

Device closure for patent foramen ovale in patients with cryptogenic stroke: which patients should get it?

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Patent foramen ovale (PFO) and cryptogenic stroke (CS) both have a high prevalence. The optimal treatment to reduce stroke recurrence after CS remains controversial. Results from clinical trials, meta-analyses, and position papers, support percutaneous PFO device closure and medical therapy compared to medical therapy alone. However, the procedure may be associated with cardiac complications including an increased incidence of new atrial fibrillation. The benefit/risk balance should be determined on a case-by-case basis with the greatest benefit of PFO closure in patients with atrial septal aneurysm and PFO with large shunts. Future studies should address unsolved questions such as the choice of medical therapy in patients not undergoing closure, the duration of antiplatelet therapy, and the role of PFO closure in patients over 60 years old.

Introduction

Cryptogenic stroke (CS) (or stroke of undetermined origin), as defined by the TOAST classification, is a brain infarction not attributable to a definite cardioembolic event, large or small artery disease, or other diseases after appropriate vascular, cardiac, and serological investigations, suspected to result from a cryptogenic embolism.^{1,2}

The relationship between CS and PFO was first reported more than 20 years ago. Percutaneous PFO closure has been proposed for stroke recurrence prevention. Multiple trials with conflicting results have been published, leading to a Class 2b recommendation for PFO closure in US stroke guidelines.³⁻⁵

Three new RCTs in 2017 (CLOSE,⁶ REDUCE,⁷ and DEFENSE⁸) and three meta-analyses in 2018-2019 have been published,⁹⁻¹¹ favouring PFO closure for CS. Consensus statements from the French Society of

Cardiology¹² and the European Society of Cardiology have been published in 2019.¹³ The recently published updated AHA stroke guidelines raised doubts about the quality of the RCTs and the strength of results.¹⁴ Many questions remain unanswered and require a critical review and evaluation.

Epidemiology, anatomy, and physiology

Anatomy

The foramen ovale (FO) allows the shunting of blood from right (RA) to left atrium (LA) *in utero*. At birth the increase in LA pressure reversing the interatrial gradient, pushes the Septum Primum against the Septum Secundum, closing the FO. A true anatomic closure occurs during the first days of life. However, in one-quarter of adults, an incomplete apposition of Septum Primum and Septum Secundum creates a 'tunnel' between RA and LA, known as a PFO. Therefore, in the absence of a paradox embolism, a PFO should be considered an anatomical variant instead of a

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true pathologic condition. Different lengths of the tunnel and different left atrial opening positions may be seen; a prominent Eustachian valve may increase blood flow from the inferior vena cava (IVC) to the PFO. In anatomic studies, the PFO diameter ranges from 1 to 19 mm.¹⁵ Septum Primum may become stretched and aneurysmal (ASA), sometimes with fenestrations, increased mobility and bulging.

Cryptogenic stroke and patent foramen ovale

Cryptogenic stroke and PFO are two conditions with high prevalence and therefore it is challenging to prove their causal relationship. About 30% of stroke in USA and a similar number (~25%) in Europe are of unknown origin.¹⁶ No gender difference in CS incidence has been shown.

The risks of recurrent stroke after CS at 1 month was 4.2% in the Oxford meta-analysis and 3% in the National Institute of Neurological Disorders and Stroke Data Bank.¹⁷ At 2 years, recurrence risk ranges from 14 to 20%, and 33% at 5 years in Olmstead county.¹⁸

The rate of CS in the population, and the rate of recurrent stroke following CS in the recent RCTs on CS and PFO was lower than previous reports, reducing the statistical power of these trials. Some studies reported a higher rate of CS recurrence in patients with ASA or atrial septum (AS) hypermobility (>10 mms) together with PFO.⁵

Patent foramen ovale and cryptogenic stroke

Patent foramen ovale is detectable in ~25% of adults (from 10 to 24% at transthoracic echocardiography, from 22-39% at transoesophageal echocardiography and from 15 to 36% at autopsy).¹⁹ Patent foramen ovale prevalence seems superior in patients with CS. Isolated PFO was found in 37% of 561 subjects (mean age 42 years) with CS and PFO + ASA in further 9%.²⁰ A strong association of PFO and CS has been shown especially if an ASA or a large right to left shunt is present.^{21,22} Some smaller studies suggest an association between PFO with small or medium shunt plus a large ASA and an increased risk of stroke recurrence.⁵

In a meta-analysis of Kent including 3000 patients with CS and in a study of Thaler, a younger age, radiographic evidence of a cortical infarct and mainly the absence of traditional vascular risk factors were associated with PFO detection.^{23,24}

However, many studies following PFO patients without a history of stroke, failed to identify an increased risk, suggesting other factors in addition to its presence causing the paradoxical embolism and the cerebral event.

Cryptogenic stroke and cardiac conditions

Most CS are considered to be due to cardiac thromboembolism based on the features on the brain imaging, mainly from undiagnosed atrial fibrillation (AF), often missed if either asymptomatic or if ECG telemetry or prolonged recording is not performed. All CS patients should undergo a 12-lead ECG and a 24-h Holter monitoring or ideally longer monitoring (48-72 h or 7 days ECG patch). Moreover, high-risk AF patients (i.e. age >65 years, hypertension,



Figure 1: Echocardiography TOE: a thrombus through the PFO.

diabetes, heart failure, or cardiac structural abnormalities) require longer monitoring. An implantable loop recorder for six months to rule out AF, particularly before a PFO closure decision, is reasonable if standard screening is negative.²⁵

The most accepted pathophysiological hypothesis to explain PFO and CS is a 'paradoxical embolism', crossing the PFO and entering the systemic circulation. Intermittent elevation of RA pressure, for example during the Valsalva manoeuvre, coughing, or caval compression, will increase right-to-left shunting and the potential risk. There are case reports of young patients with CS presenting both a PFO and deep venous thrombosis (DVT). Rarely, a thrombus has been shown on imaging passing through the PFO and straddling the AS (Figure 1).

Another potential source is thrombus formation *in situ* within the PFO or on the atrial walls if an ASA is present. It could act like a net, capturing thrombi in the right atrium (RA) and conveying them to the PFO.

Diagnostic issues

Most patients (almost 90%) with stroke or TIA have a normal transthoracic echocardiogram.

When an interatrial communication is suspected but not directly seen, a PFO may be shown using contrast imaging methods, with the passage of agitated saline bubbles into the left heart chambers within three cardiac cycles of RA opacification.

Semi-quantification of shunts may be determined by the number of bubbles crossing into the LA: small between 3 and 10 bubbles; medium between 10 and 20; large >20. Both shunt direction and degree of shunting can change according to the patient's physiologic state, ability to perform Valsalva manoeuvre, and point of saline injection.

The contrast study is typically performed via an arm vein, but sometimes blood flow within the RA may not allow for significant bubble shunting because PFO shunt flow preferentially comes from the IVC. Accordingly, in some cases with high suspicion, echocardiography (TTE, TOE, or intracardiac echocardiography) using a lower extremity vein in the alert patient capable of Valsalva manoeuvre is reported as the most sensitive method of PFO diagnosis, especially with prominent Eustachian valve.

Echocardiographic detection of shunting is diagnosed by contrast transthoracic echocardiography (cTTE), contrast transoesophageal echocardiography (cTOE), or contrast transcranial Doppler (cTCD). Sensitivity and specificity are 46% and 99% for cTTE, 89% and 92% for cTOE, and 96% and 93% for cTCD, respectively.²⁶⁻²⁸ A Valsalva manoeuvre may be necessary to increase RA pressure transiently to unmask a transient right-to-left shunt across a PFO.

The algorithm recommended by the recent ESC position paper is based on the sensibility and specificity of these exams. Depending upon availability and expertise, cTTE is recommended as the first investigation in CS to unveil a PFO, with cTOE or cTCD as alternatives if suspicion is high but the cTTE is normal. cTCD has two important limitations: (i) it does not distinguish an intracardiac shunt from an intrapulmonary shunt (e.g. pulmonary arteriovenous malformations), (ii) it does not assess the AS anatomy. In centres where cTCD is unavailable, cTTE with harmonic imaging is an alternative with the advantage of providing detailed anatomy of the IAS sometimes identifying an ASD if present for PFO device closure if indicated.

In patients with a positive contrast study result, a cTOE clarifies the anatomy thanks to the high-resolution direct view of the AS, especially at the level of the fossa ovalis. An ASA is diagnosed by cTOE if there is a fixed displacement or a hypermobile mobile fossa ovalis region of the AS toward the RA or LA, or both, exceeding 10 mm from the midline or a combined total right and left excursion of 15 mm.

The main disadvantage of cTOE is that the sedated patient cannot perform the Valsalva manoeuvre, and some PFOs remain undiagnosed. In selected cases, it may be useful to antagonize sedation.

Nakayama *et al.* proposed an echocardiographic score to define high-risk PFO. The presence of two or more high-risk PFO features (score ≥ 2) is associated with CS. These hallmarks are large-size PFO (>2 mm in height), long-tunnel PFO (>10 mm in length), ASA, hypermobile AS, prominent Eustachian valve, or Chiari's network, large right-to-left shunt at rest and during Valsalva manoeuvre, and low-angle PFO ($<10^\circ$ of PFO angle from inferior vena cava).²⁹

Management of a patient with the incidental diagnosis of a patent foramen ovale

In daily practice, a PFO may be found incidentally in a patient without any clinical signs and symptoms. In a prospective study, PFO was not shown to be predictive of future cardiovascular events after age and co-pathologies correction.³⁰ Currently, a conservative approach is recommended and there is no role for percutaneous PFO device closure for primary prevention. Patients with an incidental PFO do not require any specific treatment, and only life-style counselling is recommended e.g. avoid scuba diving and, DVT prophylaxis and treatment. The scuba diving should not exceed the 25-30m of depth using nitrox instead of compressed O₂.

Moreover, the Mist Trials showed negative results of PFO Closure for only the prevention of migraine.³¹

Secondary prevention of cryptogenic stroke in patients with patent foramen ovale: patent foramen ovale closure

Data from the randomized trials and a meta-analysis led the authors of a recent Position Paper of the European Society of Cardiology to support PFO closure in high-risk patients. These recommendations are based on the evaluation of two factors: (i) probability that the PFO has a role when other aetiologies of CS have been excluded and (ii) the probability of recurrent CS.

It should be remembered that PFO closure has potential complications. In a cohort of 730 patients who underwent PFO closure for CS, 6.3% had a recurrent stroke and/or TIA, and 3.9% had a residual right-to-left shunting.³² The incidence of new AF varies depending upon the PFO device delivered, with published rates of 13% for the Cardioform device, 4% for the Helex device, and 4% for the Amplatzer PFO device.³³ Rare complications include device thrombosis, embolism, displacement, infective endocarditis, and aortic root erosion.

Patent foramen ovale closure decision should be undertaken by a multidisciplinary team (MDT), including a neurologist, confirming that the CS is probably due to an embolic event, the PFO has high-risk features, the exclusion of other causes of embolic stroke, especially AF, and anatomical eligibility for device closure and risk of complications. The indication should be discussed with the patient with a clear and complete explanation of the benefits and risks of the procedure, additional medical therapy required, and alternative options.

Randomized studies

Several RCTs comparing PFO closure with antiplatelet and anticoagulant therapy have been reported with details of their design, study population, and device (*Table 1*). Three large RCTs (CLOSE,⁶ REDUCE,⁷ and DEFENSE-PFO⁸), and the RESPECT⁵ with prolonged follow-up, showed that PFO closure in the first 6 months (in the CLOSURE³⁴) reduces stroke relapses with no changes in mortality, in young people (<60 years) with a high-risk of PFO.

Meta-analysis

In the meta-analysis despite methodology limitations, consensus is currently that PFO device closure should be considered in CS patients with the highest risk. No differences have been reported to suggest the superiority of a specific PFO closure device (*Table 2*).

Patent foramen ovale closure indications

Clinical variables which favour a PFO device closure for secondary prevention following CS are young age, no common CV risk factors, no other potential CV causes of thromboembolism, the concomitance of DVT or DVT risk factors, ASA, or large shunt association. ASA association seems justify the PFO closure, while less agreement is about only moderate or severe shunts without an ASA or other risk factors.

Table 1 Methodological comparison of the recent randomized clinical trials on PFO closure after cryptogenic stroke

	Closure I Trial	PC Trial	Respect (2013)	Respect-Long trial	Defence - PFO	Reduce trial	Close Trial
Population	909 pts PFO + CS/TIA 6 months. PFO + CS Age: 18-60 years.	414 pts PFO + CS Age < 60 years.	980 pts PFO + CS within 270 days Age: 18-60 years	980 pts PFO + CS within 270 days Age: 18-60 years	120 pts PFO + CS Age: 18-80 years.	664 pts PFO + CS within 180 days Age: 18-59 years.	980 pts recent CS PFO-related Age: 16-60 years.
PFO risk factors:							
• Shunt	+++/++++	+++/++++	++	++	++/++++	++/++++	++/++++
• ASA	++	+++/++++	+	+	++/++++	++/++++	++/++++
Shunt + ASA							
Intervention:	PFO closure + antiplatelet (n=447)	PFO closure+ antiplatelet (n=204)	PFO closure+ antiplatelet (n=499)	PFO closure+ antiplatelet (n=499)	PFO closure + medical therapy (n=60)	PFO closure + antiplatelet (n=441)	PFO closure + antiplatelet therapy
Control:	Warfarin or ASA or both	Warfarin 6 months followed by aspirin or antiplatelet (n=211)	OAC (n=481)	OAC (n=481)	Antiplatelet or anticoagulation (n=60)	Antiplatelet (n=223)	Warfarin or DOACs Aspirin, clopidogrel or aspirin combined with extended release dipyridamole
Primary endpoint	Stroke/TIA at 2y, death from any cause at 30 days or 31 days - 2 years death from neurologic causes	Death, non-fatal stroke, TIA, peripheral embolism	Recurrent non-fatal or fatal stroke or early death after randomization	Recurrent non-fatal or fatal stroke or early death after randomization	Stroke, vascular death and TIA	Freedom from clinical evidence of ischaemic stroke	Fatal or non-fatal stroke Fatal/major procedure-related and haemorrhagic complications
Follow-up period (years)	2	4	2.6	5.9	2.8	3.2	3.2
Device	Starflex	Amplatzer	Amplatzer	Amplatzer	Amplatzer	Helix or Cardioform	Helix or Cardioform
Procedural success	86.1%	95.9%	-	-	-	-	93.7%
Primary endpoint	5.5%	3.4%	1.8%	1.8%	0%	-	1.4%
Adjusted HR (95% CI)	0.78	0.63	0.49	0.55	P=0.03	-	1.4%
P-value	P=0.37	P=0.34	P=0.08	P=0.046	P=0.013	-	0.03
Recurrent stroke	2.9%	0.5%	1.8%	1.0%	0%	1.4%	1.3%
Adjusted HR (95% CI)	0.90	0.20	0.49	0.38	P=0.013	0.23	0.03
P-value	P=0.79	P=0.14	P=0.08	P=0.007	P=0.013	P=0.002	P<0.001
Periprocedural AF	5.7%	2.9%	3.0%	1.5%	-	6.6%	6.6%
Limitations	• Failed primary endpoint. • Minimal lost-to follow-up	• Failed primary endpoint. • Baseline risks, devices used, Endpoint definitions differed among the trials: direct comparisons event rates	• Large number lost to follow-up mainly in long-term when only medication received	• Large number lost to follow-up. • Potential bias (unblinded referral for endpoint adjudication)	• Early termination for patient safety, resulting in an underpowered study	• Large number lost to follow-up • Potential bias (unblinded referral	• Rate of patient recruitment and absence of prolonged electrocardiographic

(continued)

Table 1 Continued

	Closure Trial	PC Trial	Respect (2013)	Respect-Long trial	Defence - PFO	Reduce trial	Close Trial
Summary	<ul style="list-style-type: none"> Potential bias (un-blinded referral) 	and treatment effects is difficult. <ul style="list-style-type: none"> Potential bias (un-blinded referral) 	<ul style="list-style-type: none"> Potential bias (un-blinded referral for endpoint adjudication) 	to provide the hazard ratio. <ul style="list-style-type: none"> Potential bias (un-blinded design) 	for endpoint adjudication)	monitoring to detect occult AF. <ul style="list-style-type: none"> Potential lack of detection of AF does not explain the lower rate of stroke recurrence in PFO group. Potential bias due to un-blinded design 	Reduction of subsequent stroke after PFO closure combined with antiplatelet therapy than antiplatelet therapy alone. High risk of AF
Conclusions	Incidence of recurrent stroke not significantly reduced.	Not significant risk reduction compared with medical therapy.	Incidence of recurrent stroke rate not significantly reduced.	Reduction of recurrent stroke after PFO closure than medical therapy alone during follow-up.	Reduction of recurrent stroke with PFO closure than medical therapy alone. High risk of AF	Reduction of stroke after PFO closure combined with antiplatelet therapy with antiplatelet therapy. High risk of AF	

Table 2. Characteristics of metaanalysis

	Aim	Inclusion criteria	Conclusions
Turc <i>et al.</i> ¹⁰	3560 patients Comparing closure, anticoagulation, and antiplatelet therapy to prevent stroke recurrence in PFO-associated CS.	RCTs comparing at least 2 of the 3 strategies: PFO closure, anticoagulation and antiplatelet therapy.	No blinding of participants and personnel to treatment arm, but outcomes adjudicated in a blinded fashion in all studies except in the DEFENSE-PFO. Risk of bias judged sizeable in 3 of 6 studies for high dropout rate (> 10%) in comparison to low incidence of recurrent stroke, and differential dropout rate between the closure and medical therapy arms. Not excluded selective bias in the PC Trial Clinical Events Committee discounted potential primary endpoint events more often in the antithrombotic therapy group than in the PFO closure group.
Riaz <i>et al.</i> ⁹	3560 patients Five RCTs comparing closure vs. medical therapy on stroke or side effects.	Stroke considered primary efficacy endpoint / bleeding and AF primary safety endpoints	Inclusion criteria and stroke characterization differed between studies. Closure associated with significant reduction in stroke risk compared to medical management with an increased risk of atrial arrhythmias. At subgroup analysis closure significantly reduced incidence of composite primary endpoint among patients with moderate to large shunts.
Garg <i>et al.</i> ¹¹	3457 patients Five RCTs comparing efficacy and safety of PFO closure vs. medical therapy based on PFO characteristics	CS assigned to standard medical therapy or closure. Primary outcome reduction in stroke recurrence. Secondary outcome: rates of TIA, composite outcome of stroke, TIA, and death from all causes, and rates of AF.	Low risk of bias. Large reduction in stroke recurrence in high-risk patients with aneurysm and large shunt. Risk reduction not significant in low-risk patients. No differences in mortality or major bleeding between groups. High risk of AF in PFO closure.

In a review in absence of ASA, the risk of stroke relapse was low and percutaneous PFO closure was not recommended.³⁵ However in the meta-analysis PFO closure in patients with the largest shunt was beneficial, independent of the presence of an ASA. The same indication comes from CLOSE and DEFENSE-PFO trials where selected high-risk patients, with or without ASA, in contrast to previous studies, received a benefit from PFO closure with no CS recurrence. Consequently, both French and ESC Position Papers recommend percutaneous PFO closure in CS patients with ASA or isolated PFO with large shunts. The updated AHA Stroke guidelines favour PFO closure vs. antiplatelet therapy, but not vs. anticoagulant therapy, and only in patients with the restrictive eligibility criteria of the RCTs.

Secondary prevention of cryptogenic stroke in patients with patent foramen ovale: medical therapy

Medical therapy should be considered in low-risk patients where PFO device closure is not indicated, assessing the bleeding risk vs. the PFO-stroke-related relapse risk. This evaluation should be repeated at intervals during the long-term follow-up because the characteristics of the patient may change.

Vitamin K antagonists (VKA) may be the best choice in low bleeding risk, in presence of good compliance and with adequate monitoring. DOACs need further study to extend their use in this setting. Whilst DOACs show greater antiembolic protection and a reduced bleeding risk compared to VKA in patients with AF, the results compared to antiplatelet agents in CS, have been disappointing.

Antiplatelet therapy can be an alternative when these criteria are lacking or the risk of stroke is low. Only in the RESPECT trial, the data of the medical therapy arm with anticoagulant or antiplatelet therapy are reported. Among those with indication to anticoagulation, there was no benefit of PFO closure. A full and unbiased discussion with patients regarding the various options so they can make a fully informed decision is appropriate.

What to do in daily clinical practice

The decision to recommend and proceed to a percutaneous PFO device closure should be agreed in a MDT, ideally including neurologists, and cardiologists with expertise in echocardiography, intervention, congenital heart disease, and other imaging experts if needed.

The neurologist should evaluate imaging and exams coming to the conclusion of their compatibility with an embolic event. The imaging specialists including echocardiography should confirm the diagnosis of a PFO and ASA or ASD if present, the shunt degree and PFO anatomy, and exclude other possible cardiac or vascular sources of thromboembolism. The interventional cardiologist should evaluate the feasibility and safeness of the PFO closure procedure, its possible risks, and the choice of the device, after a careful evaluation of the anatomic characteristics. The decision should be discussed in a timely manner with the patient,

and after explaining the risks and benefits of the procedure.

Currently, PFO closure is recommended only as a secondary prevention indication for patients aged from 18 to 60 years with a CS of probable cardioembolic origin in the previous 6 months, when PFO is associated with ASA or to high degree shunts (>20-25 microbubbles), especially in presence of concomitant DVT and when other causes of cardiac thromboembolism have been ruled out.

It is not currently recommended for subjects without these specific criteria, like CS more than 6 months before, TIA, age over 60 years, asymptomatic ischaemic lesions occasionally found at cerebral MRI, PFO with moderate shunt (<20 microbubbles), and, moreover, patients who need anticoagulation for other indications. These remain areas for future research.

In the specific cases, the intrinsic characteristics of the PFO may have a higher risk degree (ASA association, Chiari network, Eustachian prominent valve, long 'tunnel' PFO, stroke relapse during anti-thromboembolic treatment, DVT, and situations favouring its occurrence and recurrence, like hypercoagulability conditions, chronic pulmonary hypertension, stroke after Valsalva manoeuvre, RoPE scoring). The presence in a patient of common CV risk factors should be seen against the PFO closure indication. The ROPE score²³ assesses stroke-related vs. incidental PFO in CS. A high score suggests a high association between PFO and CS (young patients, few or no vascular risk factors, cortical infarcts with risk of recurrence of 2% at 2 years), while a low score suggests that the PFO is an incidental finding (elderly patients, deep infarcts, and vascular risk factors with a 2 years risk of recurrence of 20%). In clinical practice has not yet been validated to select the patients that benefit mostly from PFO closure.

We endorse the recommendations of Pristipino *et al.* about PFO closure according to (i) CS with a high probability of PFO role and (ii) High relapse probability. However, the answers to both these questions should be individualized. Moreover, if both conditions are present the closure is strongly suggested, if both are negative should be preferred a medical treatment. If only one of the characteristics is present it should be taken a decision only after a careful consensus.

It is strongly recommended that percutaneous PFO device closure should be undertaken in high volumes centres with dedicated follow-up. After PFO closure there is evidence to start medical therapy (aspirin 75 mg with clopidogrel 75 mg) from 1 to 6 months; followed by monotherapy for 5 years. Considering the high risk of developing AF in the first months after the procedure and of PE, it should be carefully evaluated anticoagulant instead of an antiplatelet prophylaxis for 40 days. To date, there are no clear indications on what to do in case of residual right to left shunt in patients with already closed PFO.

Conclusions

Recent RCTs and subsequent meta-analyses increased the data available to aid decision making in patients with CS and a PFO. Whilst these studies have helped to identify the

population with the greatest benefit, many questions remain in the patient group with some high-risk features but insufficient to be stratified as high-risk. Medical therapy with antiplatelet vs. anticoagulation therapy, subjects not involved in RCTs, optimal management therapy after the procedure, AF management, new percutaneous closure methods, and the role, if any, in primary prevention of closure in patients with a PFO with multiple high-risk features are topics requiring further studies to guide treatment decisions in patients with CS.

Research in the field in the next years will lead to improving and refining the evidence base for the management of CS in patients with a PFO.

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