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REVIEW

Patent foramen ovale: when does it need closure?

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Abstract

A patent foramen ovale (PFO) is present in approximately 25% of the general population. Its clinical significance is primarily in patients with cryptogenic stroke. Randomized trials have evaluated whether transcatheter PFO closure reduces recurrent stroke compared to medical therapy. Evidence outside stroke, including migraine, decompression illness, and platypnea-orthodeoxia syndrome, is limited. We reviewed major randomized controlled trials and extended follow-up studies evaluating transcatheter PFO closure in patients with cryptogenic stroke. Key trials included RESPECT, REDUCE, CLOSE, DEFENSE-PFO, and RESPECT-Late. Study populations, procedural outcomes, and post-procedural management were summarized. Non-stroke indications were evaluated using available randomized and observational data. In the RESPECT trial (n=980; mean age 46±11 years; 38% female; median follow-up 5.9 years), recurrent ischemic stroke occurred in 3.6% of patients undergoing PFO closure *vs* 5.8% with medical therapy (HR 0.55; 95% CI, 0.31–0.999; p=0.046). The REDUCE trial (n=664; mean age 45±10 years; 42% female) demonstrated a 77% relative risk reduction in recurrent stroke with closure *vs* antiplatelet therapy alone (1.4% *vs* 5.4%; p=0.002). The CLOSE trial (n=663; mean age 45±11 years; 40% female) reported no recurrent strokes in the closure group *vs* 14 events (6%) in the antiplatelet group over 5.3 years (p<0.001). DEFENSE-PFO (n=120; mean age 52±12 years; 45% female) showed stroke in 0% *vs* 12.9% with medical therapy at 2 years (p=0.013). RESPECT-Late demonstrated sustained benefit over 10 years (HR 0.54; 95% CI, 0.29–0.999; p=0.046). Pooled analysis across trials indicated a 59% lower risk of recurrent stroke with closure (HR 0.41; 95% CI, 0.20-0.83). The benefit was most pronounced in patients with large shunts or atrial septal aneurysms. Post-procedural atrial fibrillation occurred in 3-5% of patients; serious procedural complications were <2%. Dual antiplatelet therapy was administered for 3–6 months, and successful shunt elimination exceeded 90%. Evidence for PFO closure in migraine with aura or decompression illness remains limited; closure in platypnea-orthodeoxia syndrome shows symptomatic improvement based on small case series. Transcatheter PFO closure significantly reduces recurrent stroke in adults aged 18-60 years with cryptogenic stroke and high-risk anatomical features. The procedure is generally safe, with low rates of serious complications. Non-stroke indications remain investigational, and patient selection with multidisciplinary evaluation is essential to maximize benefit and minimize risk.

Key words: patent foramen ovale, cryptogenic stroke, transcatheter closure.

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Clinical significance of patent foramen ovale

A patent foramen ovale (PFO) is a common anatomical variant, present in approximately 25% of the general population.[1] In most individuals, this embryonic remnant remains clinically silent throughout life. However, in select scenarios, a PFO may serve as a conduit for right-to-left shunting, potentially allowing venous thromboemboli to bypass the pulmonary circulation and enter the systemic arterial system.[2] This paradoxical embolism has been implicated in various clinical events, most notably cryptogenic stroke. Recent evidence has reshaped how clinicians view the significance of PFO and, importantly, when closure should be considered.

Evidence supporting patent foramen ovale closure in cryptogenic stroke

The primary indication for PFO closure is secondary prevention of cryptogenic stroke in young to middle-aged adults (typically 18-60 years) with high-risk PFO features, such as a large right-

to-left shunt, atrial septal aneurysm, or prominent eustachian valve (Figure 1). Cryptogenic strokes account for nearly 30-40% of ischemic strokes,[3] particularly in younger patients without evident vascular risk factors. The initial hypothesis linking PFO to paradoxical embolism in this population prompted multiple clinical trials to assess whether percutaneous PFO closure could reduce the risk of recurrent stroke. Early trials, such as Evaluation of the STARFlex Septal Closure System in Patients With a Stroke and/or Transient Ischemic Attack Due to Presumed Paradoxical Embolism Through a Patent Foramen Ovale (CLOSURE I),[4] failed to show a significant benefit. However, these studies were limited by heterogeneity in patient selection and high rates of procedural complications.

Subsequent trials with more rigorous inclusion criteria yielded different results (Table 1). The Patent Foramen Ovale Closure or Medical Therapy After Stroke (RESPECT) trial,[5] which followed 980 patients for a median of 5.9 years, demonstrated a significant reduction in recurrent ischemic stroke with PFO closure compared to medical therapy alone (HR 0.55; 95% CI, 0.31-0.999; p=0.046). In the Septal Occluder Device for Patent Foramen Ovale PFO Closure in Stroke Patients (REDUCE) trial (n=664),[6] closure led to a 77% relative risk reduction in recurrent stroke compared to antiplatelet therapy alone (1.4% *vs* 5.4%; p=0.002). The Patent Foramen Ovale Closure or Anticoagulants *versus* Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE) trial enrolled 663 patients with cryptogenic stroke and found no recurrent strokes in the PFO closure arm *versus* 14 events in the antiplatelet-only group (p<0.001).[7] All three of these trials emphasized the importance of patient selection; closure was most beneficial in individuals aged 18 to 60 with cryptogenic stroke and no alternative source of embolism, particularly when high-risk PFO features were present. These include a large shunt size, the presence of an atrial septal aneurysm, or a prominent eustachian valve.

The Device Closure *Versus* Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale (DEFENSE-PFO) trial,[8] though smaller (n=120), also showed a significant reduction in the composite outcome of stroke, vascular death, or thromboembolic event (0% *vs* 12.9% over 2 years; p=0.013). Importantly, the trial enrolled patients up to 80 years of age, and older patients achieved benefits that were at least comparable, if not greater, than those observed in younger individuals. The RESPECT-Late study,[9] the extended follow-up from the original RESPECT trial, confirmed the long-term benefit of PFO closure. Over a median of 10 years, PFO closure remained associated with lower stroke recurrence (HR 0.54; 95% CI, 0.29-0.999; p=0.046) without an increase in mortality or serious adverse events.

A pooled meta-analysis of these trials further confirmed the benefit of PFO closure by reporting a 59% reduction in recurrent stroke risk (HR 0.41; 95% CI, 0.20-0.83).[10] Notably, this benefit came at the cost of an increased risk of new-onset atrial fibrillation, observed in up to 5% of patients post-procedure. However, in most cases, the arrhythmia was transient and managed conservatively.

Based on available randomized trial data and contemporary guideline recommendations, patients most likely to benefit from PFO closure share several defining characteristics. These include age between 18 and 60 years, a documented ischemic stroke classified as cryptogenic after comprehensive evaluation, and the absence of an alternative high-risk stroke mechanism such as atrial fibrillation, significant carotid atherosclerosis, or small-vessel disease. Anatomical features that further increase the likelihood of benefit include a large right-to-left shunt, the presence of an atrial septal aneurysm, a prominent eustachian

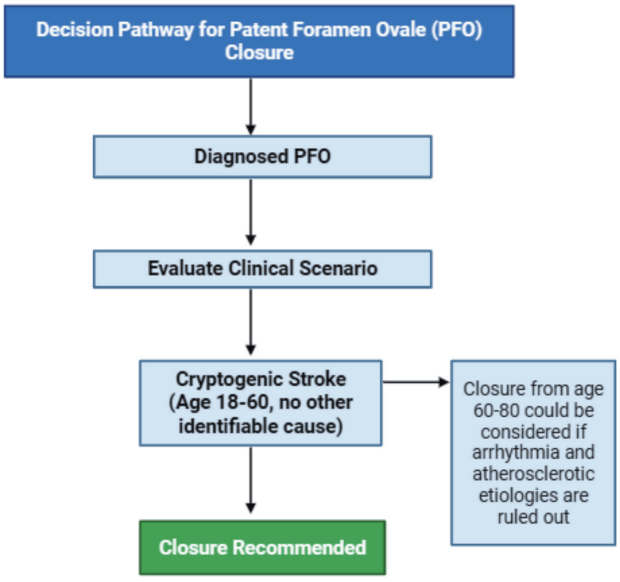

Figure 1. Decision pathway for patent foramen ovale closure.

Table 1. Summary of modern clinical trials.

	RESPECTtrial	REDUCEtrial	CLOSE trial	DEFENSE-PFOtrial
Year	2017	2017	2017	2018
Randomised	Yes	Yes	Yes	Yes
Randomized patients, n.	980	664	663	120
Follow-up time, years	5.9	3.2	5.3	2.8
Mean age, years	45.9	45.2	43	51.8
Incidence of stroke	(HR 0.55; 95% CI, 0.31 to 0.999; p=0.046)	(RR, 0.44; 95% CI, 0.24 to 0.81; p=0.02)	(HR 0.03; 95% CI, 0 to 0.26; p<0.001)	(2-year event rate 12.9%; 95% CI: 3.2 to 22.6; p=0.013)

PFO, patent foramen ovale; HR, hazard ratio; CI, confidence interval; RR,relative risk.

valve or Chiari network, and substantial shunting at rest or with Valsalva maneuver. Closure should be considered only after multidisciplinary assessment involving neurology and cardiology, with shared decision-making that accounts for patient preference and procedural risk.

Equally important in patient selection is the systematic exclusion of alternative stroke mechanisms. The benefit of PFO closure is closely linked to careful patient selection. Closure should be considered only after a comprehensive evaluation has excluded alternative causes of ischemic stroke. This includes ruling out atrial fibrillation through prolonged cardiac monitoring, assessing for large-artery atherosclerosis via carotid imaging, and evaluating for small-vessel disease or other structural heart abnormalities. Patients with identified alternative stroke mechanisms are unlikely to benefit from PFO closure, and closure in such cases may expose them to unnecessary procedural risks without reducing stroke recurrence. Therefore, multidisciplinary assessment involving neurology and cardiology is essential, with shared decision-making that integrates patient preference, anatomical features, and procedural risk.

PFO closure is not recommended in patients with a clearly identified alternative cause of stroke, such as atrial fibrillation, large-artery atherosclerosis, or small-vessel disease. Closure should also be avoided in individuals with significant comorbidities that increase procedural risk or limit life expectancy, including advanced heart failure, severe pulmonary disease, or active malignancy. Anatomical factors may preclude safe closure, for example, a very small PFO or complex septal anatomy not suitable for device placement. Additionally, closure may not be appropriate in patients for whom the procedural risks outweigh potential benefits, including those unwilling or unable to undergo long-term antiplatelet therapy or follow-up imaging. These considerations highlight the importance of multidisciplinary evaluation, incorporating both cardiology and neurology expertise, and shared decision-making to ensure patient safety and optimize clinical outcomes.

Current clinical guidelines have evolved accordingly. The 2020 American Academy of Neurology (AAN) guidelines and the 2021 American Heart Association/American Stroke Association (AHA/ASA) guidelines support PFO closure for carefully selected patients aged ≤60 years with a history of cryptogenic stroke and a high likelihood of paradoxical embolism.[11] Closure should be performed in conjunction with long-term antiplatelet therapy, and only after thorough evaluation by a multidisciplinary team including neurology and cardiology specialists. In contrast, routine closure is not recommended in patients with an alternative stroke etiology, such as atrial fibrillation or significant atherosclerosis.

Long-term data support the durability of PFO closure benefits, with studies such as RESPECT-Late demonstrating sustained reductions in recurrent stroke over a median follow-up of 10 years, without increased mortality or major adverse events. To ensure ongoing safety and efficacy, structured follow-up is recommended, including clinical assessment for recurrent neurologic events and echocardiographic imaging to confirm device position and shunt closure. Regular follow-up allows early identification of potential complications, such as device-related issues or atrial arrhythmias, and reinforces adherence to recommended antiplatelet therapy, ensuring that the long-term benefits of closure are maintained.

Although PFO closure is generally safe and effective, late complications can occur and should be considered in long-term management. These include delayed device-related issues such as erosion, embolization, or thrombus formation, as well as the possibility of recurrent stroke or transient ischemic attack, particularly in patients with residual shunting or other ongoing vascular risk factors. Late-onset atrial fibrillation may also arise beyond the early post-procedural period. These risks underscore the importance of continued clinical follow-up and periodic imaging, which allow timely detection and management of any complications, ensuring the sustained efficacy and safety of PFO closure over time.

Other potential indications

Outside of cryptogenic stroke, the evidence supporting PFO closure is less robust. One area of ongoing debate is its role in the management of migraine with aura. Observational studies have consistently reported a higher prevalence of PFO in patients with migraine, especially migraine with aura, raising the possibility of a pathophysiologic link via microembolic phenomena or vasoactive substances bypassing pulmonary filtration.[12] However, randomized trials such as Migraine Intervention with STARFlex Technology (MIST),[13] Percutaneous Closure of PFO in Migraine with Aura (PRIMA),[14] and Prospective, Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects With Migraine and PFO Using the Amplatzer PFO Occluder to Medical Management (PREMIUM)[15] failed to demonstrate a consistent reduction in migraine frequency or severity following PFO closure. While a subset of patients with frequent, refractory migraine and large right-to-left shunts may benefit, PFO closure for migraine remains investigational and is not recommended outside of clinical trials.

Similarly, the utility of PFO closure in patients with decompression illness (DCI), commonly seen in divers, has been explored. Theoretically, a PFO can allow nitrogen bubbles formed during ascent to bypass the pulmonary filter and enter systemic circulation, leading to neurologic or musculoskeletal symptoms. Case series have reported that divers with DCI and PFO are more likely to experience recurrence, and that closure may reduce this risk.[16] However, randomized data are lacking, and the decision to close a PFO in this context should be individualized, balancing the risk of recurrent DCI with procedural risks and patient lifestyle.

Another emerging area of interest is the potential role of PFO closure in patients with platypnea-orthodeoxia syndrome (POS), a rare condition characterized by positional dyspnea and arterial desaturation that improves when lying down.[17] In such patients, a PFO or other intracardiac shunt facilitates right-to-left flow in

the upright position, particularly when combined with anatomical factors such as aortic elongation or right atrial compression.[17] Case reports and small series suggest substantial symptom relief after PFO closure, and in such instances, PFO closure is generally accepted as the treatment of choice.[18]

Technical considerations and long-term outlook

From a technical standpoint, transcatheter PFO closure is a relatively low-risk procedure with a high success rate.[19] It is typically performed under local anesthesia with echocardiographic and fluoroscopic guidance. Complication rates are low, with serious adverse events occurring in fewer than 2% of patients.[19] The most common concerns include atrial arrhythmias, vascular complications, device embolization, and, rarely, cardiac erosion.[20] Use of newer, softer occluder devices and better patient selection have reduced these risks substantially.

Post-closure management generally includes dual antiplatelet therapy for 3 to 6 months, followed by lifelong single-agent therapy.[21,22] Follow-up includes clinical surveillance and, in some cases, echocardiographic imaging to confirm device positioning and shunt resolution. Long-term prognosis is excellent, particularly when closure is performed in high-risk patients after cryptogenic stroke.

Several ongoing trials and emerging device technologies may shape the future landscape of PFO closure. Newer, softer occluder devices with improved conformability and lower complication rates are under investigation, potentially reducing procedural risks such as atrial arrhythmias and device embolization. Additionally, clinical trials are exploring the benefit of PFO closure in broader patient populations, including older adults and those with non-stroke indications, as well as the use of advanced imaging for better patient selection. These developments may further refine the balance of benefits and risks and guide future guideline recommendations.

Conclusions

In conclusion, while PFO is a common and often incidental finding, its clinical significance varies widely depending on the context. The most compelling data support closure in young to middle-aged adults with cryptogenic stroke and high-risk PFO anatomy. In other scenarios, such as migraine, diving-related DCI, or platypnea-orthodeoxia, PFO closure may be beneficial for selected individuals and should be considered on a case-by-case basis. As evidence continues to evolve and device technologies improve, the role of PFO closure may further expand, but careful patient evaluation remains essential. Decisions should be guided by a multidisciplinary approach, balancing the potential benefits of PFO closure against the procedural risks and alternative treatment options.

Contributions

All the authors made a substantive intellectual contribution, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest

The authors declare no potential conflict of interest.

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