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CLINICAL REVIEW
Frontiers in cardiovascular medicine

Patent foramen ovale closure for secondary stroke prevention

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Transcatheter closure of patent foramen ovale (PFO) in patients with cryptogenic stroke is gaining momentum after the recent publication of four randomized clinical trials suggesting its benefit. This article provides a contemporary overview of the anatomy and pathophysiology of PFO, the available diagnostic tools for the assessment and risk stratification of PFO, and the current and future landscape of PFO closure devices and their optimal utilization. It also summarizes the current data on PFO closure for stroke prevention, and discusses the remaining open issues in the field of PFO closure.

Keywords Cryptogenic stroke • Patent foramen ovale • Device closure • Stroke prevention

Introduction

Paradoxical embolization via a patent foramen ovale (PFO) was first reported in the 1880s by Cohnheim and Litten who described simultaneous venous and systemic emboli in two young patients with large PFOs.[1] However, the pathological implications of PFO did not attract wide attention till Lechat *et al.*[2] reported a higher prevalence of PFO in patients with ischaemic stroke in 1988. Several concurrent studies highlighted the association between PFO and paradoxical embolization, decompression sickness, and hypoxaemia.[3–7] This has led to the development of a variety of percutaneous PFO closure devices and prospective investigations of their potential role in stroke prevention.[8–11] The enthusiasm for PFO closure for stroke prevention, once tempered by the modest observed benefit in the initial randomized trials, has resurfaced recently with the emergence of large-scale data unequivocally supporting its benefit in preventing recurrent strokes.[12] In light of the recent evidence, a multidisciplinary position paper authored by eight European societies gave strong recommendations for PFO closure in selected patients with cryptogenic stroke.[13] Given the high relevance of this topic to the daily practice of cardiovascular specialists, this narrative review aims to provide a contemporary overview of: (i) the anatomy and pathophysiology of PFO, (ii) the diagnostic assessment and risk stratification of PFO, (iii.) the current data on the utility of PFO closure for secondary stroke prevention, and (iv) the landscape of PFO closure devices and their optimal utilization.

Patent foramen ovale anatomy and pathophysiology

The foramen ovale is a separation between the septum primum and septum secundum at the anterior–superior portion of the septum. This 'tunnel-like' space is an essential component of foetal circulation that allows oxygenated placental blood to reach the arterial circulation during pregnancy. After birth, this communication closes in the majority of people but remains patent in 10–25% (*Figure 1*).[14,15] The PFO, while frequently clinically silent, can serve a pathological role by allowing thrombi to transit from the venous to the systemic circulation (paradoxical embolization). The definite proof of this concept comes from cardiac imaging and autopsy case series that documented thrombi of various sizes and shapes transiting through the PFO tunnel or wedged in it (thrombus in transit) (*Figure 2*).[16] Patent foramen ovales have wide heterogeneity in terms of their diameter, length, and relationship with the surrounding structures, but they can generally be divided into simple and complex PFOs according to certain anatomical characteristics. Simple PFOs, encountered in 45% of patients referred for device

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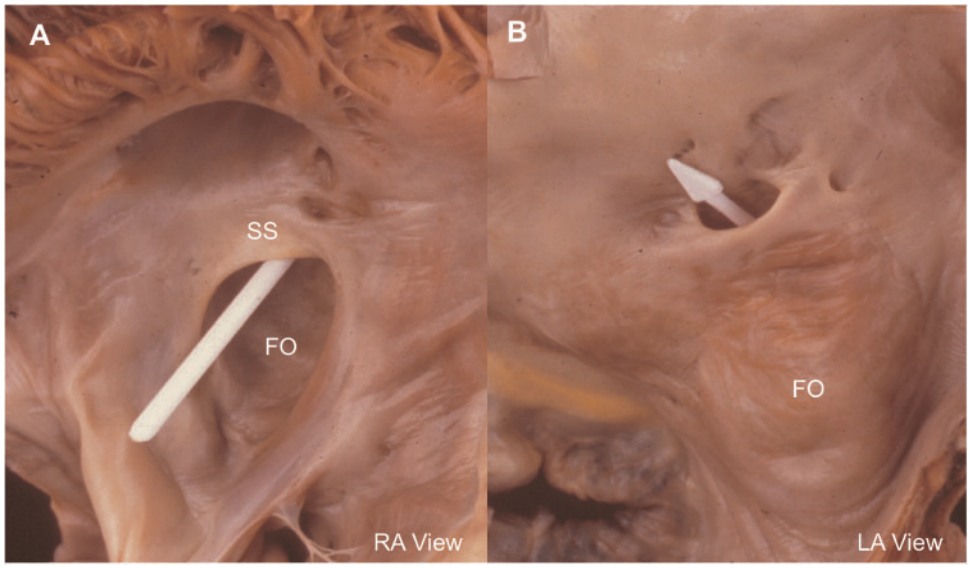


Figure 1 Gross anatomy of patent foramen ovale. A probe is passed through the patent foramen ovale which is shown from the right atrial (RA) view (*A*) and the left atrial (LA) view (*B*). FO, fossa ovalis; SS, septum secundum.

closure, are short tunnels (<8 mm length) that are not associated with atrial septal aneurysm, lipomatous septal hypertrophy, prominent Eustachian valve, or Chiari network[17] (*Figure 3*). Patent foramen ovales with one or more of these are considered complex. The complexity of a PFO has implications for the risk of paradoxical embolization as well as the approach and success of PFO closure; a PFO with an aneurysmal septum (ASA.) is associated with a larger shunt, and higher odds of paradoxical embolism than a PFO without ASA.[18,19] Atrial septal aneurysms are also associated with more 'open time' of the PFO increasing the risk of paradoxical embolism. Similarly, the presence of Eustachian valves may take part in the mechanism leading to paradoxical embolization by directing flow from the inferior vena cava into the intra-atrial septum, although this association has not been clearly documented.

Methods of patent foramen ovale detection and characterization

Transthoracic echocardiography with intravenous injection of saline micro-bubble or dedicated echo contrast mediums can be used to detect PFOs with good sensitivity and specificity. The appearance of micro-bubbles or echo contrast in the left atrium within three to six cardiac cycles after right atrial opacification is diagnostic of an intracardiac shunt.[20] The classification of shunt is estimated by the maximum number of micro-bubbles seen in the left atrium in a single frame during the first three cardiac cycles after bubbles crossing. The shunt is generally graded as small, moderate, and large, when the number of micro-bubble is 1–5, 6–30, and >30, respectively. This methodology, however, suffer from significant limitations including the lack of accounting for the number of bubbles in the right atrium, the pressure difference between the left and right atrium at the time of the shunt, and the quality of the Valsava manoeuvers commonly used to increase right atrial pressure. Transesophageal echocardiography (TOE.) offers an incremental advantage over TOE by providing detailed anatomical characterization of the PFO and hence is considered the reference standard for detection of PFOs. The accuracy of either modality depends on the incorporation of standardized imaging protocols and the performance of several injections of agitated saline or echocardiographic contrast medium with provocative manoeuvers to ensure adequate increase the right atrial pressure. The interpretation of these studies should take into consideration specific issues that might limit their yield: false negative studies may result from inadequate visualization, difficulty in preforming the Valsava manoeuver (especially with TOE), or elevated left atrial pressure preventing right-to-left (R-L) shunting.

Another diagnostic approach uses contrast enhanced transcranial Doppler (c-TCD) a simple non-invasive method that allows the detection and semi-quantitative estimation of venous-to-arterial circulation shunts.[21] Traditionally, the insonating probe is placed on the temple just above the ear, and the middle cerebral artery is interrogated. However, interrogation of any other extra-cranial artery of the same calibre is more straightforward and can serve the same purpose of detecting R-L shunting. Agitated saline is injected intravenously and special software is then used to record and count high-intensity transient signals from the interrogated vessel (bubble count). A bubble count ≥10 is consistent with a large R-L shunt. Numerous high-intensity transient signals are often described as 'showers pattern; >25 bubbles' or 'curtain pattern; uncountable', and these two patterns are associated with high risk of cryptogenic stroke [adjusted OR 12.4; 95% confidence interval (CI) 4.08–38.09] (*Figure 4*).[23] Transcranial Doppler has a high sensitivity (97%) and specificity (93%) in detecting R-L shunt, but cannot differentiate the source (intra-cardiac vs. extra-cardiac).[24] The addition of blood to

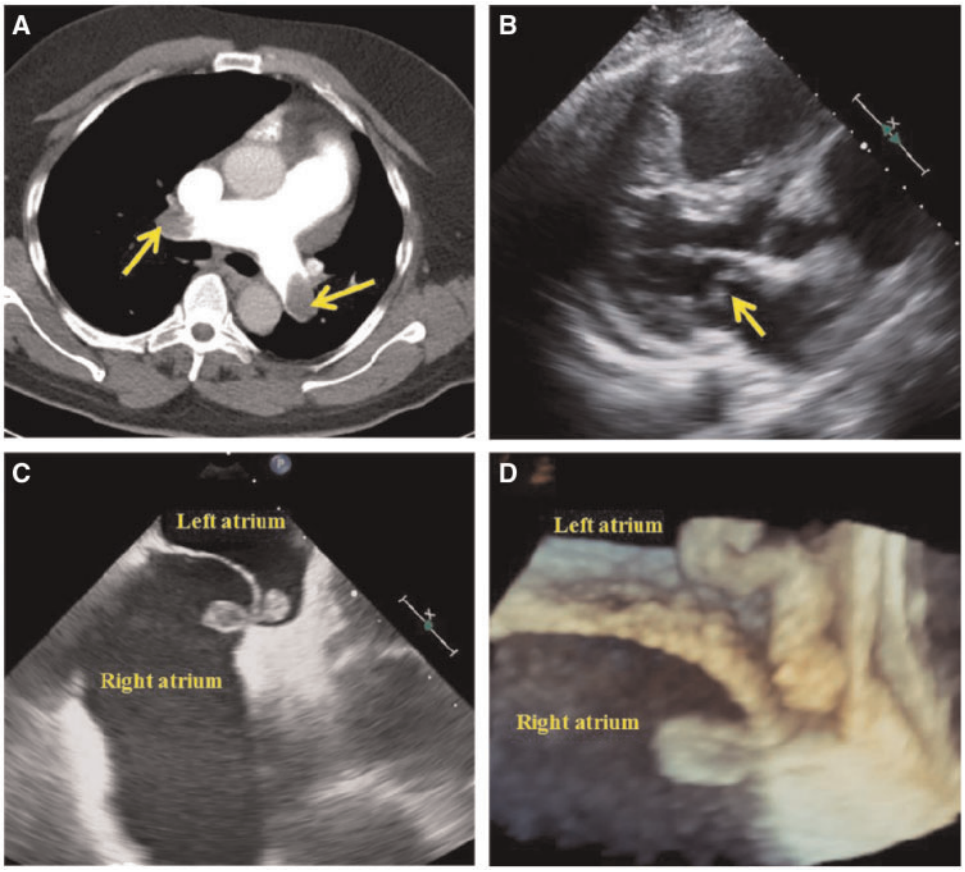


Figure 2 Multi-modality imaging of 'thrombus in transient' in a patient with a patent foramen ovale. (*A*) Bilateral pulmonary embolic on computed tomography. (*B*) Thrombus on the mitral valve on transthoracic echocardiography. (*C, D*) Large thrombus trapped in the patent foramen ovale tunnel on transesophageal echocardiography. Reproduced with permission from Biglane *et al.*[17]

agitated saline improves the sensitivity of c-TCD for the detection of R-L shunt to 100% when compared with other conventional contrast agents.[25] While echocardiography remains the most commonly used screening method for R-L shunt, c-TCD can play a complementary role in equivocal cases, and can also guide the success of shunt closure by providing an accurate estimation of residual shunt after device closure.[26]

Transcatheter patent foramen ovale closure—appraisal of the current evidence

The association between PFO and ischaemic stroke has been documented in a large number of observational studies. In a landmark study of 308 consecutive patients who underwent PFO closure ($n = 150$) or medical therapy ($n = 158$), the composite Endpoint of stroke, transient ischaemic attack (TIA), or peripheral embolism was lower in the PFO closure group (11% vs. 21%, hazard ratio [HR]= 0.43; 95% CI = 0.20–0.94; $P = 0.033$).[27] In a meta-analysis of 48 non-randomized studies including >10 000 patients, recurrent neurological event rate was 0.8/100 person-year (95% CI 0.5–1.1) in patients who underwent PFO closure vs. 5.0 (95% CI 3.6–6.9) among those who were treated medically.[28] In a Bayesian attributable risk analysis, the relationship between PFOs and cryptogenic stroke was found to be causal in ∼50% of patients.[29] Based on these observational data, interest in device closure of PFOs continued to grow. However, the enthusiasm for device closure was quickly tempered with the publication of the first round of randomized clinical trials (RCTs): CLOSURE-1, PC and RESPECT between 2012 and 2013.[30–32]

CLOSURE-1 was the first randomized trial of PFO closure for stroke prevention. It randomized 909 patients with cryptogenic stroke or TIA to medical therapy vs. PFO closure with the STARFlex Septal Occluder (NMT Medical, Inc., Boston, MA, USA) between 2003 and 2008.[28] The primary endpoint was a composite of stroke or TIA at 2 years, death from any cause during the first 30 days, or death from neurologic causes beyond 30 days. The primary endpoint occurred in 5.5% in the closure group and 6.8% in the medical treatment group (HR, 0.78; 95% CI 0.45–1.35; $P = 0.37$). The PC trial was conducted between 2000 and 2009 and assigned 414 patients with prior cryptogenic stroke, TIA, or systematic embolism to PFO closure with the Amplatzer PFO Occluder (Abbott, Santa Clara, CA,

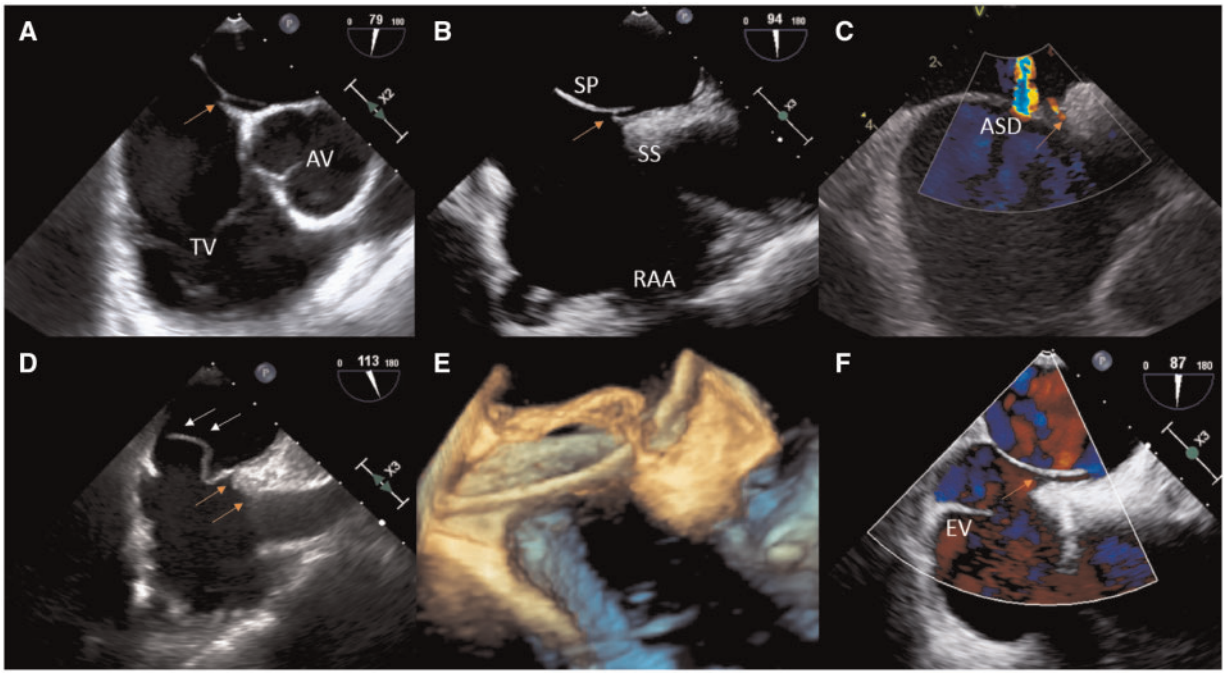


Figure 3 Various phenotypes of patent foramen ovale on echocardiography. (*A*) a simple patent foramen ovale with short tunnel. (*B*) Patent foramen ovale with thickened septum secundum. (*C*) Patent foramen ovale with small septum secundum atrial septal defect. (*D, E*) Patent foramen ovale with atrial septal aneurysm. (*F*) Long tunnel patent foramen ovale with a prominent Eustachian valve. ASD, atrial septal defect; AV, aortic valve; EV, Eustachian valve; RAA, right atrial appendage; SP, septum primum; SS, septum secundum; TV, tricuspid valve.

USA) vs. medical therapy.[29] The primary endpoint was similar to that in CLOSURE-1 and similarly occurred in comparable rates in the device closure group vs. the medical therapy group (3.4% vs. 5.2%, HR 0.63, 95% CI 0.24–1.62, $P = 0.34$). The landmark RESPECT trial recruited 980 patients with prior cryptogenic stroke or TIA between 2003 and 2011 to receive device closure with the Amplatzer PFO Occluder vs. medical therapy.[30] The primary endpoint of recurrent ischaemic stroke or early death occurred in 1.8% vs. 3.3% in the device closure vs. medical treatment arms, respectively (HR 0.49, 95% CI 0.22–1.1, $P = 0.08$).

In aggregate, these round-1 trials missed their primary end points for the intention-to-treat populations, suggesting no additional benefit of device closure over medical therapy for secondary stroke prevention in patients with PFO (*Table 1*). However, concerns were raised about certain issues with the design, recruitment, and analysis of these trials. All three trials were underpowered due to the low stroke recurrence rates, which may have resulted from insufficient length of follow-up, lenient inclusion criteria (patients with TIA were allowed), the modest numbers of PFOs with high-risk features (large R-L shunt and/or ASA), and the heterogeneity in the prescribed medical regimens (antiplatelets and anticoagulants) in the medical treatment arms.[33] The wide adoption of PFO closure at the time of round-1 trials also led to difficult and prolonged recruitment and high drop out rates, both of which may have introduced important confounding biases.[34] Nonetheless, despite the methodological flaws in these trials, key lessons were learned:

(1) Patent foramen ovale closure can be done with reasonable safety, but a differential impact of the device type was observed. In the CLOSURE-1 trial, half of the strokes in the device arm occurred within 30 days after the procedure. Also, a non-negligible number of patients had incomplete closure (13.4%), device thrombus (1.1%) and new onset atrial fibrillation (5.7%) during follow-up raising concerns about the specific closure device used (STARFlex septal occluder). A superior safety profile was observed with the Amplatzer PFO occluder used in the other two RCTs.

(2) Patent foramen ovale closure is not inferior and may be superior to medical therapy. Although statistical significant could not be established, the numerical superiority of PFO closure was seen in all three trials. Furthermore, the lack of statistical significance was often driven by the primary analysis protocol (intention-to-treat analysis). In RESPECT, patients who underwent PFO closure had lower recurrence event rate compared with those who had medical therapy but this was not statistically significant in the intention-to-treat analysis (HR 0.49, 95% CI 0.22–1.11, $P = 0.08$). Nonetheless, one-third of the events in the device group occurred in patients who had not received a device. When these patients were excluded in the per-protocol analysis, device closure was superior to medical therapy (HR 0.37, 95% CI 0.14–0.96, $P = 0.03$).

(3) (3.) Non-inferiority of PFO closure compared with medical therapy at mid-term is likely to lead to superiority of PFO closure during longer term follow-up, as late sequelae of PFO closure are extremely rare while life-long anticoagulation is likely to result in significant cumulative bleeding risks.[35,36]

(4) Patent foramen ovales are not all the same. A signal of higher magnitude of benefit of closing PFOs with patients with ASA or large

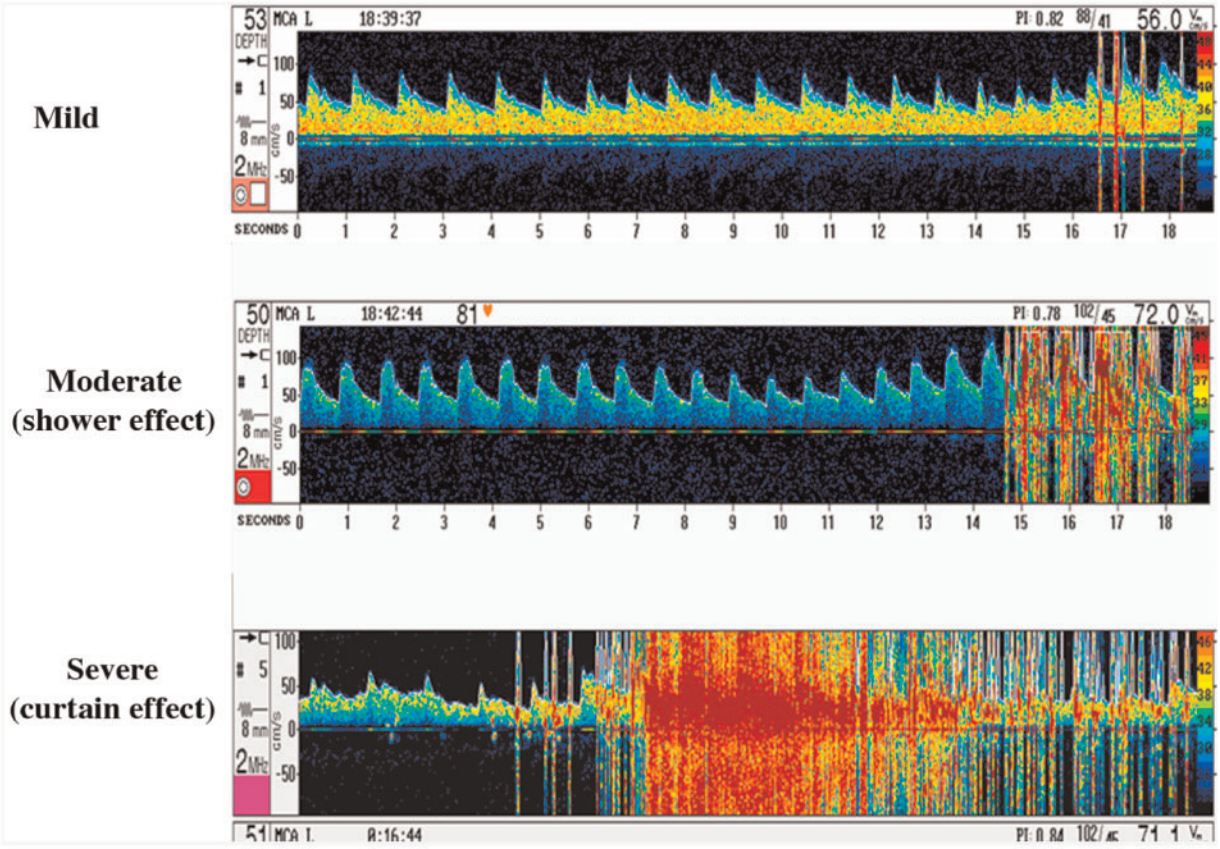


Figure 4 Contrast enhanced transcranial Doppler patterns in patients with various degrees of right-to-left shunt. MCA, middle cerebral artery. Reproduced with permission form Gonzalez-Aluja *et al.*[23]

shunt compared with lower risk patients and anatomy was seen in the RESPECT trial (HR 0.27, 95% CI 0.11–0.70) vs. (HR 0.80, 95% CI 0.43–1.47), respectively.[37]

Round-1 RCTs established the safety and the non-inferiority of PFO closure compared with medical therapy in patients with PFO and a cryptogenic stroke. However, these results were widely used to discourage PFO closure rather than signifying its role. Nonetheless, the debate on PFO closure and the interest in the procedure did not cease. Rather, three new RCTs (CLOSE, REDUCE, and DEFENSE-PFO) were launched employing stringent inclusion and exclusion criteria, and more defined protocols for medical therapy and clinical endpoints than round-1 trials.[38–40]

The CLOSE study was the first non-industry sponsored RCT in the history of PFO closure.[34] Funded by the French ministry of health, CLOSE planned to randomize 900 patients with cryptogenic stroke to PFO closure (with any device) vs. medical therapy. The study's design featured two important aspects; it included a majority of patients with high-risk PFOs (large shunt and/or septal aneurysm in >90%), and allowed separate but clearly defined arms of medical therapy (antiplatelet arm and anticoagulant arm). Due to slow enrolment and budget limitations, the trial was stopped in 2014 after enrolling 663 patients. Among these patients, the primary endpoint of any stroke occurred less frequently after device closure when compared with antiplatelet therapy (0% vs. 4.9%, HR 0.03, 95% CI 0–0.26, $P < 0.001$) but not when compared with anticoagulation therapy (1.5% vs. 3.8%, HR 0.43, 95% CI 0.1–1.5, $P = 0.17$). The REDUCE trial enrolled 664 patients to undergo PFO closure with the HELEX device (GORE, Flagstaff, Arizona) or to continue antiplatelet therapy. The study endpoints were the occurrence of clinical ischaemic stroke and the finding of new infarction on magnetic resonance brain imaging. Patent foramen ovale closure was superior to antiplatelet therapy for both endpoints (1.4% vs. 5.4%, HR 0.23, 95% CI 0.09–0.62, $P = 0.002$ and 5.7% vs. 11.3%, HR 0.51, 95% CI 0.29–0.91, $P = 0.04$, respectively). DEFENSE-PFO was the latest RCT to test the utility of PFO closure in patients with cryptogenic stroke.[36] It exclusively enrolled patients with high-risk PFOs and assigned them to PFO closure with the Amplatzer PFO Occluder vs. medical therapy. The trial was stopped prematurely after an interim analysis showed an overwhelming benefit of PFO closure in the prevention of the composite endpoint of stroke, vascular death, or major bleed (0% vs. 12%, CI 3.2-22.6, standard error 5.0). In addition to these trials, a supplemental long-term analysis of the RESPECT patient cohort was conducted at the request of the FDA. This analysis showed that during an extended follow-up (5.9 years), PFO closure was associated with a significant reduction in recurrent stroke compared with medical therapy (HR 0.55, 95% CI 0.30–1.0, $P = 0.046$).[41] The consistent finding of a striking reduction in

Table 1 Summary of the randomized clinical trials comparing patent foramen ovale device closure vs. medical therapy in patients with cryptogenic stroke

Trial	*N*	Inclusion	Device/sponsor	Control	Main primary end points	F/U	Outcomes (intention-to-treat analysis)(Intervention vs. control)
Round-1 RCTs							
Closure-I (2012)	909	Cryptogenic stroke/TIA + TEE verified PFO	Starflex Industry	ASA and/or Warfarin	Stroke/TIA/early death (30 d)/late neurologic death	2	5.5% vs. 6.8% (HR 0.78, 95% CI 0.45–1.35, $P = 0.37$)
PC Trial (2013)	414	Cryptogenic stroke/TIA/SE + TEE verified PFO	Amplatzer Industry	Any antithrombotic (antiplatelet or OAC)	Death/non-fatal stroke/TIA/SE	4.1	3.4% vs. 5.2% (HR 0.63, 95% CI 0.24–1.72, $P = 0.34$)
RESPECT (2013)	990	Cryptogenic stroke/TIA + TEE verified PFO	Amplatzer Industry	ASA/Clopidogrel/ASA + Dipyridamole/Warfarin	Ischaemic stroke/ early death	2.6	1.8% vs. 3.3% (HR 0.49, 95% CI 0.22–1.11, $P = 0.08$)
Round-2 RCTs							
CLOSE (2017)	663	Cryptogenic stroke + high-risk PFO[a]	Any Academic	(1) antiplatelet (2) warfarin or NOAC	Any stroke (Ischaemic, ICH)	5.3	(1) 0% vs. 4.9% (HR 0.03, 95% CI 0–0.26, $P < 0.001$) (2) 1.5% vs. 3.8% (HR 0.43, 95% CI 0.1–1.5, $P = 0.17$)
REDUCE (2017)	664	Cryptogenic stroke + TEE verified PFO	Cardioform Industry	ASA/Clopidogrel/ASA + Dipyridamole	(1) Clinical ischaemic stroke (2) New infarct on brain MRI	3.2[c]	(1) 1.4% vs. 5.4% (HR 0.23, 95% CI 0.09–0.62, $P = 0.002$) (2) 5.7% vs. 11.3% (HR 0.51, 95% CI 0.29–0.91, $P = 0.04$)
RESPECT LT (2017)	980	Cryptogenic stroke/TIA + TEE verified PFO	Amplatzer Industry	ASA/Clopidogrel/ASA + Dipyridamole/Warfarin	Ischaemic stroke/ early death	5.9[c]	3.6% vs. 5.8% (HR 0.55, 95% CI 0.31–0.99, $P = 0.046$)
DEFENSE-PFO (2018)	120	Cryptogenic stroke + high-risk PFO[b]	Amplatzer Academic	ASA/ASA + Clopidogrel or Cilastazol/Warfarin	Stroke/vascular death/major bleed	2.8[c]	0% vs. 12.9% (95% CI 3.2–22.6, standard error 5.0)

ASA, aspirin; CI, confidence interval; F/U, follow-up; HR, hazard ratio; ICH, intracranial haemorrhage; *N*, number; NOAC, non-vitamin K antagonist oral anticoagulants; PFO, patent foramen ovale; R-L, right-to-left; RCT, randomized controlled trial; SE, systemic embolization; TIA, transient ischaemic attack; yr., year.
[a]High-risk PFO was defined as a PFO with atrial septal aneurysm or large shunt.
[b]High-risk PFO was defined as a large or hypermobile PFO or a PFO with ASA.
[c]Median follow-up was reported.

Table 2 Summary of meta-analyses comparing device closure vs. medical therapy in patients with cryptogenic stroke

Device closure vs. medical therapy	Event rate	OR [95% CI]	I^2	NNT/NNH
Stroke recurrence[13]				
Overall[a]	1.96% vs. 4.61%	0.38 [0.18–0.80]	53%	37.7
Only in RCTs with high-risk PFOs	0.81% vs. 5.98%	0.18 [0.07–0.45]	2%	19.3
In Patients with high-risk PFOs in RCTs	1.62% vs. 5.42%	0.34 [0.15–0.76]	49%	26.3
Device closure vs. antiplatelet therapy	2.38% vs. 6.07%	0.38 [0.17–0.84]	60%	27.1
Device closure vs. OAC therapy	2.28% vs. 3.82%	0.74 [0.20–2.74]	31%	N/A
TIA recurrence[13]	3.39% vs. 3.83%	0.85 [0.59–1.22]	0%	N/A
Death[13]	0.37% vs. 0.51%	0.92 [0.31–2.71]	11%	N/A
New onset atrial fibrillation[13]				
Overall	4.92% vs. 1.02%	4.15 [2.42–7.13]	1%	25.6
Beyond 45 days	2.01% vs. 1.02%	1.80 [0.99–3.28]	0%	N/A

CI, confidence interval; I^2, heterogeneity between the included studies; N/A, non-applicable; NNH, number needed to harm; NNT, number needed to treat; OAC, oral anticoagulation; OR, odds ratio; PFO, patent foramen ovale; RCT, randomized clinical trial; TIA, transient ischaemic attack.
[a]Intention-to-treat analysis.

recurrent ischaemic events compared with medical therapy in all of round-2 RCTs was considered a tipping point for PFO closure (*Table 1*).

An important lesson from these round-2 trials was that the magnitude of benefit of device closure was highest in trials that enrolled PFO patients with high-risk features (CLOSE, DEFENSE-PFO). In an updated meta-analysis including all round-1 and round-2 trials, the impact of PFO closure on stroke recurrence was larger in patients with ASA and/or large shunt [relative risk (RR) = 0.27, 95% CI 0.11–0.70, $I^2 = 42\%$) compared with patients without these features (RR = 0.80, 95% CI 0.43–1.47, $I^2 = 12\%$).[42] In another meta-analysis, the number needed to treat to prevent an ischaemic event in patients PFO was significantly less when only patients with high-risk PFOs are treated compared with closure of any PFO (*Table 2*).[13] While the results of these RCTs settled the debate on PFO closure in patients <60 year of age who suffered a cryptogenic stroke, several important issues remain unaddressed:

First, what is the optimal method of confirmation of the cryptogenic stroke? Do all patients need screening for cardiac arrhythmia and hypercoagulopathy before considering device closure? Is an incidentally found atrial fibrillation in a 45-year-old male more likely to cause a stroke than a large PFO with ASA? What is the appropriate duration of arrhythmia screening (30-day Holter monitoring vs. 6–12 month implantable loop recording)? Does prolonged screening increase the risk of interim secondary events especially in patients with active venous thromboembolism (VTE)? In one study, early silent brain infarctions occur in up to approximately one-third of patients within 1 week of the index cryptogenic stroke.[43]

Second, how can we predict the chance of causal association between PFO and stroke, and the risk of stroke recurrence? There is currently only one risk model that addresses this issue; The ROPE score is an index that has been shown to be able to define the PFO-attributable risk in patients with cryptogenic strokes.[44] However, controversies remain about the utility of ROPE score for a number of reasons: (i) A high ROPE score not only suggests a PFO-related stroke, but also suggests very low chance of stroke recurrence, and vice versa. (ii) The ROPE score does not account for the PFO characteristics or other important variables that have been shown to be important determinants of causality of stroke by the PFO (concomitant VTE, imaging features of the stroke, etc.). Hence, the value of the ROPE score in guiding treatment decisions remains limited, and there is an unmet clinical need to develop a comprehensive risk prediction tool that incorporates the characteristics of the patient, the ischaemic event, and the PFO anatomy and physiology and their aggregate influence on individual clinical scenarios.

Third, is PFO closure appropriate in older patients (e.g. >60) with cryptogenic strokes who were excluded from RCTs? Although the risk of paradoxical embolism becomes less likely relative to other potential causes of stroke in the elderly, the PFO in this population may indeed be more dangerous due to the higher incidence of VTE in a population that is by default sicker than the younger PFO population. Mazzucco *et al.*[45] documented a significant association between PFO and cryptogenic stroke in patients >60 years of age. In another analysis from a multinational registry of cryptogenic strokes, patients' aged 60–80 (all comers, irrespective of PFO presence) had a higher risk of recurrent stroke/TIA compared with those aged <60 (HR 1.90, 95% CI 1.21–2.98).[46] Whether this reflects a higher burden of stroke risk factors and perhaps limited utility for PFO closure in this age group remains to be assessed. Nonetheless, pending further data, extensive screening for arrhythmia and other stroke risk factors may be warranted in elderly patients who are considered for PFO closure for secondary stroke prevention.

Fourth, is device closure superior to oral anticoagulation (OAC) especially the contemporary non-vitamin K antagonist oral anticoagulants? Several meta-analyses have consistently shown superiority of OAC over antiplatelet therapy when medical treatment is chosen for secondary stroke prevention.[47,48] However, comparative data of device closure vs. OAC are scarce. In the only RCT directly comparing these two strategies for secondary stroke prevention (the CLOSE trial), no significant difference in the rates of recurrent stroke at a

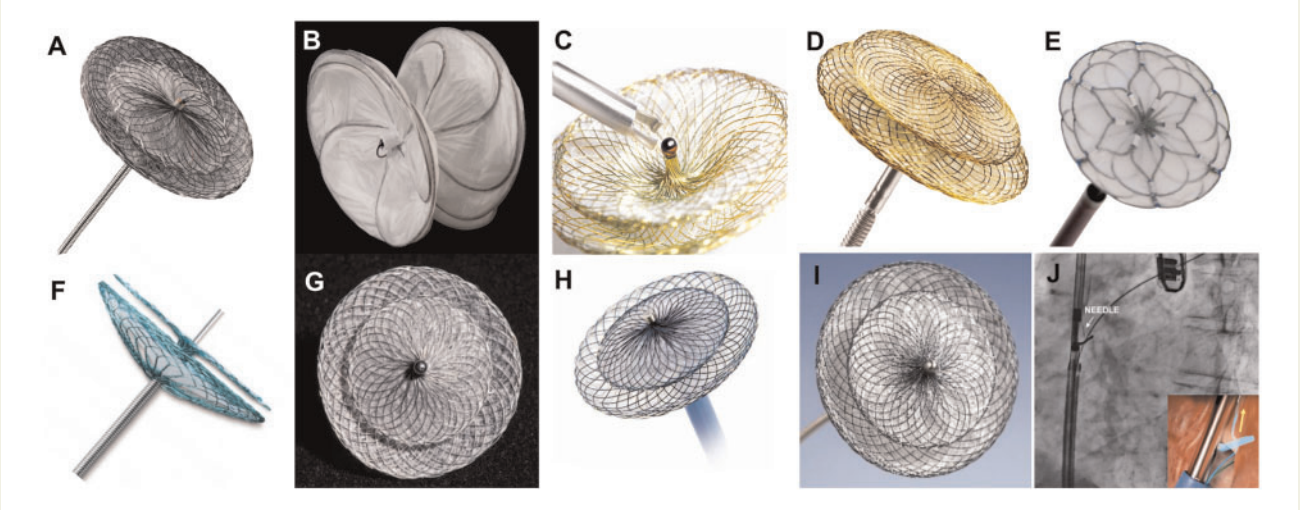


Figure 5 Landscape of contemporary patent foramen ovale occluders. (*A*) Amplatzer patent foramen ovale Occluder; (*B*) Cardioform Septal Occluder; (*C*) Figulla Flex-II patent foramen ovale Occluder; (*D*) CeraFlex™ patent foramen ovale Occluder; (*E*) Ultrasept patent foramen ovale Occluder; (*F*) Nit-Occlud patent foramen ovale; (*G*) Cocoon; (*H*) Hperion; (*I*) Cardi-O-Fix; (*J*) NobleStitch. Reprinted with permission from Gaspardone *et al.*[55]

mean follow-up of 5.3 years was observed (1.5% after device closure vs. 3.8% with OAC, HR 0.43, 95% CI 0.1–1.5, $P = 0.17$), Despite this equipoise, PFO closure might be an attractive alternative to life-long anticoagulation which may become problematic during longer follow-up (>5 years) in a population that typically enjoys a several decades life expectancy.[35,36]

The landscape of patent foramen ovale closure devices

Numerous PFO closure devices were developed and tested, but many were subsequently removed from the market [e.g. CardioSeal (NMT, Boston, MA, USA), Coherex FlatStent (Coherex Medical, Salt Lake City, UT, USA), Cierra (Cierra, Redwood City, CA, USA), etc.] due to performance inferiority to market leading devices [Helex/GSO (GORE Medical, Flagstaff, AZ, USA), and the AMPLATZER PFO]. Based on the long-term results of RESPECT and the results of the REDUCE trial, the AMPLATZER PFO occluder and the GSO received FDA approval for secondary stroke prevention in 2016 and 2018, respectively. The Amplatzer PFO occluder is a self-expandable, double-disc device made from a platinum-filled nickel-titanium (Nitinol) wire mesh. The discs contain thin polyester fabric to enhance complete sealing. The right atrial desk is larger than the left atrial desk, and both are connected with a short waist (*Figure 5A*). The GSO is a non-self-centring device that is made from five Nitinol wires encased in a thin layer of micro-porous polytetrafluoroethylene (ePTFE). When deployed, it forms two circular opposing disks that are secured in place by a locking mechanism that passes through the centre of the device (*Figure 5B*).

Despite the excellent safety profiles of the current PFO devices, further innovations have aimed to design lower profile and more biocompatible devices, although many of these closely followed the concept of the Amplatzer PFO closure device.[49] The Figulla Flex-II PFO Occluder (Occlutech, Jena, Germany) is designed with a unique braiding technique that allows for a single central pin on the right atrial disc (*Figure 5C*). This device is enhanced with two polyethylene terephthalate patches to ensure complete closure after implantation. A prospective registry included 100 patients who underwent PFO closure with the Figulla device showed promising results (successful implant 100%, residual shunt ≤1 grade 80%, AF 1%, and device embolization 1%).[50] The CeraFlex™ PFO occluder (Lifetech, Shenzhen, China) features a unique Titanium nitride coating which reduces nickel leaching from the nitinol wire and hence enhances biocompatibility (*Figure 5D*). It also has a special connecting mechanism between the device and the delivery cable that allows free rotation of the device. The Ultrasept device (Cardia, Eagan, MN, USA) consists of two round low profile discs of Ivalon (polyvinyl alcohol) that are supported by six-rounded nitinol loops (*Figure 5E*). The Nit-Occlud PFO (PFM medical, Germany) is also an ultra-low profile device that has a single-layer distal disc, which reduces the metal used in the left atrium by 50%, hence decreasing the risk of device thrombosis (*Figure 5F*). Initial data on the Nit-Occlud PFO device showed comparable efficacy and safety to the Amplatzer and Cardioform devices.[51] Other devices [Cocoon (Vascular Innovations, Nonthaburi, Thailand), Hyperion (Comed, SHSMA Corporation, Shanghai, China), and Cardio-O-fix (Starway Medical Technology, Beijing, China)] (*Figure 5G–I*) are available for PFO closure outside of the USA, but large-scale or long-term data associated with their use are limited.

The concept of deviceless PFO closure has been tested clinically for over a decade. Plausibly, eliminating permanent intra-cardiac implants is a desirable goal if similar efficacy can be demonstrated with bio-absorbable devices. Unfortunately, early experience with such devices (Biostar, NMT) documented high rates of complications including poor closure rates, higher thrombogenicity, and device material embolization leading to abandonment of this concept.[52–54]

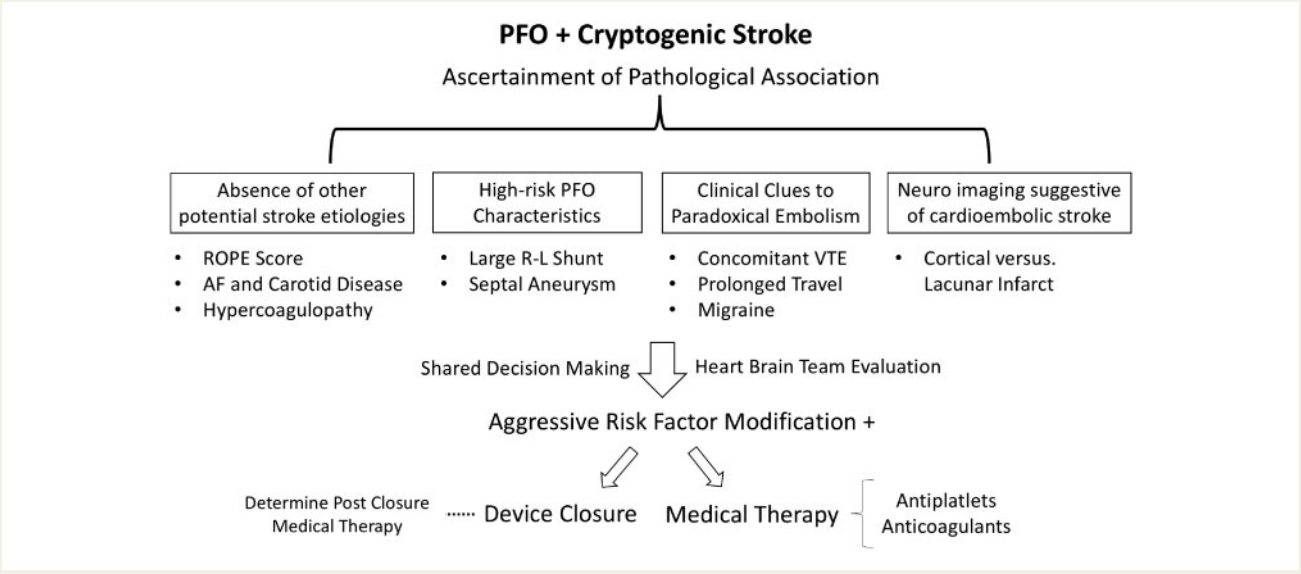


Figure 6 An algorithmic approach to patients with cryptogenic stroke and patent foramen ovale. AF, atrial fibrillation; PFO, patent foramen ovale; R-L, right-to-left; VTE, venous thromboembolism.

Suture-based devices that leave very little 'footprint' in the atrial septum have similarly been inspired by the need for a 'deviceless' PFO closure. The NobleStitch system (HeartStitch, Inc., Fountain Valley, CA, USA) consists of two dedicated catheters to capture and suture the septum secundum and the septum primum using a 4-0 polypropylene suture (*Figure 5J*), and is to date the first suture-mediated PFO closure device to be tested in a sizable cohort of patients. Early data on the feasibility of the NobleStitch demonstrated a high device closure success rate (96%), and no device-related complications.[55] However, concerns been raised about the procedural requirements [large bore access (14 French sheath), and contrast volume (median 200 mL)], and the high rate (25%) of incomplete closure at follow-up.[54] Further studies are needed to establish the role of the NobleStitch in routine PFO closure given the excellent safety and efficacy data with the widely used double-desk devices.

Putting it all together; an algorithmic approach to a patient with a patent foramen ovale and cryptogenic stroke

The wealth of emerging data on PFO closure coupled with the remaining unaddressed issues in the field may result in certain challenges to clinicians attempting to synthesize the evidence to treat individual patients (*Take home figure*). An individualized team-based approach is best suited to overcome these challenges. The first task is to ascertain a pathological association between the PFO and the stroke. There is currently no single tool that allows accurate prediction of such association. Therefore, several elements often need to be jointly examined by a cardiologist and a stroke neurologist to determine causality. These include: screening for other potential aetiologies of the ischaemic stroke, anatomical characteristics of the PFO itself, clinical clues to paradoxical embolism, and neuroimaging findings suggestive of cardioembolic stroke. Once the PFO is determined to be related to the stroke, a shared decision to proceed with device closure vs. medical therapy is made involving as an integral component a well-informed patient. Although decision aids have been shown to be an efficient method of incorporating the data and the patient's values and preferences in the decision-making process, no such tools have yet been developed for PFO closure. It is important to emphasize that device closure, albeit effective in reducing stroke recurrence, does not eliminate the need for aggressive risk factor modifications. A simplified algorithm to manage patients with cryptogenic stroke who are found to have a PFO is outlined in *Figure 6*. In addition, a recently published interactive clinical guide can be extremely useful in providing a visual illustration of the risks, benefits and level of evidence for both clinicians and PFO patients considering various secondary preventative measures.[56]

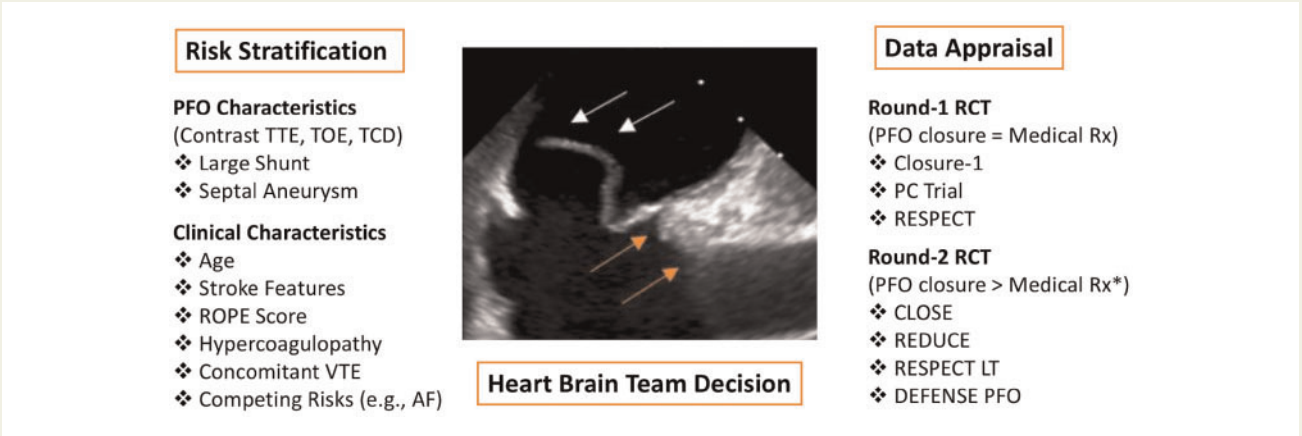
Other considerations

Patent foramen ovale closure for primary prevention prior to surgical procedure

The role of PFO in the causation of ischaemic stroke has been primarily established in ambulatory patients who experience a cryptogenic stroke. However, a potential pathological role of PFO in post-operative ischaemic strokes among patients undergoing non-cardiac surgery has been recently suggested.[57] In a retrospective study of 150 198 patients who underwent non-cardiac surgery, the estimated risks of stroke at 30-day was 5.9/1000 patients with PFO and 2.2/1000 patients without PFO (adjusted OR 2.66, 95% CI 1.96–3.63, $P < 0.001$). In addition, the presence of a PFO was associated with higher rates of ischaemic stroke at 1 year: 4.7% vs. 1.1% in patients without a PFO (aOR: 2.01, 95% CI 1.51–2.69; $P < 0.001$).[58] These provocative findings augment the argument that PFO closure may indeed become an important primary prevention strategy in certain high-risk populations.[35,36,59]

Long-term safety and efficacy

Percutaneous PFO closure is performed with excellent technical results, with success rates exceeding 98% and major complication



Take home figure Patent foramen ovale closure in patients with cryptogenic stroke. AF, atrial fibrillation; PFO, patent foramen ovale; RCT, randomized controlled trials; TCD, transcranial Doppler; TOE, transesophageal echocardiography; TTE, transthoracic echocardiography; VTE, venous thromboembolism. *Predominantly antiplatelets. Orange arrows, patent foramen ovale; White arrows, atrial septal aneurysm.

rates <1%.[34,60] Nonetheless, concerns remain about potential long-term issues with device closure such as residual R-L shunt, incident AF, free-wall device erosion, and device thrombosis. These concerns are especially important when considering device closure in young patients without clear cardiovascular risk factors. Residual R-L shunt can result from incomplete device closure or the co-existence of other sources of R-L shunt [e.g. interatrial defects or aortic valve (AV) malformations]. In RCTs, residual R-L shunt was reported in up to 25% of patients.[34,38,41] Data on the temporal progression or regression of residual shunts, their mechanisms, and their potential association with adverse events are limited. In a study of 567 patients who underwent PFO closure with the Amplatzer PFO occluder, 19.5% has residual R-L shunt at 4 ± 2 months, but this was reduced to 8.4% at 11 ± 2 months.[61] However, this could have been a result of a less aggressive screening strategy during the subsequent follow-up. Among patients with ≥moderate residual shunt at mid-term follow-up ($n = 24$), eight patients (33%) had identifiable aetiologies of their shunt (five had AV malformations, and three had residual peri-device shunt), and all were treated percutaneously. In another study of 2679 patients who underwent PFO closure, 100 (3.7%) had significant residual shunt that required intervention (1–2 additional devices).[62] All patients had complete elimination of the R-L shunt following their 2nd or 3rd device implantations. The European position paper on PFO closure suggested that shunt assessment should be an integral part of PFO closure, and recommended preforming TCD at least once beyond 6 months to assess effective closure and thereafter, if shunting persisted, annually until closure.[13]

New onset AF occurs more frequently after device closure than with medical therapy (4.9% vs. 1.0%, OR 4.15, 95% CI 2.42–7.13; number needed to harm = 25.6 at ~3 years)[13] (*Table 2*). However, the vast majority of newly detected AF events resolve within 45–60 days after device closure.[13,44] Nonetheless, further ascertainment of the transient nature of post-PFO closure AF is necessary given the substantial impact of AF and its consequences.

Device thrombosis is an extremely rare late complication of PFO closure. In a systematic safety review of PFO closure, device thrombosis was reported in 1/10 893 patient only. However, device thrombosis was reported in 2/441 patients (0.5%) in the REDUCE trial. Further studies are needed to assess the incidence of device thrombosis in clinical practice, its mechanisms [device related vs. underlying pathology (e.g. thrombophilia)], and its optimal management. Likewise, long-term data from RCT and real-world registries showed very few cases of free-wall erosion after PFO closure. The vast majority of reported device erosions in the literature occurred in patients who had atrial septal defect closure rather than PFO closure.[63,64]

Cost-effectiveness

The majority of patients considered for PFO closure after a cryptogenic stroke are of young or middle age. A plausible assumption is therefore that device closure might be more cost-effective than medical therapy in the long-term. A recent study by Leppert *et al.*[65] found that at 15 years, PFO closure vs. medical therapy improved quality-adjusted life years by 0.33 at a cost saving of $3568, representing an incremental net monetary benefit of $52 761. Additional investigations are required to assess whether this cost-effectiveness extends to subsets of patients (e.g. those with large R-L shunt, ASA, concomitant VTE, etc.), and to older patients who were not enrolled in RCTs.

The role of a collaborative heart–brain team

Patent foramen ovale is prevalent among the general population, and hence the potential for inappropriate use of PFO closure devices is high. An important source of possible inappropriate use of this technology is in patients in whom the PFO was incidental and not causally related to stroke, and in those with events that are misclassified as ischaemic (e.g. lacunar infarcts, non-specific neurological symptoms, etc.). Thus, the role of a collaborative team approach in insuring appropriate application of transcatheter PFO closure cannot be overemphasized. Attributing an ischaemic stroke to the PFO in a young patient

with ASA, concomitant DVT, and no risk factors may be straightforward. However, establishing an association between a small PFO and non-cortical infarcts or TIAs in an older patients require more scrutiny and deeper understanding of neuro-syndromes and neuroimaging, which might not be within the cardiologist skillset. On the other hand, characterizing PFO (anatomically and functionally) is not routinely undertaken by neurologists. Therefore, it is plausible that a collaborative patient-centred care will lead to optimal utilization of device closure and may potentially improve clinical outcomes.[66]

Summary

After two decades of intense debate and numerous investigations, the role of PFO closure in secondary stroke prevention is now firmly established. However, issues surrounding optimal patient selection, the long-term safety of closure devices, and the lack of comparative effectiveness studies of device closure vs. OAC or antiplatelet strategies remain open. The evolution and success of transcatheter prevention of cryptogenic stroke relies on a collaborative team approach to this complex entity, and on continuous research to address the unresolved issues in the field.

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