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REVIEW ARTICLE

Migraine and patent foramen ovale: correlation, coexistence, dependence. A narrative review

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Abstract

Objective: This review was conducted to analyze the current knowledge on the topic of the relation between migraine and patent foramen ovale (PFO) and indicate the most crucial clinical implications.

Background: Migraine is a primary headache disorder that affects a significant part of the global population. Importantly, it has been considered a risk factor for ischemic stroke, especially in women with migraine with aura. The foramen ovale is a physiological opening in the atrial septum formed during fetal life, which closes in most people in the first year after birth. However, in some people, it can be present in adulthood and is called the patent foramen ovale. PFO is more likely to occur in patients with migraine compared to the population not experiencing migraine headaches.

Methods: Two review teams, comprising migraine experts and stroke experts, were engaged in the screening process, resulting in the inclusion of 204 relevant publications. To be considered for inclusion, an article had to directly cover the topic of PFO or migraine.

Results: In the following work, we have focused on several aspects regarding the direct and indirect relationship between migraine and PFO. Although analyzing migraine pathogenesis, apart from the straight link between PFO and migraine, others are also considered, such as a prominent Eustachian valve or Chiari valve, causing a high-risk PFO or a paradoxical embolism. Regarding the clinical practice, the prevalence of PFO and migraine, indications for exact therapies, and subsequently, neuroimaging in the view of PFO and migraine, have been scrutinized. Another crucial aspect of this review is the risk of stroke in patients with migraine, considering the PFO presence. It is suggested that patients with migraine have more vascular lesions on magnetic resonance imaging and more often experience strokes. Thus, the question arises whether PFO should be closed as stroke prophylaxis in every migraine patient.

Abbreviations: AF, atrial fibrillation; ASA, atrial septal aneurysm; CN, Chiari-network; CSD, cortical spreading depression; ED, endothelial dysfunction; EV, Eustachian valve; IS, ischemic stroke; MA, migraine with aura; MIDAS, Migraine Disability Assessment Scale; MO, migraine without aura; MRI, magnetic resonance imaging; OR, odds ratio; PCT, plateletcrit; PFO, patent foramen ovale; RCT, randomized controlled trial; RLS, right-to-left shunt; SCs, stroke chameleons; SMs, stroke mimics; TCD, transcranial Doppler ultrasonography; TEE, transesophageal echocardiography; TIA, transient ischemic attack.

Conclusions: Several aspects have been explored; however, more research is needed to draw clear conclusions with further indications for clinical practice. Nevertheless, it seems that not in all patients with migraine with PFO should the closure procedure be performed, but when the PFO is of a high-risk form or there are other indications, it should at least be considered.

Plain Language Summary

This review looked at what scientists know about the connection between migraine and a small heart opening called a patent foramen ovale (PFO). It showed that people with migraine, especially with aura, often have PFO, but it is not certain whether closing this heart opening helps prevent strokes in these patients. More studies are needed, but closing PFO could be considered for some people with migraine with other indications, who have a high-risk type of PFO.

KEYWORDS
ischemic stroke, migraine, patent foramen ovale, primary headache disorders, right-to-left shunt

INTRODUCTION

Migraine is a very common disease of the nervous system and is characterized by the occurrence of spontaneous, recurrent headaches with autonomic symptoms. The pathophysiology of a migraine attack remains not entirely clear. Among the many hypotheses regarding the mechanism of its occurrence, the neurovascular theory, including disturbances in blood flow through cerebral vessels caused by a pathological vascular reaction combined with neuronal disorders, is considered by most researchers to be primary. At some point, it has been suggested that the reduction in cerebral blood flow during a migraine attack is related to the spread of the so-called cortical inhibition, depression of neuronal activity (cortical spreading depression [CSD]), and is a secondary phenomenon.[1–3] The recent study by Mehnert et al.[4] demonstrated that in all patients with migraine, regardless of aura presence, the attack starts in the hypothalamus. Thus, the aura should not be understood as blood flow disturbances preceding pathogenetic alterations leading to headache, but rather as the downstream event. Nevertheless, the possibility of blood flow changes participating in migraine pathogenesis, especially in aura, is supported by the more frequent occurrence of patent foramen ovale (PFO) in patients with migraine with aura (MA)[5–7]; however, it is more likely to begin after the molecular changes responsible for migraine headache.

The foramen ovale is a physiological opening in the interatrial septum of the heart, which is formed during fetal life and closes after birth in most people. Some healthy people have an inactive opening in place of the fetal foramen ovale, called a persistent foramen ovale, surrounded by a rim of connective tissue of the septum, forming a kind of valve. When the pressure in the right atrium increases, exceeding the pressure in the left atrium (e.g., during the Valsalva maneuver), this may be enough to open such a valve and unblock the foramen ovale. In this situation, with the clear foramen, we named it PFO.[8] The diagnostic methods for detecting PFO are transesophageal echocardiography (TEE) and transcranial Doppler ultrasonography (TCD). The topic of the relationship or just coexistence of migraine and PFO has been discussed for many years in scientific literature, both from a clinical perspective and from a potential therapeutic perspective.[9] It remains unresolved to date. Therefore, the authors of this narrative review undertook a summary of the current knowledge on this topic with an attempt to draw conclusions that can serve clinicians in making further decisions.

METHODOLOGY

Literature search

The comprehensive literature search was performed between March 20, 2025, and April 17, 2025. The high value, peer-reviewed articles were taken into consideration. Databases, including the PubMed Database and the Embase Database, were searched with additional inclusion of appropriate articles found in the reference lists. To find adequate publications, the following Medical Subject Headings terms were implicated: embolism, paradoxical; foramen ovale, patent; ischemic stroke; migraine disorders; migraine with aura; migraine without aura; stroke; with additional terms, not included among the Medical Subject Headings vocabulary, such as Chiari network; endothelial dysfunction; Eustachian valve; migraine aura; migraine pathogenesis; patent foramen ovale closure; stroke chameleons; and stroke mimics. The aspects covered in the review have been summarized in Figure 1.

Inclusion criteria

The eligible studies were those covering the broad topic of migraine of any type concerning PFO or stroke. Studies should primarily include

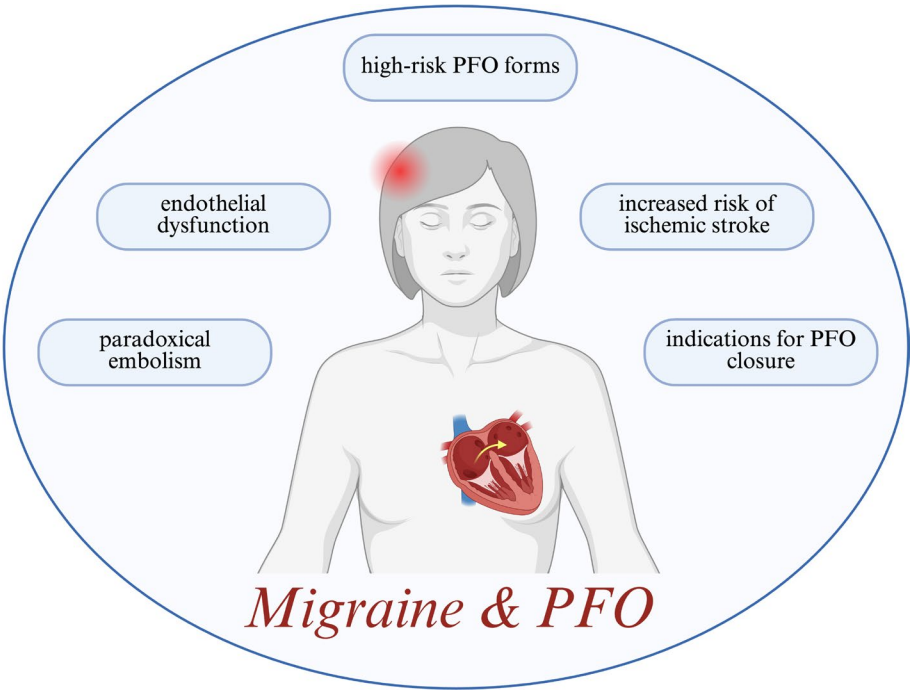

FIGURE 1 A graphical summary of aspects regarding migraine and patent foramen ovale (PFO) analyzed in the review, such as high-risk PFO, including large size, prominent Eustachian valve or Chiari network, endothelial dysfunction, as a common element pathogenesis of PFO and migraine, the increased risk of ischemic stroke, related, but not only, to paradoxical embolism, and finally, the putative indications for PFO closure. [Color figure can be viewed at wileyonlinelibrary.com]

adult populations; however, when strictly linked to the review topic, research on pediatric patients was allowed. The exclusion was based on the article type (conference abstracts), article language (other than English or Polish), and article topic (not related to the review).

Selection process

The search for eligible articles was performed by two teams: migraine experts and stroke experts, resolving discrepancies by discussion. The final selection led to the inclusion of 143 relevant publications.

MIGRAINE PATHOGENESIS

Migraine pathogenesis and PFO existence

PFO can be found in patients with migraine more frequently. Although there are debates about whether PFO is related to migraine in general or only MA, the statement that migraine is linked to PFO is likely to be relevant.[10–12] Furthermore, some suggest it may be true only for the association between migraine and large PFO.[13] Currently, one of the possible theories says that vasoactive chemicals from the venous circulation, as a result of PFO presence, can omit the pulmonary filters and reach the cerebral vascular system, leading to migraine attacks in susceptible individuals.[12,14] Those chemicals, for instance, serotonin, are known to trigger migraine attacks, but in patients without PFO, they cannot access the brain.[12,14] Genetics, impaired cerebral autoregulation, and microembolisms are listed among other factors suggested to underlie this pivotal correlation.[15] Wilmshurst et al.[16] performed a study to indicate the potential inheritance of right-to-left shunt (RLS) and its role in the inheritance of MA. The researchers demonstrated that the RLS was likely to be inherited in an autosomal dominant manner. Moreover, when a proband had migraine, other family members with migraine were more likely to have a sizeable atrial shunt.[16] According to impaired cerebral autoregulation, Guo et al.[17] demonstrated that patients with migraine with RLS had disturbed cerebral autoregulation in comparison to patients without RLS. Moreover, this was also true when comparing participants with large RLS and small RLS.[17] Finally, the most likely hypothesis about the link between migraine and PFO is microemboli presence, which can trigger CSD.[15] CSD is associated primarily with MA, which will be described thoroughly below.[15,18] However, CSD is suggested to play a role in migraine headaches as well, not only in MA.[18] In rodents, CSD was responsible for both immediate and delayed activation of the trigeminovascular system, possibly leading to aura and headache, respectively.[18,19]

Migraine pathogenesis and paradoxical embolism

Paradoxical embolism is a relatively rare cause of acute occlusion of the artery, leading to ischemia of the body organs supplied by

it.[20] It has been described as another factor playing a presumptive role in migraine pathogenesis and susceptibility. Current data suggest that paradoxical embolisms, by reaching the central nervous system, can not only be the cause of cerebrovascular events, such as stroke, as is mainly known,[20] but also other neurological conditions, such as Alzheimer's disease[21] or migraine.[22,23] Rigatelli[23] reviewed the available literature, concluding that patients with migraine with PFO have larger RLS compared to patients with PFO but without migraine. Moreover, this large shunt increased the risk of paradoxical embolism, which is one of the explanations for higher ischemic stroke (IS) rates in patients with migraine.[23] However, the migraine–stroke relation is not what we focus on in this subparagraph. It has been hypothesized that the large RLS due to the PFO's existence not only increases the risk of IS but is also related to migraine attacks themselves.[24] Dao et al.[25] conducted a study to analyze patients for potential PFO closure. Apart from stroke survivors, patients with other conditions related to PFO and paroxysmal embolism were also included. Among 416 patients, 38 had significant migraine headaches. The authors also presented a specific case of a patient whose migraine significantly decreased in severity after the PFO closure, thus hypothesizing that PFO and paradoxical embolism may be essential factors influencing the course of migraine. On the other hand, in the randomized control trial (RCT) conducted by Dowson et al.,[26] although the higher prevalence of PFO in migraine has been demonstrated, the PFO closure did not affect the primary or secondary end points compared to the control group, which were respectively: (1) migraine cessation, and (2) change in severity, frequency, and characteristics of migraine attacks. Thus, it was suggested that even though PFO is more frequent in migraine, the paradoxical embolism is not likely to induce or affect migraine course.[26,27]

Migraine pathogenesis and prominent Eustachian valve or Chiari-network

The Eustachian valve (EV) is a part of the right sinus venosus valve, particularly its intermediate part, which persisted from embryonic development.[28] It is prenatally responsible for inducing the flow of blood rich in oxygen through the foramen ovale to the left atrium. It physiologically starts to involute between 9 and 15 weeks of pregnancy, completing the process in the first years after birth.[28] However, in some cases, EV persists in the form of a floating membrane of varying sizes in the right atrium.[28] Increasing evidence suggests that persistent EV may increase the risk of paroxysmal embolism.[28,29] PFO accompanied by EV, similar to the large PFO mentioned above, is called "a dangerous form" of PFO or a high-risk PFO.[29] Kato et al.[30] described a patient with a giant EV and PFO, causing a significant RLS demonstrated in echocardiography. A patient had a history of recurrent migraine attacks, particularly hemiplegic migraine with recurrent transient hemiparesis, and finally, with migraine complications, including several migraine-triggered seizures.

Another type of right atrium remnant is a Chiari-network (CN), first described by Hans Chiari at the end of the 19th century,[31] a thin membrane that also persisted from embryonic development as an anatomical variation.[32,33] CN may be a source of a thrombus and, in combination with PFO, lead to cerebral or peripheral ischemia.[33] Thus, like EV, when CN coexists with PFO, it is considered a high-risk PFO.[29] According to the study conducted by Trabattoni et al.,[34] CN was observed in 19.9% of PFO patients, whereas EV was observed in 9% of PFO patients. Rigatelli et al.[35] explored the role of EV and CN in patients with migraine. In the echocardiography of patients with migraine, a prominent EV or CN was revealed in 82% of patients with migraine in comparison to 55.5% of patients without migraine. According to the migraine type, the presence of EV or CN was observed in 100% of individuals with MA and 60% of those without aura.[35]

Migraine pathogenesis and endothelial dysfunction

Endothelium, a simple monolayer lining the inner walls of vessels, plays a pivotal role in vascular homeostasis.[36] Endothelial dysfunction (ED) can also be called endothelial activation, which is not currently needed and leads to arterial disease.[36,37] The potential association between migraine and ED is suggested in the CSD phenomenon, which leads to increased permeability of the blood–brain barrier, endothelial damage, inflammation, and subsequent trigeminovascular neuron activation. All these alterations result in a microenvironment that promotes hypercoagulation.[38] Tietjen et al.[38] reviewed the existing literature to determine whether migraine, hypercoagulability, and PFO are linked. The researchers demonstrated that migraine, particularly with aura, correlated with increased levels of factors, such as von Willebrand factor antigen, fibrinogen, tissue plasminogen activator antigen, and endothelial microparticles, as well as thrombocytosis and erythrocytosis. Moreover, MA in patients with stroke correlated with both the thrombophilic state and PFO.[38] Lantz et al.[39] assessed endothelial function in patients with cryptogenic stroke and PFO and those with migraine. Patients with migraine did not differ significantly from healthy controls in terms of reactive hyperemia index, which stands for endothelial function (the lower score, the more impaired function). However, what can be considered interesting is that most included patients had scores indicating ED.[39] Undoubtedly, some results are contradictory, and the literature is lacking. More research is needed on this part of pathogenetic insights to draw clear conclusions.

Migraine aura from the view of PFO

There is various evidence about the correlation between PFO and not only migraine in general or MA, but strictly, migraine aura. It is believed that PFO, usually with specific variants, so-called high-risk PFO, may lead to microemboli and ischemic events.[29] Those

microemboli can, but do not necessarily, cause a transient ischemic attack (TIA) or IS; however, they may also trigger CSD.[40] In a mouse model designed by Nozari et al.,[41] air microemboli caused CSD in all mice but not infarction. Additionally, cholesterol crystals and polystyrene microspheres led to CSD in eight of 12 and eight of 16 mice, respectively. In comparison, the infusion of normal saline did not result in CSD in any case. The authors, thus, concluded that the presence of PFO, allowing venous microembolisms to reach the brain, may cause CSD and, hence, migraine aura in susceptible patients.[41] Similarly, iatrogenic microemboli in humans were able to provoke migraine aura.[42] Hadjikhani et al.[43] conducted a study evaluating functional magnetic resonance imaging (MRI) in patients with migraine, particularly during the aura phase. The researchers assessed blood oxygen level–dependent signal changes, representing the CSD phenomenon, and presented that those changes were consistent with clinical aura.[43]

MIGRAINE AND PFO IN CLINICAL PRACTICE

Epidemiology

The incidence of PFO was assessed in vivo in the healthy population and in autopsy studies of people who died. In postmortem studies, the incidence of anatomically detected PFO was estimated at an average of 26% (17%–35%).[7] Small (diameter, 0.2–0.5 cm) foramen ovale was found in 29% and larger (0.6–1.0 cm) foramen ovale was found in 6% of cases.[9] Echocardiographic studies conducted in healthy individuals showed that the incidence of PFO is, according to various authors, 8%–26%[44–48] and decreases with age, which may be related to the gradual closure of PFO during the aging process. It is believed that in people under 55 years of age, the incidence of PFO is independent of age.[49] In older people, PFO is detected less frequently.[50] In patients with cryptogenic IS, the incidence of PFO is in patients <55 years of age is approximately 46% and in patients >55 years of age, it is approximately 21%. In some studies, PFO was found in 40% of all patients with migraine, including 54% of patients with MA and 46% of patients with migraine attacks with aura only, compared with 25% of patients with migraine without aura (MO) and 25% of control individuals.[51] This study included 62 patients (48 women) with MA, 60 patients (53 women) with MO, and 65 healthy individuals (51 women). Del Sette et al.[52] demonstrated the presence of RLS in 41% of patients with MA, compared with 16% of the control group and 35% of patients with IS. Similarly, Anzola et al.[53] found PFO in 48% of patients with MA, compared to 23% of patients with MO and 20% of healthy controls.

Domitrz et al.[54] conducted the study on a group of 121 patients: 61 patients with MA, 60 with MO, and 65 healthy controls. To detect PFO, contrast TCD was performed during the Valsalva maneuver, and the presence of PFO was found in 54% of patients with MA compared to 25% of those with MO and 25% of the control group. The difference between patients with MA and patients with MO, and the difference between patients with MA and the control group, was statistically significant. There was no association between the type of migraine aura and PFO, nor did we find any association between PFO and the frequency of attacks, familial occurrence, sex, or age of patients, and PFO. In another study, the occurrence of PFO, atrial septal aneurysm (ASA), and mitral valve prolapse was assessed in 96 patients with MO (87 females), in 62 patients with MA (41 females), and 53 healthy people (40 females).[55] In comparison with the control group, only the prevalence of PFO was statistically higher in patients with migraine (35%), especially with aura (43.5%), compared to controls (21%). There were no statistically significant differences between the occurrence of ASA or mitral valve prolapse in migraine and control groups.

On the other hand, a Chinese study on a group of 3741 people over 20 years old (regardless of PFO or migraine features) confirmed the presence of PFO in 881 people.[56] The prevalence of MO in the PFO group was 12.83%, significantly higher than in the group without PFO (7.83%). Analyses of the matched samples showed that the presence of a PFO increased the risk of MO ($p < 0.001$; odds ratio (OR), 1.71; 95% confidence interval [CI], 1.19–2.47). Older results indicating a higher incidence of PFO in the migraine group were confirmed by a recent meta-analysis by Chinese researchers.[57] The authors screened various databases, and a total of 27 studies involving 8875 participants were included in their work. The results indicated a statistically significant association between PFO and migraine prevalence. Overall, individuals with migraine had higher rates of PFO compared to healthy controls. This association was stronger in the MA group. Summarizing, all the studies confirm that PFO occurs more frequently in patients with migraine, and it is particularly frequent among patients with MA.

PFO closure in migraine

Following the advent of catheter-based therapies, PFO closure has emerged as a practical solution to the problem of diseases that can be associated with PFO, including migraine, and the effect of PFO closure on migraine has been a subject of debate for over 20 years.[58] PFO closure alone does not usually lead to the disappearance of migraine attacks; however, some controlled studies[59–62] and many observational studies report improvement of migraine following PFO closure and often the disappearance of migraine aura.[63–68] Similarly, in the study by Ben-Assa et al.,[69] long-term follow-up after transcatheter PFO closure was associated with significant improvement in migraine burden, and the presence of aura was a predictor of symptom disappearance. Almost all observational studies of PFO closure suggesting improvement in migraine were conducted in individuals with a history of stroke or divers' decompression sickness, and these patients were not representative of the migraine population.[70]

According to the issue of reducing the mean number of migraine days and the total number of attacks, three major RCTs did not meet their primary efficacy end points. The Prospective, Randomized

Investigation to Evaluate Incidence of Headache Reduction in Subjects with Migraine and PFO Using the AMPLATZER PFO Occluder to Medical Management double-blind study of 230 patients with migraine with and without aura and PFO with large RLS did not meet its primary end point of at least a 50% reduction in migraine attacks compared with sham control (38.5% of participants in the study group vs. 32% of people in the control group).[71] However, a significant decrease in the mean number of migraine days per month was observed in the study group.[71] Similarly, the Migraine Intervention with STARFlex Technology study failed to achieve its intended end points—complete remission of migraine as the primary end point and ≥50% reduction in headache days as a secondary end point after 6 months of follow-up.[26] The Percutaneous Closure of PFO in Migraine with Aura study, although PFO closure reduced the number of migraine days with aura and migraine attacks with aura, did not reach a ≥50% reduction in headache days after 1 year of follow-up.[72] Also, in the CLOSE-MIG randomized trial in patients with cryptogenic stroke associated with PFO and migraine, transcatheter PFO closure combined with antiplatelet therapy did not reduce the mean annual number of migraine attacks (with or without aura) compared with antiplatelet therapy alone during a 5-year follow-up.[73] PFO closure did not result in either the complete disappearance of migraine attacks or a reduction in the use of migraine preventive therapy. The only significant difference was a reduction in the annual number of attacks with aura in patients with MA attributed to PFO closure.[73] The cited studies evaluating the effect of percutaneous PFO closure on migraine severity are included in Table 1. Additionally, PFO closure resulted in the improvement of hemiplegic migraine in several described case patients, especially the disappearance of aura.[74]

However, does percutaneous PFO closure not reduce the burden of migraine? It should be noted that in the cited studies, despite the lack of expected end points, often unrealistic, in the form of complete migraine relief, there was a significant improvement in migraine. At the same time, several available meta-analyses of RCTs have shown that transcatheter PFO closure can significantly improve symptoms in patients with migraine in terms of reducing the number of migraine days, shortening migraine attacks, and reducing the frequency of attacks. Moreover, it may be possible to help some patients experiencing migraine with a complete removal of symptoms.[76–80] However, this benefit was not associated with improved response rates or complete resolution of migraine; this raises concerns about the magnitude of the clinical benefit of PFO closure in migraine prophylaxis[77] while significantly reducing the risk of recurrent stroke after PFO closure in cryptogenic stroke.[73] Some researchers, however, believing in the persistent denial of the benefits of PFO closure in patients with migraine, especially with aura, ignore the fact that PFO closure in these patients has the additional benefit of protection against paradoxical emboli, and these patients could be suitable targets for PFO closure in the primary prophylaxis of paradoxical embolism.[67,81]

Currently, research is focused on selecting patients who may benefit most from percutaneous PFO closure for migraine and on finding appropriate biomarkers. Sommer et al.[82] performed a study of patients with migraine with PFO treated with thienopyridines that inhibit the P2Y12 receptor (clopidogrel and prasugrel in nonresponders). P2Y12 inhibitors were used as off-label agents in migraine headache therapy. None of the participants had other indications to take antiplatelet medications. The platelet reactivity units testing was performed initially in 17 responders to set the threshold value (a minimum value to cause migraine relief), which was identified as <140. Out of the rest participants, those who had the platelet reactivity units test value over 140 were offered the course of prasugrel instead. The researchers observed not only a reduction in migraine frequency after achieving adequate platelet inhibition but also a strong correlation between antiplatelet response and benefit from subsequent PFO closure, as thienopyridine-responsive patients were offered PFO closure.[82] Of the patients with PFO closure, 94% showed sustained improvement in symptoms 3 months after discontinuing antiplatelet therapy, which was not observed in the group without PFO closure.[82] In a recent study, a nomogram model was constructed to predict migraine remission by assessing factors influencing prognosis in patients with migraine with PFO after its closure. Significant predictors that were identified included high Migraine Disability Assessment Scale (MIDAS) score before closure, presence of mitigating factors, lower frequency of migraine attacks, large leakage on TCD, and elevated plateletcrit (PCT) (PCT = platelet count × mean platelet volume/10,000), although no direct association between PCT and migraine has been reported in the literature at present.[83] In a study conducted in China among 139 patients with migraine after PFO closure, the incidence of headache nonremission after the procedure was 33.09%. Smoking history, atrial fibrillation (AF), absolute lymphocyte count, platelet-to-lymphocyte ratio, and interventricular septum thickness were established as independent risk factors for headache nonremission after percutaneous PFO closure.[84] One study showed that PFO closure was associated with improvement in headache with concomitant increases in cystatin C, a neuroendocrine polypeptide implicated in many vascular diseases, and calcium, both of which were reduced in patients with MA and PFO.[85]

It should also be emphasized that after PFO closure, complications might occur, the frequency of which ranged from 0% to 12%, depending on the study. The most common complications were AF and inguinal hematoma; TIA, IS, and infective endocarditis were rare.[70] Transcatheter closure of PFO may also be a factor in triggering migraine, mainly with aura, which occurred in 7%–15% of patients after the procedure,[86,87] whereas the addition of clopidogrel to aspirin for 3 months after the procedure resulted in a lower frequency of new migraine attacks.[88]

There are no RCTs available to support PFO closure for conditions other than cryptogenic stroke, including migraine. However, this procedure appears to be most promising in patients with frequent aura or those who respond to P2Y12 inhibitors. Further clinical trials are needed to identify the specific patients with migraine who would benefit most from PFO closure.[58] Currently recruiting, the GORE RELIEF (randomized, blinded, placebo-, and sham-controlled trial) aims to optimize patient selection for

TABLE 1 A summary of the studies evaluating the effect of percutaneous PFO closure on patients with migraine, including, primarily, migraine severity, frequency, and migraine burden.

References	Country	Study design	MIG pts	Follow-up	Results
Kimmelstiel et al. 2007[59]	USA	Controlled study	*n* = 41	3 m	• 83% ↓ in MIG frequency • ↓ in MIG severity and MIDAS score • ↓ in the discontinuing medications use in 71% pts
Biasco et al. 2014[60]	Italy	Case–control study	*n* = 89 MA = 67	46 m	• NSD in MIDAS score ↓ • clinical benefit or MIG relief
Anzola et al. 2006[61]	Italy	Case–control study	*n* = 50 MA = 33	12 m	• the overall MIG score improved significantly in the study group (independent of MIG type, age and cerebrovascular risk factors) • aura disappeared significantly in the study group
Vigna et al. 2009[62]	Italy	Case–control study	*n* = 53 MA = 33	6 m	• larger ↓ in the number of all attacks in the study group • significant ↓ in the number of disabling attacks only in the study group • MIG relief in 34% of the study group • >50% ↓ in attacks in 87% of the study group
Schwerzmann et al. 2004[63]	Switzerland	Observational study	*n* = 48 MA = 37	24 m	• the headache attacks frequency ↓ by 54% in MA and 62% in MO • no ↓ in the headache attacks frequency in another headache group
Post et al. 2004[64]	Belgium	Observational study	*n* = 26 MA = 12	6 m	• significant and sustained ↓ in the MA incidence • ↓ in the frequency of migraine attacks
Trabattoni et al. 2011[65]	Italy	Observational study	*n* = 77 MA = 13	28 m	• significant ↓ (>50%) in the number and intensity of attacks in 60.5% pts • MIG disappeared in 46% pts and ↓ MIG recurrences frequency observed in 40% during 12-month follow-up • overall improvement of MIG in 89% of pts
Rigatelli et al. 2012[66]	Italy	Observational study	*n* = 80 MA = 63	11 m	• 87.5% of pts reported improvement in MIG symptoms (MIDAS scale), 12.5% reported no improvement, none of the pts reported worsening of MIG symptoms • auras ultimately cured in 96.8% of MA pts
Tarantini et al. 2015[68]	Italy	Observational study	*n* = 120 MA = 96	51 m	• complete resolution of MIG attack in 44% • reduction of symptoms in 49% of pts • 7% pts had no improvement—all pts with aura resulted completely free of aura symptoms
Wahl et al. 2010[75]	Switzerland	Observational study	*n* = 150 MA = 96	59 m	• MIG headaches improved by at least 79% pts, including 34% with complete MIG relief, an effect which for 5 years
Ben-Assa et al. 2020[69]	USA	Observational study	*n* = 110 MA = 85	36 m	• ↓ in MIG burden by >50% in 87.0% pts and symptoms completely resolved in 48% • presence of aura was associated with MIG resolution 6 months after PFO closure • the absence of RLS was associated with an improvement in MIG severity by >50%
Tobis et al. 2017[71]	USA	Randomized, double-blind, sham-controlled clinical trial	*n* = 123 MA = 80	12 m	• no 50% or more ↓ in MIG attacks in the study group • significantly greater ↓ in headache days in the study group • complete MIG remission lasting 1 year in 8.5% pts in the study group; 1% in the control group

(Continues)

TABLE 1 (Continued)

References	Country	Study design	MIG pts	Follow-up	Results
Dowson et al. 2008[26]	Great Britain	Randomized, double-blind, sham-controlled clinical trial	*n* = 74 MA = 74	6 m	• NSD in MIG headache relief between groups • greater ↓ in total MIG headache days in the study group
Mattle et al. 2016[72]	Multicenter	Randomized, double-blind, controlled trial	*n* = 53 MA = 53	12 m	• the primary end point (↓ in MIG days per m after 1 year) not achieved • greater mean ↓ in MIG days with aura per m and the number of MIG attacks with aura in the study group
Mas et al. 2021[73]	Multicenter	Randomized, controlled trial	*n* = 67 MA = 43	60 m	• NSD in the average annual number of attacks (with or without aura) • ↓ in the average annual number of aura attacks • NSD in the annual number of MIG attacks

Abbreviations: ↓, decrease; m, months; MA, migraine with aura; MIDAS, Migraine Disability Assessment Scale; MIG, migraine; MO, migraine without aura; *n*, number of patients; NSD, no significant difference; PFO, patent foramen ovale; pts, patients; RLS, right-to-left shunt.

transcatheter PFO closure using thienopyridine response as an inclusion criterion.[89]

Despite advancements, the increasing rate of PFO closure raises questions about the appropriateness of its indications. The number of PFO closures increased from 4.75 per 100,000 person-years in 2006 to 6.60 per 100,000 person-years in 2019. Strikingly, nearly half of these procedures were performed for non-Food and Drug Administration–approved indications such as migraine, TIA, platypnea–orthodeoxia syndrome, and decompression illness.[90,91] The most recent British Cardiovascular Intervention Society Position Statement emphasized that if PFO closure is considered for migraine treatment, it should only be pursued in collaboration with a neurologist specializing in migraine, with thorough disclosure of the uncertainties involved.[91] Both the 2022 Society for Cardiovascular Angiography & Interventions guidelines and the 2021 European Society of Cardiology guidelines recommend against the routine use of PFO closure for migraine but note that it may be considered in human cases for refractory, debilitating migraine treatment.[58]

PFO AS A LINKING ELEMENT BETWEEN STROKE AND MIGRAINE

Epidemiology

The prevalence of PFO is estimated to be 40% among stroke patients under the age of 55 years.[45] It is particularly common in individuals experiencing cryptogenic stroke, with an occurrence rate of 65% in this population,[92,93] which is approximately three times as high as in the general population.[94,95] Notably, up to 73% of young individuals who experienced IS without traditional vascular risk factors were found to have PFO.[96] These findings underscore a strong association between PFO and cryptogenic stroke, which itself accounts for 25%–40% of all ischemic events.[95,97–98] Nevertheless, it needs to be emphasized that PFO alone is not a general risk factor for stroke across the broader population,[99] particularly when compared to more prevalent cardiac abnormalities.[100]

Several studies have shown that PFO is significantly more prevalent in stroke patients with migraine compared to those without. This association is especially strong in cases involving MA and cryptogenic strokes.[93,101] Among patients with both conditions, the prevalence of PFO is estimated to be 79%. Notably, in cases of cryptogenic stroke accompanied by frequent migraine aura, PFO was identified in up to 93% of patients.[93] Furthermore, high-risk PFO has been recognized as a leading cause of stroke in young individuals, particularly those with MA, accounting for 17% of cases.[102] Evidence also suggests that patients with PFO who experience IS have a higher incidence of migraine.[92,103]

Ischemic stroke

Although a growing body of evidence indicates a link between migraine, particularly MA, and cryptogenic stroke in younger individuals, this association appears to be independent of both traditional vascular risk factors and the presence of PFO.[40,92] Current research has not provided definitive evidence that migraine directly increases the risk of PFO-related stroke.[104,105] It is still unclear whether PFO acts as a causal factor in individuals with migraine or is merely an incidental anatomical finding.[106]

Gollion et al.[107] demonstrated a significant association between potentially causal PFO and MA in young adults with cryptogenic stroke (OR, 3.24; 95% CI, 1.45–7.2), whereas other studies reported no such link.[92,108] These inconsistencies may arise from the need to differentiate between anatomically smaller, incidental PFOs and "high-risk" PFOs. Patients with high-risk PFOs have a higher likelihood of stroke recurrence than those with non–high-risk PFOs.[109] This is particularly evident in patients with cryptogenic stroke, where high-risk PFOs significantly increase the risk

of subsequent strokes.[110–112] Elgendy et al.[113] even pointed out the validity of using the term PFO-associated stroke in cases where PFO is considered a probable cause of the stroke, rather than classifying these patients as cryptogenic. The presence of high-risk features in PFO suggests a need for more aggressive management strategies, such as PFO closure, which has been shown to reduce stroke recurrence in these patients.[111,114] Supporting this, Snijder et al.[115] found that PFO with ASA was strongly associated with MA (OR, 2.71; 95% CI, 1.23–5.95). Nevertheless, another study showed that even high-risk PFOs in patients with MA did not significantly elevate future stroke risk.[101] Furthermore, certain anatomical features of PFO, such as a funnel-shaped left atrial opening, longer PFO tunnel length, and multiple exit points, have been linked with an increased risk of cryptogenic stroke.[116] Additionally, in a comparative study between patients with embolic stroke of undetermined source and those with migraine, echocardiographic findings were mostly similar.[104] Interestingly, the risk of paradoxical embolism score and high-risk PFO scores did not differ significantly between the groups.[104]

Right-to-left shunting, especially when associated with ASA, has been proposed as a mechanism linking PFO with stroke and MA.[117] In a study conducted by Gao et al.,[118] RLS was found in 78% of patients with cryptogenic strokes, compared to 35% in the control group. Research indicates that larger shunts carry a greater risk of stroke. Patients with massive RLS experience a higher incidence of recurrent strokes compared to those with smaller shunts.[119–121] Furthermore, the risk of stroke is elevated when RLS is combined with other factors that promote atherosclerosis. However, even in the absence of additional risk factors, RLS alone poses a significant risk for cryptogenic strokes.[122] Furthermore, Zhao et al.[123] indicated that the prevalence of permanent RLS, total RLS, and large RLS was significantly higher in patients with migraine compared with controls. The size of RLS appears to correlate with migraine severity. Martinez-Majander et al.[92] reported a rising prevalence of MA in stroke patients with increasing RLS size: from 29.2% in those without shunting to 49.4% in those with severe RLS.

Outside of the migraine context, PFO has also been studied concerning AF and pulmonary embolism. In patients with AF undergoing left atrial appendage closure, the presence of a PFO did not significantly affect the risk of IS or TIA either before or after the procedure. Only major residual leaks (>5 mm) were associated with a higher risk of cerebrovascular events during long-term follow-up.[124] In patients with acute pulmonary embolism, PFO has been linked to a significantly higher incidence of IS and overall mortality. Meta-analytic data suggest that PFO increases the odds of stroke in these patients by more than five times (OR, 5.36; 95% CI, 3.20–8.99).[125]

The accuracy of PFO diagnosis is another key factor in treatment planning. Advanced diagnostic techniques such as TEE and contrast TEE have shown greater sensitivity in detecting PFO and pulmonary arteriovenous malformations compared to transthoracic echocardiography with or without contrast.[40] Notably, contrast-enhanced TEE was shown to improve the detection rate of PFO compared to TEE with color Doppler imaging alone.[126]

Clinical importance

Following the recently published 2024 European Stroke Organization guidelines on PFO, the diagnostic workup for PFO should include a detailed evaluation of the anatomical and functional characteristics of the shunt. The guidelines recommend that TEE remains the gold standard for anatomical assessment, providing detailed information on the size of the PFO, the presence of an atrial septal aneurysm, and the morphology of the interatrial septum. Additionally, TCD with bubble study is suggested as a highly sensitive screening tool for detecting RLS, whereas TTE with bubble study can be considered as an initial, less invasive evaluation, especially in younger patients with good acoustic windows.[127] Growing evidence supports the use of percutaneous closure of PFO as an effective secondary prevention strategy in patients with cryptogenic stroke. A recent meta-analysis confirmed its superiority over antiplatelet or antithrombotic therapy alone.[128] Nonetheless, not all strokes in patients with PFO are indeed PFO-related,[127] emphasizing the importance of selecting appropriate candidates for closure.[129]

Importantly, the presence of migraine itself appears to predict a higher risk of stroke recurrence after PFO closure.[130] One study reported a stroke recurrence rate of 8.4%, with nine of 13 patients experiencing recurrent events having migraine, including four with aura. Both a risk of paradoxical embolism score below 7 (OR, 5.991) and the presence of migraine (OR, 5.932) were identified as independent predictors of recurrent stroke or TIA following closure.[130]

Antiplatelet therapy is frequently used in patients with PFO to prevent strokes, primarily when PFO closure is not performed.[131–133] Studies suggest that anticoagulation may more effectively reduce the risk of recurrent strokes in patients with PFO compared to antiplatelet therapy, although this comes with an increased risk of major bleeding.[131,132,134] The meta-analysis performed in 2024 showed that the anticoagulation approach, in comparison to antiplatelet therapy, resulted in significantly lower risk of IS in patients with embolic stroke of undetermined source and PFO.[135] Additionally, the P2Y12 platelet inhibitor has shown promise in decreasing migraine attacks, particularly in patients with PFO. This suggests that it may play a preventive role in avoiding new-onset migraine following atrial septal defect closure.[136] Nevertheless, more large-scale, randomized trials are needed to better understand the role of antiplatelet therapy or anticoagulation therapy for patients with migraine and PFO, sometimes complicated by IS, especially in comparison to other treatment options such as PFO closure.[137]

Stroke mimics and stroke chameleons

Undoubtedly, PFO remains a shared feature seen more commonly in both migraine and stroke affecting young people. Stroke mimics (SMs) refer to conditions that present with clinical symptoms similar to those of IS, leading to potential misdiagnosis and inappropriate treatment. The most common causes of SMs include

peripheral vestibular disorders, seizures, metabolic disturbances, psychiatric conditions, and, notably, migraine.[138,139] Among these, migraine, particularly MA, is the leading cause of SMs, responsible for 14.7% of misdiagnosed cases.[140] It accounts for approximately 1.79% of emergency stroke evaluations and is involved in approximately 18% of incorrect thrombolytic treatments.[141,142] Despite this, administering thrombolytic treatment to patients with MA has an extremely low risk of adverse events, with a reported rate of just 0.01%.[141,142] Migraine often overlaps symptomatically with IS, featuring visual, sensory, and motor disturbances, making them particularly susceptible to misclassification in acute neurological presentations.[143]

Several factors help differentiate migraine-related SMs from true strokes. These include younger patient age, absence of cardiovascular comorbidities, and lower scores on the National Institutes of Health Stroke Scale.[143–145] Migraine as an SM is more prevalent in younger women, who often present early in emergency settings with symptoms that can be mistaken for stroke, such as speech or vision disturbances.[143,146–147] A prior diagnosis of migraine is also inconsistently reported, present in only 47.2%–50% of patients with SM, despite up to 79.4% fulfilling diagnostic criteria for migraine at the time of presentation.[143,145] Furthermore, aura type plays a critical role in diagnosis. Although visual aura is most common,[148] sensory symptoms appear more frequently in migraine-related SMs.[143,145] Loss of sensation alone has been noted in 73.5% of migraine SM cases and is considered a major risk factor for being mistaken for stroke.[143,149] Furthermore, symptoms like vertigo and nonlocalizable neurological deficits are more common in (SM)s, including migraine, compared to true strokes.[147] Neuroimaging remains central to differential diagnosis. Perfusion computed tomography is usually normal, but combined with MRI, including arterial spin-labeled sequences, it may enhance diagnostic accuracy, especially in focal neurological deficits.[143,150]

Stroke chameleons (SCs) are cases of IS that are not immediately recognized as strokes, often due to atypical presentations or being masked by other conditions. This misidentification can lead to significant consequences, including delayed or incorrect diagnoses.[151] SCs can be understood from various perspectives. One notable aspect is that headaches are commonly reported as a symptom at the onset of IS. In one study, 27% of participants indicated that they experienced headaches at the onset of their strokes.[152] Furthermore, ischemic events may trigger headache patterns similar to migraine, which can lead to diagnostic confusion.[144,148] According to the International Headache Society, a secondary headache type may arise "in close temporal relation to another disorder known to cause headache."[148] Another related diagnostic challenge involves migrainous infarction, where ischemic symptoms occur during a migraine aura. In these cases, neuroimaging must show an ischemic lesion that corresponds anatomically with the aura symptoms presented.[148]

Because migraine can present both as SMs and SCs, a thorough assessment that combines clinical signs with imaging data is crucial to reduce the risk of misdiagnosis and improve patient outcomes.[146,153] Increasing awareness of the diagnostic complexity of migraine is essential for achieving greater accuracy.

FINAL CONSIDERATIONS AND PRACTICAL GUIDANCE FOR PATIENTS

There is relatively strong evidence that migraine is indeed related to PFO existence and that PFO and migraine co-occurrence can play a significant role in the risk of IS, especially among young populations. Nevertheless, it seems unnecessary to screen each patient with migrainefor PFO presence, in comparison to young patients with stroke, mainly those without any clear risk factors, who undoubtedly require extended diagnostics. Hence, patients with migraine should not be routinely screened for PFO; however, considering the correlation between migraine with and without PFO and stroke, one should be encouraged to eliminate any modifiable risk factors for ischemic events.

LIMITATIONS

This review acknowledges several limitations. First, the included studies show significant heterogeneity, particularly in study design, patient populations, and diagnostic criteria for migraine, stroke, and PFO. This variability limits the comparability of findings and makes it difficult to draw firm conclusions. Second, many studies relied on retrospective data or observational methods, which can introduce selection bias and limit causal inference. Third, the approaches used to diagnose PFO or migraine varied considerably among studies. For instance, some studies used TEE to diagnose PFO, whereas others relied on transthoracic echocardiography or contrast TCD. Finally, publication bias cannot be ruled out, as studies that report significant associations between PFO, stroke, and migraine may be more likely to be published. This could influence the overall interpretation of the evidence.

SUMMARY

The relationship/coexistence between migraine and PFO is still not clear, and based on current knowledge, it is not possible to make a clear decision on the specific procedure—PFO closure in patients with migraine or to recommend anticoagulant treatment—even if we consider the hypothesis of the mechanism of paradoxical embolization. This article only addresses the most critical issues, which can be summarized as follows:

1. Considering the literature to date, one can consider potential indications for PFO closure in patients with migraine (Figure 2).
2. The answer to the question of whether recurrent migraine attacks with aura in young people can be considered an indication for PFO closure remains unclear.

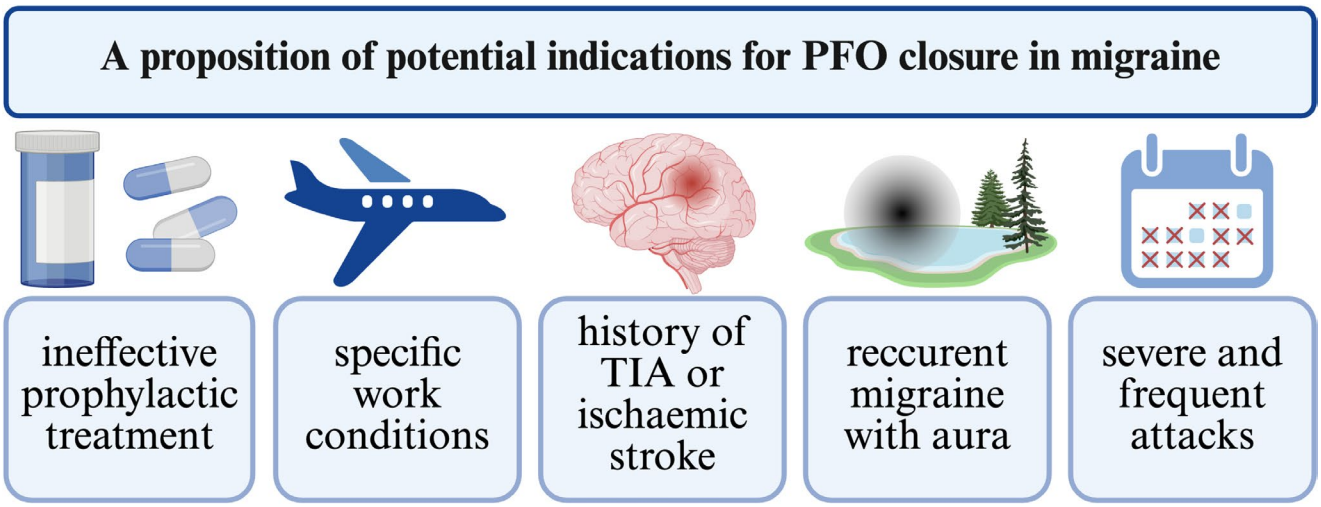

FIGURE 2 A summary of putative indications that may be considered in decision-making for PFO closure in migraine. PFO, patent foramen ovale; TIA, transient ischemic attack. [Color figure can be viewed at wileyonlinelibrary.com]

3. It seems that in severe and frequent migraine attacks with aura and ineffective prophylactic treatment, including acetylsalicylic acid, PFO closure may be an optional treatment method.
4. The size of PFO, together with other specific features, the so-called high-risk PFO, is likely to play a significant role in the risk of IS, either with or without migraine headaches.
5. The diagnosis of PFO in IS patients should be performed with the greatest possible accuracy; thus, TEE should be performed, especially when transthoracic echocardiography did not reveal any abnormality.
6. The qualification for the procedure of PFO closure should be performed in every patient with IS without other apparent reasons.
7. Additional tools for recognizing SCs or SMs are needed, because no existing tools offer sufficient accuracy in daily clinical practice.
8. Although the issue of PFO in migraine has been known for decades, more studies are required to estimate clear indications for patients with migraine and PFO management.

AUTHOR CONTRIBUTIONS

Olga Grodzka: Writing – original draft; methodology; visualization; writing – review and editing. **Michał Borończyk:** Writing – original draft. **Anna Zduńska:** Writing – original draft. **Julia Węgrzynek-Gallina:** Writing – original draft. **Izabela Domitrz:** Writing – original draft; writing – review and editing; supervision; conceptualization. **Anetta Lasek-Bal:** Writing – original draft; writing – review and editing; supervision; conceptualization.

CONFLICT OF INTEREST STATEMENT

Olga Grodzka, Michał Borończyk, Anna Zduńska, Julia Węgrzynek-Gallina, Izabela Domitrz, and **Anetta Lasek-Bal** declare no conflicts of interest.

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