Review

Beyond Anticoagulation: Understanding the Failure of Medical Therapy in PFO-Related Stroke and the Superiority of Closure

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Beyond Anticoagulation: Understanding the Failure of Medical Therapy in PFO-Related Stroke and the Superiority of Closure

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Abstract

Patent foramen ovale (PFO) is present in roughly one quarter of adults and is over-represented among younger patients with cryptogenic ischemic stroke. The past decade has produced compelling evidence from randomized trials showing that PFO closure is superior to medical therapy in preventing recurrent ischemic stroke in appropriately selected patients. Despite this, anticoagulation continues to be used when closure is not feasible, declined, contraindicated, or considered after recurrent events. The observation that some patients experience "breakthrough" stroke or transient ischemic attack (TIA) despite therapeutic anticoagulation raises a critical question: why does medical therapy fail in PFO-related stroke, and why does closure appear superior? This narrative review synthesizes the latest evidence on the pathophysiology of PFO-associated stroke, with attention to mechanisms that remain incompletely addressed by anticoagulation. It analyzes randomized trial data comparing antiplatelet therapy, anticoagulation, and transcatheter closure. It examines the role of high-risk PFO anatomical characteristics, the Risk of Paradoxical Embolism (RoPE) score, and the PFO-Associated Stroke Causal Likelihood (PASCAL) classification in understanding medical therapy failure. Additionally, the review explores whether PFO "type" predicts anticoagulation failure and highlights future research directions needed to further optimize therapy. The conclusion is clear: in the selected patients with high-risk features closure offers superior stroke prevention beyond what anticoagulation can achieve.

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1. Introduction

Patent foramen ovale (PFO) is a remnant of fetal circulation that persists in approximately 25–30% of adults, making it one of the most common congenital cardiac anomalies [1–3]. While most individuals remain asymptomatic, PFO is over-represented among patients with cryptogenic ischemic stroke, particularly those younger than 60 years, non-lacunar infarct patterns, and without or few traditional vascular risk factors. Paradoxical embolism via a PFO is estimated to account for ≈5% of all ischemic strokes and up to 10% in younger patients [1].

For many years, management of PFO-associated stroke was limited to antithrombotic therapy—either antiplatelet agents or vitamin K antagonists—based largely on observational data. Randomized control trials of device closure were initially neutral but were underpowered. More recent, larger and longer-term trials (RESPECT long-term, CLOSE, REDUCE, DEFENSE-PFO) have demonstrated that PFO closure, when combined with antiplatelet therapy, significantly reduces recurrent stroke compared with medical therapy alone in selected patients, especially those with high-risk anatomical features [4–8].

Despite this, anticoagulation remains part of clinical practice. It is used when closure is not available or declined, when there is concomitant deep venous thrombosis (DVT) or when stroke recurs despite antiplatelet therapy. Clinicians increasingly encounter patients with cryptogenic

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stroke, PFO, and recurrent events despite apparently adequate anticoagulation. Understanding why anticoagulation fails, and why closure appears superior in selected subgroups, is critical for optimizing secondary prevention strategies.

This narrative review pursues four main goals:

1. To summarize the pathophysiology of PFO-related stroke with emphasis on mechanisms that are incompletely modified by anticoagulation.
2. To review evidence comparing anticoagulation, antiplatelet therapy, and PFO closure for secondary prevention.
3. To discuss how PFO anatomy, RoPE score, and the PASCAL classification relate to medical therapy failure.
4. To propose future research directions informed by these mechanistic and clinical insights. or (in risk stratification, trial design, and individualized therapy)

2. Pathophysiology of PFO-Related Stroke: Why an Anatomic Conduit Matters

2.1. Classic Mechanisms

Multiple, potentially overlapping mechanisms have been proposed for PFO-associated stroke:

Paradoxical embolism : The traditional and most widely accepted mechanism in paradoxical embolism-migration of thrombus from the venous system through a right-to-left shunt into the arterial circulation [1,3]. Conditions that transiently increase right atrial pressure (Valsalva maneuvers, coughing, straining) may open the foramen ovale flap even in the absence of persistent right-to-left pressure gradients [1,3]. Anticoagulation reduces but does not eliminate venous thrombus formation. Residual thrombi, even small ones, may still cross the shunt. Thus, the anatomical conduit remains, providing a pathway for stroke whenever transient pressure reversal occurs.

In situ thrombus formation within the PFO tunnel : Especially in long, aneurysmal, or hypermobile septa where low-flow regions may predispose to in situ thrombus formation, which may be platelet-rich and less responsive to anticoagulation [3].

Associated atrial arrhythmias and atrial cardiopathy : A growing body of evidence suggests that structural and functional atrial abnormalities (dilation, fibrosis, impaired function, or subclinical atrial arrythmias) that predispose to thrombogenesis independent of, but sometimes co-existing with, the PFO [9].

Coexisting prothrombotic states: Patients with inherited or acquired thrombophilias, malignancy, hormonal therapy, or immobilization may continue forming venous thrombi despite therapeutic anticoagulation. The PFO provides an ongoing anatomical risk [1,9]. The central concept is that the PFO serves as a conduit enabling venous thrombi (or thrombi formed in the PFO itself) to bypass the pulmonary capillary filter and embolize to the brain. Transient elevations in right atrial pressure—during Valsalva maneuvers, coughing, defecation, heavy lifting, or even normal activities—can briefly reverse the interatrial pressure gradient and open the flap valve, permitting paradoxical embolization [1,3].

2.2. High-Risk Anatomical Features

Not all PFOs are equal. High-risk features associated with higher odds of stroke or higher recurrence on medical therapy include:

- **Large right-to-left shunt** (often defined as >20 bubbles in the left atrium on contrast echocardiography) [10,11].
- **Atrial septal aneurysm (ASA)** or marked septal hypermobility (≥10 mm excursion) [7,10].
- **Long PFO tunnel and "low-angle" PFO**, in which the angle between the PFO tunnel and the inferior vena cava or inferior atrial wall is ≤10°, potentially channeling venous flow toward the left atrium [3,12].

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- **Prominent Eustachian valve or Chiari network**, embryologic remnants that direct venous inflow from the inferior vena cava to the fossa ovalis and PFO, increasing the likelihood that venous thrombi reach the left atrium [13–16].

These features have been repeatedly linked to higher probability that the PFO is causal and to greater benefit of closure compared with medical therapy including anticoagulation.

2.3. Emerging Concept: PFO-Associated Stroke as a Multifactorial Syndrome

Recent reviews propose that "PFO-associated stroke" (PFO-AS) should be viewed as a multifactorial syndrome rather than a single mechanism disease. In addition to paradoxical embolism and in situ thrombosis, atrial cardiopathy—structural and electrophysiological remodeling of the atria without overt atrial fibrillation—may coexist and contribute to thrombogenesis [3,9].

This integrated view helps explain why simply altering coagulation (with anticoagulants) might not fully abrogate risk: thrombus formation may occur in multiple sites (venous system, PFO tunnel, left atrium), under different hemodynamic and biological conditions (platelet-rich vs fibrin-rich clot, local stasis vs systemic hypercoagulability), and in the presence of a persistent anatomical conduit that is unaffected by medical therapy.

3. Why Anticoagulation May Fail in PFO-Related Stroke

At first glance, anticoagulation should be an attractive therapy: if venous thromboembolism is the main driver of paradoxical embolism, then preventing its formation (or reducing its size) should prevent stroke. Yet multiple lines of evidence suggest that anticoagulation is not reliably superior to antiplatelet therapy in unselected patients with PFO-associated cryptogenic stroke, and it clearly does not match the effect size of PFO closure in high-risk populations [17–20].

Mechanistically, several factors underlie this apparent failure:

3.1. The Anatomic Pathway Remains Intact

Anticoagulation modifies thrombogenesis but does not remove the anatomical shunt. Even with reduced thrombus formation, any venous thrombi that do form still have direct access to the systemic circulation through the PFO when transient right-to-left gradients occur. Closure, in contrast, eliminates the conduit altogether.

This distinction is especially relevant when thrombi arise under circumstances where anticoagulation is less effective—e.g., severe stasis, very large clot burden, or underlying hypercoagulability that overwhelms therapeutic anticoagulation.

3.2. Heterogeneity of Thrombus Biology

Venous thrombi are classically fibrin-rich and responsive to anticoagulants. However, thrombi forming in low-flow pockets (e.g., within a PFO tunnel or regions of atrial cardiopathy) may have mixed platelet–fibrin composition. In these settings, antiplatelet-mediated pathways and local endothelial activation can contribute, and anticoagulation alone may be less effective [3,9].

Moreover, coexistent prothrombotic conditions—cancer-associated thrombosis, antiphospholipid antibodies, myeloproliferative disorders—may produce recurrent thrombosis despite therapeutic anticoagulation. When a PFO is present, each new thrombus represents another opportunity for paradoxical embolism.

3.3. Atrial Cardiopathy and Non-PFO Mechanisms

In some patients initially labelled as having "PFO-related" stroke, subsequent monitoring reveals atrial fibrillation, atrial flutter, or biomarkers and imaging consistent with atrial cardiopathy. In such patients, anticoagulation is indeed appropriate, but the recurrent stroke risk may arise from atrial-source thromboembolism, not paradoxical embolism.

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The NAVIGATE ESUS trial and related studies highlight that DOACs did not reduce recurrent stroke compared with aspirin in patients with embolic stroke of undetermined source (ESUS), including those with PFO, although some subgroups with left atrial enlargement appeared to benefit [18,20,21]. These findings underscore the complexity of stroke mechanisms in patients with PFO and suggest that atrial cardiopathy must be recognized and treated separately from the PFO conduit.

3.4. Real-World Limitations of Anticoagulation

In clinical practice, anticoagulation is vulnerable to:

- **Non-adherence** and missed doses (especially problematic for DOACs with short half-lives).
- **Drug–drug interactions** and variable absorption.
- **Renal or hepatic impairment** altering drug levels.

Even "breakthrough" stroke on anticoagulation may be partly explained by unrecognized periods of subtherapeutic drug exposure. Closure avoids this vulnerability by providing an anatomic solution independent of patient adherence.

3.5. Residual Risk Demonstrated in Clinical Trials

The CLOSE trial, which directly compared PFO closure, antiplatelet therapy, and anticoagulation, provides a key data point. In CLOSE, PFO closure essentially abolished recurrent ischemic stroke over a median of 5.3 years, while recurrent events occurred in both the antiplatelet and anticoagulation arms, though numbers were small and the trial was not powered for a direct comparison between medical strategies [5,19].

Pooled analyses and meta-analyses combining CLOSE with prior trials (e.g., PICSS, NAVIGATE ESUS) suggest that anticoagulation may modestly reduce recurrent stroke compared with antiplatelet therapy in patients with PFO, but the confidence intervals are wide, heterogeneity is substantial, and bleeding risks are higher [17,18,20]. These data strongly suggest that neither antiplatelet therapy nor anticoagulation alone matches the protective effect of closure in those with high-risk PFO anatomy and high PFO-causality scores.

4. Evidence Comparing Antiplatelet Therapy, Anticoagulation, and PFO Closure

4.1. PFO Closure vs Medical Therapy

The modern PFO closure trials share several features: they enrolled predominantly patients aged 18–60 years with recent cryptogenic stroke, non-lacunar infarct patterns, and a PFO; and they randomized participants to device closure plus antiplatelet therapy versus medical therapy (antiplatelet or anticoagulant) alone.

Key trials include:

- **RESPECT (long-term)** – PFO closure with the Amplatzer occluder vs medical therapy. Extended follow-up (median ≈5.9 years) showed a significant reduction in recurrent ischemic stroke with closure, particularly in those with large shunts or ASA [4]
- **CLOSE** – three-arm trial comparing closure, antiplatelet therapy, and anticoagulation. Closure virtually eliminated recurrent stroke; anticoagulation numerically reduced stroke compared with antiplatelets, but sample size was small [5]
- **REDUCE** – closure with Gore HELEX or CARDIOFORM occluders plus antiplatelet therapy vs antiplatelet therapy alone; showed a significant reduction in clinical stroke and new silent brain infarcts on MRI [6]
- **DEFENSE-PFO** – focused on high-risk PFO (large shunt, ASA, or hypermobile septum). Closure significantly reduced the composite of stroke, vascular death, or major bleeding vs medical therapy, with striking separation of Kaplan–Meier curves [7]

Individual-patient and reconstructed time-to-event meta-analyses of these and earlier trials (CLOSURE I, PC) demonstrate that PFO closure reduces recurrent stroke by approximately 40–60%

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compared with medical therapy in appropriately selected patients, with the largest benefit seen in those with high-risk anatomy [8,22].

4.2. Anticoagulation vs Antiplatelet Therapy

Several analyses have focused on whether oral anticoagulants (OACs) outperform antiplatelet therapy in PFO-associated stroke: A pooled observational analysis by Kent et al. of patients from PICSS and other datasets suggested a trend favoring anticoagulation but did not demonstrate a statistically significant difference, in part due to limited power and heterogeneity [17]. The CLOSE trial's anticoagulation arm (predominantly warfarin) showed fewer strokes than the antiplatelet arm, but sample sizes were small and confidence intervals overlapped [5,19]. NAVIGATE ESUS, which enrolled patients with ESUS (including many with PFO), found that rivaroxaban did not reduce recurrent stroke versus aspirin and increased major bleeding; subgroup analysis in those with PFO also failed to show clear benefit [18,21]. A recent meta-analysis of DOACs vs aspirin in ESUS (including NAVIGATE ESUS, RE-SPECT ESUS, ARCADIA, ATTICUS) concluded there was no reduction in recurrent stroke or systemic embolism and an increased bleeding risk with DOACs [20].

Collectively, these data support a cautious conclusion: anticoagulation may offer modest protection beyond antiplatelets in some PFO-associated stroke populations, but the advantage is uncertain, and bleeding risk may offset benefit. No evidence suggests that anticoagulation can match the risk reduction achieved by closure in high-risk PFO patients.

5. PFO Anatomy, RoPE Score, and PASCAL Classification: Linking Structure, Causality, and Medical Therapy Failure

5.1. RoPE Score

The Risk of Paradoxical Embolism (RoPE) score estimates the likelihood that a detected PFO is causally related to a cryptogenic stroke rather than incidental. It incorporates age, cortical stroke location, history of hypertension, diabetes, prior stroke/TIA, and smoking status. Higher RoPE scores (typically in younger patients with few vascular risk factors and cortical infarcts) imply a higher probability that the PFO is pathogenic [1].

However, RoPE does not include PFO anatomical features. Two patients with identical RoPE scores may have very different PFO anatomy and risk of recurrence.

5.2. PASCAL Classification

The PASCAL (PFO-Associated Stroke Causal Likelihood) system, proposed by Kent and colleagues, integrates RoPE score with high-risk anatomical features (large shunt, ASA) to categorize patients into groups where the PFO is deemed *unlikely*, *possible*, or *probable* as the cause of stroke [1,10].

- **Probable PFO-related stroke** – high RoPE score and at least one high-risk PFO feature.
- **Possible PFO-related stroke** – intermediate combinations.
- **Unlikely PFO-related stroke** – low RoPE score and absence of high-risk anatomical features.

Application of PASCAL to trial datasets demonstrates that the absolute benefit of closure is concentrated in the "probable" group, with more modest or uncertain benefit in other categories [1,11]

5.3. Does PASCAL or PFO "Type" Influence Anticoagulation Failure?

Direct evidence that specific PFO subtypes or PASCAL categories are associated with failure of anticoagulation (i.e., recurrent events despite therapeutic OAC) is limited, as very few trials have been powered to analyze this interaction. However, several lines of inference support the hypothesis that high-risk anatomy predisposes to residual risk despite anticoagulation:

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1. High-risk anatomical features (large shunt, ASA, hypermobile septum, prominent Eustachian valve/Chiari network, low-angle PFO) are associated with higher baseline risk of paradoxical embolism and stroke recurrence on medical therapy [12–14,23]
2. The greatest relative and absolute benefit of closure over medical therapy in RESPECT, REDUCE, and DEFENSE-PFO was observed in patients with these high-risk morphologies [6,7,24]
3. Observational data suggest that recurrence rates in medically managed PASCAL "probable" PFO-related stroke may approach 1–2% per year, despite antithrombotic therapy [1,11]

Mechanistically, it is intuitive that large, low-angle shunts with flow-directing structures such as Eustachian valves or Chiari networks create a more efficient conduit for paradoxical emboli. Even small thrombi, incompletely suppressed by anticoagulation, may be preferentially directed through these channels.

Thus, while hard data are still emerging, current evidence and pathophysiological reasoning strongly suggest that patients in the PASCAL "probable" category with high-risk PFO anatomy are precisely those in whom anticoagulation is most likely to fail and closure is most likely to be superior.

6. Clinical Implications and Guideline Perspectives

The 2021 AHA/ASA guideline for secondary stroke prevention recommends that in patients aged 18–60 years with a non-lacunar ischemic stroke of undetermined cause and PFO with high-risk anatomic features, PFO closure is reasonable after a multidisciplinary discussion and shared decision-making (Class IIa, Level of Evidence B-R) [25] For patients without high-risk features or with competing mechanisms of stroke, medical therapy (antiplatelet or, in selected situations, anticoagulation) is preferred.

European and other international guidelines are broadly concordant, emphasizing high-risk PFO anatomy and high RoPE scores as criteria supporting closure and acknowledging that the incremental benefit of anticoagulation over antiplatelets remains uncertain [11,23].

Anticoagulation as a long-term substitute for closure in high-risk, PASCAL-probable patients appears mechanistically and empirically suboptimal: residual stroke risk is non-trivial, and bleeding complications may accumulate over decades of therapy.

7. Future Directions

Based on the current evidence and mechanistic understanding, several avenues for future research emerge.

7.1. Direct Comparison of DOACs vs PFO Closure in PASCAL-Probable Patients

To date, no randomized trial has directly compared modern DOACs against PFO closure in a population enriched for PASCAL-probable PFO-related stroke (young, high RoPE, high-risk anatomy). The anticoagulation data are largely extrapolated from warfarin-based regimens and from ESUS populations where PFO can be incidental.

A trial that randomizes such patients to DOACs vs PFO closure plus antiplatelet therapy with stratification by PASCAL class and high-risk anatomical features would directly test whether any medical regimen can match closure in this high-risk group.

7.2. Refined Phenotyping of Atrial Cardiopathy in PFO-Associated Stroke

Emerging evidence suggests that atrial cardiopathy may coexist with PFO, particularly in older patients or those with vascular risk factors, and may contribute to thromboembolism independently of paradoxical embolism [9,20].

Prospective studies incorporating advanced echocardiography (left atrial strain, volume, stiffness), cardiac MRI, biomarkers (NT-proBNP, high-sensitivity troponin, prothrombotic markers)

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and prolonged rhythm monitoring, could identify subgroups in whom combined strategies (PFO closure plus anticoagulation) are warranted and those for whom closure alone is sufficient.

7.3. Mechanistic Imaging of Venous and In Situ Thrombus

Better understanding of where thrombi originate in PFO-associated stroke is needed. Research combining systematic venous Doppler and pelvic MR venography for occult DVT, high-resolution imaging of PFO tunnels for in situ thrombus and serial D-dimer and other coagulation markers could clarify the relative contributions of venous vs in situ vs atrial thrombus and inform which patients might still benefit from anticoagulation after closure.

7.4. Post-Closure Antithrombotic Optimization

Post-closure antithrombotic regimens vary widely (short-term dual antiplatelet therapy vs single antiplatelet, vs short-term anticoagulation). Trials focusing on high-risk subsets (e.g., device-related thrombus, strong thrombophilia, atrial cardiopathy) could optimize these regimens and minimize both stroke and bleeding risk.

7.5. Device Design and Procedure-Related Arrhythmias

A small but real increase in new-onset atrial fibrillation is observed after PFO closure, although most episodes are early and transient [4,6,7]. Future studies should define which devices and techniques minimize AF risk and device-related thrombosis and determine whether short-term prophylactic anticoagulation or tailored monitoring in high-risk patients improves outcomes.

7.6. Decision Tools Integrating PASCAL, Bleeding Risk, and Patient Preferences

Finally, development and validation of decision support tools that integrate PASCAL category, detailed anatomy, individual bleeding risk (HAS-BLED or similar), life expectancy and comorbidities, and patient values and preferences, could guide personalized therapy—particularly in gray-zone scenarios where both closure and anticoagulation are plausible options.

8. Conclusions

PFO-associated stroke lies at the intersection of anatomy, thrombosis, and atrial biology. Anticoagulation reduces but does not eliminate venous thrombus formation and leaves the anatomical conduit (PFO) intact, allowing paradoxical embolism to occur. High-risk anatomical PFO features favor persistent embolic risk despite anticoagulation. Randomized trials consistently show superiority of closure in selected patients—particularly those with large shunts, ASA, or high PASCAL "probable" classification. The concept of anticoagulation "failure" in PFO-related stroke should prompt clinicians to reassess both the mechanism (PFO-mediated vs atrial or arterial) and the anatomy (high-risk vs low-risk PFO), rather than simply intensifying or switching anticoagulant agents. In PASCAL-probable patients with high-risk anatomy, the weight of evidence and pathophysiology strongly supports closure as the preferred strategy. Anticoagulation should be reserved for established indications (atrial fibrillation, thrombosis, thrombophilia) and used as an adjunct rather than a substitute when the PFO conduit is clearly causal. Future research must directly compare DOACs with closure in high-risk populations, refine our understanding of atrial cardiopathy in PFO-associated stroke, and develop integrated decision tools that combine PASCAL classification, bleeding risk, and patient preferences. Until then, a mechanistically informed approach—recognizing the inherent limitations of medical therapy when an anatomic shunt persists—supports the emerging paradigm: beyond anticoagulation, PFO closure occupies a central role in preventing recurrent stroke in truly PFO-related cases.

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