

# Closure of patent foramen ovale for secondary prevention of cryptogenic stroke: current perspectives

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Patent foramen ovale (PFO) is found in about 25% of the population from autopsy studies. In patients with cryptogenic stroke (which accounts for about 30% of strokes), the prevalence of PFO is even higher (about 40–50%). In patients younger than 55 years of age with cryptogenic stroke, the odds ratio for the prevalence PFO is 6 (95% CI: 3.72–9.68), suggesting a very strong association between the two [1]. Over the past decade, PFO closure has been studied as a non-pharmacologic means of secondary prevention of stroke. The earlier devices used for PFO closure were the CardioSEAL and STARFlex devices (NMT Medical, Boston, MA). Currently, the Amplatzer PFO Occluder (Abbott, St. Paul, MN) and Gore Cardioform septal occluder (W. L. Gore & Associates, Inc, Flagstaff, AZ) are widely used. Essentially, these devices have a double-disc design with left and right atrial discs, deployed percutaneously through a femoral venous approach.

Earlier trials [2–4] had failed to show a significant benefit of PFO closure over medical therapy. Accordingly, in 2014, the American Heart Association/American Stroke Association guidelines recommended against routine use of PFO closure for secondary prevention of cryptogenic stroke in patients with a PFO without evidence of deep venous thrombosis [5]. However, recent trials [6–9] have shown superiority of PFO closure over medical therapy alone to prevent recurrent strokes in this population. The essential details of the individual trials are summarized in Table I. Recently published meta-analyses have also confirmed the findings from the recent trials. In a meta-analysis of 2892 patients enrolled in 4 randomized control trials [3, 6–8], PFO closure decreased the absolute risk for recurrent stroke by 3.2% (risk difference: –0.032; 95% CI: –0.050 to –0.014) compared with medical therapy [10]. In another meta-analysis that included 3440 patients enrolled in 5 major randomized trials [2, 3, 6–8], PFO closure significantly reduced recurrent stroke (OR = 0.41; 95% CI: 0.19–0.90;  $p = 0.03$ ) compared to medical therapy alone [11]. Of note, new onset atrial fibrillation was significantly more frequent after PFO closure (OR = 5.75, 95% CI: 3.09–10.70;  $p < 0.00001$ ).

What should the current evidence-based practice in patients with PFO and cryptogenic stroke be? Interpretation of conflicting results from individual trials is compounded by significant heterogeneity in study population, medical therapy and the type of device used for closure. However, this heterogeneity also provides us the opportunity to find out the

Table I. Comparison of trials on PFO closure in cryptogenic stroke

Parameter	CLOSURE-1 (2012) [2]	PC (2013) [3]	RESPECT (2013) [4]	RESPECT extended (2017) [8]	Gore REDUCE (2017) [6]	CLOSE (2017) [7]	DEFENSE-PFO (2018) [9]
Number of patients	909	414	980	980	664	663	120
Mean age [years]	45.9 ±9.5	44.5 ±10.1	45.9 ±9.9	45.9 ±9.9	45.2 ±9.4	43.3 ±10.4	51.8
Moderate/large RLS	52.90%	65.60%	75.20%	75.20%	81.30%	100%	100% <sup>1</sup>
ASA	36.60%	23.70%	35.60%	35.60%	20.40%	32.80%	10.8%
Follow-up (mean) [years]	2	4.1 <sup>2</sup>	2.1	5.9	3.2	5.3	2.8
Closure device used	STARFlex	Amplatzer PFO	Amplatzer PFO	Amplatzer PFO	Cardioform septal occluder <sup>^</sup>	11 different devices*	Amplatzer PFO
Medical therapy	Antiplatelet or AC or both	Antiplatelet or AC	Antiplatelet or AC	Antiplatelet or AC	Antiplatelet	Antiplatelet or AC	Antiplatelet or AC
Anticoagulation	34%	31%	25%	25%	0%	28.20%	21.7% <sup>3</sup>
Effective closure	86.10%	95.90%	93.50%	93.50%	94.50%	93.00%	100%
End-points	Composite of stroke or TIA, death from any cause in first 30 days, death from neurologic causes between 31 days and 2 years	Composite of death, stroke, TIA or peripheral embolism	Composite of recurrent ischemic stroke	Composite of recurrent ischemic stroke	Ischemic stroke and new brain infarction on imaging	Stroke	Composite of stroke, vascular death, or thrombolysis in myocardial infarction-defined major bleeding
Endpoints in closure device group	5.5%	3.4%	3.4%	3.6%	1.4%	0%	0%
Endpoints in medical therapy group	6.8%	5.2%	5.2%	5.8%	5.4%	6% <sup>4</sup>	6%
P-value	0.37	0.34	0.08	0.046 <sup>5</sup>	0.002	< 0.001	0.013
PFO beneficial	No	No	No	Yes	Yes	Yes	Yes

PFO – patent foramen ovale, \*approved by Interventional Cardiology Committee, <sup>^</sup>replaced Helex septal occluder, RLS – right-to-left shunt, ASA – atrial septal aneurysm, TIA – transient ischemic attack, CLOSURE-1 – 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, PC – Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism, RESPECT trial – Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment, Gore REDUCE trial – Gore HELEX Septal Occluder/GORE CARDIOFORM Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed TIA in patients with PFO, CLOSE trial – Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence, DEFENSE PFO trial – Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale. <sup>1</sup>High-risk PFO, i.e. PFO with atrial septal aneurysm, hypermobility or PFO size ≥ 2 mm on transesophageal echocardiography. <sup>2</sup>4.1 years in closure group, 4 years in medical therapy group. <sup>3</sup>25% at 30 days, 23.1% at 6 months, 21.7% at 12 months for medication-only arm, compared to 15% at 6 months, 7.7% at 30 days, 6.4% at 12 months for PFO closure arm. <sup>4</sup>AC group is 1.6% – not powered to compare, antiplatelet group only is 6%. <sup>5</sup>Subgroup analysis showed a benefit for closure in presence of substantial right-to-left shunt (p = 0.005).

subset of the population for which PFO closure is potentially effective.

First, let us discuss the differences in patient selection. The benefit of PFO closure is noted when patients with more significant shunting were included. For instance, about 80% of patients in the Gore REDUCE trial [6] (Gore Helex Septal Occluder/GORE CARDIOFORM Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed TIA in Patients With PFO) and over 75% of patients in the RESPECT trial [4, 8] (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) had at least a moderate degree of right-to-left shunt through the PFO. Similarly, in the CLOSE trial [7] (Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence), all patients had at least a moderate right-to-left shunt. In the recently published DEFENSE-PFO trial (Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale) [9], all patients had high-risk PFO, i.e. size  $\geq 2$  mm, PFO with atrial septal aneurysm, or hypermobility (phasic septal excursion into either atrium  $\geq 10$  mm) on transeophageal echocardiography.

Patent foramen ovale can be classified as small ( $< 2$  mm), medium (2–3.9 mm), or large ( $\geq 4$  mm). On bubble study, the shunt can be classified as small ( $\leq 5$  bubbles), moderate (6–25 bubbles), or severe ( $> 25$  bubbles). Patients with a large PFO or with a moderate-to-severe shunt have an increased risk of recurrent stroke and are more likely to benefit from device closure [12]. Atrial septal aneurysm, as defined by excursion of the interatrial septum by 10 mm or greater, is independently associated with an increased risk of recurrent stroke. This can sometimes be associated with a large PFO and lower rates of successful closure. Patients with lacunar stroke, caused by small vessel disease of the brain, are not likely to benefit from PFO closure. Of the earlier trials, only the RESPECT trial [4] had excluded patients presenting with lacunar infarction. The PC trial (Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism) and CLOSURE I trial [2] (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) had also included patients with TIA which were not necessarily cryptogenic in nature.

Second, we will discuss the differences in medical therapy in the control arm. In the earlier trials, medical therapy consisted of antiplatelets and/or anticoagulants, which was based on the discretion of the treating physician. In the new-

er trials, only antiplatelet agents were exclusively used in the control arm, which is consistent with current established stroke guidelines. Although in the CLOSE trial [7] there was a separate arm of patients with anticoagulant use, there was lower than expected patient enrollment, and this group was underpowered to make any meaningful comparisons. In the DEFENSE-PFO trial [9], the decision on anticoagulation was based on the treating physician's discretion (for example, at 6 months, 7.7% of patients in the PFO closure arm versus 23.1% in the control arm were on warfarin).

Third, there were significant differences in the type of device used. The STARFlex device that was originally used in the CLOSURE-1 trial is already off the market due to inferior efficacy (effective closure was 86.1%) and concerns with safety. The Amplatzer PFO Occluder and Gore Cardioform septal occluder that have superior efficacy were used in the recent trials.

Fourth, the earlier trials were underpowered to detect any significant benefit with PFO closure. The PC trial suffered from recruitment and dropout issues. The follow-up period in CLOSURE-1 and RESPECT trials was only about 2 years (as compared to 5.9 years in the RESPECT extended trial and 5.3 years in the CLOSE trial).

The Risk of Paradoxical Embolism (RoPE) Score [13] was originally developed in 2011 to identify patients with cryptogenic stroke and a PFO in whom PFO was likely to be the cause of their stroke. Components of the score include age (0–5 points, with younger age assigned more points), cortical infarct on imaging, absence of smoking, hypertension, diabetes mellitus, and prior stroke/TIA (all the above assigned 1 point each). The higher the score, the more likely the stroke is related to paradoxical embolism from the PFO. Although this has not been validated or studied in PFO closure, it is prudent to use this score to screen out patients with minimal potential benefit (especially a score of 0–3 where the stroke is likely from other etiologies). One of the main drawbacks with the score is that the size of the PFO or severity of shunt is not factored into this calculation.

Our suggested approach is as follows: PFO closure should not be routinely performed in all patients with cryptogenic stroke. In younger patients (less than 55 years of age) with cryptogenic stroke and a high risk PFO (moderate to severe right-to-left shunt; atrial septal aneurysm; increased atrial septal excursion  $\geq 10$  mm; PFO size  $\geq 2$  mm), PFO closure significantly reduces the risk of recurrent stroke compared to medical therapy alone. Of note, a higher incidence of atrial fibrillation was seen in the PFO closure group in most trials. However, when overall serious adverse events were compared, there was no significant difference be-

tween the two groups. Candidacy for anticoagulation if atrial fibrillation were to occur after device implantation should be a consideration when patients are being evaluated for this procedure.

In conclusion, we suggest shared decision-making with the patient, explaining the likelihood that the stroke is caused by the PFO, and discussing the evidence regarding efficacy and risks of the procedure.

### Conflict of interest

The authors declare no conflict of interest.

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