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Original Article

J Clin Med Res. 2019;11(2):106-113

Bleeding Complications in Warfarin-Treated Patients Admitted to the Emergency Department

Mustafa Ozturk[a], Afsin Ipekci[b], Sevil Kusku Kiyak[b], Yonca Sinem Akdeniz[b], Yavuz Aydin[b], Ibrahim Ikizceli[b], Ozgur Sogut[a, c]

Abstract

Background: Increased use of warfarin for the treatment and prophylaxis of many diseases has increased the frequency of adverse events. Emergency departments (EDs) are the first places where early interventions for bleeding and other complaints related to warfarin use are performed. This study assessed the characteristics of patients receiving warfarin and the risk factors for bleeding complication among those admitted to the ED.

Methods: Patients admitted to the ED for any reason other than trauma during a 1-year period were retrospectively reviewed. The study population consisted of 96 patients who had received warfarin and had an international normalized ratio (INR) ≥ 3. Patient demographics and medical history were recorded.

Results: The mean age of the patients (female, 52.1%) was 64.9 ± 14.5 years. Fatigue was the most common presenting complaint (61%). At least one major and/or minor bleeding event had occurred in 32 (33.3%) of the patients. Patients with (n = 32) and without (n = 64) bleeding complications did not significantly differ with respect to age, sex, reason for warfarin initiation, duration of warfarin use, concomitant diseases, and concurrent medications. There were also no significant differences in the distribution of patient admissions in terms of season at presentation, INR level, and weekly warfarin dose.

Conclusions: While the parameters evaluated in this study did not significantly differ among warfarin-treated patients, they may nonetheless pose a risk of bleeding. Further large-scale and long-term studies that take into account biological variation are required to precisely identify the risk factors for bleeding.

Keywords: Warfarin-treated patients; International normalized ratio; Major bleeding event; Minor bleeding event; Emergency department

Manuscript submitted October 22, 2018, accepted November 15, 2018

[a]Department of Emergency Medicine, University of Health Sciences, Haseki Training and Research Hospital, Istanbul, Turkey
[b]Department of Emergency Medicine, University of Istanbul Cerrahpasa, Istanbul, Turkey
[c]Corresponding Author: Ozgur Sogut, Department of Emergency Medicine, University of Health Sciences, Haseki Research and Training Hospital, Millet Street, 34096, Fatih/Istanbul, Turkey. Email: ozgur.sogut@sbu.edu.tr

doi: https://doi.org/10.14740/jocmr3669

Introduction

Warfarin is an anticoagulant used for the treatment and prophylaxis of many diseases. Due to its substantially narrow therapeutic index, determination of its therapeutic dose in clinical practice can be challenging [1, 2]. Thus, adverse events (AEs) are frequently encountered, particularly at the beginning of treatment, until the appropriate therapeutic dose is achieved. For this reason, warfarin-treated patients are closely monitored, through measurements of their international normalized ratio (INR). An INR of > 3 (and especially > 4) often results in bleeding, while inadequate anticoagulation (INR < 2) enhances the risk for thrombotic events [2]. The appropriate warfarin dose is influenced by numerous variables, including the vitamin K load in the patient's diet, hepatic function, comorbidities, concurrent medications, and CYP2C9 polymorphisms. Other factors limiting the use of warfarin are unpredictable and patient-specific dose responses, a delayed onset or delayed cessation of action, the need to monitor anticoagulation, and many drug-drug and drug-food interactions [3-5]. Moreover, because of its teratogenic effects, warfarin is contraindicated during pregnancy [6].

A warfarin dose that is too high increases the frequency of AEs and complications, particularly bleeding [7]. Although most warfarin-associated bleeding events do not cause significant problems, in rare cases they may be major and life-threatening [8-10]. A better understanding of the efficacy and safety of warfarin would allow more efficient and extensive administration while reducing the problems associated with its use. Thus, we assessed the characteristics of warfarin-treated patients as well as the risk factors leading to bleeding among patients admitted to the emergency department (ED) for warfarin-related complications.

Materials and Methods

Data from the 61,707 adult patients admitted to the ED of our hospital during a 1-year period for any reason other than trauma were retrospectively reviewed. Within this group, 309 patients on warfarin were identified and 96 patients (141 ED visits) had an INR ≥ 3. Patient demographics and medical history were recorded, together with major and minor bleeding events. Macroscopic hematuria, gastrointestinal, retroperitoneal, cranial, and intra-abdominal bleeding, bleeding requiring

hospitalization or an invasive procedure, bleeding causing a 2-unit decrease in the hemoglobin level, and bleeding requiring > 3 units of blood product transfusion were considered major bleeding events.

Clinically relevant minor bleeding was defined as skin hematoma > 25 cm^2, spontaneous nosebleed of > 5-min duration, gingival bleeding for > 5 min, any bleeding leading to hospitalization, any bleeding leading to transfusion < 3 units of blood product, or any other bleeding considered relevant by the investigator.

Statistical analyses

The data were analyzed using the Predictive Analytics Software, version 18.0 (SPSS Inc., Chicago, Il, USA). A Chi-square test was used for two-group and multiple-group comparisons of categorical variables; otherwise a Fisher's exact test was used. A P value < 0.05 was considered to indicate statistical significance. Descriptive statistics are expressed as numbers and percentages for categorical variables and as means, standard deviations, and minimums and maximums for numerical variables.

Results

The study population consisted of 96 patients (141 visits) on warfarin therapy who were admitted to the ED for any reason other than trauma and had an INR ≥ 3. The mean age of the patients was 64.9 ± 14.5 years (range: 23 - 87 years) and 52.1% of the patients were female. In terms of ED admission, 71.9% (n = 69) of the patients had been admitted once, 19 twice, and eight patients more than three times. The most common presenting complaints were fatigue (61%), shortness of breath (27.7%), and extremity pain (27%) (Table 1).

There was no bleeding complaint in 66.7% (n = 64) of the patients whereas 32 (33.3%) had experienced major and/or minor bleeding at least once. The occurrence of a bleeding event accounted for 27.7% (n = 39) of all admissions (n = 141). The frequency of major and minor bleeding and the location of the bleeding site according to the number of admissions and affected patients are shown in Table 2.

The characteristics of the 32 patients with a bleeding complication, defined as major or minor bleeding occurring at least once, and the 64 without bleeding are presented in Table 3. The two groups did not significantly differ regarding age, sex, reason for the initiation of warfarin therapy, and duration of warfarin use. There were also no significant differences regarding comorbidities and concurrent medications (Table 4). Table 5 shows the distribution of admissions in patients with and without bleeding according to season of presentation, INR level, and weekly warfarin dose.

When patients were grouped according to their presenting INR values: 102 had INR value between 3 and 4.9, 32 had INR value between 5 and 8.9, and seven patients had INR value ≥ 9.

The rate of bleeding complications (major and minor bleeding) were 26.3% in those with an INR range (3 - 4.9), 40.6% in those with an INR range of 5 - 8.9, and 22.3% in those with an INR ≥ 9. However, the difference between patients with and without bleeding regarding distribution of their admissions according to presenting INR values was not significant. (P = 0.492 and P = 0.342; Table 6).

Table 1. Distribution of Presenting Complaints of the Study Patients

Complaint*	n (%)
Fatigue	86 (61.0)
Shortness of breath	39 (27.7)
Extremity pain	38 (27.0)
Vomiting	17 (12.1)
Bloody urine	15 (10.6)
Ecchymosis	13 (9.2)
Abdominal pain	13 (9.2)
Fever	11 (7.8)
Diarrhea and vomiting	11 (7.8)
Headache	10 (7.1)
Dizziness	10 (7.1)
Weakness	10 (7.1)
Chest pain	9 (6.4)
Palpitation	8 (5.7)
Faint	7 (5.0)
Speech disorder	5 (3.5)
Nasal bleeding	4 (2.8)
Contraction	4 (2.8)

*Patients may have presented with more than one complaint; analyses were performed for 141 admissions among 96 patients.

Table 7 shows the comparison of patients with major bleeding and minor bleeding according to age, gender, presenting season and duration of warfarin use. The two groups did not significantly differ regarding sex and presenting season (both comparisons, P > 0.05). However, there were significant differences between the two groups in terms of age and duration of warfarin use (P < 0.001 and P < 0.05, respectively; Table 7).

Discussion

Warfarin accounts for a substantial proportion of ED admissions for drug-related AEs [11]. As the ED is the first hospital department to see patients with warfarin-related bleeding complications and other complaints, analyses of this population were expected to provide insights into the optimal monitoring and treatment of patients on warfarin therapy who are at risk of bleeding. We found that the most common presenting complaints were fatigue (61%), shortness of breath (27.7%), and extremity pain (27%). Major and/or minor bleeding occurred at least once in 33.3% of the patients. The most frequent major and minor bleeding events were hematuria and cutaneous

Table 2. Frequency of Major and Minor Bleeding and the Bleeding Sites According to the Number of Admissions and Patients

	Major bleeding		Minor bleeding	
	Patients (n = 96)	Admissions (n = 141)	Patients (n = 96)	Admissions (n = 141)
	n (%)	n (%)	n (%)	n (%)
Bleeding site				
Subcutaneous hematoma, ecchymosis			10 (10.4)	13 (9.2)
Hematuria	10 (10.4)	12 (8.5)		
Nasal bleeding			4 (4.2)	4 (2.8)
Hemoptysis			2 (2.1)	3 (2.1)
Lower gastrointestinal bleeding	2 (2.1)	2 (1.4)		
Intramuscular or intra-abdominal hematoma	2 (2.1)	2 (1.4)		
Intracranial hemorrhage	2 (2.1)	2 (1.4)		
Vaginal bleeding			2 (2.1)	2 (1.4)
Retinal hemorrhage			1 (1.0)	1 (0.7)
Upper gastrointestinal bleeding	1 (1.0)	1 (0.7)		
Total	17 (17.7)	19 (13.5)	19 (19.8)	23 (16.3)

Bleeding may have occurred at more than one site and may have differed in type.

bleeding, respectively. Eroglu et al [12] reported that, among warfarin users seen in the hospital, bleeding most often occurs in the gastrointestinal system (38.5%) and especially in the upper gastrointestinal tract (n = 83). In the study of Sayhan et al [13], melena-hematochezia (16.9%), hematuria (14.6%), and cyanosis of the skin (10.1%) were the most common presenting complaints among patients admitted to the ED for warfarin-associated complications.

Anthony et al [14] identified atrial fibrillation (75.6%) and venous thromboembolic disease (14.9%) as the diseases for which the initiation of warfarin is most commonly indicated whereas according to Sayhan et al [13], atrial fibrillation (27%) and coronary artery disease (19.1%) are the most common underlying diagnoses among patients seen at the ED.

Table 3. Characteristics of the Patients According to the Presence of Bleeding Complications

	Bleeding		P
	Present (n = 32)	Absent (n = 64)	
	n (%)	n (%)	
Age, year			
< 65	11 (34.4)	31 (48.4)	0.190
≥ 65	21 (65.6)	33 (51.6)	
Sex			
Male	18 (56.2)	28 (43.8)	0.248
Female	14 (43.8)	36 (56.2)	
Reasons for warfarin therapy			
Atrial fibrillation	18 (56.3)	39 (60.9)	0.659
Stroke	6 (18.8)	10 (15.6)	0.699
Cardiac valve prosthesis	3 (9.4)	6 (9.4)	1.000
Antithrombin III deficiency	3 (9.4)	2 (3.1)	-
Pulmonary embolism	2 (6.3)	3 (4.7)	-
Peripheral artery disease	1 (3.1)	3 (4.7)	-
Deep vein thrombosis	1 (3.1)	1 (1.6)	-
Duration of warfarin use			
≤ 1 year	5 (15.6)	7 (10.9)	0.527
> 1 year	27 (84.4)	57 (89.1)	

Table 4. Comorbidities and Concurrent Medications in Patients With and Without Bleeding

	Bleeding		P
	Present (n = 32)	Absent (n = 64)	
	n (%)	n (%)	
Comorbidity			
Hypertension	26 (81.3)	46 (71.9)	0.317
Heart disease	15 (46.9)	32 (50.0)	0.773
Diabetes	11 (34.4)	18 (28.1)	0.530
Chronic obstructive pulmonary disease	3 (9.4)	10 (15.6)	0.534
Cerebrovascular disease	2 (6.3)	9 (14.1)	0.327
Chronic kidney insufficiency	1 (3.1)	7 (10.9)	0.262
Chronic liver disease	0 (0)	1 (1.6)	-
Malignancy	1 (3.1)	0 (0)	-
Concurrent medication			
Antidepressants	5 (15.6)	12 (18.8)	0.705
Acetylsalicylic acid	5 (15.6)	7 (10.9)	0.513
Allopurinol	3 (9.4)	7 (10.9)	1.000
Metformin	6 (18.8)	4 (6.3)	0.079
Lipid-lowering drugs	5 (15.6)	4 (6.3)	0.155
Antibiotic	4 (12.5)	4 (6.3)	0.434
Levothyroxine	4 (12.5)	2 (3.1)	0.093
Antiepileptic	2 (6.3)	4 (6.3)	1.000
Non-steroidal anti-inflammatory drugs	1 (3.1)	2 (3.1)	-
Low molecular-weight heparin	1 (3.1)	1 (1.6)	-
Clopidogrel	0 (0)	2 (3.1)	-

In our study, the primary reasons for warfarin initiation were atrial fibrillation (59.4%) and stroke (16.7%).

McMahan et al [15] followed patients who were discharged from the hospital after the initiation of warfarin therapy until the first major bleeding and determined an annual incidence of cumulative major bleeding of 7%. In the study of Palareti et al [16], the annual incidence of bleeding (major and minor) was 7.6 per 100 patient-years. Lindh et

Table 5. Distribution of Emergency Department Admissions of Patients With and Without Bleeding According to Season, and Weekly Warfarin Dose

	Bleeding		P
	Present (n = 39)	Absent (n = 102)	
	n (%)	n (%)	
Presenting season			
Spring	10 (25.6)	29 (28.4)	0.469
Summer	11 (28.2)	26 (25.5)	
Autumn	5 (12.8)	23 (22.5)	
Winter	13 (33.3)	24 (23.5)	
Warfarin dose, mg/week			
< 35	31 (79.5)	90 (88.2)	0.306[#]
35 - 50	7 (17.9)	12 (11.8)	
> 50	1 (2.6)	0 (0.0)	

[#]Only one patient was taking warfarin > 50 mg/week and was not included in the analyses.

Table 6. Distribution of International Normalized Ratio (INR) Values in Major Bleeding, Minor Bleeding and Non-Bleeding Groups of the Study Patients

INR*	Non-bleeding n (%)	Bleeding		P
		Major bleeding n (%)	Minor bleeding n (%)	
3 - 4.9	75 (73.5)	11 (10.7)	16 (15.6)	0.492
5 - 8.9	18 (56.3)	1 (3.1)	13 (37.5)	0.342
≥ 9	6 (85.7)	1 (22.3)	0	-

*Patients had been admitted once, twice, or more than three times; analyses were performed for 141 admissions among 96 patients. Data are presented as percentages (%) or n = numbers of patients.

al [17] reported an incidence of first-time severe bleeding in warfarin-treated patients of 2.3 per 100 patient-years. A determination of the risk factors for bleeding complications in patients receiving warfarin would allow the identification of patients at risk. These patients would require close follow-up to prevent the development of serious complications or at least allow their early diagnosis. Age, sex, comorbidities, and concurrent medications are among the parameters investigated as risk factors for bleeding in patients receiving warfarin, and scoring models to predict the risk of bleeding have been proposed [18, 19].

The likelihood of warfarin use increases with age, a fact that is particularly relevant given that the elderly population is increasing worldwide. Accordingly, an increase in the prevalence of warfarin-associated complications can be expected. Although Shepherd et al [20] found no significant differences between the young and the elderly regarding the pharmacokinetics of warfarin, they postulated an increased intrinsic sensitivity to warfarin as the reason for its enhanced effect in older individuals. In our study, the mean age of the patients was 64.9 ± 14.5 years and the rate of bleeding complications in those ≥ 65 years of age was 56.3%. However, while several studies have reported that advanced age is a risk factor for major bleeding [13, 16, 21, 22], this has not been consistently demonstrated [15, 17]. In our study, bleeding complications occurred in 26.2% of patients < 65 years of age and in 38.9% of patients ≥ 65 years of age. Nevertheless, there were no significant differences between the two groups regarding the frequency of bleeding complications (P = 0.190).

Whether warfarin-associated bleeding differs by sex has also been debated, with some studies reporting female [22] or male [17] sex as a risk factor for bleeding; however, others have failed to find a sex-related association [15, 16]. In our study, the rates of bleeding complication were 39.1% in males and 28% in females; the difference was not significant (P = 0.248).

Salobir et al [23] investigated the possibility of a seasonal effect of warfarin-related complications and found that

Table 7. Comparison of Patients With Major Bleeding and Minor Bleeding According to Age, Gender, Presenting Season and Duration of Warfarin Use

	Bleeding		P
	Major (n = 32)	Minor (n = 64)	
	n (%)	n (%)	
Age, year			
<65	5 (38.5)	8 (61.5)	< 0.001
≥ 65	10 (34.5)	19 (65.5)	
Sex			
Male	9 (36)	16 (64)	0.326
Female	5 (29.4)	12 (70.6)	
Presenting season			
Spring	2 (15.4)	11 (84.6)	
Summer	4 (36.4)	7 (63.6)	0.372
Autumn	3 (50)	3 (50)	
Winter	5 (41.7)	7 (58.3)	
Duration of warfarin use			
≤ 1 year	1 (20)	4 (80)	0.027
> 1 year	12 (32.4)	25 (67.6)	

Data are presented as percentages (%) or n = numbers of patients.

patients had the lowest INR in summer and the highest INR in autumn. In addition, the rate of an INR < 2 was higher in summer, and the rate of an INR > 4 was higher in autumn. We evaluated patients with an INR ≥ 3 and found no significant difference between those with and without bleeding regarding the seasonal distribution of their ED admission.

In warfarin users, INR must be maintained within the therapeutic range, but despite close monitoring, this is often not the case. In a multi-center study, the mean time in which the INR was in the patient's therapeutic range did not exceed 77%, even in Sweden, where the rate was the highest [24]. Patients receiving warfarin are frequently admitted to the ED and generally have an INR outside the therapeutic range [25]. There is a close relationship between INR and the risk of bleeding, which increases at INR > 4 [26]. Landefeld et al [27] reported that for each 1.0-unit increase in the INR, the odds ratio for major and minor bleeding during the week following the measurement increases by 80% and 50%, respectively. Palareti et al [16] reported an increased risk of bleeding in patients with an INR > 4.5. Lindh et al [17] investigated the predictors of severe bleeding during warfarin therapy and determined that the risk of bleeding was not significantly associated with the target INR, the time spent out of the target INR range, and the requirement for warfarin dosing. Eroglu et al [12] reported no significant correlation between the INR value and the severity of bleeding. In the study of Anthony et al [14], among patients receiving warfarin and presenting at the ED, 43.8% had an INR within the therapeutic range, 22.4% had an INR lower than the therapeutic range, and 33.8% had an INR higher than the therapeutic range. The present study evaluated patients with an INR ≥ 3. When divided into three groups according to the distribution of INR values, the highest total (major and minor bleeding) and minor bleeding rates was found in the patient group with INR between 5 and 8.9 (40.6% and 37.5%, respectively). Additionally, patients with an INR range ≥ 9 had the major bleeding rate (22.3%). However, no significant difference was found between the bleeding groups and the non-bleeding group in terms of INR levels (P = 0.492 and P = 0.342; Table 6).

Some studies have investigated the time to first bleeding complaint in patients receiving warfarin. Landefeld and Goldman [21] reported cumulative rates of major bleeding of 3%, 11%, and 22% at 1, 12, and 48 months after therapy initiation, respectively. They also found that the monthly risk of major bleeding decreased from 3% during the first month of ambulatory treatment to 0.3% per month after the first year of treatment. In another study, 39% of the patients receiving warfarin had their first bleeding attack within the first 3 months, and 47% had it after the first year [28]. Zhang et al [22] reported that warfarin use for ≥ 120 days in a year increased the risk of bleeding. In our study, while 11.5% of the patients receiving warfarin for up to 1 year had at least one major or minor bleeding event, the rate was 89.5% in those receiving the drug for > 1 year; however, there were no differences between the groups with and without bleeding according to duration of warfarin use. Even if the warfarin dose remains unchanged, the INR may change because of biological variation [29]. Zhang et al [22] reported no relationship between the daily warfarin dose and bleeding prevalence. In the present study, among the three groups of patients established according to their presenting warfarin dose, bleeding occurred in 25.6% of patients with a presenting dose < 35 mg/week and in 36.8% of patients in whom the presenting warfarin dose was 35 - 50 mg/week. The only patient with a presenting dose > 50 mg/week also had a bleeding complication. Although the rate of bleeding complications appeared to increase with increasing drug dose, when this patient was excluded there were no significant differences between patients with and without bleeding regarding the distribution of their admissions according to the presenting drug dose (P = 0.306).

As warfarin users are usually older, they are more likely to have comorbidities such as hypertension, cardiac disease, diabetes mellitus, chronic obstructive pulmonary disease, cerebrovascular disease, chronic kidney insufficiency, chronic liver disease, and malignancy. Landefeld and Goldman [21] reported the following risk factors for major bleeding in warfarin users: a history of stroke or gastrointestinal bleeding, the presence of any serious comorbidity (recent myocardial infarction, renal insufficiency, or severe anemia), and atrial fibrillation. McMahan et al [15] found that the presence of a comorbid condition (hypertension, diabetes mellitus, chronic obstructive pulmonary disease, cancer, acute myocardial infarction, stroke) was not associated with the risk of major bleeding in warfarin users, whereas an association was determined for alcohol abuse, chronic renal insufficiency, and gastrointestinal bleeding history. In the present study, the difference between patients with and without bleeding regarding comorbidities was not significant. However, the risk of warfarin-related major bleeding was found to be significantly increased in patients aged over 65 years and taking warfarin longer than 1 year (P < 0.001 and P = 0.027, respectively).

Warfarin users usually receive several concurrent drugs because of comorbidities. Drugs affecting warfarin metabolism may impact the INR depending on their ability to inhibit or activate the CYP2C9 enzyme. Lindh et al [17] found that the use of drugs that potentially interact with warfarin was an independent risk factor for severe bleeding. In the study of Zhang et al [22], concurrent use of warfarin and cephalosporin or metronidazole was associated with an increased risk of bleeding vs. warfarin use alone. By contrast, the concurrent use of warfarin with amiodarone, fibric acid derivatives, or nonsteroidal anti-inflammatory drugs did not increase the bleeding risk. McMahan et al [15] found that the use of drugs known to influence prothrombin levels was not associated with major bleeding. In our study, there were no differences between patients with and without bleeding complications regarding the use of concurrent medications that may potentially interact with warfarin.

Conclusions

Warfarin therapy is almost always long-term and the drug may be needed for the lifetime of some patients. This requires long-term patient follow-up for complications, particularly bleeding. Thus, a limitation of this study was its retrospective and cross-sectional design. Nonetheless, it showed that the rates of major and minor bleeding events were relatively high among

warfarin-treated patients admitted to the ED for any reason other than trauma. Although the incidence of these events was not statistically significant, our results demonstrate the risk of bleeding in this population. Further large-scale and long-term prospective studies that take into account biological variation may allow a precise determination of bleeding risk in patients on warfarin.

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