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OUTCOMES OF WARFARIN THERAPY FOR SECONDARY PREVENTION OF ISCHEMIC STROKE: A RETROSPECTIVE, FOLLOW-UP STUDY[1]

İSKEMİK İNMENİN İKİNCİL KORUNMASINDA VARFARİN TEDAVİSİNİN SONUÇLARI: RETROSPEKTİF BİR TAKİP ÇALIŞMASI

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Abstract: Aim: Anticoagulant prophylaxis is recommended because cardioembolic ischemic stroke is associated with worse functional outcomes, increased recurrence rates, and higher mortality. This study aimed to investigate the rates of recurrent ischemic attacks and bleeding complications in patients receiving warfarin following ischemic stroke.

Method: In this retrospective analysis, a total of 181 individuals who were initiated on warfarin therapy following an ischemic stroke were included in the study. These patients were subsequently monitored for a duration spanning from 1 month to as long as 16 years. The acute ischemic stroke diagnosis was established using the Trial of Org 10172 in Acute Stroke Treatment classification criteria. Patient follow-up periods, international normalized ratio (INR) levels, ischemic events, and bleeding were recorded and evaluated.

Results: In the patient cohort, 97 (53.6%) were women and 84 (46.4%) were men. The recurrent ischemic stroke rate was 7.2%, major bleeding rate was 3.3%, and minor bleeding rate was 12.7%. While the average INR value during recurrent ischemic stroke was 1.69±0.31, the average INR value during bleeding complications was observed to be 3.15±1.38. The rate of minor bleeding was related to duration of warfarin use and non-valvular atrial fibrillation.

Conclusion: Our results show that long-term warfarin use and non-valvular atrial fibrillation are risk factors for bleeding.

Keywords: Ischemic Stroke, Warfarin, Anticoagulant, Ischemic Attacks

Öz: Amaç: Kardiyoembolik iskemik inme daha kötü fonksiyonel sonuçlar, artmış nüks oranları ve daha yüksek mortalite ile ilişkili olduğu için antikoagülan profilaksisi önerilmektedir. Bu çalışmanın amacı, iskemik inme sonrası varfarin alan hastalarda tekrarlayan iskemik atak oranlarını ve kanama komplikasyonlarını araştırmaktır.

Yöntem: Bu retrospektif çalışmaya iskemik inme sonrası varfarin başlanan ve 1 ay ile 16 yıl arasında takip edilen 181 hasta dahil edildi. Akut iskemik inme tanısı Trial of Org 10172 in Acute Stroke Treatment sınıflamasına göre konuldu. Hastaların takip süreleri, uluslararası normalleştirilmiş oran (INR) düzeyleri, iskemik olaylar ve kanama kaydedildi ve değerlendirildi.

Bulgular: Hasta kohortunun 97'si (%53.6) kadın ve 84'ü (%46.4) erkekti. Tekrarlayan iskemik inme oranı %7,2, majör kanama oranı %3,3 ve minör kanama oranı %12,7 idi. Tekrarlayan iskemik inme sırasında ortalama INR değeri 1.69±0.31 iken, kanama komplikasyonları sırasında ortalama INR değeri 3.15±1.38 olarak gözlendi. Minör kanama oranı varfarin kullanım süresi ve non-valvüler atriyal fibrilasyon ile ilişkiliydi.

Sonuç: Sonuçlarımız uzun süreli varfarin kullanımının ve non-valvüler atriyal fibrilasyonun kanama için risk faktörü olduğunu göstermektedir.

Anahtar Kelimeler: İskemik İnme, Varfarin, Antikoagülan, İskemik Ataklar

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INTRODUCTION

Stroke is a medical condition with a bleak outlook, impacting over 12 million individuals globally on an annual basis, as reported by Hindsholm et al. (Hindsholm et al., 2023). In the United States alone, close to 795,000 individuals experience a stroke annually with a total annual cost of more than $34 billion (Shah et al., 2022). Ischemic stroke, which affects more than 11 million people worldwide each year, accounts for 85% of strokes and is the most common (Boot et al., 2020). As per the criteria established by the Trial of Org 10172 in Acute Stroke Treatment (TOAST) study, ischemic stroke can be attributed to five distinct etiological factors, which include cardioembolism, small vessel blockage, atherosclerosis in large arteries, other well-defined causes, and origins that cannot be determined (Adams et al., 1993). The frequency of cardioembolic stroke, which constitutes approximately 30% of ischemic strokes, is gradually increasing. Causes of cardiac-related stroke include arrhythmias such as atrial fibrillation, atrial flutter and sick sinus syndrome, left atrial appendage, left atrial or ventricular thrombus, endocarditis, mitral stenosis, bioprosthetic or mechanical valve, heart tumors such as fibroelastoma and myxoma (Chew & Piccini, 2023; Dakay et al., 2018; Sloane & Camargo, 2019).

Non-valvular atrial fibrillation (NVAF) stands out as the leading contributor to cardioembolic strokes (Ferro, 2003). NVAF affects 2-3% of the population and is the most frequent arrhythmia in the US and Europe (Kirchhof, 2017). Ischemic stroke caused by NVAF is associated with worse functional outcomes, increased recurrence rates, and higher mortality (Gao & Passman, 2022). Hence, it is of utmost significance to implement preventive measures in order to avert recurrent incidents in individuals who have experienced cardioembolic strokes due to non-valvular atrial fibrillation (NVAF) (Song et al., 2021). Current clinical recommendations advise the use of long-term oral anticoagulant (OAC) therapy for specific ischemic stroke patients, as indicated by Hindricks et al. (Hindricks et al., 2021). Research has demonstrated that OAC treatment can reduce the likelihood of ischemic stroke by around two-thirds, as observed in the study by Ruff et al. (Ruff et al., 2014). In addition, it has also been shown that percutaneous left atrial appendage occlusion, which lowers bleeding risk and mortality, may be an alternative to oral anticoagulants (Chen et al., 2021; Paiva et al., 2021).

Warfarin, dabigatran, apixaban, rivaroxaban and edoxaban are commonly used anticoagulant agents (Bir & Kelley, 2021). The efficacy of warfarin as the primary anticoagulant for preventing secondary cardioembolic strokes, has been confirmed in many randomized studies (Kamel & Healey, 2017; Song et al., 2021). Nevertheless, factors like the elevated bleeding risk associated with warfarin utilization and the requirement for rigorous international normalized ratio (INR) monitoring restrict its application (Cha et al., 2017; Jung et al., 2015). In NVAF studies for

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primary and secondary prevention, it is recommended that the INR value be between 2.0 and 3.0 for maximum protection from ischemic stroke in patients receiving anticoagulant treatment. An INR value below 2.0 results in an increase in the risk of ischemic stroke (Go et al., 2003). It has been shown that the average annual major bleeding rates are 0.9%-2.7% and the average annual fatal bleeding rates are 0.07%-0.7% (Kahwati et al., 2022). The primary objective of this investigation was to assess the adverse outcomes, such as the recurrence of ischemic strokes and bleeding events, among patients who had experienced ischemic strokes arising from various underlying causes and were currently under warfarin therapy.

MATERIALS AND METHODS

Patients diagnosed with first or recurrent acute ischemic stroke as a result of clinical and radiological evaluation at the Neurology Clinic of Başkent University Faculty of Medicine and who were receiving on warfarin or antiplatelet therapy together with warfarin were included in this retrospective study. Approval for the study was received from the clinical ethics committee of Başkent University (KA11/254). The diagnosis of acute ischemic stroke was made according to the TOAST classification. Ischemic stroke risk factors were determined using techniques such as brain magnetic resonance imaging (MRI), diffusion MRI, carotid MR angiography, electrocardiography (ECG), echocardiography and Holter. A total of 249 patients, receiving warfarin alone or antiplatelet therapy together with warfarin, were evaluated retrospectively. Sixty-eight patients who did not come for follow-up were excluded from the study. One hundred eighty one patients receiving warfarin treatment and were followed up were included in the study. It was observed that a patient was under follow-up in our department because she had been using warfarin for 16 years.

Duration of warfarin use, regular INR monitoring, recurrent vascular events and bleeding complications, and INR values during recurrent vascular events and bleeding complications were recorded in detail. Patients were grouped as those using warfarin for less than 1 year, between 1-5 years, and over 5 years. The regular INR group was composed of patients who came for monthly INR monitoring. The irregular INR group comprised cases with INR control that took more than a month. The optimal INR value was determined as 2-3. Bleeding requiring the administration of two or more units of erythrocyte suspension, cerebral hemorrhage, and bleeding requiring urgent transfusion were considered major bleeding complications. All other bleeding was recorded as minor bleeding complications. Risk factors of patients with

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recurrent ischemic stroke were determined through examinations and re-categorized according to the TOAST classification.

Statistical Analysis

SPSS software version 15.0 was performed for statistical analyses. Numerical data were summarized using mean, standard deviation, median, and the range of values. Categorical variables were summarized by presenting the count and percentage. The normal distribution of numerical variables was assessed using the Kolmogorov-Smirnov test, and the homogeneity of variances among groups was assessed using the Levene test. To compare numerical variables among more than two groups, parametric tests like one-way analysis of variance or Welch analysis of variance were utilized, while the non-parametric Kruskal-Wallis test was applied when appropriate. Pairwise comparisons were made using Tukey's HSD, Games-Howell, and Bonferroni-corrected Mann-Whitney U tests. Categorical variables were compared between groups using the Chi-square test. Statistical significance was set at a p-value less than 0.05.

RESULTS

In the study, 97 (53.6%) of the patients were women and 84 (46.4%) were men. Among the recurrent vascular events during warfarin use, recurrent ischemic stroke was observed in 7.2% of the patient group, transient ischemic attack was observed in 0.6%, acute myocardial infarction was observed in 1.1% and splenic embolism was observed in 0.6%. Major bleeding complications were determined in six (3.3%) of the patients and minor bleeding complications were determined in 23 (12.7%). Of the patients who developed major bleeding complications, three had gastrointestinal tract bleeding, two had subdural hematoma, and one had a rectus muscle hematoma. Minor bleeding complications included epistaxis (n=11), hematuria (n=6), hematochezia (n=3), intramuscular hematoma (n=1), ecchymosis (n=1), and vaginal bleeding (n=1). During follow-up, two patients died of subdural hematoma, six patients died of sepsis, and two patients died of cardiac reasons. These two patients who developed subdural hematoma were not included among the major bleeding complications, and the outcome of death was evaluated separately. When major bleeding complications and cerebral-related deaths were considered together, the fatal complication rate was found to be approximately 4.4% (Table 1).

Table 1. Distribution of Recurrent Vascular Events, Bleeding Complications and Mortality of the Patients Included in the Study

	Number (n)	Percentage (%)
Recurrent vascular events		
Ischemic CVD	13	7.1
TIA	1	0.6
MI	2	1.1
Systemic embolism	1	0.6

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Bleeding complications		
Major	6	3.3
Minor	23	12.7
Mortality		
Cerebral	2	1.1
Non-cerebral	8	4.4

CVD: Cerebrovascular disease, **TIA**: Transient ischemic attack, **MI:** Myocardial infarction

Recurrent ischemic stroke was observed in 4.7% of patients using warfarin for less than one year, in 5.4% of patients using warfarin for 1-5 years, and in 10.9% of patients using warfarin for more than 5 years. There was no significant difference between the groups. While there was no significant difference in the rates of major bleeding complications according to the duration of warfarin use, minor bleeding complications were observed more frequently as the duration of warfarin use increased (p = 0.023). No significant relationship was found between the death rates of both cerebral and non-cerebral causes according to the duration of warfarin use (Table 2).

Table 2. Recurrent Vascular Events, Bleeding Complications and Mortality Rates According to Warfarin Treatment Durations

	≤1 year (n=43)	**1-5 years (n=74)**	**>5 years (n=64)**	***p* value**
Ischemic CVD	2 (4.7%)	4 (5.4%)	7 (10.9%)	0.363
TIA	0 (0%)	1 (1.4%)	0 (0%)	0.407
MI	0 (0%)	1 (1.4%)	1 (1.6%)	0.576
Systemic embolism	-	-	1 (1.6%)	0.352
Major bleeding	1 (2.3%)	3 (4.1%)	2 (3.1%)	0.873
Minor bleeding	3 (7%)	6 (8.1%)	14 (21.9%)	**0.023**
Cerebral deaths	0 (0%)	1 (1.4%)	1 (1.6%)	0.576
Non-cerebral deaths	1 (2.3%)	1 (1.4%)	6 (9.4%)	0.060

CVD: Cerebrovascular disease, **TIA**: Transient ischemic attack, **MI:** Myocardial infarction.

When risk factors for bleeding complications were evaluated, minor bleeding complications were observed in 27.3% of those with a history of NVAF, while minor bleeding complications were observed in 10.7% of those without NVAF. The difference was found to be statistically significant (p = 0.040). No significant association of other risk factors with bleeding complications was observed (Table 3).

Table 3. Bleeding Complication Rates According to Risk Factors

		Major Complication		**Minor Complication**	
		Number (%)	**p**	**Number (%)**	**p**
Gender	Men (n=84) Women (n=97)	4 (%4.8) 2 (%2.1)	0.418	14 (%16.7) 9 (%9.3)	0.206
Hypertension	No (n=44) Yes (n=137)	1 (%2.3) 5 (%3.6)	1.000	6 (%13.6) 17 (%12.4)	1.000
Coronary Artery Disease	No (n=119)	3 (%2.5)	0.414	15 (%12.6)	1.000

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	Yes (n=62)	3 (%4.8)		8 (%12.9)	
Diabetes Mellitus	No (n=124) Yes (n=57)	5 (%4) 1 (%1.8)	0.667	13 (%10.5) 10 (%17.5)	0.230
Hyperlipidemia	No (n=128) Yes (n=53)	4 (%3.1) 2 (%3.8)	1.000	19 (%14.8) 4 (%7.5)	0.273
Cerebrovascular Disease	No (n=152) Yes (n=29)	6 (%3.9) 0 (%0)	0.591	16 (%10.5) 7 (%24.1)	0.064
Atrial Fibrillation	No (n=159) Yes (n=22)	6 (%3.8) 0 (%0)	1.000	17 (%10.7) 6 (%27.3)	***0.040***
Hypothyroidism	No (n=163) Yes (n=18)	6 (%3.7) 0 (%0)	1.000	22 (%13.5) 1 (%5.6)	0.477
Chronic Liver Failure	No (n=169) Yes (n=12)	6 (%3.6) 0 (%0)	1.000	22 (%13) 1 (%8.3)	1.000
History of TIA in the last 6 months	No (n=169) Yes (n=12)	5 (%3) 1 (%8.3)	0.341	23 (%13.6) 0 (%0)	0.368
Malignancy	No (n=177) Yes (n=4)	6 (%3.4) 0 (%0)	1.000	22 (%12.4) 1 (%25)	0.422
Connective Tissue Disease	No (n=178) Yes (n=3)	6 (%3.4) 0 (%0)	1.000	23 (%12.9) 0 (%0)	1.000
Hyperthyroidism	No (n=179) Yes (n=2)	6 (%3.4) 0 (%0)	1.000	22 (%12.3) 1 (%50)	0.239
Obesity	<30 (n=151) ≥30 (n=30)	5 (%3.3) 1 (%3.3)	1.000	18 (%11.9) 5 (%16.7)	0.547
Cigarette	No (n=154) Yes (n=27)	5 (%3.2) 1 (%3.7)	1.000	17 (%11) 6 (%22.2)	0.120
Alcohol	No (n=177) Yes (n=4)	6 (%3.4) 0 (%0)	1.000	23 (%13) 0 (%0)	1.000

When the etiology of cases with recurrent ischemic stroke was regrouped according to TOAST, there was no significant difference between the initial etiology and the etiology of recurrent ischemic stroke (p = 1.000) (Table 4).

Table 4. TOAST Relationship Between Initial and Recurrent Ischemic Stroke

	Initial TOAST classification	
	Cardioembolic	Undefined etiology
TOAST classification of recurrent events		
Cardioembolic	9 (90%)	1 (10%)
Undefined etiology	2 (50%)	2 (50%)

Some (40.3%) of the patients only received warfarin, 57.5% received warfarin + aspirin, and 2.2% received warfarin + clopidogrel. Patients using antiplatelets together with warfarin additionally had coronary artery disease. No statistically significant findings were found in terms of recurrent ischemic events and bleeding complications between these treatment groups (Table 5).

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Table 5. Rates of Recurrent Ischemic Events and Bleeding Complications According to Different Treatment Groups

	Recurrent Ischemic Events		Major Bleeding		Minor Bleeding	
	n (%)	*p*	n (%)	*p*	n (%)	*p*
Warfarin (n=73)	5 (6.8%)		3 (4.1%)		8 (11%)	
Warfarin+Aspirin (n=104)	7 (6.7%)	0.532	3 (2.9%)	0.792	14 (13.5%)	0.703
Warfarin+Clopidogrel (n=4)	1 (25%)		0 (0%)		1 (25%)	

Recurrent ischemic stroke was observed at a rate of 7.1% among those who regularly monitored INR monthly, and at a rate of 8.3% among those who monitored INR irregularly. In patients with regular INR monitoring, major bleeding was detected in 3.6% and minor bleeding was detected in 13%. Among patients with irregular INR monitoring, a minor bleeding complication was observed in one patient. No significant difference was detected between the groups. The mean INR value in patients with major bleeding complications was 3.15±1.38. It was observed that two of these patients had subdural hematoma even though their INR levels were within the optimum INR values (2.35 and 2.87). However, these two patients were in the group using warfarin + aspirin due to undefined etiology. It was observed that the mean INR value in patients with minor bleeding complications was 3.19±1.54. An INR value above the optimum limit is a risk factor for bleeding complications, but complications can also occur when it is within therapeutic limits. It was determined that the INR level at the time of recurrent stroke was below 2 in 11 of the 13 patients who had recurrent ischemic stroke. The INR level of a patient who had a transient ischemic attack was 3.4 (Table 6).

Table 6. INR Values During Recurrent Ischemic Events and Bleeding Complications

INR value during recurrent ischemic events	1.69±0.31 1.74 [1.00 – 2.08]
INR value during major bleeding complications	3.15±1.38 2.68 [2.04 – 5.80]
INR value during minor bleeding complications	3.19±1.54 2.54 [1.64 – 8.00]

(Values are Given as Mean±SD, Median [Min-Max])

Paroxysmal atrial fibrillation (PAF) was detected by Holter in 48.8% of patients with normal sinus rhythm on ECG. This finding shows that PAF can be detected in a majority of patients with normal sinus rhythm on ECG, and that Holter should be performed in suspected patients (Table 7). Recurrent ischemic stroke was observed in 9.7% of patients with no history of AF but with AF detected on their ECG and in 6.3% of patients with normal sinus rhythm. Recurrent ischemic stroke was detected in 10.8% of the patients with PAF detected in Holter.

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Table 7. Comparison of ECG and Holter Findings

		Holter			
		N/A	**NVAF**	**NSR**	**PAF**
ECG	**Chronic NVAF**	22	0	0	0
	New diagnosis NVAF	26(83.9%)	2(6.5%)	0	3(9.7%)
	NSR	36(28.3%)	2(1.6%)	24(18.9%)	62(48.8%)
	Sinus bradycardia	0	1	0	0

ECG: Electrocardiography, **NVAF:** Non-valvular atrial fibrillation, **NSR:** Normal sinus rhythm, **PAF:** Paroxysmal atrial fibrillation

DISCUSSION

This study focused on assessing the occurrences of recurrent ischemic strokes and bleeding events among individuals receiving warfarin treatment following an initial ischemic stroke. Among the patients, major bleeding was observed in 3.3%, while minor bleeding was observed in 12.7% of cases. Notably, minor bleeding was linked to the prolonged use of warfarin and the presence of non-valvular atrial fibrillation (NVAF).

Stroke prevention is a top priority due to its status as a major global cause of both fatalities and neurological impairments. More precisely, patients with non-valvular atrial fibrillation (NVAF) face a fivefold increase in their risk of experiencing an ischemic stroke, but this risk soars to a factor of 17 in individuals with atrial fibrillation (AF) coupled with mitral stenosis (Wolf et al., 1978). Lansberg et al (Lansberg et al., 2012) reported that the annual hemorrhagic transformation in patients using OAC was between 0.6% and 1% 32. Within two weeks after NVAF-induced stroke, the risk of developing early recurrent cerebral embolism was reported to be approximately 0.1% and 1.3% per day (Hart et al., 1983). In the RAF investigation, which involved the assessment of 1,029 patients, the recurrence rate of ischemic events was determined to be 7.6%, major bleeding was 1.4%, and symptomatic cerebral bleeding was 3.6% (Paciaroni et al., 2015). According to the RAF study, it is advisable to begin anticoagulant therapy within a timeframe of four to 14 days for preventing recurrent ischemic strokes, with the exception of patients who have large ischemic lesions linked to cerebral hemorrhage. According to findings by Mac Grory et al. (Mac Grory et al., 2019), the resumption of oral anticoagulant (OAC) therapy in patients with atrial fibrillation (AF) following a cardioembolic stroke is advised to be delayed until at least 48 hours have passed, as there is a risk of recurrence. In cases of valvular AF, individuals not receiving OAC therapy face an eightfold greater incidence of embolic events compared to those who are on OAC therapy. As a result, it is highly advised to utilize oral anticoagulants (OACs) for the purpose of secondary stroke prevention in individuals who have experienced cardioembolic strokes (Bir & Kelley, 2021).

Warfarin holds the position as the most commonly employed oral anticoagulant across the globe, serving both primary and

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secondary roles in preventing ischemic strokes. Bleeding or thromboembolism may occur as a result of the use of warfarin, which has a narrow therapeutic window (Ma et al., 2022). While warfarin reduces the risk of ischemic stroke in patients with NVAF by approximately 66 percent, it may cause a slight increase in the rate of major bleeding or intracerebral hemorrhage by 1.4%-4.5% per year (Kim et al., 2009; Marti-Fabregas & Mateo, 2009). The recurrence rate in the first year after cardioembolic ischemic stroke is approximately 10%. In the studies of Ravvaz et al. (Ravvaz et al., 2021), it was determined that 558 (7.67%) of 7,274 newly diagnosed AF patients who receiving warfarin treatment experienced bleeding or ischemic events. Bleedings (4.97%) were detected twice as frequently as ischemic events (2.71%). Gastrointestinal bleeding was observed in 198 patients, intracranial bleeding was observed in 29 patients, other major bleeding was observed in 134 patients, transient ischemic attack was observed in 182 patients and systemic embolic events were observed in 15 patients. Since warfarin is superior to aspirin in preventing stroke in NVAF patients, anticoagulant treatment is also recommended in valvular AF (Bir & Kelley, 2021). In the European Atrial Fibrillation Trial investigation, involving the assessment of 1,007 patients who had experienced ischemic stroke and had NVAF, it was observed that the recurrence of ischemic strokes decreased by 66% among those treated with warfarin and by 14% among those using aspirin. The reported annual risk rates for ischemic stroke were 4% for the warfarin group, 10% for the aspirin group, and 12% for the placebo group ("Silent brain infarction in nonrheumatic atrial fibrillation. EAFT Study Group. European Atrial Fibrillation Trial," 1996). An examination comparing warfarin to standard-dose direct oral anticoagulants (DOACs) revealed that there were no discernible distinctions between the two groups in relation to the risk of major bleeding, with rates of 5.94% and 5.05%, respectively. However, patients receiving DOACs exhibited a reduced likelihood of experiencing fatal bleeding and intracranial bleeding. Moreover, researchers observed a higher risk of major gastrointestinal bleeding in patients treated with standard DOAC than in patients treated with warfarin, 2.54% versus 1.95%, respectively. In the same study, it was reported that the risk of major bleeding in patients taking low-dose DOACs (4.34%) was lower than in patients taking warfarin (5.94%) (Carnicelli et al., 2022). In the study where 2,337 patients were evaluated between January 1, 2015 and December 31, 2020, 315 (13.4%) patients experienced another ischemic stroke attack. In the same study, ischemic stroke was observed in 12.6% of those taking warfarin, 12.8% of those taking DOACswitch, and 8.7% of those taking fixed DOACsame within one year. Within one year, 5.3% of those taking warfarin, 1.6% of those taking DOACswitch and 1.5% of those taking DOACsame had intracranial hemorrhage (Ip et al., 2023).

In our investigation, we noted significant bleeding issues in 3.3% of the patients, minor bleeding incidents in 12.7%, and

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recurrent ischemic episodes in 7.2% of the cases. Of the patients who developed major bleeding complications, three were gastrointestinal system bleeding, two were subdural hematoma, and one was rectus muscle hematoma. The mortality rate during follow-up was 5.5% (2 patients due to subdural hematoma, 6 patients due to sepsis, and 2 patients due to cardiac reasons). When major bleeding complications and cerebral-related deaths were evaluated together, the fatal complication rate in our study was determined as 4.4%. The incidence of recurrent ischemic attacks was related to the duration of warfarin use. In our study, no significant difference was determined in recurrent ischemic stroke between the patient groups receiving warfarin and warfarin plus aspirin treatment (n=73, n=104, respectively) (6.8% vs. 6.7%, respectively). This may be due to keeping the INR values between 2.0 and 3.0 in both groups. There was no notable distinction observed in the incidence of major bleeding complications among the treatment groups. Combination therapy can be applied in patient groups at high risk for concomitant coronary artery disease and ischemic stroke, as long as the INR level is kept at the optimum level. As a matter of fact, we frequently encounter combination therapy applications in our clinical practice. The bleeding rates and recurrent ischemic attack rates we obtained in our study are similar to previous study results.

For patients taking warfarin, the dose should be carefully adjusted and careful and consistent INR monitoring should be performed. Because the effectiveness of warfarin depends on therapeutic INR control. The ideal INR range is 2.0–3.0 (2.5–3.5 in the presence of a mechanical valve), and the effectiveness of warfarin decreases when INR falls below 2.0 (Gong et al., 2022). According to the American Heart Association (AHA), monthly INR control is necessary to keep the INR value between 2.0-3.0, but longer follow-ups, such as a 2-month break, may be recommended in patients whose INR value remains stable (European Heart Rhythm et al., 2006). Song et al (Song et al., 2021) compared the effects of hirudin plus aspirin and warfarin in patients with ischemic stroke due to NAVF. The INR values in the warfarin group at 1, 2, 3, 6, 9 and 12 months were observed to be 2.00, 1.98, 2.20, 2.34, 1.97 and 2.42, respectively. In the same study, the time in therapeutic range (TTR) of patients taking warfarin was determined to be 66.5% and the INR value was determined to be < 2 in 31.4% ± 19.3% of the total treatment period. A sole patient experienced an INR value exceeding 3 for a duration of 1.3 months, and this particular individual encountered a non-fatal intracranial hemorrhage three months after the onset of the stroke. In the study, where 77.9% of the patients achieved INR stability, seven (6.25%) major complications were identified in the hirudin plus aspirin group and 14 (12.84%) major complications in the warfarin group. In the study where the INR was kept between 2.0 and 3.0 throughout the study, the recurrent ischemic stroke rate was observed to be 2.57% in the warfarin group. In another study, it was determined that the risk of bleeding in chronic liver patients with

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an INR value of < 3 was higher than in warfarin users. It has been reported that as the INR value increases above 3, the risk of bleeding in warfarin users increases (Afzal et al., 2022). Similar to our study, in a retrospective study by Moriyasu et al. (Moriyasu et al., 1993), 68 patients who had previously had a cardioembolic ischemic stroke and were under warfarin treatment were followed for 39±27 months for recurrent stroke and bleeding complications. While recurrent ischemic stroke was observed in three patients (4.4%), major bleeding complications were detected in 12 patients (17.6%). In the same study, the average INR value during recurrent ischemic stroke was determined as 2.2 and the average INR value during bleeding complications was determined as 3. In our study, while the average INR value during recurrent ischemic stroke was 1.69±0.31, the average INR value during bleeding complications was determined as 3.15±1.38. Recurrent ischemic stroke was observed at a rate of 7.1% among those who regularly monitored INR monthly, and at a rate of 8.3% among those who monitored INR irregularly. This result suggests that regular INR monitoring will reduce the rate of recurrent ischemic stroke.

The limitations of our study are that it is retrospective, single-center, has a limited follow-up period, no TTR calculation, no randomization, and a small number of patients. Our results should be confirmed with prospective studies with larger sample sizes and longer follow-up periods.

In conclusion, we evaluated the recurrent stroke attacks and bleeding complications in patients receiving warfarin after ischemic stroke that we followed in our clinic. Rates of recurrent stroke attacks and bleeding complications were consistent with previous studies. NAVF and long-term warfarin use were determined as risk factors for minor bleedings. Monthly INR monitoring and keeping INR between 2.0 and 3.0 is important for the effectiveness of warfarin.

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