Factors Associated with Ischaemic Stroke Development Despite Oral Anticoagulant Therapy in Patients with Non-Valvular Atrial Fibrillation

Emre Ozdemir[1], Muhammed Mucahit Tiryaki[2], Zeynep Emren[3], Ozgen Safak[4], Enise Tiryaki[5] and Aysen Suzen Ekinci[6]

[1]*Department of Cardiology, Ataturk Research and Training Hospital, Izmir Katip Celebi University, Izmir, Turkiye*
[2]*Department of Cardiology, Mus Government Hospital, Mus, Turkiye*
[3]*Department of Cardiology, Cigli Research and Training Hospital, Bakircay University, Izmir, Turkiye*
[4]*Department of Cardiology, Faculty of Medicine, Balikesir University, Balikesir, Turkiye*
[5]*Department of Neurology, Mus Government Hospital, Mus, Turkiye*
[6]*Department of Neurology, Ataturk Research and Training Hospital, Izmir, Turkiye*

ABSTRACT

Objective: To evaluate the effectiveness of the most popular risk scores (CHADS2, CHA2DS2-VASc, and ATRIA scores) in predicting stroke events in patients with non-valvular atrial fibrillation (NVAF) who were already receiving oral anticoagulant therapy (OAT).

Study Design: An observational study.

Place and Duration of the Study: Department of Cardiology, Ataturk Research and Training Hospital, Izmir Katip Celebi University, Izmir, Turkiye, from January 2020 to December 2023.

Methodology: Patients with NVAF who were on OAT were divided into two groups. Group 1 consisted of patients who had not experienced a stroke while on OAT, and Group 2 consisted of patients who had experienced at least one stroke while on OAT at the time of inclusion. Continuous variables were presented as mean or median values and were compared using Student's t-test or Mann-Whitney U test, depending on the type of data distribution.

Results: There were 162 patients in Group 1 and 129 patients in Group 2, the majority being females. The median age of patients was 76 years (IQR: 71-82) in Group 1 and 75 years (IQR: 68-81) in Group 2. Comorbidities were statistically similar in both groups except for hyperlipidemia. Treatment for atrial fibrillation (AF) was also statistically similar in both groups. The CHA2DS2-VASc and ATRIA stroke scores showed statistically significant differences between the groups. In univariate analysis, hyperlipidemia and ATRIA stroke score were >8, and in multivariate analysis, only ATRIA stroke score was >8, which showed a correlation with estimating the risk of ischaemic stroke (IS) events under oral anticoagulation (OAC). The ATRIA stroke score showed a strong correlation Spearman's rho test and in the ROC curve.

Conclusion: The CHA2DS2-VASc, CHADS, and ATRIA risk scores have proven effective in primary IS prophylaxis. The ATRIA stroke score system for secondary prevention appears to be more effective than the most popular score systems.

Key Words: *Non-valvular atrial fibrillation, ATRIA stroke score, CHA2DS2-VASc, Oral anticoagulation, Ischaemic stroke*.

How to cite this article: Ozdemir E, Tiryaki MM, Emren Z, Safak O, Tiryaki E, Ekinci AS. Factors Associated with Ischaemic Stroke Development Despite Oral Anticoagulant Therapy in Patients with Non-Valvular Atrial Fibrillation. *J Coll Physicians Surg Pak* 2025; **35(06)**:712-716.

INTRODUCTION

Stroke is one of the leading causes of disability and death, with atrial fibrillation (AF) being a major risk factor for this condition. AF can be divided into two groups: Valvular AF and non-valvular AF (NVAF).[1] In patients with NVAF, non-vitamin K oral anticoagulants (NOACs) or vitamin K-antagonist oral anticoagulants (VKAOCs) can be used as oral anticoagulation therapy (OAT) to lower the risk of ischaemic stroke (IS).[1,2]

Correspondence to: Dr. Emre Ozdemir, Department of Cardiology, Ataturk Research and Training Hospital, Izmir Katip Celebi University, Izmir, Turkiye
E-mail: emreozdemir27@yahoo.com.tr

Received: January 16, 2025; Revised: April 18, 2025; Accepted: May 21, 2025
DOI: https://doi.org/10.29271/jcpsp.2025.06.712

Observational studies have shown that approximately 10-30% of strokes in AF patients occur while on OAT, putting this group at a high risk of morbidity and mortality due to high rates of IS recurrence.[2]

Potential underlying causes for this situation may include interruption of oral anticoagulation (OAC), inappropriate OAC dosing, and the presence of additional risk factors.[3] Various scoring systems, such as CHADS2, CHA2DS2-VASc, and ATRIA stroke scores, are useful for determining additional risk factors.[4] Some studies have shown that the ATRIA stroke score is better at predicting stroke in patients while on OAT compared to CHADS2 and CHA2DS2-VASc scores.[5]

This score system can also be used for primary prevention in patients with NVAF. However, there are limited data on stroke risk calculation in patients with NVAF who are already on OAT.

This study aimed to evaluate the effectiveness of the most popular risk scores (CHA2DS2-VASc and ATRIA stroke scores) along with clinic and laboratory parameters in predicting stroke events in patients with NVAF who are already on OAT.

METHODOLOGY

Patients were scanned on OAT due to NVAF from January 2020 to December 2023 at the Department of Cardiology, Ataturk Research and Training Hospital, Izmir Katip Celebi University, Izmir, Turkiye. All data collected were retrospective and consecutive. Twenty-one patients were excluded because of insufficient data documenting stroke history. Patients were divided into two groups. Group 1 consisted of patients who had no stroke on OAT, and Group 2 consisted of patients who had at least one stroke on OAT at the time of inclusion.

The study variables included Diabetes Mellitus (regulated blood glucose with at least one hypoglycemic agent), arterial hypertension (regulated blood pressure with at least one antihypertensive), coronary artery and carotid artery diseases (coronary lesion >50%), chronic kidney disease (persistent abnormalities in kidney structure or function for more than three months, manifesting as either low GFR or the presence of a marker of kidney damage), atrial fibrillation (documented any atrial fibrillation period), left ventricular ejection fraction (LVEF), age, haemoglobin (Hb), and thyroid-stimulating hormone levels were noted.[6] In patients who underwent VKAOC, an international normalised ratio (INR) of 2.0 to 3.0 and an annual time in the therapeutic range (TTR) above 70% were considered appropriate treatments. For NOACs patients, the agent used as described and suggested in the literature was accepted as the appropriate treatment.[7]

The ATRIA stroke score is based on four age categories, prior stroke, female gender, renal function, a history of diabetes, congestive heart failure, and hypertension.[8] The CHA2DS2-VASc scoring system includes heart failure, hypertension, age, diabetes mellitus, prior stroke, vascular disease, and female gender.[9] NVAF is accepted as AF in patients with moderate-to-severe mitral stenosis of rheumatic origin or mechanical prosthetic valve replacement.[10,11]

Statistical analyses were conducted using the Statistical Package for Social Sciences 15.0 software (SPSS, Chicago, IL, USA). The Kolmogorov-Smirnov test was utilised to determine if the data followed a normal distribution. Continuous variables were reported as mean (standard deviation, SD) or median (interquartile range, Q1-Q3) values and were compared using either Student's t-test or Mann-Whitney U test, depending on the data distribution. Variables with a p-value of <0.1 in the comparative analysis were included in the univariate analysis. Variables with a p-value of <0.05 were further evaluated using multivariate logistic regression analysis. The correlation between risk scores and cognitive function was assessed using Spearman's rho test. The predictive value of the risk scores was determined through receiver operator analysis, and the area under the curve of the risk scores was compared using the DeLong test. A p-value of <0.05 was considered statistically significant.

RESULTS

In the current study, 312 patients on OAT due to NVAF were scanned from January 2020 to December 2023. Twenty-one patients were excluded due to insufficient data. There were 162 patients in Group 1, and 129 patients in Group 2.

In the present study's population, the stroke rate on OAT was 44.3%, with a female dominance of 99 (61.1%) patients in Group 1 and 88 (68.2%) in Group 2 (p = 0.209). The median age was 76 (IQR: 71-82) years in Group 1 and 75 (IQR: 68-81) years in Group 2 (p = 0.181). Comorbidities were statistically similar in both groups, except for hyperlipidemia, which was 17 (10.5%) patients in Group 1 and 32 (24.8%) in Group 2 (p = 0.001, Table I). Appropriate treatment for AF was statistically similar in both groups (Table I).

Table I: Clinic and laboratory parameters of patients.

Variables	Group 1 CVE (-) n = 162	Group 2 CVE (+) n = 129	p-value
	n (%)	n (%)	
Female gender n (%)	99 (61.1%)	88 (68.2%)	0.209
Age median (IQR)	76 (71-82)	75 (68-81)	0.181
Arterial hypertension	131 (81.3%)	102 (79%)	0.625
Coronary arterial disease	45 (27.9%)	24 (18.1%)	0.063
Ejection fraction % median (IQR)	60 (52-60)	60 (860-60)	0.089
Diabetes mellitus	60 (37.2%)	53 (41%)	0.508
Hyperlipidemia	17 (10.5%)	32 (24.8%)	0.001
Chronic kidney disease	12 (7.4%)	7 (5.5%)	0.497
Smoking	13 (8.0%)	9 (6.9%)	0.912
Cancer	7 (4.3%)	9 (6.9%)	0.323
Valve replacement	1 (1.2%)	1 (0.7%)	0.622
Coagulation disorder	1 (0.6%)	0	0.371
Carotid arterial disease	4 (2.4%)	4 (3.1%)	0.497
Appropriate treatment	102 (62.9%)	92 (71.3%)	0.133
Thyroid stimulating hormone mU/L median (IQR)	1.3 (0.8-1.99)	1.41 (0.88-2.45)	0.306
Hemoglobine g/dL median (IQR)	12.5 (11.13.65)	12.5 (10.8-13.9)	0.660
CHA2DS2-VASc score	4 (3-4)	5 (5-6)	<0.001
ATRIA stroke score	7 (5-8)	10 (9-11)	<0.001

Continuous variables were presented as median (interquartile range, Q1-Q3) values and were compared with Mann-Whitney U test depending on the type of data distribution. Qualitative variables were presented as frequencies and percentages and were compared with Chi-square test.

Table II: Distribution of anticoagulant medical treatment for both groups.

Variables	Group 1 CVE (-) n = 162	Group 2 CVE (+) n = 129	p-value	Variables	Group 1 CVE (-) n = 162	Group 2 CVE (+) n = 129	p-value
	n (%)	n (%)			n (%)	n (%)	
Warfarin	58 (33.8%)	51 (39.5%)	0.312	Rivaroxaban	42 (40.4%)	25 (32.1%)	0.535
				Edoxaban	8 (7.7%)	8 (10.2%)	
				Apixaban	29 (27.9%)	21 (27%)	
NOAC	104 (66.2)	78 (60.5%)		Dabigatran	25 (24.0%)	24 (30.7%)	

Variables were presented as frequencies and percentages and were compared with Chi-square test.

Table III: Analysis for estimating ischaemic stroke development despite oral anticoagulant therapy in patients with non-valvular atrial fibrillation.

Variable	Univariate analysis				Multivariate analysis			
	HR	95% CI		p-value*	HR	95% CI		p-value**
Hyperlipidemia	2.974	1.470	5.311	0.002	1.717	0.740	3.983	0.208
ATRIA stroke score (>8)	25.256	13.580	46.970	<0.001	23.724	12.711	4.4278	<0.001
Ejection fraction	1.025	0.999	1.052	0.057	-	-	-	-

**p-values were determined with univariate logistic regression analysis. **p-values were determined with multivariate logistic regression analysis.*

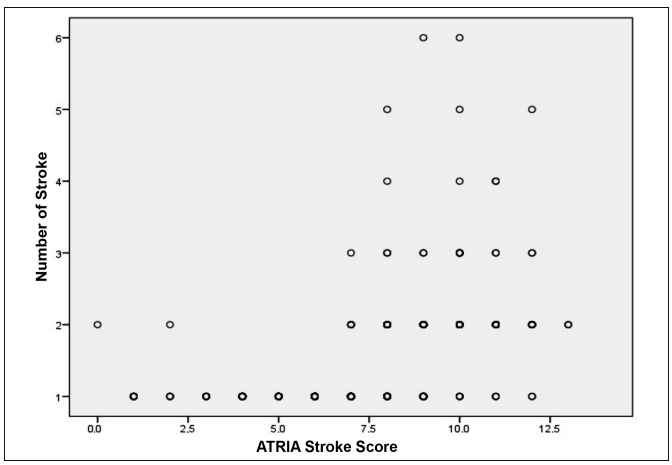

Figure 1: ATRIA stroke score and recurrent stoke correlation.

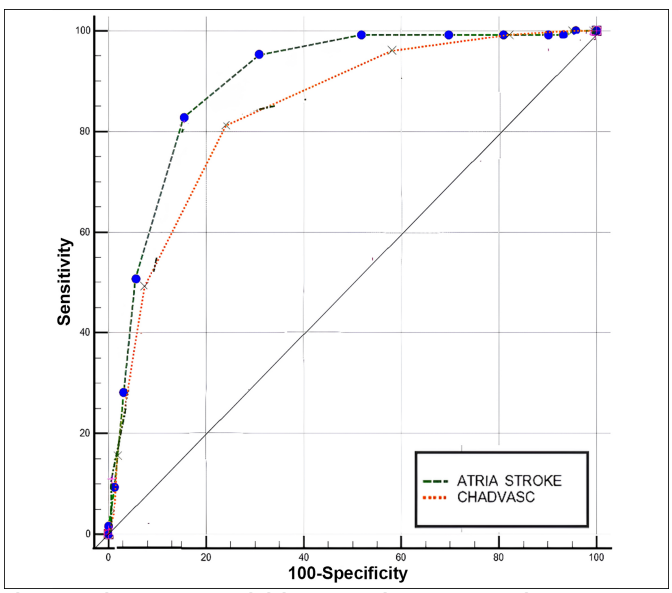

Figure 2: The ROC curve of risk score and recurrent stroke events. Area under curve (AUC) of ATRIA stroke score is 0.831 with 0.782-0.872, 95% confidence interval, p-value <0.001 and AUC of CHA2DS2-VASc score is 0.842 with 0.795-0.882, 95% confidence interval, p-value <0.001.

The appropriate treatment of NOAC and VKA in both groups was similar, with subgroups of NOAC (Rivaroxaban, Edoxaban, Apixaban, Dabigatran) types distributed statistically similarly in both groups (Table II).

In the current study, the authors evaluated the most popular risk scores (CHA2DS2-VASc, Atria stroke scores). The CHA2DS2-VASc score median was four (IQR: 3-4) in Group 1 and five (IQR: 5-6) in Group 2 with p <0.001. In univariate analysis for estimating ischaemic stroke development despite OAT in patients with NVAF, the hazard ratio (HR) was 2.974, 95% confidence interval (CI) was 1.470-5.311, p-value was 0.002 for hyperlipidemia, and HR: 25.256, 95% CI: 13.580-46.970, p <0.001 for ATRIA stroke score over 8 points (Table III). Also, in multivariate analysis for estimating ischaemic stroke development despite OAT in patients with NVAF, HR: 23.724, 95% CI: 12.711-4.4278, p <0.001 for ATRIA stroke score over 8 points (Table III).

Spearman's rho correlation analysis evaluated all score systems, where the CHA2DS2-VASc score reached a moderate positive correlation with recurrent stroke events (rho: 0.591, p <0.001 and rho: 0.609, p <0.001). ATRIA stroke score had a strong correlation with rho: 0.671 and p <0.001. Supported by this data, the logarithmic increase of recurrent stroke and ATRIA stroke risk score can also be seen in Figure 1.

In the ROC curve as seen in Figure 2, HR: 0.842, CI: 0.795–0.882, p <0.001 for CHA2DS2-VASc score; HR: 0.900, 95% CI: 0.859–0.932, p <0.001 for ATRIA stroke score were detected (Figure 2). When the authors compared these AUC values, the AUC of ATRIA stroke score was different from the CHA2DS2-VASc score (p = 0.04, Figure 2).

DISCUSSION

IS is a significant cause of mortality and morbidity.[1] AF is associated with approximately one-third of IS cases.[12] NOACs and Vitamin K antagonists (VKA) are common treatment

strategies for stroke prevention in NVAF.[9] However, patients with AF may still experience IS despite OAT. Randomised clinical trials, real-life studies, and meta-analyses have shown failure of oral anticoagulants in 1-2% of NVAF patients per year.[13-15]

In this study, the median age was 75 years for Group 1 and 76 years for Group 2. These data are similar but slightly higher than studies by Khanevski *et al*. and Kocaman *et al*. There was a female predominance in this study, while the studies by Khanevski *et al*. and Kocaman *et al*. showed male gender dominance.[16,17] These differences may be due to the study centre being a referral centre for the Aegean region, resulting in a cohort of more complicated patients.

The stroke rate on OAT in this study was 44.3%. This rate is higher than the 26.4% reported in a meta-analysis and the 43.7% reported in a study from Sweden by Eriksson and Olsson.[18,19] This higher rate may be attributed to the limited socio-cultural status of the cohort, despite appropriate treatment rates in the population.

Hypertension was found to be the strongest factor for IS in the present study, aligning with findings from Khanevski *et al*.[16] Study by Kolmos *et al*. showed diabetes mellitus, coronary heart disease, and smoking as the risk factors.[20] In this study, a statistical difference was found in hyperli-pidemia between Group 1 and 2 (Table I).

For clinicians, the CHA2DS2-VASc and ATRIA stroke score systems are frequently used to stratify the stroke risk in patients with AF. There are different studies about risk scores, with the most revealing that the CHA2DS2-VASc and ATRIA stroke score are effective in predicting IS in patients with AF. Van Dem Ham *et al*.'s and Paciaroni *et al*.'s studies showed an independent association between a high CHA2DS2-VASc score and IS.[21,22]

On the other hand, another study showed no significant association between the risk of recurrent ischaemic stroke or any stroke with CHADS2, CHA2DS2-VASc, and ATRIA scores.[4]

In this study, CHA2DS2-VASc and ATRIA stroke scores had statistical significance in IS under OAC (Table I). The authors also found that hyperlipidemia and an ATRIA stroke score >8 had a correlation with estimating the IS event in univariate analysis, and only an ATRIA stroke score >8 in multivariate analysis (Table III). The ATRIA stroke score had a strong correlation in Spearman's rho test and in the ROC curve (Figure 1). These data are valuable as these are the most commonly used scores for clinicians.

The main limitation of this study was being a single-centre study and in retrospective cohort.

To the best of the authors' knowledge, this is the first study to evaluate the effectiveness of popular IS score systems in NVAF for secondary prevention of IS. However, the present study has a limited population, and larger studies are needed on this subject.

CONCLUSION

Although the usage of NOACs has improved the ability to prophylactically prevent IS in NVAF, predicting which patients will experience IS despite appropriate OAC treatment and monitoring them more closely remained an issue. The CHA2DS2-VASc, CHADS, and ATRIA stroke scores have proven themselves in primary IS prophylaxis. The ATRIA stroke score system for secondary prevention appears to be more effective than the most popular score systems.

ETHICAL APPROVAL:
Ethical approval was obtained from the Local Ethics Committee for the study (2023/0165). The study was conducted in compliance with the Declaration of Helsinki and adhered to all applicable ethical guidelines and regulations.

PATIENTS' CONSENT:
Written or verbal consent was obtained from all patients during necessary situations and procedures.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
EO: Conception, design, analysis of the data, and writing of the study.
MMT, ET: Data collection and acquisition of the data.
ZE: Statistical analysis and data collection.
OS, ASE: Critical revision and drafting of the work.
All authors approved the final version of the manuscript to be published.

REFERENCES

1. Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS, *et al*. Heart disease and stroke statistics-2022 update: A report from the American Heart Association. *Circulation* 2022; **145(8)**:e153-639. doi: 10.1161/CIR.0000000000001052.
2. Meinel TR, Branca M, De Marchis GM, Nedeltchev K, Kahles T, Bonati L, e*t al*. Prior anticoagulation in patients with ischaemic stroke and atrial fibrillation. *Ann Neurol* 2021; **89(1)**:42-53. doi: 10.1002/ana.25917.
3. Yaghi S, Liberman AL, Henninger N, Grory BM, Nouh A, Scher E, *et al*. Factors associated with therapeutic anti-coagulation status in patients with ischaemic stroke and atrial fibrillation. *J Stroke Cerebrovasc Dis* 2020; **29(7)**: 104888. doi: 10.1016/j.jstrokecerebrovasdis.2020.104888.
4. Yu I, Song TJ, Kim BJ, Heo SH, Jung JM, Oh KM, *et al*. CHADS2, CHA2DS2-VASc, ATRIA, and Essen stroke risk scores in stroke with atrial fibrillation: A nationwide multi-

centre registry study. *Medicine* 2021; **100(3)**:e24000. doi: 10.1097/md.0000000000024000.

5. Aspberg S, Chang Y, Atterman A, Bottai M, Go AS, Singer DE. Comparison of the ATRIA, CHADS2, and CHA2DS2 VASc stroke risk scores in predicting ischaemic stroke in a large Swedish cohort of patients with atrial fibrillation. *Eur Heart J* 2016; **37(42)**:3203-10. doi: 10.1093/eurheartj/ehw077.
6. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, *et al*. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150(9)**:604-12. doi: 10.7326/0003-4819-150-9-200905050-00006.
7. Zhao S, Hong X, Cao J, Cai H, Du S, Ma P. Appropriate dosing regimens of non-vitamin K antagonist oral anticoagulants for treatment of patients with non-valvular atrial fibrillation: An evidence-based consideration. *Front Pharmacol* 2020; **11**:1293. doi: 10.3389/fphar.2020.01293.
8. Singer DE, Chang Y, Borowsky LH, Fang MC, Pomernacki NK, Udaltsova N, *et al*. A new risk scheme to predict ischaemic stroke and other thromboembolism in atrial fibrillation: The ATRIA study stroke risk score. *J Am Heart Assoc* 2013; **2(3)**:e000250. doi: 10.1161/JAHA.113.000250.
9. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, *et al*. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021; **42(5)**:373-498. doi: 10.1093/eurheartj/ehaa612.
10. Martins RP, Galand V, Colette E, Behar N, Pavin D, Leclercq C, *et al*. Defining nonvalvular atrial fibrillation: A quest for clarification. *Am Heart J* 2016; **178**:161-7. doi: 10.1016/j.ahj.2016.05.014.
11. Giancaterino S, Hsu J. Valvular atrial fibrillation: A confusing and obsolete definition. *J Am Coll Cardiol* 2019; **73(25)**: 3360-1. doi: 10.1016/j.jacc.2019.04.039.
12. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, *et al*. Worldwide epidemiology of atrial fibrillation: A global burden of disease 2010 study. *Circulation* 2014; **129(8)**:837-47. doi: 10.1161/CIRCULA TIONAHA.113.005119.
13. Yao X, Abraham NS, Sangaralingham LR, Bellolio MF, McBane RD, Shah ND, Noseworthy PA. Effectiveness and safety of dabigatran, rivaroxaban, and apixaban *versus* warfarin in nonvalvular atrial fibrillation. *J Am Heart Assoc* 2016; **5(6)**:e003725. doi: 10.1161/JAHA.116.003725.
14. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007; **146 (12)**:857-67. doi: 10.7326/0003-4819-146-12-200706190-00007.
15. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, *et al*. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: A meta-analysis of randomised trials. *Lancet* 2014; **383(9921)**:955-62. doi: 10.1016/S0140-6736(13)62343-0.
16. Khanevski AN, Bjerkreim AT, Novotny V, Naess H, Thomassen L, Logallo N, *et al*. Recu*rrent* ischaemic stroke: Incidence, predictors, and impact on mortality. *Acta Neurol Scand* 2019; **140(1)**:3-8. doi: 10.1111/ane.13093.
17. Kocaman G, Duruyen H, Kocer A, Talip A. Recurrent ischaemic stroke characteristics and assessment of sufficiency of secondary stroke prevention. *Noro Psikiyatr Ars* 2015; **52(2)**:139. doi: 10.5152/npa.2015.7499.
18. Mohan KM, Wolfe CD, Rudd AG, Heuschmann PU, Kolominsky-Rabas PL, Grieve AP. Risk and cumulative risk of stroke recurrence: A systematic review and meta-analysis. *Stroke* 2011; **42(5)**:1489-94. doi: 10.1161/STROKEAHA.110.602615.
19. Eriksson SE, Olsson JE. Survival and recurrent strokes in patients with different subtypes of stroke: A fourteen-year follow-up study *Cerebrovasc Dis* 2001; **12(3)**:171-80. doi: 10.1159/000047700.
20. Kolmos M, Christoffersen L, Kruuse C. Recurrent ischaemic stroke–A systematic review and meta-analysis. *J Stroke Cerebrovasc Dis* 2021; **30(8)**:105935. doi: 10.1016/j.jstrokecerebrovasdis.2021.105935.
21. van Den Ham HA, Klungel OH, Singer DE, Leufkens HG, van Staa TP. Comparative performance of ATRIA, CHADS2, and CHA2DS2-VASc risk scores predicting stroke in patients with atrial fibrillation: Results from a national primary care database. *J Am Coll Cardiol* 2015; **66(17)**:1851-9. doi: 10.1016/j.jacc.2015.08.033.
22. Paciaroni M, Agnelli G, Caso V, Silvestrelli G, Seiffge DJ, Engelter S, *et al*. Causes and risk factors of cerebral ıschaemic events in patientswith atrial fibrillation treated with non-vitamin k antagonist oral anticoagulants for stroke prevention. *Stroke* 2019; **50(8)**:2168-74. doi: 10.1161/STROKEAHA.119.025350.