

REVIEW ARTICLE

Patent foramen ovale-associated stroke:
Historical evolution, clinical presentations,
randomized trials, and closure strategiesAbdallah G. Aloteiby¹, Baker M. Ayyash¹, and Ziyad M. Hijazi*¹

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Abstract

Patent foramen ovale (PFO) is increasingly recognized as an important contributor to cryptogenic ischemic stroke, particularly in younger patients without traditional vascular risk factors. Although present in about one-quarter of the general population, its higher prevalence among patients with otherwise unexplained stroke has raised questions regarding a causal relationship. The most widely accepted mechanism is paradoxical embolism, in which thrombotic material from the venous circulation bypasses the pulmonary filter through a transient right-to-left interatrial shunt. Over time, specific anatomical and clinical factors such as shunt size, the presence of an atrial septal aneurysm, and the overall vascular risk profile have been shown to help differentiate incidental PFO from clinically significant cases. Randomized clinical trials have demonstrated a reduction in recurrent ischemic stroke with percutaneous PFO closure in carefully selected patients, with benefit driven by appropriate patient selection and high-risk anatomical features. Despite these clinical trials and evidence, several uncertainties remain, including the management of older patients, the role of anticoagulation, and the significance of post-procedural atrial fibrillation, which is more common after closure but is typically transient. There is now increasing emphasis on individualized risk stratification using tools such as the Risk of Paradoxical Embolism (RoPE) score and PFO-Associated Stroke Causal Likelihood (PASCAL) classification. This review summarizes the current understanding of PFO-associated stroke, including pathophysiology, clinical presentation, randomized evidence, treatment strategies, and future directions, including emerging evidence on head-to-head device comparison and bioresorbable closure technology.

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1. Introduction

Ischemic stroke is a major cause of morbidity and mortality worldwide. While many cases are attributed to established mechanisms such as large artery atherosclerosis, cardioembolism, or small vessel disease, a substantial proportion—particularly in younger patients—remains unexplained despite comprehensive evaluation and is classified as cryptogenic stroke.^{1,2}

Among the potential contributors to cryptogenic stroke, patent foramen ovale (PFO) has become one of the most extensively studied and debated entities. PFO is present

in approximately one-quarter of the general population, yet its prevalence is notably higher among patients with cryptogenic stroke, especially in younger age groups. This discrepancy has long prompted debate regarding whether PFO represents an incidental finding or a true causal mechanism of embolic stroke in selected patients.^{3,4}

The central pathophysiological concept linking PFO to stroke is paradoxical embolism, whereby thrombotic material from the venous circulation gains access to the arterial system through a transient right-to-left interatrial shunt. Over time, additional anatomical and clinical factors such as shunt size, the presence of atrial septal aneurysm (ASA), and the absence of conventional vascular risk factors have been recognized as key determinants of the likelihood that a PFO is causally related to a stroke event.^{1,5}

In parallel with increasing understanding of the underlying pathophysiology, the management of PFO-associated stroke has undergone a substantial evolution. Early randomized trials comparing percutaneous closure with medical therapy produced largely inconclusive results, leading to uncertainty regarding the clinical value of intervention. However, subsequent studies guided by improved patient selection, longer follow-up periods, and advances in device technology consistently demonstrated a reduction in recurrent ischemic stroke with transcatheter closure in appropriately selected patients.^{6–10}

Importantly, the current challenge is no longer simply determining whether PFO closure is effective, but rather to identify the patients most likely to benefit. This has led to the development of structured risk stratification approaches that integrate clinical features, anatomical characteristics, and competing stroke mechanisms into individualized decision-making.

In this context, this review provides a comprehensive and clinically focused synthesis of current evidence of PFO-associated stroke, including its pathophysiology, clinical presentation, randomized trial data, treatment strategies, and future directions.

2. Historical evolution of the patent foramen ovale–stroke concept

Recognition of PFO as a potential cause of cryptogenic stroke has evolved substantially since the late 1990s. Early observational data demonstrated a markedly increased prevalence of PFO among patients with cryptogenic stroke, particularly in younger adults, in whom persistent interatrial communication was identified far more frequently than in the general population. These observations formed the basis for suspecting a causal relationship between PFO and otherwise unexplained cerebral ischemic events.^{1,3}

The association was first described by Cohnheim in 1877, though clinical implications were not fully appreciated until contrast echocardiography demonstrated a strong association between PFO and cryptogenic stroke.¹¹ This association is most commonly explained by paradoxical embolism, a mechanism whereby thrombi originating in the venous circulation bypass the pulmonary vascular bed through a transient right-to-left interatrial shunt and enter the systemic arterial circulation. As cryptogenic stroke became better defined as a clinical entity, this mechanism became increasingly plausible, particularly in younger patients without conventional vascular risk factors or another clear cause of stroke.

Management strategies evolved alongside these insights. Early approaches involved surgical closure in selected patients with presumed PFO-related stroke, but these were gradually replaced by percutaneous transcatheter techniques as interventional cardiology advanced and closure device technology matured.^{12,13} The transition toward catheter-based closure was driven by the premise that eliminating the interatrial communication would reduce the risk of recurrent embolic events.

A major shift came with the introduction of randomized controlled trials. The first generation of such trials, CLOSURE I, RESPECT, and the PC Trial, failed to demonstrate clear superiority of PFO closure over medical therapy alone, and their largely neutral results led to considerable debate about the clinical value of the intervention.^{3,8,14,15} These findings shaped early guideline positions, which generally advised against routine closure in unselected patients.^{8,16,17}

Later studies helped identify the factors contributing to these mixed outcomes. Differences in patient populations, relatively short follow-up, and inclusion of patients without high-risk PFO features likely contributed to the weaker treatment effect seen in early trials. Later studies adopted more stringent selection criteria, concentrating on patients with large right-to-left shunts, ASA, or both, anatomical characteristics associated with a greater probability of PFO-mediated embolism. This refinement produced a markedly different evidence landscape. The CLOSE and REDUCE trials, together with the extended follow-up data from RESPECT, collectively established that percutaneous PFO closure significantly reduces the risk of recurrent ischemic stroke in appropriately selected patients.^{3,6,8,18}

An important regulatory milestone occurred in October 2016, when the United States Food and Drug Administration granted its first approval of a PFO closure device specifically for secondary stroke prevention, based on evidence from the RESPECT trial.¹⁸ This decision marked the transition of PFO closure from a debated

investigational procedure to an accepted treatment option for carefully selected patients with cryptogenic stroke.

Diagnostic approaches also evolved significantly during this period. Transesophageal echocardiography with agitated saline contrast became the cornerstone of PFO detection and anatomical characterization. Alongside these technical refinements, more structured risk stratification tools were introduced to estimate the probability that a detected PFO was causally related to the index stroke. The Risk of Paradoxical Embolism (RoPE) score and, subsequently, the PFO-Associated Stroke Causal Likelihood (PASCAL) classification system have improved clinical decision-making by systematically integrating patient age, vascular risk factor burden, and PFO anatomical characteristics into a coherent probabilistic framework.^{19,20}

Overall, the evolution of the PFO–stroke concept reflects a progressive transition from epidemiological suspicion to mechanistic plausibility, and ultimately to evidence-based clinical intervention. What began as an anatomical observation of uncertain significance has since become a clinically actionable target in selected patients with cryptogenic stroke and high-risk PFO anatomy, driven by decades of iterative scientific and clinical investigation.

3. Pathophysiological mechanisms linking patent foramen ovale to stroke

The link between PFO and ischemic stroke is explained by several interrelated mechanisms that allow embolic material to reach the cerebral circulation. Although PFO is common in the general population and is usually asymptomatic, certain physiological and anatomical conditions can transform this otherwise benign interatrial communication into a clinically relevant pathway for embolism. Understanding these mechanisms is essential to distinguish incidental PFO from cases in which the defect is likely to play a causal role in stroke.

3.1. Paradoxical embolism

The most widely accepted mechanism linking PFO to ischemic stroke is paradoxical embolism. In this scenario, thrombi originating in the venous system, most commonly from deep vein thrombosis of the lower extremity or pelvic veins, enter the right atrium and traverse the interatrial septum through the PFO when a transient right-to-left pressure gradient develops. Once in the systemic circulation, the embolus may reach the cerebral vasculature and precipitate an ischemic event.

Under normal physiological conditions, left atrial pressure exceeds right atrial pressure, maintaining a left-

to-right gradient that prevents spontaneous shunting. However, any maneuver that transiently elevates right atrial pressure can reverse this gradient. Such pressure changes occur commonly during activities that increase intrathoracic pressure, including coughing, straining, sneezing, or performing a Valsalva maneuver. During these brief episodes, blood and potentially any entrained embolic material may pass through the PFO tunnel and enter the systemic arterial circulation. This dynamic shunting process forms the physiological basis of the paradoxical embolism hypothesis and explains how embolic events can arise even in individuals with otherwise structurally normal hearts.^{1,5}

3.2. Venous thromboembolism and embolic sources

The paradoxical embolism model inherently involves venous thromboembolism as an upstream source of PFO-associated stroke. Several studies have documented higher rates of deep venous thrombosis in patients with cryptogenic stroke and PFO compared with other stroke populations. Although an identifiable venous thrombus is not always present at the time of stroke, transient or previously resolved thrombosis may still account for the embolic source. In addition, conditions that increase the risk of thrombosis, such as prolonged immobility, inherited thrombophilia, malignancy, and hormonal therapy, may further increase the likelihood of paradoxical embolic events in individuals with a PFO.^{1,5}

3.3. Role of atrial septal aneurysm and shunt size

Not all PFOs carry the same clinical risk. Growing evidence suggests that certain anatomical features significantly influence the likelihood of embolic events, particularly the presence of an ASA and a large right-to-left shunt. ASA is characterized by excessive mobility of the interatrial septum, typically defined by a phasic excursion of several millimeters into either atrium during the cardiac cycle. This increased motion may facilitate intermittent opening of the PFO tunnel and promote right-to-left shunting (Figure 1).

Large shunt size has likewise been consistently associated with a higher probability that a detected PFO is causally related to stroke. Greater shunt volumes allow more blood and therefore a larger potential load of embolic particles to cross the interatrial communication during transient pressure changes. Observational data and subgroup analyses from randomized trials show that patients with both large shunts and coexisting ASA benefit the most from transcatheter closure, highlighting the importance of these features in risk stratification and treatment decisions.^{14,21–24}

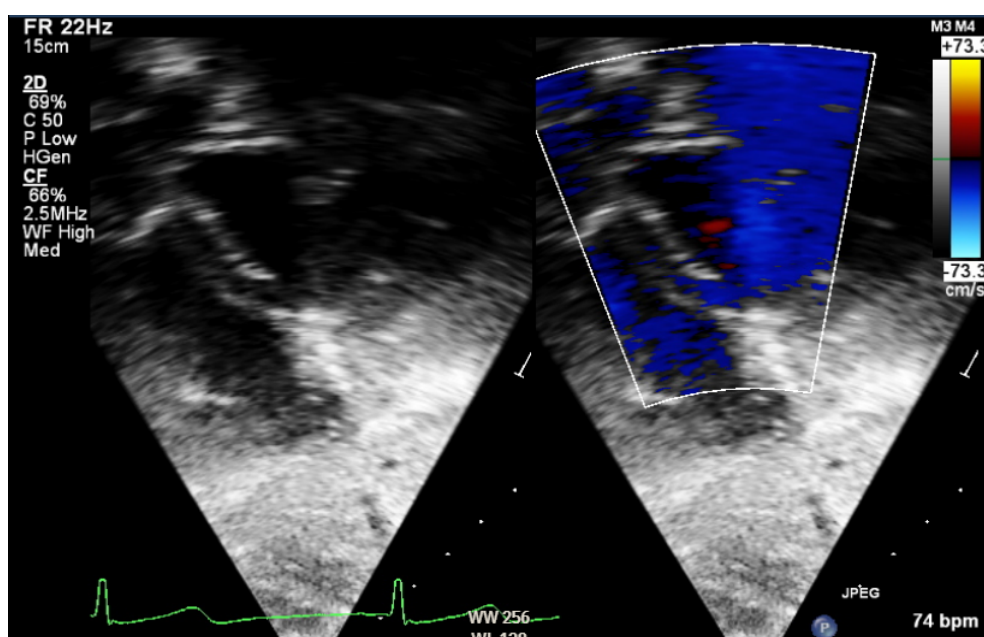


Figure 1. Transthoracic echocardiogram with color flow Doppler demonstrating a patent foramen ovale (PFO) with an associated atrial septal aneurysm (ASA). The left panel shows the hypermobile interatrial septum with characteristic bowing consistent with ASA. The right panel demonstrates predominantly right-to-left color flow Doppler signal across the PFO, illustrating the pathophysiological mechanism of paradoxical embolism through which venous embolic material may gain access to the systemic circulation. The coexistence of PFO and ASA represents a high-risk anatomical phenotype associated with increased stroke recurrence risk and the greatest benefit from percutaneous closure. Source: Authors' own work.

3.4. *In situ* thrombus formation

Beyond paradoxical embolism arising from a peripheral venous source, a second and mechanistically distinct pathway has been proposed in which thrombus forms directly within the PFO tunnel itself. The overlapping, unfused segments of septum primum and septum secundum create a redundant, slit-like channel in which flow is often sluggish, an environment that in principle favors local clot formation independent of any venous source. For years this mechanism remained largely theoretical, supported mainly by scattered case reports of thrombus caught in transit across the septum, most often identified incidentally at autopsy or during emergency surgery for a large embolus, since the transient nature of the finding made it difficult to capture on routine imaging.

This has changed with the introduction of high-resolution optical coherence tomography (OCT), which allows direct, *in vivo* visualization of the PFO tunnel's endocardial surface at a resolution far exceeding conventional echocardiography. In a preliminary OCT study performed during PFO catheterization, *in situ* thrombus was identified in all 11 patients with a recent stroke, compared with only 1 of 7 patients without stroke (100% vs. 14.3%; $p < 0.001$), an early but striking signal

that the tunnel itself could harbor a genuine embolic source.²⁵ This finding was subsequently confirmed and substantially extended in a larger cross-sectional study of 117 patients with PFO, none of whom had conventional vascular risk factors, divided into stroke or transient ischemic attack (TIA), migraine, and asymptomatic groups. *In situ* thrombus was detected in 83.7% of the stroke group and 57.1% of the migraine group, but in none of the asymptomatic patients ($p < 0.001$), and its presence was independently associated with stroke risk (odds ratio, 4.59; 95% confidence interval [CI], 1.26–16.69). Thrombus burden was not trivial: patients with stroke had a median of 7 discrete thrombi per PFO (interquartile range [IQR], 3–12), and abnormal endocardium, most often surface irregularity or discontinuity, was found in nearly three-quarters of patients with thrombus but in none without it, suggesting that endocardial injury within the tunnel may itself promote local thrombogenesis.²⁶

This body of work has a direct, and empirically supported, bearing on antithrombotic management, rather than resting on mechanistic reasoning alone. In the same cohort, stroke patients already receiving anticoagulation at the time of OCT had a strikingly lower thrombus burden than those on antiplatelet therapy or no antithrombotic treatment (median 1 thrombus [IQR, 0–3] vs. 9 [IQR, 5–13];

$p < 0.001$), a difference that persisted when anticoagulated patients were compared specifically against those on antiplatelet therapy alone ($p < 0.001$).²⁶ This is the first clinical evidence linking antithrombotic strategy to actual thrombus burden within the PFO tunnel, and it supports favoring anticoagulation over antiplatelet therapy when *in situ* thrombus is identified or strongly suspected, until the thrombus has resolved or the defect has been closed. The finding is observational, drawn from a single-center cohort, and no randomized trial has tested antithrombotic strategy specifically in this setting. In practice, most operators favor a period of anticoagulation with imaging follow-up before proceeding to elective closure, reserving urgent intervention for recurrent embolization despite treatment.

3.5. Hemodynamic triggers of shunting

The propensity for right-to-left shunting through a PFO ultimately comes down to the pressure relationship between the two atria: anything that raises right atrial pressure relative to left atrial pressure, even briefly, can open the gradient in the wrong direction. A Valsalva maneuver does exactly this. Straining raises intrathoracic and right atrial pressure while venous return and left atrial filling drop, narrowing or briefly reversing the normal left-to-right gradient across the septum—which is why bubble-contrast echocardiography and transcranial Doppler are timed around the release of strain rather than the strain itself. Doppler grading of shunt severity uses the same signal-counting approach as echocardiographic bubble studies, running from a handful of countable signals up to an innumerable “curtain” pattern that marks a large shunt, and the grade correlates reasonably well with anatomical shunt size and, in several series, with stroke risk.²⁷

Several conditions raise right heart pressure in a sustained rather than transient fashion, and these too promote shunting. Obstructive sleep apnea is the best example. Recurrent hypoxemia and hypercapnia during apneic episodes raise pulmonary vascular resistance, right ventricular afterload, and ultimately right atrial pressure, which may reopen or unmask a PFO that would otherwise stay functionally closed. Direct pressure measurements confirming this in isolated OSA are still lacking, but the epidemiological signal is hard to ignore: in a series of 100 consecutive patients with OSA studied by contrast transcranial Doppler, right-to-left shunting was found in 72%, roughly three times the autopsy-based prevalence in the general population, and 65% of these patients shunted at rest, with no Valsalva maneuver at all.²⁸ Shunting that shows up without provocation points to a persistently altered pressure gradient, not one that only opens under transient strain. Pulmonary hypertension and right ventricular dysfunction from other causes likely act the

same way. However, pulmonary hypertension on its own has not been reliably linked to a higher PFO prevalence—it may be the hypoxemia and the swings in ventilatory pressure, not the elevated pressure itself, that matter. Add these sustained states to the transient triggers above, and it becomes easier to understand why two anatomically similar PFOs can behave so differently or why a single resting study might miss shunting altogether.

3.6. Emerging non-mechanical pathogenic mechanisms

Although PFO and atrial septal defect are frequently discussed together as interatrial communications, their clinical consequences differ in ways that matter at the bedside. PFO creates an intermittent right-to-left conduit that can carry venous embolic material into the systemic circulation; atrial septal defect produces sustained right heart volume overload and carries its own set of structural and arrhythmic sequelae, often in combination with other congenital lesions. A recent clinical update on both conditions underscores that distinguishing between them—precisely, on imaging and in clinical context—is not a formality but a prerequisite for choosing the right therapeutic target.²⁹

Separately, the mechanical model of paradoxical embolism has never fully accounted for why some patients with modest shunts suffer recurrent stroke, why closure does not eliminate risk in everyone, or why the majority of adults with demonstrable right-to-left shunting remain asymptomatic throughout life. A prospective study by Tworek *et al.*³⁰ offers a partial answer. In 92 patients under 55 years with PFO and prior cryptogenic stroke compared with 56 controls, interleukin-18 was more than twice as high in the PFO group (268.0 vs. 121.0 pg/mL; $p < 0.001$), galectin-3 and 3-nitrotyrosine were also significantly elevated, and, critically, all three markers were significantly intercorrelated ($r = 0.29$ – 0.57 ; all $p \leq 0.002$) and remained associated on multivariable analysis. High-sensitivity C-reactive protein, vascular cell adhesion molecule 1, and intercellular adhesion molecule 1 were unremarkable, suggesting the signal reflects selective activation of inflammatory, fibrotic, and nitrosative pathways rather than nonspecific systemic inflammation. The implication is that a state of chronic vascular vulnerability, distinct from the embolic event itself, may co-exist with the anatomical defect and independently condition stroke risk in certain patients.

3.7. Integrating pathophysiology with clinical risk stratification

Because PFO is present in approximately one quarter of the adult population, determining when it represents a true pathogenic substrate rather than an incidental

finding remains a central clinical challenge. Contemporary approaches address this by integrating clinical characteristics, anatomical features, and neuroimaging findings to estimate the probability of PFO-mediated stroke. The RoPE score incorporates variables such as patient age, the absence of traditional vascular risk factors, and infarct imaging pattern to generate a probabilistic estimate of causal relevance. More recently, the PASCAL classification has refined this process further by combining clinical probability estimates with anatomical parameters, including shunt size and the presence of ASA, to categorize strokes as probably, possibly, or unlikely related to the PFO.^{19,20}

These frameworks reflect a broader shift in the field. Rather than treating all PFOs as clinically equivalent, current approaches recognize that the likelihood of causality varies across patients. Integrating mechanistic understanding with structured risk stratification is therefore central to informed clinical decision-making regarding diagnostic evaluation and potential PFO closure.

4. Clinical presentation and patient characteristics of patent foramen ovale-associated stroke

Patients with PFO-associated stroke tend to share a relatively consistent demographic and clinical profile across observational studies and randomized trials. The condition most commonly affects young to middle-aged adults, typically between 18 and 60 years of age, with mean ages in major studies ranging from approximately 40 to 51 years.^{2,5,6,15,31–38} This age distribution stands in contrast to the broader ischemic stroke population, in which incidence rises sharply with advancing age and is generally driven by well-established vascular risk factors.

Although the majority of studies have concentrated on patients younger than 60 years, more recent studies have begun to explore the clinical relevance of PFO in older individuals, with some cohorts including patients aged 60 years or older and mean ages approaching the late sixties. These emerging data suggest that PFO may remain clinically relevant in selected older patients, though the probability of competing stroke mechanisms increases substantially with age.

4.1. Factors associated with clinical silence or stroke in patent foramen ovale

A question that follows naturally from the epidemiology of PFO is why, given its presence in roughly a quarter of the adult population, only a small minority of carriers

ever experience a PFO-related embolic event. Several of the anatomical and clinical factors already discussed converge to answer this. Shunt size is the most consistently implicated variable: a small, restrictive PFO permits only intermittent, low-volume flow even during provocation, whereas a large shunt, particularly when accompanied by an ASA, allows a substantially greater embolic load to cross with each transient pressure reversal.^{14,20–24} The burden of venous thromboembolism upstream of the shunt adds a second layer of variability, since a patient with inherited thrombophilia or another prothrombotic tendency presents a thrombus to the shunt far more often than one without such a tendency, even if the two PFOs are anatomically identical.^{1,5,39,40} The frequency of Valsalva-type maneuvers in daily life is a further determinant: because shunting is fundamentally pressure-dependent, individuals whose occupations, habits, or medical conditions involve frequent straining, heavy lifting, or chronic cough create more opportunities for the right-to-left gradient to reverse than someone with an identical PFO but a sedentary routine. Finally, the pulmonary vascular bed ordinarily filters small venous emboli that reach the right heart without crossing the septum; a large shunt effectively bypasses this protective filtration for material below the tunnel diameter, while a small or absent shunt leaves it largely intact.^{1,5} Taken together, it is this interaction of anatomy, thrombotic supply, and maneuver frequency, rather than the presence of a PFO per se, that separates the asymptomatic majority from the minority in whom the defect becomes clinically manifest.

4.2. Index neurological events

The predominant clinical presentation in this population is cryptogenic ischemic stroke, defined as a cerebral infarction without an identifiable cause despite thorough diagnostic evaluation. Across clinical trials and cohort studies, cryptogenic stroke represents the index event in the majority of patients evaluated for PFO.^{2,3,5,6,9,17,18,22,33,38,41–57}

Among enrolled patients, ischemic stroke accounts for approximately 62%–71% of index events, while TIA represents 28%–33% of presentations.^{12,21,31,58} A smaller subset of patients presents with systemic embolic manifestations, such as peripheral arterial embolism, though these events are considerably less frequent. Neurological outcomes following the index event are often favorable. In several randomized trials, approximately 80% of patients had modified Rankin Scale scores of 0–1 after the initial stroke, reflecting minimal residual disability and likely related to the younger age and lower burden of comorbid disease in this population.^{6,9}

4.3. Stroke characteristics and imaging patterns

Distinctive neuroimaging patterns have been observed in PFO-associated stroke. Infarcts commonly appear embolic in character, frequently involving superficial cortical territories or multiple vascular distributions.⁵⁹ A notable feature is the relatively high proportion of events affecting the vertebrobasilar circulation; approximately 40% of strokes in certain cohorts involve the posterior circulation, substantially exceeding the roughly 20% contribution of the posterior circulation to total cerebral blood flow.¹⁰ This posterior predominance is generally read as further support for an embolic mechanism, since a purely thrombotic or small-vessel process would not be expected to favor one vascular territory so consistently—though the same source also allows that non-embolic mechanisms in a subset of presumed cryptogenic strokes cannot be fully excluded, so the finding is supportive rather than definitive.¹⁰ Infarct size varies considerably, with some patients exhibiting large territorial infarctions consistent with embolic occlusion of major cerebral arteries.

This posterior circulation predominance has clinical implications that go beyond its mechanistic significance. At the bedside, a patient presenting with an isolated posterior circulation infarct, particularly a cerebellar or occipital lesion, in the absence of vertebrobasilar atherosclerosis, dissection, or another clear large-artery explanation, should prompt a heightened index of suspicion for a cardioembolic or paradoxical embolic source, including

PFO, rather than being attributed by default to small-vessel or posterior circulation-specific pathology. This is because a bloodborne embolus entering the aortic arch has no anatomical reason to preferentially seek the anterior circulation, so a pattern of infarction that involves the posterior circulation, whether alone or in combination with anterior territory lesions, is considerably more consistent with a proximal embolic source than with a mechanism confined to a single vascular distribution. Recognizing this pattern therefore has genuine differential-diagnostic value, reinforcing rather than reducing the diagnostic effort directed toward transesophageal echocardiography and prolonged rhythm monitoring in patients whose infarct pattern includes posterior circulation involvement. Infarct location is also one of the imaging variables embedded directly in the RoPE score, in which a cortical, subcortical, or cerebellar pattern, as opposed to a small, deep, penetrator-territory lesion more typical of small-vessel disease, increases the estimated probability that the stroke is embolic and that an identified PFO is causally relevant rather than incidental.^{10,19}

4.4. Patent foramen ovale anatomical characteristics

The anatomical features of the PFO vary widely among patients and carry important prognostic implications. Shunt size ranges from small to large interatrial communications, and the presence of a moderate or large right-to-left shunt has been consistently associated with greater stroke risk (Figure 2).

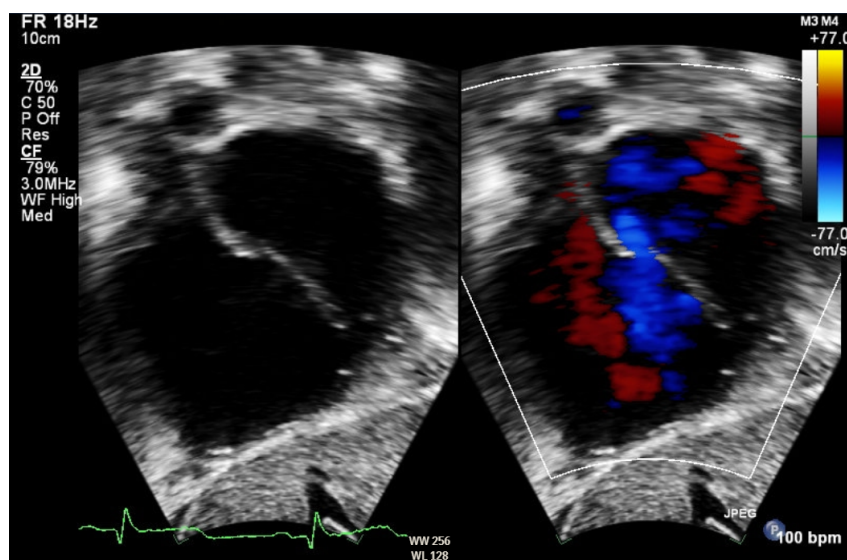


Figure 2. Transthoracic echocardiogram with color flow Doppler demonstrating a patent foramen ovale (PFO) with a right-to-left interatrial shunt. The right panel demonstrates a high-velocity color flow signal across the interatrial septum, reflecting a hemodynamically significant right-to-left shunt through which venous embolic material may paradoxically enter the systemic arterial circulation. Shunt size is one of the strongest anatomical predictors of recurrent stroke risk and is independently associated with the greatest benefit from percutaneous PFO closure. Source: Authors' own work.

In one major randomized trial population, approximately 81% of patients had moderate or large shunts, reflecting the deliberate enrichment of higher-risk anatomical phenotypes within the trial cohort.²²

The presence of an ASA represents another anatomically important feature, reported in approximately 23%–28% of patients with PFO-associated stroke.^{7,12,60} ASA is defined by excessive mobility of the interatrial septum and is thought to facilitate intermittent opening of the PFO tunnel, thereby increasing susceptibility to paradoxical embolic events. Additional high-risk anatomical characteristics, including PFO diameter of ≥ 2 mm and septal hypermobility with a phasic excursion of ≥ 10 mm, have been incorporated into contemporary risk stratification frameworks and have directly informed the inclusion criteria of major randomized closure trials.^{9,6}

4.5. Comorbid conditions and vascular risk factors

Consistent with the cryptogenic nature of the index stroke, conventional vascular risk factors are relatively uncommon in PFO cohorts compared with other stroke populations. Across studies, hypertension has been reported in approximately 25%–31% of patients, diabetes mellitus in 2%–7%, and hyperlipidemia in 27%–44%.^{12,56,62} In one cohort, roughly 40% of patients carried at least one conventional vascular risk factor, though the overall burden remained considerably lower than that typically observed in atherosclerotic stroke populations.

A subset of patients has demonstrated an elevated prevalence of thrombophilia or hypercoagulable states, which may act synergistically with PFO to heighten the risk of paradoxical embolism. Associations with inherited thrombophilic disorders and hematologic abnormalities have been reported, and in one study, recurrent stroke or TIA was attributable to thrombophilia or a hematologic condition in 62.5% of affected patients.^{39,40}

4.6. Diagnostic evaluation

Diagnostic evaluation is based on a combination of cardiac imaging and neurological assessment. Transesophageal echocardiography with agitated saline contrast remains the standard method for detecting PFO and assessing right-to-left shunting, while transcranial Doppler provides a noninvasive alternative for identifying microembolic signals.^{1,12,44,63}

Brain imaging with magnetic resonance imaging or computed tomography (CT) is performed to confirm the presence and to characterize the pattern of cerebral infarction, supporting the diagnosis of an embolic event.⁷ In some studies, neuroimaging has also been repeated during follow-up to assess for recurrent events.⁶⁴

Once a PFO is confirmed, the work-up should not stop at echocardiography and brain imaging—what comes next determines the treatment strategy as much as the PFO itself does. Rhythm monitoring should run at least thirty days, since paroxysmal atrial fibrillation missed on a short recording gets misfiled as cryptogenic stroke. The left atrial appendage and native valves should also be evaluated independently of the PFO. Vascular imaging—CT or magnetic resonance angiography of the neck and head vessels, carotid duplex, and the aortic arch—rules out large-artery disease as a competing or coexisting source. Thrombophilia testing (factor V Leiden, prothrombin G20210A, protein C and S, antithrombin III, antiphospholipid antibodies) matters less for diagnosis than for treatment: a confirmed thrombophilic disorder is one of the clearer reasons to favor anticoagulation over antiplatelet therapy after closure.^{39,40} Lower-extremity duplex looks for a venous source; CT pulmonary angiography should be performed if concurrent pulmonary embolism is suspected. An active deep vein thrombosis changes the plan on its own — anticoagulation first, closure later, since dislodging clot during device deployment is a real risk. Atypical presentations warrant a look for occult malignancy, since a cancer-driven hypercoagulable state changes both the presumed mechanism and the risk-benefit math on closure. And a basic metabolic panel—fasting glucose, glycated hemoglobin, lipids—still belongs in the work-up, if only to make sure a competing atherosclerotic cause is not being missed. None of this is optional once the PFO itself has been found; it is what turns a single anatomical finding into an actual treatment decision.

These diagnostic steps are best understood not as isolated tests but as a sequential pathway. Evaluation begins with brain imaging to confirm an infarct of embolic appearance, followed by the standard cryptogenic stroke workup used to exclude alternative mechanisms. PFO-specific testing may then be performed using transesophageal echocardiography and transcranial Doppler to confirm and characterize the shunt.^{1,12,44,63} The resulting anatomical and clinical findings can be integrated using the RoPE score and PASCAL classification to estimate the probability that the PFO is causally related to the index event.^{19,20} This process culminates in a multidisciplinary decision, weighing this causal-likelihood estimate against age, bleeding risk, and patient preference, to arrive at a course of action among closure, antiplatelet therapy, or anticoagulation.

5. Treatment strategies for patent foramen ovale-associated stroke

The management of patients with PFO and cryptogenic stroke has changed significantly over the past three decades. Two main strategies have been explored:

percutaneous transcatheter closure of the PFO and medical therapy aimed at preventing thromboembolism. Initially, antithrombotic therapy was standard, but advances in interventional cardiology led to catheter-based closure to prevent paradoxical embolism. As randomized trial data accumulated, these two strategies were increasingly compared in controlled settings to determine whether anatomical closure of the interatrial communication could reduce the risk of recurrent ischemic events beyond what medical therapy alone could achieve.^{2,3,14,22–24}

5.1. Percutaneous patent foramen ovale closure: Devices and procedural techniques

5.1.1. Closure devices

Multiple transcatheter occlusion devices have been evaluated for percutaneous PFO closure across randomized trials and observational studies. The Amplatzer PFO Occluder (Abbott, Abbott Park, IL, USA) has been the most extensively studied and widely deployed system, with numerous trials and registries reporting outcomes with this device.^{11,21,32,60,64–68} Reported device sizes include 18 mm, 25 mm, 30 mm, and 35 mm variants, allowing procedural tailoring based on the anatomical characteristics of the interatrial septum.^{3,37}

Other devices evaluated in clinical studies include the Gore Helex Septal Occluder (W. L. Gore & Associates, USA) and the Gore Cardioform Septal Occluder (W. L. Gore & Associates, USA).^{8,10,69} Device performance has varied across systems, particularly with respect to complete closure rates and procedural safety profiles.

The Occlutech Figulla Flex II PFO Occluder (Occlutech GmbH, Germany) represents an additional transcatheter closure system with regulatory approval in Europe since 2011 and in Canada since 2019, though it remains investigational in the United States. The device consists of nitinol wire mesh discs connected by a thin flexible nitinol bridge, with biocompatible polyethylene terephthalate patches to promote tissue ingrowth, and disc sizes ranging from 18 to 35 mm.

Comparative outcomes between the Occlutech Figulla and the Amplatzer Occluder have been evaluated in observational studies. In a two-center Italian registry of 406 consecutive patients, procedural success was 99.5% with both devices, and residual grade ≥ 2 right-to-left shunt at 12-month follow-up was 4.5% in each group with no significant difference.⁶⁰ The only outcome favoring the Figulla device was a significantly lower rate of supraventricular arrhythmias compared with the Amplatzer Occluder (9% vs. 17%; $p = 0.02$), with no deaths or recurrent embolic events in either group. More recently,

a single-center registry from Lucerne comparing both devices in patients undergoing PFO closure between 2017 and 2022 similarly demonstrated equivalent outcomes, with effective closure rates of 96.6% for the Amplatzer and 94.5% for the Occlutech Figulla Flex II at six-month follow-up ($p = 0.30$). Available observational evidence therefore suggests comparable closure efficacy between the two devices, with a potentially favorable arrhythmic profile for the Occlutech system.^{60,70}

Long-term effectiveness is further determined by the rate of complete anatomical closure of the interatrial communication, typically assessed by follow-up echocardiography at 6–12 months post-procedure.

5.1.2. Evolution of procedural techniques

Procedural approaches to PFO closure have evolved considerably with increasing operator experience and advances in imaging technologies. Early procedures were commonly performed under general anesthesia with transesophageal echocardiographic guidance.^{11,37}

As experience accumulated, simplified protocols emerged. Many centers demonstrated that PFO closure could be performed safely using fluoroscopic guidance alone, reserving intracardiac echocardiography (ICE) for cases involving complex septal anatomy.^{37,57} This procedural simplification was accompanied by shorter procedure times. In one series, mean fluoroscopy time decreased from 8.6 ± 3.4 min in early cases to 3.4 ± 1.9 min with increasing operator experience.³¹

Procedures have also transitioned toward performance under local rather than general anesthesia, facilitating shorter recovery times and enabling same-day discharge. In one series, 97.6% of patients were discharged on the day of the procedure, reflecting both the safety and logistical efficiency of contemporary PFO closure programs.^{11,57}

5.1.3. Post-procedural management

Effective long-term management after PFO closure extends well beyond the index procedure and depends on a structured approach to antithrombotic therapy, imaging surveillance, and recognition of device-related complications.

Antithrombotic management following closure—including the duration of dual antiplatelet therapy and the transition to long-term monotherapy—is discussed in detail in the Medical Therapy section below.

Surveillance for residual shunting is a second essential component of post-procedural care. Follow-up echocardiography with agitated saline contrast, typically performed at 6 to 12 months, allows detection of a persistent

right-to-left shunt across the closure device. Patients with a residual moderate or large shunt after attempted closure face a substantially elevated risk of recurrent events, with a composite stroke/TIA rate of 2.32 per 100 patient-years compared with 0.75 in patients achieving complete closure, corresponding to a hazard ratio of 3.05 (95% CI, 1.65–5.62). At five years, the cumulative probability of recurrent stroke or TIA was 9.3% in patients with residual shunting compared with 2.5% in those with complete closure.⁷ These findings justify systematic imaging follow-up rather than assuming procedural success based on an uncomplicated implantation alone, and a clinically significant residual shunt identified on surveillance imaging should prompt consideration of repeat closure or continued antithrombotic therapy pending reassessment.

Device-related thrombus, though uncommon with contemporary devices, represents a third area requiring specific management. When thrombus is identified adherent to the closure device on follow-up imaging, the standard approach is therapeutic anticoagulation until the thrombus resolves, generally confirmed by serial echocardiography over a period of approximately three to six months, rather than proceeding directly to further intervention. This mirrors the management of intracardiac thrombus in other settings and reflects the same underlying principle discussed in relation to native *in situ* PFO tunnel thrombus: a fixed, endothelium-poor surface within the heart is managed with anticoagulation until resolution is demonstrated, with mechanical intervention reserved for thrombus that persists or embolizes despite adequate anticoagulation.

5.2. Medical therapy regimens

5.2.1. Antiplatelet therapy

Medical therapy has long been the standard approach for patients with cryptogenic stroke and PFO. Antithrombotic strategies have varied across clinical trials, reflecting changes in practice over time.

Following device closure, most studies used dual antiplatelet therapy—typically aspirin combined with clopidogrel—for a period of one to six months, followed by long-term single antiplatelet therapy for secondary prevention. In some protocols, aspirin was combined with extended-release dipyridamole instead, depending on study design and regional practice patterns.^{12,15}

5.2.2. Anticoagulation strategies

Earlier randomized trials often allowed oral anticoagulation as part of the medical therapy arm. For example, the RESPECT trial permitted treatment with aspirin, warfarin, clopidogrel, or aspirin combined with dipyridamole at the

discretion of the treating physician.¹⁵ In several studies, warfarin anticoagulation targeting an International Normalized Ratio of 2.0–3.0 was used, and in one trial approximately 25.2% of patients received anticoagulant therapy.³ Other protocols used six-month courses of anticoagulation.^{11,12,64}

5.2.3. Antiplatelet versus anticoagulation: Comparative efficacy and patient selection

Although the CLOSE trial's three-arm design allowed a direct comparison between anticoagulation and antiplatelet therapy, the number of medical-arm events was too small for this comparison alone to be conclusive. A broader perspective comes from a network meta-analysis incorporating data across trials with differing medical-arm compositions, which estimated that anticoagulation was associated with approximately 71 fewer recurrent strokes per 1,000 patients treated compared with antiplatelet therapy, at the cost of approximately 12 additional major bleeding events per 1,000 patients treated.³⁵ Both credible intervals cross the null, so this should be read as a plausible trade-off rather than a settled result.

The role of direct oral anticoagulants (DOACs) in this setting remains undefined by dedicated trial evidence; their use is extrapolated entirely from experience in other cardioembolic indications, and no randomized study has yet tested a DOAC specifically in PFO-associated stroke.

A more selective group of patients may derive greater benefit from anticoagulation in preference to antiplatelet therapy: those with documented or strongly suspected inherited thrombophilia, in whom recurrence has been shown to be disproportionately common,^{39,40} those with a suspected venous thrombotic source, and those with another strong prothrombotic tendency. In these patients, closure alone addresses the anatomical substrate but does not correct an ongoing prothrombotic tendency, which is why a combined or anticoagulation-based strategy is often favored on mechanistic grounds, even though dedicated randomized comparisons in this specific subgroup are lacking.

5.2.4. Evolution of medical therapy in later trials

As the management of cryptogenic stroke evolved, later trials increasingly focused on antiplatelet therapy alone in the medical treatment arm. Both the CLOSE and Gore REDUCE trials restricted their control groups to antiplatelet therapy, reflecting a shift toward antiplatelet-based strategies in patients without a clear indication for anticoagulation.¹⁸ The CLOSE trial was particularly notable for including a separate randomization arm comparing oral anticoagulation with antiplatelet therapy, allowing a direct

three-way comparison between device closure, antiplatelet therapy, and anticoagulation within a single study.^{6,71}

5.3. Patient selection and contraindications

5.3.1. Selection criteria

Patient selection evolved substantially across successive trial generations. Early studies often enrolled patients with PFO regardless of anatomical characteristics, resulting in heterogeneous populations and potentially diluting treatment effects.¹⁸ Later trials refined enrollment by focusing on patients with high-risk anatomical features more likely to indicate a causal relationship between the PFO and the index stroke. For example, the CLOSE trial restricted inclusion to patients with large interatrial shunts or coexisting ASA¹⁸, while the DEFENSE-PFO trial required at least one high-risk feature, such as a PFO diameter ≥ 2 mm, ASA, or marked septal hypermobility.^{9,71} These enriched populations likely had a higher baseline probability of PFO-mediated embolism and were therefore more likely to benefit from closure.

5.3.2. Exclusion criteria

Across trials, patients with an identifiable alternative cause of stroke were consistently excluded. Common exclusion criteria included large-artery atherosclerosis, small-vessel disease, uncontrolled hypertension or diabetes, autoimmune conditions, recent substance abuse, and independent indications for long-term anticoagulation.^{10,11,19,64} Patients with contraindications to antiplatelet or anticoagulant therapy were also generally excluded.^{11,19}

5.3.3. Stratification variables

Several trials incorporated pre-specified stratification variables to ensure balanced randomization and enable subgroup analyses. These commonly included age (e.g., <45 vs. ≥ 45 years), the presence of ASA, and the number of prior embolic events. Such stratification allowed investigators to assess whether treatment effects varied across different clinical and anatomical risk profiles.

6. Major randomized clinical trials of patent foramen ovale closure

The potential benefit of percutaneous PFO closure for secondary prevention of cryptogenic stroke has been evaluated in several randomized trials over the past two decades. Early studies reported largely neutral results, whereas later trials, guided by improved patient selection and advances in device technology, demonstrated a significant reduction in recurrent stroke risk.

Together, these trials form the foundation of current clinical recommendations for PFO closure in carefully selected patients with cryptogenic stroke⁶⁻¹⁰ (Table 1).

6.1. Early randomized trials

6.1.1. CLOSURE I trial

The CLOSURE I trial was the first large randomized study designed to evaluate whether transcatheter PFO closure could reduce recurrent neurological events compared with medical therapy. Patients with cryptogenic stroke or TIA were randomized to closure using the STARFlex device or to medical therapy.

The trial did not demonstrate a significant reduction in the primary composite endpoint of stroke, TIA, or death. This neutral result has been attributed to heterogeneous patient selection, inclusion of patients with likely incidental PFO, and limitations related to the device used. Notably, the study population was not enriched for high-risk anatomical features, such as large shunts or ASA, which were later shown to influence treatment benefit.⁸

6.1.2. PC trial

The PC Trial evaluated PFO closure using the Amplatzer device compared with medical therapy in patients with cryptogenic embolism. Although recurrent events were numerically lower in the closure group, the difference did not reach statistical significance. The relatively small sample size and low event rates limited statistical power. Despite its neutral primary outcome, the trial supported the safety and feasibility of closure with newer-generation devices.⁸

6.1.3. RESPECT trial

The RESPECT trial was among the largest studies in this field. Patients with cryptogenic stroke were randomized to closure with the Amplatzer device or to medical therapy. Initial analyses showed a trend toward reduced recurrent stroke with closure, but this did not reach statistical significance in the intention-to-treat analysis. Extended follow-up later demonstrated a significant reduction in recurrent ischemic stroke with closure. Subgroup analyses suggested greater benefit in patients with large shunts or ASA, findings that subsequently informed the design of subsequent trials.^{7,8}

6.2. Later positive trials

6.2.1. CLOSE trial

The CLOSE trial applied stricter selection criteria, enrolling only patients with high-risk PFO features, including large shunts or ASA. Patients were randomized to closure using

Table 1. Summary of major randomized controlled trials of percutaneous patent foramen ovale closure for secondary stroke prevention

Trial	N	Device	Follow-up	Key inclusion criteria	Absolute event rate, closure vs. medical (ARD)	Primary result	Key finding
CLOSURE I (2012) ⁵	909	STARFlex	2 years	Cryptogenic stroke or TIA; any PFO anatomy	2.9% vs. 3.1% (ARD −0.2%)	Neutral (HR 0.78, $p = 0.37$)	No benefit; STARFlex device associated with higher AF and thrombus rates
PC Trial (2013) ⁶⁵	414	Amplatzer PFO Occluder	4.1 years	Cryptogenic embolism; any PFO anatomy	3.4% vs. 5.2% (ARD −1.8%)	Neutral (HR 0.63, $p = 0.34$)	Numerically fewer events with closure; underpowered; confirmed device safety
RESPECT (2013/2017) ^{3,7}	980	Amplatzer PFO Occluder	5.9 years (extended)	Cryptogenic stroke; any PFO anatomy; age 18–60	0.58 vs. 1.07 per 100 PY (ARD −0.49 per 100 PY)	Positive on extended f/u (HR 0.55, $p = 0.046$)	Initial ITT analysis neutral; extended follow-up showed significant stroke reduction; first FDA-approved device (2016)
CLOSE (2017) ⁶	663	Multiple (Amplatzer predominant)	5.3 years	Cryptogenic stroke; large shunt or ASA; age 16–60; 3-arm design	0% vs. ~8.9%* (ARD ~−8.9%)	Strongly positive (HR 0.03, $p < 0.001$)	Zero recurrent strokes in closure arm; high-risk anatomy enrichment key to positive result; also compared anticoagulation vs. antiplatelets
REDUCE (2017) ²²	664	GORE Helex/Cardioform	3.2 years	Cryptogenic stroke; any PFO; antiplatelet control arm only	1.4% vs. 5.4% (ARD −4.0%)	Positive (HR 0.23, $p = 0.002$)	Significant reduction in recurrent stroke and new brain infarctions; silent infarct rates similar between groups
DEFENSE-PFO (2018) ⁹	120	Amplatzer PFO Occluder	2 years	Cryptogenic stroke; high-risk PFO only (diameter ≥ 2 mm, ASA, or hypermobility)	Composite endpoint; per-arm binary rate not separately reported	Positive (composite endpoint)	Significant reduction in stroke, vascular death, or major bleeding; exclusively high-risk anatomy; 100% procedural success

Abbreviations: AF: Atrial fibrillation; ARD: Absolute risk difference; ASA: Atrial septal aneurysm; f/u: Follow-up; HR: Hazard ratio; ITT: Intention-to-treat; PFO: Patent foramen ovale; TIA: Transient ischemic attack.

various devices, predominantly the Amplatzer device plus antiplatelet therapy, antiplatelet therapy alone, or anticoagulation.^{6,8}

The trial demonstrated a marked reduction in recurrent stroke with closure, with no recurrent strokes observed in the closure group during follow-up. These findings provided strong evidence supporting closure in carefully selected patients.

6.2.2. REDUCE trial

The REDUCE trial compared closure using Gore devices with antiplatelet therapy alone. The study showed a significantly lower rate of recurrent ischemic stroke in the closure group.

In addition, fewer new brain infarctions were observed with closure, supporting the concept that eliminating the

right-to-left shunt reduces both clinical and subclinical embolic events.^{8,10}

6.2.3. DEFENSE-PFO trial

The DEFENSE-PFO trial focused exclusively on patients with high-risk anatomical features. Despite its smaller sample size, it demonstrated a significant reduction in the composite endpoint of stroke, vascular death, or major bleeding with closure.⁹

6.3. Overall evidence and synthesis

Across randomized trials and meta-analyses, percutaneous PFO closure has been associated with a significant reduction in recurrent stroke compared with medical therapy alone, with relative risk reductions ranging from approximately 39% to 77%.

In contrast, effects on TIA have been less consistent, and no significant differences in overall mortality have been observed between treatment strategies.^{2,8,14,16,23,24}

6.4. Evolution of evidence

Taken together, the progression of randomized evidence reflects a shift from early neutral findings to consistent evidence of benefit in later trials. This transition was driven by improved patient selection, particularly the identification of high-risk anatomical features, and advances in device technology.

Collectively, these trials established that PFO closure reduces recurrent stroke risk in carefully selected patients, particularly those with large right-to-left shunts or ASA, and form the basis of current guideline recommendations.

All major randomized trials to date compared percutaneous PFO closure against medical therapy, leaving the question of comparative device performance unanswered. The OCCLUFLEX trial (NCT05069558) addresses this gap as the first multicenter randomized controlled trial designed to compare PFO closure devices directly. The trial randomizes 450 patients with cryptogenic stroke across 48 centers in the United States, Canada, and Europe in a 1:1 ratio to receive either the Occlutech Figulla Flex II PFO Occluder or a standard-of-care device—the AMPLATZER Talisman PFO Occluder or the Gore CARDIOFORM Septal Occluder—using a noninferiority framework. The primary endpoint is effective PFO closure at 12 months by echocardiographic bubble study, the secondary endpoint is nonfatal recurrent stroke through 12 months, and the safety endpoint includes all device- and procedure-related serious adverse events, including post-procedural atrial fibrillation. Unlike prior randomized trials that excluded patients older than 60 years, OCCLUFLEX imposes no upper age limit. Results are pending and are

expected to provide the first randomized evidence to guide device selection in clinical practice.⁷²

7. Evidence synthesis and clinical outcomes

7.1. Stroke recurrence

The most consistent finding across randomized trials is a reduction in recurrent ischemic stroke among patients undergoing PFO closure compared with those managed medically.

This benefit was not uniform and was most pronounced in patients with high-risk anatomical features, such as large right-to-left shunts or coexisting ASA, supporting a stronger causal relationship between the PFO and the index event in these subgroups.

Across randomized trials and meta-analyses, PFO closure has been associated with relative risk reductions of approximately 39%–77%, with a number needed to treat of roughly 25 to 46 patients to prevent one stroke over 2–5 years.^{2,14,22–24,45,54}

Absolute event rates make the same point differently. Medical therapy arms in these trials have shown recurrent stroke rates of roughly 1.1 to 5.4 per 100 patient-years; after closure, that drops to about 0.47 to 0.61 per 100 patient-years, and the gap holds up across meta-analyses using different pooling methods.^{2,7,14,19,22} Extended follow-up cohorts put freedom from recurrent neurological events after closure at roughly 99% at one year, 99% at two years, and 97% at five years—a small annual event rate, compounded over time, still adding up to a durable benefit in patients who are typically young enough for that timeframe to matter.⁶⁶

Although absolute event rates were relatively low, reflecting the younger and lower-risk populations studied, the consistency of these findings across trials strengthens confidence in the observed benefit. No significant differences in overall mortality have been observed between closure and medical therapy.

7.2. Silent cerebral infarction

Neuroimaging findings provide additional insight into the effects of PFO closure. In the REDUCE trial, the overall rate of new brain infarctions was lower in the closure group. However, when silent infarcts were considered separately, rates were similar between groups, suggesting that the primary benefit of closure lies in preventing clinically apparent stroke.^{8,10}

7.3. Long-term outcomes

Long-term follow-up has been critical in demonstrating the benefit of PFO closure. Initial analyses, particularly

from the RESPECT trial, were inconclusive, but extended follow-up revealed a significant reduction in recurrent stroke with closure.^{7,8}

These findings highlight that, in populations with low annual event rates, meaningful differences between treatment strategies may only become evident over time.

7.4. Overall interpretation of evidence

Taken together, the pattern of evidence supports a clear but patient-specific benefit of PFO closure. The greatest benefit is observed in individuals with high-risk anatomical features and a low burden of competing vascular risk factors.^{6–10}

The shift from early neutral trials to consistently positive results reflects improved patient selection and advances in procedural techniques. At the same time, the lack of a consistent effect on TIA reinforces the importance of focusing on stroke-specific endpoints when evaluating treatment benefits.

8. Safety and adverse events of patent foramen ovale closure

Although percutaneous PFO closure has demonstrated clear benefit in selected patients, its clinical value must be considered alongside its safety profile. Across randomized trials and observational studies, the procedure has been generally well tolerated, with low rates of serious complications.

The most consistently reported adverse event is new-onset atrial fibrillation. Rates of major bleeding and overall mortality are similar between closure and medical therapy, suggesting no excess overall harm with the interventional approach.^{2,22,24,45,73}

8.1. Atrial fibrillation

Among reported complications, atrial fibrillation is the most frequent and clinically relevant. Meta-analyses consistently show a higher incidence following PFO closure, with an approximately four- to six-fold increase compared with medical therapy alone.^{2,14,23,24,45}

However, the timing and behavior of these arrhythmias are important. In most cases, atrial fibrillation occurs early after the procedure and is typically transient. One analysis reported that nearly three-quarters of cases resolved within 45 days, suggesting a predominantly procedural rather than chronic mechanism.²

This pattern is supported by individual studies, which report early post-procedural atrial fibrillation rates of around 9%, with persistent arrhythmia observed

in a smaller proportion of patients during longer-term follow-up.^{32,39,61} Reassuringly, some data suggest that patients who develop atrial fibrillation do not necessarily experience higher rates of subsequent ischemic events, although this finding should be interpreted with caution.³⁹

Device type may also influence risk. The Amplatzer Occluder has been associated with lower rates of atrial fibrillation compared with earlier-generation devices used in initial trials, which were linked to higher arrhythmic risk. This distinction highlights how improvements in device design have contributed to both enhanced efficacy and improved safety profiles.^{16,43}

This reassurance should be weighed against the limitations of the underlying data. Follow-up in most of these cohorts extends only a few years, monitoring for recurrence was not always systematic beyond the immediate post-procedural window, and device-specific differences in atrial fibrillation incidence complicate pooling across studies. In the absence of larger cohorts with rigorous, extended rhythm and neurological follow-up, it would be premature to treat post-procedural atrial fibrillation as reliably benign, particularly in a population that has, by definition, already demonstrated a predisposition to embolic stroke.

Given this uncertainty, a pragmatic monitoring and management approach is warranted. Rhythm monitoring for at least 30 days after device closure is reasonable, since this window captures the great majority of clinically relevant episodes described above. When atrial fibrillation is detected, the decision to anticoagulate should follow standard CHA₂DS₂-VASc-based risk stratification; because nearly all of these patients already carry a point for prior stroke or TIA, most will meet a guideline threshold favoring anticoagulation if atrial fibrillation is confirmed. For transient, early post-procedural atrial fibrillation that resolves within the initial monitoring period, the duration of anticoagulation can reasonably be individualized according to recurrence on further monitoring, bleeding risk, and patient preference. Atrial fibrillation that persists beyond approximately six weeks, or that recurs after an initial course of treatment, should generally be managed as any other case of atrial fibrillation meeting a CHA₂DS₂-VASc indication, namely with long-term anticoagulation, since a persistent arrhythmia at this stage is less likely to reflect a purely transient post-procedural phenomenon.

8.2. Procedural and device-related complications

Serious procedural and device-related complications are uncommon but clinically important when they occur. Across studies, such events have been reported in approximately 1.4% to 5.9% of patients.^{3,6,22}

Pericardial complications, including effusion and, rarely, cardiac tamponade, have been described, with some cases requiring invasive intervention.^{21,42} Device embolization is another recognized complication, occurring infrequently but occasionally necessitating surgical retrieval when percutaneous removal is not feasible.^{7,11,57,74,75}

Other rare events include air embolism, cardiac perforation, transient ischemic episodes, and transient electrocardiographic changes. Although infrequent, these complications highlight the importance of operator experience and careful patient selection.^{11,37,75}

Device-specific differences further illustrate the evolution of safety. Thrombus formation has been reported more commonly with earlier-generation devices, while it appears to be rare with newer systems, including the Amplatzer device.^{42,64} Similarly, structural complications, such as device frame fractures, were primarily observed with earlier-generation platforms and are now seldom reported.⁷⁴ These observations highlight the impact of technological advances on improving procedural safety.

Importantly, overall rates of serious adverse events appear similar between PFO closure and medical therapy in most studies, supporting the overall safety of the interventional approach.

8.3. Vascular access and minor complications

Access-site complications are relatively infrequent and are usually minor. Reported events include groin hematomas, pseudoaneurysms, and, less commonly, arteriovenous fistulas requiring intervention.^{9,12,37,61} Transient arrhythmias other than atrial fibrillation have also been described but are generally self-limited.^{12,63}

In contemporary practice, PFO closure is typically well tolerated. Observational data suggest low in-hospital complication rates and a high proportion of same-day discharges, reflecting improvements in procedural techniques and peri-procedural care.^{32,57}

8.4. Bleeding and thrombotic events

Unlike atrial fibrillation, major bleeding does not appear to be increased with PFO closure. Across multiple studies, bleeding rates are similar between closure and medical therapy, with no consistent advantage for either approach.^{24,33,54,73,76}

When bleeding occurs, it is more often related to antithrombotic therapy rather than the procedure itself. In particular, anticoagulation is associated with an increased risk of intracranial and gastrointestinal bleeding over time.^{11,35} Isolated bleeding events, such as gastrointestinal hemorrhage, have been reported but remain uncommon.⁶⁴

Venous thromboembolism has been observed in some studies, with slightly higher rates reported in the closure group in certain trials; however, overall event rates remain low.^{7,22}

8.5. Mortality and overall safety

Across randomized trials and pooled analyses, no meaningful difference in all-cause mortality has been observed between PFO closure and medical therapy.^{2,24,45} Several studies have reported no early deaths and no deaths attributable to neurological causes during follow-up.^{5,36} Long-term observational data further support these findings, demonstrating comparable survival between treatment strategies.⁷⁷

Similarly, overall rates of serious adverse events are broadly comparable between groups. In most studies, PFO closure does not result in an increased risk of major adverse outcomes compared with medical therapy, reinforcing its overall safety in appropriately selected patients.^{2,3,22,34,76}

8.6. Overall perspective on safety

Taken together, the available evidence indicates that percutaneous PFO closure is a safe intervention when performed in experienced centers. The main trade-off is an increased risk of atrial fibrillation, which typically occurs early after the procedure and is often transient.^{2,14,23,24,45}

Other complications, including device- and procedure-related events, are uncommon, and there is no consistent increase in major bleeding or mortality.^{2,22,24,45,73} From a clinical perspective, this safety profile supports the use of PFO closure in carefully selected patients, where the reduction in recurrent ischemic stroke outweighs the relatively modest procedural and arrhythmic risks.

9. Heterogeneity of treatment effect and patient selection

One of the most important insights from the accumulated evidence is that the benefit of PFO closure is not uniform across all patients. Instead, the treatment effect varies according to PFO anatomical characteristics, patient age, vascular risk profile, and the likelihood that the index stroke is truly PFO-mediated rather than incidental.

This heterogeneity helps explain the differing results between early and later trials and underpins the current emphasis on careful patient selection.^{14,19,20,46,48,61,76}

9.1. Shunt size

Among anatomical factors, shunt size appears to be one of the strongest modifiers of treatment benefit. Meta-analyses have shown that patients with moderate-to-large or large right-to-left shunts derive substantially greater benefit

from PFO closure compared with those with small shunts. In contrast, patients with small shunts show little or no clear benefit.

The clinical relevance of this difference is reflected in the number needed to treat, which is significantly lower in patients with larger shunts compared with the overall population.^{14,46,48,76}

These findings help explain why earlier trials that enrolled patients irrespective of anatomical risk often reported weaker results, whereas later studies enriched for patients with large shunts were more likely to demonstrate a clear treatment effect.^{14,18,71}

Quantitative grading criteria help standardize what constitutes a “large” shunt in practice. On agitated saline contrast studies, shunt severity is conventionally classified using the International Consensus Criteria: no microembolic signals (negative), 1–10 signals (mild/small shunt), more than 10 signals without a curtain pattern (moderate shunt), and a curtain pattern, in which individual signals can no longer be distinguished (large/severe shunt). Transcranial Doppler applies the same signal-based framework and is regarded as a highly sensitive, noninvasive complement to echocardiography for both initial shunt detection and grading.²⁷ Anatomical diameter provides a complementary quantitative threshold: a PFO diameter of 2 mm or greater was among the defining high-risk anatomical criteria in the DEFENSE-PFO trial, alongside ASA and septal hypermobility, and this cutoff has since been widely adopted as a practical anatomical marker of high-risk PFO morphology.^{9,61} Together, these echocardiographic, Doppler-based, and anatomical thresholds allow a more reproducible classification of

shunt severity than descriptive terminology alone, and directly support the anatomical criteria embedded in contemporary risk stratification and closure trial eligibility.

9.2. Atrial septal aneurysm

Atrial septal aneurysm adds an important dimension to treatment-effect heterogeneity. Patient-level analyses have shown that individuals with both a large shunt and coexisting ASA derive the greatest reduction in recurrent stroke following PFO closure. In contrast, patients with small shunts and no aneurysm appear to gain little benefit²⁰ (Table 2).

This interaction is clinically significant, as it suggests that ASA should be considered in conjunction with shunt size rather than in isolation. The presence of both features identifies a subgroup in whom the PFO is most likely to be causally related to the index event and in whom closure provides the greatest absolute benefit.^{20,23}

9.3. Age-related effects

The relationship between age and treatment benefit is complex and closely linked to overall stroke mechanism. Risk stratification tools such as the RoPE and PASCAL scores, which incorporate age alongside vascular risk factors, have shown that patients with higher scores, typically younger individuals without traditional vascular risk factors, derive greater benefit from PFO closure.¹⁹

Within the age range studied in most randomized trials (18–60 years), treatment benefit appears to be broadly consistent across age groups. However, the magnitude of benefit is influenced by the likelihood that the stroke is PFO-mediated rather than related to alternative vascular mechanisms.⁵³

Table 2. Effect of patent foramen ovale closure on recurrent stroke by shunt size and atrial septal aneurysm status

Anatomical category	aHR (95% CI)	ARR at 2 years	Clinical implication
Large shunt + ASA	0.15 (0.06–0.35)	5.5% (2.7%–8.3%)	Greatest benefit; closure strongly recommended
Large shunt, no ASA	0.27 (0.14–0.56)	1.0%	Meaningful relative benefit; individualized decision
Small shunt + ASA	0.36 (0.17–0.78)	1.0%	Moderate relative benefit; careful case selection
Small shunt, no ASA	0.68 (0.41–1.13)	1.0%	Little or no benefit; closure not routinely indicated

Note: Data are from an individual patient data meta-analysis of six randomized clinical trials involving 3,740 patients. The median follow-up was 57 months. The interaction *p*-value was 0.02. Adapted from Mas *et al*.

Abbreviations: aHR: Adjusted hazard ratio; ARR: Absolute risk reduction; ASA: Atrial septal aneurysm; CI: Confidence interval.

In older patients, available data are more limited and less definitive. Observational studies suggest that selected individuals over 60 years of age may still benefit from closure, particularly when high-risk anatomical features are present. At the same time, these patients tend to have higher overall recurrence and adverse event rates, reflecting a greater burden of competing stroke mechanisms.^{32,61}

9.4. Vascular risk factors and thrombophilia

The burden of conventional vascular risk factors also influences both baseline recurrence risk and response to PFO closure. Hypertension, higher overall vascular risk profiles, and thrombophilia have all been associated with recurrent events following closure. These findings suggest that anatomical closure does not eliminate non-PFO-related stroke mechanisms, and that some patients remain at risk due to coexisting vascular or hematologic factors.^{39,40,78,79}

Thrombophilia is particularly relevant in this context. Cohort data have shown that a substantial proportion of recurrent stroke or TIA events may be attributable to underlying thrombophilic or hematologic conditions.³⁹ Similarly, systematic reviews have reported higher recurrence rates in patients with thrombophilia compared with those without.

These observations highlight that, in patients with hypercoagulable states, PFO closure alone may be insufficient, and a more comprehensive secondary prevention strategy, including appropriate antithrombotic therapy, may be required.⁴⁰

9.5. Residual shunt and recurrence after closure

Residual shunting after attempted closure is an important determinant of long-term outcomes. Patients with persistent moderate or large residual shunts have higher rates of recurrent events compared with those who achieve complete closure. This relationship links technical success directly to clinical effectiveness and highlights the importance of appropriate device selection and post-procedural follow-up.

It also provides a mechanistic explanation for why devices with higher rates of complete closure are associated with better long-term neurological outcomes.^{7,42}

These findings underscore that the benefit of PFO closure depends less on the presence of a PFO than on the likelihood that it is pathogenic. Large shunts, the presence of ASA, a low burden of competing vascular risk factors, and successful complete closure define the profile of patients most likely to benefit.^{14,19,20}

In practice, these variables are not weighed in isolation but integrated at the bedside: age sets the baseline probability of an embolic mechanism, neuroimaging pattern and PFO anatomy refine it, and the RoPE score and PASCAL classification formalize this into a single estimate of causal likelihood that guides the choice between closure, antiplatelet therapy, and anticoagulation.

10. Explanations for the divergent findings of early and later trials

The contrast between early neutral trials and later positive studies is a defining feature of the PFO literature. Accumulating evidence suggests that this shift reflects important changes in trial design, patient selection, device performance, comparator therapy, and duration of follow-up, rather than the simple accumulation of more data.^{14,16,18,20,35,43,51,52}

10.1. Anatomical enrichment

Early trials enrolled patients across a broad range of PFO anatomical characteristics, a strategy that likely diluted the treatment effect by including many individuals with small shunts or otherwise low-risk features.¹⁸ In contrast, later studies deliberately enriched their populations for patients with high-risk anatomical features, particularly large shunts, ASA, or both.^{6,9,18,71} This shift in enrollment fundamentally increased the likelihood that the PFO was causally related to the index stroke and, consequently, the probability that closure would provide clinical benefit.^{14,20}

10.2. Device evolution

Device technology has evolved substantially over time. The device used in CLOSURE I was later recognized to have a less favorable safety and efficacy profile, with higher rates of atrial fibrillation and device-related thrombus formation.

In contrast, later studies used newer-generation devices such as the Amplatzer and GORE systems, which demonstrated higher rates of complete closure and improved safety profiles.

Consistent with this, pooled analyses restricted to Amplatzer-based studies have shown more favorable stroke outcomes compared with analyses that included earlier-generation devices.^{16,42,43}

10.3. Medical therapy heterogeneity

The comparator arm also evolved over time. Earlier trials often allowed a combination of antiplatelet therapy and anticoagulation, whereas later studies—such as CLOSE and REDUCE—restricted medical therapy to antiplatelet agents alone.

Because anticoagulation may be more effective than antiplatelet therapy in preventing recurrent stroke in some patients, earlier trial designs may have made the medical arm more competitive, thereby reducing the apparent benefit of PFO closure.^{10,18,35,51}

10.4. Duration of follow-up

Follow-up duration also played an important role. In populations with low annual event rates, treatment effects may take several years to become evident. Meta-regression analyses have suggested that longer follow-up is associated with a greater observed benefit of PFO closure. The RESPECT trial provides a clear example of this pattern: initial analyses were neutral, whereas extended follow-up demonstrated a significant reduction in recurrent stroke.^{7,52}

These four factors together explain the shift from early uncertainty to later confidence in the benefit of PFO closure. As trials increasingly focused on appropriate patient selection, used improved device technology, applied more consistent comparator strategies, and incorporated longer follow-up, the treatment effect became more apparent.

11. Special populations and real-world practice

Although randomized trials provide the foundation of evidence, a growing body of observational data has expanded understanding of how PFO closure performs in populations underrepresented in trials and in routine clinical practice. While these data do not carry the same level of evidence as randomized studies, they offer important insights into clinically relevant scenarios.

11.1. Older patients

Most randomized trials limited enrollment to patients 60 years of age or younger. However, more recent observational studies have examined outcomes in older adults. In one cohort of patients aged 60 years or older, PFO closure was associated with lower rates of composite ischemic stroke or TIA, particularly among those with high-risk anatomical features.

At the same time, recurrence and adverse event rates were higher in this group overall, reflecting the greater influence of competing vascular mechanisms in older patients. These findings highlight the importance of careful patient selection and individualized clinical decision-making in this population.^{32,61}

The biological basis for this pattern is straightforward. Older patients accumulate, over time, a growing set of alternative explanations for stroke that simply have not had time to develop in a younger person: subclinical

atrial fibrillation becomes more common, atherosclerotic disease of the large vessels progresses, and small-vessel disease from long-standing hypertension or diabetes becomes more prevalent. A high-risk PFO does not disappear or become less anatomically significant with age, but it must increasingly compete with these other plausible mechanisms for causal attribution to any given stroke. This is reflected in the lower RoPE and PASCAL scores typically seen in older patients, and it explains why closure can still provide a real, measurable benefit in carefully selected older individuals with high-risk anatomy and few competing risk factors, while providing progressively less benefit as the burden of alternative vascular disease grows.^{19,20}

11.2. Patients with transient ischemic attack, thrombophilia, or recurrent events

Evidence in patients presenting with TIA rather than stroke is more limited. However, registry data suggest that procedural success and long-term neurological outcomes may be comparable to those observed in stroke cohorts, despite generally lower RoPE scores.⁸⁰

Patients with thrombophilia or multiple prior embolic events represent a higher-risk subgroup, in whom recurrence may persist even after closure.^{39,40,81} In these individuals, PFO closure may still provide benefit, but management often requires a broader assessment of thromboembolic risk and consideration of adjunctive medical therapy.

11.3. Timing of intervention

In randomized trials, PFO closure was typically performed within six to nine months of the index event. Observational data suggest that delayed closure may still be associated with favorable outcomes, although robust randomized evidence beyond these timeframes is limited.⁸²

This is clinically relevant, as delays in referral and diagnostic evaluation are common in real-world practice, and decisions regarding closure often occur outside the strict timelines of clinical trials.

11.4. Procedural simplification and durability

Real-world procedural practice has evolved alongside advances in device technology and operator experience. Contemporary observational series demonstrate that PFO closure can be performed with low complication rates, often using simplified fluoroscopy-guided approaches and enabling same-day discharge.^{32,57}

Long-term follow-up supports the durability of newer devices, with low rates of recurrent stroke and little evidence of late structural device failure.^{32,64,74,77}

These observations extend the clinical relevance of randomized trial data, suggesting that PFO closure remains both effective and feasible in routine practice when performed in experienced centers. At the same time, they highlight the importance of individualized clinical decision-making in patients who fall outside traditional trial populations, including older individuals and those with thrombophilia.^{32,39,61,77,80,82}

12. Current guideline recommendations

Guideline recommendations now reflect a decade of accumulated trial data, pooled analyses, and better patient selection—though the major documents don't all get there the same way. The common ground: PFO closure is recommended or strongly considered in patients 18 to 60 years old with a cryptogenic ischemic stroke, no alternative cause identified, and high-risk PFO anatomy.^{7,8,21,31,83}

The 2021 AHA/ASA secondary prevention guideline actually issues two recommendations here, and the stronger one is easy to overlook. Before it says anything about closure versus medical therapy, it gives a Class I recommendation—its highest category—to making that decision jointly among patient, cardiologist, and neurologist, weighing the probability that the PFO is actually causal. Only then does it address closure itself: Class IIa for choosing transcatheter closure plus long-term antiplatelet therapy over antiplatelet therapy alone, in patients 18 to 60 with a nonlacunar stroke of undetermined cause and high-risk PFO anatomy.⁸⁴ Where the anatomy is not high-risk, the same guideline downgrades to Class IIb, calling the benefit of closure “not well established” rather than endorsing or ruling it out.

The 2024 European Stroke Organisation (ESO) guideline gets to the same place through a formal GRADE process: closure plus antiplatelet therapy beats antiplatelet therapy alone in patients 18–60, with the benefit concentrated in large shunts, ASA, or both, and it builds the PASCAL classification directly into patient selection.⁸³

The European position paper arrives at the same starting point by a different route. A formal consensus of eight European scientific societies—including the European Association of Percutaneous Cardiovascular Interventions and the ESO—independently rates interdisciplinary, individualized decision-making as a “strong” statement in its own right, ahead of any statement about closure thresholds.⁸⁵ Two documents developed independently converging on process before they converge on any specific anatomical threshold is worth noting: neither treats PFO closure as a decision one specialty should make alone.

Age 60 is where these documents diverge most. The

AHA/ASA guideline is the most explicit: closure in patients older than 60 “should rarely be performed, and only in very unusual clinical circumstances,” since no randomized trial has enrolled this age group.⁸⁴(pe412) The ESO guidelines are less categorical, treating closure past 60 as a case-by-case decision reserved for high-risk anatomy and an otherwise clean work-up, rather than excluding it outright.⁸⁵

Within the medical therapy arm, guidance increasingly distinguishes antiplatelet therapy from anticoagulation rather than treating medical management as a single strategy. Antiplatelet therapy remains the default for most patients, while anticoagulation is generally favored when a specific thrombophilic disorder is confirmed, a venous thromboembolic source is identified or strongly suspected, or *in situ* thrombus within the PFO tunnel is suspected, recognizing that no dedicated randomized trial has compared the two strategies head-to-head in these subgroups.^{6,35,39,40}

The shift across all of these documents is the same: PFO is not a yes/no finding to close or ignore anymore. It is a condition managed across patient selection, procedural technique, choice of antithrombotic strategy, and structured follow-up after the fact.^{61,83}

13. Controversies and future directions

Despite substantial progress, several important controversies remain. One relates to the management of patients older than 60 years, in whom observational data are increasingly supportive but randomized evidence remains limited.⁶¹ Another area of uncertainty involves patients with thrombophilia, who may remain at elevated risk despite closure and may require anticoagulation-based strategies that have not been fully evaluated in randomized trials.^{35,39,40}

Furthermore, the relative role of PFO closure versus anticoagulation also remains incompletely defined. While closure has demonstrated clear benefit over antiplatelet therapy in selected patients, direct randomized comparisons with anticoagulation are limited.^{6,35} This question is particularly relevant for individuals with strong prothrombotic tendencies or borderline anatomical risk profiles.

Additional unresolved issues include the clinical significance of residual shunting, the long-term implications of post-procedural atrial fibrillation, and the interpretation of TIA-only presentations.^{7,39,80}

Looking ahead, further progress in the field is likely to depend less on expanding closure to broader populations and more on refining patient selection. In this

context, integrating anatomical features with clinical risk stratification tools such as the RoPE score and PASCAL classification represents one of the most promising directions for future research and clinical practice.^{19,20,61}

Beyond the question of device selection, the long-term consequences of leaving a permanent metallic implant within the interatrial septum have prompted the development of bioresorbable PFO closure devices. Current nitinol-based occluders raise concerns regarding chronic low-grade inflammation, device thrombus, arrhythmia, and potential interference with future transseptal procedures—including radiofrequency ablation, left atrial appendage occlusion, and transcatheter edge-to-edge mitral valve repair.

A further debate concerns the routine versus selective use of ICE during the closure procedure. While ICE offers direct visualization of septal anatomy and transseptal puncture, its routine use adds procedural time, cost, and complexity. Comparative data suggest that fluoroscopy-guided closure, with ICE reserved for anatomically complex cases, achieves complication rates statistically indistinguishable from routine ICE guidance, including arrhythmic complications (1.3% vs. 1.2%) and vascular complications (0.5% vs. 2.3%).⁵⁷ This has supported a shift toward selective rather than routine ICE use in experienced centers, simplifying the procedure and enabling same-day discharge in the great majority of patients, while reserving ICE for cases where septal anatomy is unclear on fluoroscopy alone.

Health economic considerations also remain underexplored in most reviews of this topic. A detailed cost-effectiveness analysis pooling five randomized trials (3,404 patients) found that PFO closure reached conventional cost-effectiveness (defined as less than US\$50,000 per quality-adjusted life-year gained) at 2.7 years after the procedure, despite an initial excess cost driven almost entirely by procedural expenditure.⁸⁶ Beyond this threshold, the cumulative cost of medical therapy was projected to exceed that of closure after approximately 55 years of follow-up, reflecting the front-loaded cost of the procedure against the long-term, recurrent costs of medical management and recurrent events. These findings support the economic, as well as clinical, rationale for closure in appropriately selected younger patients with high-risk anatomy, though cost-effectiveness thresholds and healthcare financing structures vary considerably across countries and should not be assumed to generalize uniformly.

Finally, screening and management strategies in high-risk occupational populations, particularly divers

and pilots, warrant specific mention, since even a single paradoxical embolic event can be catastrophic in these groups. Current European position statements advise against routine PFO screening in either recreational divers or conventional pilots, given the mismatch between the high background prevalence of PFO and the low absolute incidence of decompression sickness or altitude-related events. However, selective screening is considered reasonable in professional divers with high-risk work activity and in select military pilots undertaking intensive high-altitude flight activity, given the disproportionate consequences of a single event in these occupations.⁸⁵ Registry data support a graded, risk-stratified approach in divers: in the DIVE-PFO registry of 829 divers, a screening and risk-stratification strategy using shunt grading was associated with a significant reduction in decompression sickness across all groups, with divers found to have a high-grade shunt offered either catheter-based closure or a conservative diving strategy, while those with low-grade shunts were advised toward conservative diving alone; no decompression sickness events occurred in the closure group during follow-up.⁸⁷ These occupational contexts illustrate that the threshold for considering closure may reasonably be lower than in the general population, even though formal randomized trial data specific to divers and pilots remain absent.

Bioresorbable devices address these limitations by providing temporary mechanical closure during the endothelialization period, after which the device degrades completely, leaving only native fibrous septal tissue without a permanent implant.

The first randomized controlled trial evaluating this technology was published in *Circulation* in 2026. Zhang *et al.*⁸⁸ randomized 190 patients with PFO across seven centers to receive either a novel biodegradable device composed of polydioxanone and poly-L-lactic acid ($n = 96$) or a conventional nitinol device ($n = 94$). Both materials carry established FDA approval for clinical use in surgical sutures and intravascular stents since the 1980s. At six-month follow-up, successful PFO closure was achieved in 90.63% of patients in the biodegradable group and 91.49% in the nitinol group, confirming noninferiority. No deaths, device embolism, thrombus formation, or erosion were observed in either group throughout the entire 24-month study period, with zero cases of atrial fibrillation recorded in either group at any timepoint. The biodegradable device fully disappeared on echocardiography in all patients by 24 months after implantation, leaving no residual device material. While these findings represent an important proof of concept, the limited sample size, short follow-up, single-country enrollment, and use of a Chinese nitinol

control device necessitate larger multinational trials before this technology can be considered for routine clinical practice.⁸⁸

14. Conclusion

Our understanding of PFO-associated stroke has evolved considerably over time. What was once seen as an incidental anatomical finding is now recognized, in selected patients, as a potentially modifiable cause of embolic stroke. This shift has been driven not only by randomized trials but also by a deeper understanding of heterogeneity of PFO anatomy and stroke mechanisms.

Current evidence shows that percutaneous PFO closure can reduce the risk of recurrent ischemic stroke, particularly in younger patients with high-risk anatomical features such as large right-to-left shunts or an associated ASA. At the same time, this benefit is not seen in all patients. The presence of competing vascular risk factors, thrombophilia, or alternative stroke mechanisms reduces the likelihood that the PFO is causally related to the index event and therefore reduces the expected benefit of closure.

From a safety perspective, closure is generally well tolerated. The main trade-off is an increased risk of atrial fibrillation, which in most cases occurs early after the procedure and is often transient.

As a result, the field has moved away from a simple yes-or-no approach to PFO closure. Instead, clinical decisions are increasingly guided by individualized risk assessment. Tools such as the RoPE score and the PASCAL classification help estimate how likely it is that a PFO is causally related to stroke, and support more tailored decision-making.

Looking ahead, the key challenge is not to expand closure to broader populations, but to better define which patients derive the greatest benefit. Important questions remain, particularly regarding older patients, the role of anticoagulation in higher-risk groups, and the long-term implications of post-procedural atrial fibrillation.

Ultimately, management of PFO-associated stroke requires an individualized approach, where anatomical findings, clinical context, and evolving evidence are integrated to guide the best treatment strategies.

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Ziyad M. Hijazi is a consultant for Occlutech GmbH

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