NORTHWESTERN MEDICAL JOURNAL

Northwestern Med J. 2024;4(1):41-47
DOI: 10.54307/NWMJ.2024.87

RESEARCH ARTICLE

Emergency department admissions and hemorrhage risk in patients on warfarin-containing drugs: a retrospective study

Oya Güven[1], **Merve Demireller**[2]

[1]Department of Emergency Medicine, Kırklareli University, Kırklareli Training and Research Hospital, Kırklareli, Türkiye.
[2]Department of Emergency Medicine, Kırklareli Training and Research Hospital, Kırklareli, Türkiye.

Cite as: Yazar A. Güven O, Demireller M. Emergency department admissions and hemorrhage risk in patients on warfarin-containing drugs: a retrospective study. Northwestern Med J. 2024;4(1):41-47.

ABSTRACT

Aim: Warfarin-containing medications are commonly prescribed anticoagulants for preventing and treating arterial and venous thromboembolism. As such, it may present a risk of hemorrhage. In this study, we aimed to investigate the occurrence of hemorrhage associated with warfarin, along with the contributing factors, by analyzing data obtained from emergency requests.

Methods: Patients who presented to the emergency department within one year and requested an INR analysis have been included. Among these patients, the demographic characteristics and risk factors of patients using warfarin and having signs of hemorrhage and those with increased INR levels and hemorrhage symptoms without using warfarin were studied retrospectively.

Results: Two hundred and seventy-three patients were included in the study. Two hundred and eleven patients (76.9%) were taking warfarin, 94.8% of whom had initiated the drug for cardiac reasons. INR value below 2.5 were found in 39.3% of these patients. Only 8.1% were identified with hemorrhage.

Conclusion: Warfarin poses a significant challengefor clinicians and patients due to its associated risk of hemorrhage. In this study, the risk of major hemorrhage was generally low.

Keywords: emergency department, hemorrhage, INR, warfarin

Corresponding author: Oya Güven **E-mail:** ersinoya@yahoo.com
Received: 03.02.2023 **Accepted:** 12.12.2023 **Published:** 30.01.2024

INTRODUCTION

Warfarin, which contributes significantly to the anticoagulant efficacy, is usually prescribed to cardiac and neurological patients. It is the medication of choice for patients with atrial fibrillation (AF), pulmonary embolism (PE), and stroke. Its effectiveness is measured by the International Normalized Ratio (INR). Its interaction with food is high. For example, yogurt bacteria effectively increase the production of vitamin K from the intestine. Therefore, it is inappropriate for warfarin users to eat too much yogurt (Table 1) (1). Warfarin inhibits the activation of vitamin K-dependent coagulation factors (Factors II, VII, IX, and X) and regulatory proteins (proteins C, S, and Z) (2). It typically demonstrates effectiveness within two to seven days. Because of its slow onset of action, it is not preferred in acute situations. Treatment begins with heparin (3). Genetic variation and the cytochrome p450 system metabolizing warfarin cause inter-individual variability and affect dose-response estimation (4,5). Consequently, the INR level is checked regularly.

Low molecular weight heparin (LMWH) should be initiated with warfain and stop after INR level reached 2. The INR rate for patients treated with warfarin varies depending on the underlying condition but is typically targeted at 2.0 to 3.5. An INR below 2.0 is associated with an increased risk of thromboembolism. An INR greater than 4.0 indicates an elevated risk for hemorrhage (6).

The most feared side effect of warfarin is hemorrhage. It can occur with minor trauma (even when brushing teeth) or spontaneously. It can be seen as a subcutaneous, intramuscular, ocular, gastrointestinal (GIS), or intracranial hemorrhage or hematuria, epistaxis, or menometrorrhagia. In addition, side effects such as dizziness, headache, nausea, vomiting (indicative of intracranial hemorrhage), and allergic reactions may develop. Consequently, patients on warfarin should be warned about potential problems and advised to adopt lifestyle precautions.

Systematic follow-up and patient education are essential for successful treatment. Although fatal hemorrhage is generally not observed, emergency departments are the first point of care for acute hemorrhage. In this study, the variety of hemorrhage observed in people on warfarin was examined by analyzing data from emergency department (ED) admissions.

MATERIALS AND METHODS

Study design

From January 1 to December 31, 2020, the records of 507 patients who applied to the ED for any reason and had their INR levels tested were analyzed. A total of 273 patients on warfarin and patients with INR>2.5 who were not on warfarin were included in the study. Patients diagnosed with acute hemorrhaging who were registered in the system but did not have an INR analysis request were excluded from the study. Demographic

Table 1. Drugs and foods that affect warfarin level.

Drugs that increase the effect of warfarin	Paracetamol, antibiotics (penicillin, cephalosporins, chloramphenicol, trimethoprim-sulfamethoxazole, ciprofloxacin, erythromycin, sulfonamides), amiodarone, cimetidine, cortisone, etoposide, fluconazole, lovastatin, quinidine, thyroid hormone, tricyclic antidepressants, vitamin E
Drugs that reduce the effect of warfarin	Anti-thyroid drugs, ascorbic acid, azathioprine, barbiturates, carbamazepine, oral contraceptives, spironolactone, teicoplanin, mercaptopurine, antihistamines
Foods containing high doses of vitamin K	Cabbage, spinach, chard, parsley, purslane, lettuce, chickpeas, liver, green tea, broccoli, Brussels sprouts, turnip, fish oil
Foods containing moderate doses of vitamin K	Asparagus, cauliflower, cheese, peas, coffee, avocado
Foods containing low doses of vitamin K	Red meat, chicken, eggs, milk, bread, butter, carrots, celery, corn, green beans, onions, rice, tomatoes, potatoes, peppers, peanuts, pumpkin, apples, oranges, strawberries

characteristics of the patients were recorded. If the patient was on warfarin, had signs of hemorrhage and/or complained of having a hemorrhage on admission, the reason for starting warfarin was also noted. In the case of hemorrhage, the factors affecting the condition were examined.

In this study, major hemorrhages were defined as intracranial or retroperitoneal bleeding requiring hospitalization, two or more units of blood transfusions, or those occurring in critical areas. Those classified as minor hemorrhage were skin hematoma larger than 25 cm^2, spontaneous epistaxis or gingival hemorrhage lasting longer than five minutes, any hemorrhage that did not require hospitalization, or any hemorrhage that required less than 2 units of blood transfusion (7).

Statistical analysis

Descriptive statistics, including mean, standard deviation, median, minimum, maximum, frequency and ratio, were calculated using SPSS 28.0. The Kolmogorov-Smirnov test was used to measure the distribution of variables. The Mann-Whitney U test was used to analyze independent quantitative data, and the Chi-square and Fischer tests were used to analyze independent qualitative data. $p<0.05$ was accepted as statistically significant level.

RESULTS

Of the total patients examined, 163 were women (59.7%) and 110 were men (40.3%). The mean age was 68.6±15.4 years. Of these, 211 were on warfarin, with an average age of 66.9±15.1 years.

The INR of 190 people (69.6%) was >2.5. and hemorrhages occurred in 24 patients (8.8%). Ten patients (41.7%) were found to have major hemorrhage, and five (29.4%) of these patients were on warfarin (Table 2). The most common symptom observed in patients, whose INR level were checked was cardiac (chest pain [20.5%]) (Figure 1).

In 200 patients (94.8%) on warfarin, the prescriptions were predominantly for cardiac reasons (94.8%), with neurological prescriptions following (2.8%), and pulmonary prescriptions constituting 2.4% (Table 3). In the warfarin group, the utilization of various medications (especially cardiac drugs such as calcium channel blockers and angiotensin-converting enzyme inhibitors) was significantly higher ($p<0.05$). In addition, cardiac symptoms (25.6%) were the most common reason for ED utilization in this group.

High level of INR was also detected in the non-warfarin group. The highest INR level among these patients was reported for patients on rivaroxaban (53.2%) and apixaban (11.2%), respectively. The other patients had a history of liver disease (4.8%), addiction

Table 2. Demographic characteristics of all patients.

		Min-Max	Median (Q1-Q3)	Mean±SD / n (%)
Age		18.0-96.0	71.0 (58-81)	68.6±15.4
Gender	Female			163 (59.7%)
	Male			110 (40.3%)
INR value	<2.5			83 (30.4%)
	>2.5			190 (69.6%)
Hemorrhage	No			249 (91.2%)
	Yes			24 (8.8%)
Minor hemorrhage				14 (58.3%)
Major hemorrhage				10 (41.7%)

SD: Standard Deviation, INR: International Normalized Ratio

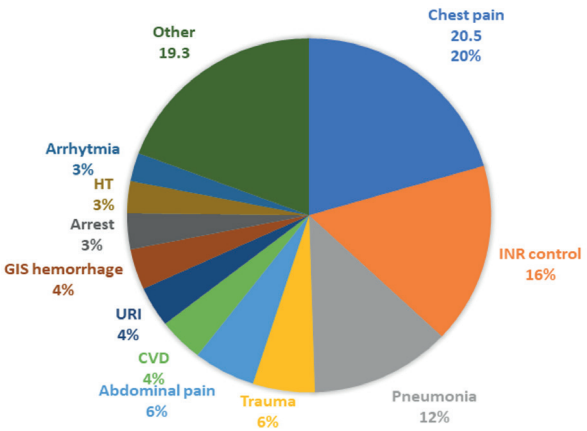

Figure 1. Reasons for admission and diagnosis in all patients.

CVD: cerebrovascular disease, stroke; URI: upper respiratory infection; HT: hypertension; INR: International Normalized Ratio; GIS: gastrointestinal; Other: headache, Covid pneumonia, urinary tract infection, gastritis etc.

(1.6%), and dabigatran use (1.6%). In other patients, it was impossible to determine the cause of the high INR (27.6%). No anticoagulant or antiaggregant drugs were found in the records of the patients not receiving warfarin. There was no significant difference in hemorrhage rates between the warfarin and non-warfarin groups (p >0.05). However, the incidence of prior hemorrhage was significantly higher in the warfarin group compared to the non-warfarin group (p <0.05). The incidence of minor hemorrhage was higher in patients with acute hemorrhage (70.6%) (Table 4).

Table 3. Outcomes for patients using warfarin.

		Median (Q1-Q3)	Mean±SD / n (%)
Age		68 (54-81)	66.9±15.1
Warfarin Usage	No		62 (23.1%)
	Yes		211 (76.9%)
Usage Period (Year)		3.0 (1-8)	4.4±3.2
Cause of onset of medication.	Arrhythmia		173 (82.0%)
	CVD		6 (2.8%)
	Valve Repl.		27 (12.8%)
	PE		5 (2.4%)

SD: Standard Deviation; CVD: Cerebrovascular disease, stroke; Valve Repl: Heart valve replacement; PE: Pulmonary embolism

The rate of hemorrhage was high (62.5%) in males. Patients with an INR higher than 2.5 who did not have hemorrhages were predominant (69.1%). The percentage of patients on warfarin who did not experience hemorrhages (77.9%) was higher than the rate of those who did. The most common presentation of hemorrhage was GI hemorrhage (41.7%), followed by epistaxis (25%) (Table 5).

Table 4. INR levels and occurrences of hemorrhage in warfarin users and others.

		Warfarin (-)		Warfarin (+)		p
		n	%	n	%	
INR value	<2.5	0	0%	83	39.3%	**0.000 x^2**
	>2.5	62	100%	128	60.7%	
Hemorrhage	No	55	88.7%	194	91.9%	0.429 x^2
	Yes	7	11.3%	17	8.1%	
Minor hemorrhage		2	28.6%	12	70.6%	0.058 x^2
Major hemorrhage		5	71.4%	5	29.4%	
Hemorrhage history	No	62	100%	188	89.1%	**0.007 x^2**
	Yes	0	0%	23	10.9%	

X^2: Chi-square test (Fischer test); INR: International Normalized Ratio

Table 5. Distribution of hemorrhagic patients.

		Hemorrhage (-)		Hemorrhage (+)		p
		Mean±SD / n (%)	Median (Q1-Q3)	Mean±SD / n (%)	Median (Q1-Q3)	
Age		68.7±15.7	71.0 (58-82)	67.2±13.0	67.5 (57-77)	0.440 m
Gender	Female	154 (61.8%)		9 (37.5%)		**0.020** X^2
	Male	95 (38.2%)		15 (62.5%)		
INR value	< 2.5	77 (30.9%)		6 (25.0%)		0.547 X^2
	> 2.5	172 (69.1%)		18 (75.0%)		
Warfarin usage	No	55 (22.1%)		7 (29.2%)		0.429 X^2
	Yes	194 (77.9%)		17 (70.8%)		
Previous hemorrhage	(-)	233 (93.6%)		17 (70.8%)		**0.000** X^2
	(+)	16 (6.4%)		7 (29.2%)		
Cause of application or diagnosis						
GIS		25 (10.0%)		10 (41.7%)		**0.000** X^2
Cardiac		70 (28.1%)		0 (0.0%)		**0.003** X^2
Respiratory		60 (24.1%)		1 (4.2%)		**0.025** X^2
INR control		45 (18.1%)		0 (0.0%)		**0.023** X^2
Neurological		28 (11.2%)		1 (4.2%)		0.282 X^2
Trauma		13 (5.2%)		2 (8.3%)		0.629 X^2
Urology		5 (2.0%)		4 (16.7%)		**0.004** X^2
Epistaxis		0 (0.0%)		6 (25.0%)		**0.000** X^2
Infection		3 (1.2%)		0 (0.0%)		1.000 X^2

SD: Standard Deviation, m Mann-Whitney U test / X^2 Chi-square test (Fischer test)

Complaints reported by patients experiencing hemorrhage

GIS: Gastrointestinal hemorrhage; Respiratory: Hemoptysis; Neurological: Intracranial hemorrhage; Trauma: Arrest (vascular injury and intra-abdominal hemorrhage), Rectus hematoma; Urology: Hematuria

DISCUSSION

This study showed that patients on warfarin generally did not have severe hemorrhage. Warfarin is frequently used in cardiology (8). Because the risk of heart disease increases with age, it is anticipated that people who use warfarin are more likely to be in the older population. This may account for the higher mean age of the study sample. Lindh et al.[9] found that men had a higher rate of hemorrhage. Similar results were observed in the present study. Genetic factors, lifestyle, and consistent drug use may have influenced this result.

Many studies have shown that the annual incidence of major hemorrhage in patients using warfarin ranges from 0.4% to 7.2% (10,11). Rates of minor hemorrhage can be up to 15.4% per year (11,12). This study determined that a history of warfarin use and a high level of INR did not make a significant difference in hemorrhage rates. According to the literature, many patients who develop bleeding experience minor bleeding (epistaxis). This study found that antihypertensive drugs were the most frequently used medications among patients taking warfarin. Therefore, epistaxis may have developed as a result

of high blood pressure. In addition, in the literature, the rate of major hemorrhage was low (29.4%) in the warfarin user group, and the most common type was GI hemorrhage (13). If the INR is below 1.5, surgery can be performed with minimal risk of hemorrhage. If the INR rate is between 4.5 and 10.0 and there is no hemorrhage, the warfarin dose should be skipped. If hemorrhage is detected, intravenous (IV) vitamin K, fresh frozen plasma (PFC), and prothrombin complex (PCC) concentrate should be administered (14).

Furthermore, it was observed that patients in this study self-reported the use of anticoagulant drugs. However, as the specific drug names were unknown, the INR levels were measured. Upon thorough examination of the prescription records, it was discovered that not all patients were prescribed warfarin. Moreover, the INR is routinely included in emergency tests, serving as a crucial indicator for emergency surgeries. In this study, the INR levels of patients who use anticoagulants other than warfarin, especially rivaroxaban, vary significantly. Therefore, it is appropriate for the emergency physician to request the INR level for all patients presenting with a situation that requires urgent medical intervention such as unconscious patients who have taking anticoagulant medication. This study also included data on the COVID-19 pandemic. In older patients with symptoms of COVID-19 or a history of nearly cured from COVID-19, INR levels may have increased without warfarin use since anticoagulants (LMWH) were added to their treatment.

The therapeutic and hemorrhagic risk thresholds for warfarin are closely aligned, posing a challenge for clinicians managing patients on this medication. However, the majority of patients in the warfarin group in this study exhibited no signs or history of hemorrhage. Consequently, the risk of hemorrhage associated with warfarin may be less pronounced than initially perceived. Hylek et al.[15] reported a 4.4% risk of major hemorrhage in patients with INR > 6, noting that there was a low level of risk because patients were followed up frequently. Çat et al.[16] found that the risk of minor and major hemorrhage increases as the level of INR increases. Similar findings were observed in this study. According to this result, although the number of patients on warfarin admitted to the ED is high, effective hemorrhage control could be achieved more efficiently when managed under the supervision of the physician who initially prescribed the drug.

Visser et al.[17] stated that metabolism would be impaired in patients with heart failure taking warfarin. They stated that due to the effect of the disease, hepatic veins will be affected, and drug metabolism will be impaired. Therefore, the INR level and bleeding risk will increase. The dose of warfarin may need to be monitored frequently in this group of patients. Most patients in this study were on warfarin for cardiac reasons, and the mean duration of use was more than three years. Therefore, the elevated level of INR may have increased as a result, but the risk of major hemorrhage have not increased.

Meeker et al.[18] found ineffective levels of INR in 49% of ED patients with a history of warfarin use. We also had similar results in our study. Still, since it was not possible to determine whether the patients discontinued the drug or whether other factors may have affected the INR level in these retrospective studies, generalizations cannot be made from the specified results.

Studies have shown that the effect of warfarin is higher and the risk of hemorrhage increases in the elderly (19,20). The main reason for this could be attributed to the existence of comorbidities and the concurrent use of multiple drugs. The risk of hemorrhage due to warfarin use is not very high in the literature. Different anticoagulants can be considered for elderly patients with poor drug compliance, those unable to control INR, and individuals dependent on others for medication management. Because of these factors, it may be more advisable to use warfarin in younger patients.

Contrary to common perception, warfarin may not be as high-risk as widely believed. The risks associated with its use can be minimized by advising patients on lifestyle changes, risk factor control, and regular INR monitoring.

Ethical approval

This study has been approved by the Kırklareli University Health Sciences Institute Ethics Committee (approval date 25/05/2021, number PR0330R0/10). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: OG, MD; Concept: OG; Design: MD; Data Collection or Processing: OG, MD; Analysis or Interpretation: OG; Literature Search: OG; Writing: OG, MD. All authors reviewed the results and approved the final version of the article.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Turkish Society of Hematology. Coumadin usage guide. 2019. Available at: https://www.thd.org.tr/thd_halk (Accessed on August 21, 2021).
2. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008; 133(6 Suppl): 160S-198S. [Crossref]
3. Hirsh J, Fuster V, Ansell J, Halperin JL; American Heart Association/American College of Cardiology Foundation. American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. J Am Coll Cardiol. 2003; 41(9): 1633-52. [Crossref]
4. Thacker SM, Grice GR, Milligan PE, Gage BF. Dosing anticoagulant therapy with coumarin drugs: is genotyping clinically useful? Yes. J Thromb Haemost. 2008; 6(9): 1445-9. [Crossref]
5. Kanagasabapathy P, Chowdary P, Gatt A. Alternatives to warfarin-the next generation of anticoagulants. Cardiovasc Ther. 2011; 29(6): e80-8. [Crossref]
6. Wittkowsky AK, Devine EB. Frequency and causes of overanticoagulation and underanticoagulation in patients treated with warfarin. Pharmacotherapy. 2004; 24(10): 1311-6. [Crossref]
7. Lip GY, Andreotti F, Fauchier L, et al. Bleeding risk assessment and management in atrial fibrillation patients. Thromb Haemost. 2011; 106(6): 997-1011. [Crossref]
8. Ertas F, Duygu H, Acet H, Eren NK, Nazli C, Ergene AO. Oral anticoagulant use in patients with atrial fibrillation. Turk Kardiyol Dern Ars. 2009; 37(3): 161-7.
9. Lindh JD, Holm L, Dahl ML, Alfredsson L, Rane A. Incidence and predictors of severe bleeding during warfarin treatment. J Thromb Thrombolysis. 2008; 25(2): 151-9. [Crossref]
10. Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. Arch Intern Med. 2005; 165(10): 1095-106. [Crossref]
11. DiMarco JP, Flaker G, Waldo AL, et al. Factors affecting bleeding risk during anticoagulant therapy in patients with atrial fibrillation: observations from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. Am Heart J. 2005; 149(4): 650-6. [Crossref]
12. Ozturk M, Ipekci A, Kiyak SK, et al. Bleeding Complications in Warfarin-Treated Patients Admitted to the Emergency Department. J Clin Med Res. 2019; 11(2): 106-13. [Crossref]
13. Eroğlu SE, Altınok DA, Özpolat Ç, Akoğlu H, Onur ÖE, Akoğlu ÜE. The investigation of the relation between INR levels and risk of complication in patients with a history of warfarin use. Marmara Medical Journal. 2012; 25(3): 138-42.
14. Tran HA, Chunilal SD, Harper PL, et al. An update of consensus guidelines for warfarin reversal. Med J Aust. 2013; 198(4): 198-9. [Crossref]
15. Hylek EM, Chang YC, Skates SJ, Hughes RA, Singer DE. Prospective study of the outcomes of ambulatory patients with excessive warfarin anticoagulation. Arch Intern Med. 2000; 160(11): 1612-7. [Crossref]
16. Çat BG, Çavuş UY, Bakır M, Yılmaz D, Yıldırım S. Emergency Department Visits due to the Bleeding Complication of Warfarin. The Anatolian Journal of Family Medicine. 2020; 3(1): 59-63. [Crossref]
17. Visser LE, Bleumink GS, Trienekens PH, Vulto AG, Hofman A, Stricker BHC. The risk of overanticoagulation in patients with heart failure on coumarin anticoagulants. Br J Haematol. 2004; 127(1): 85-9. [Crossref]
18. Meeker E, Dennehy CE, Weber EJ, Kayser SR. Emergency department management of patients on warfarin therapy. Ann Emerg Med. 2011; 58(2): 192-9. [Crossref]
19. Shepherd AM, Hewick DS, Moreland TA, Stevenson IH. Age as a determinant of sensitivity to warfarin. Br J Clin Pharmacol. 1977; 4(3): 315-20. [Crossref]
20. Fihn SD, Callahan CM, Martin DC, McDonell MB, Henikoff JG, White RH. The risk for and severity of bleeding complications in elderly patients treated with warfarin. Ann Intern Med. 1996; 124(11): 970-9. [Crossref]