

Beyond Stroke—Investigating Heart-Brain Connections in Migraine and Pain: A Mini Review

Roshni Riaz Memon^{1*}, Muqadas Bhatti², Umar Aziz³, Javeria Nawaz⁴, Vicky Kumar⁵, Haris Muhammad⁶, Ali Ather⁷,
Aparna Iyer⁸

¹Ziauddin University, Karachi, Pakistan

²Department of Public Health, Bahria University, Karachi, Pakistan

³Department of Medicine, Jinnah Sindh Medical University, Karachi, Pakistan

⁴Department of Medicine, Dow University of Health Sciences, Karachi, Pakistan

⁵George Washington University, Washington, D.C, USA

⁶Newark Beth Israel Medical Centre, New Jersey, USA

⁷Shalamar Medical and Dental College, Lahore, Pakistan

⁸Maimonides Medical Centre, New York, USA

Article Info

Article Notes

Received: September 11, 2025

Accepted: November 10, 2025

*Correspondence:

*Dr. Roshni Riaz Memon, Ziauddin University, Karachi, Pakistan; Email: roshniriaz36@gmail.com

©2025 Memon RR. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License.

Keywords

Patent Foramen Ovale

Cryptogenic Stroke

Pain Syndromes

Interdisciplinary Care

PFO Closure Outcomes

Migraine with Aura

Abstract

The patent foramen ovale (PFO), a congenital interatrial communication caused by incomplete septal closure, has long been recognised as a factor contributing to cryptogenic stroke, especially among younger adults. However, recent evidence has expanded its clinical relevance, revealing a strong association between PFO and migraine with aura. This emerging link has sparked interest in evaluating PFO closure not only for secondary stroke prevention but also as a possible treatment for neurovascular pain syndromes. Randomised controlled trials such as PRIMA and PREMIUM have assessed the impact of transcatheter PFO closure on migraine frequency. While these studies showed modest reductions, the varied outcomes highlight the complexity of the PFO–migraine relationship. Despite this variability, transcatheter closure with nitinol-based occluders remains a safe and effective procedure, achieving long-term closure rates of over 98% with few complications.

Recent advances, including biodegradable occluders studied in the BioMetal trial, reflect increasing momentum towards personalised and biocompatible treatment approaches. Overall, these developments suggest that PFO closure could provide meaningful relief for carefully selected migraine sufferers—particularly those with frequent aura and refractory symptoms. Going forward, collaboration between cardiologists, neurologists, and pain specialists will be crucial to understanding the underlying mechanisms and refining patient selection. As knowledge advances, PFO closure holds promise as a transformative intervention that links cerebrovascular health and chronic pain management.

Introduction

Patent foramen ovale (PFO) is a congenital heart defect, persisting in 20-25% of the population, and results from the failure of an embryonic fetal communication between the right and left atria¹. Most PFOs remain asymptomatic throughout life, but they can be associated with conditions including cryptogenic stroke and systemic arterial embolism¹. PFO closure, a medical procedure that seals the PFO, has emerged as a secondary prevention option for patients with cryptogenic stroke and cerebrovascular events². Recent trials favour PFO closure over medical therapy, especially in patients under 60 with cryptogenic, embolic-appearing stroke, and high-risk features such as atrial septal aneurysm or large right-to-left shunt².

Traditionally studied in the context of stroke and paradoxical embolism, PFO is now increasingly linked to migraine, particularly migraine with aura, where its prevalence rises from 20–30% in the general population to 40–60% among affected patients³. To create a comprehensive and focused synthesis, we conducted a narrative review of peer-reviewed literature published from 2000 to 2025, searching databases such as PubMed, Scopus, and Google Scholar. Our search included terms like “patent foramen ovale,” “migraine with aura,” “systemic pain,” “neurovascular coupling,” and “autonomic dysfunction.” Articles were chosen based on their relevance to the link between PFO, migraine, and systemic pain syndromes, emphasising mechanistic, clinical, and interventional studies. We also examined reference lists of key papers to find additional sources. All peer-reviewed articles published in any language that explored the relationship between PFO and migraine (with or without aura), systemic pain, or autonomic dysfunction- focusing on pathophysiology, clinical aspects, or interventions- were included. Studies involving humans, such as observational, cohort, case-control, and randomized controlled trials, were eligible. We excluded non-peer-reviewed works, editorials, commentaries, conference abstracts without full texts, animal studies unless relevant for mechanisms, and articles lacking methodological rigor or core relevance themes.

This review discusses the growing role of PFO closure in migraine and systemic pain beyond stroke prevention. It summarises current evidence, underlying mechanisms, gaps in research concerning non-stroke applications, and opportunities for collaboration among cardiology, neurology, and pain medicine.

Understanding PFO Anatomy and Pathophysiology

Among atrial septal defects, a patent foramen ovale is a subset that results from a remnant of normal fetal anatomy⁴. About 50% of six-month-old infants have a PFO⁵. Patent foramen ovale (PFO) is an opening between the atrial septum secundum and primum at the fossa ovalis. It allows fetal blood flow into the systemic circulation. After birth, as pulmonary circulation develops, the functional PFO begins to close, usually completing anatomical closure around 12 months. PFO mainly increases stroke risk through paradoxical embolism.

A paradoxical embolism can occur when a blood clot in the venous system crosses an intracardiac defect or atrioventricular malformation and enters the systemic circulation. When a PFO is present, any sustained increase in right-sided heart pressures can elevate the risk of this condition⁶. The risk of cryptogenic stroke rises with larger defects and interatrial aneurysm, possibly due to increased thrombus formation or larger size of PFOs linked to aneurysmal tissue⁷.

The primary reason that PFO remains asymptomatic in numerous individuals is that its anatomical structure, essentially a small flap, tends to maintain stable dimensions and does not undergo physical expansion. However, the risks associated with its presence can become more apparent or severe due to other changing health factors⁸. For example, the amount of blood flowing through the PFO can fluctuate, and while most people with a PFO don't show any symptoms, it can be linked to complications like cryptogenic stroke or transient ischemic attack (TIA). These minute emboli, with no evident origin, may bypass the pulmonary circulation and reach the brain directly, thereby contributing to paradoxical embolism. They are also associated with the initiation of migraine episodes and are intricately linked to migraines accompanied by aura⁹.

PFO and Cryptogenic Stroke- The Established Connection

Cryptogenic stroke, which accounts for nearly 40% of ischemic strokes, presents a persistent diagnostic and therapeutic challenge¹⁰. Unlike strokes with known causes like atrial fibrillation or carotid artery disease, cryptogenic strokes don't have a clear cause, making it harder to prevent them. In younger adults, a common heart defect called patent foramen ovale (PFO) has become a major contributor to these strokes. This defect occurs when the atrial septum doesn't close fully¹¹.

A patent foramen ovale (PFO) can cause paradoxical embolism, in which blood clots or other embolic material bypass the lungs and enter the bloodstream, potentially reaching the brain¹². This is a key factor in recurring ischemic events, especially in patients without common vascular risk factors. Typically, secondary prevention has relied on antiplatelet agents or anticoagulants; however, these treatments carry a risk of bleeding and may not entirely prevent recurrence. As a result, transcatheter PFO closure has become a more attractive option as a definitive treatment. This minimally invasive procedure uses occluder devices to close the septal defect, lowering the risk of embolic stroke¹³.

Several large-scale, randomised controlled trials—RESPECT, CLOSE, REDUCE, and DEFENSE-PFO—have demonstrated that PFO closure is more effective than medical therapy for specific patients, especially those under 60 with large shunts or atrial septal defects aneurysms^{14,15}. Although there are concerns about increased risk of atrial fibrillation after the procedure, recent studies, including Liu et al., indicate no significant rise in arrhythmia risk after closure¹⁶. These findings have led to updated clinical guidelines, making PFO closure a viable option for stroke prevention in appropriately selected patients.

PFO and Migraine with Aura-Emerging Evidence

Patent Foramen Ovale, present in 20-30% of adults, shows a notably higher prevalence among migraine patients¹⁷, particularly those having migraine with aura (MA), ranging from 46.3% to 88%¹⁸, and massive right-to-left shunts in 38.9% of MA patients¹⁹. Chronic migraine is also notable in individuals with PFO, with one study reporting 66% prevalence¹⁸. The right-to-left shunt in PFO bypasses pulmonary filtration, allowing microemboli or vasoactive substances such as serotonin to enter systemic circulation, triggering cortical spreading depression (CSD). These chemicals are usually metabolised in the lungs, but reaching the brain unfiltered can trigger hyperexcitability in neurons, contributing to migraine attacks¹⁷.

Several trials investigated PFO closure for migraine. The MIST²⁰ trial studied the efficacy of transcatheter PFO closure with STARFlex implant on 432 patients; it reported no significant cessation of migraine headache between the implant and sham group. However, exploratory analysis revealed that the implant group showed a greater reduction in headaches, which may be attributed to the exclusion of outliers with a higher headache frequency. Adverse events included tamponade, pericardial effusion, retroperitoneal bleed, and oozing of the groin post-procedure. The trial had several limitations, including unrealistic endpoints, a small sample size, a short follow-up period, and confounding medications.

Another randomised controlled trial, PRIMA²¹, reported the effect of the Amplatzer PFO Occluder. Among 705 patients, 83 completed the follow-up. The outcomes were non-significant; no adverse events with permanent sequelae were reported, and five without permanent sequelae were reported. Limitations included the absence of a sham intervention, early termination of patient enrolment, and the inclusion of a specific population of migraine patients.

PREMIUM²², a double-blinded sham group trial with a population of 230 patients also used Amplatzer PFO Occluder. The trial yielded similar results to those previously reported, with no significant reduction in migraine frequency. One serious adverse event (transient atrial fibrillation) was reported in 205 patients in the PFO group. Limitations include the assumption that the treatment group would have twice the response rate of the control group, given the sample size, rendering the study underpowered.

A meta-analysis, Zhang et al, 2022.²³ reported a greater reduction in migraine frequency with PFO closure, which contrasts with the findings of the previously mentioned trial. Some patients presented the opposite finding, but this

difference was not statistically significant due to the smaller number of studies and sample sizes. Subgroup analysis revealed a notable reduction in headaches and complete cessation of migraines in the MA group compared to those without aura. In rare cases, migraine attacks increased after PFO closure, possibly due to platelet activation and elevated serotonin that could be controlled by antiplatelet therapy²⁴.

Research has identified several biomarkers associated with PFO in migraine patients. Calcitonin Gene-Related Peptide (CGRP) emerges as a promising biomarker. The concentration correlates positively with right-to-left shunt grades and headache severity scores, demonstrating diagnostic value with 72.55% sensitivity and 78.43% specificity²⁵. Additionally, cystatin-C and calcium levels were lower in the PFO group, which led to migraine improvement²⁶. CGRP represents the most substantiated biomarker with clinical relevance for migraine diagnosis and treatment monitoring²⁵.

Critical Appraisal of Clinical Trials

The MIST, PRIMA, and PREMIUM trials have significantly advanced our understanding of the potential effects of PFO closure on migraine outcomes; however, due to several methodological issues, their findings should be interpreted with caution. In the PRIMA trial, for example, only 83 of 705 patients completed follow-up, limiting statistical power and increasing the risk of type II errors due to the small sample size and high dropout rate²¹. Furthermore, some studies used extremely stringent or unrealistic primary endpoints, such as the MIST trial's emphasis on total migraine cessation, which may have overshadowed significant gains in headache frequency or severity²⁰. It was also challenging to determine whether benefits were maintained or whether delayed complications materialised, given the comparatively brief follow-up periods in many trials.

Taken together, these concerns highlight the need for larger, independently funded studies with longer follow-up, standardised diagnostic criteria, and outcomes that more accurately reflect patients' actual experiences, such as quantifiable improvements in quality of life or a 50% or greater reduction in migraine days. With these refinements, future studies could more clearly define the actual therapeutic value of PFO closure beyond its well-established role in stroke prevention. Table 1 summarises key randomised controlled trials and meta-analyses assessing the role of PFO closure in migraine patients, highlighting study designs, inclusion criteria, primary outcomes, and study limitations across different interventions.

Table 1: Summary of major clinical trials and meta-analysis evaluating the efficacy and safety of patent foramen ovale (PFO) closure for migraine management

Sno	Trial Name	Sample size	Device Used	Design	Inclusion criteria	Exclusion Criteria	Outcomes	Limitations
1.	MIST ²⁰	432	STARfex	Double-blind sham controlled	Migraine with aura frequent attacks	Non-Aura migraine, confounding with medications	No significant cessation; exploratory reduction in headaches	Unrealistic endpoints, short follow-up, small sample, adverse events
2.	PRIMA ²¹	705	Amplatzer PFO Occluder	Randomized controlled trial	Specific migraine patients.	No specific exclusion criteria listed.	No significant reduction, five adverse events without permanent sequelae.	Absence of sham intervention, early termination of patient enrolment, and the inclusion of a specific population of migraine patients
3.	PREMIUM ²²	230	Amplatzer PFO Occluder	Double-blinded sham group trial	Migraine patients	No specific exclusion criteria listed.	No significant reduction, adverse event (transient atrial fibrillation).	Assumed treatment group response twice the control group, underpowered study
4.	Zhang et al. 2022 ²³	1165	N/A	Meta-analysis	Studies on PFO closure for migraine	Limited studies, smaller sample size	Higher reduction in migraine frequency, cessation of migraines in those with aura	Smaller sample sizes, conflicting findings in some studies

Device Closure: Mechanism and Outcomes

Transcatheter PFO closure uses nitinol-based devices, such as the Amplatzer and Gore devices, to close the septal defect, achieving >95% effective closure. These devices act as scaffolds for the septum and become rapidly endothelialized, resulting in ~98% occlusion in long-term follow-up²⁷. The procedure is performed through femoral venous access under fluoroscopic/echo guidance. The device is positioned by deploying overlapping left- and right-atrial discs across the defect, forming a characteristic “Pacman” shape on fluoroscopy, and then gently pulled to ensure stability before final release. Patients generally undergo short-term dual antiplatelet therapy (1-6 months) after the procedure, followed by single-agent therapy and early monitoring for atrial arrhythmias²⁸. PFO closure has an impeccable safety record. While complications are rare, the most common complication is transient periprocedural atrial fibrillation, which is generally treatable. Thrombus formation, device embolisation, residual shunt, or erosion are rare and largely preventable with careful technique²⁷.

There’s promising evidence that closing a PFO can provide relief for people with migraines. In a combined analysis of two major studies involving a total of 337 patients, researchers found that those who underwent PFO closure experienced a reduction in monthly migraine days from approximately 3.1 to 1.9. In fact, the percentage of patients who were completely migraine-free after closure was 9.0%, compared with only 0.7% beforehand²⁹.

Observational studies also showed positive results. 86 adolescents had undergone the procedure, and 83% of patients in this study reported experiencing a 50% or greater reduction in migraine frequency, whereas 54% were completely free of migraines after the procedure. The most significant improvement appeared to be among patients with migraine with aura³⁰. Meta-analyses support these findings, noting significantly more headache-free days and fewer attacks with closure compared to medical therapy²³.

Follow-up data suggest that migraine benefits persist over time. In a series with an average follow-up of about 50 months, the occlusion remained greater than 98%, and no recurrent strokes occurred. After PFO closure, patients reported significantly improved quality of life, as evidenced by decreased headache severity and increased overall well-being, as reflected in SF-36 scores²⁷. While more research is always beneficial, the existing data suggest that PFO closure could be a game-changer for people struggling with migraines.

Intersection with Pain Medicine

Migraine, a chronic neurological disorder, is characterised by recurrent intense headaches that last 4-72 hours, accompanied by nausea and sensitivity to light and sound³¹. Affecting 15-29% of the general population, migraine is ranked among the top 20 most disabling lifetime conditions by the World Health Organization (WHO)³¹. As an evolutive neurological disorder, migraine exists on

a spectrum from episodic to chronic forms and involves complex pathophysiological mechanisms including genetic or epigenetic factors, inflammatory processes, and central sensitization^{32,33}.

There is growing interest in the overlap between migraine and other chronic pain syndromes such as fibromyalgia and chronic fatigue. Limited direct evidence is available that links PFO to these syndromes; however, the shared mechanisms, such as central sensitization, endothelial dysfunction, and systemic inflammation, suggest a potential common pathway. A bidirectional relationship exists between migraine and fibromyalgia, with fibromyalgia patients showing 1.89 times higher risk of developing migraine, while migraine patients have 1.52 times greater risk of developing fibromyalgia³³. Therefore, the role of pain specialists is vital in managing migraine with comorbid pain syndromes, which requires individualised, multidisciplinary approaches across cardiology and neurology for optimal care for PFO patients.

PFO has been increasingly implicated in migraine and other systemic pain syndromes through various interconnected mechanisms (Table 2). The primary pathway involves right-to-left shunting of blood that bypasses pulmonary filtration, allowing microemboli to enter cerebral circulation and potentially trigger cortical spreading depression, a process linked to migraine aura and pain activation^{32,34,35}. Similarly, bypassing pulmonary clearance allows vasoactive substances (e.g., serotonin, bradykinin) to reach the cerebral circulation, where they can activate pain pathways^{32,35}. PFO has also been associated with impaired cerebral autoregulation, leading to unstable cerebral blood flow and heightened susceptibility to migraine and pain disorders^{32,34}. In addition, genetic predispositions affecting vascular and neural development, or structural brain changes like white matter alterations, have also been observed in migraine patients with PFO³². By enabling the systemic spread of inflammatory mediators and microemboli, PFO may promote systemic inflammation and neurovascular dysfunction, both of which are characteristic of chronic pain syndromes^{32,35}.

Future Directions and Clinical Implications

Closing PFO can enhance cognition and reduce impairment. Early studies have shown promising results; although it is becoming more accepted as a treatment for migraines, the critical aspect to address is conducting rigorous clinical trials: conditions need to be well defined, outcomes clearly specified, and follow-up extended over time. A significant breakthrough involves identifying a unique profile or “fingerprint” pattern linked to headaches presumed to be secondary to PFO; this could ultimately distinguish them from more typical migraines and will be a focus for future research³⁶. Moreover, as the therapeutic options for PFO closure expand, so does the need for personalised medicine. Not all patients with migraines or cryptogenic strokes respond equally well to closure, highlighting the importance of predictive tools to identify the best candidates. Advances in genomics, machine learning, and clinical phenotyping are expected to facilitate personalised risk assessments and outcome predictions in the near future, allowing clinicians to move beyond a generic approach. Although traditional markers such as CGRP and calcium are generally recognised as reliable research biomarkers, emerging techniques like contrast-enhanced transcranial Doppler and high-resolution MRI are being explored for more precise characterisation of shunt dynamics and cerebral perfusion abnormalities³². These developments may help define a neurovascular signature for migraine associated with PFO, leading to more targeted interventions.

As PFO closure is increasingly considered not only for stroke prevention but also for migraine and cognitive issues, it is crucial to consider the ethical aspects of this procedure. The procedure is generally safe and minimally invasive; however, the risks should not be underestimated, especially when it is offered for conditions like chronic migraine, which are not immediately life-threatening. Clear and compassionate communication is vital to inform patients that PFO closure for migraine is still in its early stages and is somewhat experimental. Therefore, informed consent should encompass not only the technical details

Table 2: Pathophysiological Pathways Linking PFO to Systemic Pain

Mechanism or Pathway	Impact on Brain/Pain System	Potential Pain Syndromes Affected
Microemboli & CSD ^{32,34,35}	Microemboli triggers cortical spreading depression, activating pain pathways	Migraine aura, headache
Vasoactive Substance Bypass ^{32,35}	Vasoactive agents bypass lung filtration, enter the brain/systemic circulation	Migraine, systemic pain, central pain sensitisation
Impaired Cerebral Autoregulation ^{32,34}	Disrupted blood flow regulation sensitises pain-processing neural structures	Migraine, chronic pain, fatigue
Genetic/Structural Factors ³²	Shared genetic risk, brain structure changes affecting pain processing	Migraine, chronic pain
Systemic Inflammation ^{32,35}	The passage of inflammatory mediators increases neurovascular dysfunction	Migraine, fibromyalgia, others

CSD: Cortical Spreading Depression; PFO: Patent Foramen Ovale

but also the patient's expectations, potential benefits, and uncertainties. Moving forward, interdisciplinary collaboration will be vital. Cardiologists, neurologists, radiologists, and pain specialists must work together to design trials and contribute to international registries that record outcomes, complications, and patient-reported benefits³⁷. These efforts will help refine clinical guidelines and support the idea that PFO closure could become a paradigm-shifting intervention in neurovascular medicine.

Conclusion

Emerging evidence continues to highlight the complex relationship between patent foramen ovale (PFO), migraine with aura, and systemic pain syndromes. Increasing data suggest that PFO closure could be a promising treatment, especially for patients experiencing aura in more than half of their attacks, who do not respond to standard preventive therapies, and who have a significant right-to-left shunt. However, the varied results from clinical trials emphasise the need for improved patient selection criteria and validated biomarkers. Identifying indicators such as microembolic load, platelet activation profiles, or genetic factors could support more personalised treatments and help avoid unnecessary procedures.

While encouraging, current limitations, including small sample sizes, brief follow-up periods, and differences in diagnostic and procedural standards across studies, highlight the need for standardised protocols and large, multicentre randomised trials to yield more definitive evidence of causality and benefit. Future research should focus on collaboration among neurologists, interventional cardiologists, and translational scientists to develop integrated diagnostic, risk assessment, and follow-up tools after PFO closure. As our understanding of underlying mechanisms advances, PFO closure—guided by specific biomarkers and patient-centred approaches—could become a targeted treatment for refractory migraine, potentially improving outcomes and quality of life for patients.

Acknowledgment

The authors received no financial support for the research, authorship, or publication of this manuscript. No external contributions were involved in the development of this work.

Conflict of Interest

The authors declare no conflict of interest related to this study.

References

1. Ten questions on patent foramen ovale | Italian Journal of Cardiology - Official Journal of the Italian Federation of Cardiology and the Italian Society of Cardiac Surgery. Available from: <https://www.giornaledicardiologia.it/archivio/4521/articoli/45210/>
2. Miranda B, Fonseca AC, Ferro JM. Patent foramen ovale and stroke. *J Neurol*. 2018; 265(8): 1943-9. Available from: <https://pubmed.ncbi.nlm.nih.gov/29680895/>
3. Kumar P, Kijima Y, West BH, et al. The Connection Between Patent Foramen Ovale and Migraine. *Neuroimaging Clin N Am*. 2019; 29(2): 261-70. Available from: <https://pubmed.ncbi.nlm.nih.gov/30926116/>
4. Sposato LA, Albin CSW, Elkind MSV, et al. Patent Foramen Ovale Management for Secondary Stroke Prevention: State-of-the-Art Appraisal of Current Evidence. *Stroke*. 2024; 55(1): 236-47. Available from: <https://pubmed.ncbi.nlm.nih.gov/38134261/>
5. Patent Foramen Ovale - PubMed. Available from: <https://pubmed.ncbi.nlm.nih.gov/29630203/>
6. Paradoxical Embolism - StatPearls - NCBI Bookshelf. Available from: <https://www.ncbi.nlm.nih.gov/sites/books/NBK470196/>
7. Hara H, Virmani R, Ladich E, et al. Patent foramen ovale: current pathology, pathophysiology, and clinical status. *J Am Coll Cardiol*. 2005; 46(9): 1768-76. Available from: <https://pubmed.ncbi.nlm.nih.gov/16256883/>
8. Shah AH, Horlick EM, Kass M, et al. The pathophysiology of patent foramen ovale and its related complications. *Am Heart J*. 2024; 277: 76-92. Available from: <https://pubmed.ncbi.nlm.nih.gov/39134216/>
9. Kumar P, Tobis JM. The Multiple Clinical Manifestations of Patent Foramen Ovale. *Struct Heart*. 2020; 4: 159-68. Available from: <https://doi.org/10.1080/24748706.2020.1733719>
10. Cheng T, Gonzalez JB, Testai FD. Advances and ongoing controversies in PFO closure and cryptogenic stroke. *Handb Clin Neurol*. 2021; 177: 43-56. Available from: <https://doi.org/10.1016/B978-0-12-819814-8.00009-3>
11. Rakhimova I, Semenova Y, Khaibullin T, et al. Cryptogenic Stroke and Embolic Stroke of Undetermined Source: Risk Factors and Approaches for Detection of Atrial Fibrillation. *Curr Cardiol Rev*. 2022; 18: e211221199213. Available from: <https://doi.org/10.2174/1573403X18666211221145714>
12. Kumar S, Selim MH, Caplan LR. Medical complications after stroke. *Lancet Neurol*. 2010; 9: 105-18. Available from: [https://doi.org/10.1016/S1474-4422\(09\)70266-2](https://doi.org/10.1016/S1474-4422(09)70266-2)
13. Kent DM, Dahabreh IJ, Ruthazer R, et al. Anticoagulant vs. antiplatelet therapy in patients with cryptogenic stroke and patent foramen ovale: an individual participant data meta-analysis. *Eur Heart J*. 2015; 36: 2381-9. Available from: <https://doi.org/10.1093/eurheartj/ehv252>
14. Pan X, Xu L, Zhou C, et al. Meta-analysis of patent foramen ovale closure versus medical therapy for prevention of recurrent ischemic neurological events: Impact of medication type. *Medicine (Baltimore)*. 2021; 100: e26473. Available from: <https://doi.org/10.1097/MD.00000000000026473>
15. Hammad A, Ahmad A, Khraisat O, et al. Patent foramen ovale closure vs medical therapy in secondary prevention of stroke and TIA: A systemic review and meta-analysis. *Cardiovasc Revasc Med*. 2025. Available from: <https://doi.org/10.1016/j.carrev.2025.06.037>
16. Liu Y, Wu Y, Xiong L. Surgical vs. drug therapy in patients with patent foramen ovale and cryptogenic stroke. *Herz*. 2021; 46: 250-4. Available from: <https://doi.org/10.1007/s00059-020-04921-3>
17. Liu K, Wang BZ, Hao Y, et al. The Correlation Between Migraine and Patent Foramen Ovale. *Front Neurol*. 2020. Available from: <https://doi.org/10.3389/fneur.2020.543485>
18. Diving into the Comorbidity Between Migraine and Patent Foramen Ovale n.d. Available from: <https://www.migrainedisorders.org/diving-into-the-connection-between-migraine-and-patent-foramen-ovale/>

19. Tembl J, Lago A, Sevilla T, et al. Migraine, patent foramen ovale and migraine triggers. *J Headache Pain*. 2007; 8: 7-12. Available from: <https://doi.org/10.1007/s10194-007-0359-x>
20. Dowson A, Mullen MJ, Peatfield R, et al. Migraine Intervention With STARFlex Technology (MIST) Trial: A Prospective, Multicenter, Double-Blind, Sham-Controlled Trial to Evaluate the Effectiveness of Patent Foramen Ovale Closure With STARFlex Septal Repair Implant to Resolve Refractory Migraine Headache. *Circulation*. 2008; 117:1397-404. Available from: <https://doi.org/10.1161/CIRCULATIONAHA.107.727271>
21. Mattle HP, Evers S, Hildick-Smith D, et al. Percutaneous closure of patent foramen ovale in migraine with aura, a randomized controlled trial. *Eur Heart J*. 2016; 37: 2029-36. Available from: <https://doi.org/10.1093/eurheartj/ehw027>
22. Tobis JM, Charles A, Silberstein SD, et al. Percutaneous Closure of Patent Foramen Ovale in Patients With Migraine. *J Am Coll Cardiol*. 2017; 70: 2766-74. Available from: <https://doi.org/10.1016/j.jacc.2017.09.1105>
23. Zhang Y, Wang H, Liu L. Patent Foramen Ovale Closure for Treating Migraine: A Meta-Analysis. *J Intervent Cardiol*. 2022. Available from: <https://doi.org/10.1155/2022/6456272>
24. Danese E, Montagnana M, Lippi G. Platelets and migraine. *Thromb Res*. 2014; 134: 17-22. Available from: <https://doi.org/10.1016/j.thromres.2014.03.055>
25. Li C, Yu Y, Li N, et al. Calcitonin gene-related peptide: a possible biomarker in migraine patients with patent foramen ovale. *BMC Neurol*. 2024. Available from: <https://doi.org/10.1186/s12883-024-03615-1>
26. Dong B, Li X, Zhang L, et al. Effects of patent foramen ovale in migraine: a metabolomics-based study. *J Physiol*. 2025; 603: 809-35. Available from: <https://doi.org/10.1113/JP286772>
27. Evola S, Camarda EA, Triolo OF, et al. Clinical Outcomes and Quality of Life after Patent Foramen Ovale (PFO) Closure in Patients with Stroke/Transient Ischemic Attack of Undetermined Cause and Other PFO-Associated Clinical Conditions: A Single-Center Experience. *J Clin Med*. 2023. Available from: <https://doi.org/10.3390/jcm12185788>
28. Eltelbany M, Gattani R, Ofosu-Somuah A, et al. Transcatheter PFO closure for cryptogenic stroke: current approaches and future considerations. *Front Cardiovasc Med*. 2024. Available from: <https://doi.org/10.3389/fcvm.2024.1391886>
29. Mojadidi MK, Kumar P, Mahmoud AN, et al. Pooled Analysis of PFO Occluder Device Trials in Patients With PFO and Migraine. *J Am Coll Cardiol*. 2020; 77: 667-76. Available from: <https://doi.org/10.1016/j.jacc.2020.11.068>
30. Mi Z, He G, Li C, et al. Efficacy and safety of transesophageal ultrasound-guided patent foramen ovale closure for migraine in adolescents. *Front Pediatr*. 2023. Available from: <https://doi.org/10.3389/fped.2023.1296825>
31. Muthyala N, Qadrie ZL, Suman A. Migraine & Migraine Management: A Review. *Pharmatutor*. 2018. Available from: <https://doi.org/10.29161/PT.v6.i4.2018.8>
32. Cao W, Shen Y, Zhong J, et al. The Patent Foramen Ovale and Migraine: Associated Mechanisms and Perspectives from MRI Evidence. *Brain Sci*. 2022. Available from: <https://doi.org/10.3390/brainsci12070941>
33. Penn IW, Chuang E, Chuang TY, et al. Bidirectional association between migraine and fibromyalgia: retrospective cohort analyses of two populations. *BMJ Open*. 2019. Available from: <https://doi.org/10.1136/bmjopen-2018-026581>
34. Nozari A, Dilekoz E, Sukhotinsky I, et al. Microemboli may link spreading depression, migraine aura, and patent foramen ovale. *Ann Neurol*. 2010; 67: 221-9. Available from: <https://doi.org/10.1002/ana.21871>
35. Fuller CJ, Jesurum JT. Migraine and Patent Foramen Ovale: State of the Science. *Crit Care Nurs Clin North Am*. 2009; 21: 471-91. Available from: <https://doi.org/10.1016/j.ccell.2009.07.011>
36. Reisman M, Fuller CJ. Is patent foramen ovale closure indicated for migraine? *Circ Cardiovasc Interv*. 2009; 2: 468-74. Available from: <https://doi.org/10.1161/CIRCINTERVENTIONS.109.876128>
37. Liu J, Liu Y, Sheng Y. Global research trends and frontiers in patent foramen ovale closure: a comprehensive bibliometric analysis (2004-2024). *Front Neurol*. 2025. Available from: <https://doi.org/10.3389/fneur.2025.1618910>