatal cases, the

TABLE 7: Clinical, laboratory, treatment characteristics and types of bleeding compared to initial INR values of patients.

	≤5.00 (n=176)	5.01-9.00 (n=143)	>9.00 (n=199)	p
Gender				
Male, *n (%)*	68 (38.6)	77 (53.8)	83 (41.7)	**0.020**
Female, *n (%)*	108 (61.4)	66 (46.2)	116 (58.3)	
Age, *year±SD*	63.5±13.6	63.4±13.1	65.2±13.3	0.224
Warfarin dose, *mg/wk±SD*	29.9±9.0	32.6±11.6	33.2±11.2	**0.021**
Hb, *mg/dL±SD*	10.4±2.6	10.7±2.7	10.2±2.6	0.255
Platelet, *10^3/µL*	247.8±73.8	268.2±88.7	273.6±116.9	0.124
SBP, *mmHg±SD*	119.3±20.6	125.4±28.0	116.4±22.0	**0.002**
DBP, *mmHg±SD*	73.5±14.4	75.9±15.1	72.4±14.0	0.099
Pulse, *beat/min±SD*	86.4±15.4	88.1±19.7	91.2±19.4	**0.030**
SI, *mean±SD*	0.8±0.2	0.8±0.4	0.9±0.5	**0.004**
MSI, *mean±SD*	1.0±0.3	1.1±1.1	1.2±1.4	**0.010**
Bleeding Type, *n(%)*				
1	9 (5.1)	4 (2.8)	11 (5.5)	0.577
2	108 (61.4)	86 (60.1)	112 (56.3)	
3a	38 (21.6)	36 (25.2)	61 (30.7)	
3b	13 (7.4)	9 (6.3)	11 (5.5)	
3c	8 (4.5)	8 (5.6)	4 (2.0)	
5	8 (4.5)	13 (9.1)	7 (3.5)	
FFP need, *n (%)*				
Yes	103 (58.5)	136 (95.1)	196 (98.5)	**<0.001**
No	73 (41.5)	7 (4.9)	3 (1.5)	
FFP, *unit±SD*	1.7±0.5	2.2±0.8	2.8±1.0	**<0.001**
PRC need, *n (%)*				
Yes	43 (24.4)	34 (23.8)	58 (29.1)	0.341
No	133 (75.6)	109 (76.2)	141 (70.9)	
ES, *unit±SD*	2.8±0.9	3.0±1.9	2.5±0.9	0.072
Lenght of stay, *day±SD*	1.9±1.7	2.2±2.4	1.9±1.2	0.451
Mortality	11 (6.4)	14 (10.1)	12 (6.2)	0.344

SD: Standard deviation; INR: International normalized ratio; Hb: Hemoglobin; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; SI: Shock index; MSI: Modified shock index; FFP: Fresh frozen plasma; PRC: packed red cell.

leading cause among all causes (~%35) and bleeding-related mortality causes (~%46) was GIS bleeding. Intracranial bleeding was the second most common cause (~%19 and %25, respectively). In fact, when intracranial bleeding is excluded, the most significant result of our study is that the most important factor that contributes to mortality is the hemodynamic condition of the patient on presentation rather than the site of the bleeding.

Ansell J and colleagues reported that the desired INR value (2-3) for anticoagulation could be reached using 5 mg/day oral warfarin.[16] Fanikos et al. reported that the average warfarin dose used by patients who developed bleeding complications was 5.15 mg, and Nargis and colleagues reported that their patients were taking 5 mg of warfarin at the daily treatment dose.[10,15] Garcia DA and colleagues reported that bleeding was not solely dependent on warfarin and that additional factors may also have been responsible for the bleeding and that bleedings that occurred within the first month were particularly related to the patient's unique characteristics.[7] The average warfarin dose of our patients was 31.9±10.7 mg/week. That is to say, the average dose was approximately 4.55 mg, which is close to the normal daily dose recommended to

most patients. In 344 (66.4%) of the patients, the INR levels were identified to be above 5, although the patients were taking the recommended oral dose. The rate of patients with INR values of ≥3 was approximately 90%. This condition strongly suggests that there are factors other than the warfarin dose that affect the INR levels. However, in our study, despite the presence of a statistical relationship between the warfarin dose and high INR levels, no significant relationship was determined between the severity of the bleeding and mortality. This also suggested that other factors independent of the warfarin dose may have led to major bleeding and mortality. In the literature, there are reports of interactions between warfarin and genetic structure, food consumed, drugs, and underlying chronic diseases.[14,17] However, the direct effect of these factors on the occurrence or severity of bleeding is unknown. Therefore, there appear to be other factors that need to be questioned.

In a study, the rate of major bleeding in patients using warfarin was reported as 1-12%.[13] Unverir and colleagues reported the rate of patients with major bleeding as 21.6%. They concluded that the high levels could be related to sociocultural differences and interruptions in the follow-up of the bleeding profile.[14] Weber JE and colleagues reported that the bleeding risk increased further when the INR level rose above 5.[18] There are also studies reporting that the association between INR levels and the severity of bleeding is weak. For example, Denizbasi et al. reported that the INR values of patients and the severity of their complications did not run a parallel course and that the rate of bleeding was 82%.[19] Similarly, Levine et al. claimed that there was no clear connection between major bleeding or the bleeding rate and the anticoagulant effects.[20] Eroglu and colleagues also expressed that they did not identify a relationship between the INR levels and the severity of bleeding.[11] In our study, the rate of mortality directly related to bleeding was identified as 5.4%. However, no relationship was established between the INR values and the bleeding types or mortality. Therefore, the presence of additional factors that may cause major bleeding should be considered.

It is recommended to discontinue the drug and observe the patients with high INR levels and no bleeding, to discontinue the drug in patients with bleeding complications, and to administer vitamin K, FFP or prothrombin complex concentrates in cases of major bleeding.[6] Dentali et al. recommended administration of intravenous vitamin K and coagulation factors in patients with major bleedings, but did not express a definite statement about the most suitable dose or type of coagulation factor.[21] It was identified that in other studies, these patients were treated with vitamin K together with FFP and/or PRC based on the indications stated in guidelines.[11,15] In our study, a significant increase was determined in the patients' FFP needs and the amount administered as the INR value increased (≥9). Unverir and colleagues delivered vitamin K to 28.6% of the patients.[14] They attributed this high rate to the high number of bleeding complications or the possibility of vitamin K having been delivered to some patients for wrong indications. Alay and colleagues reported that the transfusion need was higher in patients with high INR values or in those presenting with major bleeding and that the management of the bleeding required more time.[22] In our study, 59.8% of the patients were administered FFP alone, and 24.1% were administered FFP together with vitamin K. Although approximately 64% of the patients did not suffer from severe bleeding the rate of patients who were administered FFP was rather high. This can be explained by reasons such as the high rate of patients with increased INR levels, bleeding at sites that may lead to functional defects despite the amount of bleeding being low, the unavailability of oral vitamin K preparations in our country and the reluctance to use IV vitamin K, and the tendency to correct high INR levels with FFP even in the absence of severe bleeding.

LIMITATIONS

Due to the fact that the study was a single-center study, it cannot be claimed that the results it presents can be generalized. We are unaware of the patient population in our region using warfarin

during the study period. Therefore, we were unable to calculate how many of the patients using warfarin at therapeutic doses actually suffered from bleeding. Since the study only included patients presenting with bleeding complaints, the patient population that did not suffer bleeding despite high INR values was not evaluated, and a comparison could not be made. An important limitation of the study is that the medications used by patients concomitantly with warfarin were not taken into account. A significant portion of the patients were in the older age group and had multiple medical problems. They used a wide variety of drugs and they had different dietary habits. Therefore, It was not possible to assess the warfarin interaction with each drug or food. No comparison to patients using NOACs presenting with bleeding complaints was made. The study included only those who were admitted to the emergency department with bleeding complaints when using warfarin. Therefore, the patient population that did not show any bleeding despite the high INR values was not evaluated and no comparison was made.

CONCLUSION

Although NOACs are introduced into medical use daily, the use of warfarin continues at considerable rates across the world. Problems related to dose adjustment, food and drug interactions, and difficulties in INR monitoring make bleeding complications related to warfarin use a current agenda. In our study conducted in patients presenting to the emergency unit with bleeding complaints while using warfarin, it was observed that more than half of the patients were 65 years of age or older, and that there was no significant difference with respect to gender. It was observed that 2/3 of the patients used warfarin for valvular heart disease and atrial fibrillation, that a significant portion of the bleedings were minor bleedings, and that GIS bleedings were prominent among the causes of fatal bleedings. Moreover, it was observed that the most important factor that contributed to mortality was the patient's hemodynamic condition on presentation. Although they were taking warfarin at therapeutic doses, the warfarin value was higher than 5 in 2/3 and higher than 3 in 4/5 of the patients. However, no relationship was identified between the INR levels and the severity of bleeding or mortality.

In final words, patients using warfarin can suffer from fatal and non-fatal bleeding even at therapeutic doses. Patients should be informed thoroughly about this; they should be recommended to avoid drugs and foods that increase the effect of warfarin and to regularly attend INR follow-ups. As emergency unit doctors, the hemodynamic data of patients presenting to the emergency service with bleeding complaints related to warfarin use should be assessed carefully, and aggressive interventions and close monitorization should be performed in unstable patients.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Sedat Kocak, Birsen Ertekin;* ***Design:*** *Esma Erdemir Öztürk, Sedat Kocak, Birsen Ertekin;* ***Control/Supervision:*** *Defne Dundar, Esma Erdemir Öztürk, Sedat Kocak, Birsen Ertekin;* ***Data Collection and/or Processing:*** *Tarık Acar, Defne Dundar, Esma Erdemir Öztürk, Sedat Kocak, Birsen Ertekin;* ***Analysis and/or Interpretation:*** *A. Sadık Girisgin, Defne Dundar, Esma Erdemir Öztürk, Sedat Kocak, Birsen Ertekin;* ***Literature Review:*** *M. Refik Medni, Esma Erdemir Öztürk, Sedat Kocak, Birsen Ertekin;* ***Writing the Article:*** *Sedat Kocak, Birsen Ertekin;* ***Critical Review:*** *Sadık Girisgin, Tarık Acar, Defne Dundar, Esma Erdemir Öztürk, Sedat Kocak;* ***References and Fundings:*** *M.Refik Medni, Tarık Acar, Defne Dundar, Sedat Kocak, Birsen Ertekin;* ***Materials:*** *A. Sadık Girisgin, Tarık Acar, Sedat Kocak, Birsen Ertekin.*

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