VIA MEDICA

REVIEW ARTICLE

Journal of Transfusion Medicine
2023, vol. 16, no. 4, 246–252
DOI: 10.5603/jtm.99302

ISSN 1689-6017
e-ISSN 2080-1505

Thrombophilia and ischemic stroke

Jacek Musiał

Prof. Andrzej Szczeklik 2nd Department of Internal Medicine, Jagiellonian University, Collegium Medicum, Kraków, Poland

Summary

Ischemic stroke is mainly provoked by atherosclerotic changes in cerebral arteries or thromboembolic episodes related to cardiac arrhythmias. Less frequently, especially in the younger patients stroke may be related to hypercoagulable states. Detection of thrombophilia requires specialized diagnostic procedures and in some situations change patients' management. Presence of thrombophilia may influence decision to close patent foramen ovale in a patient after ischemic stroke. On the other hand, antiphospholipid syndrome diagnosis influences the choice of antithrombotic treatment in the secondary prevention of stroke.

Keywords: ischemic stroke; inherited thrombophilia; atiphospholipid syndrome; patent foramen ovale

J. Transf. Med. 2022; 16: 246–252

Introduction

Congenital thrombophilia is mainly associated with an increased risk of episodes of venous thromboembolism [1]. However, arterial thrombosis in the form of ischemic stroke already appears in the original description of the first family with congenital thrombophilia — antithrombin deficiency, originally described by Egeberg in 1965 [2]. More commonly, however, arterial thrombosis is associated with an acquired thrombophilia, such as antiphospholipid syndrome, in about a third of cases [3]. In the latter case, for reasons that are not fully explained, most episodes are ischemic stroke [4].

Stroke is the second most common cause of death worldwide (nearly 11% of all deaths) and the most common factor leading to adult disability [5, 6]. The primary cause of stroke is atherosclerosis of the intracerebral arteries and small arteries of the brain, often arising as a consequence of hypertension, and strongly associated with the presence of classic cardiovascular risk factors [7]. The second major cause is strokes caused by embolic episodes due to cardiac arrhythmias (primarily atrial fibrillation), persistent foramen ovale (paradoxical embolism), or valvular defects, and valvular prostheses [7]. However, in about 30% of ischemic strokes, especially in young people, the cause cannot be established. Such a stroke is referred to as a cryptogenic stroke [8]. It is therefore worthwhile to determine the role of congenital and acquired thrombophilia in episodes of ischemic stroke, especially in younger people, where the causes of such stroke are not obvious. This raises the question of whether diagnosis for such a defect can lead to a favorable change of patient management.

Congenital thrombophilia

Data on the role of congenital thrombophilia in adult ischemic stroke patients are divergent. While

Correspondence address: prof. dr hab. n. med. Jacek Musiał, II Department of Internal Medicine, Jagiellonian University, Medical College, ul. Skawińska 8, 31–066 Kraków, Polska, e-mail: jacek.musial@uj.edu.pl
Translation: mgr Krystyna Dudziak

Received: 21.11.2023 Accepted: 21.12.2023 Early publication date: 31.12.2023

some large observational studies have found no increased prevalence of thrombophilic defects in ischemic stroke patients [9], others have pointed to an increased proportion of patients with factor V type Leiden gene mutations, or prothrombin G20210A gene mutations, particularly in younger people with stroke [10, 11]. Finally, a large meta-analysis of available studies published four years ago indicated that the presence of particular types of congenital thrombophilia is associated with a slightly increased risk of ischemic stroke in adults, with the exception of (rare) antithrombin deficiency [12]. The odds ratio (OR) here was not high: 1.25 (95% CI: 1.08–1.44); 1.48 (95% CI: 1.22––1.80); 2.13 (95% CI: 1.16–3.90); and 2.26 (95% CI: 1.34–3.80 for factor V Leiden, prothrombin gene G20210A mutation, protein C deficiency, and protein S deficiency, respectively.

Although congenital thrombophilia increases the risk of ischemic stroke to a small extent, especially in younger people without other significant cardiovascular risk factors, the finding of its presence, neither allows to determine the risk of recurrent episodes, nor currently changes the management of patients after stroke [13, 14].

One specific topic within the study of the impact of congenital thrombophilia on the incidence of ischemic stroke is the problem of patent foramen ovale (PFO). The defect is the result of the lack of permanent postnatal closure of the foramen ovale by the close fusion of the septum primum and septum secundum of the atrial septum. Such a defect is observed in about 25% of people [15], and with the availability of transesophageal echocardiography, the detection of PFO in ischemic stroke survivors is not difficult today. The junction between the right and left atrium predisposes small thrombi to enter the systemic circulation, which can result in arterial paradoxical embolism, including ischemic stroke.

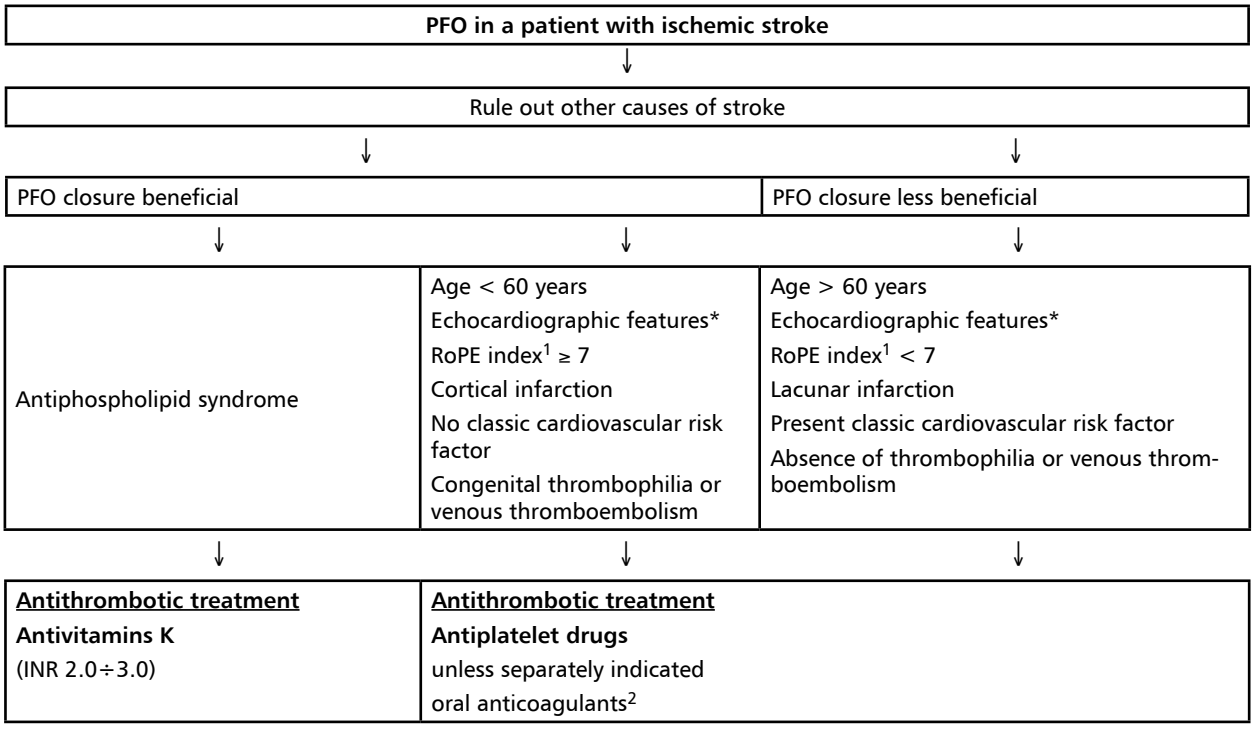
A discussion of the factors determining surgical percutaneous closure of PFO is beyond the scope of this paper. These include both echocardiographic parameters and clinical factors, as included in the RoPE score [16]. It should only be noted here that the procedure, according to recommendations [17, 18], should be especially considered in a group of patients with PFO under 60 years of age who have had a cryptogenic stroke. A newer more precise term here is: embolic stroke of undetermined source (ESUS). PFO closure is associated in such patients with a significant reduction in the relative risk of recurrent stroke (RR 0.36) compared to conservative management (anticoagulant treatment) [19]. Such a procedure is particularly indicated for patients with thrombophilia, as a current systematic review and meta-analysis of available studies showed them to have a higher risk of stroke recurrence (hazard rate HR = 2.41; 95% CI: 1.44–4.06), compared to patients with PFO and cryptogenic stroke without accompanying thrombophilia [20]. After PFO closure, the risk of such recurrence was just below the level of statistical significance (OR = 2.07; 95% CI: 0.95–4.48). In conclusion, the prevailing view today is that in patients with a history of cryptogenic stroke and established persistent foramen ovale, associated with thrombophilia, the appropriate management is surgical closure of the PFO [14, 20, 21].

It should be emphasized that the studies and systematic review cited above, concerning post stroke patients with known persistent foramen ovale and concomitant thrombophilia, mostly included cases of congenital and acquired thrombophilia together. A similar case was with, studies of patients in whom the decision was made to forgo surgery and undertake conservative treatment. The drug groups used include antiplatelet agents, antivitamin K, and more recently, direct oral anticoagulants (DOACs). Current pooled studies indicate that no study has been able to demonstrate superiority in the selection of any of the aforementioned drug groups with regard to the effectiveness of ischemic stroke prevention [21, 22].

Currently, there is a lack of data on the indications and duration of anticoagulant treatment in thrombophilic patients undergoing surgical PFO closure. The general recommendations of the European Society of Cardiology prescribe dual antiplatelet therapy for 1–6 months after PFO closure and single antiplatelet therapy for 5 years [23]. It seems that, with the exception of patients with antiphospholipid syndrome (see below), patients with congenital thrombophilia after PFO closure are subject to the above general rules of management.

An important question arises about the indications for diagnosis of congenital thrombophilia in patients who have had a stroke and are diagnosed with PFO. Data from daily practice indicate that in about two thirds of these patients, no thrombophilia testing is performed [24]. This resonates with current views in Europe that routine diagnostics for thrombophilia in patients after a cerebral ischemic episode in whom the presence of a PFO has been confirmed is not needed [14, 23]. It is understood that congenital thrombophilia should be included in the management plan only if it has already been

Figure 1. Management of patients after ischemic stroke and diagnosed persistent oval hole (modified from [14])



*The degree of leakage, the number of microbubbles after injection of shaken saline, the presence of atrial septal aneurysm

[1]an index taking into account the presence/absence of clinical factors affecting the risk of stroke in PFO: hypertension, diabetes, stroke or transient cerebral ischemia (TIA), smoking

[2]vitamin K antagonists or direct oral anticoagulants (DOACs)

previously identified [14]. The data presented above, however, indicate that such a diagnosis should nevertheless be indicated, both for congenital thrombophilia and especially for the co-occurrence of antiphospholipid syndrome (see below). This is because the finding of thrombophilia can influence both the decision to surgically close a PFO and the choice of anticoagulant treatment.

The principles of management of post stroke patients with persistent foramen ovale are shown in Figure 1.

Antiphospholipid syndrome

Antiphospholipid syndrome is characterized by the coexistence of antiphospholipid antibodies (aPL) in the blood of the patient with clinical manifestations, mainly in the form of venous thrombosis, arterial thrombosis, and thrombosis of small vessels, and in women also obstetric complications. New classification criteria for antiphospholipid syndrome, published in 2023 [25], allow us to classify a patient as APS if we confirm the persistent presence of antiphospholipid antibodies in moderate, or high titers, along with a range of clinical manifestations, among which arterial thrombosis is mentioned. Laboratory classification criteria include the presence of lupus anticoagulant (LA), measured by coagulometric methods, and/or anticardiolipin antibodies (aCL) and/or antibodies directed against beta2 glycoprotein I ($a\beta_2$ GPI) in the IgG and IgM classes. Arterial thrombosis as a clinical criterion must meet the condition of excluding other equally or more likely causes of its occurrence. The reader will find a broader discussion of these issues at "New classification criteria for antiphospholipid syndrome — 2023" Journal of Transfusion Medicine 2023, vol. 16, no. 3, 103–109 (https://journals.viamedica.pl/journal_of_transfusion_medicine/article/view/97795).

Signs of central nervous system ischemia associated with antiphospholipid syndrome include ischemic stroke, episodes of transient cerebral ischemia (TIA, transient ischaemic attack), and hyperintense white matter foci of presumed ischemic etiology found on imaging studies (MRI) [26]. A current systematic review of available studies indicates that among people under the age of 50 who have had an ischemic stroke, or TIA, antiphospholipid antibodies are found in about 17% of cases [27].

As with most of the clinical manifestations of APS, it is difficult to establish a strict, specific relationship between single types of antiphospholipid antibodies and stroke [28]. The strongest association with all thrombotic complications here is the presence of lupus anticoagulant. To determine the risk of thrombotic complications, we now rather use the so called antibody profile. A high risk profile, both for the occurrence of a thrombotic episode (including stroke) and its recurrence, is associated with the persistent presence of all three types of antibodies (triple positivity) [29, 30]. The same was true for a high risk profile carried by the presence of two types of antibodies, including lupus anticoagulant and aCL, or $a\beta_2$ GPI, especially in the IgG class and at high titers. In contrast, low thrombotic risk is associated with the transient presence of single aPL at low/moderate titers [31]. There are indications that thrombotic risk may also increase in patients with APS and the co-occurring clinical criterion of moderate thrombocytopenia [32].

Since stroke occurs most often in the context of arteriosclerosis in the elderly, the question arises in whom we should carry out diagnostic testing for antiphospholipid syndrome. Such testing is particularly indicated in cases of cryptogenic stroke, and in younger people; some recommendations here suggest an age limit of < 50 years [33]. A contemporary survey indicates that any age limit for the diagnosis of antiphospholipid syndrome in stroke patients is used by only about 30% of investigators [26]. This is because antiphospholipid syndrome may also occur in the elderly [34]. Here, however, the diagnostic approach would have to be individualized due to the frequent coexistence of many other classic cardiovascular risk factors. The pathogenetic role of detected antiphospholipid antibodies may be questionable here, and their presence incidental. Conversely, the finding of aPL with a high risk profile in an elderly person not burdened with classical risk factors will argue more strongly for such a role.

To date, the optimal time after stroke for aPL laboratory testing has not been determined. The effect of anticoagulants or acute phase proteins on the results of lupus anticoagulant testing of lupus anticoagulant determinations [33] dictates that determinations should be delayed beyond the acute phase of stroke. However, the tests should be performed as soon as possible, as the results may influence a fundamental change in treatment.

In the treatment of antiphospholipid syndrome after ischemic stroke, first of all, all classic cardiovascular risk factors should be identified and any modifiable factors should be vigorously combated [31]. Secondary thromboprophylaxis is based on indefinite administration of vitamin K antagonists (VKA) preparations with maintenance of an INR between 2.0 and 3.0 [31]. In case of ineffectiveness, it is recommended to either increase the intensity of anticoagulation with VKA to an INR of 3.0÷4.0, or to administer VKA in doses that maintain the INR between 2.0÷3.0 and add acetylsalicylic acid (ASA) in low doses 75–100 mg [31]. At this point, it should be noted that in the case of other episodes associated with ischemia of the central nervous system (TIA, probably vascularized white matter lesions), the management in daily practice includes the administration of acetylsalicylic acid in low doses, the use of dual antiplatelet therapy (ASA + clopidogrel), or the administration of other antiplatelet drugs.

The introduction of direct oral anticoagulants (DOAC) for treatment and prophylaxis of APS patients has created a potentially attractive alternative to the cumbersome use of VKA in the treatment of APS patients. In 2018, the first study comparing treatment with rivaroxaban 20 mg daily with warfarin (INR 2.0–3.0) in patients with triple positive APS was published [35]. It showed a lower efficacy of rivaroxaban, manifested by a higher rate of arterial thrombotic episodes. International recommendations, published just a year later, included the recommendation that DOACs should not be used in patients with arterial thrombosis burdened by antiphospholipid antibodies with a high risk profile [31, 36]. However, they were allowed to be used in patients with venous thrombosis, and in patients without high risk profile aPL. Nevertheless, two meta analyses have now been published, including further clinical studies of the effects of DOACs compared to VKA in APS patients, including patients after episodes of venous thromboembolism, and patients with aPL with a lower risk profile, including the presence of dual antibody types (double positivity) [37, 38]. Included in the analysis were studies conducted in the US, UK, Spain, and, as mentioned, Italy. They included a total of 472 subjects. Three studies used rivaroxaban, and one used apixaban. The analysis indicated that the use of DOACs compared to warfarin increases the risk of recurrent arterial thrombosis by about 3–5 times, with no effect on the risk of recurrent venous thrombosis. Among the increased episodes of arterial thrombosis, ischemic stroke predominated. Its risk of recurrence increased (10 to 13 times) with DOAC use compared to warfarin [37, 38]. These findings

Table 1. Diagnosis and management of APS in patients after ischemic stroke

Indications for APS diagnosis in patients after ischemic stroke
• Patients after ischemic stroke/transient cerebral ischemic episode < 50 years of age
• Patients after cryptogenic stroke/embolic stroke of unknown source (ESUS[1])
• Post ischemic stroke patients with associated systemic autoimmune disease (mainly systemic lupus erythematosus)
• Patients after ischemic stroke who have had prior venous thrombosis
• Women after ischemic stroke with prior complications of pregnancy
Recommended diagnostic tests
• Lupus anticoagulant coagulometric methods, three step procedure
• aCL, IgG and/or IgM classes; by ELISA method[2]
• aβ2 GPI of IgG and/or IgM class; ELISA method[2]
Treatment of APS in post stroke patients
• Vitamin K antagonists (INR 2.0÷3.0), or
• Vitamin K antagonists (INR 2.0÷3.0) + acetylsalicylic acid at low doses (75–100), or
• Vitamin K antagonists (INR 3.0÷4.0)
• Elimination/treatment of classic modifiable cardiovascular risk factors

[1]ESUS — embolic stroke of undetermined source

[2]ELISA an immunoenzymatic method is recommended for determining moderate/high levels of antiphospholipid antibodies (aPL). Automated platforms can also be used to determine aPL, but for which there are no defined levels of moderate/high levels of aPL

should lead to changes in recommendations for secondary thromboprophylaxis in patients with the thrombotic form of antiphospholipid syndrome [39]. Warfarin should be used not only in patients with aPL with a high risk profile and a history of arterial thrombosis, but also in patients after a history of venous thrombosis and those who are potentially at lower thrombotic risk (presence of two types of aPL, or only persistent presence of one type of antibody at higher titers) [40]. Because of the important implications of the diagnosis of antiphospholipid syndrome for the mode of thromboprophylaxis in people with ischemic stroke, the diagnosis of APS must be made on the basis of strict criteria [26], as confirmation of APS diagnosis influences strongly antithrombotic prophylaxis. Vitamin K antagonists should be probably instituted as soon as the first positive aPL determination indicating increased thrombotic risk becomes available, even before confirmation of persistent aPL positivity after next 3 months [27]. Diagnosis and management of APS in patients after ischemic stroke are presented in Table 1.

Conflict of interest: none declared

References

1. Zawilska K. Trombofilia wrodzona. W: Zakrzepy i zatory, pod red. Windyga J, Pasierski T, Torbicki A. PZWL, Warszawa 2014: 53–68.
2. Egeberg O. Thrombophilia caused by inheritable deficiency of blood antithrombin. Scand J Clin Lab Invest. 1965; 17: 92, doi: 10.3109/00365516509077290, indexed in Pubmed: 14260761.
3. Musiał J. Zespół antyfosfolipidowy. W: Zakrzepy i zatory, pod red. Windyga J, Pasierski T, Torbicki A. PZWL, Warszawa 2014: 69–84.
4. Cervera R, Piette J, Font J, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis & Rheumatism. 2002; 46(4): 1019–1027, doi: 10.1002/art.10187, indexed in Pubmed: 11953980.
5. World Health Organization. The top 10 causes of death. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.
6. Adamson J, Beswick A, Ebrahim S. Is stroke the most common cause of disability? J Stroke Cerebrovasc Dis. 2004; 13(4): 171–177, doi: 10.1016/j.jstrokecerebrovasdis.2004.06.003, indexed in Pubmed: 17903971.
7. Niewada M, Członkowska A. Zakrzepy i zatory tętnic mózgowych. W: Zakrzepy i zatory, pod red. Windyga J, Pasierski T, Torbicki A. PZWL, Warszawa 2014: 347–369.
8. Yaghi S, Bernstein R, Passman R, et al. Cryptogenic Stroke. Circul Res. 2017; 120(3): 527–540, doi: 10.1161/circresaha.116.308447, indexed in Pubmed: 28154102.
9. Ridker PM, Hennekens CH, Lindpaintner K, et al. Mutation in the gene coding for coagulation factor V and the risk of myocardial infarction, stroke, and venous thrombosis in apparently healthy men. N Engl J Med. 1995; 332(14): 912–917, doi: 10.1056/NEJM199504063321403, indexed in Pubmed: 7877648.
10. Hamedani AG, Cole JW, Mitchell BD, et al. Meta-analysis of factor V Leiden and ischemic stroke in young adults: the importance of case ascertainment. Stroke. 2010; 41(8): 1599–1603, doi: 10.1161/STROKEAHA.110.581256, indexed in Pubmed: 20616326.
11. Jiang B, Ryan KA, Hamedani A, et al. Prothrombin G20210A mutation is associated with young-onset stroke: the genetics of

early-onset stroke study and meta-analysis. Stroke. 2014; 45(4): 961–967, doi: 10.1161/STROKEAHA.113.004063, indexed in Pubmed: 24619398.
12. Chiasakul T, De Jesus E, Tong J, et al. Inherited thrombophilia and the risk of arterial ischemic stroke: a systematic review and meta-analysis. J Am Heart Assoc. 2019; 8(19): e012877, doi: 10.1161/JAHA.119.012877, indexed in Pubmed: 31549567.
13. Majmundar S, Thapa S, Miller ES, et al. Low value of inherited thrombophilia testing among patients with stroke or transient ischemic attack: A three-year retrospective study. J Stroke Cerebrovasc Dis. 2023; 32(10): 107308, doi: 10.1016/j.jstrokecerebrovasdis.2023.107308, indexed in Pubmed: 37633204.
14. Swan D, Connors JM, Thachil J. Dilemmas in hematology: consults in patients with arterial thrombosis. J Thromb Haemost. 2023; 21(3): 421–432, doi: 10.1016/j.jtha.2023.01.002, indexed in Pubmed: 36696207.
15. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. Mayo Clin Proc. 1984; 59(1): 17–20, doi: 10.1016/s0025-6196(12)60336-x, indexed in Pubmed: 6694427.
16. Thaler DE, Di Angelantonio E, Di Tullio MR, et al. The risk of paradoxical embolism (RoPE) study: initial description of the completed database. Int J Stroke. 2013; 8(8): 612–619, doi: 10.1111/j.1747-4949.2012.00843.x, indexed in Pubmed: 22883936.
17. Messé S, Gronseth G, Kent D, et al. Practice advisory update summary: Patent foramen ovale and secondary stroke prevention. Neurology. 2020; 94(20): 876–885, doi: 10.1212/wnl.0000000000009443, indexed in Pubmed: 32350058.
18. Kavinsky C, Szerlip M, Goldsweig A, et al. SCAI Guidelines for the management of patent foramen ovale. Journal of the Society for Cardiovascular Angiography & Interventions. 2022; 1(4): 100039, doi: 10.1016/j.jscai.2022.100039.
19. Turc G, Calvet D, Guérin P, et al. CLOSE investigators. closure, anticoagulation, or antiplatelet therapy for cryptogenic stroke with patent foramen ovale: systematic review of randomized trials, sequential meta-analysis, and new insights from the CLOSE study. J Am Heart Assoc. 2018; 7(12), doi: 10.1161/JAHA.117.008356, indexed in Pubmed: 29910193.
20. Hviid CVB, Simonsen CZ, Hvas AM. Recurrence risk in patients with cryptogenic stroke, patent foramen ovale, and thrombophilia: a systematic review and meta-analysis. Thromb Haemost. 2019; 119(11): 1839–1848, doi: 10.1055/s-0039-1693739, indexed in Pubmed: 31378004.
21. Farjat-Pasos JI, Nuche J, Mesnier J, et al. Transcatheter patent foramen ovale closure in stroke patients with thrombophilia: current status and future perspectives. J Stroke. 2022; 24(3): 335–344, doi: 10.5853/jos.2022.01697, indexed in Pubmed: 36221936.
22. Geisler T, Keller T, Martus P, et al. Apixaban versus aspirin for embolic stroke of undetermined source. NEJM Evid. 2023; 3(1), doi: 10.1056/evidoa2300235.
23. Pristipino C, Sievert H, D'Ascenzo F, et al. European position paper on the management of patients with patent foramen ovale. General approach and left circulation thromboembolism. Eur Heart J. 2018; 40(38): 3182–3195, doi: 10.1093/eurheartj/ehy649, indexed in Pubmed: 30358849.
24. Dębski M, Abdelrahman A, Alshehri H, et al. Contemporary management of patent foramen ovale: a multinational survey on cardiologists' perspective. J Interv Cardiol. 2021; 2021: 6955791, doi: 10.1155/2021/6955791, indexed in Pubmed: 34602869.
25. Barbhaiya M, Zuily S, Naden R, et al. 2023 ACR/EULAR antiphospholipid syndrome classification criteria. Ann Rheum Dis. 2023; 82(10): 1258–1270, doi: 10.1136/ard-2023-224609, indexed in Pubmed: 37640450.
26. Cohen H, Werring D, Chandratheva A, et al. Survey on antiphospholipid syndrome diagnosis and antithrombotic treatment in patients with ischemic stroke, other brain ischemic injury, or arterial thromboembolism in other sites: communication from ISTH SSC subcommittee on lupus anticoagulant/antiphospholipid antibodies. J Thromb Haemost. 2023; 21(10): 2963–2976, doi: 10.1016/j.jtha.2023.06.020, indexed in Pubmed: 37391096.
27. Sciascia S, Sanna G, Khamashta MA, et al. APS Action. The estimated frequency of antiphospholipid antibodies in young adults with cerebrovascular events: a systematic review. Ann Rheum Dis. 2015; 74(11): 2028–2033, doi: 10.1136/annrheumdis-2014-205663, indexed in Pubmed: 24942381.
28. Mittal P, Quattrocchi G, Tohidi-Esfahani I, et al. Antiphospholipid syndrome, antiphospholipid antibodies, and stroke. Int J Stroke. 2023; 18(4): 383–391, doi: 10.1177/17474930221150349, indexed in Pubmed: 36571450.
29. Pengo V, Ruffatti A, Legnani C, et al. Incidence of a first thromboembolic event in asymptomatic carriers of high-risk antiphospholipid antibody profile: a multicenter prospective study. Blood. 2011; 118(17): 4714–4718, doi: 10.1182/blood-2011-03-340232, indexed in Pubmed: 21765019.
30. Pengo V, Ruffatti A, Legnani C, et al. Clinical course of high-risk patients diagnosed with antiphospholipid syndrome. J Thromb Haemost. 2010; 8(2): 237–242, doi: 10.1111/j.1538-7836.2009.03674.x, indexed in Pubmed: 19874470.
31. Tektonidou MG, Andreoli L, Limper M, et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. Ann Rheum Dis. 2019; 78(10): 1296–1304, doi: 10.1136/annrheumdis-2019-215213, indexed in Pubmed: 31092409.
32. Vreede AP, Bockenstedt PL, McCune WJ, et al. Cryptic conspirators: a conversation about thrombocytopenia and antiphospholipid syndrome. Curr Opin Rheumatol. 2019; 31(3): 231–240, doi: 10.1097/BOR.0000000000000595, indexed in Pubmed: 30747734.
33. Devreese KMJ, de Groot PG, de Laat B, et al. Guidance from the Scientific and Standardization Committee for lupus anticoagulant/antiphospholipid antibodies of the International Society on Thrombosis and Haemostasis: Update of the guidelines for lupus anticoagulant detection and interpretation. J Thromb Haemost. 2020; 18(11): 2828–2839, doi: 10.1111/jth.15047, indexed in Pubmed: 33462974.
34. Zuily S, Clerc-Urmès I, Bauman C, et al. APS ACTION Investigators. Cluster analysis for the identification of clinical phenotypes among antiphospholipid antibody-positive patients from the APS ACTION Registry. Lupus. 2020; 29(11): 1353–1363, doi: 10.1177/0961203320940776, indexed in Pubmed: 32703117.
35. Pengo V, Denas G, Zoppellaro G, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. Blood. 2018; 132(13): 1365–1371, doi: 10.1182/blood-2018-04-848333, indexed in Pubmed: 30002145.
36. Zuily S, Cohen H, Isenberg D, et al. Use of direct oral anticoagulants in patients with thrombotic antiphospholipid syndrome: Guidance from the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. J Thromb Haemost. 2020; 18(9): 2126–2137, doi: 10.1111/jth.14935, indexed in Pubmed: 32881337.

37. Giarretta I, Ageno W, Dentali F. Lack of efficacy of direct oral anticoagulants compared to warfarin in antiphospholipid antibody syndrome. Haematologica. 2022; 107(11): 2737–2741, doi: 10.3324/haematol.2022.281586, indexed in Pubmed: 35861020.
38. Khairani CD, Bejjani A, Piazza G, et al. Direct oral anticoagulants vs vitamin K antagonists in patients with antiphospholipid syndromes: Meta-analysis of randomized trials. J Am Coll Cardiol. 2023; 81(1): 16–30, doi: 10.1016/j.jacc.2022.10.008, indexed in Pubmed: 36328154.
39. Crowther MA, Jones AE, Witt DM. Warfarin is the preferred therapy for patients with thrombotic APS: back to the future. J Am Coll Cardiol. 2023; 81(1): 31–33, doi: 10.1016/j.jacc.2022.10.015, indexed in Pubmed: 36328156.
40. Hart R, Catanese L, Perera K, et al. Embolic stroke of undetermined source. Stroke. 2017; 48(4): 867–872, doi: 10.1161/strokeaha.116.016414, indexed in Pubmed: 28265016.