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Review Article

Patent foramen ovale: Unanswered questions

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Abstract

The foramen ovale is a remnant of the fetal circulation that remains patent in 20–25% of the adult population. Although long overlooked as a potential pathway that could produce pathologic conditions, the presence of a patent foramen ovale (PFO) has been associated with a higher than expected frequency in a variety of clinical syndromes including cryptogenic stroke, migraines, sleep apnea, platypnea–orthodeoxia, deep sea diving associated decompression illness, and high altitude pulmonary edema. A unifying hypothesis is that a chemical or particulate matter from the venous circulation crosses the PFO conduit between the right and left atria to produce a variety of clinical syndromes. Although observational studies suggest a therapeutic benefit of PFO closure compared to medical therapy alone in patients with cryptogenic stroke, 3 randomized controlled trials (RCTs) did not confirm the superiority of PFO closure for the secondary prevention of stroke. However, meta-analyses of these RCTs demonstrate a significant benefit of PFO closure over medical therapy alone. Similarly, observational studies provide support for PFO closure for symptomatic relief of migraines. But one controversial randomized study failed to replicate the results of the observational studies while another two demonstrated a partial benefit. The goal of this review is to discuss the clinical conditions associated with PFO and provide internists and primary care physicians with current data on PFO trials, and clinical insight to help guide their patients who are found to have a PFO on echocardiographic testing.

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Abbreviations

- PFO, patent foramen ovale;
- RLS, right-to-left shunt;
- ASA, atrial septal aneurysm;
- POD,platypnea–orthodeoxia;
- OSA, obstructive sleep apnea;
- DS, decompression sickness;
- TEE, transesophageal echocardiogram;
- TCD, transcranial Doppler;
- TTE, transthoracic echocardiogram;
- TIA, transient ischemic attack;
- RCT, randomized clinical trial

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1. Embryology and anatomy

Since fetal lungs in utero are incapable of oxygenating blood, the fetus is dependent on the maternal circulation for oxygen delivery via the placenta. Oxygenated blood returning to the right atrium via the umbilical vein needs to be delivered to the brain and vital organs before further loss of oxygen occurs. To facilitate this rapid transit, an inter-atrial communication evolved in all mammals, known as the foramen ovale [1].

After birth, the foramen ovale flap (the septum primum) physiologically closes against the septum secundum when pulmonary vascular resistance and right atrial pressure decrease. During the first two years of life, irreversible closure of the inter-atrial communication occurs; however, in 20–25% of the population this foramen remains patent [1].

A patent foramen ovale (PFO) is like a trap door between the atria with a spectrum of possible states of flow. At rest there may be no flow between the atria, or if the flap is partially open, there may be a left-to-right shunt since pressure in the left atrium is greater than the right. However, a transient right-to-left shunt (RLS) may occur during certain physiologic maneuvers that reverse the inter-atrial pressure gradient by increasing venous return to the right atrium, such as coughing, sneezing, deep breathing and the Valsalva maneuver [2].

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An atrial septal aneurysm (ASA), a saccular deformity of the atrial septum that protrudes 15 mm in the direction of either atria, is associated with 15% of PFOs and is often seen with the largest size PFO [3] and [4].

2. PFO imaging

The most accurate test for determining the presence of a PFO is a right heart catheterization with documentation of a guidewire crossing the atrial septum. The standard non-invasive method for diagnosing a PFO is transesophageal echocardiography (TEE) using agitated saline contrast [5]. Transcranial Doppler (TCD) is a more sensitive and less uncomfortable method for diagnosing PFO with a sensitivity of 97% and specificity of 93%[6]. Transthoracic echocardiogram (TTE) with bubble study is a less expensive, non-invasive test compared to TEE with comparable specificity[7] and [8]. However, conventional TTE has a 46% sensitivity; some studies report improvements in sensitivity when equipped with harmonic imaging capability [9] and [10]. If there is clinical suspicion for PFO, our preferred diagnostic strategy is an initial TCD screening test followed by TEE.

3. Clinical syndromes associated with PFO

3.1. PFO and stroke

The idea that a PFO could function as a conduit for a venous thrombus to pass from the right to left atrium to produce an embolic stroke was first hypothesized in the late 19th century. However, it was not until the widespread use of echocardiography that a more definitive connection was established [Fig. 1]. In 1988, two relatively small observational studies (total 100 patients) were published describing an increased prevalence of PFO (40–50% versus 10–15%; $p < 0.001$) in patients < 40–55 years old with cryptogenic stroke [11] and [12]. Subsequently, this association was also confirmed in older patients[13].

The presence of ASA increases the risk of an initial stroke (meta-analysis of four studies: OR 4.96, 95% CI 2.37–10.39) as well as recurrent stroke (OR 23.93, 95% CI, 3.09–185.42) [12] and [14]. It is hypothesized that ASA allows greater blood flow through the PFO canal, increasing the chance of a thrombus passing from the venous to arterial system [15] and [16].

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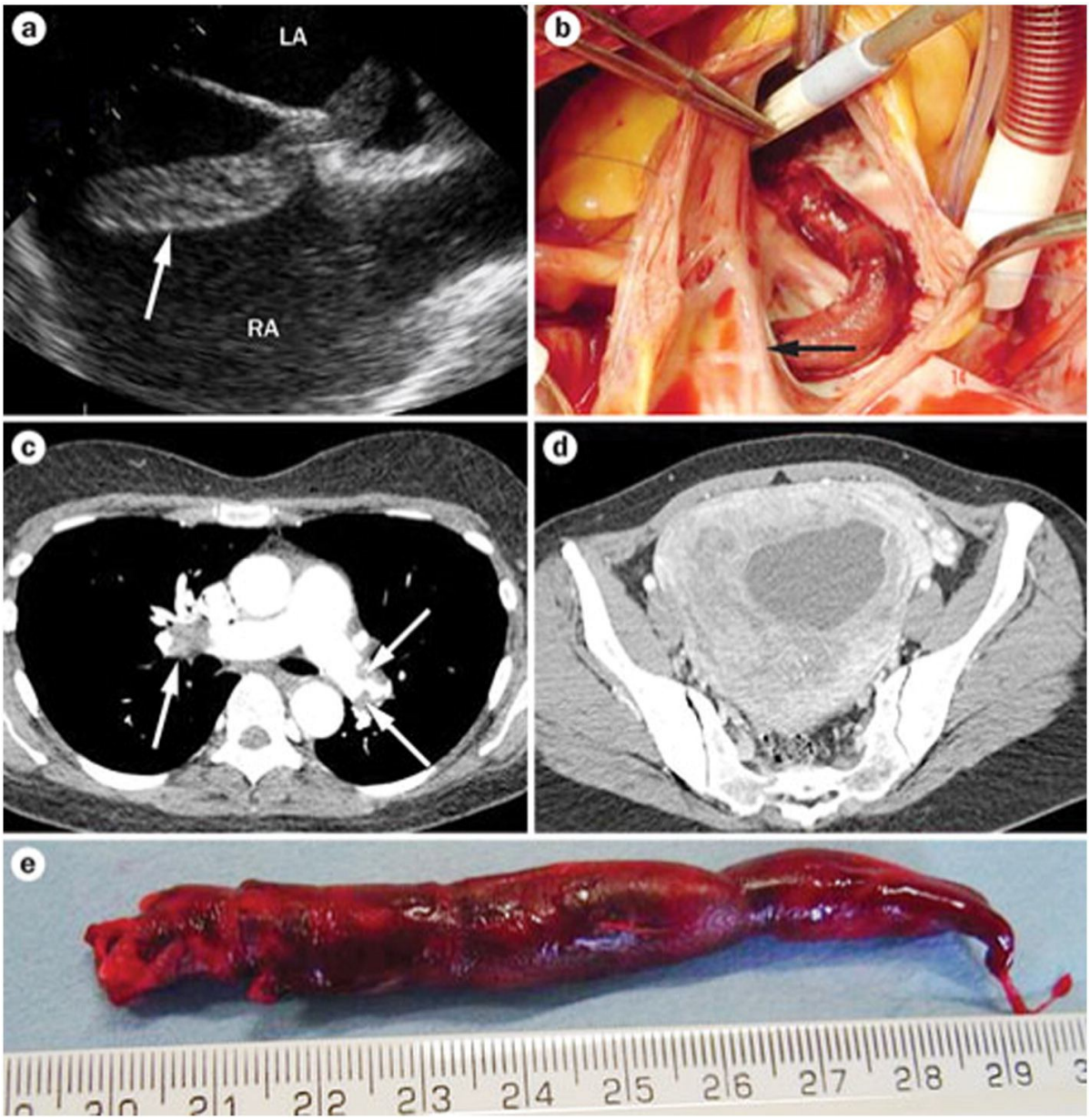

Fig. 1.

Thrombus in transit through a patent foramen ovale.

a) Bicaval two-dimensional TEE image of a large thrombus lodged in a PFO (arrow). b) The same patient at surgery with the thrombus seen in the right atrium passing through the PFO (arrow). c) Large pulmonary emboli found in both main pulmonary arteries (arrows). d) Multifibroid uterus compressing the pelvic veins, which are laden with thrombi. e) The excised thrombus.

Abbreviations: LA, left atrium; PFO, patent foramen ovale; RA, right atrium; TEE, transesophageal echocardiography.

Although observational studies have demonstrated that medical therapy with antiplatelets or antithrombotics lowers recurrent stroke events, the WARSS study (Warfarin Aspirin Recurrent

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Stroke Study), a randomized study including 2206 patients, did not demonstrate a difference in recurrent events in patients with cryptogenic stroke taking warfarin versus aspirin; the recurrence rate was high in both groups at 8%/year[17]. PICCS (Patent Foramen Ovale in Cryptogenic Stroke Study) was a substudy of the WARSS trial that evaluated the recurrence rate in 630 patients who had a PFO identified by TEE [18]. In patients > 65 years old, those with cryptogenic stroke and a PFO had a 2-year recurrence rate of 38% versus 14% in patients without a PFO (2.7 times higher; p = 0.01). There was however no difference in recurrence rate in cryptogenic stroke patients with and without a PFO who were younger than 55 and those aged 55 to 64 (p = 0.15; 2-year event rates, 2% versus 9%; and p = 0.70; 2-year event rates, 10% versus 14%) [19]. We assume this finding, which is inconsistent with most other observational studies, is due to the unknown biases of recruitment of the patient population.

A meta-analysis of 48 observational studies compared 10,327 patients with cryptogenic stroke/TIA who had a PFO and underwent PFO closure versus medical therapy. The medical therapy group had a 6.3 fold increased event rate of recurrent neurological events compared to the closure group [20]. Based on these observations, it was hypothesized that a randomized trial would prove that PFO closure was preferable to medical therapy to prevent recurrent cryptogenic stroke.

3.1.1. Stroke RCTs [Table 1A]

3.1.1.1. Closure I trial: device closure of patent foramen ovale or medical therapy for cryptogenic stroke

Closure I was the first randomized controlled trial comparing medical therapy (aspirin, Coumadin or both) versus medical therapy plus percutaneous PFO closure for the secondary prevention of stroke or transient ischemic attack (TIA) [21]. Patients aged 18–60 years who had cryptogenic stroke or TIA were enrolled; all patients had a TEE-confirmed PFO.

Of 909 patients, 447 were randomized to PFO closure using the STARFlex device (NMT Medical, Boston, Massachusetts; Fig. 2) and 462 to medical therapy. Contrary to many observational studies, the results did not demonstrate superiority of percutaneous PFO closure compared to medical therapy. The primary composite endpoint of stroke, TIA and mortality at 2 years occurred in 5.5% in the device group versus 6.8% in the medical therapy group (p = 0.37). There was also no difference in the endpoint of stroke (2.9% versus 3.1%; p = 0.79) or TIA (3.1% versus 4.1%; p = 0.44) after a 2-year follow-up. The incidence of major vascular complications (3.2% versus 0%) and atrial fibrillation (5.7% vs 0.7%) was higher in the device

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arm ($p < 0.001$ for both). Device closure was associated with a residual RLS in 14% of patients in the closure group.

Table 1A.

Summary of randomized controlled trials of percutaneous patent foramen ovale closure in stroke and/or transient ischemic attack.

Cryptogenic stroke trials

Trial	Patient selection	Medical group	Treatment group	Follow up	Primary endpoint	Results
CLOSURE I	Patients aged 18–60 years old with a cryptogenic stroke or a TIA and a PFO [n = 906]	Aspirin, warfarin or both.	PFO closure with STARFlex device plus aspirin and Coumadin for the first month followed by aspirin for 2 years	2 years	Composite of stroke, TIA, early death from any cause and late neurologic death	Closure with the device did not offer benefit compared to medical therapy alone for the prevention of recurrent stroke or TIA.
RESPECT	Patients aged 18–60 years old with cryptogenic stroke and PFO [n = 980]	Aspirin, warfarin, clopidogrel or aspirin plus extended release dipyridamole	PFO closure with Amplatzer device followed by ASA plus clopidogrel for the first month and ASA for 5 months	Median 2.1 years	Composite of recurrent ischemic non-fatal and fatal stroke and early death	No benefit associated with PFO closure in primary intention to treat analysis. However, in pre-specified per-protocol and as-treated analyses closure was superior to medical therapy alone.
PC	Patients aged less than 60 with a PFO and a stroke, TIA or peripheral embolic event [n = 414]	Antiplatelet or antithrombotic therapy	Closure with the Amplatzer device followed by Aspirin for at least 5–6 months plus clopidogrel or ticlopidine for 1–6 months	Mean 4 years	Composite of death, non-fatal stroke, TIA or peripheral embolism	Closure of PFO did not reduce recurrent embolic events or death compared to medical therapy.

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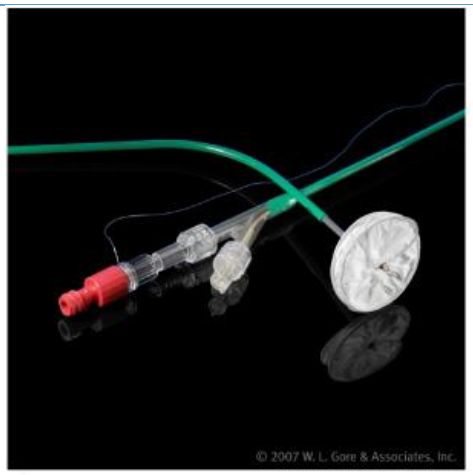

a) Gore Helex Septal Occluder

b) STARFlex PFO implant device

c) Amplatzer PFO Occluder

Fig. 2.

PFO occluding devices.

a: Gore Helex Septal Occluder.

b: STARFlex PFO implant device.

c: Amplatzer PFO Occluder

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Discrepancies between results of prior observational studies and this randomized trial for PFO closure in cryptogenic stroke were mainly attributed to the closure device used, which may have contributed to a higher than expected rate of recurrent cryptogenic stroke in the device group. The STARFlex device had an unfavorable safety profile with a high rate of thrombogenesis and atrial fibrillation. Of 26 patients who developed atrial fibrillation, 23 occurred in the device arm with 3 of those developing a recurrent stroke. Safety concerns with this device along with its lower efficacy of complete PFO closure had also been observed in prior studies [22] and [23].

3.1.1.2. RESPECT trial: closure of patent foramen ovale versus medical therapy after cryptogenic stroke

The RESPECT trial was a prospective, multicenter (69 sites), controlled and event-driven trial which enrolled patients between 18–60 years old who had a cryptogenic stroke and a PFO identified by TEE. After a stroke, 980 patients were randomized within 270 days to either closure with the Amplatzer PFO occluder [Fig. 2] (499 patients) or medical therapy with aspirin, warfarin, clopidogrel, or aspirin plus extended-release dipyridamole (481 patients) [24]. The choice of which medical therapy was left to the discretion of the treating neurologist. At a mean follow-up of 2.6 ± 2.0 years, there was no significant difference in the primary endpoint of recurrent ischemic nonfatal stroke, fatal ischemic stroke and early death after randomization (with all of the events being non-fatal ischemic strokes) when closure was compared to medical therapy (0.66% versus 1.38%; p = 0.08). However, a subgroup analysis of the intention-to-treat group suggested that PFO closure is beneficial in patients with a substantial shunt size and an ASA. In the pre-specified per-protocol and as-treated analyses, closure was superior to medical therapy in the prevention of recurrent stroke (p = 0.03 and p = 0.007 respectively). The rate of serious adverse events did not differ between the two groups; total incidence of atrial fibrillation was also similar (3.0% versus 1.5%, p = 0.13). At a 6 month follow-up, 93.5% in the device arm met the criteria for effective PFO closure as defined by a shunt grade of 0 or 1 by TEE.

The RESPECT trial was limited by a high dropout rate (17%) in the medical therapy group. Lack of blinding (no sham procedure) might have resulted in loss of 83 patients from that group, some of whom may have received closure of PFO with one of the FDA-approved off-label devices. In addition, 3 patients assigned to the closure group who had a recurrent stroke never received a device; this explained the discrepancies between the intention-to-treat and per-protocol results.

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3.1.1.3. PC trial: percutaneous closure of patent foramen ovale in cryptogenic embolism

The PC trial enrolled 414 patients, aged < 60 years, who had a PFO and a prior ischemic stroke, TIA or peripheral thromboembolic event at 29 centers worldwide [25]. Patients were assigned to medical therapy with either antiplatelet or oral anticoagulation therapy or closure with the Amplatzer PFO Occluder. After a 4-year follow-up, there was no difference in the primary endpoint of death, nonfatal stroke, TIA or peripheral embolism between the closure and medical therapy groups (3.4% vs 5.2%; p = 0.34). Individually, there was no difference in the incidence of nonfatal stroke (0.5% versus 2.4%; p = 0.14) and TIA (2.5% versus 3.3%; p = 0.56) when comparing closure to medical therapy. One of the major limitations of the study was that it was significantly underpowered with a high risk of a type II error. In addition, the clinical presentation of TIA can be nonspecific (e.g. from a migraine aura) and enrollment of these patients may have resulted in inclusion of patients with an alternative initial diagnosis. Lastly, lack of blinding may have permitted use of off-label PFO occluding devices among patients in the medical therapy group.

When analyzing these trials, several factors should be noted; all the trials were limited by slow recruitment and unexpectedly low event rates. Higher risk patients were less likely to be randomized, and more likely to receive PFO closure with an off-label device without being enrolled in the RCT. For example, during the recruitment period for the CLOSURE I trial, utilization of off-label PFO closure versus referral to the randomized trial was 3:1 with higher risk patients preferentially being referred to off-label device closure [26]. There is still uncertainty whether PFO is a causal or incidental finding in cryptogenic stroke. Just because a PFO is present, does not prove that the stroke was due to a paradoxical embolus. It is likely that some subjects had incidental PFOs, such as in the presence of unrecognized atrial fibrillation. This presumably should be equally distributed in a randomized population. An additional study is also underway to investigate the role of PFO closure on secondary prevention of cryptogenic stroke. The REDUCE study is a randomized, multi-center study designed to compare PFO closure using the GORE HELEX occluder [Fig. 2] with medical therapy in patients with a history of cryptogenic stroke or imaging confirmed transient ischemic attack. The trial has completed its recruitment phase and the results are eagerly awaited.

3.1.1.4. Meta-analyses of the stroke trials

Following completion of the three stroke RCTs, several meta-analyses pooled data from these studies, in an attempt to increase the sample size, reduce type II errors and explore the

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possibility that a subgroup of patients may benefit from PFO closure [27], [28], [29],[30] and [31]. Khan et al demonstrated that PFO closure, regardless of the device used, was beneficial compared to medical therapy for the prevention of recurrent neurological events (HR 0.67, 95% CI 0.44–1.00) with more robust data when only RESPECT and PC trials were pooled together (HR 0.54, 95% CI 0.29–1.01) even with an intention-to-treat analysis [32]. The RESPECT and PC trials used the same Amplatzer PFO device which justifies pooling data from these trials. Nevertheless, current guidelines from the AHA do not support PFO closure in the event of cryptogenic stroke or TIA unless a DVT is identified [33].

3.2. PFO and migraines

In the 1990s, it was observed that patients with a history of migraines, who underwent PFO closure for an unrelated reason, often had symptomatic migraine relief. As distinguished from the general population where PFO is present in 20% of people, 30–50% of migraineurs with aura have a PFO [34] and [35]. The prevalence of PFO is not increased in people who have migraine without aura compared to the general population[36]. In 2000, Wilmshurst et al. reported relief of migraines in patients undergoing PFO closure for cryptogenic stroke or deep sea decompression illness. PFO closure symptomatically improved or completely relieved migraines with and without aura in 18/21 subjects [37]. Subsequently, over 11 observational reports with 1632 subjects have corroborated these findings [Table 2] [23], [37], [38], [39], [40], [41], [42], [43], [44],[45], [46], [47] and [48].

These observations suggest that there may be a physical or chemical agent that passes from the venous to the arterial circulation that can trigger migraine. Current hypotheses suggest a chemical trigger (as opposed to an embolus) that is normally metabolized by the lungs. While there is no consensus on one particular chemical trigger, studies point to the role of the nitric oxide pathway in inducing migraines, possibly through histamine or serotonin [49] and [50]. Alternatively, it may just be the presence of hypoxemic venous blood or lower pH which may act as the migraine trigger. PFO closure leads to appropriate lung oxygenation of all venous blood.

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Table 1B.
Summary of randomized controlled trials of percutaneous closure of patent foramen ovale for migraine.

Migraine trials

Trial	Patient selection	Medical group	Treatment group	Follow up	Primary endpoint	Results
MIST	Patients with a PFO and severe, recurrent, debilitating, drug resistant migraines with aura [n = 432]	Sham procedure	PFO Closure with STARFlex device	6 months follow up	Complete headache cessation	No significant difference in endpoints
PRIMA	Patients with a PFO and frequent, drug-resistant migraine with aura [n = 107]	3 months of clopidogrel and 6 months of aspirin	PFO closure with Amplatzer device plus 3 months of clopidogrel and 6 months of aspirin	1 year	Reduction in mean migraine days	No difference in mean reduction in migraine with aura days. Reduction in total migraine with aura days or attacks, ≥ 50% reduction in migraine days, freedom from migraine, and freedom from migraine with aura were all significant favoring closure
PREMIUM	Patients with a PFO and frequent severe, daily debilitating migraines with and without aura [n = 230]	Sham procedure	PFO closure with Amplatzer device	Up to 12 months	Reduction in migraine attacks per month	No difference in reduction in migraine attacks. Significant reduction in total headache days in device group, especially in migraineurs with aura

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Table 2.
Observational studies of the prevalence of migraine in patients referred for PFO closure and the effect of closure on migraine.

Study	Prevalence # migraines	% closed	% migraine improved/cured	Length of follow-up (months)
Wilmshurst (2000)[37]	21/37	59%	86%	30
Morandi (2003) [48]	17/62	27%	88%	6
Schwerzmann (2004) [23]	48/215	22%	81%	12
Post (2007) [40]	26/66	39%	65% (cured)	6
Reisman (2005) [41]	57/162	35%	70%	12
Azarbal, Tobis (2005) [42]	37/89	42%	76%	18
Donti, Giardini (2006) [43]	35/131	27%	91%	20
Anzola (2006) [39]	50/163	100%	88%	12
Kimmelstiel (2007)[46]	24/41	59%	83%	3
Papa (2009) [47]	28/76	37%	82%	12
Khessali (2012)[a][45]	204/590	40%	76%	12
Meta-analysis	547/1632	33.5%	80.5%	13 ± 7.5

a Migraine with aura.

3.2.1. Migraine RCTs [Table 1B]

3.2.1.1. MIST trial: migraine intervention with STARFlex technology

he MIST trial was the first randomized, double-blinded, clinical trial aimed at evaluating the effect of PFO closure on migraine headaches [51]. The study population consisted of patients with recurrent, debilitating, and drug-resistant migraines with aura. A total of 432 patients were screened using a TTE bubble study; 60% had a RLS, the majority of which were attributed to PFO (63%). Patients were randomized in a 1:1 ratio to PFO closure with the STARFlex device or a sham procedure (skin incision in the groin). Participants were required to keep a daily

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headache diary to record their migraine events. After a 6-month follow-up, the treatment groups were unblinded and a repeat TTE was performed to assess for residual RLS.

The primary endpoint was complete headache cessation. Secondary endpoints included change in incidence, severity, frequency, and character of migraines or an overall change in quality of life. Although the MIST trial demonstrated a high prevalence of RLS in patients who had migraine with aura (60%), there was no significant difference in primary or secondary endpoints between the two groups. Cessation of headaches was reported in 3/74 patients in the closure group and 3/73 in the sham group. Migraine frequency was reduced by 42% in the treatment arm versus 23% in the sham arm but ultimately was not statistically significant. A major concern of the MIST trial was the high complication rate in the closure group. Serious adverse events occurred in 16 patients, 10 of which were in the device arm; major procedural complications included pericardial effusion (2 patients; 1 developed tamponade), retroperitoneal bleed (1 patient), atrial fibrillation (2 patients), and severe chest pain (2 patients).

Results of MIST were disappointing as prior observational studies had shown a significant reduction in migraine frequency following PFO closure. Two theories could potentially explain the discrepancies between clinical observations and this RCT [52]:

1. Prior observational studies analyzed a different population of patients with cryptogenic stroke who also had migraines while MIST only included patients with frequent or daily migraines refractory to medical therapy.

2. The STARFlex device was not completely effective in closing the PFO, resulting in large, residual RLS. Some controversy has unfolded regarding the MIST trial's accuracy in reporting residual shunts at the 6-month follow-up [53]. Assuming that the trial's negative results were attributable in part to the possible 1/3 of patients having failed PFO closure, then it is reasonable to expect that benefits would only be seen in those with effective PFO closure. However, even in the remaining 2/3 of patients with adequate closure, there was no significant decrease in migraine frequency, but if the 2 subjects with chronic daily migraines are excluded, then a statistically significant decrease in headache frequency was seen.

3.2.1.2. PRIMA trial: percutaneous closure of patent foramen ovale in migraine with aura

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The PRIMA trial was a randomized, open-label, multicenter (20 cites in Canada and Europe) trial that evaluated the efficacy of percutaneous PFO closure in reducing migraine with aura in patients refractory to medical treatment. The study included 107 migraineurs with aura with onset before age 50, who had > 3 migraine attacks or 5 migraine days per month (but < 14 headache days per month), failed multiple migraine medications, and had a PFO. Patients were randomized to either PFO closure with the Amplatzer device (AGA Medical, Golden Valley, Minnesota; Fig. 2) plus 3 months of clopidogrel and 6 months of aspirin (53 patients) or the same medical therapy without PFO closure (54 patients).

As with MIST, the PRIMA study demonstrated a high incidence of RLS among migraine with aura patients (40%). There was no significant difference in the primary endpoint of a mean reduction in migraine days at 1-year follow-up between closure and medical therapy (− 2.9 ± 4.7 versus − 1.7 ± 2.4, p = 0.17). However, secondary endpoints including reduction in migraine with aura days (− 2.4 ± 3.6 versus − 0.6 ± 2.7, p = 0.01), reduction in migraine with aura attacks (− 2.0 ± 2.0 versus − 0.5 ± 1.5, p < 0.01), ≥ 50% reduction in migraine days (37.5% versus 14.6%, p = 0.02), as well as freedom from migraine (10% versus 0%, p < 0.05) and migraine with aura (40% versus 10%, p < 0.05) were all significant in favor of closure. Only 1 patient in the closure group had a major vascular complication with bleeding and another had atrial fibrillation requiring cardioversion; no adverse events occurred in the medical group. Despite some limitations including lack of blinding, high post-randomization dropout rate (1 patient in closure group and 11 in medical group), failure of 12 of the 53 patients (23%) in the device group in actually getting the device (8 patients withdrew consent and 4 failed device implantation), the PRIMA trial demonstrates that migraine with aura appears to respond favorably to PFO closure.

3.2.1.3. PREMIUM trial: prospective randomized investigation to evaluate incidence of headache reduction in subjects with migraine and PFO using the Amplatzer PFO occluder compared to medical management

The PREMIUM trial is a randomized, double-blinded, sham-controlled study evaluating the effect of PFO closure using the Amplatzer PFO occluder in patients with frequent severe, debilitating migraine headaches. Subjects were screened by review of a 60-day migraine diary. Patients enrolled had 6–14 headache days per month and had failed ≥ 3 preventative medications. A TCD screening bubble study, followed by a right heart catheterization at the time of randomization, was used for PFO recognition. A total of 230 subjects were randomized to either a sham procedure plus medical therapy (107 patients) or percutaneous PFO closure plus medical therapy (123 patients). Subjects were required to maintain a headache diary

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3 months prior to and 10–12 months after randomization. Comparison of headache frequency was made between the last 3 months of observation and the baseline. Subjects were unblinded at the end of one year and those assigned to medical therapy had the option of undergoing PFO closure.

The primary efficacy endpoint was a > 50% reduction in the number of migraine attacks per month; the study however showed no difference in the primary endpoint between the device and sham group (38% vs 32%, p = 0.3). Secondary endpoints included a reduction in the total number of headache days with the results showing a significant reduction in the device group (3.4 vs 2.0 days, p = 0.03). Of the patients with primarily migraines with aura, there was a significant reduction in the number of headache days (49% vs 23%, p = 0.015) with complete remission of migraines occurring in 8.6% of patients in the device group versus only 1 (0.9%) in the sham group (p = 0.02). While the results of this study did not show a significant reduction in migraine attack frequency, it did reduce the total number of days with migraine and the procedure was safe. Additionally, in patients having migraine predominantly with aura, there was a significant decrease in the total headache days with a substantial proportion having complete resolution, which is a rare finding with any medical therapy. The study population differed from the MIST trial by enlisting patients with and without aura, having no restriction on age of onset, and excluding people with chronic daily migraines (> 15 headache days per month). It is possible that the failure to see a decrease in migraine attack frequency in this study may be related to the inclusion of patients having migraines without aura. In addition, the endpoint of migraine attacks is less likely to show a statistical difference due to the small numbers, compared with migraine days, which was successful in reaching its endpoint for the PREMIUM Trial.

3.3. PFO and platypnea–orthodeoxia

Platypnea–orthodeoxia (POD) is a rare condition in which patients experience dyspnea and become hypoxic when upright, with relief when recumbent. POD may occur due to a ventilation perfusion mismatch associated with hepatic and pulmonary disease. However, increased RLS through a PFO in the upright position has also been associated with POD [54]. It is hypothesized that age-associated anatomical changes such as elongation of the aorta, stretching of the atrial septum, and diaphragmatic paralysis produce increased RLS through a pre-existing PFO and result in substantial arterial desaturation in the upright position.

In 1995, Lanzberg et al. described the long term relief of symptoms in 8 patients with POD who underwent PFO closure [55]. Later in 2013, Blanche et al described a case series of 5 patients

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with POD who underwent successful closure of PFO with subsequent improvement in oxygenation and symptom resolution [56]. Patients experienced immediate and sustained long term symptomatic relief while achieving immediate normal oxygen levels (oxygen saturation increased from 85 ± 11% to 95 ± 6%) after PFO closure[57]. One recent study demonstrated that percutaneous PFO closure improved or completely resolved orthostatic dyspnea and hypoxemia in 11/17 (65%) patients with POD (upright SaO2 increased from 76 ± 5% to 92 ± 8%, $p < 0.0001$) [58].

3.4. PFO and obstructive sleep apnea

Obstructive sleep apnea (OSA) is associated with increased cardiovascular and all-cause morbidity and mortality. The prevalence is > 10% in the general population and higher in older and obese patients. Over the past two decades, the prevalence of OSA has increased presumably due to an increase in obesity [59] and [60]. Prevalence of PFO in OSA patients has been reported to be 40–69% [61] and [62]. While the pathophysiologic contribution of PFO to OSA has not been fully elucidated, patients with OSA and a PFO may be more prone to develop hypoxia at a lower severity of hypopnea due to RLS through the PFO. Case reports have described significant symptomatic improvement and decreased hypopnea after PFO closure in OSA patients [63] and [64]. More robust evidence, such as a RCT is needed to further support these observations.

3.5. PFO and deep sea diving (decompression sickness)

In the presence of reduced environmental pressure, nitrogen microbubbles can form in the vasculature with resultant arteriolar obstruction of end-organ blood supply. This may result in non-specific constitutional symptoms within 30 min of reaching surface pressure, manifested as central or peripheral nerve symptoms, rash, or hypoxemia. With the advent of improved decompression measures, the incidence of decompression syndrome (DS) has been reduced over time, but still occurs in one out of every 1000 divers [65].

In 1989, Wilmshurst et al reported that patients who experienced DS had a higher prevalence of PFO (65% versus 23%); the prevalence of PFO among divers is 27% which is similar to the general population [66] and [67]. Further risk quantification in a larger observational cohort study revealed a five-fold increased risk of developing DS in divers with a PFO, with increased risk correlating to PFO size. Two case series reported successful results after PFO closure in divers who experienced DS, all of whom resumed diving without further incidents [68] and [69]. Subsequently, other studies have reported long term prevention of DS following PFO

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closure [70]. Although there are no specific guidelines on PFO closure for DS, percutaneous closure is often offered as a treatment option especially in professional divers.

3.6. PFO and high altitude pulmonary edema

Allemann et al demonstrated a four-fold increased incidence of PFO in those susceptible to developing high altitude pulmonary edema, compared to resistant mountain climbers[71]. PFO size correlated with the degree of arterial hypoxemia. The hypothesized mechanism involves a cycle of high altitude hypoxia producing pulmonary vasoconstriction and hypertension. In those with a PFO, increased right sided pressures would exacerbate the RLS and result in worsening arterial hypoxemia, altered alveolar-arterial gradients, and capillary leakage leading to pulmonary edema. PFO closure has been reported to have benefits in some cases following elimination of RLS [72]. The development of headaches at altitudes above 8000 ft is also more common in subjects with a PFO (unpublished data).

4. Safety of percutaneous PFO closure

There are 3 percutaneous closure devices that are commonly used off-label: the Amplatzer ASD occluder or the Cribriform ASD occluder (AGA Medical, Golden Valley, Minnesota), and the Helex septal occluder (W.L. Gore and Associates, Flagstaff, Arizona); the Amplatzer PFO occluder was only available for the randomized trials. The CarioSEAL–STARFlex device is no longer manufactured [Fig. 2].

Overall, about 8000 PFO closure procedures are performed every year in the United States using various devices [73] with nearly 90% of patients having complete closure of their PFO within 1 year [74]. The main risk with PFO closure with any device is that 1 in 500 patients develop severe chest pain, presumably due to an enhanced inflammatory response with dense fibrous tissue, and exacerbation of migraine. In one retrospective multicenter study, 50% of the devices which were removed secondary to chest pain (7/14 devices) had a nickel allergy to the PFO device based on a skin patch test. Chest pain attributed to a nickel allergy is often associated with the Amplatzer device which has higher nickel content than the Helex device. Of note, treatment with steroids and/or non-steroidal anti-inflammatory drugs should be attempted prior to device explantation. [75]. The migraines may respond to the anti-platelet agent, clopidogrel, but if the chest pain persists, it can only be relieved by surgical removal of the device [75].

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CardioSEAL–STARFflex was associated with a higher rate of thrombus formation [3.6% versus 0% with Amplatzer and Helex], atrial fibrillation [5% versus 1.4% with Amplatzer and 1.3% with Helex] [22], residual RLS (up to 15% of cases), and longer mean hospital stay [75]. Amplatzer devices have a higher rate of complete PFO closure and a low rate of atrial fibrillation and thrombus formation [76]. Safety results of the RESPECT trial demonstrated no significant difference in all-cause serious adverse events comparing closure with the Amplatzer PFO occluder to medical therapy (23.0% and 21.6%, respectively; P = 0.65) [24]. However, the Amplatzer device is associated with a higher incidence of nickel allergy which has been associated with prolonged migraines and chest pain after device implantation. Of the devices that undergo explantation, 18% of patients are found to have a nickel allergy and 5% of explanted devices have evidence of erosion [75].

5. Summary

A PFO is present in approximately 20–25% of adults [1]. Although most people who have a PFO remain asymptomatic, the presence of PFO has been associated with numerous medical conditions. It is estimated that 1 in 1000 people per year who have a PFO will develop a cryptogenic stroke [22]. The pathological effect of a PFO is potentially mediated via two mechanisms: 1. A passageway for blood clots, platelet plugs, or nitrogen bubbles to the systemic circulation; or 2. A significant RLS that leads to arterial hypoxemia, or passage of other chemicals that may trigger a migraine with aura, or high altitude sickness.

A TTE bubble study, traditionally utilized for PFO diagnosis, has a low sensitivity. TCD screening for a RLS detects almost all significant PFOs and can be followed by a TEE to obtain an accurate picture of the septal anatomy.

Despite multiple observational studies demonstrating the positive impact of PFO closure on cryptogenic stroke and migraine, the results of RCTs are controversial. Due to the lower risk patients that agreed to participate, the risk of recurrent stroke is low in patients in the RCTs, making it difficult to demonstrate a substantial reduction of risk using device closure. In spite of this, a meta-analysis of the RCTs using the Amplatzer device, RESPECT and PC, demonstrates a benefit of percutaneous PFO closure compared to medical treatment alone. Procedural risks associated with modern closure devices are low. For these reasons, it was difficult to enroll patients into the stroke trials, as high-risk patients with large PFOs and recurrent strokes are often apprehensive about leaving closure to chance, and tend to prefer closing their PFOs off-label, outside the RCTs. If medical therapy is chosen, the recent meta-analysis by Kent et al showed no difference between use of oral anticoagulation (warfarin) and

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antiplatelet therapy (aspirin, clopidogrel, ticlopidine, or aspirin plus dipyridamole) [78]. If medical therapy is chosen, a recent meta-analysis by Kent et al showed no difference between use of oral anticoagulation (warfarin) and antiplatelet therapy (aspirin, clopidogrel, ticlopidine, or aspirin plus dipyridamole) [78]. Given the lack of an obvious difference, the need for monitoring and dose adjustment, and the higher risk of bleeding with warfarin, antiplatelet therapy may be preferred compared to oral anticoagulation [79]. However, more randomized controlled trials are needed in this regard.

Data on PFO closure in migraine is limited, but the PRIMA Trial suggests that patients with migraine and aura may respond favorably. The results of the PREMIUM trial confirm this and suggest that migraineurs with frequent aura (present in > 50% of attacks) are especially responsive to PFO closure. Percutaneous PFO closure in patients with platypnea–orthodeoxia is safe and effective in closing the RLS and reestablishing normal arterial oxygen levels. However, POD is rare, so a RCT will never be performed for this condition. Small observational studies have shown promise in diminishing symptoms of sleep apnea via PFO closure [35], [36] and [37]. It will be necessary to perform a randomized study to prove that closure will reduce OSA symptoms.

The emergence of both observational studies and RCTs led to a 50 fold increase in the number of PFO closures between 1998 and 2004 [77]. From the perspective of the primary care physician, deciding which patient to refer for patent foramen ovale closure still remains a commonly encountered but unanswered clinical question. Based on the existing data from the RCTs, there is still controversy about PFO closure for migraine or cryptogenic stroke prevention. The recent advent of the ROPE score may help identify patients who have cryptogenic stroke and PFO in whom the ischemic event is more likely to be attributed to the PFO. On the ROPE scale, higher scores are assigned to younger patients without vascular risk factors and infarcts located superficially in the brain (infarcts deemed more likely to be embolic [80]) Furthermore, referral to a neurologist and cardiologist for PFO evaluation should be considered in high risk patients including those with ASAs and large shunts. Long term follow-up indicates that PFO closure is relatively safe with a mean follow-up of 7 years in some studies [44].

We are still learning much about the pathophysiology of PFO, this remnant of the fetal circulation, which appears to be more problematic than previously thought possible.

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Conflict of interest statement

Dr. Tobis is a consultant for St. Jude Medical, Inc. and W.L. Gore, Inc.; NO funding was provided by these companies to write this review. Dr. Tobis is also a primary investigator of the PREMIUM trial and co-investigator of the RESPECT trial. All other authors have nothing to disclose.

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