Review

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Pill or plug? Rethinking secondary stroke prevention for PFO patients

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Abstract

Although patent foramen ovale (PFO) is common in the general population, it is notably more prevalent among patients with cryptogenic stroke (CS). The optimal management of PFO remains uncertain, with ongoing debate over the effectiveness of medical therapy compared to closure procedures. Medical treatments typically include antiplatelet drugs such as aspirin, clopidogrel, and dipyridamole, which aim to prevent arterial thrombus by inhibiting platelet aggregation, or anticoagulants like warfarin and direct oral anticoagulants (DOACs), which work on the coagulation cascade to reduce venous thrombus formation and embolic risk. In contrast, closure techniques aim to eliminate the anatomical conduit for emboli. Transcatheter closure using devices such as Amplatzer or Gore has demonstrated high success and safety rates, with evidence from trials including RESPECT, CLOSE, and REDUCE supporting reduced risk of recurrent CS. However, atrial fibrillation remains a common early complication. To address concerns about implants or nickel allergies, the NobleStitch EL suture system offers a promising device-free alternative. Patient selection for closure relies on risk stratification tools such as the RoPE and PASCAL scores, while contraindications include cardiac thrombus, endocarditis, or other potential embolic sources. Overall, current evidence indicates that closure may benefit carefully selected patients, yet medical therapy remains crucial, especially when closure is contraindicated or patient preference guides the decision. Further research is required to refine selection criteria, weigh long-term safety against efficacy, and clarify the comparative benefits of medical versus closure strategies. This review aims to synthesize the available evidence.

Keywords: anticoagulation, antiplatelet therapy, medical therapy, patent foramen ovale (PFO), PFO closure, stroke

Introduction

Ischemic stroke remains a major global health challenge, affecting millions of lives worldwide, and approximately 40% of them are classified as cryptogenic. Previous studies have identified patent foramen ovale (PFO) to be prevalent in 25% of the general population and approximately 40%–50% in patients with cryptogenic stroke (CS)[1]. Therefore, if not effectively managed, PFO can pose a higher risk of stroke recurrence, which presents a significant challenge due to rising stroke-related complications, including physical disability, bowel and bladder issues, UTI, and pneumonia[2–4]. Therefore, efficient management of PFO in CS patients has become essential.

Currently available therapies for secondary prevention of CS include antiplatelet agents and anticoagulants. While this treatment offers some benefit, many patients continue to experience recurrent neurological events, with a concern of higher risks of bleeding. This has led to clinical trials and observational studies assessing the efficacy of PFO closure as an alternative to medical therapy. Previous trials, including REDUCE, CLOSE, DEFENSE-PFO, and the long-term follow-up of RESPECT, have suggested

HIGHLIGHTS

- Stroke causes 5 M + deaths yearly; 40% of ischemic strokes are cryptogenic.
- Antiplatelets and anticoagulants help prevent recurrent cryptogenic strokes.
- PFO closure is explored as an alternative to reduce stroke recurrence risks.
- Antiplatelets are safe, affordable, and widely used in medical stroke therapy.
- Anticoagulants may reduce strokes more than antiplatelets but raise bleeding risk.

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that PFO closure can be superior to medical treatment alone, whereas few trials have reported the opposite. These trials, along with meta-analyses such as that by Hammad *et al*[5], also highlighted atrial fibrillation as a possible risk factor for PFO closure; however, a recently published randomized controlled trial (RCT) by Liu *et al*[6] found no significant association between atrial fibrillation and PFO closure.

To provide a better understanding of the existing evidence, this narrative review aims to evaluate the efficacy of PFO closure compared to medical therapy for the secondary prevention of ischemic stroke and transient ischemic attack (TIA) and assess its safety profile to offer practical, evidence-based recommendations for the management of CS in patients with PFO.

Methodology

A comprehensive literature search was performed across PubMed, Scopus, and Embase for publications from January 2000 to September 2025. The search used keywords such as "Patent Foramen Ovale," "cryptogenic stroke," "closure," "antiplatelet," "anticoagulant," "Amplatzer," "Gore," "NobleStitch," and "RoPE score." To expand coverage, a seeding method was employed: relevant articles prompted reviews of their references for additional relevant studies. Inclusion criteria were peer-reviewed clinical trials, meta-analyses, and observational studies that assessed medical therapy or closure methods for PFO in patients with CS. Exclusions included case reports, non-English publications, and studies on non-CS populations.

Pathophysiology and Mechanism

The foramen ovale is an opening between the left and right atria that allows blood to pass through it during fetal life. It forms when the septum primum fails to fuse with the septum secundum. Usually, after birth, pressure in the left atrium causes the foramen ovale to close; however, sometimes it persists, resulting in a PFO. Later in life, this creates an intracardiac right-to-left shunt, allowing venous thrombi to bypass the lungs and enter arterial circulation directly. This phenomenon, known as paradoxical embolism, enables the clot to travel to the brain, where it can occlude cerebral arteries and ultimately result in stroke and TIA[7,8]. Where it can occlude cerebral arteries and ultimately result in stroke and tia. In patients with cryptogenic stroke, where no conventional etiology, such as large-vessel atherosclerosis or atrial fibrillation,n is identified, the presence of a PFO provides a plausible pathogenic mechanism. Figure 1 illustrates this pathway, demonstrating how a PFO permits a thrombus to circumvent the pulmonary circulation and access the cerebral circulation, in contrast to the typical atrial anatomy.

Several studies have attributed various risk factors to the occurrence of stroke in patients with PFO. Among them, a significant concern is the development of deep venous thrombosis (DVT)[8], since it can directly lead to paradoxical embolism and ultimately escalate the chances of stroke. Moreover, both the size of the PFO and the degree of shunting are essential, with larger defects and greater shunt volumes associated with a higher risk of stroke than smaller defects and lower shunt volumes[7]. Other potential risk factors include young age and the presence of an atrial septal aneurysm[7]. Additionally, male gender and hypertension have also emerged as independent predictors of stroke in PFO patients[9].

Various diagnostic modalities are utilized to detect PFO. Initial diagnosis can be made by using transthoracic echocardiography and transcranial Doppler (TCD) ultrasound, combined with a bubble test. These techniques are preferred due to their non-invasive nature, lower cost, and higher sensitivity (particularly of TCD)[10,11]. The transesophageal echocardiogram (TEE) bubble study is further used to confirm the diagnosis. It is considered a gold standard due to its ability to provide more detailed, direct images of the heart[11].

Medical therapy for PFO-related stroke/TIA

For patients with PFO and a history of CS or TIA, medical therapy remains a foundation stone of management, primarily when device closure is not performed or feasible. Antiplatelet therapy and anticoagulants are two primary approaches, each with distinct mechanisms of action and associated risk profiles. Antiplatelet therapy, such as aspirin, clopidogrel, and dipyridamole, inhibits platelet aggregation and reduces thrombus formation in the arteries[12]. Antiplatelets are readily used due to their ease of administration, relatively low cost, and promising safety profile. Clinical trials such as RESPECT and REDUCE, although primarily designed to assess device closure, included medical therapy arms that were mainly antiplatelet-based, providing indirect evidence for their effectiveness[13,14]. The primary limitation of antiplatelets is the ongoing risk of recurrence, especially in patients with high-risk anatomical features such as a large shunt or atrial septal aneurysm, or in those with an underlying tendency toward venous thromboembolism (VTE)[15].

Single antiplatelet therapy (SAPT) vs Dual antiplatelet therapy (DAPT)

Currently, there are no large-scale RCTs directly comparing the effectiveness of single antiplatelet therapy (SAPT) versus dual antiplatelet therapy (DAPT) in preventing stroke or TIA, regardless of whether patients have undergone PFO closure. Three short-duration RCTs, enrolling patients within 12–24 hours of stroke, indicated that DAPT was associated with lower rates of recurrent stroke compared to SAPT[16–18]. However, two longer trials lasting over 18 months did not demonstrate a significant advantage for DAPT over SAPT[19,20]. Guidance remains based on procedural protocols, observational studies, and expert consensus. The European Stroke Organisation (ESO) 2024 guidelines recommend initiating DAPT, followed by a long-term SAPT regimen, as per routine procedures used in most trials. There are also no evidence-based recommendations regarding the optimal duration of SAPT[21].

Anticoagulants, traditionally with vitamin K antagonists such as warfarin and DOACs, target the coagulation cascade, preventing thrombus formation on the venous side and embolic propagation through the PFO. DOACs are increasingly being used to avoid thrombosis in patients with CS and thrombophilic predisposition. For instance, a retrospective cohort of 160 patients reported lower rates of recurrent VTE and thrombotic events in patients with thrombophilia, supporting its effectiveness as compared to standard anticoagulants[22]. Building on this, the 2025 Guidelines for DOACs by Tran *et al* suggest that DOACs are highly effective in managing atrial fibrillation, VTE, and thrombophylaxis post-surgery. For patients with high-risk diseases such as inherited thrombophilia, DOACs are readily indicated, except for those with antiphospholipid syndrome, especially the triple-positive types, who would benefit from

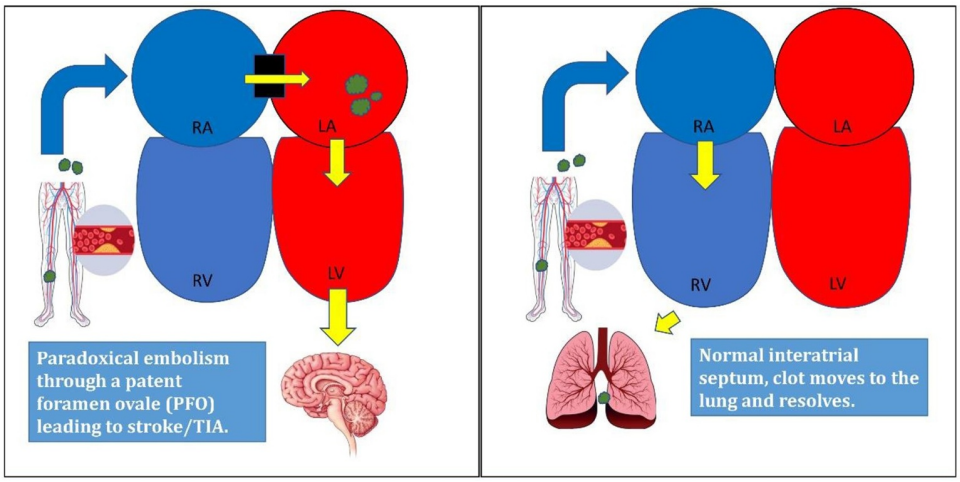

Figure 1. A schematic comparison of a normal interatrial septum (right) and a patent foramen ovale (left) illustrating paradoxical embolism and the potential pathway of a thrombus resulting in stroke or transient ischemic attack (TIA).

Warfarin instead[23]. Although high-quality literature backed clinically for the use of DOACs is evident, trials reporting on PFO-specific populations are lacking and limited to observational and cohort studies. Consequently, further prospective studies are needed to strengthen the evidence base in this subgroup.

Data from the CLOSE trial directly compared anticoagulants with antiplatelets, showing a trend toward fewer recurrent strokes in the anticoagulation group[24]. This aligns with findings from a systematic review and meta-analysis, which suggests that standard anticoagulation may be more effective than antiplatelet therapy in preventing recurrent ischemic events[15]. However, warfarin is associated with a more pronounced bleeding risk, which has driven interest toward DOACs as a safer alternative[25]. Although the evidence is not entirely consistent, a large systematic review and meta-analysis of over 13 000 patients treated with either DOACs or antiplatelets found no significant difference in stroke prevention between the two strategies[26].

Overall, clinical evidence suggests that antiplatelet therapy is safe, convenient, and effective for many patients, particularly those with lower-risk PFO anatomy or without thrombotic risk factors. Anticoagulation may be more effective at preventing recurrence, especially in patients with VTE or high-risk anatomical features; however, it requires careful assessment of bleeding risk[15,27]. Furthermore, data remain limited as few trials have specifically compared antiplatelet and anticoagulant strategies. Most evidence on anticoagulation is derived from studies conducted before the introduction of DOACs.

Patient selection is therefore essential. For younger patients with CS and high-risk PFO anatomy who may not be suitable for closure, anticoagulation can be considered. Conversely, for patients at a higher risk of bleeding with comorbidities, or for whom ease of use is a priority, antiplatelet therapy remains a reasonable option. The choice between SAPT and DAPT has not been extensively researched. Current guidelines, including those from the American Academy of Neurology and the American Heart Association/American Stroke Association, generally regard both strategies as acceptable. Individual risk-benefit analysis, comorbidities, and patient preferences guide the primary decision[28,29]

PFO closure:Techniques and Devices

For patients with a CS and a PFO, clinicians use transcatheter closure as a potent therapeutic strategy to prevent recurrence. This intervention primarily employs two FDA-approved devices: the Amplatzer™ PFO Occluder and the Gore™ Cardioform Septal Occluder. The Amplatzer features a nitinol mesh and polyester fabric, providing high radial strength and achieving closure rates of over 95%. Conversely, the Gore Cardioform device consists of a nitinol frame covered with expanded polytetrafluoroethylene (ePTFE), offering superior flexibility and conformability that may reduce the risk of erosion in complex anatomies[30]. Both devices promote rapid endothelialization and high anatomic closure rates across complex and straightforward PFO anatomies, supporting long-term benefits in preventing secondary strokes, as evidenced by real-world patient outcomes[31].

While these implantable devices have demonstrated excellent efficacy, some patients may prefer alternatives due to concerns about the permanence of implants, nickel exposure, or future procedural needs. For such cases, a “deviceless” option called the NobleStitch EL suture-mediated system is gaining attention. Although it shows promise as an alternative, further studies are needed to fully clarify its benefits[32].

New clinical data have significantly expanded our understanding of its performance. In the most significant available cohort to date (703 patients with a median follow-up of 4 years), Gaspardone *et al* reported that the system achieved effective closure (residual shunt ≤ grade 1) in roughly 89% of patients and did so without any recurrent strokes or TIAs; only one patient had a brief episode of atrial fibrillation[33]. When we compare this with traditional double-disc occluders like Amplatzer or Gore Cardioform, we see that devices typically achieve closure rates above 95% but also carry a measurable risk of new-onset atrial fibrillation, usually around 5%–6%

and reaching up to 21% in some studies[34]. In contrast, NobleStitch studies have not reported device-related atrial fibrillation, and a recent retrospective comparison has also suggested that arrhythmias were found only in the device-treated patients (three of 55) despite having similar technical success rates[32].

Regulatory pathways also differ. The NobleStitch EL holds a CE mark in Europe for PFO closure; however, in the United States, it is cleared by the FDA only for general cardiovascular suturing, not specifically for PFO[35]. Although these emerging data are encouraging – especially for patients who prefer not to have a permanent implant – the current evidence base remains predominantly observational. Therefore, it is crucial to conduct larger, well-designed randomized trials to determine whether suture-mediated closure can consistently match, or even exceed, the results of standard occluder-based device closure[32,33].

The PFO closure procedure involves several key steps. The operator inserts a catheter into the femoral vein and guides it through the PFO under fluoroscopic and echocardiographic imaging (intracardiac or transesophageal). They then deploy the device, typically starting with the left atrial disc and overlapping it with the right atrial disc to cover the septum. The classical "Pacman sign" on fluoroscopy, along with the gentle tug test, confirms adequate device stability and closure before release. Post-procedure management typically consists of short-term dual antiplatelet therapy (usually between 1 and 6 months) followed by single antiplatelet therapy adjusted to the patient's bleeding risk as well as other parameters. Patients undergo early mobilization and rhythm monitoring to detect potential atrial fibrillation[30,36].

PFO closure is primarily used in the secondary prevention of CSs, where no alternative cause has been identified. To determine the likelihood that the PFO caused the stroke, clinicians use tools like the RoPE score and PASCAL classification, discussed later on. These tools consider factors such as patient age, vascular risk factors, stroke patterns, and PFO characteristics (e.g., large shunt or atrial septal aneurysm). By assessing these details, health care providers can identify patients who would benefit most from closure[37]. Although most studies have focused on younger adults, a growing body of observational data supports the careful use of PFO closure in older patients (≥60 years) when the likelihood of the PFO causing the stroke is strong, and other potential causes have been ruled out[38]. There are, however, absolute contraindications to the procedure. Closure should not be attempted if there is any thrombus within the heart, if there is active infective endocarditis, or if there is any other, more probable embolic source identified as atrial fibrillation or unstable atherosclerotic plaque[30,36].

Experienced centers report that transcatheter PFO closure maintains an excellent safety profile with very low rates of major vascular or device complications[31]. Nevertheless, atrial fibrillation remains the most frequently observed periprocedural complication, typically presenting in the early postoperative phase due to local irritation or stretch, and it usually responds well to standard treatment. Long-term follow-up data suggest that beyond the first few months, patients do not experience a significant increase in atrial fibrillation risk[39]. Clinicians may encounter rare complications, including device-related thrombus, device embolization, residual shunt, and cardiac erosion; however, these can be prevented by applying proper technique and selecting the appropriate device size.

Key Clinical Trials Comparing Closure vs Medical Therapy

For decades, the management of CS in patients with PFO has been a subject of ongoing clinical debate, particularly concerning the prevention of recurrence through device closure or medical therapy. Initial observational studies suggested a potential benefit of device closure; however, these findings were not sufficiently conclusive to warrant a change in clinical practices. Following a series of RCTs that featured enhanced design and more meticulous patient selection, the treatment paradigm has shifted from predominantly medical therapy to PFO closure. Table 1 provides a summary comparing the major trials and recent meta-analyses, outlining study design, patient populations, primary outcomes, and adverse events.

A multicenter, RCT called RESPECT 2017 compared PFO closure with Amplatzer PFO Occluder to medical therapy (aspirin, warfarin, clopidogrel)[13]. The population consists of 980 adult patients aged 18–60 years (499 in the closure group vs 481 in the medical therapy group), with a median follow-up of 5.9 years. The study found a significant reduction in recurrent ischemic stroke in the first group, specifically with large shunts or atrial septal aneurysms. The relative difference in the rate of recurrent ischemic stroke between PFO closure and medical therapy alone was significant; however, the rate of VTE was higher in the closure group, exceeding that in healthy populations, which suggests that CS and PFO slightly increase the long-term risk of venous thromboemboli. A total of 25 serious adverse events were observed in 499 patients in the leading intervention group. The trial is randomized, which strengthens its reliability; however, an open-label design could introduce bias that might affect the outcome. There was a higher dropout rate in the medical therapy group (33%), which may have skewed the results. Selecting adults aged 18–60 would limit the implications to older people or those with multiple comorbidities.

Another triple-armed trial, CLOSE 2017[24], consisted of PFO closure plus long-term antiplatelet therapy with an antiplatelet-only group and an anticoagulation group. The trial included 663 patients with recent CS attributed to device-induced closure with an associated atrial septal aneurysm or large right-to-left interatrial shunt. The median follow-up period was 5.3 years. The rate of recurrent stroke was significantly lower with PFO closure plus long-term antiplatelet therapy than with antiplatelet therapy alone. The number of serious adverse events did not differ significantly between the treatment groups. However, the risk of atrial fibrillation was considerably higher in the closure group, with cases detected within 1 month after the procedure, but did not recur during the follow-up period of 4.4 years. In the antiplatelet therapy group, patients with PFO and atrial septal aneurysm had a stroke. Randomization across three arms strengthens the comparison. However, the three-arm design may add complexity, variation in drug choice, dosing, and lack of adherence to the treatment. Generalizability is restricted because the trial only enrolled patients with large shunts associated with atrial septal aneurysms.

Furthermore, the REDUCE trial[14], consisting of 664 patients with CS and PFO, compared closure with the Gore device vs

Table 1

A comprehensive summary of all major trials and recent meta-analysis pertaining to medical therapy and PFO device closure.

Study Name	Sample size	Intervention	Study Design	Inclusion criteria	Exclusion Criteria	Main Outcomes	Adverse Events	Limitations
RESPECT	980	• PFO closure group: PFO closure. • Medical therapy group: antithrombotic therapy	Multicenter, randomized, open-label, controlled clinical trial.	Patients aged 18–60 with a history of cryptogenic ischemic stroke and confirmed PFO		Lower incidence of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death, in PFO closure group versus medical therapy group.	Serious adverse events occurred in 40.3% of the PFO closure group versus 36.0% with medical therapy ($P = 0.17$). Periprocedural atrial fibrillation (7 cases) resolved before discharge. Pulmonary embolism and deep-vein thrombosis were slightly higher in the PFO closure group (0.41 vs. 0.11 and 0.16 per 100 patient-years, respectively). Other events included allergic reactions, cardiac perforation, bleeding, hematoma, and vasovagal reactions.	The trial did not require prolonged cardiac monitoring, though occult atrial fibrillation is rare in cryptogenic stroke among 18–60-year-olds. Unequal follow-up duration also introduced variability, as some medical-therapy patients may have been lost to follow-up after receiving off-label PFO closure.
CLOSE	663	• PFO closure group: PFO closure followed by long-term antiplatelet therapy Antiplatelet only group: antiplatelet therapy alone • Anticoagulation group: oral anticoagulation	Multicenter, randomized, open-label, superiority trial.	Patients aged 16 to 60 who had a recent cryptogenic stroke linked to a PFO with atrial septal aneurysm or large shunt.	-	Significant reduction in stroke incidence in the PFO closure group.	Serious adverse events occurred in 35.7% of the PFO closure group, 33.2% of the antiplatelet-only group, 33.9% of the antiplatelet comparator group, and 33.2% of the anticoagulation group. Procedural complications affected 5.9% of PFO closure patients. Atrial fibrillation/flutter was more common after PFO closure (4.6% vs 0.9%), mostly within one month. Bleeding rates were 0.8% in PFO closure, 2.1% in antiplatelet-only, 2.3% in antiplatelet comparator, and 5.3% in anticoagulation groups.	The trial faced a lower-than-expected recruitment rate and did not include prolonged ECG monitoring, limiting its ability to detect cases of occult atrial fibrillation.
REDUCE	664	• PFO closure group: percutaneous PFO closure plus daily antiplatelet therapy. • Antiplatelet only group: only antiplatelet therapy.	Multinational, prospective, randomized, controlled, open-label trial	Patients aged 18 to 59 years who had a cryptogenic ischemic stroke within 180 days prior to enrolment.	Patients were excluded for significant large-vessel disease, small-vessel lacunar strokes, uncontrolled diabetes or hypertension, autoimmune disease, recent substance abuse, or any indication for anticoagulation.	Fewer strokes and infarctions in the PFO closure group compared to the antiplatelet-only group.	Serious adverse events occurred in 23.1% of PFO closure patients versus 27.8% in the antiplatelet-only group. Device-related events affected 1.4% of PFO closure patients. Atrial fibrillation/flutter was higher after PFO closure (6.6% vs 0.4%). There were 2 deaths in the PFO closure group, and bleeding rates were 1.8% versus 2.7% in the antiplatelet-only group.	A number of patients in the antiplatelet-only group (14 in total) underwent PFO closure outside the trial, which may have affected group integrity. Additional limitations include differing dropout rates between groups, introducing possible misclassification bias, and a low overall event count, which limits the strength of subgroup analyses.

(*Continues*)

Table 1

(Continued).

Study Name	Sample size	Intervention	Study Design	Inclusion criteria	Exclusion Criteria	Main Outcomes	Adverse Events	Limitations
DEFENSE-PFO	120	• Closure group: PFO closure (mainly with Amplatzer PFO Occluder). • Medical therapy group: antiplatelet therapy (90.2%) or anticoagulation (9.8%).	Randomized, controlled, open-label trial.	Patients with cryptogenic stroke and a high-risk PFO, defined as having: • Atrial septal aneurysm (≥10 mm excursion), or • Large PFO (≥2 mm separation at rest, or ≥2 mm with Valsalva), or • Hypermobile interatrial septum.	Major risk factors for cardioembolism (e.g., AF >30s), > 50% stenosis in a relevant cerebral artery, other specific stroke causes.	Primary Endpoint (Composite of stroke, vascular death, or TIMI major bleeding at 2 years): • 0% in closure group (0/60). • 12.9% in Medical therapy group (6/60); all were recurrent strokes. Absolute risk reduction: 12.9% ($P = 0.013$).	New atrial fibrillation occurred in 1.6% of the closure group (transient, periprocedural), and pericardial effusion also affected 1.6%. No device embolization, erosion, or thrombosis was reported.	
Hammad et al.	16 698	• Closure: PFO closure (various devices). • Medical therapy: antiplatelet or anticoagulant therapy.	Systematic review and meta-analysis (6 RCTs, 26 observational studies).	Patients with PFO and cryptogenic stroke or TIA.		PFO closure reduced recurrent ischemic neurological events, all-cause mortality, and major bleeding compared to medical therapy.	Atrial Fibrillation: Remained a safety concern, potentially linked to thromboembolic risk if new-onset.	
Satpathy et al. (2025)	20 999	• Closure: PFO closure. • Medical therapy: standard medical therapy.	Retrospective cohort study (U.S. Medicare data).	Patients >60 years hospitalized with ischemic stroke and PFO.		Lower risk of recurrent stroke with closure (1.65 vs 2.66 events/100 patient-years; HR 0.62, $P = 0.007$).	Short-term (30-day): Overall safety event rates were similar between groups. Long-term: Incidence of venous thromboembolism (VTE) and atrial fibrillation/flutter was higher in the device closure group.	
Mir et al	4416	• PFO closure + antiplatelet therapy • Antiplatelet therapy alone • Anticoagulation therapy alone	Systematic review and network meta-analysis	Included RCTs comparing PFO closure with antiplatelet or anticoagulation therapy, as well as trials comparing anticoagulation with antiplatelet therapy in patients with PFO and cryptogenic stroke.	-	In patients under 60, PFO closure likely reduces recurrent ischemic stroke compared with antiplatelet therapy but offers no clear advantage over anticoagulation. Closure carries risks of persistent atrial fibrillation and device-related complications, while anticoagulation carries a higher risk of major bleeding.	PFO closure likely provides a meaningful reduction in ischemic stroke recurrence compared with antiplatelet therapy, with moderate-certainty evidence (RD −87 per 1000 over 5 years). Compared with anticoagulation, it offers little or no difference in stroke prevention but likely has a lower major bleeding risk. However, PFO closure increases persistent atrial fibrillation and device-related complications. Anticoagulation may reduce stroke recurrence versus antiplatelets but probably increases major bleeding risk.	The small sample size, single-center recruitment, and short 90-day follow-up may limit the study's statistical power and the assessment of aspirin-plus-clopidogrel efficacy and safety.

antiplatelet therapy with a median follow-up of 3.2 years. The study reported a lower stroke recurrence rate in the closure group compared to the medical therapy group. Atrial fibrillation was highly reported in the PFO group, with rare findings of device-related complications. The findings of the trial are robust, but the small sample size and short follow-up period may weaken the validity of results. As mentioned in the study limitations, the differential dropout rate between the two study groups might lead to inaccurate probability value (*P*-value).

Much work has been done on PFO closure devices, with trials confirming cost benefits and efficacy[32,39,40]. Retrospective 2025 studies, including Satpathy *et al*[38], used Medicare fee-for-service data (2016–2022) to identify patients over 60 hospitalized with ischemic stroke and diagnosed with PFO or atrial septal defect, with≥6 months of prior coverage. Out of 20 999 beneficiaries (device group n = 1132; control n = 19 867), the device group had a lower risk of recurrent stroke (1.65 vs 2.66 events/100 patient-years; HR 0.62, *P* = 0.007). 30-day safety events were similar; however, VTE and atrial fibrillation or flutter were more common in the device group. In U.S. patients over 60, PFO closure reduced recurrent stroke risk compared to medical therapy, with an acceptable safety profile.

Additionally, research by Goessinger[37] involved 330 patients. The study collected data from patients who underwent PFO closure between 2010 and 2015 to evaluate the combined endpoint of TIA, stroke, or death from stroke at short- and long-term follow-up. The mean age of the patients was 49 (±12) years, with 55.5% being male. Before PFO closure, 86% of patients had experienced a stroke, and 19% had multiple neurological events. Procedure-related complications occurred in 2.4% of patients.

Recently, Hammad *et al* (2025)[5] provided strong evidence supporting PFO closure. Analyzing 32 studies with 16 698 patients, including six RCTs and observational studies, they found that PFO closure reduced recurrent ischemic neurological events compared to medical therapy. The study highlighted the benefits of PFO closure over anticoagulants, aligning with the CLOSE 2017 results but not supported by the RESPECT study. Outcomes lacked strong subgroup validation, particularly for TIA recurrence. PFO closure also decreased all-cause mortality and major bleeding, especially among older males with shunts and atrial septal defects. AF remains a safety concern, potentially linked to thromboembolic risk if new. While the findings are robust and significant, earlier meta-analyses involved fewer patients, showed inconclusive results favoring closure, and did not analyze mortality or major bleeding differences between groups, marking a significant leap forward in the clinical trial landscape[25,27,41].

Considering all these factors, along with clinical evidence, research suggests there's no specific tipping point in the balance that favors either approach. Instead, this highlights the need for a patient-centered practice where the patient's needs and demographics are prioritized. Figure 2 also highlights the evolution of evidence associated with PFO closure and medical therapy over time.

Patient selection and risk Stratification

Optimal management of patients with PFO and CS or TIA remains debated. Increasing attention is now being given to patient selection and risk stratification to minimize complications such as procedural risks and atrial fibrillation. Recent guidelines from the European Stroke Organisation (ESO) recommend PFO closure for patients aged 18–60 years with PFO-associated stroke, particularly those with large right-to-left shunts and atrial septal aneurysms, using the PFO-Associated Stroke Causal Likelihood (PASCAL) classification system for patient selection[21]. This is further supported by the American Academy of Neurology (AAN), which advises closure in carefully selected patients under 60 with embolic-appearing strokes, reporting a 3.4% 5-year stroke risk reduction versus a 3.9% periprocedural complication rate and 0.33% annual risk of new atrial fibrillation[29].

High-risk anatomical features significantly influence clinical decision-making for closure versus medical therapy (Table 2). These include atrial septal aneurysm, hypermobility, large PFO size, and specific anatomical variants[42]. In real-world practice, patients with high-risk PFO features are significantly more likely to undergo closure, with these characteristics serving as independent predictors of the closure decision alongside undetermined stroke etiology[43]. The DEFENSE-PFO trial demonstrated a complete elimination of primary endpoints in the closure group, compared to 12.9% event rates in the medical therapy group among patients with high-risk PFO characteristics[42]. However, PFO closure is consistently associated with increased risk of new-onset atrial fibrillation, with odds ratios ranging from 3.45 to 5.74 across studies[5,44].

Predictive tools, such as the Risk of Paradoxical Embolism (RoPE) score, help estimate the probability that a stroke is PFO-attributable. Calculated from factors such as age, absence of hypertension or diabetes, and cortical infarct location, a RoPE score ≥7 indicates a high likelihood and correlates with greater closure benefit[45]. Supporting this threshold, Morais *et al* found that RoPE scores ≤6 independently predicted a higher risk of recurrent ischemic events and mortality after PFO closure[46]. Complementary tools include the PASCAL classification, which integrates RoPE with anatomical risks to categorize causality as "probable," "possible," or "unlikely."

Chronological age could further refine patient selection, as randomized trials have demonstrated that the most significant benefit of PFO closure is in patients aged 18–60 years[21,42,47]. The American Academy of Neurology recommends PFO closure only after thorough evaluation to exclude alternative stroke mechanisms, particularly in patients younger than 60 years with embolic-appearing infarcts and no other identified stroke etiology[29]. The benefit of PFO closure is most evident in carefully selected young patients with few to no vascular risk factors. Conversely, patients with additional vascular risk factors show diminished benefit, with higher rates of recurrent stroke or TIA observed in older patients (age >55) and those with diabetes and hypertension. Therefore, shared decision-making is paramount and should involve multidisciplinary teams, including[48] Neurologists, cardiologists, and primary care providers, to ensure patients are fully informed about the risks, benefits, and uncertainties of each option, thereby optimizing individualized care. Figure 3 shows a stepwise approach to clinical decision-making for PFO evaluation in CS.

Controversies and Ongoing Debates

Managing a PFO in patients with CS presents a complex challenge at the intersection of cardiology and neurology. As new evidence and treatment options emerge, the decision between

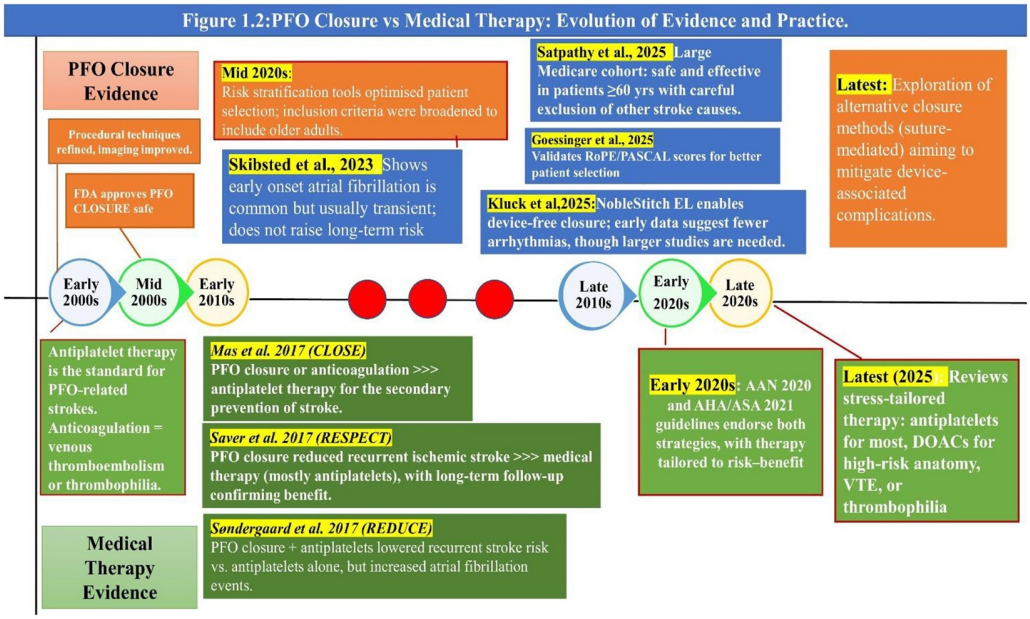

Figure 2. A chronological overview illustrating how key clinical trials, guideline shifts, and emerging technologies have shaped the management of Patent Foramen Ovale (PFO) related stroke from the early 2000s to 2025. ASA, atrial septal aneurysm; PASCAL, PFO-Associated Stroke Causal Likelihood; PFO, patent foramen ovale; RoPE, risk of paradoxical embolism.

percutaneous closure and medical therapy becomes increasingly nuanced, requiring careful consideration of risk assessment, personalized treatment strategies, and the balance between intervention benefits and potential complications. A central issue in this debate is the cost-effectiveness of PFO closure. When appropriately applied, it can enhance quality-adjusted life years (QALYs) and reduce long-term healthcare costs. However, even slight reductions in treatment efficacy can significantly affect cost-effectiveness, highlighting the importance of selecting suitable candidates for intervention[49,50]. The absence of a universally accepted diagnostic algorithm for PFO-related stroke further complicates treatment decisions and contributes to variability in clinical practice[51].

Additionally, PFO closure is associated with a higher risk of new-onset atrial fibrillation (AF), itself a potential cause of stroke, raising concerns about substituting one risk for another[39].

Future research should focus on refining treatment strategies through innovative, evidence-based approaches. More RCTs involving elderly patients are needed, as most existing studies primarily include younger adults, leaving outcomes for those over sixty underexplored[5]. While awaiting these results, it is essential to improve long-term risk assessments, including AF, device-related complications, and mortality. Understanding differences among closure devices, procedural techniques, and anticoagulation strategies is also crucial. Evaluating the safety and effectiveness of each device, exploring sex-based differences, and examining anatomical interactions will help optimize patient outcomes[47,52,53]. Current research has overlooked important pathophysiological factors such as concurrent venous thrombosis and consistent PFO evaluation, which are vital for understanding complications like cryptogenic and embolic stroke[8].

Preventive strategies involving medication either alongside or instead of PFO closure require more straightforward guidelines, especially in cases involving DVT. Variations in treatment protocols, regional practices, and device types further complicate matters. Establishing standardized post-closure care and monitoring for complications would be beneficial, while identifying effective antiplatelet or anticoagulant regimens is critical for patients who decline or are ineligible for device procedures[51]. Inadequate evaluations, such as overreliance on the RoPE score, increase the risk of misdiagnosis. Moreover, inconsistencies in stroke definitions across studies hinder the ability to draw broad

Table 2

Patient selection and risk stratification factors for PFO closure.

Factor	Higher risk (favors closure)	Lower risk (favors medical therapy)
Anatomy	Large shunt, atrial septal aneurysm (ASA), associated structures (Eustachian valve, Chiari network)	Small shunt, isolated PFO without aneurysm
RoPE score	High (younger age, cortical infarct, no vascular risk factors)	Low (older age, vascular risk factors present)
Age	<60 years	>60 years (higher likelihood of alternative stroke causes)
Comorbidities	Few or absent	Hypertension, diabetes, atrial fibrillation, hyperlipidemia
Lifestyle	Healthy, modifiable risk factors	Persistent vascular/lifestyle risks
Decision-making	Patient is willing for an invasive procedure, values stroke reduction	Prefers medical management, concerned about procedural risks

PFO, patent foramen ovale; RoPE, risk of paradoxical embolism.

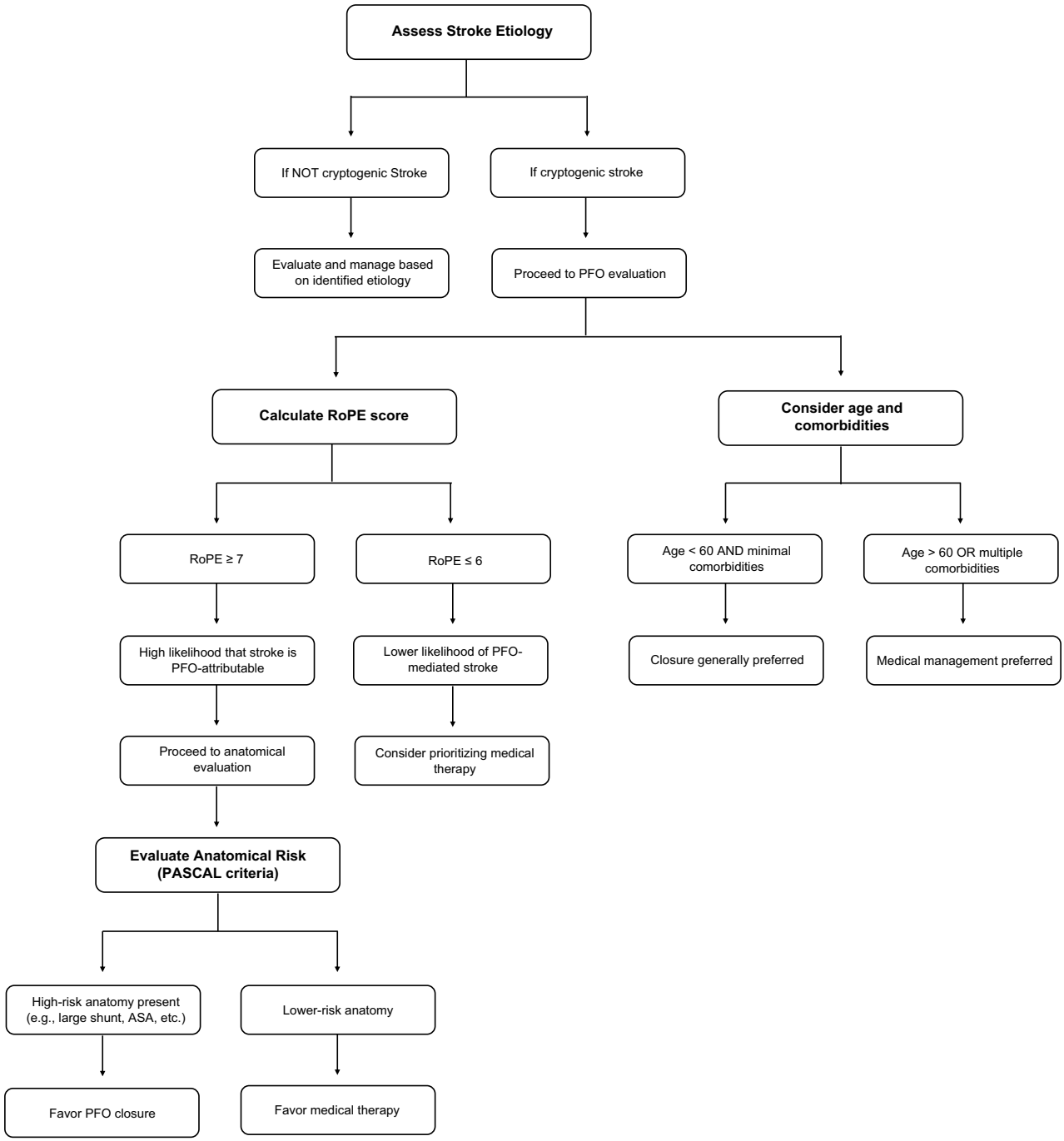

Figure 3. A stepwise algorithm outlining the evaluation of stroke etiology, use of RoPE score, incorporation of age and comorbidities and anatomical risk assessment (PASCAL criteria) to guide clinicians on personalized decision making.

conclusions[42,46]. Emerging data suggest that suture-mediated closure may reduce device-related arrhythmias, but further research is needed to confirm its advantages and determine the most appropriate patient population.

Conclusion

For years, the connection between PFO and stroke has been debated. Recent RCTs show that closing a PFO can lower the risk of recurrent events in patients with CS. However, in real-world clinical practice, treating stroke patients with a coexisting PFO presents some challenges. These findings mark a significant shift in clinical practice, highlighting the need for updated protocols and evidence-based treatment adjustments. Additionally, multiple studies point to age as a key factor, indicating that all-cause mortality and neurological event rates are significantly higher in older patients; however, these differences are less pronounced in younger individuals. This emphasizes that clinicians

should avoid a one-size-fits-all approach and instead adopt a personalized strategy that considers age, anatomical features, and the risk of stroke recurrence.

Collaboration between specialists is crucial to balance stroke risk reduction with the management of arrhythmia and thromboembolic risks. Integrating PFO closure into treatment embodies personalized medicine, with interventions tailored to each patient's profile. As precision medicine advances, treating PFO in CS is likely to become more sophisticated, relying on data and focusing on individual patients, marking a new chapter in cerebrovascular treatment.

This narrative review adheres to the Transparency in the Reporting of Artificial Intelligence in Research (TITAN) guideline[54].

All AI-assisted text was thoroughly reviewed, edited, and refined by the authors. The conceptualization, literature interpretation, synthesis of ideas, and manuscript writing were performed entirely by the authors, ensuring the academic rigor, accuracy, and originality of the review.

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Consent

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Author contributions

R.R.M. (Pakistan) conceived the idea, designed the manuscript outline, conducted the primary literature review, and drafted the initial version. She also coordinated communication among co-authors and integrated revisions into the final manuscript. U.A., H.W., M.B., J.N., M.W., R.K.M., V.K., H.M. contributed to data interpretation, contextual insights, and refinement of the draft. R.K.M. (Nepal) provided a critical review, intellectual input, and shaped the discussion; he will serve as the corresponding author and guarantor. All authors read and approved the final manuscript.

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Guarantor

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