Patent Foramen Ovale and Atrial Septal Defect

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KEYWORDS

• Patent foramen ovale • Atrial septal defect • Transcatheter closure • Echocardiography

KEY POINTS

- The foramen ovale fails to close after birth in up to 25% to 30% of individuals.
- Patients with patent foramen ovale (PFO) are mostly asymptomatic, but having a PFO has been associated with embolic strokes, migraines (especially with aura), and rarely platypnea-orthodeoxia syndrome.
- Transcatheter PFO closure may be considered for secondary stroke prevention in embolic stroke patients with a high Risk of Paradoxical Embolism (RoPe) score.
- Atrial septal defects (ASDs), while often treated in childhood, may sometimes go undetected into late adulthood.
- For ASD patients with significant shunt (Qp/Qs $\geq$1.5) or right heart volume overload, closure is recommended, via surgery or transcatheter methods, considering expertise and anatomy.

Video content for this article is at http://www.interventional.theclinics.com.

INTRODUCTION

Foramen ovale is a normal prenatal interatrial communication, permitting the transfer of oxygenated blood from the right atrium to the left atrium.[1] Typically, in around 75% of individuals, this opening naturally closes during the neonatal period as pulmonary resistance decreases and blood flow through the lungs increases, resulting in higher left-sided resistance.[2] Nevertheless, in approximately 15% to 35% of adults, the foramen ovale persists, leading to the condition known as patent foramen ovale (PFO).[3,4] A possible link between PFO and stroke was first proposed in the late nineteenth century.[5] Association between PFO and embolic ischemic stroke, migraine headaches, platypnea-orthodeoxia syndrome (POS), and decompression sickness has been described,[6–8] and up to 40% to 50% of young patients with embolic stroke of undetermined source may be diagnosed with PFO.[9] Transcatheter PFO closure has emerged as an effective treatment to reduce the risk of recurrent stroke.[10–13]

Anatomy and Pathophysiology

The human fetus develops in a relatively low oxygen environment. Oxygenated blood from the mother's side of the placenta enters the fetal side through numerous villi, which later merge to form the umbilical vein. This vein then divides to supply the hepatic circulation and join the ductus venosus. The oxygenated blood from the ductus venosus enters the right atrium and is preferentially directed to the left atrium through the foramen ovale. This mixed blood, along with a small amount of blood from the pulmonary veins, flows into the ventricle and ascending aorta, supplying the carotid arteries and the coronaries, ultimately supporting the developing brain and heart of the fetus.[14]

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The formation of the interatrial septum is a complex process. Initially, a primitive heart tube forms, which is suspended from the mesocardium.[15] The tube undergoes a looping process, leading to the formation of the primary atrium. The growth of the primary atrial septum (septum primum) toward the atrioventricular cushion results in an opening at its distal edge, known as the primary atrial foramen or ostium primum. As the muscular septum primum grows downward, its superior portion becomes fenestrated. These fenestrations eventually merge to form the foramen secundum, ensuring the continued flow of blood from the right to the left side of the system during the rest of gestation. Once the foramen secundum is fully formed, the ostium primum closes, and the septum primum becomes the flaplike valve of the foramen ovale.[16]

Around 75% of individuals experience spontaneous fusion of the septum primum with the septum secundum by the age of 2, resulting in the closure of the PFO.[17] However, in the remaining individuals, a tunnel-like oblique crescent-shaped defect persists, known as PFO.

Symptomatology and Clinical Manifestations

Stroke

While most patients with PFO are asymptomatic, the most concerning clinical manifestation is ischemic stroke caused by paradoxic embolism. Paradoxic emboli originate in the systemic venous circulation and pass into the systemic arterial circulation through a PFO.[18] Around 20% to 40% of ischemic strokes have an unknown cause, termed as cryptogenic strokes, and patients with cryptogenic stroke often have a higher prevalence of PFO.[19,20] A meta-analysis of case-control studies found a significant association between the presence of a PFO, atrial septal aneurysm (ASA), or both and ischemic stroke in patients under the age of 55 years (with odds ratios of 3.1, 6.1, and 15.6, respectively).[21]

The Risk of Paradoxical Embolism (RoPe) study conducted a patient-level meta-analysis of 12 cryptogenic stroke cohorts, revealing a correlation between the prevalence of PFO and the likelihood of PFO being the underlying cause of stroke when vascular risk factors like hypertension, diabetes, smoking, and prior transient ischemic attack (TIA) were absent and a cortical infarct was present.[22] In the same study, the presence of a PFO along with an ASA was identified as a significant predictor of recurrent stroke in the cryptogenic stroke cohorts.[22] However, other studies like the Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS) and the Spanish right-to-left shunt multicenter study (CODICIA) studies did not find PFO with an ASA to be a significant predictor of an increased risk of recurrent stroke.[23,24]

Migraine

Migraine is a prevalent condition affecting approximately 10% of adults, with a higher incidence in women.[25] Over the past 2 decades, research has indicated a link between PFO and migraine, particularly migraine with aura. Although migraine headaches have been linked to PFO, routine screening for PFO is not recommended in migraine patients.

Data on PFO closure and improvement of migraine are debatable. Studies have demonstrated that closing PFO in patients with large PFO detected through transcranial Doppler (TCD) with subclinical brain magnetic resonance imaging (MRI) lesions resulted in a significant decrease in both the frequency and severity of migraines.[26] These brain lesions may suggest silent thromboembolism and could put these patients at higher risk of future embolic events. Similarly, PFO closure significantly reduced migraine symptoms in patients with high-risk PFO characteristics, such as a curtain shunt pattern on TCD and transesophageal echocardiogram (TEE) (indicating more extensive shunting), right-to-left shunting during normal respiration, ASA, and presence of eustachian valve.[27]

The Migraine Intervention with STARFlex Technology (MIST) and percutaneous closure of patent foramen ovale in patients with migraine (PREMIUM) randomized control trials, which involved patients with migraine and PFO, found no difference between PFO device closure and sham treatment in terms of headache cure at the 6-month endpoint and no difference in reduction in responder rate.[28,29] Likewise, the percutaneous closure of PFO in migraine with aura (PRIMA) study, which focused on patients with migraine with aura, showed no statistically significant difference between the PFO device closure group and the medical management group in terms of reducing monthly migraine days.[30] On the other hand, there has been some limited evidence that clopidogrel might decrease migraine episodes in patients after transcatheter PFO closure.[31,32] Future trials bear the responsibility of identifying individuals who would derive the most benefit from PFO closure, primarily by considering high-risk PFO characteristics, best evaluated through TEE. In addition, they may also include individuals with subclinical brain lesions on imaging for assessment.

Decompression sickness

Decompression sickness occurs when a diver surfaces from a dive and nitrogen bubbles, which typically dissipate in the lungs, enter the systemic circulation through a right-to-left shunting pathway like PFO. These bubbles may then embolize to the brain, causing ischemic lesions. Although rare, there have been reports of paradoxic embolism through a PFO, which has been identified as a cause of conditions like myocardial infarction or renal embolism.[33,34] A prospective, nonrandomized study involving 104 scuba divers with a history of significant decompression sickness found that transcatheter PFO closure was associated with a reduction in symptomatic and asymptomatic decompression sickness, as evidenced by ischemic brain lesions observed on MRI.[35] To date, the guidelines do not recommend routine PFO closure in patients with prior decompression illness without a prior PFO-associated stroke.[36]

Platypnea-orthodeoxia syndrome. POS is an uncommon condition characterized by dyspnea and hypoxia that worsen when a person is upright but improve when they lie down. In most adults with PFO, significant right-to-left shunt resulting in hypoxia is not present; however, perturbations in right heart physiology can induce right-to-left shunt such as in pulmonary thromboembolism, right ventricular myocardial infarction, pneumothorax, hydrothorax, pericardial effusion, or after pneumonectomy or in chronic situations such as pulmonary hypertension, severe tricuspid regurgitation, pulmonic valve stenosis, or regurgitation.[37,38] However, the subacute and chronic development of POS often occurs in the absence of these clinical events, suggesting that another process may play a role.

To diagnose this condition, it may be necessary to perform a transthoracic echocardiography (TTE) or TEE with bubble contrast and agitated saline both in recumbent and upright positions.[39] Cardiac MRI or CT can be used to detect any abnormalities in the aorta.[40] Transcatheter PFO closure can improve symptoms in individuals with POS.[41]

Diagnosis

Various ultrasound methods, such as TTE, TEE, and TCD, can be employed to identify PFO. In recent times, three-dimensional echocardiography (3DE), CT, and MRI have also been utilized for this purpose.

Echocardiography

Agitated saline is a commonly used method to diagnose right-to-left shunts. The criteria for a positive contrast study on TTE or TEE vary, but it is generally agreed upon that a right-to-left shunt is diagnosed if at least 3 micro-bubbles appear in the left atrium, either spontaneously or after provocative maneuvers such as coughing or performing the Valsalva maneuver, within 3 cycles of complete opacification of the right atrium.[8] During the Valsalva maneuver, the increased filling of the right atrium raises its pressure, leading to the opening of the foramen ovale. A proper Valsalva maneuver can be achieved by applying a calibrated strain (40 mm Hg measured by spirometry) sustained for 10 seconds.[42] Studies have indicated that the sensitivity of detecting a PFO is improved when contrast injection is performed through the femoral vein rather than the antecubital vein.[43] When contrast is flowing through the inferior vena cava, it is directed toward the interatrial septum, often potentiated by a eustachian valve, while contrast injected through the superior vena cava is directed toward the tricuspid valve.[44] Most echocardiographic laboratories still prefer using the antecubital vein because of its easy accessibility.

Studies have demonstrated that TEE exhibits a very pronounced correlation with autopsy findings, exhibiting a sensitivity and specificity of nearly 100% in diagnosing PFO.[45] Because of its exceptional sensitivity and superior image resolution, which allows for detailed analysis of the interatrial septal area and PFO morphology, TEE is currently considered the gold standard for diagnosing and characterizing PFO. In some cases, obtaining a good Valsalva maneuver during TEE may be challenging, particularly if the patient is heavily sedated, in comparison to TTE or TCD examinations.[46]

Advanced imaging: 3DE, CT, and MRI

Advanced imaging techniques such as 3DE using reconstruction methods and real-time analysis have been utilized to assess various medical conditions, including PFO. In a recent comparison, real-time 3D TTE demonstrated significantly higher diagnostic accuracy than contrast TTE, with a sensitivity of 83% versus 44% ($P<.001$).[47]

Limited studies involving contrast-enhanced MRI and cardiac CT demonstrated good agreement with TEE in diagnosing PFO.[39,47] However, larger studies have revealed that both these modalities are less effective than TEE in detecting PFO.[48,49]

Management

Treatment for preventing strokes in patients with PFO is increasingly becoming evident, with

growing support for transcatheter PFO closure in specific populations. Other available treatment options include antiplatelet therapy or anticoagulant therapy. It is important to consider patient selection in therapeutic decision-making, as not all PFOs are likely to be responsible for strokes given the high prevalence of PFO in the general population.[50] Recent guidelines from the Society of Cardiovascular Angiography and Interventions (SCAI) provide valuable insights for PFO management based on an expert panel review of the available literature.[36]

Medical therapy

Currently, the decision whether antiplatelet therapy or anticoagulant therapy is more suitable for patients with cryptogenic stroke and PFO is debatable, as evidenced in the medical arms of published randomized PFO closure trials. In the Warfarin-Aspirin Recurrent Stroke Study (WARSS), no significant difference in recurrent stroke or death prevention was found between warfarin and aspirin in patients with cryptogenic stroke.[51] In the PICSS, which was a subset of the larger WARSS study focusing on patients who underwent TEE examination, it was observed that warfarin-treated cryptogenic stroke patients with PFO had comparable 2-year risk of stroke or death compared with those receiving antiplatelet treatment.[23] The PFO-ASA study showed that recurrent stroke occurred more frequently with aspirin therapy in patients with PFO and ASA, suggesting the need for additional preventive strategies for high-risk PFO anatomy.[8] A meta-analysis of retrospective studies also indicates that anticoagulation might be more beneficial than aspirin therapy in preventing recurrent neurologic events in patients with PFO and cryptogenic stroke.[52] Considering these findings, the recently published guidelines by the SCAI recommend transcatheter PFO closure as a preferred option over antiplatelet or anticoagulant therapy for patients with cryptogenic stroke and PFO.[50]

PFO Closure Trials

For stroke

Data on PFO closure clinical trials are summarized in **Table 1** (**Fig. 1**).[11–13,28–30,53–55] The CLOSURE trial aimed to determine whether percutaneous PFO closure using the STARFlex device reduces the risk of recurrent stroke or TIA in patients with cryptogenic stroke or TIA.[13] However, the trial found that PFO closure did not significantly reduce the 30-day rate of recurrent stroke/TIA, all-cause mortality, or death from neurologic causes when compared to medical therapy. The trial included 909 patients and had a follow-up of 2 years. Adverse events such as atrial fibrillation and periprocedural vascular complications were more common in the device group. The study is subject to several limitations. Primarily, its statistical power is insufficient to detect a significant difference in the primary outcome. In addition, scrutiny has been directed toward the inclusion of patients with TIA. Furthermore, it is essential to acknowledge that the STARFlex device is no longer in circulation, raising concerns about the applicability of the findings to contemporary medical devices.

Similarly, the RESPECT (Randomized evaluation of recurrent stroke comparing PFO closure to established current standard of care treatment) trial aimed to determine whether closing a PFO using Amplatzer reduces recurrent stroke in patients with cryptogenic ischemic stroke compared to medical therapy alone.[11] In an intention-to-treat analysis, the study found that PFO closure did not significantly reduce nonfatal ischemic stroke, stroke mortality, or early all-cause mortality when compared to medical therapy at 2.6 years of follow-up. Subgroup analyses suggested potential benefits for patients with substantial shunts, ASAs, or superficial location of infarcts. Moreover, the per-protocol analysis demonstrated a significant decrease in rate of recurrent stroke in the device group. Following this, a prolonged follow-up of the RESPECT trial spanning a median of 5.9 years revealed a sustained advantage in the device group in both types of analyses, demonstrating a 62% relative reduction in the risk of stroke.[11]

The Gore REDUCE trial was a multicenter study comparing septal occluders (the Helex device, a first-generation septal occluder which was then replaced during the study by the Cardioform device, a second-generation device) with medical therapy in patients aged 18 to 60 years who had recently experienced a cryptogenic stroke. Patients were randomly assigned (2:1) to receive either transcatheter PFO closure or antiplatelet therapy. The study involved extensive testing to rule out other potential causes of stroke, and individuals with significant cardiovascular risk factors were excluded.[12] Over a median follow-up of 3.2 years, the device arm had a lower rate of recurrent ischemic stroke than the medical therapy group (1.4% vs 5.4%). This reduction in stroke recurrence was statistically significant and did not come with a significant increase in serious adverse events. However, atrial fibrillation occurred more frequently in the closure group (6.6% vs 0.4%), with most cases

Table 1
Clinical trials for transcatheter patent foramen ovale closure

Anticoagulation vs Antiplatelet Therapy for Treating Recurrent Strokes in Patients with PFO								
Author, Year of Publication	**Type of Study**	**Number of Patients Included**	**Age in Years**	**Study Population**	**Treatment**	**Follow-up in Years**	**Primary Endpoint**	**Outcome by Medical Treatment**
Mohr et al, 2002	Randomized double-blind clinical trial	2206	63 ± 11.3	Patients with cryptogenic stroke	Warfarin vs aspirin	2 years	Death or recurrent stroke	HR = 1.13; CI (0.92-1.38), *P* = 0.25
Homma et al,[23] 2002	Randomized double-blind clinical trial	630	59 ± 12.2	Patients with cryptogenic stroke	Warfarin vs aspirin	2 years	Death or recurrent stroke	HR = 0.52; CI (0.16-1.67), *P* = 0.28
Mas et al,[8] 2001	Prospective multicenter study	581	18-55	Patients with cryptogenic stroke ± high-risk feature PFO	Aspirin vs no aspirin	4 years	Recurrent neurological events	HR = 3.91; CI (1.59-9.59), *P* = 0.003
Agarwal et al,[52] 2012	Meta-analysis of observational studies			Patients with cryptogenic stroke	Anticoagulation vs antiplatelet		Recurrent neurological events	RR = 0.58; CI (0.41-0.82)

Patent Foramen Ovale Transcatheter Closure Trials										
Trial Name	Year Published	Number of Patients	Age	Indication	High-Risk Features	Population	Device Used	Follow-up (Years)	Primary Endpoint	Outcome
CLOSURE	2012	909	18-60	Cryptogenic stroke/TIA	–	PFO closure vs medical therapy	StarFlex	2	Composite of stroke and death	HR = 0.78, [0.45, 1.35], $P = 0.37$
PC	2013	414	18-60	Ttroke/TIA/ Thromboembolic event	-	PFO closure vs medical therapy	Amplatzer PFO Occluder	4.1	Composite of death, nonfatal stroke, TIA, or peripheral embolism	HR = 0.63, [0.24, 1.62], $P = 0.34$
RESPECT	2017	980	18-60	Cryptogenic stroke	-	PFO closure vs medical therapy	Amplatzer PFO Occluder	5.9	Recurrent stroke or death	HR = 0.55, [0.31, 0.99], $P = 04$
CLOSE	2017	663	16-60	Cryptogenic stroke/TIA	+	PFO closure vs medical therapy	Amplatzer PFO Occluder + 10 others	5.3	Recurrent stroke or silent brain infarction	HR = 0.03, [0, 0.26], $P < 0.001$
Gore REDUCE	2017	664	18-59	Cryptogenic stroke/TIA	-	PFO closure vs medical therapy	GSO and HELEX	3.2	Recurrent stroke	HR = .23, [0.09, 0.62], $P = .002$
DEFENSE-PFO	2018	120	18-80	Cryptogenic stroke/TIA	+	PFO closure vs medical therapy	Amplatzer PFO Occluder	2.8	Composite of stroke, vascular death, or major bleeding	0% vs 12.9%, log $P = .013$
MIST	2008	147	20-61	Migraine	-	PFO closure vs Sham procedure	StarFlex	0.5	Cessation of migraine headache 91 to 180 days after the procedure	4.0% vs 4.1%, $P = 0.51$
PRIMA	2016	107	20-62	Migraine	-	PFO closure vs medical therapy	Amplatzer PFO Occluder	1	Reduction in monthly migraine days	No difference
PREMIUM	2017	220	18-65	Migraine	-	PFO closure vs Sham procedure	Amplatzer PFO Occluder	1	50% reduction in migraine attacks and adverse events	No difference

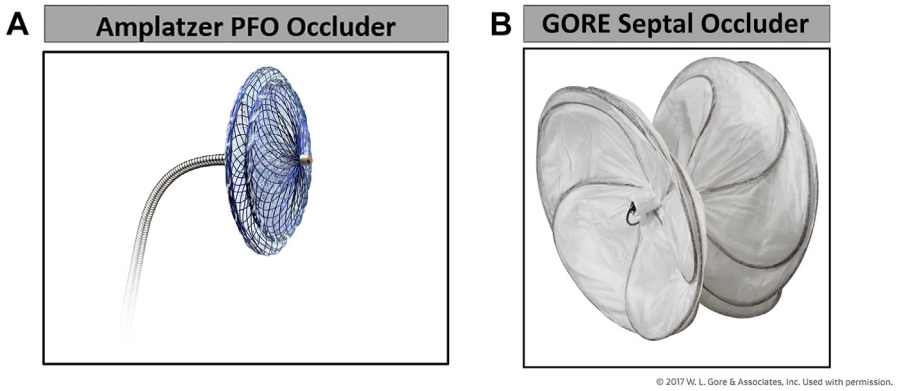

Fig. 1. Common patent foramen ovale occluder devices. [*A*] Amplatzer, Amplatzer Talisman, and Talisman are trademarks of Abbott or its related companies. (Reproduced with permission of Abbott, ©2024. All rights reserved; and [*B*] GORE® CARDIOFORM Septal Occluder. See Instructions for Use for complete device information, including approved indications and safety information.)

(83%) happening within the first 45 days after the procedure. On the other hand, sustained atrial fibrillation (lasting longer than 14 days) occurred only in 2.7% of patients in the device group.[12]

The DEFENSE-PFO trial enrolled 120 patients who had recently experienced a cryptogenic ischemic stroke and had a high-risk PFO.[55] These patients were divided into 2 groups: One underwent transcatheter PFO closure using the Amplatzer PFO occluder, while the other received medical therapy. High-risk PFO was defined as a PFO with ASA, hypermobility (septal excursion of $\geq$10 mm), or a size of $\geq$2 mm. After a 2-year follow-up, the primary endpoint, which included stroke, vascular death, or thrombolysis in myocardial infarction (TIMI)-defined major bleeding, occurred in 12.9% of the medical group but was not observed in the PFO closure group (P = .013). The closure group experienced no ischemic strokes, vascular deaths, major bleeding events, hemorrhagic strokes, TIAs, or systemic embolisms.[55]

In a recent meta-analysis that included the major clinical trials investigating PFO closure vs medical therapy, it was found that recurrent neurologic events were more frequent in the medical therapy group than in the PFO closure group.[56] The former study also showed that patients with a low RoPe score (with vascular comorbidities and without high-risk PFO features) had higher hazard ratio of recurrent neurologic events than patients with a high RoPe score, defined as $\geq$7, or those with high-risk PFO features on echocardiography. In short, the greatest advantage of PFO closure is observed in patients with the highest likelihood that the initial stroke was directly linked to the PFO. This categorization has the potential to assist in making personalized decisions for individuals with cryptogenic stroke and PFO.

For migraine. In a meta-analysis that included 2 studies (PRIMA and PREMIUM trials), a total of 337 patients were analyzed, 176 randomized to PFO closure and 161 to medical therapy alone.[57] At 1 year of follow-up, the meta-analysis demonstrated that PFO closure was associated with significant reduction in monthly migraine days (−3.1 days vs −1.9 days; P = .02), a notable decrease in monthly migraine attacks (−2.0 vs −1.4; P = .01), and a greater number of subjects experiencing complete cessation of migraines (9% vs 0.7%; $P < .001$).

Limitations of PFO clinical trials

In the CLOSURE (Evaluation of the STARFlex septal closure system in patients with stroke and/or TIA due to presumed paradoxic embolism through a PFO) study, most events in both the closure and medical therapy groups were found to be unrelated to PFO and PTE.[13] Various alternative explanations were identified, including conditions like atrial fibrillation, subcortical lacunar infarcts, aortic arch atheroma, complex migraine, and vasculitis. This suggests that the initial neurologic event might not have been linked to PFO and PTE. The trial participants may not have been the most suitable population for studying PFO closure, as only a third of them exhibited high-risk features like ASA, and approximately half had significant shunting. In addition, excluding patients with hypercoagulable testing or deep vein thrombosis (DVT) might have removed individuals whose stroke mechanism was likely related to PTE.

The RESPECT trial has several limitations, including a relatively high withdrawal rate of 17% in the medical therapy group and 9% in the closure group.[11] Moreover, some patients did not adhere strictly to the trial protocol, which had significant implications on outcomes. Notably, in the intention-to-treat population, three out of nine patients who experienced recurrent ischemic stroke in the closure group did not have the closure device in place at the time of the recurrence. Despite these limitations, an extended follow-up of the RESPECT trial, with a median duration of 5.9 years, demonstrated continued benefits in the closure group, with a remarkable 62% relative risk reduction in stroke.

In the PC (Comparing Percutaneous closure of PFO using the Amplatzer PFO Occluder with medical treatment in patients with cryptogenic embolism) trial, difficulty recruiting patients and the inclusion of TIA in the primary endpoint were the main limitations.[53]

It is important to note that some patients in the antiplatelet-only group (14 in total) opted for PFO closure outside of the trial. In addition, there were differences in the dropout rates between the two study groups, which could introduce bias either toward or away from a neutral outcome. Moreover, the trial had a relatively low number of total events, which makes it challenging to conduct detailed subgroup analyses and draw firm conclusions.[12]

For DEFENSE-PFO, the trial had several limitations, including early termination for patient safety, resulting in insufficient statistical power to establish the hazard ratio. Furthermore, the lower-than-expected patient recruitment was due in part to the publication of consecutive clinical trials favoring PFO closure, especially the CLOSE trial, which had similar stringent entry criteria. In addition, because the trial was conducted in only 2 centers, there is a possibility of selection bias among enrolled patients, although it cannot be entirely ruled out.[55]

CLOSE trial had few limitations, including a lower-than-anticipated patient recruitment rate and the absence of extended electrocardiographic monitoring to identify hidden atrial fibrillation.[54] It is important to note that when the trial protocol was developed, prolonged electrocardiographic monitoring was not part of the standard evaluation for cryptogenic stroke. However, it is worth mentioning that the effectiveness of extended monitoring in young cryptogenic stroke patients has not been established. In addition, the possibility of not detecting atrial fibrillation does not explain why the PFO closure group had a lower rate of stroke recurrence.[54]

Indications

Stroke

After the PC and RESPECT trials, the Amplatzer PFO Occluder received Food and Drug Administration (FDA) approval in October 2016 for treating PFO-associated stroke in patients aged 18 to 60 years. The 2021 American Heart Association (AHA)/ASA guidelines suggested the following: (1) A multidisciplinary team approach involving a cardiologist and neurologist is needed for managing nonlacunar ischemic stroke. (2) Choosing PFO closure over medical therapy in patients with high-risk PFO anatomy, such as ASA or large shunt, is reasonable. However, it remains uncertain whether transcatheter PFO closure provides more benefits than medical therapy for patients with low-risk PFO anatomy.[58]

Other conditions

The latest SCAI guidelines advise against the regular use of PFO closure for patients with migraine or prior decompression illness. Nonetheless, they do offer a conditional recommendation considering the low certainty of evidence, suggesting closure may be considered for POS when other potential causes of hypoxia have been ruled out. In addition, closure might also be considered in cases of systemic embolism without a previous PFO-associated stroke once other possible embolic causes have been excluded.[50]

Devices

The GORE CARDIOFORM Septal Occluder, which was FDA approved for PFO closure on March 30, 2018, is a platinum-filled Nitinol wire frame covered with expanded PTFE. The delivery system is composed of a 10 Fr. (OD) 75-cm braided, precurved delivery catheter with a radiopaque distal marker. The device has central, left, and right atrial eyelets. Each eyelet is formed of 5 petals to cover the septal wall. The device is repositionable and retrievable. The device is available in diameters of 20, 25, and 30 mm.

The Amplatzer PFO occluder is a self-expanding, double-disk device made of 0.005-inch nitinol wire and polyester patches sewn within each disk to occlude blood flow. The waist is thin and mobile, and the right atrial disk is larger than the left atrial disk in contrast to the Amplatzer ASO device. The device was approved for PFO closure by the U.S. FDA on October 28, 2016. There are 4 available sizes (18, 25, 30, and 35 mm). Sheath size can be 8 or 9 Fr. depending on device size.

Procedural Details

Transcatheter PFO closure is performed in the cardiac catheterization laboratory under

conscious moderate sedation. The procedure is guided by both fluoroscopy and ultrasound, typically using intracardiac echocardiography (ICE) or TEE. The femoral veins are accessed for venous entry with an 11-Fr. sheath for the Gore device (or 7-Fr. sheath which will be later exchanged to an 8- or 9-Fr. delivery sheath for the Amplatzer device) and an 8-Fr. (25 cm) sheath below for ICE catheter. With the ICE catheter in the right atrium, the interatrial septum is examined carefully to determine the complexity of the PFO. A bubble study can be performed through the opposite femoral venous sheath, but is not required. A right-heart catheterization (RHC) is performed using a 7-Fr. wedge catheter via the right common femoral vein access.

Intravenous heparin is given to achieve the appropriate activated clotting time (ACT) level of >250 seconds. The same wedge catheter or a multipurpose catheter with a 0.035-inch guidewire is advanced across the PFO into the left atrium under ICE and fluoroscopic guidance. Once across the PFO, once the guidewire is placed in the left superior pulmonary vein, it is exchanged for an extra-stiff 0.035-inch Amplatz superstiff wire. The subsequent steps differ depending on the device used.

For the GORE CARDIOFORM Septal Occluder device

The delivery catheter is advanced over the Amplatz wire in a monorail system and positioned in the left atrium. The wire is then removed, and the left atrial disk is deployed away from the roof and appendage. The right atrial disk is then deployed, straddling the septum. The occluder is locked, the locking loop is verified (Video 1), and the retrieval cord is removed to deploy the device.

For amplatzer devices

A delivery sheath (8 or 9 Fr. depending on the device size, 45° curve) is advanced across the PFO over the Amplatz wire. The wire is then removed. The device is loaded onto the delivery cable and introduced into the delivery sheath in the left atrium. The left atrial disk is opened, and the system is pulled against the interatrial septum. The sheath is withdrawn to expose the right atrial disk, and the device position is confirmed before releasing it.

After the procedure, vascular closure devices (such as VASCADE) can be used to obtain hemostasis in the femoral venous accesses. Other alternative strategies would include a figure-of-8 suture and manual pressure.

Complications

Transcatheter PFO closure is generally a safe procedure, with most complications being mild in nature. The most common reported complication is the development of atrial arrhythmias, such as atrial fibrillation and atrial flutter, with rates varying between studies.[11,13,50–53] Device thrombosis and embolization are uncommon complications.[59] Major bleeding due to vascular injury occurred in less than 0.5% of cases in RESPECT and PC trials.[11,53] Pericardial effusion or tamponade has been reported in about 0.3% of patients.[28] Device erosion has been associated with the Amplatzer septal occluder used for atrial septal defect (ASD) closure but generally considered low risk. With Gore devices, however, there has been a report of 2 cases of pericardial tamponade thought to be related to wireframe fracture and perforation.[60] Air embolism is a potentially severe complication that can be avoided through proper flushing and careful fluoroscopy during device insertion into the delivery sheath.

ATRIAL SEPTAL DEFECTS

Introduction

ASDs are recognized as one of the prevalent congenital heart abnormalities in adults. The estimated occurrence of ASDs in adults is 0.88 cases per 1000 individuals.[61] Most patients remain asymptomatic until their second to fourth decades of life, thus leading to a delay in diagnosis. During this period, increased blood flow in the pulmonary vasculature can trigger remodeling in the pulmonary blood vessels and consequently impact the direction of shunting and the perfusion of vital organs.

Anatomy and Pathophysiology

Four primary types of defects in the atrial septum lead to ASDs. The most common is the ostium secundum defect, accounting for around 80% of cases, arising from a lack of tissue at the fossa ovalis. Ostium primum defects are linked to tissue deficiency near atrioventricular valves and often involve a cleft in the left-sided valve, sometimes termed partial atrioventricular septal defect. Sinus venosus defects are more common in the upper part of the sinus venosus and often coincide with anomalous pulmonary venous return. The least-frequent type, coronary sinus defects, known as unroofed coronary sinuses, are often overlooked in conventional imaging.[62]

In ASD cases, hemodynamics is guided by Ohm's law, tied to fluid flow in the pulmonary vascular bed. Shunting is influenced by factors such as end-diastolic filling pressures, compliance, and defect size. Significant ASDs can lead to right atrium and ventricle enlargement over time due to increased left-to-right flow.

While pulmonary pressures are usually lower than systemic pressures, some cases develop pulmonary hypertension, pulmonary vascular remodeling, leading to bidirectional shunting and cyanosis or Eisenmenger syndrome.[62,63]

Clinical Presentation

ASDs are usually asymptomatic, and the diagnosis is often incidental. However, a minority of patients might exhibit signs of an unrepaired ASD through a comprehensive medical history and clinical evaluation. This history often uncovers a gradual decline in exercise capacity, sometimes marked by subtle or even obvious shortness of breath during physical activity. This alteration typically takes place over months to years, although it can be more abrupt if pulmonary arterial hypertension (PAH) is present. Arrhythmias including atrial fibrillation or atrial flutter may be the presenting sign. Paradoxic embolism resulting in stroke or ischemia of other organ systems may also occur.

Diagnosis

Physical examination

An outflow tract murmur during systole, caused by increased pulmonary flow, and a fixed split in the second heart sound due to delayed pulmonic valve closure could be appreciated. Ostium primum ASDs may have associated mitral and tricuspid regurgitation murmurs.

Electrocardiographic

The electrocardiogram results show signs of an enlarged right atrium (P-pulmonale), a shifted electrical axis to the right, increased muscle mass in the right ventricle (evident as a tall R wave in V1), and a partial right bundle branch block pattern (rSR′ or rsR′ pattern in leads V1-V3) in cases of secundum ASDs. In primum ASD, left-axis deviation might be observed. First-degree atrioventricular block is a possible finding in all types of ASDs.

Imaging

Echocardiography is the main modality for diagnosing ASDs.[61] TTE is limited by "septal dropout," which can lead to incorrect positive ASD diagnoses, but saline contrast echocardiography improves accuracy. TTE reveals right atrial and right ventricular enlargement, assesses pulmonary artery pressure, and estimates the left-to-right shunt using the pulmonary flow to systemic flow (Qp/Qs) ratio, although this is infrequently utilized due to inaccuracy. TTE also identifies associated anomalies like pulmonary or mitral valve disease. Complete evaluation including cross-sectional imaging via cardiac MRI or CT before transcatheter ASD closure can exclude partial anomalous pulmonary venous return, which if present would necessitate surgical intervention (Fig. 2). Three-dimensional echocardiography, CT, and MRI are important tools for ASD assessment, with MRI providing defect visualization, shunt measurement, and right ventricular assessment, and contrast-enhanced cardiac CT offering similar anatomic insight.

Invasive assessment

RHC is generally one of the final diagnostic steps, especially when contemplating defect repair. RHC is essential for assessing shunt flow and is particularly valuable in quantifying shunting degree and direction, and additional left heart catheterization including crossing the ASD for pulmonary venous oximetry sampling may be required if there is suspicion for bidirectional or right-to-left shunt. Intracardiac echocardiography can be performed alongside RHC if preoperative echo images are insufficient for defect assessment, especially when considering percutaneous closure. Intracardiac echocardiography offers additional high-resolution visualization of the interatrial septum and provides real-time 2-dimensional imaging guidance during percutaneous closure procedures.

Management

Indications for ASD repair

Decisions regarding repairing ASDs are based on clinical and anatomic considerations. Small

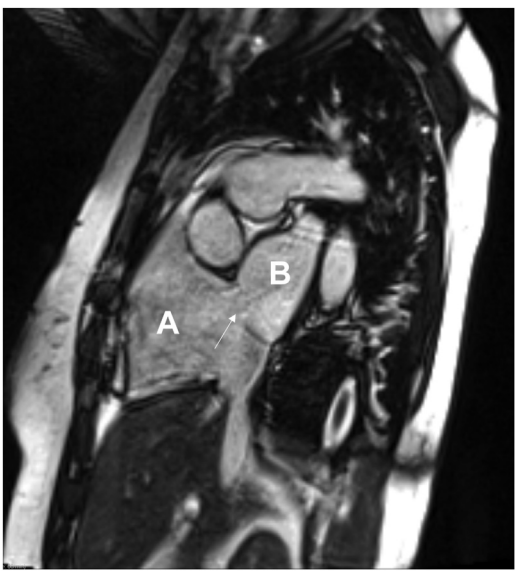

Fig. 2. Cardiac MRI demonstrating a large secundum atrial septal defect. (A) Right atrium; (B) left atrium; arrow: atrial septal defect.

ASDs might close naturally during childhood, but larger defects can lead to hemodynamic maladaptation and clinical symptoms if left untreated. Repair decisions involve factors like defect size, location, shunt's hemodynamic impact, and presence of PAH. The current guidelines from.

ACC/AHA advocate for the closure of ASD when a significant shunt (Qp/Qs $\geq$ 1.5) and right-sided volume overload exist (Class I).[63] This pertains to both symptomatic and asymptomatic patients, as long as the pulmonary artery systolic pressure is under 50% of the systemic pressure and the pulmonary vascular resistance remains lower than one-third of the systemic vascular resistance. The closure, especially in the presence of symptoms or right-sided heart enlargement, aims to halt any further deterioration and facilitate the restoration of normal dimensions on the right side.

Contraindications for ASD repair

It is not recommended to close ASDs for patients with substantial right-to-left shunt or severe PAH (pulmonary vascular resistance [PVR] >8 Wood units or irreversible pulmonary vascular occlusive disease).[63,64] Emerging data suggest that those with pulmonary artery pressure less than two-thirds of systemic arterial pressure, PVR less than two-thirds of systemic resistance, or positive response to pulmonary vasodilator testing might be considered for closure, often using a fenestrated device to ensure a proper "pop-off." Relative contraindications for percutaneous cases encompass defects larger than 36 mm, inadequate margins for device anchoring, or device interference with atrioventricular valves or venous drainage.[64]

Surgical repair approaches and results

Other than in secundum ASDs, the primary method for ASD repair involves surgery, which necessitates an open sternotomy approach and the use of cardiopulmonary bypass for direct visualization of the defect. Autologous pericardial or synthetic patches made of materials like polyester polymer (Dacron) or polytetrafluoroethylene are often used for surgical repair. Ostium primum defects can be more complex, as the patch must be attached at the crux of the ventricular septum and atrioventricular valves. Mitral valve repair or even replacement might be necessary. For sinus venosus defects, where partial anomalous pulmonary venous return is common, patch closure diverts anomalous drainage into the left atrium[65]; however, proof of concept and a growing body of data suggest that transcatheter repair of sinus venosus defects may eventually become an accepted standard.[66,67] Surgical repair before 25 years of age offers a 30-year survival rate comparable to matched controls; however, repair between 25 and 40 years results in slightly attenuated survival.[65] Although surgical ASD repair in adulthood reduces mortality significantly, it does not notably impact the risk of present or future atrial arrhythmias. Although mortality from ASD repair is low, complications such as atrial arrhythmia, bleeding, pneumothorax, and pericardial or pleural effusions can occur.[68]

Percutaneous repair approaches and results

Transcatheter closure provides an established alternative to surgical repair for secundum ASDs. Commonly used devices in the US include the Amplatzer Septal Occluder (Abbott) Gore Cardioform ASD occlude (GCA) (W.L. Gore and Associates), and Gore Cardioform Septal Occluder (GSO) (W.L. Gore and Associates) (**Fig. 3**, Video 2).

The Amplatzer Septal Occluder is particularly popular due to ease of implantation and availability in sizes suitable for larger defects. It is a self-expandable, double-disk device made of nitinol wire mesh that is tightly woven into 2 disks with a 3- to 4-mm connecting waist between the 2 disks. GSO is described earlier in the PFO section. It can be used to close secundum ASDs <17 mm. Similar to the GSO, the GCA consists of a nitinol wire frame covered by PTFE. It has left and right atrial discs and an intra-disc region or waist between the discs that occupies the defect and prevents shunting of blood between the left and right atria. It is available in 5 sizes—27, 32, 37, 44, and 48 mm—and can treat a defect range of 8 to 35 mm.

Procedural Details

ASD closure, a catheter-based procedure, involves conscious sedation, ICE, and fluoroscopic guidance (**Fig. 4**). ICE offers benefits over TEE due to avoiding general anesthesia and enhanced views of the right side of the interatrial septum. The AcuNav ICE catheter (Siemens Medical Solutions, Diamond Bar, CA) is commonly used. Femoral venous access (into both femoral veins) is established using ultrasound guidance. A complete RHC measures shunt fraction, pressures, and capillary wedge pressure. For complex septal anatomy, TEE may be preferred. The ICE catheter evaluates the septum's structure and measurements. The deficient or absent rims are assessed to ensure suitability for closure. "Stop-flow" balloon sizing is performed by inflating a soft,

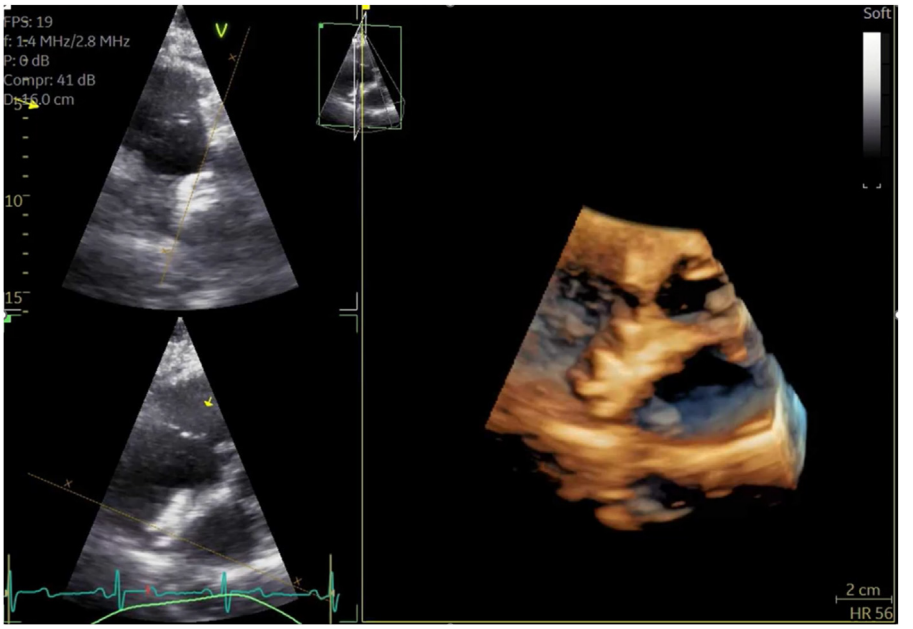

Fig. 3. Three-dimensional transthoracic echocardiogram showing an Amplatzer Septal Occluder.

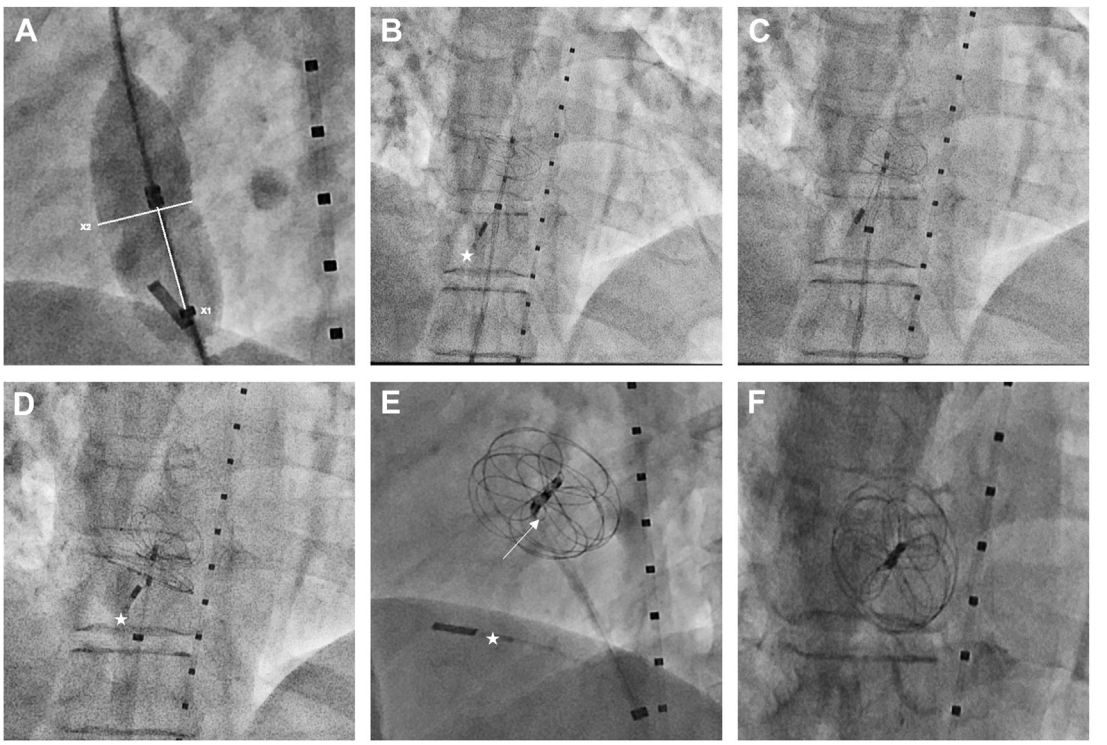

Fig. 4. Intracardiac echocardiography guided implantation of a Gore Cardioform Septal Occluder for a small atrial septal defect (ASD). (*A*) Balloon sizing of ASD using Biplane measurements, X1: 15-mm length between balloon dots, X2: ASD size based on balloon indentation. (*B*) Deployment of left atrial disc. (*C*) Flattening of left atrial disc on the atrial septum. (*D*) Deployment of right atrial disc. (*E*) Locking loop (*arrow*). (*F*) Device released. *Intracardiac echocardiography catheter.

compliant balloon across the ASD while monitoring cessation of color Doppler flow across the ASD. Once the flow is occluded, the size of the balloon at the level of the ASD is measured in 2 views to optimize device size selection. Subsequent steps vary based on the device chosen.

For the Amplatzer Septal Occluder, the device is loaded onto the delivery cable and inserted into the sheath. After positioning, the device's atrial disks are sequentially deployed using fluoroscopy in left anterior oblique (LAO) cranial projection. Once satisfactory positioning is confirmed, the device is released by rotating the delivery cable counterclockwise.

The GCA, once positioned, is deployed by sliding and pushing mechanisms, ensuring proper disc apposition and defect closure.

Complications

Risks tied to percutaneous closure encompass arrhythmias, atrioventricular block, device erosion, and thromboembolism. Device embolization and malpositioning occur rarely (less than 1%), usually due to improper sizing or placement.[69–72] Other rare complications include wire frame fracture in the case of Gore occluder devices and thrombus formation on the device[73]

SUMMARY

PFO is present in up to 15% to 35% of adults. It holds clinical significance, especially in embolic stroke. Transcatheter closure is effective, particularly in high-risk PFO cases, including ASAs. PFO's role in other conditions, like migraine and decompression sickness, is an ongoing research focus. A multidisciplinary approach with interventional cardiologists and neurologists is key for patient care. ASDs encompass various defect types, with ostium secundum being the most prevalent. Indications for repair depend on clinical and anatomic factors, with guidelines suggesting closure for significant shunts and right-sided volume overload. The choice of repair depends on patient characteristics and defect type and size. Percutaneous closure is exclusively utilized for secundum ASDs. Both surgical and percutaneous repair methods have their advantages and considerations.

CLINICS CARE POINTS

- The foramen ovale allows oxygenated blood transfer, closing naturally in most but persisting in 15% to 35%, leading to patent foramen ovale (PFO).
- PFO is linked to cryptogenic ischemic stroke, migraine, decompression sickness, and platypnea-orthodeoxia syndrome.
- Recent guidelines from the Society of Cardiovascular Angiography and Interventions (SCAI) recommend transcatheter PFO closure as the preferred option over antiplatelet or anticoagulant therapy for patients with cryptogenic stroke and PFO, emphasizing its effectiveness in reducing the risk of recurrent stroke.
- Atrial septal defects (ASDs) are common congenital heart abnormalities, often asymptomatic until adulthood, with potential delayed diagnosis and impact on pulmonary vascular remodeling.
- ASDs, categorized into four primary types, lead to hemodynamic changes, causing right atrium and ventricle enlargement, and in significant cases, pulmonary hypertension and bidirectional shunting with potential cyanosis.
- Diagnosis of ASDs involves physical examinations, electrocardiography, and echocardiography; management decisions are based on clinical factors, with repair options including surgical and percutaneous closure, each having specific indications, contraindications, and potential complications.

DISCLOSURE

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SUPPLEMENTARY DATA

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REFERENCES

1. Dattilo PB, Kim MS, Carroll JD. Patent foramen ovale. Cardiol Clin 2013;31:401–15.
2. Homma S, Sacco RL. Patent foramen ovale and stroke. Circulation 2005;112:1063–72.
3. Di Tullio MR. Patent foramen ovale: echocardiographic detection and clinical relevance in stroke. J Am Soc Echocardiogr 2010;23:144–55. quiz 220.
4. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10

decades of life: an autopsy study of 965 normal hearts. Mayo Clin Proc 1984;59:17–20.
5. Schräder R. Indication and techniques of transcatheter closure of patent foramen ovale. J Interv Cardiol 2003;16:543–51.
6. Handke M, Harloff A, Olschewski M, et al. Patent foramen ovale and cryptogenic stroke in older patients. N Engl J Med 2007;357:2262–8.
7. Lechat P, Mas JL, Lascault G, et al. Prevalence of patent foramen ovale in patients with stroke. N Engl J Med 1988;318:1148–52.
8. Mas JL, Arquizan C, Lamy C, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. N Engl J Med 2001;345:1740–6.
9. Lamy C, Giannesini C, Zuber M, et al. Clinical and imaging findings in cryptogenic stroke patients with and without patent foramen ovale: the PFO-ASA Study. atrial septal aneurysm. Stroke 2002;33:706–11.
10. Carroll JD, Saver JL, Thaler DE, et al. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. N Engl J Med 2013;368:1092–100.
11. Saver JL, Carroll JD, Thaler DE, et al. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. N Engl J Med 2017;377:1022–32.
12. Søndergaard L, Kasner SE, Rhodes JF, et al. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. N Engl J Med 2017;377:1033–42.
13. Furlan AJ, Reisman M, Massaro J, et al. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. N Engl J Med 2012;366:991–9.
14. Morton SU, Brodsky D. Fetal physiology and the transition to extrauterine life. Clin Perinatol 2016;43:395–407.
15. Anderson RH, Brown NA, Webb S. Development and structure of the atrial septum. Heart 2002;88:104–10.
16. Anderson RH, Webb S, Brown NA. Clinical anatomy of the atrial septum with reference to its developmental components. Clin Anat 1999;12:362–74.
17. Hara H, Virmani R, Ladich E, et al. Patent foramen ovale: current pathology, pathophysiology, and clinical status. J Am Coll Cardiol 2005;46:1768–76.
18. Meacham RR, Headley AS, Bronze MS, et al. Impending paradoxical embolism. Arch Intern Med 1998;158:438–48.
19. Meier B, Lock JE. Contemporary management of patent foramen ovale. Circulation 2003;107:5–9.
20. Cabanes L, Mas JL, Cohen A, et al. Atrial septal aneurysm and patent foramen ovale as risk factors for cryptogenic stroke in patients less than 55 years of age. A study using transesophageal echocardiography. Stroke 1993;24:1865–73.
21. Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. Neurology 2000;55:1172–9.
22. Kent DM, Ruthazer R, Weimar C, et al. An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke. Neurology 2013;81:619–25.
23. Homma S, Sacco RL, Di Tullio MR, et al. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in cryptogenic stroke study. Circulation 2002;105:2625–31.
24. Serena J, Marti-Fàbregas J, Santamarina E, et al. Recurrent stroke and massive right-to-left shunt: results from the prospective Spanish multicenter (CODICIA) study. Stroke 2008;39:3131–6.
25. Schwedt TJ, Demaerschalk BM, Dodick DW. Patent foramen ovale and migraine: a quantitative systematic review. Cephalalgia 2008;28:531–40.
26. Vigna C, Marchese N, Inchingolo V, et al. Improvement of migraine after patent foramen ovale percutaneous closure in patients with subclinical brain lesions: a case-control study. JACC Cardiovasc Interv 2009;2:107–13.
27. Rigatelli G, Dell'Avvocata F, Ronco F, et al. Primary transcatheter patent foramen ovale closure is effective in improving migraine in patients with high-risk anatomic and functional characteristics for paradoxical embolism. JACC Cardiovasc Interv 2010;3:282–7.
28. Dowson A, Mullen MJ, Peatfield R, et al. Migraine Intervention with STARFlex Technology (MIST) trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache. Circulation 2008;117:1397–404.
29. Tobis JM, Charles A, Silberstein SD, et al. Percutaneous closure of patent foramen ovale in patients with migraine: the premium trial. J Am Coll Cardiol 2017;70:2766–74.
30. Mattle HP, Evers S, Hildick-Smith D, et al. Percutaneous closure of patent foramen ovale in migraine with aura, a randomized controlled trial. Eur Heart J 2016;37:2029–36.
31. Wilmshurst PT, Nightingale S, Walsh KP, et al. Clopidogrel reduces migraine with aura after transcatheter closure of persistent foramen ovale and atrial septal defects. Heart 2005;91:1173–5.
32. Guo Y, Shi Y, Zhu D, et al. Clopidogrel can be an effective complementary prophylactic for drug-refractory migraine with patent foramen ovale. J Investig Med 2020;68:1250–5.
33. Agostoni P, Gasparini G, Destro G. Acute myocardial infarction probably caused by paradoxical embolus in a pregnant woman. Heart 2004;90:e12.
34. Iwasaki M, Joki N, Tanaka Y, et al. A suspected case of paradoxical renal embolism through the patent foramen ovale. Clin Exp Nephrol 2011;15:147–50.

35. Billinger M, Zbinden R, Mordasini R, et al. Patent foramen ovale closure in recreational divers: effect on decompression illness and ischaemic brain lesions during long-term follow-up. Heart 2011;97:1932–7.
36. Kavinsky CJ, Szerlip M, Goldsweig AM, et al. SCAI guidelines for the management of patent foramen ovale. Journal of the Society for Cardiovascular Angiography & Interventions 2022. Available at: https://www.jscai.org/article/S2772-9303(22)00023-0/fulltext.
37. Agrawal A, Palkar A, Talwar A. The multiple dimensions of Platypnea-Orthodeoxia syndrome: a review. Respir Med 2017;129:31–8.
38. Babu S, Zhu Z, Chavez M, et al. PFO closure after pulmonary valve intervention in patients with hypoxemia due to right-to-left intracardiac shunt. Methodist Debakey Cardiovasc J 2022;18:90–5.
39. Soliman OII, Geleijnse ML, Meijboom FJ, et al. The use of contrast echocardiography for the detection of cardiac shunts. Eur J Echocardiogr 2007;8:S2–12.
40. Dundon BK, Psaltis PJ, Worthley SG. Cardiac magnetic resonance and "augmented" right-to-left intracardiac shunting through a patent foramen ovale. J Invasive Cardiol 2008;20:197–8.
41. Guérin P, Lambert V, Godart F, et al. Transcatheter closure of patent foramen ovale in patients with platypnea-orthodeoxia: results of a multicentric French registry. Cardiovasc Intervent Radiol 2005;28:164–8.
42. Desai AJ, Fuller CJ, Jesurum JT, et al. Patent foramen ovale and cerebrovascular diseases. Nat Clin Pract Cardiovasc Med 2006;3:446–55.
43. Gin KG, Huckell VF, Pollick C. Femoral vein delivery of contrast medium enhances transthoracic echocardiographic detection of patent foramen ovale. J Am Coll Cardiol 1993;22:1994–2000.
44. Hamann GF, Schätzer-Klotz D, Fröhlig G, et al. Femoral injection of echo contrast medium may increase the sensitivity of testing for a patent foramen ovale. Neurology 1998;50:1423–8.
45. Schneider B, Zienkiewicz T, Jansen V, et al. Diagnosis of patent foramen ovale by transesophageal echocardiography and correlation with autopsy findings. Am J Cardiol 1996;77:1202–9.
46. Rana BS, Thomas MR, Calvert PA, et al. Echocardiographic evaluation of patent foramen ovale prior to device closure. JACC Cardiovasc Imaging 2010;3:749–60.
47. Monte I, Grasso S, Licciardi S, et al. Head-to-head comparison of real-time three-dimensional transthoracic echocardiography with transthoracic and transesophageal two-dimensional contrast echocardiography for the detection of patent foramen ovale. Eur J Echocardiogr 2010;11:245–9.
48. Nusser T, Höher M, Merkle N, et al. Cardiac magnetic resonance imaging and transesophageal echocardiography in patients with transcatheter closure of patent foramen ovale. J Am Coll Cardiol 2006;48:322–9.
49. Hur J, Kim YJ, Lee H-J, et al. Cardiac computed tomographic angiography for detection of cardiac sources of embolism in stroke patients. Stroke 2009;40:2073–8.
50. Alsheikh-Ali AA, Thaler DE, Kent DM. Patent foramen ovale in cryptogenic stroke: incidental or pathogenic? Stroke 2009;40:2349–55.
51. Mohr JP, Thompson JL, Lazar RM, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. N Engl J Med 2001;345:1444–51.
52. Agarwal S, Bajaj NS, Kumbhani DJ, et al. Meta-analysis of transcatheter closure versus medical therapy for patent foramen ovale in prevention of recurrent neurological events after presumed paradoxical embolism. JACC Cardiovasc Interv 2012;5:777–89.
53. Meier B, Kalesan B, Mattle HP, et al. Percutaneous closure of patent foramen ovale in cryptogenic embolism. N Engl J Med 2013;368:1083–91.
54. Mas J-L, Derumeaux G, Guillon B, et al. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. N Engl J Med 2017;377:1011–21.
55. Lee PH, Song J-K, Kim JS, et al. Cryptogenic stroke and high-risk patent foramen ovale: the defense-PFO trial. J Am Coll Cardiol 2018;71:2335–42.
56. Turc G, Calvet D, Guérin P, et al. Closure, anticoagulation, or antiplatelet therapy for cryptogenic stroke with patent foramen ovale: systematic review of randomized trials, sequential meta-analysis, and new insights from the close study. J Am Heart Assoc 2018;7:e008356.
57. Mojadidi MK, Kumar P, Mahmoud AN, et al. Pooled analysis of PFO occluder device trials in patients with PFO and migraine. J Am Coll Cardiol 2021;77:667–76.
58. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the american heart association/american stroke association. Stroke 2021;52:e364–467.
59. Goel SS, Aksoy O, Tuzcu EM, et al. Embolization of patent foramen ovale closure devices: incidence, role of imaging in identification, potential causes, and management. Tex Heart Inst J 2013;40:439–44.
60. Kumar P, Orford JL, Tobis JM. Two cases of pericardial tamponade due to nitinol wire fracture of a gore septal occluder. Cathet Cardiovasc Interv 2020;96:219–24.
61. Marelli AJ, Ionescu-Ittu R, Mackie AS, et al. Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010. Circulation 2014;130:749–56.
62. Bradley EA, Zaidi AN. Atrial septal defect. Cardiol Clin 2020;38:317–24.

63. Stout KK, Daniels CJ, Aboulhosn JA, et al. 2018 AHA/ACC guideline for the management of adults with congenital heart disease: a report of the american college of cardiology/american heart association task force on clinical practice guidelines. Circulation 2019;139:e698–800.
64. Fraisse A, Latchman M, Sharma S-R, et al. Atrial septal defect closure: indications and contra-indications. J Thorac Dis 2018;10:S2874–81.
65. Geva T, Martins JD, Wald RM. Atrial septal defects. Lancet 2014;383:1921–32.
66. Rosenthal E, Qureshi SA, Jones M, et al. Correction of sinus venosus atrial septal defects with the 10 zig covered Cheatham-platinum stent - an international registry. Cathet Cardiovasc Interv 2021;98:128–36.
67. Thakkar AN, Chinnadurai P, Breinholt JP, et al. Transcatheter closure of a sinus venosus atrial septal defect using 3D printing and image fusion guidance. Cathet Cardiovasc Interv 2018;92:353–7.
68. Murphy JG, Gersh BJ, McGoon MD, et al. Long-term outcome after surgical repair of isolated atrial septal defect. Follow-up at 27 to 32 years. N Engl J Med 1990;323:1645–50.
69. Yang M-C, Wu J-R. Recent review of transcatheter closure of atrial septal defect. Kaohsiung J Med Sci 2018;34:363–9.
70. Levi DS, Moore JW. Embolization and retrieval of the Amplatzer septal occluder. Cathet Cardiovasc Interv 2004;61:543–7.
71. McElhinney DB, Quartermain MD, Kenny D, et al. Relative risk factors for cardiac erosion following transcatheter closure of atrial septal defects: a case-control study. Circulation 2016;133:1738–46.
72. DiBardino DJ, McElhinney DB, Kaza AK, et al. Analysis of the US food and drug administration manufacturer and user facility device experience database for adverse events involving amplatzer septal occluder devices and comparison with the Society of Thoracic Surgery congenital cardiac surgery database. J Thorac Cardiovasc Surg 2009;137:1334–41.
73. Sommer RJ, Love BA, Paolillo JA, et al. ASSURED clinical study: new GORE® CARDIOFORM ASD occluder for transcatheter closure of atrial septal defect. Cathet Cardiovasc Interv 2020;95:1285–95.