Received: August 14, 2025
Accepted: November 17, 2025

Acad Med J 2025;5(3):199-205
UDC: 616.831-005.1-085.273.53
https://www.doi.org/10.53582/AMJ2553199r
Case report

"BREAKTHROUGH" ISCHEMIC STROKE ON NOAC THERAPY IN NEWLY DIAGNOSED NONVALVULAR ATRIAL FIBRILLATION: A CASE REPORT

Rexhepi Arbana[1], Haliti Gazmend[1], Isaki Çlirim[1], Arsovska Anita[2], Gashpar Glorija[3], Karimani Jetmir[4]

[1]PHI Clinical Hospital Tetovo, Tetovo, Republic of North Macedonia
[2]University Clinic for Neurology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia
[3]PHI Specialized Hospital for Geriatric and Palliative Medicine "13 November", Skopje, Republic of North Macedonia
[4]PHI General Hospital "Ferid Murad", Gostivar, Republic of North Macedonia
e-mail: arbana.rexhepi@gmail.com

Abstract

Introduction: Nonvalvular atrial fibrillation (NVAF) accounts for 20–30% of cardioembolic strokes. Despite the preference for nonvitamin K antagonist oral anticoagulants (NOACs) over vitamin K antagonists, ischemic stroke still occurs in 1–2% of patients. These "breakthrough strokes" are linked to high recurrence and mortality, and optimal secondary prevention remains unclear.

Case report: A 65-year-old male with NVAF on rivaroxaban presented with left hemiparesis and central facial palsy. One month prior, he experienced transient perceptual disturbance and expressive aphasia. Workup revealed paroxysmal atrial fibrillation, mild carotid atheromatosis, and normal echocardiography. Brain CT showed leukoaraiosis and cortical atrophy; MRI demonstrated a subacute ischemic lesion in the right periventricular region. NOAC adherence and dosing were appropriate. Persistent neurological deficits and mild cognitive impairment (MoCA: 22) were noted. Management included low molecular weight heparin prophylaxis, dual antiplatelet therapy, high-dose statin, antihypertensives, and supportive measures.

Discussion: Stroke, despite anticoagulation, may result from suboptimal dosing, alternative etiologies such as small vessel disease, or non-AF-related embolism. Data from a large Hong Kong cohort study suggest that continuing the same NOAC is associated with better outcomes, while switching to another NOAC or to warfarin increases recurrence risk. Conversely, some studies report benefit from switching in select cases, highlighting the need for individualized strategies.

Conclusion: Breakthrough ischemic stroke in NVAF patients on NOAC therapy is multifactorial and carries a poor prognosis. Continuation of the same NOAC may be favorable when alternative mechanisms are excluded, but randomized trials are required to guide optimal secondary prevention.

Keywords: stroke, ischemic attack, transient anticoagulants, factor Xa inhibitors, secondary prevention, treatment failure, atrial fibrillation

Introduction

Nonvalvular atrial fibrillation accounts for approximately 20 to 30 percent of all cardioembolic strokes, with a particularly high burden among the elderly population[1,2]. In recent years, nonvitamin K antagonist oral anticoagulants (NOACs) have become the preferred therapeutic option over vitamin K antagonists for both primary and secondary prevention of ischemic stroke in patients with nonvalvular atrial fibrillation[1-5]. Nevertheless, ischemic stroke still occurs in 1 to 2 percent of patients receiving oral anticoagulant therapy[1,3,6,7]. Patients who experience an ischemic stroke, despite ongoing anticoagulation, represent a particularly high-risk group. Compared to individuals without prior anticoagulant therapy, these patients have significantly higher rates of stroke recurrence and mortality[8-10]. This highlights the critical importance of personalized and optimized secondary stroke prevention strategies in this vulnerable population.

Case report

We present the case of a 65-year-old right-handed male, a retired lawyer, non-smoker and non-drinker, who presented to our clinic with complaints of left-sided facial droop and weakness in the left upper and lower limbs. On the day of symptom onset, the patient awoke at 8 a.m. feeling unusually tired and, contrary to his long-standing morning routine, chose not to go to his regular coffee shop or take a shower. Approximately one hour later, he proceeded to shower, but upon exiting the bathroom, he felt unsteady and had to hold onto nearby objects to prevent himself from falling. Gradually, he recognized that his instability was not due to dizziness but to a notable weakness in his left leg, accompanied by impaired function of his left hand, which made it difficult for him to maintain balance. Despite the symptoms, he opted not to seek immediate medical attention, expecting spontaneous resolution. However, six hours later, prompted by his wife's insistence, he presented for evaluation.

One month earlier, he had consulted a neurologist in a private institution following two brief, alternating neurological episodes. The first episode occurred in the late afternoon, around 5 p.m., while he was taking a walk. He described a surreal perceptual disturbance, as though the surrounding environment—including the asphalt, buildings, traffic lights, and utility poles—had distorted and shifted from their usual locations. He had the impression that the ground beneath him was flowing like a stream and that his visual surroundings were unfamiliar and displaced. Importantly, he remained fully conscious and oriented, retaining detailed recollection of the event without confusion or disorientation. The symptoms resolved spontaneously after approximately ten minutes, shortly after reaching his son's workplace.

Later that evening, at around 11:30 p.m., while seated in the dining room, he experienced a sudden inability to produce speech. Although fully aware of what he intended to say, he was unable to construct sentences or name everyday objects such as a table, chair, or door—though he clearly understood their purpose. This episode lasted approximately fifteen minutes. That night, he sought medical care and was advised to consult a neurologist. The following day, further investigations were performed, including a 24-hour Holter ECG, carotid ultrasound, transthoracic echocardiogram, and laboratory analysis. The carotid ultrasound revealed early atheromatous changes, the echocardiogram was unremarkable, while the Holter ECG demonstrated polymorphic ventricular premature contractions and short runs of atrial fibrillation. The clinical presentation was interpreted as transient ischemic attacks, and the patient was prescribed: rivaroxaban 20 mg once daily, perindopril/indapamide 2/0.65 mg once daily, rosuvastatin/ezetimibe 5/10 mg once daily, and cerebronal once daily.

During hospitalization, two native brain CT scans (Figure 1 and Figure 2) performed one week apart revealed intracranial atheromatous vascular changes, leukoaraiosis, and global cortical reductive changes with secondary ventricular dilatation, without radiologic evidence of acute ischemic stroke. Despite treatment, the patient's left-sided weakness persisted. With

preserved insight and awareness of his neurological deficits, he gradually began to exhibit signs of depression and emotional lability in the days that followed. He also reported a subjective decline in cognitive function, including decreased concentration, forgetfulness, and reduced verbal fluency, which he attributed to the period following administration of the SARS-CoV-2 vaccine. Therapeutically, the patient was managed with low molecular weight heparin for deep vein thrombosis prophylaxis, dual antiplatelet therapy, high dose statin therapy along with antihypertensive, gastroprotective, and other symptomatic medications.

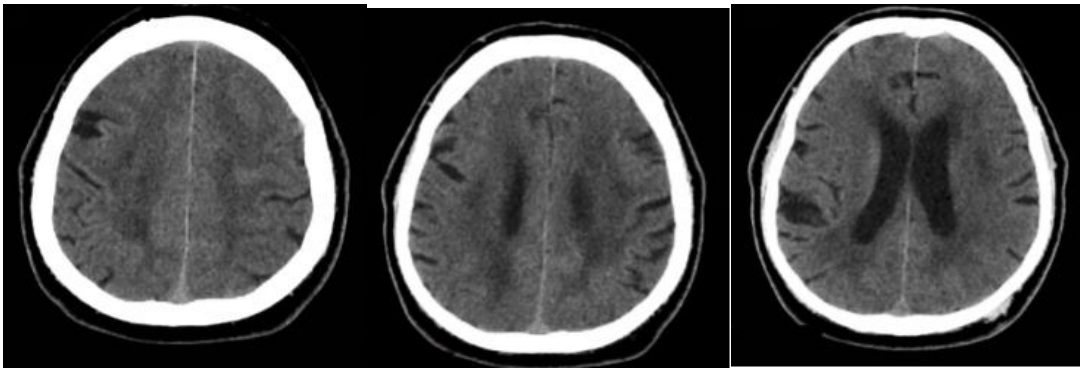


Fig. 1 First native CT scan

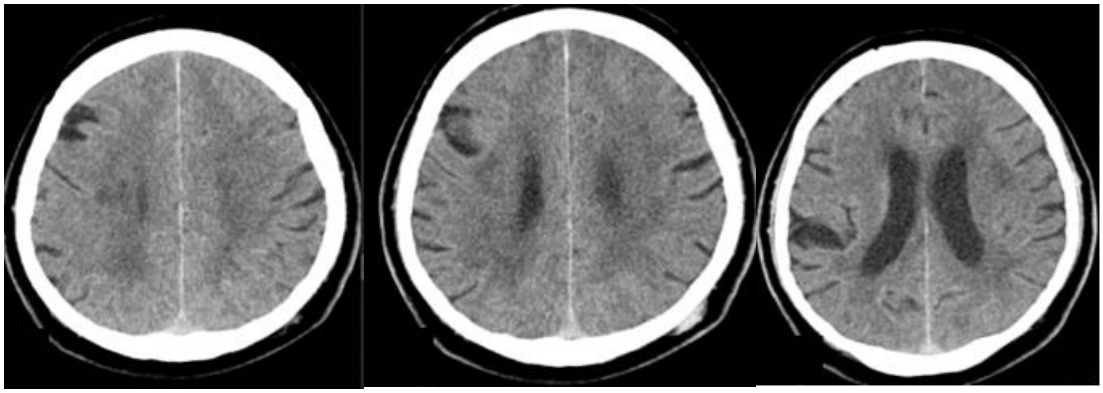


Fig. 2. Control native CT scan

On admission

Physical examination: The patient was alert and fully oriented to time, place, person, and situation. Vital signs were as follows: blood pressure 100/60 mmHg, pulse 85 bpm, respiratory rate 14 breaths per minute, body temperature 36.4 °C, body weight 79 kg, and height 174 cm. The skin was warm, dry, and exhibited good turgor, with no evidence of abnormal pigmentation, bleeding, rash, or lesions. Respiratory excursions were full and symmetrical, with clear breath sounds on auscultation anteriorly and posteriorly. No rales, rhonchi, wheezing, or pleural rubs were appreciated. Vocal and tactile fremitus were normal. Cardiac examination revealed a regular rate and rhythm, with normal intensity of the first and second heart sounds; the second heart sound was physiologically split. No additional heart sounds or murmurs were detected.

Neurological examination: There was no enophthalmos, exophthalmos, or ptosis. Extraocular movements were intact in all directions, with no evidence of strabismus or nystagmus. Pupils were equal, round, and reactive to light and accommodation. Visual fields were intact on confrontation testing. Mild facial asymmetry was observed, with a flattened left nasolabial fold and left-sided facial palsy of central origin. Muscle strength in the left upper and lower limbs was mildly reduced (grade 4/5), consistent with a mild hemiparesis. The left

plantar reflex was positive, demonstrating dorsiflexion of the great toe without fanning of the other toes.

Clinical scales: NIHSS: 3; Modified Rankin Scale (mRS): 1; CHADS-VASc score: 4; HAS-BLED score: 1

Laboratory analysis: White blood cells: 10.60 × 10/L; lymphocytes: 19.05%; monocytes: 9.50%; neutrophils: 70.75%; sedimentation rate: 19 mm/h; red blood cells: 4.76 × 10^{12}/L; hemoglobin: 10.02 mmol/L; hematocrit: 0.45 L/L; platelets: 283.30 × 10/L; glucose: 6.90 mmol/L; blood urea nitrogen: 3.90 mmol/L; creatinine: 91 µmol/L; uric acid: 369 µmol/L; total protein: 75 g/L; albumin: 41 g/L; AST: 23 U/L; ALT: 35 U/L; LDH: 154 U/L; CK: 65 U/L; CK-MB: 13 U/L; sodium: 135 mmol/L; potassium: 3.42 mmol/L; chlorides: 92 mmol/L; calcium: 2.44 mmol/L; iron: 14.20 µmol/L; total cholesterol: 3.64 mmol/L; triglycerides: 1.53 mmol/L; HDL cholesterol: 1.27 mmol/L; LDL cholesterol: 1.70 mmol/L; C-reactive protein: 5.70 mg/L.

Hemostasis parameters: PT: 11.2 s; aPTT: 33.4 s; TT: 19.1 s; INR: 0.99; D-dimers: 190 ng FEU/mL.

Montreal Cognitive Assessment (MoCA): The patient scored 22 points, indicating mild cognitive impairment, with observed deficits particularly in the domain of working memory and attention.

A few days following the discharge, a brain MRI, a transcranial and a carotid doppler ultrasound (Figures 3,4,5,6) were performed. While the doppler ultrasonography revealed no discernible abnormalities, the brain MRI revealed a subacute ischemic lesion at the height of the right lateral ventricle posterior horn and supraventriculary, along with leukoaraiosis.

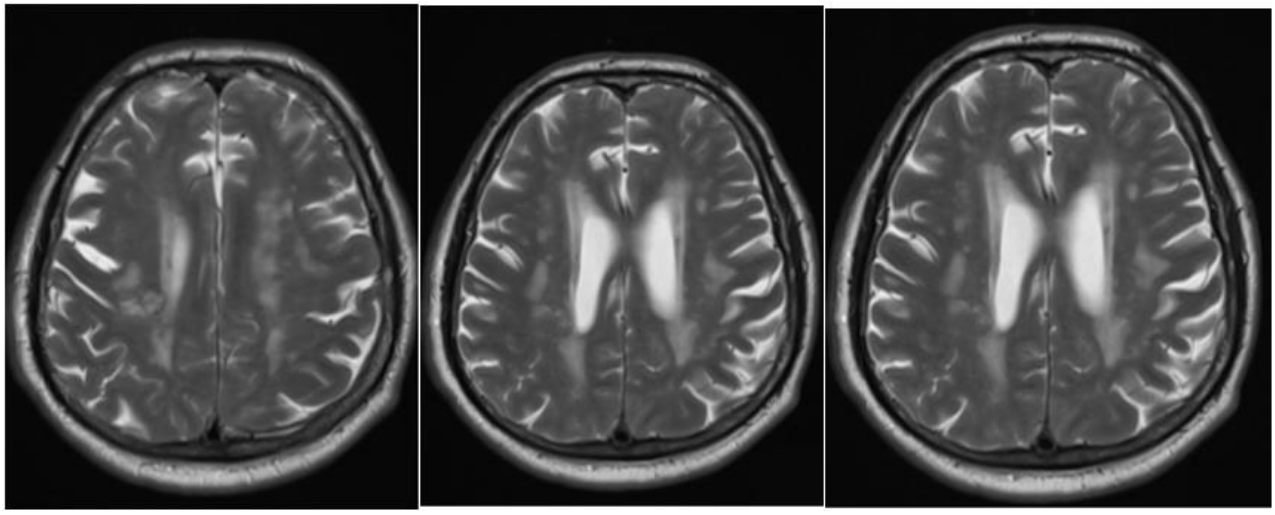
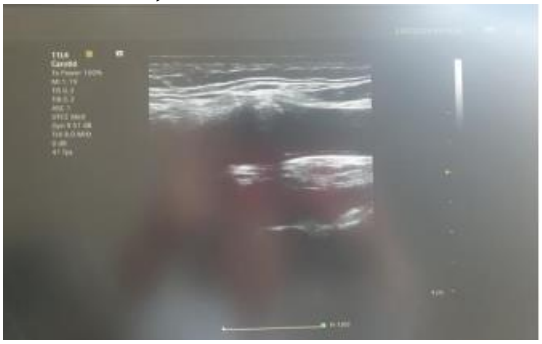


Fig. 3. Brain MRI (T2 and FLAIR) shows a subacute ischemic lesion adjacent to the posterior horn of the right lateral ventricle and supraventricular corona radiata, with restricted diffusion and low ADC signal. Leukoaraiosis is noted in para/periventricular regions, corona radiata, and centrum semiovale.



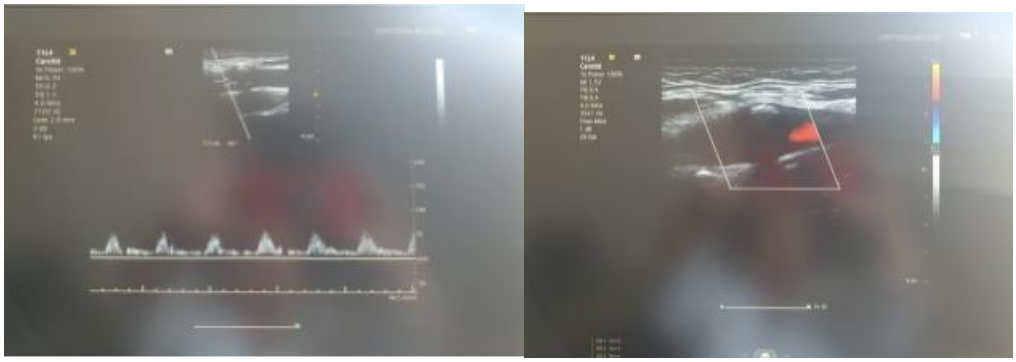


Fig. 4. Right Carotid Artery Doppler Ultrasound

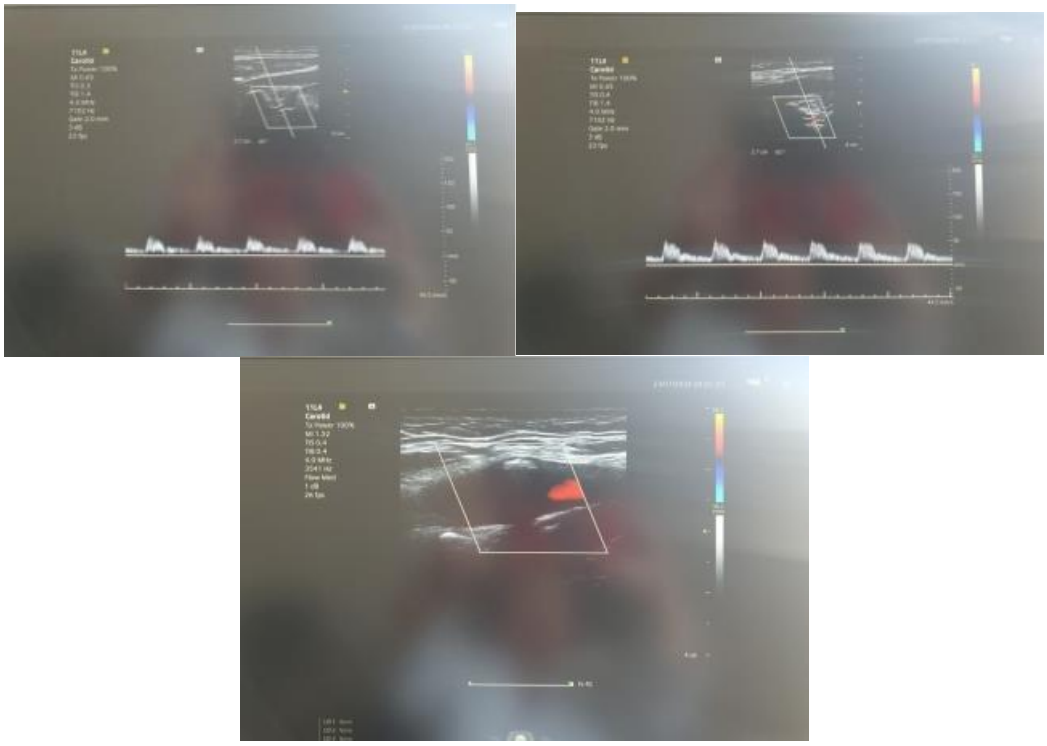


Fig. 5. Left Carotid Artery Doppler Ultrasound

Discussion

Patients with atrial fibrillation who experience an ischemic stroke, despite oral anticoagulation, face a challenging clinical scenario. Studies report an annual recurrence rate of approximately 7% and a three-month mortality of up to 12.6% in this subgroup[8]. Several potential mechanisms may underlie such "breakthrough strokes". These include inappropriate dosing of the anticoagulant, coexisting stroke etiologies unrelated to atrial fibrillation, such as intracranial atherosclerosis, cerebral small vessel disease, or patent foramen ovale, as well as true cardioembolic strokes that occur despite optimal anticoagulation. In a significant proportion of cases, the etiology remains undetermined[1,6]. Moreover, in patients receiving vitamin K antagonists, genetic polymorphisms affecting CYP2C9 and VKORC1 enzymes may alter drug metabolism, leading to subtherapeutic or unstable anticoagulant levels despite apparent adherence[6]. Due to the heterogeneity of this patient population, no universally accepted guidelines exist for secondary prevention following breakthrough stroke. Nonetheless, several therapeutic strategies have been proposed. These include continuing with the same NOAC, switching from one NOAC to another, transitioning from NOAC to a VKA, adding antiplatelet therapy to anticoagulation, or considering left atrial appendage

occlusion[1,3,6]. A large population-based observational study from Hong Kong involving 2,237 patients with ischemic stroke despite NOAC therapy provided valuable real-world insight[7]. Among these patients, 71% remained on the same NOAC, 20% were switched to another NOAC, 5% were transitioned to warfarin, 15% received the addition of an antiplatelet agent, and 3.7% were switched from 110 mg to 150 mg dabigatran twice daily. After a median follow-up of 16.5 months, switching between NOACs or to a VKA was associated with an increased risk of recurrent ischemic stroke. Importantly, the addition of antiplatelet therapy did not confer a reduction in recurrence risk. Continuing the same anticoagulant was associated with a more favorable outcome[7]. In contrast, a Taiwanese cohort analysis suggested that switching anticoagulants may reduce recurrence risk, highlighting the variability in outcomes across populations and underscoring the need for individualized treatment decisions[5]. Further supporting this complexity, a real-world clinical study including 77 patients with recurrent ischemic stroke despite NOAC therapy reported that 25% of events were attributed to suboptimal dosing. Most of these patients were elderly and had impaired renal function, which may have contributed to reduced drug clearance or underdosing. Based on observed outcomes, apixaban was suggested as the most favorable NOAC in the post-stroke setting, followed by rivaroxaban, dabigatran, and edoxaban[7]. Additionally, a pooled analysis of seven prospective cohort studies including 5,413 patients with atrial fibrillation and recent ischemic stroke revealed that patients with stroke, despite anticoagulation, had a significantly higher risk of recurrence when compared to anticoagulation-naïve patients, even when CHADS-VASc scores were similar [6]. This finding suggests that stroke in anticoagulated individuals may involve mechanisms not fully addressed by traditional thromboembolic risk scores and warrants deeper diagnostic scrutiny.

Conclusion

Patients with atrial fibrillation who suffer a breakthrough ischemic stroke. despite NOAC therapy. exhibit a higher risk of recurrence and worse overall prognosis. Although various strategies for secondary prevention have been explored, current evidence suggests that continuing the same NOAC may be the most effective option, particularly when other etiologies are excluded and risk factors are carefully managed. Future randomized studies are needed to determine optimal post-stroke anticoagulation strategies in this high-risk population.

Conflict of interest statement. None declared.
Written informed consent for publication was obtained from the patient.

References

1. Galea R, Seiffge D, Räber L. Atrial Fibrillation and Ischemic Stroke despite Oral Anticoagulation. *J Clin Med* 2023; 12(17): 5784. https://doi.org/10.3390/jcm12175784.
2. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-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.
3. Lip GYH, Banerjee A, Boriani G, Chiang CE, Fargo R, Freedman B, *et al*. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. *Chest* 2018; 154(5): 1121-1201. doi: 10.1016/j.chest.2018.07.040.
4. Arsovska A. Update in the management of acute ischemic stroke. *Academic Medical Journal* 2021; 1(1): 11-17.

5. Arsovska A, Pejkov H, Poposka L, Doneva A, Angelova A, Rexhepi A, *et al*. Generation x–challenges in anticoagulation!. *Acad Med J* 2022; 2(2): 139-153. doi: 10.53582/AMJ2222139a
6. Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haeusler KG, *et al*. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. *Europace* 2021; 23(10): 1612-1676. doi: 10.1093/europace/euab065.
7. Ip YMB, Lau KK, Ko H, Lau L, Yao A, Wong GL, *et al*. Association of Alternative Anticoagulation Strategies and Outcomes in Patients With Ischemic Stroke While Taking a Direct Oral Anticoagulant. *Neurology* 2023; 101(4): e358-e369. doi: 10.1212/WNL.0000000000207422.
8. Chao TF, Potpara TS, Lip GYH. Atrial fibrillation: stroke prevention. *Lancet Reg Health Eur* 2024; 37: 100797. https://doi.org/10.1016/j.lanepe.2023.100797.
9. Paciaroni M, Agnelli G, Falocci N, Caso V, Becattini C, Marcheselli S, *et al*. Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation: Effect of Anticoagulation and Its Timing: The RAF Study. *Stroke* 2015; 46(8): 2175-2182. doi: 10.1161/STROKEAHA.115.008891.
10. Seiffge DJ, De Marchis GM, Koga M, Paciaroni M, Wilson D, Cappellari M, *et al*. Ischemic Stroke despite Oral Anticoagulant Therapy in Patients with Atrial Fibrillation. *Ann Neurol* 2020; 87(5): 677-687. doi: 10.1002/ana.25700.