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ORIGINAL RESEARCH

Evaluation of Patients Hospitalized Due to Bleeding Complications Associated with Warfarin Treatment*

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ABSTRACT

The most significant complication of warfarin therapy is bleeding. The disadvantages of warfarin include its narrow therapeutic range and drug-drug interactions. This study aimed to determine the severity of bleeding events associated with warfarin treatment, mortality, and factors that may influence these outcomes. A total of 119 patients hospitalized due to bleeding complications associated with warfarin use between January 2007 and December 2010 were included in the study. Demographic and clinical data—including age, gender, comorbidities, International Normalized Ratio (INR), and mortality—were analyzed. Bleeding severity was classified according to the Fihn criteria as minor bleeding and major bleeding (severe, life-threatening and fatal bleeding). Fifty-six patients (51.4%) were female,53 (48.6%) were male, and 53.2% of the patients were aged 65 years and older. Hypertension (50.5%) and diabetes mellitus (22.0%) were the most common comorbid conditions. The primary indications for warfarin use were atrial fibrillation (35.8%), followed by cardiovascular diseases (32.1%), history of stroke (26.6%), and prosthetic heart valve (22.0%). The most common presenting symptoms were ecchymosis and upper gastrointestinal bleeding. Major bleeding was significantly more common in males (p=0.046). Ninety-eight percent (n=107) of patients experiencing bleeding had supratherapeutic INR values. Mortality was significantly higher in patients aged 65 years and older (p=0.029). There was no significant difference between genders in terms of overall bleeding event frequency and mortality. In conclusion, advanced age and labile INR are significant factors in warfarin-related bleeding events. Mortality due to warfarin-related bleeding is significantly higher in older patients.

Keywords: Oral anticoagulant therapy. Warfarin. Bleeding. Haemorrhage.

Varfarin Tedavisine Bağlı Kanama Komplikasyonları Nedeniyle Hastaneye Yatırılan Hastaların Değerlendirilmesi

ÖZET

Varfarin tedavisinin en önemli komplikasyonu kanamadır. Varfarinin, terapötik aralığının dar olması ve ilaç-ilaç etkileşimleri dezavantajları arasında yer almaktadır. Çalışmada varfarin tedavisine bağlı kanama olaylarının şiddeti, mortalite ve etki edebilecek faktörlerin belirlenmesi amaçlandı. Ocak 2007-Aralık 2010 tarihleri arasında varfarin kullanımına bağlı kanama nedeniyle hastaneye yatırılan 109 hasta dahil edildi. Demografik ve klinik özellikler -yaş, cinsiyet, eşlik eden hastalıklar, INR düzeyi ve mortalite- analiz edildi. Kanama şiddeti Fihn kriterlerine göre minör kanama ve major kanama (ciddi, hayatı tehdit edici ve fatal kanama) olarak sınıflandırıldı. Hastaların; 56'sı kadın (%51,4), 53'ü (%48,6) erkek, %53,2'si 65 yaş ve üzerindeydi. Komorbid hastalıklar içinde birinci sıklıkta hipertansiyon (%50,5), ikinci sıklıkta diabetes mellitus (%22,0) saptandı. Varfarin kullanım endikasyonları arasında en sık atriyal fibrilasyon (%35,8), sonrasında kardiyovasküler hastalıklar (%32,1), geçirilmiş stroke (%26,6) ve prostetik kalp kapağı (%22,0) gelmekte idi. En sık geliş semptomu ekimoz ve üst gastrointestinal kanama idi. Majör kanama erkek cinsiyette anlamlı şekilde yüksekti (p=0,046). Kanama geçiren hastaların %98'i (n=107) supraterapötik INR değerine sahipti. Mortalite ileri yaş (≥65 yaş) hastalarda anlamlı şekilde yüksekti (p=0,029). Genel kanama olaylarının sıklığı ve mortalite açısından her iki cinsiyet arasında fark yoktu. Sonuç olarak ileri yaş ve labil INR varfarin ilişkili kanama olaylarında etkilidir. Varfarine bağlı kanama olaylarında mortalite ileri yaş hastalarda anlamlı şekilde daha yüksektir.

Anahtar Kelimeler: Oral antikoagulan tedavi. Varfarin. Kanama. Hemoraji.

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Warfarin was introduced in 1954 and has since become widely used in anticoagulant therapy worldwide[1]. Its disadvantages include a narrow therapeutic range, variability of dosage between patients, frequent drug-drug and food interactions, and the need for dose monitoring using the International Normalized Ratio (INR)[2]. In 2010, direct oral anticoagulants (DOACs) were introduced, replacing warfarin in the prevention of venous thromboembolism (VTE) recurrence and in preventing complications such as stroke and systemic embolism secondary to atrial fibrillation (AF). However, in patients with prosthetic heart valves, antiphospholipid antibody syndrome, and a history of gastrointestinal (GI) bleeding, warfarin remains the treatment of choice[3].

Bleeding is the major complication of anticoagulant therapy. Bleeding that leads directly to death or requires symptomatic treatment or transfusion of two or more units of blood is classified as major bleeding[4]. The risk of major bleeding with warfarin is higher in the geriatric population and in patients with cancer[5,6]. Particularly, advanced age and polypharmacy contribute to over-anticoagulation and an increased risk of bleeding with warfarin treatment. Numerous drugs, including antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), central nervous system agents, and platelet-inhibiting medications, have been reported to interact with warfarin[7,8]. Bleeding events associated with warfarin and the resulting hospitalizations lead to increased treatment costs[9].

Although bleeding is a major complication of anticoagulant therapies, the benefits of these drugs in reducing thromboembolic events remain significant. Therefore, the aim of the present study was to determine the severity of bleeding complications associated with warfarin therapy and to identify factors affecting morbidity and mortality.

Material and Method

Study Population

A total of 109 patients admitted to the Emergency Internal Medicine Service of Ankara Numune Education and Research Hospital between January 01, 2007 and December 31, 2010 due to complications associated with warfarin use were retrospectively evaluated. Data reviewed including the indication for drug use, comorbid conditions, reason for hospital admission, daily medication dose, INR at the time of admission, prothrombin time, hematocrit level, treatment for bleeding, length of hospital stay, bleeding severity, and mortality. The upper limit of INR was accepted as 4.5 for patients with prosthetic heart valves and 4.0 for other patients. Values above these limits were defined as supratherapeutic. Because laboratory results did not provide a numeric value for INR levels >10, these patients were categorized as having an INR >10. The average daily warfarin dose was calculated by dividing the total dose by the number of days according to the dosing regimen and was recorded.

Bleeding severity was classified according to the Fihn criteria[10] and divided into two main groups as minor and major bleeding events:

1. Minor bleeding: reported but not requiring additional testing, follow-up or visits,
2. Major bleeding: divided into three subgroups as; (i) severe bleeding: requiring treatment, medical evaluation, or ≤2 units of blood transfusion, (ii) life-threatening bleeding: causes irreversible end-organ damage; or requires surgical or angiographic intervention; or two of the following: loss of ≥3 units of blood, systolic hypotension (<90 mmHg), critical anemia (hematocrit ≤20%), (iii) fatal bleeding: bleeding directly leading to the patient's death.

Statistical Analysis

Data were analyzed using SPSS for Windows 11.5 software package. Descriptive statistics for continuous variables were expressed as mean ± standard deviation or median (minimum-maximum), and categorical variables were expressed as number of cases and (%). The data were analyzed using Pearson's Chi-Square or Fisher's Exact Chi-Square tests. A p-value of <0.05 was considered statistically significant in all analyses.

Results

Demographic Data

We analyzed a total of 109 patients, 56 (51.4%) females and 53 (48.6%) males in the study. Fifty-three percent of the patients were 65 years of age or older. Among patients aged 65 and older, 79% had at least one comorbid condition, and among patients aged 80 and older, 88% had at least one comorbidity. Regarding comorbidities, hypertension was the most common (55 patients, 50.5%), followed by diabetes mellitus (24 patients, 22.0%) and heart diseases (15 patients, 13.8%). In terms of the duration of warfarin use, most patients (66 patients, 60.6%) had been on the medication for over one year, followed by those who had used it for between 3 months and 1 year (32 patients, 29.4%). The mean length of hospitalization was 2 (range: 1-45) days. The average daily warfarin dose was 4.95 mg/day in 58 patients aged 65 and over, and 4.82 mg/day in 51 patients under 65 years of age. The demographic and clinical characteristics of the cases are presented in Table I.

Table I. Demographic and clinical characteristics of patients

Variable	n=109 (%)
Age	
<65 years	51 (46.8%)
≥65 years	58 (53.2%)
Gender	
Female	56 (51.4%)
Male	53 (48.6%)
Comorbidities	
Hypertension	55 (50.5%)
Diabetes mellitus	24 (22.0%)
Pulmonary disorder	3 (2.8%)
Malignancy	7 (6.4%)
Other	27 (24.8%)
Concomitant medications	
Aspirin (acetylsalicylic acid)	24 (22.0%)
Digoxin	10 (9.2%)
Antihypertensives	46 (42.2%)
Antibiotics	12 (11.0%)
PPIs	45 (41.3%)
NSAIDs	22 (20.2%)
Duration of warfarin treatment before bleeding	
3 weeks-3 months	11 (10.1%)
3 months-1 year	32 (29.4%)
>1 year	66 (60.5%)
Treatment for bleeding	
FFP	104 (95.4%)
Blood transfusion	39 (35.8%)
Vitamin K	22 (20.2%)
Surgery	1 (0.9%)
Follow-up without treatment	1 (0.9%)
Duration of hospitalization (days)	2 (1-45)

[1] Data are expressed as n (%) and median (IQR)
[2] PPIs: Proton pump inhibitors, NSAIDs: Nonsteroidal anti-inflammatory drugs, FFP: Fresh frozen plasma

Indications for Warfarin Use and INR levels

Among the patients, 39 (35.8%) were using warfarin for atrial fibrillation (AF), 35 (32.1%) for atherosclerotic cardiovascular disease (ASCVD), 29 (26.6%) for stroke, 24 (22.0%) for prosthetic heart valves, 5 (4.6%) for pulmonary thromboembolism (PTE), and 4 (3.7%) for deep vein thrombosis (DVT). Some patients had more than one indication for warfarin treatment (Graph 1). Ninety-eight percent of the patients (n=107) experienced bleeding with supratherapeutic INR levels, whereas only 1.9% (n=2) experienced bleeding within the therapeutic INR range.

Bleeding Symptoms and Severity

Regarding presenting complaints, the most common symptom was ecchymosis (37.6%), followed by GI bleeding symptoms (28.4%) and hematoma (13.8%) (Table II).

Table II. Symptoms and frequency of bleeding

Clinical sign	n=109 (%)
Upper gastrointestinal bleeding	29 (26.6%)
Lower gastrointestinal bleeding	2 (1.8%)
Ecchymosis	41 (37.6%)
Hematoma	15 (13.8%)
Epistaxis	13 (11.9%)
Hematuria	12 (11.0%)
Gingival bleeding	11 (10.1%)
Vaginal bleeding	3 (2.8%)
Intracranial hemorrhage	1 (0.9%)
Hemarthrosis	1 (0.9%)

According to the Fihn criteria, 62 patients (56.9%) experienced minor bleeding, 28 (25.7%) experienced severe bleeding, and 19 (17.4%) experienced life-threatening or fatal bleeding. Overall, 6 patients (5.5%) died (Table III). Among the patients followed-up for bleeding, 22% (n=24) were concurrently using aspirin. Among patients with major bleeding, 61.7% (n=29) had upper GI bleeding. In these cases, the use of acetylsalicylic acid was observed in 44.8% (n=13) and NSAID use in 55.2% (n=16) of the patients, both of which were statistically significantly higher ($p<0.001$).

Table III. Severity of bleeding and mortality

Variable	n=109 (%)
Severity of bleeding	
[1] Minor bleeding	62 (56.9%)
[2] Severe bleeding	28 (25.7%)
[3] Life-threatening and fatal bleeding	19 (17.4%)
Mortality	6 (5.5%)

[1] Reported but not requiring additional testing, follow-up, or visits
[2] Requiring treatment, medical evaluation, or transfusion of at least two units of blood
[3] Causing myocardial infarction, surgical/angiographic intervention, or irreversible sequelae and bleeding that directly causes the patient's death

In the major bleeding group, a statistically significant difference in gender distribution was observed, with males exhibiting a higher prevalence of major bleeding ($p=0.046$). There was no statistically significant difference between the major bleeding group and the non-major bleeding group in terms of age, duration of warfarin use, presence of comorbid conditions, indications for drug use, or INR levels at presentation ($p>0.05$). The incidence of bleeding events in the therapeutic range (INR<4) was notably low (1.9%) at the study group due to the majority being managed as outpatients. The absence of statistically significant difference in INR levels between patients with and without major bleeding events may be attributed to the majority of patients

requiring hospitalization were in the supratherapeutic INR values (98.1%).

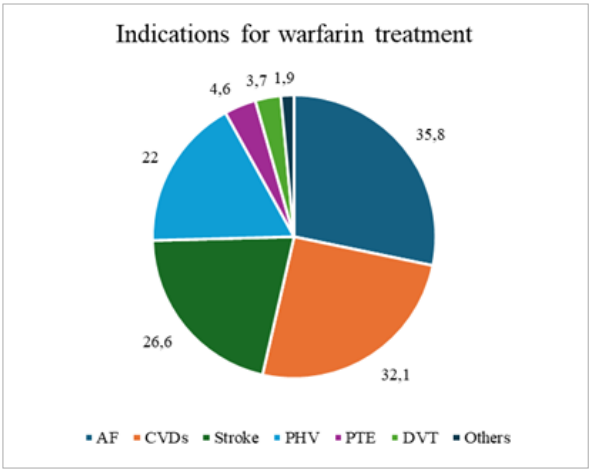
Factors Affecting Mortality

When evaluated separately, patients aged 65 years and older and those aged 80 years and older exhibited significantly higher mortality (p=0.029 and p=0.002, respectively). No significant difference in mortality was observed with regard to gender (p>0.05). Additionally, there were no statistically significant differences in mortality based on the duration of drug use, comorbid conditions, indications for drug use, presenting symptoms, or INR levels (p>0.05). The lack of statistical difference in mortality in patients with comorbidities may be related to the high rate of comorbid conditions in the patients included in the study. Factors affecting mortality are presented in Table IV.

Table IV. Factors affecting mortality

Variable	Mortality		*P value*
	No (n=103)	Yes (n=6)	
Age groups			**0.029**
<65 years	51 (49.5%)	0 (0%)	
≥65 years	52 (50.5%)	6 (100.0%)	
Gender			1.000
Female	53 (51.5%)	3 (50.0%)	
Male	50 (48.5%)	3 (50.0%)	
Duration of anticoagulation			0.110
3 weeks-3 months	11 (10.7%)	0 (0%)	
3 months-1 year	28 (27.2%)	4 (66.7%)	
>1 year	64 (62.1%)	2 (33.3%)	
Comorbid disease	72 (69.9%)	6 (100.0%)	0.180
Indications for warfarin			
AF	36 (34.9%)	3 (50.0%)	0.664
CVDs	33 (32.0%)	2 (33.3%)	1.000
Stroke	27 (26.2%)	2 (33.3%)	0.656
PHV	24 (23.3%)	0 (0%)	0.335
DVT	5 (4.9%)	0 (0%)	1.000
PTE	4 (3.9%)	0 (0%)	1.000
Symptoms			
Ecchymosis	40 (38.8%)	1 (16.7%)	0.406
Gastrointestinal bleeding	29 (28.2%)	2 (33.3%)	1.000
Hematoma	13 (12.6%)	2 (33.3%)	0.191
Hematuria	12 (11.7%)	0 (0%)	1.000
Gingival bleeding	11 (10.7%)	0 (0%)	1.000
INR			0.822
<4	2 (1.9%)	0 (0%)	
4-10	42 (40.8%)	2 (33.3%)	
>10	59 (57.3%)	4 (66.7%)	

AF: atrial fibrillation, CVDs: cardiovascular diseases, PHV: prosthetic heart valve, DVT: deep vein thrombosis, PTE: pulmonary thromboembolism



[1] *AF: atrial fibrillation, CVDs: cardiovascular diseases, PHV: prosthetic heart valve, PTE: pulmonary thromboembolism, DVT: deep vein thrombosis*
[2] *Some patients had multiple indications for warfarin treatment.*

Figure 1:
Distribution of indications for warfarin treatment

Discussion and Conclusion

Oral anticoagulant therapy is widely used in the treatment of deep venous thrombosis and pulmonary embolism, as well as in the prevention of systemic thromboembolism. The most common complication of long-term anticoagulant use is bleeding[11]. The number of patients presenting to emergency departments with life-threatening bleeding due to anticoagulant therapy is increasing every day[12]. Particularly in elderly patients, the risk of major bleeding is observed at a higher rate due to increased comorbidities and the concomitant prescription of multiple medications[6,13].

The most well-known risk factors for warfarin-related bleeding are treatment intensity and INR levels. Regardless of the indication, moderate-intensity warfarin therapy (INR 2.0-3.0) significantly reduces the risk of bleeding compared to high-intensity warfarin therapy (INR >2.5-3.0)[14,15]. In patients with prosthetic heart valves, an INR below 2 increases the incidence of thromboembolic events. While the frequency of major bleeding increases moderately when INR is in the range of 3-4, it rises markedly when INR exceeds 4[16]. One of the reasons for switching from warfarin to new-generation DOACs is that these drugs require 64% less monitoring and 32% have labile INR values[17]. In the present study, bleeding events were found to be significantly higher in patients with supratherapeutic INR values.

Clinical studies have reported that the incidence of serious bleeding episodes in patients on warfarin therapy ranges from 2% to 13%[18]. The frequency of major bleeding is higher in elderly patients (aged ≥65 years). As the incidence of comorbidities increases in

the elderly, the number of concomitantly used medications also rises. In a study evaluating 17,661 elderly patients, the rate of hospitalizations due to warfarin-related bleeding was calculated as 4.1 per 100 patient-years, and hospitalization rates were found to be significantly higher in those using aspirin and/or clopidogrel concurrently[19]. Advanced age was identified as an independent predictor of mortality (HR: 1.03) in patients using warfarin for mechanical heart valve[20]. Ron P. et al. introduced the HAS-BLED score (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly [>65 years], Drugs/alcohol concomitantly) to determine the risk of major bleeding in patients with AF receiving anticoagulant therapy. According to this scoring system, advanced age and labile INR are among the risk factors[21]. In our study, mortality was found to be significantly higher in the patient group aged 65 years and older.

NSAIDs are frequently prescribed medications that are associated with GI bleeding. In patients receiving warfarin therapy, the use of NSAIDs approximately doubles the probability of GI bleeding. This increased risk is especially pronounced in elderly patients and can occur even without changes in INR levels. Additionally, NSAIDs have been associated with an increased risk of bleeding through other mechanisms[22]. Polymorphisms in cytochrome enzymes (particularly CYP2C9) may increase the tendency to bleed by affecting the metabolism of both NSAIDs and warfarin[23,24]. Besides antiplatelet agents and NSAIDs, warfarin interacts with many other drugs—including various antimicrobial agents, SSRIs, mirtazapine, and loop diuretics—, which may increase the risk of bleeding. Proton pump inhibitors (PPIs), on the other hand, reduce hospitalizations due to GI bleeding[25]. In our study, concomitant medications most commonly used with warfarin were antihypertensive agents and PPIs.

Some studies have reported that bleeding events in patients on warfarin are more frequently observed in females, although other studies have not supported this finding[26,27]. In a study by Nekkanti et al., warfarin-related bleeding was detected more frequently in females (60.65%)[28]. However, another study evaluating 54,568 patients found that bleeding events were less frequent in females (HR: 0.52)[29]. A meta-analysis of 37 studies reported no statistically significant difference in warfarin-related major bleeding events between males and females[30]. In the this study, although the number of female patients was higher, there was no statistically significant difference in bleeding events between genders.

DOACs have become widely prescribed medications instead of warfarin therapy for AF and VTE. They have similar or better efficacy and safety profiles compared with warfarin therapy[31]. The incidence of major bleeding events in patients receiving DOACs is 2-3.5% annually. In a meta-analysis evaluating 4735 patients, the most common indication for DOACs was AF (82%), followed by VTE (14%). Intracranial hemorrhage (ICH) was the most frequently reported bleeding complication, accounting for 55% of cases, while other types of bleeding were comparatively less prevalent. Mortality was 20.2% in patients with ICH[32]. In a study evaluating 125,195 AF patients receiving warfarin treatment, the incidence of bleeding was 3.8% per year, and the most common bleeding events were in the first month of treatment[33]. In our study group, AF was the most frequent indication for warfarin therapy, consistent with findings reported in studies evaluating DOACs. The majority of bleeding events were observed after the first year of treatment.

The limitations of our study are its retrospective design and the fact that some patients may not have been included due to coding errors after diagnosis. Additionally, a relatively small number of cases were included, and the study was limited to a single medical center. As DOACs were not yet licensed during the study period, patients using these drugs could not be included in the study.

In conclusion, treatment intensity and INR levels, as well as age and drug interactions, influence the severity of warfarin-related bleeding events at varying degrees. Bleeding events remain the major complication of warfarin therapy and warrant careful management, especially in elderly patients due to the associated higher mortality rate.

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