Patent foramen ovale and atrial septal defects: A focused overview

Abstract

The foramen ovale is a key fetal cardiac structure enabling oxygenated blood flow from the right to the left atrium, bypassing the non-functional fetal lungs. Postnatally, this opening typically closes due to increased left-sided atrial pressure. However, the closure remains incomplete in approximately 25%-30% of adults, resulting in a Patent Foramen Ovale (PFO), which can have significant clinical implications. PFO has been associated with cryptogenic strokes, migraines, Platypnea-Orthodeoxia Syndrome (POS) and decompression sickness. In cryptogenic strokes, PFO serves as a potential pathway for paradoxical embolism. Migraine, particularly with aura, has shown a correlation with PFO, although trials like MIST and PREMIUM did not support routine PFO closure for migraines.

Diagnosis of PFO includes Transthoracic (TTE) and Transesophageal Echocardiography (TEE), with TEE being the gold standard due to its high sensitivity and specificity. Management strategies for PFO-associated strokes involve medical therapy (antiplatelets or anticoagulants) and transcatheter closure. Trials such as CLOSURE, RESPECT and DEFENSE-PFO demonstrated variable outcomes, with newer guidelines advocating closure in high-risk cases.

Atrial Septal Defects (ASDs) manifest later in life with potential complications like atrial arrhythmias and Eisenmenger syndrome. Diagnosis primarily relies on echocardiography, with cardiac Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) providing further assessment. Management depends on defect type and size, with percutaneous closure preferred for ostium secundum defects. Surgical repair is reserved for larger defects or associated structural abnormalities. Complications of percutaneous procedures include arrhythmias and device embolization. Overall, optimal patient selection and multidisciplinary collaboration are essential to achieving positive outcomes in managing PFO and ASD.

Keywords: Left Atrium • Antiplatelets • Transcatheter closure • Echocardiography • Atrial arrhythmias

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Introduction

The foramen ovale is a normal interatrial prenatal communication that plays a key role in fetal blood circulation, allowing oxygenated blood to pass from the right atrium to the left atrium, avoiding the not-yet-functioning fetal lungs [1]. Normally, this opening closes shortly after birth due to changes in pressure that occur with breathing, driving the pulmonary resistance down, leading to an increase in pulmonary circulation blood flow and increased left-sided resistance, ultimately causing the septum primum to seal against the septum secundum, effectively closing the foramen ovale [2]. However, in about a third of adults, this process is incomplete, leading to a PFO [3]. The medical implications of PFO have been considered since the late 19th century, linking it to

diverse conditions such as unexplained embolic strokes, migraines, platypnea-orthodeoxia syndrome and decompression sickness [4-6].

Literature Review

Anatomy and pathophysiology

During gestation, the human fetus grows in a relatively low-oxygen environment, necessitating a unique circulatory path. Blood rich in nutrients and oxygen from the placenta reaches the fetus *via* the umbilical vein, which is partly directed into the liver circulation as well as into the ductus venosus. This vessel transports the blood to the right atrium, from where it preferentially moves to the left atrium through the foramen ovale, ensuring essential organs like the brain and heart receive oxygenated blood necessary for their development [7]. The heart's septal structures, particularly the interatrial septum, form in complex stages; the septum primum grows toward the endocardial cushions, resulting in an opening at its distal edge known as the ostium primum. As the muscular ostium primum grows downwards, its superior portion becomes fenestrated and forms the foramen secundum, which plays a crucial role in maintaining blood flow from the right to the left system during the rest of gestation. Once the foramen secundum is fully developed, the ostium primum closes and forms the septum primum, later becoming the valve structure of the foramen ovale [8]. Postnatally, decreased pulmonary vascular resistance and increased left atrial pressure result in the fusion of the septum primum to the septum secundum, closing the passage between the atria. A failure in this fusion process occurs in around 25% of the population, leaving a PFO, which in turn provides a potential route for emboli to cross between the right and left circulation [9].

Symptomatology and clinical manifestations

Stroke: PFOs are typically clinically silent, but they can exhibit certain clinical manifestations concerning. Paradoxical embolism is of primary concern, where emboli from the venous system bypass the pulmonary filtration and enter the systemic arterial circulation, potentially causing an embolic ischemic stroke. In fact, almost one-third of ischemic strokes have unknown causes and are hence termed cryptogenic strokes and patients who experienced a cryptogenic stroke have a higher prevalence of PFOs compared to the rest of the population [10]. Moreover, up to 50% of young individuals who experience a cryptogenic embolic stroke will be diagnosed with a PFO [11].

Interestingly, a patient-level meta-analysis of 12 cryptogenic stroke cohorts conducted by Kent et al., known as the Risk of Paradoxical Embolism (RoPE) study, showed a correlation between the prevalence of PFO and the likelihood of it being the cause of cryptogenic stroke in individuals who lacked classical cerebrovascular risk factors, were under the age of 65 and had evidence of a cortical brain infarct on presentation [12]. Furthermore, the presence of an Atrial Septal Aneurysm (ASA) along with a PFO was associated with higher rates of recurrent embolic strokes in these groups [13].

Migraine

Migraine, especially those presenting with aura, have been correlated with PFO. While the underlying pathophysiological explanation remains ambiguous, the hypothesis suggests that microembolic phenomena or unfiltered biologically active compounds might trigger migraines. Despite the association, current clinical guidelines do not support routine PFO screening in migraine patients and randomized controlled clinical trials exploring PFO closure for migraine management, such as MIST (Migraine Intervention with STARFlex Technology) 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), found no difference between PFO device closure and sham procedure regarding headache cure or responder rate at 6-month [15,16]. However, other studies have shown that PFO closure in individuals with large shunts detected by Transcranial Doppler (TCD) and subclinical brain Magnetic Resonance Imaging (MRI) lesions or in individuals with high-risk PFO characteristics seen on TCD and TEE, resulted in a significant reduction in both severity and frequency of migraines [17,18]. Future trials are therefore needed to involve these patients with high PFO risk features and subclinical brain MRI lesions and determine whether PFO closure proves beneficial.

Rare manifestations

Decompression sickness, particularly affecting divers, involves nitrogen bubbles forming during rapid ascents that can enter the systemic circulation through a PFO, potentially causing ischemic embolic events. Current guidelines do not recommend routine closure of the PFO in individuals with prior decompression sickness unless they have experienced PFO-associated strokes [19-21].

Finally, POS is another rare condition linked to PFO, characterized by dyspnea and hypoxia that worsen when upright and improve when supine. This is attributed to a significant right-to-left shunt through a PFO, as seen on echocardiography, triggered by positional shifts and/or changes in right heart dynamics, particularly conditions that increase the pressures in the right heart [22,23]. PFO closure could improve symptoms in patients with POS [24].

Diagnosis

Multiple ultrasound methods, such as TTE, TEE and TCD have been involved in visualizing, assessing and diagnosing PFOs.

Agitated saline is the main method used to identify the presence of a right-to-left shunt during TTE or TEE: The appearance of at least 3 microbubbles in the left atrium, spontaneously or after provocative maneuvers such as coughing or Valsalva, within 3 cycles after opacification of the right atrium is considered diagnostic of an intracardiac shunt. TEE is considered the gold standard test in diagnosing PFOs, given its near 100% sensitivity and specificity, as shown in autopsy studies with near-perfect correlation. TEE also allows for the detailed characterization of the PFO and other interatrial structures, given its superior image resolution.

The use of Three-Dimensional Echocardiography (3DE) during TTE has become more prevalent and has been shown to increase the sensitivity in detecting PFOs compared to the TTE contrast study [25]. Finally, contrast-enhanced cardiac MRI and cardiac CT have shown good agreement with TEE in PFO diagnosis. However, TEE remains the gold standard given superior sensitivity, ability to characterize the PFO, its lesser cost and higher availability [26].

Management

In patients with a history of cryptogenic stroke and a PFO, management options to prevent the recurrence of these strokes include medical therapy like antiplatelet or anticoagulant medication and procedural closure using transcatheter devices. Surgical closure can be considered concomitantly when a patient is undergoing a cardiovascular surgery for another indication. The key to minimizing procedural risks and maximizing its benefits is appropriate patient selection. Only patients with cryptogenic strokes and high RoPE scores (age less than 65, no traditional cerebrovascular risk factors and cortical embolic strokes on presentation) should be considered for PFO closure. Those are the patients in whom the PFO is least likely to be an "innocent" bystander. Emerging 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.

Medical therapy

Choosing between antiplatelet and anticoagulant therapy for patients with cryptogenic stroke and PFO remains uncertain. The Warfarin-Aspirin Recurrent Stroke Study (WARSS) found no significant difference in preventing recurrent strokes or death between warfarin and aspirin in cryptogenic stroke patients [27]. Similarly, the PICSS (Patent Foramen Ovale in Cryptogenic Stroke Study), a subset of WARSS focused on patients who underwent TEE, showed that warfarin-treated patients had similar stroke and death rates over two years compared to those on antiplatelet treatment. In contrast, the PFO-ASA (Patent Foramen Ovale-Atrial Septal Aneurysm) study noted more frequent strokes with aspirin in patients with PFO and ASA, indicating the need for additional prevention strategies for high-risk PFOs. A meta-analysis of retrospective studies suggests anticoagulation might be more effective than aspirin in reducing recurrent neurological events for these patients.

In light of these studies and the limited potential benefits of medical therapy compared to transcatheter interventions, the recent SCAI guidelines recommend transcatheter PFO closure over medical therapy alone for patients with cryptogenic stroke attributed to PFO [28].

PFO closure trials

Several major trials on PFO closure and medical therapy, highlighted in Table 1, have influenced current management practices. The CLOSURE trial assessed the STARFlex device's ability to lower recurrent stroke or (transient ischemic attack) TIA risk compared to medical therapy alone in patients with cryptogenic stroke or TIA but found no significant reduction in outcomes, including recurrent stroke/TIA at 30 days, overall mortality, or neurological death over two years, involving 909 patients [29]. Complications such as post-operative atrial fibrillation and peri-operative vascular bleeding were more frequent in the device cohort. The main limitations of the CLOSURE trial are the inclusion of TIA patients, the withdrawal of the STARFlex device from use and inadequate statistical power to identify significant differences in the primary outcome [30].

The RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) trial compared the Amplatzer device to medical therapy alone and showed no significant difference in nonfatal ischemic strokes, stroke mortality, or all-cause mortality over a follow-up of 2.6 years in an intention-to-treat analysis. However, a subgroup analysis hinted at benefits from closure for patients with large shunts, ASAs, or cortical strokes. Moreover, long-term follow-up over a median of 5.9 years revealed a relative reduction of 62% in the risk of stroke in the device cohort [31].

The Gore REDUCE (Gore Helex Septal Occluder/Gore Cardioform Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed TIA in Patients with Patent Foramen Ovale (PFO); NCT00738894) trial compared septal occluders against medical therapy in patients aged 18 to 60 with a recent cryptogenic stroke. Results showed lower recurrent ischemic stroke rates in the device group (1.4%) than the medical group (5.4%) over 3.2 years, despite a higher atrial fibrillation incidence [32].

Similarly, the DEFENSE-PFO (Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients with High-Risk Patent Foramen Ovale) trial studied the Amplatzer PFO closure device. However, it focused on 120 patients with high-risk PFO and revealed no strokes, vascular deaths, or major bleeding in the

device group versus a 12.9% event rate in the medical group after a two-year follow-up. This trial defined high-risk PFOs as those associated with hypermobile ASA (excursion ≥ 1 cm), or size exceeding 2 mm [33].

A meta-analysis conducted by Turc et al., included major PFO closure trials, confirmed fewer recurrent neurological events with PFO closure versus medical therapy, especially in patients with elevated RoPe scores (>7), or PFO with high-risk features. These findings underscore again the advantage of PFO closure in patients whose initial strokes were most likely PFO-related, suggesting personalized treatment pathways for those with cryptogenic strokes and PFO [34].

For migraines, a meta-analysis incorporated two trials, PRIMA (Percutaneous Closure of PFO in Migraine with Aura) and PREMIUM, accounting for 337 patients, 176 of whom underwent PFO closure and 161 received only medical therapy. After one year, the analysis showed that PFO closure significantly reduced monthly migraine days (3.1 vs. 1.9 days; p=.02), decreased the frequency of migraine attacks (2.0 vs. 1.4; p=.01) and resulted in

more patients experiencing total migraine cessation (9% vs. 0.7%; p<.001).

Limitations of PFO clinical trials

Clinical trials examining PFO closure face several challenges, including difficulties in patient recruitment, accurately defining study populations and addressing the complex nature of cryptogenic strokes and recurrent embolic events (Table 1). Understanding whether the initial neurological events are linked with a PFO is key, as diagnostic variations and alternative embolic sources could dilute closure effects. For instance, in the CLOSURE trial, most neurological events in either group were found to be unrelated to PFO and caused by other conditions such as atrial fibrillation, aortic arch atheroma and vasculitis. Finally, variability in adherence rates, patient retention and follow-up practices on hidden conditions, like occult atrial fibrillation, also affected the results of some of those trials. This again stresses the importance of having better-designed RCTs, focusing on patients with no traditional cerebrovascular risk factors, younger in age and cortical/ischemic embolic infarcts on presentation.

	Table 1: PFO closure trials for cryptogenic stroke/tia: Outcomes and devices.						
Trial name	Year published	Patients	Age (Years)	Device used	Follow-Up (Years)	Primary outcome	Outcome
CLOSURE	2012	909	18-60	StarFlex	2	Composite of stroke and death	No significant benefit (HR=0.78, p=0.37)
PC	2013	414	18-60	Amplatzer PFO Occluder	4.1	Composite of death, nonfatal stroke, TIA, or peripheral embolism	No significant benefit (HR=0.63, p=0.34)
RESPECT	2017	980	18-60	Amplatzer PFO Occluder	5.9	Recurrent stroke or death	Significant benefit (HR=0.55, p=0.04)
CLOSE	2017	663	18-60	Amplatzer PFO Occluder and others	5.3	Recurrent stroke or silent brain infarction	Strong benefit (HR=0.03, p<0.001)
Gore REDUCE	2017	664	18-59	GSO and HELEX	3.2	Recurrent stroke	Significant benefit (HR=0.23, p=0.002)
DEFENSE-PFO	2018	120	18-80	Amplatzer PFO Occluder	2.8	Composite of stroke, vascular death, or major bleeding	Significant benefit (0% vs. 12.9%, p=0.013)

Indications

Following the PC (Comparing Percutaneous closure of PFO using the Amplatzer PFO Occluder with medical treatment in patients with cryptogenic embolism) and RESPECT trials, the Amplatzer PFO Occluder was FDA-approved in October, 2016 for treating PFO-related stroke in patients aged 18 to 60. The 2021 AHA/ASA (American Heart Association/American Stroke Association) guidelines recommend: a) A team approach with a cardiologist and neurologist for managing non-lacunar ischemic stroke, b) Preferring PFO closure over medical therapy in patients with high-risk PFO anatomy, like ASA or a large shunt, is a reasonable approach. However, it's unclear if transcatheter PFO closure offers more benefits than medical therapy for those with low-risk PFO anatomy [35].

Devices and potential associated complications

The GORE CARDIOFORM Septal Occluder, FDA-approved for PFO closure on March 30, 2018, features a platinum-filled Nitinol wire frame covered with expanded PTFE (Polytetrafluoroethylene). It includes a 10 Fr. 75 cm braided, pre-curved delivery catheter with a distal radiopaque marker. The device has three eyelets with five petal structures each, designed to cover the septal wall. Importantly, this device is repositionable and retrievable, available in 20 mm, 25 mm and 30 mm diameters.

The Amplatzer PFO Occluder is another available device, approved by the FDA on October 28, 2016, for PFO closure. It is a self-expanding, double-disk device made from 0.005 inch Nitinol wire with polyester patches in each disk to prevent blood flow. It features a thin, mobile waist, with the right atrial disk larger than the left, differing from the Amplatzer ASO device. It comes in four sizes (18, 25, 30 and 35 mm), with sheath sizes of 8 or 9 Fr. depending on the device size.

Although generally safe, transcatheter PFO closure can lead to complications, the most common being atrial arrhythmias such as atrial fibrillation and flutter (Figure 1). Rarely, issues like device thrombosis or migration may arise. More serious complications such as major bleeding, pericardial effusion and tamponade are rare, with an incidence of <0.5% as reported in the PC and RESPECT trials. Finally, air embolism is another severe complication that can be avoided with proper flushing and careful fluoroscopy during device insertion into the delivery sheath.
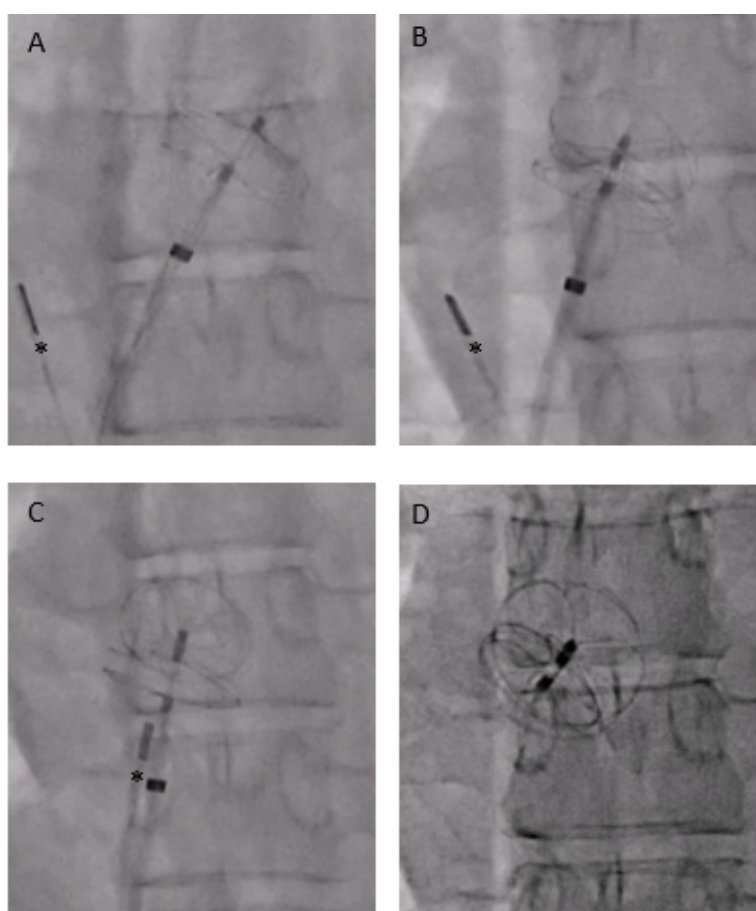

Figure 1: Intracardiac echocardiography guided implantation of a Gore Cardioform Septal Occluder for Patent Foramen Ovale (PFO). **Note:** A) Deployment of the left atrial disc; B) Flattening of the left atrial disc on the atrial septum; C) Deployment of the right atrial disc; D) Device released; *Intracardiac echocardiography catheter.

Atrial septal defects

ASDs are among the common congenital heart defects in adults, with an estimated occurrence of 0.88 in 1000 individuals [36]. ASDs are often diagnosed late as most cases are asymptomatic until the second to fourth decades of life. During this period, increased blood flow through the pulmonary arterial system caused by the left to right shunt causes remodeling of the pulmonary arteries. In extreme cases, this remodeling can be severe and irreversible, affecting the direction of the shunt, causing bidirectional flow and cyanosis, known as Eisenmenger syndrome.

ASDs are categorized into four main types, each with its specific anatomical defect. The most common ASD is the ostium secundum type, resulting from the absence of tissue in the fossa ovalis. Ostium secundum accounts for about 80% of ASDs. The second most common type is the ostium primum ASD, often referred to as partial atrioventricular septal defect, given the lack of tissue near the atrioventricular valves and is often associated with a cleft in the mitral valve. Sinus venosus defects are associated with partial anomalous pulmonary venous return. Finally, the least common type of ASDs is coronary sinus defects, also known as unroofed coronary sinus and is often associated with persistent left superior vena cava. Those are often missed on conventional cardiac imaging.

ASDs typically exhibit no symptoms initially but can manifest through gradually diminishing exercise tolerance, dyspnea on exertion, or notable atrial arrhythmias such as atrial fibrillation or atrial flutter. Paradoxical embolisms causing peripheral or cerebral ischemic conditions may also be the initial clinical manifestation of ASD.

Discussion

Physical exam features that should raise a suspicion of an ASD include a systolic flow murmur across the pulmonic valve and a fixed splitting of S2 caused by the increased flow through the pulmonic valve secondary to the left or right shunt. Moreover, in cases of ostium primum, one could also notice a tricuspid or a mitral regurgitant murmur. On electrocardiography, the presence of right atrial enlargement, right axis deviation, right ventricular hypertrophy, an incomplete right bundle branch block and a first-degree AV block should also raise suspicion of an ASD.

ASD diagnosis remains primarily echocardiographic, using agitated saline to enhance the echocardiographic diagnostic accuracy. Findings on TTE include an enlarged right atrium and right ventricle, elevated Pulmonary Artery Systolic Pressure (PASP) and increased pulmonary flow compared to flow across the Left Ventricular Outflow Tract (LVOT), with the ability to assess Qp:Qs ratio [36]. TTE will also be able to identify certain associated conditions like tricuspid or mitral valve regurgitation (ostium primum). More advanced imaging modalities also play a role (cardiac MRI and CT) in the diagnosis and evaluation of ASD, primarily in assessing for anomalous pulmonary venous return, providing visualization of the defect, as well as accurately measuring the degree of shunt MRI.

Finally, Right Heart Catheterization (RHC) is one of the last diagnostic tools used in assessing ASD, especially when considering defect repair. This procedure can quantify shunt degree and direction by calculating Qp:Qs. This is crucial to determine indications and contraindications for defect repair.

Management

While small ASDs might close spontaneously, larger defects will cause progressive pulmonary vascular remodeling, leading to clinical deterioration and will need to be repaired before the development of Eisenmenger syndrome. The current guidelines from. The current ACC/AHA (American College of Cardiology/ American Heart Association) guidelines recommend closure of ASD in the presence of a significant shunt (Qp:Qs>1.5) and right-sided volume overload (class I) [37]. This includes both symptomatic and asymptomatic individuals, as long as the PASP is under 50% of the systemic pressure and the Pulmonary Vascular Resistance (PVR) remains lower than one-third of the systemic vascular resistance. The repair is aimed at preventing further pulmonary vascular remodeling and restoring normal dimensions on the right side. Contraindications to repair include severe PVR>8; or substantial right to left shunt.

Repair of other than secundum ASDs is mainly surgical. This necessitates an open sternotomy approach and the use of a cardiopulmonary bypass to allow direct visualization of the defect. Associated defects such as mitral or tricuspid valve regurgitation and anomalous pulmonary venous return are also repaired surgically as part of the same procedure [38]. Surgical repair done before the age of 25 offers a 30-year survival benefit compared to matched cohorts. However, this does not affect the risk of present or future atrial arrhythmias, which remain elevated despite the repair [39].

Transcatheter closure is a recognized alternative to surgery for secundum atrial septal defects. Widely used devices in the U.S. include the Amplatzer Septal Occluder, Gore Cardioform ASD Occluder and Gore Cardioform Septal Occluder. The Amplatzer is favored for its simple deployment and suitability for larger defects. It features a self-expanding, double-disk design from nitinol wire. he Gore devices use a nitinol wire frame covered with PTFE and are available in sizes that can treat defects from 8 to 35 mm. Relative contra-indications to percutaneous repair include large defects >36 mm, insufficient margins for device anchoring and device interference with AV valves or venous drainage [40]. The Amplatzer Septal Occluder can treat defects as large as 38 mm.

Potential complications linked with percutaneous ASD closure include arrhythmias, AV block, embolism, rarely device erosion and thromboembolism. Matching appropriate device choice to defect size helps reduce the risks of device embolization [41,42].

Conclusion

PFO is found in around 1/3 of adults and holds clinical importance, particularly pertaining to embolic strokes. Transcatheter closure demonstrated efficacy in high-risk PFO and those associated with ASAs. The role of PFO closure in other conditions, such as migraines and decompression sickness, remains the focus of ongoing research. Appropriate patient selection through an effective multidisciplinary team, including interventional cardiologists and neurologists, is key to maximizing benefits from PFO closure while minimizing unnecessary risks. ASDs include various types, with ostium secundum being the most common. Repair decisions are based on clinical and anatomical considerations, with guidelines recommending closure for significant shunts and right-sided volume overload. The method of repair-surgical or percutaneous-depends on the patient's characteristics and the specific defect's type and size, with percutaneous closure being used exclusively for secundum ASDs. Each repair option has its own benefits and considerations.

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