

REVIEW

Comparative Effectiveness of Patent Foramen Ovale Closure and Medical Therapy in Cryptogenic Stroke: A Focused Review of Current Evidence

Ioana Georgescu^{1,2}, Andreea Badea^{1,2*}, Alexandru Andrei Badea³, Florentina Cristina Plesa^{1,2}, Florina Anca Antochi⁴, Ovidiu Cristian Chiriac^{5,6}, Carmen Adella Sirbu^{1,2,7}

¹ Neurology Department, "Dr. Carol Davila" Central Military Emergency University Hospital, 010825 Bucharest, Romania;

² Clinical Neuroscience Department, University of Medicine and Pharmacy "Carol Davila", 050474, Bucharest, Romania;

³ Cardiology Department, "Dr. Carol Davila" Central Military Emergency University Hospital, 010825 Bucharest, Romania;

⁴ Neurology Department, Emergency University Hospital Bucharest, 050098 Romania;

⁵ Discipline of Balneophysiokinetotherapy and Rehabilitation, Department of Specific Disciplines, Faculty of Midwifery and Nursing, University of Medicine and Pharmacy "Carol Davila", 050474, Bucharest, Romania; ovidiu-cristian.chiriac@drd.umfcd.ro;

⁶ Department of Rehabilitation, Physical Medicine and Balneology I, "Dr. Carol Davila" Central Military Emergency University Hospital, 010825 Bucharest, Romania;

⁷ Academy of Romanian Scientists, 050045 Bucharest, Romania.

*Correspondence: andreea.plesa@rez.umfcd.ro

Abstract: Background: Patent foramen ovale (PFO) is an anatomical variant in which the normal fetal interatrial passage persists after birth. It is estimated to be present in approximately 25% of adults. Furthermore, it appears to be involved in 50% of cryptogenic strokes. A cryptogenic stroke means the etiology remains unknown despite a thorough assessment (including arterial imaging, echocardiography, rhythm monitoring, and relevant laboratory testing, such as lipid profile and hemoglobin A1c). Secondary prevention options after a PFO-associated stroke consist of antiplatelet therapy, anticoagulant therapy, or percutaneous closure of the PFO, and it is still debatable which option is better. Objective: To critically review the available evidence regarding PFO closure vs. medical therapy as the optimal therapeutic option for secondary prevention after PFO-associated cryptogenic stroke, and to discuss relevant factors for patient selection. Methods: We conducted a focused review and searched the PubMed database for relevant literature on the subject. We included records about patients with PFO and a history of stroke. We chose to include only the free full-text sources. On the other hand, studies regarding children, studies comparing different devices or techniques, and observational studies on long-term complications and recurrence predictors were excluded. Results: Eight records were included, comprising 3750 participants, all diagnosed with PFO and stroke, to compare different therapeutic strategies for preventing stroke recurrence (PFO closure versus medical therapy). Conclusions: The results indicated that closure of PFO may provide greater protection against recurrent stroke than medical therapy alone in adequately selected patients with PFO-associated cryptogenic stroke. Additionally, given the lack of recent studies, further research is warranted to improve patient selection and evaluation of medium- and long-term prognosis.

Keywords: patent foramen ovale (PFO), stroke, PFO closure, antiplatelet, anticoagulant, cryptogenic stroke

INTRODUCTION

Being an important cause of death, but also disability, ischemic stroke has an increasing incidence in young adults (1). Most patients have residual neurological deficits six months after the event (2). Data show that almost 35% of ischemic strokes could be cryptogenic, meaning the etiology remains unknown despite careful assessment (at least arterial imaging, echocardiography, rhythm monitoring, and relevant laboratory testing, such as lipid profile and hemoglobin A1c) (3). It is also important to evaluate thyroid function, as hypothyroidism seems to be an independent risk factor for neurological events (4). On the other hand, data suggest that in acute ischemic stroke, significant derangement in thyroid hormones occurs (hypothalamo-pituitary-thyroid axis damage), with some encouraging the use of low

Citation: Georgescu I, Badea A, Badea AA, Plesa FC, Antochi FA, Sirbu CA. *Comparative Effectiveness of Patent Foramen Ovale Closure and Medical Therapy in Cryptogenic Stroke: A Focused Review of Current Evidence*. R. J. Mil. Med. 2026; CXXIX(5): 507-513

<https://doi.org/10.55453/rjmm.2026.129.5.4>

Academic Editor: Octavian Vasiliu

Received: 13 June 2026

Revised: 30 July 2026

Accepted: 02 August 2026

T3 levels as an indicator of poor prognosis (5). Previous studies have reported that women tend to experience stroke at an older age than men. Furthermore, obesity, active smoking, and the presence of the C allele of the angiotensin II type 1 receptor gene have been associated with an increased risk of stroke in women, highlighting the contribution of both genetic and environmental factors to cerebrovascular disease (6). Among cryptogenic strokes, a subset of patients with embolic stroke of undetermined source (ESUS) was described (Table 1) (7).

Table 1: Diagnostic criteria for embolic stroke of undetermined source (ESUS), adapted from Hart et al. (7)

Non-lacunar stroke on CT or MRI (Lacunar stroke being defined as a subcortical infarct ≤ 1.5 cm (≤ 2 cm on MRI diffusion images) in the distribution of the small, penetrating cerebral arteries)
Absence of extracranial or intracranial atherosclerosis causing $\geq 50\%$ luminal stenosis in arteries supplying the area of ischaemia
No major-risk cardioembolic source of embolism
• Permanent or paroxysmal atrial fibrillation • Sustained atrial flutter • Intracardiac thrombus • Prosthetic cardiac valve • Atrial myxoma or other cardiac tumours • Mitral stenosis • Myocardial infarction (within last 4 weeks) • Left ventricular ejection fraction less than 30% • Valvular vegetations • Infective endocarditis
No other cause of stroke identified
• Arteritis • Dissection, • Migraine/vasospasm • Drug misuse • Others

Patent foramen ovale (PFO) is defined as the persistence into adulthood of a normal embryological communication between the two atria (8). About 25% of adults have PFO (9). It appears to be involved in 50% of cryptogenic strokes (10) and 10% of all strokes in young adults (18-60 years) (11).

Due to the high prevalence of both PFO and cryptogenic stroke, including ESUS, it is very hard to prove an actual link between them. It is generally accepted that PFO can lead to stroke through paradoxical embolism, and increases in right-to-left shunting (Valsalva maneuver) amplify the risk. Also, another possible mechanism is represented by in situ thrombus formation (within the PFO or atrial septal aneurysm) (9).

The reported rate of recurrent stroke after cryptogenic stroke associated with PFO appears to be higher in older patients than in younger patients, suggesting other possible causes in addition to paradoxical embolism (11).

To evaluate the likelihood of PFO being the cause of stroke, there are two risk scores clinicians use in everyday practice. The RoPE (Risk of Paradoxical Embolism) score includes clinical and paraclinical data, but also behavioral features and age (12). PFO-Associated Stroke Causal Likelihood (PASCAL) classification includes the RoPE score and anatomical features of PFO (13). A high RoPE score (≥ 7) suggests a higher probability that the detected PFO is causally related to the index stroke rather than being an incidental finding. Furthermore, by integrating the RoPE score into the PASCAL classification system, we can establish the possibility/probability of stroke being related to PFO (14). Those two scores are also used in patient selection for PFO closure, but we must mention that several limitations have been pointed out. RoPE score does not prove causality, but probability (15). It also ignores PFO anatomic features; it is derived from retrospective data; and it has limited utility in older patients, who often receive low scores due to the presence of other vascular risk factors, so the score may underestimate the role of PFO in those cases. On the other hand, PASCAL classification does not prove causality either, but classifies the likelihood of PFO-related stroke. In addition, it demands detailed ultrasonography, and the results could be altered by the technique or operator experience (16).

Secondary prevention options after a PFO-associated stroke consist of antiplatelet therapy, anticoagulant therapy, or percutaneous closure of PFO (17). It is still debatable which option is better, with some studies showing superiority of PFO closure compared to antiplatelet and anticoagulant therapy, while others claim no difference in outcome or inconclusive evidence for either of them (18).

The aim of this focused review is to critically summarize current evidence comparing PFO closure with medical therapy for secondary prevention after PFO-associated cryptogenic stroke, with particular emphasis on patient selection and medium- and long-term outcomes. Also, several studies have reported an association between elevated cardiac biomarkers and increased stroke severity: higher CK-MB concentrations during the acute phase of ischemic stroke have been observed in patients with more severe neurological deficits, indicating that myocardial involvement may accompany extensive cerebrovascular injury (19).

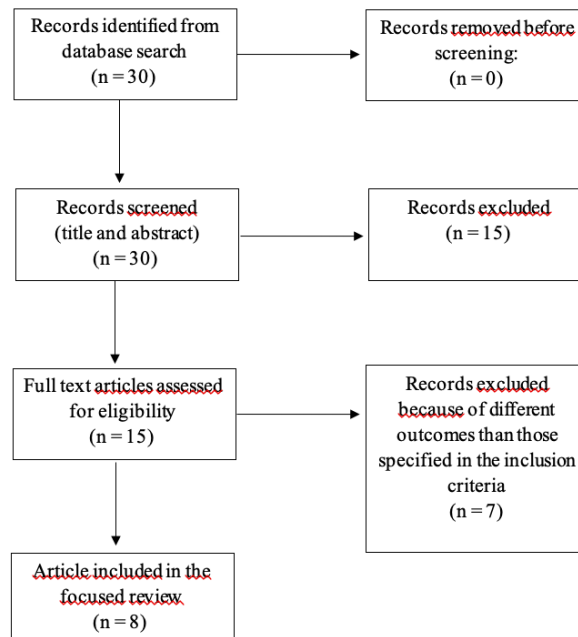
MATERIALS AND METHODS

A structured literature search was conducted in PubMed/MEDLINE for articles published between 01 January 2010 and 31 December 2025. We searched PubMed database for suitable literature data on the comparison of PFO closure with medical therapy for secondary prevention of recurrent cerebrovascular events in patients with PFO-associated cryptogenic stroke using PubMed MeSH terms, such as ("Patent Foramen Ovale"[Mesh] OR "patent foramen ovale"[tiab] OR PFO[tiab]) AND ("Stroke"[Mesh] OR "Ischemic Stroke"[Mesh] OR "ischemic stroke"[tiab] OR "cerebral infarction"[tiab] OR TIA[tiab]) AND ("Heart Septal Defects, Atrial/surgery"[Mesh] OR closure[tiab] OR occlusion[tiab] OR "device closure"[tiab] OR "transcatheter closure"[tiab]) AND ("Recurrence"[Mesh] OR recurrence[tiab] OR recurrent[tiab] OR "stroke recurrence"[tiab]). Regarding the inclusion criteria, we selected records of patients with PFO and a history of stroke, and we filtered our results by study design (clinical studies, clinical trials, multicenter studies, observational studies, randomized controlled studies) and date of publication. Also, we chose to include only free full-text sources. On the other hand, according to our exclusion criteria, studies of children, studies comparing different devices or techniques, and observational studies that focused on long-term complications and recurrence predictors were excluded from the review. The selected studies were narratively synthesized, with emphasis on study design, population characteristics, therapeutic strategies, recurrent stroke outcomes, and follow-up duration. The findings were interpreted qualitatively, with particular attention to differences in patient selection and medical treatment across trials.

RESULTS

We identified 30 records from the PubMed database search. No record was removed before screening. Half of the studies (n = 15) were excluded after screening by title and abstract. After that, a full-text article assessment led to the exclusion of another 7 studies due to outcomes that differed from those specified in the inclusion criteria. Finally, 8 records were included in the review process. The selection process is also illustrated through the following diagram (Figure 1).

Figure 1: Flow diagram of the search papers (20)



In the end, selected studies were compiled in an Excel spreadsheet, from which we extracted data on authors, study acronym, study type, year of publication, number of participants, randomization rate, primary endpoint, and comparison in the discussion and conclusions. We chose to include those studies that compared PFO closure and antiplatelet therapy to medical therapy alone (antiplatelet therapy/anticoagulation). We reviewed eight records, involving 3750 participants, all of whom were diagnosed with PFO and stroke, designed to compare different therapeutic strategies to prevent stroke recurrence (PFO closure vs medical therapy alone).

CLOSURE I (21) was a multicenter, randomized, open-label trial published in 2012 and one of the earliest reports on the subject. It included 909 patients, randomly assigned in equal proportions to two groups: one group underwent PFO closure in addition to antiplatelet therapy, and the other received medical therapy alone (warfarin, aspirin, or both). Primary endpoints were stroke recurrence, transient ischemic attack, and death. In the end, this trial found no significant difference between the two management strategies in terms of stroke recurrence. PC TRIAL (22), also a multicenter, randomized, open-label trial, published one year later, in 2013, included 414 patient, with a randomization ratio of 1:1, distributed in two arms: patients who had PFO closure as well as antiplatelet therapy (aspirin/ticlopidine/clopidogrel) and patients who recieved medical therapy only (antiplatelet therapy alone or oral anticoagulation alone - left to the discretion of the treating physician). Primary endpoints consisted of death, nonfatal strokes, transient ischemic strokes, and peripheral embolism. The results showed no significant difference between the two treatment options. The RESPECT (23) trial was a multicenter, randomized, open-label trial published in 2013, enrolling 980 patients randomized in a 1:1 ratio into two groups: those who underwent PFO closure in addition to antiplatelet therapy and those who received medical therapy exclusively (aspirin, clopidogrel, warfarin, or aspirin plus extended-release dipyridamole). It was one of the first major trials to suggest significantly lower stroke recurrence with PFO closure. Primary endpoints were stroke recurrence and death. This trial had a follow-up in 2017 (24), and the results were consistent with the initial findings. The CLOSE trial (25), another randomized, multicenter, open-label trial published in 2017, included 663 patients randomized by a 1:1:1 ratio in three groups: patients who had PFO closure besides antiplatelet therapy, patients who were given antiplatelet therapy alone (clopidogrel, aspirin, or aspirin combined with extended-release dipyridamole), and patients who received oral anticoagulation exclusively (vitamin K antagonists or direct oral anticoagulants). Its primary endpoint was stroke recurrence. The findings illustrated a significantly lower rate of stroke recurrence with PFO closure. Otherwise, the effects of oral anticoagulant therapy as compared with antiplatelet therapy on the risk of stroke recurrence could not be determined. The Gore REDUCE trial (26), also a multicenter, randomized, open-label trial published in 2017, included 664 patients randomized in two arms by a 2:1 ratio: patients with PFO closure along with antiplatelet therapy and patients who took antiplatelet therapy solely (aspirin, aspirin combined with extended-release dipyridamole, or clopidogrel). Primary endpoints included stroke recurrence, transient ischemic attack, and death. Final data illustrated significantly lower rates of stroke recurrence with PFO closure. This study had a follow-up in 2021 (27), and the results were consistent with the initial findings. The DEFENSE-PFO trial (28), a randomized, open-label, multicenter trial published in 2018, including 120 patients randomized by a 1:1 ratio in two groups, one with patients who had PFO closure plus antiplatelet therapy and one with patients who received medical therapy alone (aspirin, aspirin and clopidogrel, aspirin and cilostazol or warfarin), showed significantly lower rates of stroke recurrence with closure of the PFO in combination with medical therapy than with medical therapy alone. Its primary endpoints were stroke recurrence, death, and major bleeding (Table 2).

Table 2: Selected studies aiming to compare PFO closure and medical therapy alone (antiplatelet therapy/anticoagulation).

No.	Study	Type of study	Year	Number of participants	Primary endpoint	Comparison in study	Conclusions
1	CLOSURE I	Multicenter, randomized, open-label trial	2012	909 (1:1)	Stroke , death	PFO closure (as soon as possible, preferably 7days) plus antiplatelet therapy vs medical therapy alone (warfarin, aspirin or both)	No significant difference
2	PC Trial	Multicenter, randomized, open-label clinical trial	2013	414 (1:1)	Death, nonfatal stroke, transient ischemic attack, peripheral embolism	PFO closure (as soon as possible) plus antiplatelet therapy (aspirin/ticlopidine/clopidogrel) vs medical therapy alone (antiplatelet therapy alone or oral anticoagulation alone - left to the discretion of the treating physician)	No significant difference
3	RESPECT	Multicenter, randomized, open-label trial	2013	980 (1:1)	Stroke, death	PFO closure (within 21 days) plus antiplatelet therapy vs medical therapy alone (aspirin, warfarin, clopidogrel or aspirin combined with extended-release dipyridamole)	Recurrent ischemic stroke was significantly lower with PFO closure plus antiplatelet therapy than with antiplatelet therapy alone.
4	RESPECT follow up		2017				
5	CLOSE	Multicenter, randomized, open-label trial	2017	663 (1:1:1)	Stroke	PFO closure (within 21 days) plus antiplatelet therapy vs antiplatelet therapy alone (aspirin, clopidogrel, or aspirin combined with extended-release dipyridamole) vs oral anticoagulation alone (vitamin K antagonists or direct oral anticoagulants)	Recurrent ischemic stroke was significantly lower with PFO closure plus antiplatelet therapy than with antiplatelet therapy alone. The effects of oral anticoagulant therapy as compared with antiplatelet therapy on the risk of stroke recurrence could not be determined.
6	Gore REDUCE	Multicenter, randomize, open-label trial	2017	664 (2:1)	Stroke, transient ischemic attack, death	PFO closure (within 90 days - median of 28 days) plus antiplatelet therapy vs antiplatelet therapy alone (aspirin, aspirin combined with extended-release dipyridamole or clopidogrel)	Recurrent ischemic stroke was significantly lower with PFO closure plus antiplatelet therapy than with antiplatelet therapy alone.
7	Gore REDUCE follow up		2021				
8	DEFENSE-PFO	Multicenter, randomized, open-label trial	2018	120 (1:1)	Stroke, death, major bleeding	PFO closure (as soon as possible) plus antiplatelet therapy vs medical therapy alone (aspirin, aspirin combined with clopidogrel, aspirin combined with cilostazol or warfarin)	Recurrent ischemic stroke was significantly lower with closure of the PFOn combination with medical therapy than with medical therapy alone

DISCUSSION

We reviewed eight records, six of them being multicenter randomized open-label trials and two of them being follow-ups. The findings demonstrated a relative benefit from PFO closure in terms of stroke recurrence. Two out of eight records (25%) indicated no significant difference when comparing PFO closure and antiplatelet therapy to medical therapy alone (antiplatelet therapy/anticoagulation), while the rest of them (six out of eight, 75%) indicated superiority of PFO closure and antiplatelet therapy in stroke recurrence. We also noticed that the two studies demonstrating similar therapeutic efficacy were among the earliest large trials on this topic, while more recent studies suggest a definite benefit of PFO closure on stroke recurrence. Future research could focus on better scores to determine the causality of PFO in cryptogenic stroke, optimal therapeutic options, optimal medical therapy alone, and best imaging techniques (contrast-enhanced transthoracic echocardiogram, contrast-enhanced transoesophageal echocardiogram, contrast-enhanced transcranial Doppler).

An additional challenge in interpreting the available trials is the heterogeneity of medical therapy used in the control groups. “Medical therapy” encompassed antiplatelet agents, oral anticoagulation, or combinations of different agents, and treatment allocation was sometimes left to the discretion of the treating physician. Consequently, the available evidence more robustly addresses the question of PFO closure versus heterogeneous medical management than the specific comparative efficacy of closure versus antiplatelet therapy or anticoagulation individually. The optimal medical strategy for patients who do not undergo closure therefore remains less clearly defined.

Taken together, current evidence suggests that the clinical question has shifted from whether PFO closure is generally effective to identifying which patients are most likely to derive a net benefit from the procedure. The available randomized evidence supports closure in appropriately selected patients with PFO-associated cryptogenic stroke, particularly when alternative stroke mechanisms have been carefully excluded and clinical and anatomical features increase the likelihood of PFO causality.

Limitations

This focused review had several limitations. First, the available randomized evidence is based on a relatively small number of trials, with few recent large-scale randomized studies, none of which have been published. There were only two follow-up studies, so it is difficult to appreciate accurate long-term efficacy and prognosis. Furthermore, in PFO closure groups, different devices were used, and at the same time, in medication-alone groups, the choice between antiplatelet therapy and anticoagulation, as well as which specific drug was used, varied between trials, making it hard to draw a reliable conclusion.

Future directions

Age represents another unresolved issue in the explored domain. Most randomized trials supporting PFO closure predominantly enrolled younger patients, whereas evidence in individuals older than 60 years remains substantially more limited. In older patients, competing mechanisms of stroke—including occult atrial fibrillation and atherosclerotic disease—become increasingly prevalent, while the RoPE score tends to assign a lower probability of PFO causality because of age and accompanying vascular risk factors. Whether carefully selected older patients with high-risk PFO anatomy may nevertheless benefit from closure remains an important area for future investigation.

CONCLUSION

This focused review aimed to compare different therapeutic strategies to prevent stroke recurrence (PFO closure vs medical therapy alone). Current evidence supports PFO closure as an effective strategy for reducing recurrent stroke in appropriately selected patients with PFO-associated cryptogenic stroke. However, treatment decisions should incorporate clinical characteristics, PFO anatomy, the likelihood of a causal relationship between the PFO and the index event, competing stroke mechanisms, and the risks associated with both interventional and medical strategies. Also, we would like to point out the need for further research, considering that the latest large-scale study on this subject was published in 2018 and that access to diagnostic investigations and closure procedures has improved in recent years. It is expected that more data on this topic would optimize patient selection and evaluation of medium- and long-term prognosis.

Conflicts of interest and sources of funding

The authors declare no conflict of interest.

This research received no external funding.

Acknowledgments

No generative AI was used in the production of this article.

Authors' contribution

Conceptualization, I.G., A.B., F.A.A., and C.A.S.; methodology, I.G., A.B., F.A.A., and A.A.B.; software, A.A.B.; validation, A.A.B. and C.A.S.; formal analysis, I.G., F.C.P., and A.A.B.; investigation, I.G. and A.B.; resources, C.A.S., and F.C.P.; data curation, I.G. and A.B.; writing—original draft preparation, I.G. and A.B.; writing—review and editing,

A.A.B. and C.A.S.; visualization, I.G. and A.A.B.; supervision, C.A.S., and F.C.P. ; project administration, A.A.B., F.A.A., and C.A.S. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

References

1. Srivastava A, Tsiplova K, Taylor A, Pikula A, Mandzia J, Mikulik R, et al. Prevalence, causal classification, and prognosis of patent foramen ovale in young patients with embolic strokes of undetermined source. *J Am Heart Assoc.* 2025;14(9):e038948. doi:10.1161/JAHA.124.038948.
2. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. Heart disease and stroke statistics—2021 update: a report from the American Heart Association. *Circulation.* 2021;143(8):e254-e743. doi:10.1161/CIR.0000000000000950.
3. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, et al. 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. *Stroke.* 2021;52(7):e364-e467. doi:10.1161/STR.0000000000000375.
4. Li J, Liu H, Li Y. Hypothyroidism is a risk factor for transient ischemic attack: a meta-analysis. *Saudi Med J.* 2025;46(2):117-123. doi:10.15537/smj.2025.46.2.20240508.
5. Lamba BMS, Sharma S, Gupta P. Alteration of levels of thyroid hormones in acute ischemic stroke and its correlation with severity and functional outcome. *Rom J Mil Med.* 2019;122(3):52-63. doi:10.55453/rjmm.2019.122.3.8.
6. Nica S, Cirstoiu F, Nica R, Toma M, Cimponeriu D, Cimpoesu D. The interactions between risk factors for ischemic stroke. *Rom J Mil Med.* 2021;124(1):119-123.
7. Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, et al. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol.* 2014;13(4):429-438. doi:10.1016/S1474-4422(13)70310-7.
8. Gillebert JP, Abdul-Samad O, Shapiro LM, Rana BS, Calvert PA. Patent foramen ovale closure in 2019. *Interv Cardiol.* 2019;14(1):34-41. doi:10.15420/icr.2018.33.2.
9. Kottoor SJ, Arora RR. Cryptogenic stroke: to close a patent foramen ovale or not to close? *J Cent Nerv Syst Dis.* 2018;10:1179573518819476. doi:10.1177/1179573518819476.
10. Pristipino C, Sievert H, D'Ascenzo F, Mas JL, Meier B, Scacciatella P, et al. European position paper on the management of patients with patent foramen ovale. General approach and left circulation thromboembolism. *Eur Heart J.* 2019;40(38):3182-3195. doi:10.1093/eurheartj/ehy649.
11. Homma S, Di Tullio MR, Sacco RL, Sciacca RR, Mohr JP; PICSS Investigators. Age as a determinant of adverse events in medically treated cryptogenic stroke patients with patent foramen ovale. *Stroke.* 2004;35(9):2145-2149. doi:10.1161/01.STR.0000135773.24116.18.
12. Thaler DE, Di Angelantonio E, Di Tullio MR, Donovan JS, Griffith J, Homma S, 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.
13. Kent DM, Saver JL, Kasner SE, Nelson J, Carroll JD, Chatellier G, et al. Heterogeneity of treatment effects in an analysis of pooled individual patient data from randomized trials of device closure of patent foramen ovale after stroke. *JAMA.* 2021;326(22):2277-2286. doi:10.1001/jama.2021.20956.
14. Caso V, Turc G, Abdul-Rahim AH, Castro P, Hussain S, Lal A, et al. European Stroke Organisation (ESO) guidelines on the diagnosis and management of patent foramen ovale (PFO) after stroke. *Eur Stroke J.* 2024;9(4):800-834. doi:10.1177/23969873241247978.
15. Kent DM, Wang AY. Patent foramen ovale and stroke: a review. *JAMA.* 2025;334(16):1463-1473. doi:10.1001/jama.2025.10946.
16. Kent DM, Saver JL, Ruthazer R, Furlan AJ, Reisman M, Carroll JD, et al. RoPE-estimated attributable fraction correlates with benefit of patent foramen ovale closure: an analysis of 3 trials. *Stroke.* 2020;51(10):3119-3123. doi:10.1161/STROKEAHA.120.029350.
17. Turc G, Calvet D, Guérin P, Sroussi M, Chatellier G, Mas JL; 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):e008356. doi:10.1161/JAHA.117.008356.
18. Patel U, Dengri C, Pielykh D, Baskar A, Tar MI, Patel G, et al. Secondary prevention of cryptogenic stroke and outcomes following surgical patent foramen ovale closure plus medical therapy vs medical therapy alone: an umbrella meta-analysis of eight meta-analyses covering seventeen countries. *Cardiol Res.* 2023;14(5):342-350. doi:10.14740/cr1526.
19. Manea MM, Dragos D, Ghenu MI, Enache II, Stoican IC, Ciulavu C, et al. The neurocardiogenic impact of ischemic stroke: intricacies of cardiac enzymes and the vegetative system. *Rom J Mil Med.* 2025;128(1):36-42. doi:10.55453/rjmm.2025.128.1.5.
20. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021;372:n71. doi:10.1136/bmj.n71.
21. Furlan AJ, Reisman M, Massaro J, Mauri L, Adams H, Albers GW, et al.; CLOSURE I Investigators. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. *N Engl J Med.* 2012;366(11):991-999. doi:10.1056/NEJMoa1009639.
22. Meier B, Kalesan B, Mattle HP, Khattab AA, Hildick-Smith D, Dudek D, et al.; PC Trial Investigators. Percutaneous closure of patent foramen ovale in cryptogenic embolism. *N Engl J Med.* 2013;368(12):1083-1091. doi:10.1056/NEJMoa1211716.
23. Carroll JD, Saver JL, Thaler DE, Smalling RW, Berry S, MacDonald LA, et al.; RESPECT Investigators. Closure of patent foramen ovale versus medical

therapy after cryptogenic stroke. *N Engl J Med*. 2013;368(12):1092-1100. doi:10.1056/NEJMoa1301440.

24. Saver JL, Carroll JD, Thaler DE, Smalling RW, MacDonald LA, Marks DS, Tirschwell DL; RESPECT Investigators. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. *N Engl J Med*. 2017;377(11):1022-1032. doi:10.1056/NEJMoa1610057.

25. Mas JL, Derumeaux G, Guillon B, Massardier E, Hosseini H, Mechtouff L, et al.; CLOSE Investigators. Patent foramen ovale closure or anticoagulation vs antiplatelets after stroke. *N Engl J Med*. 2017;377(11):1011-1021. doi:10.1056/NEJMoa1705915.

26. S ndergaard L, Kasner SE, Rhodes JF, Andersen G, Iversen HK, Nielsen-Kudsk JE, et al.; Gore REDUCE Clinical Study Investigators. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. *N Engl J Med*. 2017;377(11):1033-1042. doi:10.1056/NEJMoa1707404.

27. Kasner SE, Rhodes JF, Andersen G, Iversen HK, Nielsen-Kudsk JE, Settergren M, et al.; Gore REDUCE Clinical Study Investigators. Five-year outcomes of PFO closure or antiplatelet therapy for cryptogenic stroke. *N Engl J Med*. 2021;384(10):970-971. doi:10.1056/NEJMc2033779.

28. Lee PH, Song JK, Kim JS, Heo R, Lee S, Kim DH, et al. Cryptogenic stroke and high-risk patent foramen ovale: the DEFENSE-PFO trial. *J Am Coll Cardiol*. 2018;71(20):2335-2342. doi:10.1016/j.jacc.2018.02.046.