

Patent Foramen Ovale Closure: What Are the Indications?

A summary of lessons learned from positive randomized trial data.

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An estimated 700,000 people experience an ischemic stroke in the United States every year. In 25% to 30% of these patients, the etiology cannot be determined, and the stroke is labeled as cryptogenic.¹ A patent foramen ovale (PFO) occurs in one out of every four adults,² but nearly half of people with cryptogenic stroke have a PFO.³ A number of observational studies have suggested that implantation of a PFO-occluding device can reduce the risk of recurrent stroke or transient ischemic attack compared with medical therapy in patients with cryptogenic stroke.⁴ It is hypothesized that the PFO acts as a conduit for thrombus to pass from the venous to the arterial circulation; the paradoxical embolization can travel to the brain or systemic circulation. This article summarizes the lessons learned from six randomized clinical trials and presents an evidenced-based approach for identifying stroke patients who may benefit most from percutaneous PFO closure.

EARLY RANDOMIZED TRIALS

Contrary to previous observational studies, three early randomized clinical trials could not demonstrate superiority of percutaneous PFO closure over medical therapy for secondary prevention of stroke in a primary analysis.⁵⁻⁷ The first of these trials, CLOSURE I, randomized patients with an index cryptogenic cerebrovascular event to receive the StarFlex device (NMT Medical, Inc.) or medical therapy.⁵ The trial failed to show a difference between device closure and medical therapy. In addition, the device was linked to a high incidence of atrial fibrillation (AF), thrombosis, and residual right-to-left shunt.^{8,9}

The PC trial randomized patients with cryptogenic embolism to percutaneous closure with the Amplatzer

PFO occluder (Abbott Vascular, formerly St. Jude Medical) or medical therapy. The trial only demonstrated a non-significant trend in favor of PFO closure; the Amplatzer device was not associated with any increased rate of serious adverse events, major bleeding, thrombosis, or AF.⁶ It is thought that the PC trial was unable to corroborate the findings of previous observational studies because the trial was underpowered, with risk of type II error. In addition, the PC trial included patients with transient ischemic attack and noncerebral embolism, which was different than the cohort in the observational studies, although cerebrovascular imaging had to be positive.⁹⁻¹²

Although initial data from the RESPECT trial failed to show enhanced efficacy of PFO closure with the Amplatzer device in an intention-to-treat analysis,⁷ results of long-term follow-up (median, 5.9 years) showed a 45% relative risk reduction in recurrent stroke and a remarkable 62% relative risk reduction in recurrent cryptogenic stroke.¹³ Recurrent stroke prevention was enhanced in patients with certain echocardiographic features (ie, large shunt, atrial septal aneurysm). Compared with medical therapy, patients who received the Amplatzer PFO occluder had no increased rate of serious adverse events, major bleeding, AF, or thrombosis.

A pooled patient-level analysis of the three early randomized trials corroborated that percutaneous PFO closure reduced the incidence of recurrent stroke compared with medical therapy in patients with cryptogenic ischemic stroke.¹⁴ Based on these findings, the US Food and Drug Administration approved the Amplatzer PFO occluder for percutaneous PFO closure in patients with stroke presumed to be from paradoxical embolism after evaluation by a neurologist and cardiologist.¹⁵

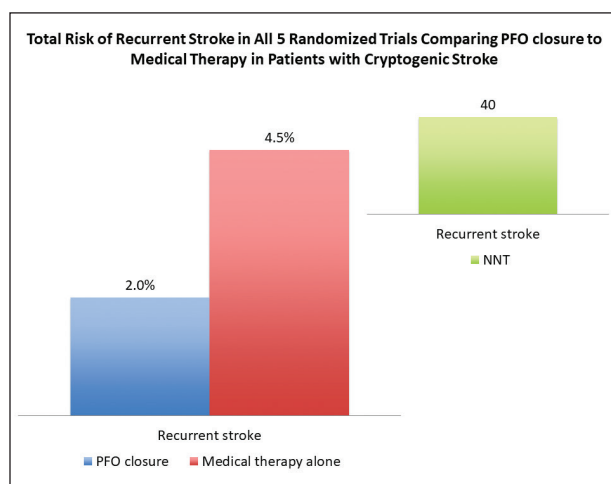


Figure 1. Risk of recurrent stroke in all clinical trials comparing transcatheter PFO closure to medical therapy in patients with cryptogenic stroke. NNT, number needed to treat. Mojadidi MK, Mahmoud AN, Elgendy IY. Percutaneous patent foramen ovale closure for cryptogenic stroke: learning from clinical trial and error. *J Thorac Dis.* 2017;9:4222–4225. With permission from AME Publishing Company.

NEWER RANDOMIZED TRIALS

In September 2017, two additional randomized trials, CLOSE and Gore REDUCE, were published.^{16,17} The CLOSE trial found that percutaneous PFO closure had greater efficacy for secondary stroke prevention compared with antiplatelet therapy alone at a mean follow-up of 5.3 ± 2.0 years (0% vs 6%; hazard ratio [HR], 0.03; 95% confidence interval [CI], 0–0.26; $P < .001$). Such a remarkable outcome of zero strokes in 5 years after PFO closure had never been demonstrated in previous trials. The CLOSE trial only included patients with an atrial septal aneurysm or large right-to-left shunt.¹⁶ The Gore REDUCE trial showed similar results, with fewer recurrent strokes in patients who received a Helex or Cardioform septal occluder (Gore & Associates) at a median of 3.2 years (1.4% vs 5.4%; HR, 0.23; 95% CI, 0.09–0.62; $P = .002$). The trial utilized CT and magnetic resonance cerebrovascular imaging in all patients to exclude stroke from large artery atherosclerosis and small vessel disease (lacunar infarcts). Additionally, patients in Gore REDUCE underwent longer inpatient AF monitoring, and those with uncontrolled risk factors were excluded.¹⁷ Both the CLOSE and Gore REDUCE studies reported no difference in serious adverse events or major bleeding between percutaneous PFO closure and medical therapy; however, device closure resulted in a more than fourfold greater incidence of AF in both studies ($P < .05$ for both).

Subsequently, a study-level meta-analysis of all five randomized clinical trials further confirmed that in patients with cryptogenic stroke, percutaneous PFO clo-

sure reduced the risk of recurrent stroke compared with medical therapy (2.0% vs 4.5%; risk ratio, 0.42; $P = .027$) (Figure 1). However, the study also demonstrated a four-fold increased risk of AF or flutter in patients who received a device, and the risk was device dependent (Figure 2).¹⁸

More recently, the DEFENSE-PFO trial was published.¹⁹ This smaller study randomized 120 patients to PFO closure or medical therapy, including only cryptogenic stroke patients who had high-risk PFOs (ie, atrial septal aneurysm, intermittent septal hypermobility, shunt size > 2 mm). At a 2.8-year median follow-up, the study reported significantly higher cerebrovascular events in patients randomized to medical therapy compared to PFO closure (2-year event rate, 12.9%; 95% CI, 3.2%–22.6%; standard error, 5.0). Corroborating results of the CLOSE trial, zero strokes were also reported in the DEFENSE-PFO trial within 2.8 years (median) among cryptogenic stroke patients who had high-risk PFOs and underwent PFO closure.¹⁹

SAFETY OF PERCUTANEOUS PFO CLOSURE

A number of different PFO-occluding devices were utilized in the clinical trials: CLOSURE I used the StarFlex device; the PC, RESPECT, and DEFENSE-PFO studies used the Amplatzer PFO occluder; the Gore REDUCE study evaluated the Helex or Cardioform septal occluder; and the CLOSE study permitted 11 different devices.

Chest pain has been reported as an infrequent complication related to device implantation, attributed to enhanced inflammation and sometimes associated with nickel allergy.²⁰ The Amplatzer device contains more nickel than other devices but was not found to be associated with more chest pain events in the PC and RESPECT studies compared with medical therapy ($P =$ nonsignificant for both). Additionally, the DEFENSE-PFO trial did not report any chest pain events associated with the Amplatzer device. However, an observational study of approximately 14,000 PFO device implantations reported an incidence of 1 in 500 in which implants resulted in surgical removal, most frequently from persistent, severe chest pain, which was thought to be due to allergy-mediated scar tissue formation in half of the cases.²⁰

Safety outcomes from clinical trials demonstrated no statistical difference in all-cause serious adverse events (including major bleeding) comparing percutaneous PFO closure to medical therapy. The CLOSURE I study had the highest incidence of device thrombosis, which was reported in two patients, compared with zero cases in the PC, RESPECT, DEFENSE-PFO, and Gore REDUCE studies. All trials, except for studies using the Amplatzer PFO occluder (ie, PC, RESPECT, DEFENSE-PFO), demonstrated a significantly increased incidence of AF or flutter in patients who underwent PFO device implantation. Most postdevice atrial arrhythmias in the trials occurred early

(< 45 days) and were usually characterized by a single episode that aborted with medical therapy, no intervention, or cardioversion. One observational study suggested that the progression of AF after PFO closure to permanent AF is infrequent at 3.8%.²¹ Data from randomized trials indicate that the risk of stroke from device-associated AF is rare (~0.2% of patients randomized to a device), and the majority of patients do not need long-term anticoagulation (anticoagulation was discontinued in 70% of patients in the CLOSE trial in whom it was started).

DISCUSSION

Results from the pooled analysis of the three early randomized trials, the more recent RESPECT (long-term follow-up), CLOSE, Gore REDUCE, and DEFENSE-PFO trials, and the meta-analysis that included the newer trials of cryptogenic stroke confirm that percutaneous PFO closure is more effective for secondary prevention of stroke compared with medical therapy.^{13,16-19} Subgroup analyses of the RESPECT study further demonstrated that secondary prevention of stroke was enhanced when PFO closure was performed in patients with a large shunt or atrial septal aneurysm.^{7,13} In support of this observation, the DEFENSE-PFO and CLOSE trials demonstrated a remarkable finding of zero strokes in

2 and 5 years, respectively, when closure was performed for stroke patients with a high-risk PFO (atrial septal aneurysm, intermittent hypermobile septum, or large PFO).

A major differentiation between the earlier trials with statistically nonsignificant data and more recent significantly positive data is the inclusion of patients who had an index stroke that was more likely due to paradoxical embolism in the four recently published trials (RESPECT, CLOSE, Gore REDUCE, and DEFENSE-PFO). The results of these four trials and lessons learned from the earlier studies have led to the recognition of a high-risk cohort of stroke patients who would benefit most from PFO closure.

When recommending PFO closure for a patient who had a stroke of uncertain origin, the question arises whether the PFO was the pathway through which a venous thrombus arrived on the arterial side or if the PFO was just “an innocent bystander.” The RoPE study attempted to separate detected PFOs in cryptogenic stroke patients into those likely to be the culprit (and therefore requiring closure) from those likely to be an innocent bystander (and therefore to be left alone).²² With the RoPE score, individual patients could be provided with a probability that their PFO was or was not attributed to their stroke by considering their age, infarct pattern, smoking status, and other comorbidities.

However, a major limitation of the RoPE score is that it does not take other clinical findings into account, the presence of which also make it more likely that the stroke was due to paradoxical embolism. These include coexisting venous thromboembolism, stroke occurring after straining, and certain echocardiographic features of the PFO anatomy (ie, atrial septal aneurysm, large PFO). The RESPECT, CLOSE, and DEFENSE-PFO trials showed that stroke patients who have these echocardiographic features benefit most from PFO closure. Additionally, use of methods such as the RoPE score may lead to the assumption that a PFO cannot cause a stroke in the presence of any other known cause of stroke; however, this is

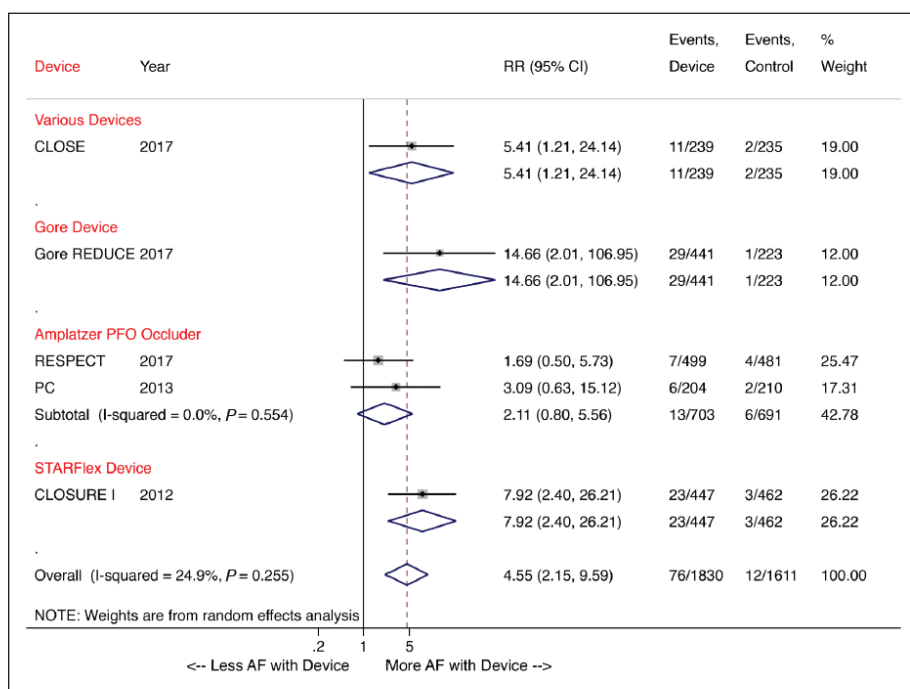


Figure 2. The risk ratio (RR) of AF or flutter by random effects meta-analysis according to the type of PFO occlusion device used in different randomized clinical trials. Adapted from Mojaddidi MK, Elgendy IY, Cutting WB, et al. Percutaneous patent foramen ovale closure for cryptogenic ischemic stroke: is it time for new guidelines? *AME Med J.* 2017;2:173. With permission from AME Publishing Company.

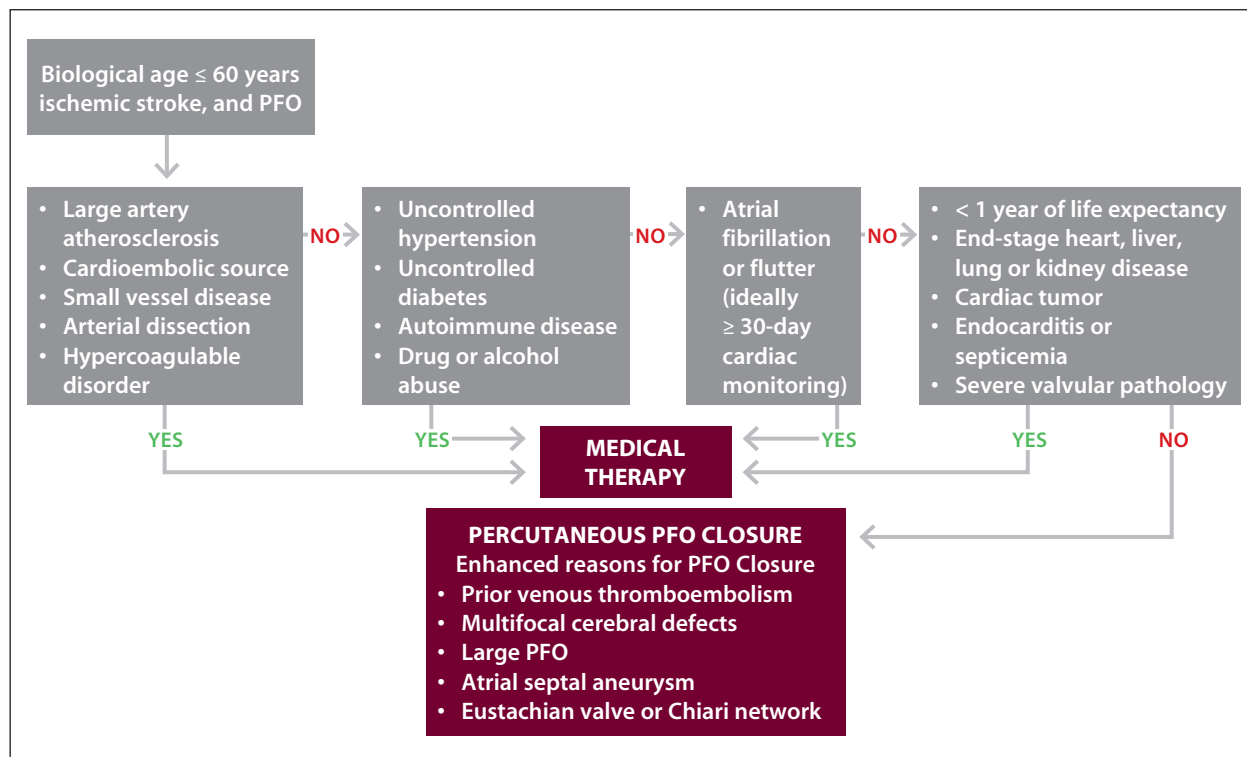


Figure 3. Evidence-based algorithm for PFO closure in ischemic stroke patients for highest clinical yield based on randomized trials. Patients can expect the greatest benefit from percutaneous PFO closure if they have no other cause of cardiovascular stroke on imaging/laboratory analyses, no uncontrolled risk factors, no AF or flutter, and no poor prognostic markers. However, there are situations in which it is impossible to prove the precise etiology of the stroke. In those cases, because the risk of PFO closure is very low, it may be prudent to treat whatever is possible, such as lowering cholesterol but also closing a PFO. Adapted from *J Am Coll Cardiol*, 71, Cryptogenic stroke and patent foramen ovale, Mojadidi MK, Zaman MO, Elgendy IY, et al, 1035–1043, 2018, with permission from Elsevier.

counterintuitive. For example, a young ischemic stroke patient who is found to have a large PFO with an atrial septal aneurysm will likely benefit from PFO closure, even in the presence of AF for short duration. There are also many other examples of strokes that do not have these echocardiographic characteristics and randomized clinical trials included these patients, and still a benefit of PFO closure was shown over medical therapy. There are patients 60 to 70 years of age who have a cryptogenic stroke associated with a PFO and no evidence for atherosclerotic disease. These patients were not included in the randomized trials, but neurologists often consider PFO closure for them.

Although the guidelines in Canada and Europe are already up to date to reflect the most recent randomized data,²³⁻²⁵ United States guideline recommendations are in the process of being updated to support percutaneous PFO closure as first-line treatment in all patients who are 18 to 60 years of age who have a stroke that is attributed to paradoxical embolism.

The identification and management of a patient's stroke related to a PFO requires a multidisciplinary team involving a neurologist, cardiologist, and other health care professionals specializing in stroke care. Neurologists should make the initial diagnosis of cryptogenic stroke, and cardiologists are tasked with ensuring that other cardiovascular culprits and uncontrolled risk factors have been identified prior to recommending PFO closure.

Given the risk of early postclosure AF and the potential for undetected AF as a cause for the index stroke, cardiologists should ideally use prolonged ≥ 30 -day cardiac monitoring as a routine part of the stroke workup.^{26,27} Risk of device-associated AF is a concern and should be discussed with all patients, along with other procedure-related risks, prior to PFO closure. Multidisciplinary stroke teams can facilitate the cryptogenic stroke evaluation to ensure that PFO closure is recommended for stroke from no other likely etiology (Figure 3).²⁸

CONCLUSION

In patients with cryptogenic stroke, randomized trials have shown a recurrent stroke risk of approximately 1% per year in the medically treated arm with no clear-cut therapeutic difference between antiplatelet and oral anticoagulation therapy with warfarin or novel oral anticoagulants, in the absence of atrial arrhythmias.²⁹⁻³¹ Although the CLOSE trial showed a nonsignificant 56% lower risk of stroke with oral anticoagulation versus antiplatelet therapy, the study was underpowered given that anticoagulation was contraindicated in many patients.³² Until a randomized trial is conducted to compare the safety and efficacy of oral anticoagulation to PFO closure in patients with cryptogenic PFO-mediated stroke, percutaneous PFO closure should be considered the most effective and safest treatment to reduce the risk of recurrent stroke in accordance with randomized evidence-based data.³³ ■

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