Transcatheter Closure Of Patent Foramen Ovale (PFO): A Review

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Introduction

Patent foramen ovale (PFO) is a common abnormality, occurring in 20–35% of the population. In the majority of infants, closure of the foramen ovale occurs soon after birth, as negative intrathoracic pressure associated with the first breaths closes the PFO. In some cases, the primum and secundum atrial septa fail to fuse and closure remains incomplete. There is continuing communication between the right and left atria, particularly during actions that cause a sudden rise and fall in intrathoracic pressure, such as coughing, sneezing or straining. The changes can be mimicked by asking the patient to perform and then release a Valsalva manoeuvre (Calvert et al., 2011).

In majority of people, PFO will remain undetected or appear only as an incidental finding during cardiac investigation. However, some PFOs may open widely and provide a conduit for material such as thrombi, air or vasoactive peptides to travel from the venous to arterial circulation – a paradoxical embolus. This is associated with cerebral embolism (cryptogenic stroke), systemic embolus, migraine with aura, and decompression sickness in divers. Percutaneous PFO closure in carefully selected individuals provides a practical solution to this problem (Gibeltt et al., 2019).

This review will highlight the current evidence for PFO closure, discuss who should be considered for this treatment and review how the procedure should be safely undertaken.

PFO Embryology

The foramen ovale is necessary for blood flow across the fetal atrial septum. During early embryonic stages, the atrium is composed of a single cavity. The development of the atrial septum begins 4 - 5 weeks after conception, usually

between days 27 and 37 postconception. At this stage, the primordial single atrium divides into right and left sides by formation and fusion of two septa: the septum primum and septum secundum. The first structure to develop is the primary atrial septum. This originates from the craniodorsal wall of the atrium and grows toward the endocardial cushions. The septum primum is at first crescent-shaped, creating a large window connecting the left and right atrium. It grows from the primordial atrial roof toward the endocardial cushions, partially dividing the common atrium into right and left halves. The endocardial cushions are formed on the dorsal and ventral walls of the atrioventricular canal, approach each other, and fuse, dividing the atrioventricular canal into right and left sides. The foramen primum results, allowing oxygenated blood flow from the right to the left atrium. As the septum primum grows toward the endocardial cushions, perforations develop. These perforations form a large central window, through programmed cell death, before the septum primum and endocardial cushions fuse (Hara et al., 2005).

The window made as these perforations fuse is the ostium secundum, which also allows blood flow from the right to the left atrium. On the right side of the septum primum, another crescent-shaped membrane grows from the ventrocranial atrial wall: the septum secundum. It gradually grows and overlaps part of the ostium secundum, forming an incomplete septal partition as an oval-shaped window. The septum secundum develops by an infolding of the atrial walls, growing downward around the right atrial aspect of the septum primum, and forming a thick arc over the ostium secundum. A hole remains inferiorly in the septum secundum where the septum primum is exposed on the right atrial side. This region is called the fossa ovalis and is composed only of the septum primum. The two septa eventually fuse together in the areas where they overlap, including around the edges of the fossa ovalis. However, at the anterosuperior edge of the fossa ovalis (adjacent to the aortic root) they remain unfused. This

tunnel, or "flap valve," permits the right-to-left shunting of blood that is necessary for normal fetal circulation. It is this window that becomes the foramen ovale (Dattilo, Kim and Carroll, 2013).

The remaining septum primum forms a flap-like valve over the foramen ovale, which typically closes by fusing with the growing septum secundum after birth. The ostium secundum leads to continuous blood flow from the right to left side of the heart, allowing blood to bypass the fetal pulmonary circulation during fetal development (Asrress et al., 2015)

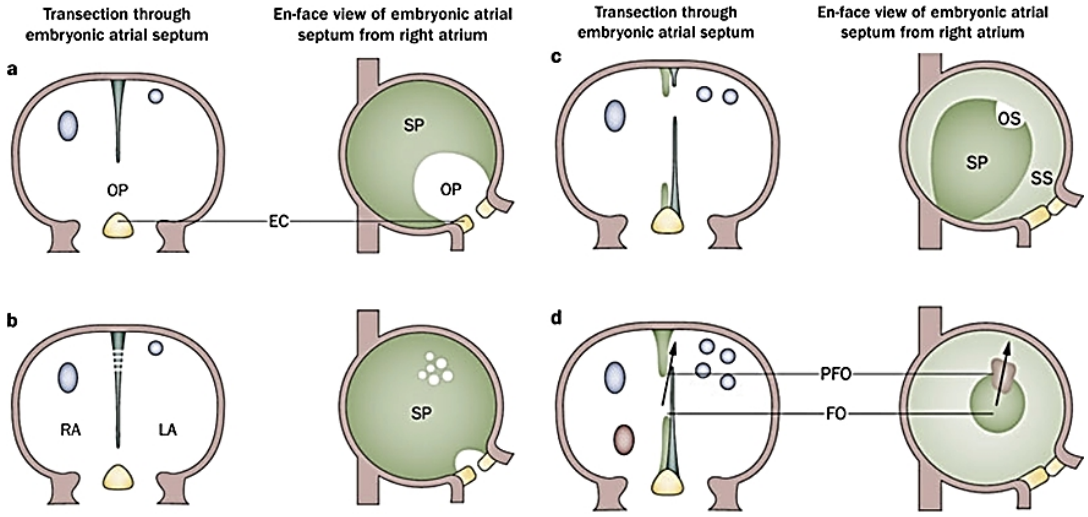

Figure 1: (A) The septum primum grows from the roof of the atria. (B) Fenestrations develop within the septum primum. (C) The septum secundum develops by an infolding of the atrial walls. The ostium secundum acts as a conduit for right-to-left shunting of oxygenated blood. (D) At the anterior superior edge of the fossa ovalis, the primum and secundum septa remain unfused, which constitutes a PFO. Arrow denotes blood flowing through the PFO from the embryonic RA to the LA. The blue and pink dots represent the development of the caval and pulmonary venous inflow to the atria. EC, endocardial cushion; FO, fossa ovalis; OP, ostium primum; OS, ostium secundum; SP, septum primum; SS, septum secundum. (Quoted from Calvert et al., 2011).

In utero, oxygenated blood from the placenta enters the inferior vena cava and the right atrium; it then crosses the foramen ovale to enter the systemic circulation. Most blood flow from the superior vena cava is routed through the tricuspid valve and enters the right ventricle. At birth, right heart pressures and pulmonary vascular resistance drop as pulmonary arterioles open in reaction to

oxygen filling the alveoli. Left atrial pressure may also rise as the amount of blood returning from the lungs increases. Either or both of these mechanisms cause flap closure against the septum secundum. The septum primum and septum secundum begin to fuse after birth and this fusion is complete by age 2 in about 75% of individuals, but patency persists in the other 25%. The patent foramen ovale (PFO) is a residual, oblique, slit-shaped defect resembling a tunnel. The reasons why the septa fail to close and produce a PFO are unknown but are likely related to multifactorial inheritance (Kiserud, 2005)

PFO Anatomy

The prevalence of probe-patent PFO is about 27%, with decreasing prevalence at each decade of life. The mean diameter in the 1st decade is 3.4 mm and in the 10th decade is 5.8 mm, perhaps reflecting size-based selection over time where larger PFOs remain patent and smaller defects close (Hagen, Scholz and Edwards, 1984).

An alternative explanation could be that the PFO is small in the pediatric age group but enlarges as the heart grows. There are no studies with a serial reliable method of quantitating the size of a PFO. Greater PFO size increases the risk of paradoxical embolism, and the heterogeneity of size and morphology are pertinent to interventional device closure selection (Anderson, Brown and Webb, 2002).

The anatomy of a PFO can be highly variable, which has important implications when considering an appropriate closure device. The dimensions and position of the tunnel can vary and must be carefully defined before PFO closure. Some PFOs consist of a tunnel that is long, with the septa tightly opposed, whereas others open widely. In some PFO tunnels, the septum primum is held away

from the septum secundum by a fold of tissue on the left atrial side, a so-called PFO with fixed opening (Hara et al, 2005)

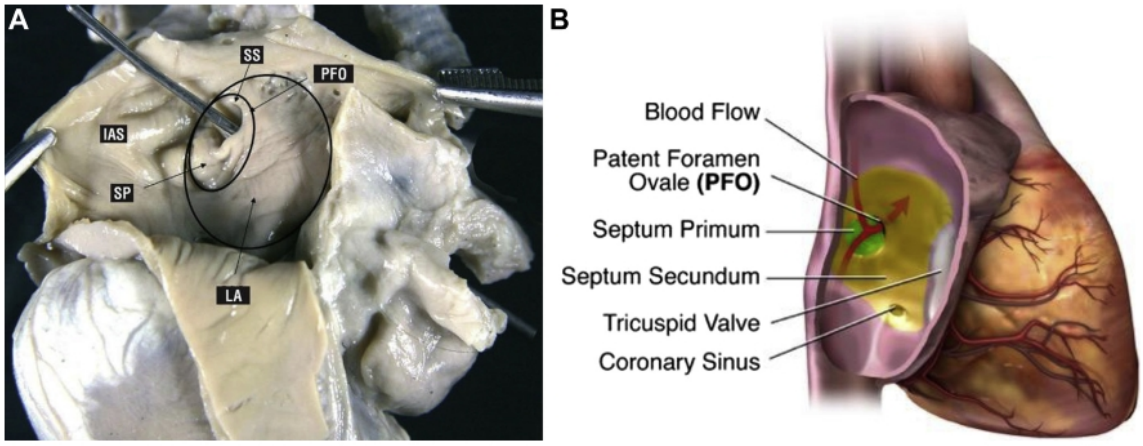

Figure 2: (A) Photograph of autopsy specimen from LA perspective demonstrating PFO by way of the passage of a metal probe; it also demonstrates adjacent structures. SP, septum primum; SS, septum secundum. (B) The septum primum is dark green, and the septum secundum is light green. A PFO typically exists at the anterior superior border adjacent to the aortic root. The arrow denotes the passage of blood through the PFO from the right to left atrium. (Quoted from Cruz-Gonzalez et al, 2008)

Anatomic variations and clinical importance

With the increasing frequency of percutaneous closure of PFO, it is important to have a clear understanding of the anatomy that will be closed with the procedure. The common goal of all closure devices is to successfully stop interatrial shunting through the PFO. However, anatomic variations can be challenging for the operator and, depending on the device, it is possible to have clinically relevant residual shunting after device placement. The increasing use of 3D TEE has allowed more accurate preoperative assessment and characterization of PFO associated anatomical variations that previously remained undetected (Rana et al., 2010a).

Many different classifications of PFO defects have been proposed. One classification describes PFOs as either simple or complex. For a PFO to be classified as simple, it should not have any of the complex PFO characteristics.

Both 2D and 3D TEE can help to better visualize the anatomy. Standard closure devices can close the majority of simple PFOs (Rana et al., 2010a).

The Characteristics of complex PFOs (Aggeli et al., 2018) are:

- Concomitant atrial septal aneurysm
- Tunnel length ≥ 8 mm: A tunnel length >8 mm is a challenge for devices with short non-stretchable waists, because of difficulties in their deployment. Narrow tunnels increase this problem further.
- Multiple atrial septum fenestrations: requires special attention by the operator before device closure
- Large Eustachian valve/ridge or Chiari network: It has been reported that a Eustachian valve can act as an obstacle for placement of PFO-occluding devices by limiting the space close to the fossa ovalis on the right atrial side. As a result, a residual shunt may persist. However, this may be device dependent and is unlikely to be an important issue with current closure devices. A Chiari network is redundant tissue attached to the Eustachian valve and may also interfere with device placement leading to catheter entrapment or device entanglement (Aydin et al., 2011)
- Hybrid defect: Coexistence of additional fossa ovalis defects, apart from the PFO. Hybrid defects include either 1 or multiple (cribriform) small or larger fossa ovalis defects. When percutaneous closure is pursued, all of these defects should be closed
- Septum secundum thickness >1cm: usually because of excessive adipose tissue, may make the PFO harder to close with a percutaneous approach and larger or softer devices should be utilized.
- Altered anatomy because of enlargement of the aortic root

Diagnosis & imaging of PFO

A number of diagnostic imaging modalities can be utilized to directly or indirectly detect and quantify a PFO, all with different advantages and limitations (Zito et al, 2009).

Direct visualization of the interatrial septum, most commonly by ultrasonography, and less frequently by cardiac computed tomography (CT) or magnetic resonance imaging (MRI), can help identify the defect and its anatomic characteristics. (Mahmoud et al., 2017).

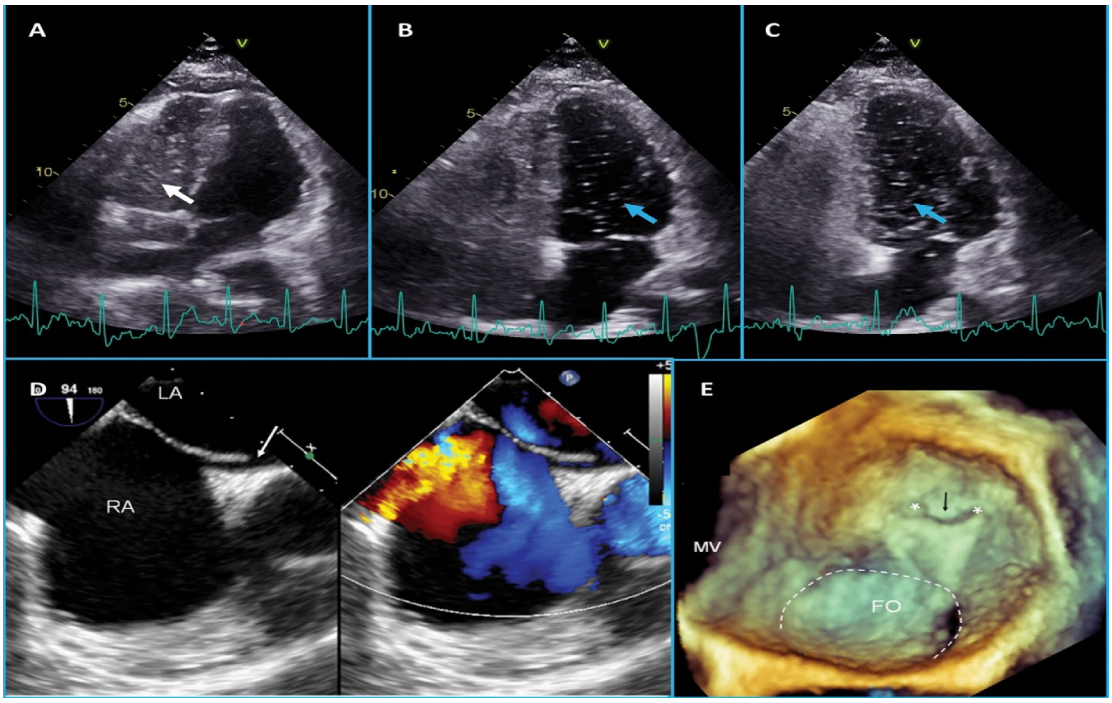

Figure 3: The top panels show a transthoracic bubble study demonstrating a PFO. (A) Apical four-chamber view. Agitated saline after intravenous injection is seen to fill the right ventricular cavity (white arrow). (B and C) Agitated saline bubbles are seen in the left atrium and ventricle within three cardiac cycles (blue arrows).
Bottom panels. (D) 2D transoesophageal echocardiography image (90 degrees) of a PFO (white arrow), with shunting evident on the colour flow Doppler. (E) The same PFO is seen in 3D, viewed from the left atrium. The points of attachment of the septum primum tissue are shown (white asterisks). The PFO opening into the left atrium is seen between these two points (black arrow). The septum secundum tissue is behind, and this overlap of tissue extends to the roof of the fossa ovalis, demarcated by the white dotted line. The PFO tunnel therefore extends from the top of the fossa ovalis to the PFO opening. FO = fossa ovalis; LA = left atrium; MV = mitral valve; PFO = patent foramen ovale; RA = right atrium. Quoted from Giblett et al., 2019

Transthoracic echocardiography (TTE) with agitated saline bubble study remains the most commonly used modality to screen for a PFO and exclusion of other shunts and common cardiac sources of embolism. Transesophageal echocardiography (TEE) with bubble study allows the clinician to diagnose a PFO with direct visualization of the atrial septal anatomy (Silvestry et al, 2015).

Transcranial Doppler (TCD) bubble study has emerged as an acceptable alternative to TTE for PFO screening; it carries a higher sensitivity than TTE and TEE, with a negative test virtually excluding a PFO (Mojadidi et al., 2014).

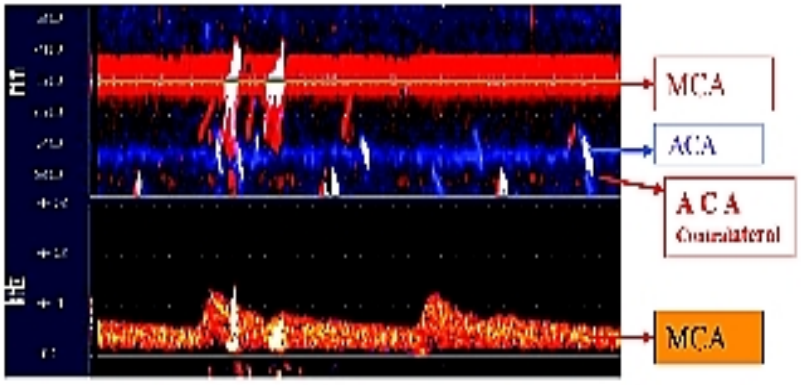

Figure 4: Embolic tracks (ETs) of bubbles on the power mmode (upper panel) and microembolic signals (MESs) on the single-gate spectrogram of the middle cerebral artery (MCA; lower panel). The boxes to the right of the display, from the top downward, indicate 2 ETs in the MCA red band, 4 ETs in the ipsilateral anterior cerebral artery (ACA) blue band, 4 ETs in the contralateral ACA red band, and 2 MESs in the spectrogram also displayed as ETs in the MCA band. Note the single gate Doppler detects only those bubbles passing the MCA while the power mode detects both ETs in the MCA and ETs in the ACAs. Time base = 2 seconds, stretched to accentuate the slopes of the ET (Quoted from Spencer et al., 2004).

Catheter probing and angiography are used to document and categorize a PFO ad hoc or complement prior imaging.

Imaging assessment of a PFO, for diagnostic and interventional purposes, is crucial to aid clinicians in making management decisions and planning potential percutaneous closure of an offending right-to-left shunt.

Table 1: Advantages and Limitations of Transthoracic Echocardiography (TTE), Transcranial Doppler (TCD), Transesophageal Echocardiography (TEE), Intracardiac Echocardiography (ICE), and Angiography for the Diagnosis of PFO.

Imaging Modality	Advantages	Limitations
TTE	• Readily available • Cost-effective • Excellent safety • Easy to perform	• Low resolution • Less sensitive than TCD • Images may be limited by patient's body habitus and poor echocardiographic windows • Often difficult to differentiate between PFO, ASD, and pulmonary shunts
TCD	• Highly sensitive • Cost-effective • Excellent safety • Easy to perform	• Positive test based on an arbitrary cutoff • Inability to differentiate between PFO, ASD, and pulmonary shunts (i.e., lower specificity) • Inability to visualize atrial septum
TEE	• Highly accurate imaging modality • Can visualize atrial septal anatomy • Accurate assessment of PFO size • Accurate assessment of shunt severity • Differentiates PFO from ASD and pulmonary shunts • Useful for closure planning • In addition to diagnosing PFO, can detect other sources of embolism	• Semi-invasive procedure • Need for sedation • Difficulty performing Valsalva with a probe in the esophagus while typically being sedated • Carries a risk of complications • May not be used in patients with esophageal stricture, diverticula, cancer, or varices • Difficulty in uncooperative patients with swallowing dysfunction
ICE	• Detailed visualization of atrial septal anatomy • Allows guidance during device deployment • Residual shunt assessment post-PFO closure • Performance without general anesthesia • Second operator not needed	• Need for second venous access • Increased risk of vascular access-related complications • Possible limitations by operator inexperience • Procedural cost
Angiography	• Accurate • Less uncomfortable than TEE • Combinable with device closure	• Needs catheterization laboratory • X-ray exposure

Quoted from Mahmoud et al., 2017

Indications and evidence for PFO Closure

Embolic Stroke of Undetermined Source (ESUS)

Also referred to as "cryptogenic stroke" which is a stroke in which, despite extensive investigations, a clear cause cannot be found. This would include the exclusion of AF; atherosclerotic disease; carotid dissection; and intracerebral pathology, such as haemorrhage or space-occupying lesions (Adams et al., 1993).

The cause of stroke remains unknown in up to 40% of patients with a stroke diagnosis. In PFO, the presumed cause of stroke is paradoxical embolus. Since the cause is known, the term is a misclassification but remains in use throughout the literature. Paradoxical embolus was first described by Zahn in 1881(**Giblett et al., 2019**) The mechanism of stroke in PFO is translocation of venous thrombus to the arterial circulation under haemodynamic conditions where the

PFO is opened. The opening of a PFO occurs during rapid fall and rise in right atrial pressure (e.g. after straining or coughing). Transient increase in right atrial pressure to greater than that of the left atrium opens a communication, and thrombus can transit at that brief moment. Several case studies demonstrating thrombus across a PFO support this mechanism (Choong et al., 2008; Madani and Ransom, 2007; Kim and Girardi, 2008), as do studies demonstrating the associations of venous thrombosis and PFO with cryptogenic stroke (Cramer et al., 2004)

Observational Studies

Several studies have demonstrated an association between cryptogenic stroke and patent foramen ovale (PFO). Observational studies suggest that the prevalence of PFO in patients with cryptogenic stroke may range between 44% and 66% (Hara et al., 2005).

- ***Observational Studies of Medical Therapy for PFO-Associated Stroke***

The initial treatment strategy for PFO-associated stroke was noninvasive, primarily with antiplatelet therapy, usually acetylsalicylic acid, or anticoagulation therapy such as warfarin.

When medical therapy alone was investigated, meta-analyses showed a significantly lower risk of recurrent neurological events when cryptogenic stroke patients were treated with oral anticoagulation compared to antiplatelet therapy, albeit with a concomitant increased incidence of bleeding (Agrawal et al., 2012).

- ***Observational Studies of PFO Closure for Stroke***

Numerous observational studies and meta-analyses have demonstrated that transcatheter PFO closure is associated with a significant reduction in the rate of

recurrent neurological events when compared with standard medical management, among patients with an index stroke of no other determined source (Agrawal et al., 2012).

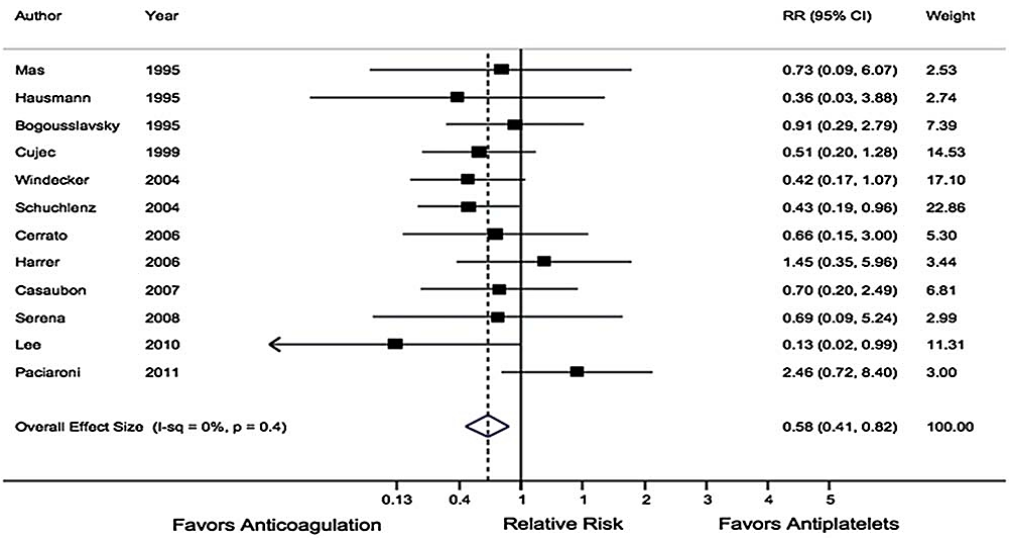

Figure 5: Incidence of recurrent neurological events in the anticoagulation and antiplatelet arms: forest plot comparing the risk of recurrent neurological events between the anticoagulation and antiplatelet subgroups of the medical management arm. CI : confidence interval; RR : relative risk. (Quoted from Agarwal et al. 2012)

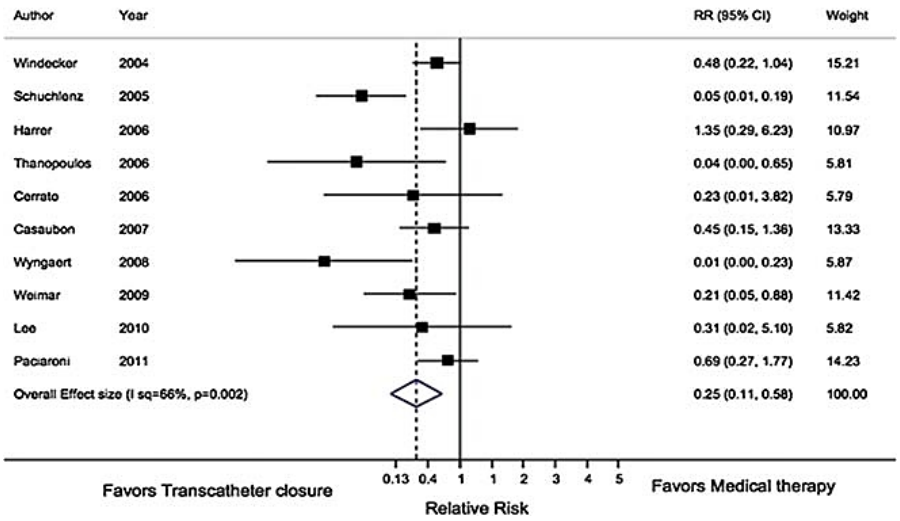

Figure 6: Forest plot comparing the risk of recurrent neurological events between the transcatheter closure and medical management arms in comparative studies. CI : confidence interval; RR : relative risk. (Quoted from Agarwal et al. 2012)

Observational studies showed that transient atrial fibrillation or flutter was the most frequent complication associated with transcatheter PFO device closure (Agrawal et al., 2012).

Early Randomized trials

Two early randomised controlled trials, CLOSURE I (Evaluation of the STARFlex® Septal Closure System in Patients With a Stroke or TIA Due to the Possible Passage of a Clot of Unknown Origin Through a PFO) (Furlan et al., 2012) and PC (PFO and Cryptogenic Embolism) (Meier et al., 2013), did not demonstrate superiority of closure compared to medical therapy.

These trials were confounded by a high crossover rate, failure to randomise those patients whose strokes were most likely to have been caused by PFO, limited power and the introduction of bias through inconsistent use of anticoagulants in the medical therapy group (Messé and Kent DM, 2013)

Furthermore, the STARFlex occluder used in CLOSURE I was a poor device that has been abandoned in Europe owing to concerns about residual defects and left-sided thrombus formation (Thaler and Wahl, 2012).

The Risk for paradoxical embolism (RoPE) score

Using the RoPE score, Kent and Thaler (2011) presented a simple method that can help to identify whether a PFO in a patient with cryptogenic stroke may be causally related to that stroke.

Given the strength and consistency of each variable included within the RoPE score, the calculated score allows clinicians to identify cryptogenic stroke patients with PFO who will benefit most from PFO-specific therapy, thereby

allowing for the proper use of finite resources and avoiding unnecessary interventions (Thaler et al., 2013).

Table 2: RoPE Score Calculator

Characteristic	Points	RoPE Score
No history of hypertension	1	
No history of diabetes	1	
No history of stroke or TIA	1	
Nonsmoker	1	
Cortical infarct on imaging	1	
Age, years		
18–29	5	
30–39	4	
40–49	3	
50–59	2	
60–69	1	
≥70	0	
Total score (sum of individual points)		
Maximum score (a patient <30 years with no hypertension, no diabetes, no history of stroke or TIA, nonsmoker, and cortical infarct)		10
Minimum score (a patient ≥70 years with hypertension, diabetes, prior stroke, current smoker, and no cortical infarct)		0

RoPE, Risk of Paradoxical Embolism; *TIA*, transient ischemic attack.

(Quoted from Kent, Ruthazer and Weimar, 2013)

Table 3: PFO Prevalence (Confirmed by TCD/TEE) in Cryptogenic Stroke Patients by RoPE Score Using Control Rate of 25%.

Cryptogenic Stroke Patients with PFO (n = 1324)		
RoPE Score	**No. of Cryptogenic Stroke Patients with PFO**	**Estimated 2-y Stroke/TIA Recurrence Rate (Kaplan–Meier), % (95% CI)**
0–3	108	20 (12–28)
4	148	12 (6–18)
5	186	7 (3–11)
6	236	8 (4–12)
7	263	6 (2–10)
8	233	6 (2–10)
9–10	150	2 (0–4)

PFO, patent foramen ovale; *RoPE*, Risk of Paradoxical Embolism; *TIA*, transient ischemic attack.

(Quoted from Kent, Ruthazer and Weimar, 2013)

However, cryptogenic stroke patients who have a PFO should be evaluated meticulously, since a detailed history, physical examination, and

echocardiography may identify risk factors that are not considered by the RoPE score. Treating physicians should also be cautioned not to fall into the conjecture that a PFO cannot cause a stroke in the presence of another stroke etiology, as this assumption is counterintuitive and not implemented with any other medical condition.

The RoPE score is based on clinical criteria and it does not include any anatomical or functional characteristics. In 2017, Rigatelli et al. assessed the potential role of a modified anatomical-functional RoPE (AF-RoPE) score in guiding selection of patients with cryptogenic stroke for device closure or medical therapy. The AF-RoPE score resulted in a more precise separation of patients with stroke and PFO, implying that anatomic and functional characteristics of a given PFO can better guide the selection of patients for PFO closure.

Table 4: AF-RoPE Score Calculator

Characteristic	Points	RoPE Score
No history of hypertension	1	
No history of diabetes	1	
No history of stroke or TIA	1	
Nonsmoker	1	
Cortical infarct on imaging	1	
Curtain R-L shunt *(by TCD)*	1	
Persistent R-L shunt at rest	2	
ASA types 3 - 5	2	
Tunnel-like PFO	2	
Age, years		
18–29	5	
30–39	4	
40–49	3	
50–59	2	
60–69	1	
≥70	0	

AF-RoPE, anatomical–functional Risk of Paradoxical Embolism; *ASA*, atrial septal aneurysm; *PFO*, patent foramen ovale; *R-L*, right-to-left; *TIA*, transient ischemic attack.

(*Quoted from, Rigatelli et al., 2017)*

Newer randomized trials

A number of recent randomised trials have demonstrated that PFO closure is superior to medical therapy. The results of these randomised controlled trials are summarised in Table 6.

Table 6: Summary of randomised controlled trials comparing PFO closure to medical therapy

Study	Device	n	Endpoints	Results	Comments
CLOSURE I[9]	STARFlex Septal Closure System	909	Composite of death (0–30 days), neurological death (≥31 days), stroke or TIA at 2-year follow-up	Non-significant reduction in primary endpoint (HR 0.78; 95% CI [0.45–1.35]; p=0.37)	Poor effective closure at 2 years, with evidence of left atrial thrombus formation in closure group
PC-Trial[10]	AMPLATZER PFO Occluder	414	Composite of death, stroke, TIA or peripheral embolism at mean 4.5 years	Non-significant reduction in primary endpoint (HR 0.63; 95% CI [0.24–1.62]; p=0.34)	Underpowered trial with substantial cross-over during follow-up
RESPECT[13,14]	AMPLATZER PFO Occluder	980	Composite of early death, stroke or TIA	Non-significant reduction in primary endpoint at median follow-up of 2.1 years (HR 0.49; 95% CI [0.22–1.11]; p=0.08). Subsequent long-term follow up (median 5.9 years) showed significant reduction with closure (HR 0.55; 95% CI [0.31–0.99]; p=0.046)	Benefit for closure in early as-treated analysis
GORE REDUCE[15]	Helex Septal Occluder or Cardioform Septal Occluder	664	Co-primary endpoints of clinical stroke and incidence of new brain infarction	Significant reduction in clinical stroke at median follow-up of 3.2 years (HR 0.23; 95% CI [0.09–0.62]; p=0.002). Significant reduction in new brain infarction (relative risk 0.51; 95% CI [0.29–0.91]; p=0.04)	2:1 randomisation to PFO closure
CLOSE[16]	Multiple devices	663	Stroke	Significant reduction in stroke with occlusion compared to antiplatelet therapy only (HR 0.03; 95% CI [0.00–0.26]; p<0.001)	1:1:1 randomisation PFO closure versus antiplatelets versus anticoagulation
DEFENSE PFO[17]	AMPLATZER PFO Occluder	120	Stroke, vascular death or Thrombolysis In Myocardial Infarction-defined major bleeding at 2-year follow-up	Significant reduction in primary endpoint with PFO closure. No events in PFO closure arm versus a 12.9% 2-year event rate in medication-only arm (p=0.013)	

PFO = patent foramen ovale; TIA = transient ischaemic attack.

(Quoted from Giblett et al., 2019)

The early results of the RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) trial did not show benefit for PFO closure; however, recently, an extended follow-up of patients demonstrated that there was a reduction in ischaemic stroke compared with medical therapy (Carroll et al. 2013; Saver et al., 2017)

The GORE-REDUCE (Gore® Septal Occluder Device for PFO Closure in Stroke Patients) trial demonstrated a significant reduction in clinical ischaemic stroke compared with antiplatelet therapy alone (Søndergaard et al., 2017)
In the CLOSE (PFO Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence) trial, no patients who underwent PFO closure experienced an ischaemic stroke, compared with 14 in the antiplatelet group (Mas et al., 2017).

Finally, the DEFENSE-PFO (Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk PFO) study showed a reduction in the composite endpoint of stroke, vascular death and Thrombolysis In MI-defined major bleeding at 2 years with PFO closure compared with medical therapy (Lee et al., 2017)

Several meta-analyses have confirmed that PFO closure reduces the risk of ischaemic stroke in patients with cryptogenic stroke and PFO.

These have shown that the overall absolute reduction in risk is low (1.0 per 100 patient-years), but this needs to be weighed against the long period of time that young patients are likely to be at risk. It is thought that patients with atrial septal aneurysm or large shunts may obtain greater benefit (Turc eta al., 2018).
Notably, in these trials and meta-analyses, AF was shown to occur more frequently after PFO closure than with medical therapy alone. This did not seem to counteract the overall stroke reduction in this population (Abo-Salem et al., 2018)

Participants enrolled in these trials were young, with most studies only including those under the age of 60 years. Participants were required to have symptoms consistent with a stroke, with confirmation of ischaemia/infarction on

brain imaging. Confirmation of PFO with TEE was also a requirement for enrolment. The studies excluded patients with an alternative attributable cause for their stroke, and participants could be enrolled no more than 6–9 months after the index stroke. One of the major alternative explanations for embolic stroke is AF, and this was excluded in all patients (Darmoch et al., 2018)

Migraine with Aura

Migraine is a common disorder in young people and is associated with aura in approximately a 1/3 of cases (Burch et al., 2015; Lipton et al., 2003). Migraine with aura has been associated with right-to-left shunts, including PFO (Schwerzmann et al., 2005). Larger shunts have been found to be particularly associated with migraine with aura (Anzola et al., 2006)

The mechanism for the relationship between migraine and PFO is proposed to be the transfer of a vasoactive substance, usually filtered by the pulmonary circulation, into the systemic circulation.(Finocchi and Del Sette, 2015)

Non-randomised studies of PFO closure have reported improvement in patients' symptoms after closure (Butera et al. 2010).

The MIST (Migraine Intervention With STARFlex Technology) trial randomised patients with refractory migraine with aura to percutaneous PFO closure or a sham procedure. The trial showed no difference in cessation of headache or reduction in headache-free days but closure group had lower number of attacks per day. However, the trial assessed a population with a relatively low frequency of migraine, and there was a large number of residual shunts after closure. These problems may have negatively influenced the results (Dowson et al., 2008).

More recently, the PRIMA (Percutaneous Closure of PFO In Migraine With Aura) (Mattle et al., 2016) and PREMIUM (Prospective, Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects With Migraine and PFO Using the AMPLATZER PFO Occluder to Medical Management) (Tobis et al., 2017) trials were negative for their primary endpoints and, while there were some reductions in headache, the effects were small and occurred at the expense of procedural complications.

Overall, there is not enough evidence for PFO closure at present to offer a routine recommendation for therapy for this indication. PFO closure may rarely be considered in carefully selected individuals through a neurology multidisciplinary team, provided there is appropriate consent for procedural risk and with an understanding that an improvement in symptoms would not be certain.

The recent European position paper on the management of patients with PFO has recommended that migraine is treated with conventional therapies and PFO closure to be considered only in clinical trials or for compassionate use in migraine with aura (Pristipino et al., 2021).

Decompression Illness

Decompression illness is a condition suffered by divers and high-altitude pilots who rapidly transition from high- to low-pressure environments. The sudden change in pressure results in formation of nitrogen bubbles within tissues that accumulate in the venous circulation. These are filtered from the blood-stream via pulmonary capillary diffusion. However, if return to low pressure (ascent from depth in the case of divers) is too rapid, then this pulmonary filtration process is overwhelmed and gas bubbles enter the systemic arterial circulation. These bubbles continue to enlarge and result in tissue trauma and even vessel

occlusion. This can produce a range of symptoms, including muscle and joint pain, headache, dizziness, fatigue, rash, paraesthesia, breathing difficulties, confusion, motor incoordination and paralysis (Butler and Hills, 1979).

The presence of a right-to-left shunt such as a PFO allows nitrogen bubbles to bypass the pulmonary filter. Diving profiles are designed to limit the time at depth and slowly ascend toward the surface in order to minimise the risk of decompression sickness (Wilmshurst, Byrne and Webb-Peploe, 1989).

The occurrence of a decompression illness despite such measures implies an increased risk of right-to-left shunt, and investigation for PFO should be considered (Torti et al., 2004).

A longitudinal, non-randomised follow-up study showed a reduction in both symptomatic neurological events and total brain lesions among recreational divers with PFO and decompression illness who had PFO closure, compared with those continuing to dive without closure (Billinger et al., 2011).

In cases where a professional diver wishes to continue diving, a PFO closure could be recommended. The alternatives – stopping diving or curtailing provocative dive profiles – should also be considered. For recreational diving, the risk–benefit analysis for continued diving with a PFO closure is unclear, but some risk remains (Pristipino et al., 2021).

Systemic Embolization

Most paradoxical emboli are likely to present as ischaemic strokes, given the anatomy of the aortic arch. However, systemic embolization to the gut, limbs and myocardium has been described (Ahmed et al., 2003; Kleber et al., 2017; Pavoni et al., 2012)

There is no evidence from randomised controlled trials that closure of PFO in the case of otherwise unexplained systemic embolisation is protective. Nonetheless, it seems logical that closure would be indicated in select cases in a similar manner to that of cryptogenic stroke.

Platypnoea–orthodeoxia Syndrome

Platypnoea–orthodeoxia syndrome (POS) is a rare condition characterised by upright positional desaturation and dyspnea that relieved by recumbence in individuals with a PFO. Alteration of the geometry of the atrial septum allows continuous streaming of deoxygenated blood from the inferior vena cava across the PFO in certain body positions. Typically, the desaturation is seen with the patient seated, while oxygen saturations are normal when the patient is lying flat (Godart et al., 2000).

Distortion of the atrial septal geometry may be caused by chest surgery, such as pneumonectomy, aortic dilatation and aortic surgery, or it may not have an identifiable cause. Occasionally, a tricuspid regurgitant jet can be directed across the PFO. POS is unrelated to underlying cavity pressures and responds well to PFO closure, provided that pulmonary artery pressure is not markedly elevated, which is usually not the case. A case series of 54 patients demonstrated that percutaneous closure could be achieved in a safely and effectively (Shah et al., 2016)

Patient Selection For PFO Closure For Stroke

A PFO is present in 40-60% of patients with cryptogenic stroke, but not all of these patients have paradoxical embolism as the culprit of their stroke. To assess if a detected PFO is the likely culprit of stroke or just an "innocent bystander," the RoPE (Risk of Paradoxical Embolus) score was developed in an effort to determine which PFO should be closed (Kent and Thaler, 2011).

The RoPE score considers a patient's age, cerebral infarct pattern, smoking status, and other comorbidities. However, a major limitation of the RoPE score is that it does not factor in that the absolute risk of paradoxical embolism increases with age and other clinical features such as coexisting venous thromboembolism, straining prior to stroke, and echocardiographic features of the PFO anatomy (atrial septal aneurysm or large shunt), all of which may suggest stroke from paradoxical embolism (Giblett et al., 2019).

The clinical trials varied in their patient enrollment criteria. Based on lessons learned from these trials, a multidisciplinary team is recommended inclusive of a neurologist, cardiologist, and other healthcare professionals trained in stroke management (Mojadidi, Mahmoud and Elgendy, 2017).

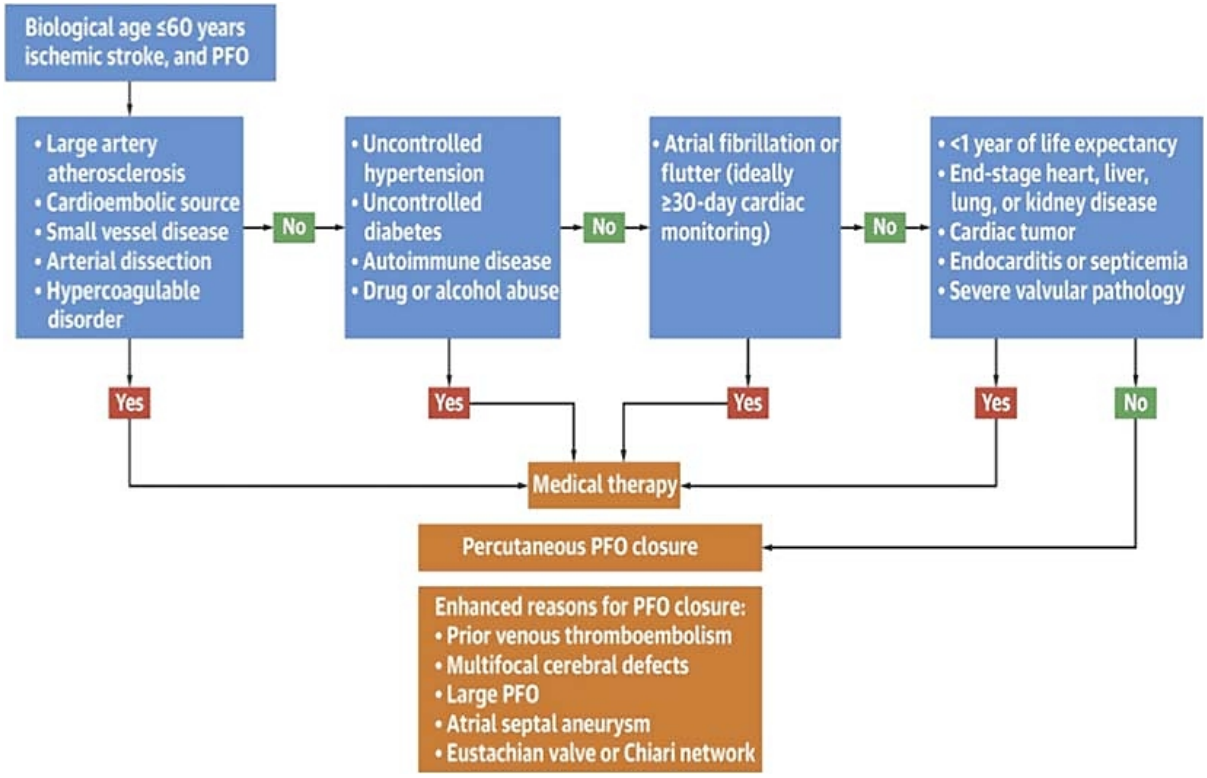

Figure 7: Evidence-Based Algorithm For PFO Closure In Ischemic Stroke Patients For Highest Clinical Yield Based On Randomized Trials. Patients can expect the greatest benefit from percutaneous PFO closure if they have no other cause of cardiovascular stroke on imaging/laboratory analyses, no uncontrolled risk factors, no atrial fibrillation or flutter, and no poor prognostic markers. However, there are situations where 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. PFO, patent foramen ovale. (Quoted from Mojadidi et al., 2018)

Neurologists should diagnose the cryptogenic stroke while cardiologists would facilitate in the detection of PFO and high-risk anatomical features and rule out other cardiovascular culprits (as illustrated in Figure 7), to ensure that PFO closure is performed for all strokes caused by paradoxical embolism (Mojadidi et al., 2018)

The PFO Closure Procedure

Pre-Procedure Investigations

Since the most common indication for closure is cryptogenic stroke, an emphasis should be placed on work-up for other potential causes of stroke. Brain imaging should be undertaken to confirm the diagnosis of a stroke of embolic topography. Lacunar strokes are not likely to be embolic in nature. Carotid imaging should be undertaken to exclude significant plaque disease.

Thrombophilia screening should be considered but is complex, with results that are sometimes inconsistent and often with a need for repeated investigations. Many thrombophilias predispose to venous more than arterial thrombosis, making interpretation of the results difficult, and this should be done in conjunction with haematologists with an interest in thrombosis.

AF is the most common source of thrombus, with studies suggesting that 13% of patients with AF have cardiac thrombus. Among patients with non-valvular AF, the thrombus was located in the left atrial appendage in 90% (Blackshear and Odell, 1996).

The presence of AF in the context of a stroke is an indication for anticoagulation, and closure of a PFO is not indicated. No study has shown that closure of a PFO confers additional benefit (**Giblett et al., 2019)**

ECG monitoring is mandatory to exclude AF, and the duration depends upon the patient's risk factors. Conclusive evidence for the best strategy to diagnose paroxysmal AF is lacking (Sanna et al., 2014).

A minimum of 72-hour ambulatory surface ECG recording has been recommended in young patients (<50 years) with no risk factors, while in those aged >50 years using 6 months of implantable loop recording (ILR). Although ILR has the advantage of extended rhythm surveillance, it is prone to false positives and false negatives (Cotter et al., 2013; Podd et al., 2016).

Transthoracic echocardiography (TTE) is the key first-line investigation for the exclusion of intracardiac thrombus. Cardiac thrombus is associated with a number of conditions apart from AF, including MI, atrial myxoma, left ventricular aneurysm, non-compaction cardiomyopathy, left ventricular failure and mitral stenosis. All of these need to be excluded prior to consideration of closure of PFO (D'Andrea et al.2021).

Bubble contrast echocardiography is a key investigation when working up patients with cryptogenic stroke. In order for a PFO to cause a stroke, it needs the ability to produce a right-to-left shunt. Bubble contrast studies are initially performed using TTE, with no sedation necessary. Agitated saline is injected into a peripheral venous cannula (ideally in the left antecubital fossa), and the patient is asked to perform a Valsalva maneuver or to sniff. With TEE imaging, abdominal hand compression and release may be an alternative to Valsalva maneuver. In the presence of a cardiac shunt, bubbles should appear in the left side within 3-5 cardiac cycles of complete opacification of the right atrium. Late appearance of bubbles may reflect pulmonary transit. The procedure may require multiple repeats to confirm the diagnosis.

A positive bubble study in the setting of cryptogenic stroke is an indication for detailed TEE. This allows the structural team to accurately define the position and anatomy of a PFO. The study will also exclude the presence of alternative shunts, such as ventricular septal defects, anomalous pulmonary venous drainage and sinus venosus defects (Rana et al., 2010b)

The diagnosis of cryptogenic stroke and PFO will require the input of multiple specialties, including stroke physicians or neurologists, cardiac imaging specialists, radiologists and interventional cardiologists. Some centres use the Risk of Paradoxical Embolism (RoPE) score to help multidisciplinary teams classify the relationship between the stroke and the PFO (Thaler, Ruthazer and Weimar, 2014).

Consideration of the investigations and the patient as a whole should be undertaken in a multidisciplinary setting.

The Closure Procedure

PFO closure is routinely performed as a day-case procedure. The procedure can be performed in a standard catheter laboratory with fluoroscopic guidance and physiological monitoring. Since patients undergoing this procedure will obtain no immediate symptomatic benefit, with only the long-term risk of stroke being reduced, all possible steps to reduce complications should be taken, i.e. the procedure should be, as far as possible, complication-free. This means using ultrasound-guided femoral venous access (if needed), echocardiographic guidance, adequate anticoagulation and special care to reduce risk of air embolus. Informed patient consent should clarify all related issues.

The use of periprocedural guidance with TEE or intracardiac echocardiography (ICE) is different among centres worldwide. Some centers prefer fluoroscopic-

only guidance. General anaesthesia is generally required in case of TEE guidance.

The procedure is undertaken from the femoral vein and adequate anticoagulation should be administered (unfractionated heparin 80–100 IU/kg).

Giblett et al., 2019 described the technique of closure using a double-disc device as follows (figure 8 shows the steps):

- The PFO is crossed with a 6 Fr multipurpose diagnostic catheter.
- A 0.035 inch J-tipped guide wire is passed into a pulmonary vein (usually the left upper).
- This may be exchanged for a stiff wire to assist delivery of balloons.
- Balloon sizing of the PFO can be performed using quantitative angiographic tools. A left anterior oblique (LAO) fluoroscopic projection may assist with this, as the septum is seen in profile. Compliant balloons with marked graduations are used, but balloon sizing can still shorten and widen the PFO. This may be desirable if there is a particularly long PFO tunnel, but it can enlarge the hole, thus necessitating a larger device. Similar (and potentially more accurate) information can be obtained through TEE assessment.
- After sizing, an appropriate device can be selected and its delivery sheath introduced into the left atrium. The left atrial disc is deployed, followed by the right disc. Throughout this procedure, ensuring that the delivery sheath remains de-aired and flushed is crucial to minimise the risk of air or thrombotic embolism.
- Once the device is placed, confirmation of adequate positioning with echocardiography and fluoroscopy should be performed prior to device release. It is important at this point to ensure that the right atrial disc covers the lip of the septum secundum (Pacman sign), so that the disc will remain on the right

atrial side and not slip into the PFO tunnel. If the device is found to malpositioned after release, it can still be recovered using a large gooseneck snare.

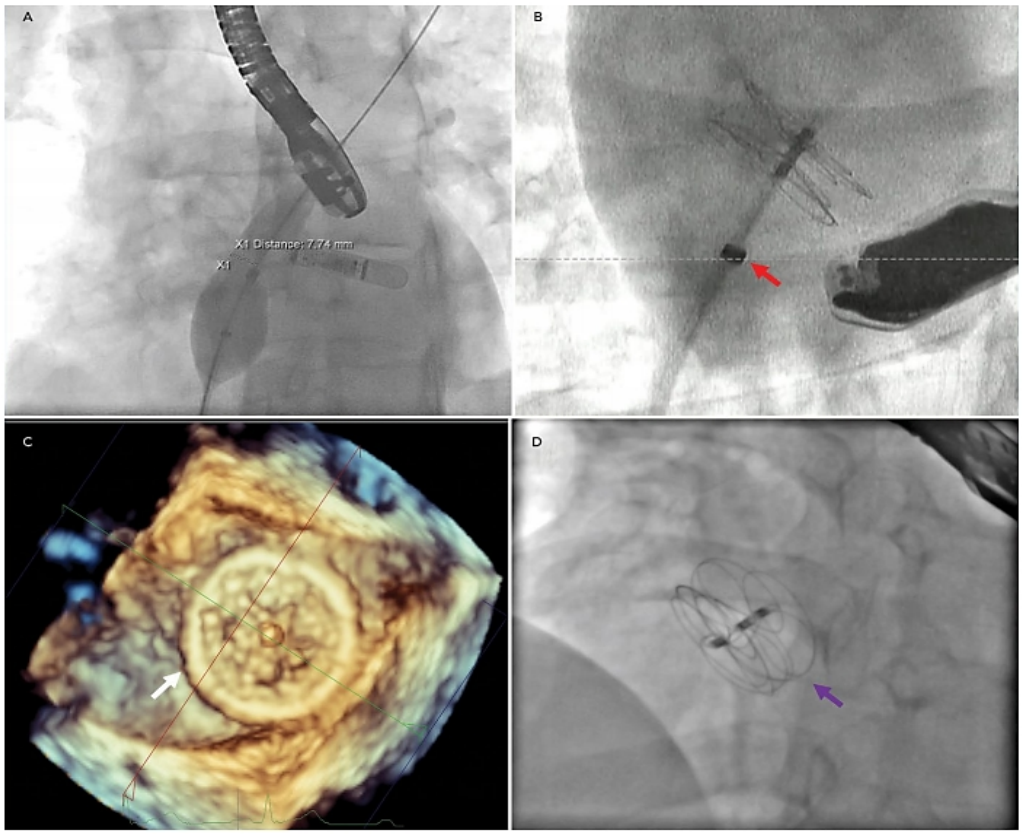

Figure 8: Percutaneous closure of a PFO (A) Wire crossing a PFO into the left upper pulmonary vein. A sizing balloon is deployed and the quantitative angiographic analysis to size the defect is shown. (B) The Gore Cardioform septal occluder has been deployed through the delivery sheath (red arrow) but has not yet been released. (C) 3D transoesophageal echocardiography image of the device (white arrow) viewed from the left atrium. (D) The device is shown in place after release (purple arrow). Quoted from Giblett et al., 2019.

The optimal regimen of antithrombotic therapy after device deployment remains uncertain. Aspirin and clopidogrel are usually given for 6 months, but evidence for this is limited and practice has varied markedly between trials. Some operators preload patients with antiplatelets, but again the evidence for this is uncertain.

Single antiplatelet therapy, usually clopidogrel 75 mg daily, is continued indefinitely.

The patient should undergo TTE prior to discharge and at 6 weeks to exclude pericardial effusion and device embolization. Closure rates are high with modern devices, and the principal objective is to stop the PFO flap valve opening wide, which occurs as soon as the device is deployed.

Complete closure depends upon endothelialisation of the device and can take up to 6 months, after which time a repeat bubble study can be undertaken to confirm complete closure, although this is not mandated unless the patient plans to dive.

Nietlispach and Meier, 2015 described a frugal way (i.e., guided by fluoroscopy only), with a high success rate and without any significant in-hospital complications using Amplatzer PFO Occluder:

- night at hospital
- Antibiotics (oral cephalosporin), 2 or 3 doses, 1st before, 2nd at discharge (outpatient), 3rd next morning (inpatient)
- No echocardiographic guidance
- Heparin bolus 5000 U before puncture
- Local groin anesthesia
- Access: right femoral vein
- 0.035 regular U-tip guidewire, exchange length not required
- Multipurpose or right Judkins catheter to pass defect if wire fails to pass spontaneously.
- 9 French single 45 degrees curve 60-80 cm TorqVue sheath (10 F for 40/40 mm Cribriform Occluder or other brands)
- Right atrial contrast medium injections for position control (left anterior oblique view without any overlap of discs)
- Unrestricted physical activity after a few hours

- Acetylsalicylic acid 100 mg for 2-5 months, starting after procedure without loading (Clopidogrel 75 mg for 1 month, starting after procedure without loading)
- Instruction for prophylaxis against endocarditis for 2-6 months
- TEE (less ideally TTE or TCD exam) at about 3-6 months (1 month after stopping platelet inhibitors)

Closure Devices

A large number of devices with varying shapes and sizes have been marketed, with many achieving CE mark status in the EU. In the US, the need for evidence from randomised controlled trials prior to approval means fewer devices have been approved by the FDA (Food and Drug Administration). Figure 9 shows PFO closure devices approved by FDA in 2ry prevention of cryptogenic strokes.

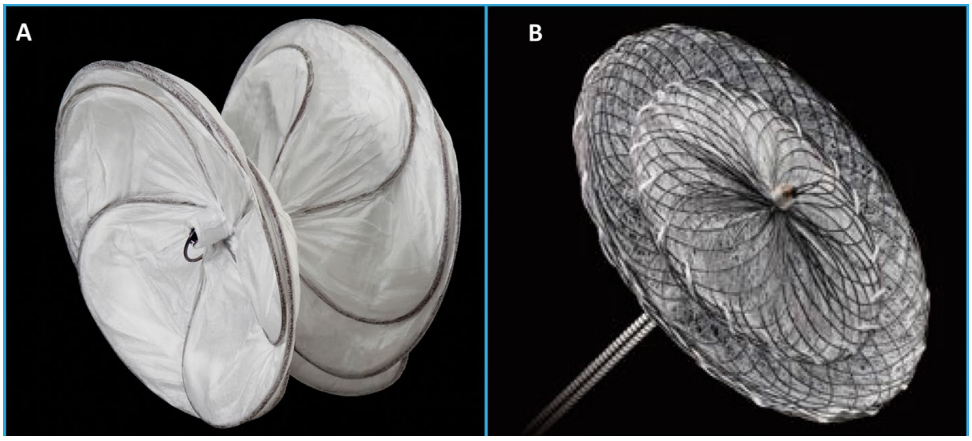

Figure 9: (A) The Gore Cardioform septal occluder. (B) The AMPLATZER PFO Occluder. These devices are both FDA-approved for PFO closure and are the two most widely deployed occluders (Quoted from Giblett et al., 2019)

Double Disc Devices

- ***Amplatzer PFO Occluder:*** The Amplatzer PFO occluder, consisting of a nitinol wire mesh and polyester, is a self-expanding double-disc device with a smaller left and a larger right atrial disc (except for the 30 mm version, where the right and the left disc each comprise 30 mm) and a central waist.

The Amplatzer PFO Occluder was the first dedicated PFO occluder and is the most widely investigated and used device for percutaneous PFO closure. Procedural success rates are close to 100%, and effective closure rates are as high as 95% at 6 months. Thrombus formation on the device is exceedingly rare, as is clinically relevant new-onset atrial fibrillation (Stortecky et al., 2015)

- ***CardioSEAL Device:*** The CardioSEAL device is a self-expanding, double square disc device, made out of a nickel-cobalt-based alloy covered by Dacron. Each disc consists of 4 arms. Safety and efficacy of this device have been reported in observational studies (Van den Branden et al., 2010). The device is no longer manufactured.

- ***STARFlex Device:*** The STARFlex device, a self-expanding, double square disc device, is similar to the CardioSEAL device. It is also made out of a nickel-cobalt-based alloy and covered by Dacron. The device was associated with an increased risk of atrial fibrillation and device thrombus formation (Staubach et al., 2009) and is no longer on the market.

- ***Figulla II PFO Occluder:*** The design of this occluder is similar to that of the Amplatzer PFO Occluder, with slight changes such as a lower-profile left atrial disc and the absence of a hub on the left atrial side (Krizanic et al., 2008). The safety and efficacy of this device have been shown in smaller registries and case series (Baglini et al., 2013). Because of assumed patent infringement concerns, it was not introduced in the United States.

- ***Gore HELEX Septal Occluder:*** The HELEX device consists of a single nitinol wire frame covered with expanded polytetrafluoroethylene (ePTFE) with a left atrial, central, and right atrial eyelet and a locking loop holding

the device together (Zahn et al., 2001). This device was effective but technically challenging to deploy and is no longer commercially available. It was replaced by the next-generation occluder based on a similar principle, the Gore Cardioform Septal Occluder.

- ***Gore Cardioform Septal Occluder:*** The Cardioform device is a double disc device made out of a nitinol frame, covered by expanded polytetrafluoroethylene (ePTFE).

  Although reported success rates are high, a lower complete closure rate has been reported with this device (Pristipino et al., 2019). On the other hand, this device is preferred by some operators who argue that it is better tolerated by patients (fewer patients complaining of chest discomfort than with the Amplatzer series of occluders). The group at UCLA (University of California, Los Angeles) has reported that the Cardioform device has the highest complete closure rate of any device based on transcranial Doppler bubble study assessment for residual shunting (Tobis, 2019).

  There has not been a report of atrial erosion with the HELEX or Cardioform devices, but there are 2 cases of hemopericardium out of 40,000 sold devices due to a fractured nitinol wire (Rhodes and Goble, 2014; Smith et al., 2014). Of all Amplatzer PFO device implants, there were 2 erosions reported (Amin et al., 2008).

Non Double-Disc Devices

- ***FlatStent Occluder:*** The FlatStent Occluder consists of a polyurethane foam and a nitinol-based wire framework (Ruygrok, 2010). The design of the FlatStent Occluder is based on the assumption that systems minimizing the amount of material exposed to the circulating blood might reduce device-

related complications such as thrombus formation, erosion, or atrial arrhythmias.

However, experience with this device is limited, and it remains to be determined whether the concept translates into similar outcomes as with the double-disc devices (Reinthaler et al., 2015)

- ***NobleStitch EL Occluder:*** This system for PFO closure uses, similar to some femoral vascular closure devices, a stitch technology to suture the septum primum and secundum, producing an "S-shape" closure of the PFO. It emerged out of similar devices tested over the past decade with unsatisfactory results. First experience with this device was recently reported in the NobleStitch EL Italian registry of 192 patients. Procedural success was achieved in 96% of patients, but at a mean follow-up of 200 days, an exceedingly high rate (11%) of significant residual right-to-left residual shunt was found (Gaspardone et al., 2018).

- ***Radiofrequency Fusion:*** Some studies investigated the use of thermal radiofrequency for percutaneous PFO closure without leaving behind an implanted device. However, closure rates of about 50% (as reported in small registries) were substantially lower than those achieved with established devices, and further device development was suspended (Sievert et al., 2009).

Safety of percutaneous PFO closure

Percutaneous PFO closure is a safe, effective, and durable procedure. Primary technical success approaches 100%, and rates of effective closure at 6 months were 94-96% with the Amplatzer PFO Occluder, and 86% with the STARFlex device (Meier et al., 2013).

Residual shunts, which are associated with increased rates of recurrent events, can be treated successfully with a second device (Susuri et al, 2017).

Randomized trials showed excellent safety results for percutaneous PFO device closure. Albeit rare, device or procedure-related complications may occur. It is estimated that over a million patients were treated with PFO closure over the past few decades; of these, only a limited number of serious or lethal complications have been reported (Meier and Nietlispach, 2017).

Atrial fibrillation, mostly occurring only intra- or early post-procedural, has been reported in about 5% of patients after percutaneous PFO closure (Rigatelli et al., 2016), with lower rates observed with the Amplatzer PFO occluder (Pristipino et al., 2019).

Device thrombus formation may rarely occur, and few cases of atrial erosion have been reported (Scacciatella et al., 2014).

Despite the general safety of the devices and the procedure, there are reports of the necessity of surgical removal for a variety of reasons. In a global survey of 13,736 percutaneous PFO device implantations performed over 9 years at 18 institutions in Europe and the USA, 38 devices (0.28% [95% confidence interval: 0.20-0.37%]) required surgical removal. There were a wide range of causes cited for these removals. The most common cause for explantation was chest pain in 14 patients, often believed to be secondary to nickel allergy to the PFO occluding device. Other causes for explantation included persistence of a residual shunt in 12 cases, which would have been corrected percutaneously in many institutions; these further included the presence of thrombus on 4 devices, pericardial effusion in 2, perforation of the atrium or aortic root in 2, recurrent

stroke in 1, endocarditis in 1, and undocumented reasons in 2 patients (Verma and Tobis, 2011).

However, The vast majority of PFO closure procedures are performed safely with minimal complications

Conclusion

The followings are key points & recommendations from European position paper on the management of patients with PFO (Pristipino et al., 2019):

1. PFO is present in about 25% of the general population. PFO can play a pathogenic role in cryptogenic left circulation thromboembolism.
2. There is no gold standard for diagnosing PFO. A combination of TTE, TEE, and TCDs may be required. The paper adopted the following algorithm for PFO detection: If TTE is positive, pursue TEE for corroboration. If TCD is positive, pursue TEE for corroboration. If TTE is negative or equivocal, pursue TCD, and if TCD is negative, stop investigation.
3. Patients with PFO and left circulation arterial embolism of unknown cause despite a comprehensive workup should be classified as having PFO-related embolism instead of cryptogenic embolism.
4. To rule out causes other than PFO, patients with left circulation embolism and PFO should undergo a 12-lead ECG and either inpatient telemetry or 24-hour Holter monitoring to evaluate for atrial fibrillation (AF). Patients ≥65 years or patients 55-64 years with AF risk factors should undergo 6 months of AF monitoring with an implantable cardiac monitor.
5. An atrial septal aneurysm, a moderate-to-severe shunt, and atrial septal hypermobility have been strongly associated with a causal role of PFO in cryptogenic stroke in some studies.
6. The risk of paradoxical embolism (RoPE) score attempts to predict how likely a PFO is causal in the setting of a cryptogenic stroke. The RoPE score can be

used to guide management decisions, but should be used in conjunction with other parameters, such as the presence of atrial septal aneurysm or deep venous thrombosis/pulmonary embolism.

7. The risk of recurrence in a PFO-associated stroke is likely quite low based on observational/randomized studies. An atrial septal aneurysm may convey a higher risk of recurrence. The authors' meta-analysis of randomized clinical trials suggests a recurrent stroke risk on medical therapy of 4.6% over 3.8 years of follow-up.
8. There are no definitive data to guide the selection of an antiplatelet versus oral anticoagulation (OAC) with vitamin K antagonists for secondary stroke prevention after PFO-related stroke. While OAC may be superior to antiplatelets in preventing PFO-related stroke, OAC also increases the risk of both intracranial and major extracranial hemorrhage. OAC may be preferred if the patient has a low hemorrhagic risk, high compliance is expected, and proper anticoagulant monitoring can be guaranteed.
9. The role of direct oral anticoagulants (DOACs) is not clear and is an important area for future research. Future research should include a randomized controlled trial of secondary prevention with a DOAC compared to PFO closure in patients with PFO-related left circulation embolism.
10. Percutaneous PFO closure results in complete closure at 1 year in 93-96%.
11. After PFO closure, it is reasonable to continue dual antiplatelet therapy for 1-6 months and then continue single antiplatelet therapy for ≥5 years.
12. In the authors' meta-analysis with 3.8 mean years of follow-up, the number needed to treat with PFO closure to prevent 1 stroke in all patients was 37 (95% CI, 26-68) and in patients with high-risk features (e.g., atrial septal aneurysm), it was 21 (95% CI, 16-61).
13. It is the position of the authors that patients ages 18-65 years with a confirmed cryptogenic stroke, transient ischemic attack, or systemic embolism with a high

probability of a causal role of their PFO should undergo percutaneous PFO closure.

14. Interdisciplinary collaboration with an interventional cardiologist and a relevant specialist (e.g., neurologist) and active collaboration with the patient are key in decision-making regarding PFO management.
15. Antibiotic prophylaxis against endocarditis before an invasive procedure or surgical intervention should be pursued for all patients within the first 6 months after closure.

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