JAMA | Review

Patent Foramen Ovale and Stroke
A Review

David M. Kent, MD, MS; Andy Y. Wang, MD

IMPORTANCE A patent foramen ovale (PFO), an opening between the right and left atria during normal fetal development that fails to close after birth, is present in approximately 25% of all adults. Paradoxical embolism, a venous thromboembolism that travels to the systemic circulation typically through a PFO, accounts for about 5% of all strokes and 10% of strokes in younger patients.

OBSERVATIONS Approximately 50% of patients 60 years or younger with an embolic stroke of undetermined source (cryptogenic stroke) have a PFO, compared with 25% of the general population. The Risk of Paradoxical Embolism (RoPE) score incorporates clinical characteristics (age, history of stroke or transient ischemic attack, diabetes, hypertension, smoking, cortical infarct on imaging) to predict the likelihood that embolic stroke of undetermined source was caused by a PFO. Among patients in the lowest RoPE score category (score <3), PFO prevalence was similar to that in the general population (23%), while PFO prevalence was 77% in patients with a RoPE score of 9 or 10. The PFO-Associated Stroke Causal Likelihood (PASCAL) classification system combines the RoPE score and anatomical criteria from echocardiography (large shunt, atrial septal aneurysm) to classify PFO as the "probable," "possible," or "unlikely" cause of otherwise cryptogenic stroke. PFO closure reduces recurrent ischemic stroke in patients 60 years or younger with cryptogenic stroke. In a pooled analysis of 6 trials (3740 patients), the annualized incidence of stroke over a median follow-up of 57 months was 0.47% (95% CI, 0.35%-0.65%) with PFO closure vs 1.09% (95% CI, 0.88%-1.36%) with medical therapy (adjusted hazard ratio, 0.41 [95% CI, 0.28-0.60]). However, the benefits and harms of closure were highly heterogeneous across the trial populations. In patients categorized as PASCAL "probable" (ie, younger patients without vascular risk factors and high-risk PFO anatomical features), there was a 90% decreased relative rate of recurrent ischemic stroke after PFO closure at 2 years (hazard ratio, 0.10 [95% CI, 0.03-0.35]; absolute risk reduction, 2.1% [95% CI, 0.9%-3.4%]). PASCAL "unlikely" patients (eg, older patients with vascular risk factors and no high-risk PFO anatomical features) did not have a lower recurrent stroke rate with PFO closure but had higher risk of procedure- and device-related adverse events, such as atrial fibrillation.

CONCLUSIONS AND RELEVANCE Patent foramen ovale is present in approximately 25% of all adults and is a common cause of stroke in young and middle-aged patients. The PASCAL classification system can help guide patient selection for PFO closure. Percutaneous PFO closure substantially reduces the risk of stroke recurrence in well-selected patients younger than 60 years after cryptogenic stroke.

Multimedia
Supplemental content
CME at jamacmelookup.com

Author Affiliations: Predictive Analytics and Comparative Effectiveness Center, Tufts Medical Center/Tufts University School of Medicine, Boston, Massachusetts (Kent); Department of Neurology, University of California San Francisco (Wang).

Corresponding Author: David Kent, MD, MS, Predictive Analytics and Comparative Effectiveness (PACE) Center, Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, 800 Washington St, Box 63, Boston, MA 02111 (david.kent@tuftsmedicine.org).

JAMA. doi:10.1001/jama.2025.10946
Published online July 28, 2025.

A patent foramen ovale (PFO), a persistent small conduit from fetal circulation permitting a right-to-left interatrial shunt, is present in approximately 25% of all adults and may be an incidental finding on echocardiogram. However, up to 30% of all strokes are cryptogenic, defined as unexplained despite an extensive evaluation for causes of stroke. Among patients with cryptogenic stroke, approximately 50% have a PFO, which may result in paradoxical embolism, in which a venous embolus directly accesses the cerebral arterial circulation. Over the last several decades, devices designed to close a PFO have been shown to be effective in preventing stroke recurrence in well-selected young and middle-aged patients with PFO.[1-6] In 2020, an international working group of stroke experts recommended that stroke nomenclature be updated to remove PFO-associated stroke from the cryptogenic category.[7]

This review presents the epidemiology of PFO-associated stroke, compares device closure with medical therapy, and discusses algorithms for the probabilistic identification of causal vs incidental PFO to support clinical decision-making. It also reviews other aspects of clinical management of PFO-associated stroke (see **Box**).

Box. Questions Commonly Asked About Patent Foramen Ovale (PFO) and Stroke

How Is the Diagnosis of a Cryptogenic Stroke Established?
Initial evaluation of stroke includes head computed tomography angiography or brain magnetic resonance angiography to assess for large-vessel atherosclerosis, electrocardiography to assess for atrial fibrillation, and echocardiography to evaluate for a cardioembolic source. If this testing is unrevealing, the diagnosis of cryptogenic stroke is made. If the infarct appears embolic based on neuroimaging findings, it is classified as an embolic stroke of undetermined source.

Among Patients With a PFO-Associated Stroke, Which Factors Suggest That the PFO Is a Causal Rather Than Incidental Finding?
Absence of vascular disease risk factors such as diabetes, hypertension, and smoking, and presence of a cortical infarct on a neuroimaging study, especially in patients younger than 60 years, suggest that a PFO is the cause of stroke. Other factors that increase this likelihood are a PFO with a large shunt or an atrial septal aneurysm and a cerebral infarction that occurred during a Valsalva maneuver or in the presence of a deep venous thrombosis.

Do All Patients With Cryptogenic Stroke Who Have a PFO Benefit From PFO Closure?
Randomized trials have demonstrated reduced rates of recurrent stroke after closure of a PFO in selected patients 60 years or younger with cryptogenic stroke. However, those classified by the PASCAL (PFO-Associated Stroke Causal Likelihood) system as "unlikely" to have had a stroke causally related to their PFO do not appear to benefit from PFO closure and have a higher risk of device-related adverse events such as atrial fibrillation.

Methods

A comprehensive search strategy was developed in collaboration with a university librarian to query PubMed for English-language studies of PFO and stroke, published from January 1, 2014, to May 17, 2025 (Supplement). Identified articles were manually evaluated, along with their relevant references, and additional key publications and clinical trials were included. A total of 867 articles were identified. Of these, we included 79 articles (27 systematic reviews/meta-analyses, 23 cohort studies, 15 randomized clinical trials, 8 expert statements or position papers, and 6 guidelines).

Embryology of Patent Foramen Ovale

During normal prenatal development, the foramen ovale is formed by the incomplete closure of the septum primum and septum secundum, 2 structures in the fetal interatrial septum. The foramen ovale allows oxygenated blood from the placenta to bypass the nonfunctional fetal lungs and access the fetal arterial circulation. At birth, blood flow through the pulmonary vasculature increases, causing a marked increase in left atrial pressure that pushes the septum primum against the septum secundum, functionally closing the foramen ovale, which then seals over the first year of life. However, in approximately 25% of individuals, the edges of the septum primum and secundum do not fully fuse, leaving a small opening, resulting in a PFO.

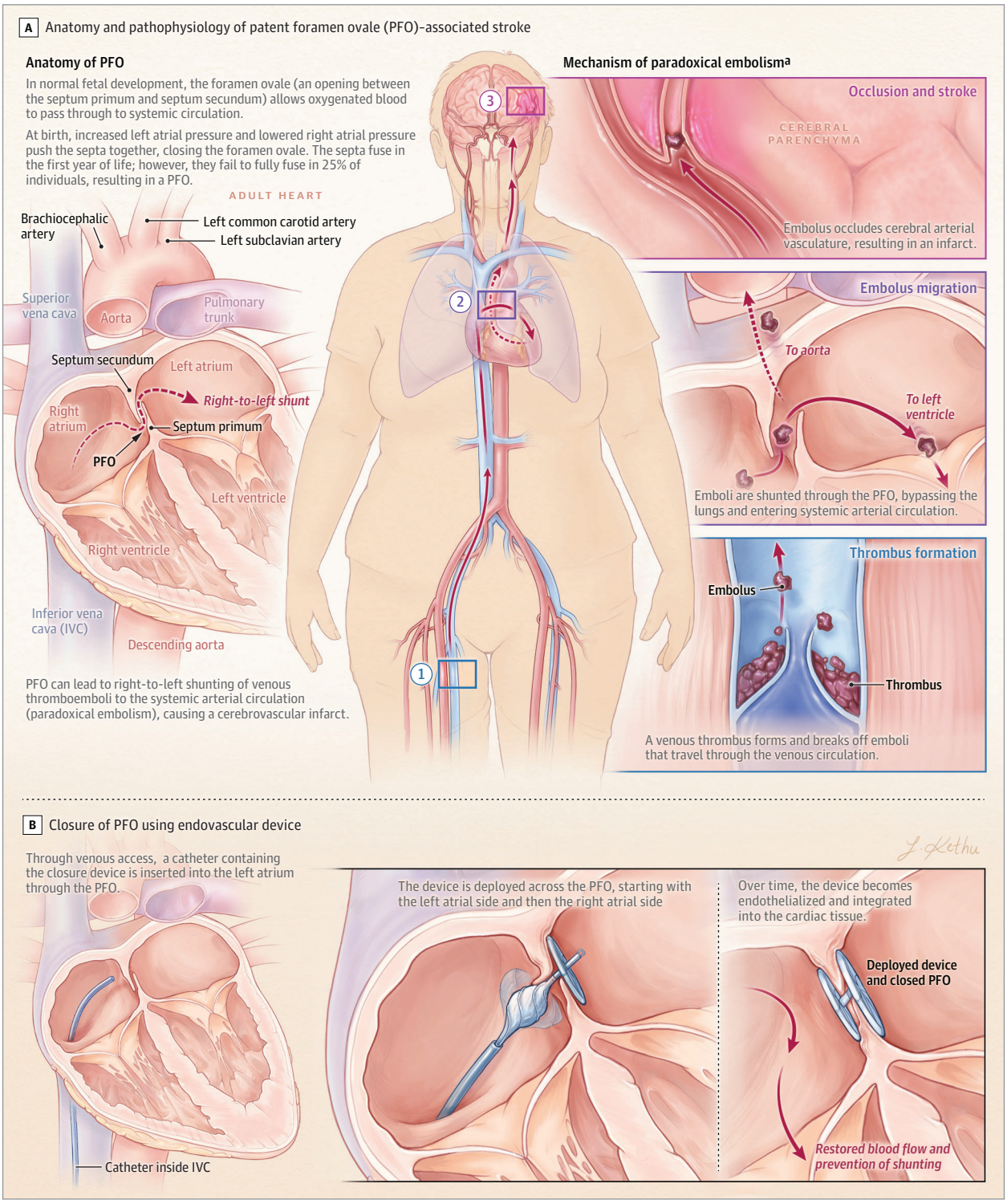
Pathophysiology of PFO-Associated Stroke

Most PFOs have a small diameter (mean, 4.9 mm [range, 1-19 mm]) and do not cause hemodynamically significant shunting of blood. However, they are large enough to permit emboli from a venous thrombus to bypass filtration in the pulmonary vasculature and access the systemic arterial circulation. This "paradoxical embolism" can cause symptomatic strokes by occluding a branch in the cerebral arterial circulation (**Figure 1**). Another potential mechanism for PFO-associated stroke is in situ thrombus formation around the interatrial tunnel, giving rise to a cerebral embolism.[8,9]

Clinical Epidemiology of PFO-Associated Stroke

Prior to the advent of contrast echocardiography, paradoxical emboli were considered a rare cause of stroke, with only 128 cases reported before 1972.[6] Subsequent epidemiologic studies reported an increased prevalence of PFO in patients with otherwise cryptogenic stroke.[10,11] In a meta-analysis of 23 case-control studies (n = 1154 cases and 1852 controls), the summary odds ratio for PFO in patients with cryptogenic stroke vs control patients with ischemic stroke of known cause was 2.9 (95% CI, 2.1-4.0).[11] However, among those younger than 55 years, the odds ratio for presence of a PFO was 5.1 (95% CI, 3.3-7.8). These associations have been used to estimate that among patients with cryptogenic stroke, PFO is the likely cause of stroke (rather than an incidental finding) in 80% of patients younger than 55 years (95% CI, 75%-84%) compared with 52% (95% CI, 34%-66%) in older patients.[11,12] It has been estimated that approximately 5% of all ischemic strokes and 10% of all ischemic strokes in young and middle-aged adults can be attributed to a PFO.[12]

Figure 1. Mechanism of Patent Foramen Ovale



[a]Other potential mechanisms for PFO-associated stroke such as in situ thrombus formation are not illustrated.

Assessment and Diagnosis of PFO-Associated Stroke

The diagnosis of PFO-associated stroke requires (1) determining if the stroke is cryptogenic; (2) detecting a PFO; and (3) determining whether the PFO is the likely cause of stroke or an incidental finding.

Is the Stroke Otherwise Cryptogenic?

The term "cryptogenic stroke" is a diagnosis of exclusion when no source of stroke is identified after a comprehensive workup.[13] Evaluation for the cause of stroke includes a history and physical examination and assessment of (1) infarct location, volume, and number on brain magnetic resonance imaging or head computed tomography (CT) that often is suggestive of etiology (eg, lacunar infarct indicates small vessel disease); (2) large vessel patency with CT angiogram, magnetic resonance angiogram, or carotid ultrasound; (3) valvular or atrial disease, including left atrial thrombosis with transthoracic echocardiography (TTE); (4) cardiac rhythm with electrocardiogram (ECG) and telemetry; and (5) complete blood cell count and coagulation laboratory tests.[14] Additional testing may include digital subtraction angiography (an endovascular technique using fluoroscopy that provides direct visualization of the blood vessels), transcranial doppler to detect right-to-left shunt, prolonged cardiac rhythm monitoring (eg, Holter monitor or implantable loop recorder), if ECG or telemetry does not identify atrial fibrillation, lumbar puncture if vasculitis is suspected, evaluation for occult malignancy (eg, thoraco-abdomino-pelvic CT), and genetic testing for gene variants associated with increased stroke risk such as in CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). This testing helps determine the etiology of strokes, which most commonly includes cardioembolism from atrial fibrillation (27.7%), small vessel disease (23.7%), large artery atherosclerosis (23.3%),[15] and other more rare causes such as moyamoya disease and vasculitis (5.3%).[16-18] If no cause for stroke is identified, it is considered cryptogenic (20.0%).[7]

The term *embolic stroke of undetermined source* was introduced in 2014 to standardize the definition of strokes with an embolic appearance on neuroimaging with no clear mechanism after diagnostic workup.[19] Embolic stroke of undetermined source may be caused by covert paroxysmal atrial fibrillation and emboli from nonstenotic intracranial and extracranial large vessel atherosclerosis and can affect patients both with and without a PFO.[20,21]

Among patients with otherwise cryptogenic stroke and PFO, the duration of cardiac monitoring that should be performed to detect covert atrial fibrillation, defined as atrial fibrillation not detected by routine ECG, is uncertain.[22] Additionally, although longer duration of cardiac monitoring (up to 3 years) is associated with increased likelihood of detecting atrial fibrillation, it is unclear whether atrial fibrillation first identified during long-term follow-up should be considered a cause of an initial stroke,[23-27] particularly when the paroxysmal atrial fibrillation burden (ie, the proportion of total monitored time that the patient is the patient is in atrial fibrillation) is extremely low, such as less than 0.1% (ie, the proportion of total monitored time that the patient is in atrial fibrillation).[28-31] The 2021 American Heart Association/American Stroke Association guideline recommends cardiac monitoring to evaluate for atrial fibrillation for at least 24 hours after an ischemic stroke.[32] In contrast, a consortium of 8 European societies proposes 6 months of cardiac monitoring for patients with cryptogenic stroke at high risk of atrial fibrillation (eg, uncontrolled hypertension or diabetes, left ventricular hypertrophy, left atrial enlargement, or heart failure) before making a decision about PFO closure.[33,34]

Identification of PFO

Most patients in high-income countries who have a stroke initially undergo transthoracic echocardiography to evaluate for structural heart disease or a thrombus, and PFO may be identified with this testing. Patients being evaluated for PFO as a cause of stroke typically undergo TTE with a bubble study, which is performed by injecting agitated saline into a vein while the patient performs a Valsalva maneuver to increase right atrial pressure. PFO is diagnosed by visualizing microbubbles in the left atrium within 3 cardiac cycles, indicating a right-to-left shunt across the atrial septum. A transthoracic echocardiograph with bubble study has a pooled sensitivity of 71% (95% CI, 50%-86%) and specificity of 99% (95% CI, 93%-100%) for identifying a PFO[35] but is considered inadequate to rule out a PFO. Transcranial doppler ultrasound with a bubble study is another noninvasive study that can detect right-to-left shunting and has a pooled sensitivity of 96% (95% CI, 93%-98%) and specificity of 90% (95% CI, 83%-95%) for detection of PFO.[35] However, because TCD detects microbubbles within the cerebral circulation, it does not directly visualize the atrial septum and cannot differentiate PFO from other shunts.

The criterion standard for PFO identification is TEE with a bubble study (see related video) to evaluate the shunt size and anatomy of the PFO, as well as surrounding structures such as an atrial septal aneurysm or a Eustachian valve, which is an embryological remnant in the right atrium that may increase blood flow across a PFO. Transesophageal echocardiography, which involves insertion of an ultrasound probe into the esophagus to visualize the heart, is typically performed with patients receiving conscious sedation. A meta-analysis of 4 prospective studies (n = 164) comparing TEE and bubble study with PFO identification during autopsy, cardiac surgery, or cardiac catheterization yielded a sensitivity of 89% (95% CI, 81%-95%) and specificity of 91% (95% CI, 82%-97%).[36] However, some PFOs may still be missed due to patient intolerance of the TEE probe because of anxiety or uncontrolled gag reflex, difficulty performing the Valsalva maneuver while sedated, or limited operator experience.

Determining if the PFO Is Causal or Incidental

Risk of Paradoxical Embolism Score and PASCAL Classification

Among patients with otherwise cryptogenic stroke, a PFO is more likely to be identified in those without typical stroke risk factors.[37] The Risk of Paradoxical Embolism (RoPE) score (**Table 1**, top) was developed from an analysis of 8 databases that included 3023 patients with cryptogenic stroke who were systematically evaluated for PFO.[3,8] The RoPE score includes 6 clinical characteristics (age, history of stroke or transient ischemic attack [TIA], diabetes, hypertension, smoking, cortical infarct on imaging) and ranges from 0 to 10 (Table 1, top; **Table 2**).[38] The variation in prevalence across RoPE score stratum can be used to estimate the PFO-attributable fraction—the likelihood that a PFO identified in a patient with cryptogenic stroke is causally related to the stroke—according to Bayes theorem (Table 2). Among patients in the lowest RoPE score category (score <3, older patients with multiple stroke risk factors), the

prevalence of PFO was 23%, similar to that in the general population, suggesting a PFO-attributable fraction near zero.[38] The prevalence of PFO in patients with cryptogenic stroke and a RoPE score of 9 or 10 was 77%, suggesting a PFO-attributable fraction of approximately 90% in these patients.[38]

The RoPE score has been independently validated in studies of patients with otherwise cryptogenic stroke.[42,43] For example, in the ASTRAL database of 455 patients with PFO and otherwise cryptogenic stroke, the prevalence of PFO in each RoPE score stratum was similar to that in the RoPE database—ranging from 23% (95% CI, 21%-26%) in those with a RoPE score 3 or less to 72% (95% CI, 68%-75%) in those with a RoPE score of 9 or 10.[43] Because an attributable fraction is estimated and not a directly observable quantity, validation of the PFO-attributable fraction requires randomized data that examines the agreement between PFO-attributable fraction and the observed relative treatment effect of PFO closure across different RoPE strata.

Several limitations of the RoPE score have been noted. Studies have shown that patients with high RoPE scores may have a low risk of stroke recurrence.[38] In a study of 1324 patients with PFO-associated stroke, Kaplan-Meier estimates for stroke/TIA 2-year recurrence rates were 2% (95% CI, 0%-4%) in patients with a RoPE score of 9 or 10, so the absolute benefit of PFO closure in patients most at risk of having a recurrent PFO-attributable stroke may be limited. Additionally, the RoPE score does not incorporate PFO anatomical features associated with increased paradoxical embolism risk[44,45]—ie, a large shunt size (defined as >20 bubbles appearing within the right atrium within 3 cardiac cycles after venous injection of agitated saline) and atrial septal aneurysm (defined as ≥10 mm of excursion of the septal wall from midline).

The PFO-Associated Stroke Causal Likelihood (PASCAL) classification system includes the RoPE score and echocardiographic findings, with high-risk anatomical features defined as a large shunt and/or an atrial septal aneurysm (Table 1, bottom). Based on the PASCAL classification system, PFO is considered the "probable," "possible," or "unlikely" cause of otherwise cryptogenic stroke.

Table 1. Calculation of the RoPE Score and PASCAL Classification[a]

Characteristic		Points
RoPE score calculator[b]		
No history of hypertension		1
No history of diabetes		1
No history of stroke or transient ischemic attack		1
Nonsmoking		1
Cortical infarct on imaging		1
Age, y		
18-29		5
30-39		4
40-49		3
50-59		2
60-69		1
≥70		0
Total RoPE Score (sum of individual points)		X
PASCAL classification system[c]		
High RoPE score (≥7)	High-risk PFO feature (LS and/or ASA)	PFO-related stroke
Absent	Absent	Unlikely
Absent	Present	Possible
Present	Absent	
Present	Present	Probable

Abbreviations: ASA, atrial septal aneurysm (defined as ≥10 mm of excursion from midline); LS, large shunt (defined in the database as >20 bubbles in the left atrium on transesophageal echocardiogram); PASCAL, PFO-Associated Stroke Causal Likelihood; PFO, patent foramen ovale; RoPE, Risk of Paradoxical Embolism; .

[a] Adapted with permission from *Neurology*.[38]

[b] The RoPE score assesses the probability that a PFO discovered in the setting of an otherwise cryptogenic stroke was pathogenically related to the stroke rather than an incidental finding. The RoPE score ranges from 0 to 10, with scores of 0 to 3 indicating a negligible likelihood that the stroke is attributable to the PFO and a score of 10 indicating an approximately 90% probability that the stroke is attributable to the PFO.

[c] PASCAL combines the RoPE score with the presence or absence of high-risk PFO features to determine the likelihood that the PFO was causally related to the index stroke.

Other Potential Risk Factors for Paradoxical Embolism

Additional clinical factors not included in the RoPE score that may be associated with increased risk of paradoxical embolism include Valsalva at stroke onset; recent prolonged travel; sleep apnea; presence of a deep vein thrombosis or pulmonary embolism at presentation; hypercoagulability; migraine; and other anatomical features, such as the presence of a Chiari network or a Eustachian valve.[11,46-49]

Treatment of PFO-Associated Stroke

Percutaneous PFO closure is performed by insertion of a closure device via a catheter into the right atrium via the femoral vein. The device is deployed across the PFO, where it covers the PFO and becomes integrated into the cardiac tissue over time (Figure 1).

The first 3 randomized trials of patients with PFO-associated stroke treated with PFO closure and aspirin vs medical therapy alone (eg, either antiplatelet or anticoagulation medications) reported no statistically significant difference in the primary end points of stroke, TIA, or embolic events at 2-year follow-up (CLOSURE trial[39] [909 patients]), at 2.5-year follow-up (RESPECT trial[1] [980 patients]), and at 4-year follow-up (PC trial[41] [914 patients]).[50] However, a study of patients in the RESPECT trial at mean follow-up of 5.9 years reported 21 additional strokes and a recurrent ischemic stroke rate of 3.6% in the PFO closure group (18/499 patients) vs 5.8% in the medical therapy group (28/481 patients) (hazard ratio [HR], 0.55 [95% CI, 0.31-1.00]; $P = .046$).[1] The extended RESPECT,[51] REDUCE,[2] and CLOSE[3] trials, all published in 2017, and the DEFENSE-PFO trial,[40] published in 2018, all reported benefit of PFO closure in patients with PFO-associated stroke. Meta-analysis of 6 randomized trials (3560 patients) (Table 2) reported a lower rate of recurrent ischemic stroke with PFO closure (2%) vs medical therapy alone (4.6%) (relative risk, 0.44 [95% CI, 0.23-0.85]; $P = .01$) at a median follow-up of 57 months (IQR, 24-64).[33,52-54] Based on these results, guidelines now recommend PFO closure in selected patients (ie, aged <60 years with cryptogenic stroke).[32,33,55] The heterogeneity in clinical trials for antithrombotic therapy regimens that accompanies mechanical closure prohibits definitive

Table 2. PFO Closure Randomized Trials[a]

Trial (No. of patients in database)	Age, mean, y (inclusion criteria)	Atrial septal aneurysm, %	Large shunt, %	TIA as index event, %	PFO closure		Standard medical therapy		Baseline rhythm detection before enrollment	High-risk vs low-risk PFO features	Postclosure rhythm monitoring[b]
					PFO closure devices used	Antithrombotic given with device	Antiplatelet	Anticoagulant			
CLOSE,[3] 2017[c] (n = 663)	43 (16-60)	32	94	0	11 Types: double-disk (82%), STARFlex, double umbrella (18%)	Aspirin + clopidogrel for 3 mo followed by aspirin, clopidogrel, or aspirin + dipyridamole	Aspirin, clopidogrel or aspirin + dipyridamole	93% Received warfarin, 7% received DOAC[d]	Holter monitoring	Only high-risk	12-Lead ECG every follow-up visit
CLOSURE I,[39] 2012 (n = 909)	46 (8-60)	37	53	28	STARFlex (double umbrella)	Aspirin + clopidogrel for 6 mo followed by aspirin	Aspirin	25% Received warfarin	12-Lead ECG	Both	12-Lead ECG every follow-up visit
DEFENSE-PFO,[40] 2018 (n = 120)	52 (NR)	57	NR	0	Amplatzer (double-disk)	Recommended aspirin + clopidogrel for at least 6 mo after procedure, but could be any antithrombotic	Aspirin, clopidogrel, aspirin + clopidogrel, or aspirin + cilostazol	25% Received warfarin	Holter or prolonged cardiac monitoring	Only high-risk	NR
PC,[41] 2013 (n = 414)	44 (<60)	24	65	18	Amplatzer (double-disk)	Recommended aspirin + thienopyridine for 1-6 mo followed by aspirin for total at least 5-6 mo but could be any antithrombotic or none	Aspirin or thienopyridine	30% Received warfarin	Holter monitoring	Both	12-Lead ECG every follow-up visit
REDUCE,[2] 2017 (n = 664)	45 (18-59)	20[e]	84	0	Gore Helex (double-disk) or Cardioform septal occluder (double-disk)	Clopidogrel (300 mg) load periprocedure (if not already taking), 75 mg daily for 3 d, followed by same antiplatelet regimen as antiplatelet-only group	Aspirin, clopidogrel, or aspirin + dipyridamole	0%	12-Lead ECG	Both	12-Lead ECG every follow-up visit
RESPECT,[1] 2013, 2017 (n = 980)	46 (18-60)	36	49	0	Amplatzer (double-disk)	Aspirin + clopidogrel for 1 mo followed by aspirin for at least 5 mo	Aspirin, dipyridamole, clopidogrel or aspirin + dipyridamole	25% Received warfarin	12-Lead ECG or Holter monitoring	Both	ECG or Holter only at 1-mo follow-up

Abbreviations: DOAC, direct oral anticoagulant; ECG, electrocardiogram; NR, not reported; PFO, patent foramen ovale.

[a] Adapted with permission from *Neurology*. 2013;81(7):619-625.

[b] In addition to telemetry during hospitalization of PFO closure procedure, and if there was a concern for arrhythmia on postclosure follow-up, cardiac monitoring was performed at the discretion of the clinical team.

[c] CLOSE trial was the only trial designed in a 1:1:1 ratio comparing PFO closure vs antiplatelet vs anticoagulant. Data presented here compare PFO closure vs antiplatelet groups only. No clinical data on PFO closure vs anticoagulation groups were reported.

[d] Anticoagulation group only.

[e] For the closure group only.

recommendations that favors a single approach for all patients (Table 2). Nonetheless, the European Stroke Organization guidelines suggest dual antiplatelet therapy for 1 to 6 months following closure, and long-term single antiplatelet therapy, in part because the cause of the stroke is rarely certain.[35]

However, even after PFO closure, patients with cryptogenic stroke and PFO have a higher stroke risk at 4-year follow-up (2.5% [95% CI, 1.5%-4.0%]) after closure compared with the general population (0.4% [95% CI, 0.3%-0.6%]; HR, 6.3 [95% CI, 3.1-12.6]).[56] Stroke recurrence risk in patients after PFO closure is associated with cardiovascular risk factors such as age and modifiable risk factors such as hypertension, diabetes, dyslipidemia, and smoking status,[57] underscoring the importance of managing vascular risk factors even after PFO closure.

Adverse Effects of PFO Closure

PFO closure is generally considered safe but serious adverse effects may occur, including atrial fibrillation/flutter (3.7%), vascular complications consisting of hemorrhage/hematoma and vascular complication requiring surgical repair (3.0%), hematoma/hemorrhage (2.7%), cardiac tamponade/perforation (0.5%), pneumothorax/hemothorax (0.1%), and death (0.3%), based on a retrospective cohort study using claims data from 1887 patients.[58] In an analysis of pooled individual patient data from 6 randomized clinical trials (RCTs) of device closure of PFO after stroke,[59] the number of patients experiencing any serious adverse event was similar in the PFO closure group (28.7%) and medical therapy group (26.4%) (risk difference, 1.97% [95% CI, −0.89% to 4.82%]) over a median follow-up of 57 months. However, atrial fibrillation was higher in the PFO closure group (5.0%) than the medical therapy group (1.1%) (risk difference, 3.77% [95% CI, 2.65%-4.89%]), although more than one-half of this risk difference was due to periprocedural atrial fibrillation, which is often transient.[60] The risk of atrial fibrillation onset beyond the periprocedural period (>45 days after the procedure) was 2.4% in the PFO closure group vs 0.8% in the medical therapy group (risk difference, 1.38% [95% CI, 0.56%-2.19%]).[59] Additionally, venous thromboembolism was 1.4% in the PFO closure group vs 0.5% in the medical therapy group (risk difference, 0.87% [95% CI, 0.22%-1.51%]); bleeding was similar across treatment groups (1.4% with closure vs 1.7% with medical therapy).[59] Other rare potential device-related complications that were not quantified in these trials include nitinol allergic reactions due to nickel exposure and device dislodgement, fracture, and infection.

Variation in the Effects of PFO Closure Based on RoPE Score and PASCAL Classification

The individual patient meta-analysis of 6 RCTs (n = 3740) investigated the benefit of PFO closure in reducing recurrent stroke across the RoPE score and the PASCAL classification system.[59] In this pooled analysis, the annualized incidence of stroke over a median follow-up of 57 months was 0.47% (95% CI, 0.35%-0.65%) with PFO closure vs 1.09% (95% CI, 0.88%-1.36%) with medical therapy (adjusted HR, 0.41 [95% CI, 0.28-0.60]). For patients with a higher risk of paradoxical embolus as the cause of their stroke (RoPE score ≥7), the relative reduction in the rate of recurrent stroke was significantly greater (HR, 0.21 [95% CI, 0.11-0.42]) compared with patients with a lower risk of paradoxical embolus as the cause (RoPE score <7; HR, 0.61 [95% CI, 0.37-1.00]; P = .02). (**Figure 2**).[59] The reduction in risk of recurrent stroke is similar to the calculated attributable fractions of 40% in those with RoPE scores less than 7 and 80% in those with RoPE scores 7 or greater (Table 2).[59,61,62]

Using the PASCAL classification system (Table 1, bottom), among patients classified as PASCAL "probable" based on the presence of high-risk anatomical features and a high RoPE score, PFO closure was associated with a 90% relative decrease in the rate of stroke recurrence over a median 57 months (HR, 0.10 [95% CI, 0.03-0.35]; absolute risk reduction, 2.1% [95% CI, 0.9%-3.4%]) (Figure 2A). PASCAL "possible" patients had an intermediate degree of relative benefit (HR, 0.38 [95% CI, 0.22-0.65]), although similar to PASCAL "probable" patients on the clinically important absolute scale—with a 2-year risk difference in recurrent stroke with closure of approximately 2% in both the PASCAL "probable" and "possible" categories[59] (Figure 2B). In contrast, patients in the PASCAL "unlikely" category had no reduction in the rate of recurrent stroke with PFO closure (HR, 1.14 [95% CI, 0.53-2.46]). The difference in effects across PASCAL strata was highly statistically significant (P = .003 over a median follow-up of 57 months).

Rates of device-related safety outcomes have been reported to be higher in the PASCAL "unlikely" group than in the "probable" or "possible" groups. For example, in the pooled analysis of 6 RCTs, the absolute risk increase of postperiprocedural atrial fibrillation (occurring >45 days after randomization) over a median follow-up of 57 months was 4.41% (95% CI, 1.02%-7.80%) in the PASCAL "unlikely" category, 1.53% (95% CI, 0.33%-2.72%) in the "possible" category, and 0.65% (95% CI, −0.41% to 1.71%) in the "probable" category. The increased risk of atrial fibrillation among device-treated patients in the PASCAL "unlikely" category likely is due to their older age and increased vascular risk factors, which are associated with procedure-related atrial fibrillation.[43]

While the PASCAL classification system considers a large shunt or an atrial septal aneurysm as high-risk anatomical features for PFO, a pooled analysis of 6 trials (n = 3740) indicated that patients with both of these high-risk PFO features received the most benefit from PFO closure.[63] These patients had both the highest recurrence rate with medical therapy (5.9% at 2 years) and the lowest recurrence with closure (0.4% at 2 years). At 2 years, their absolute risk reduction of recurrent stroke was 5.5% (95% CI, 2.7%-8.3%), compared with 1.0% in patients with only 1 or none of these high-risk features.[63]

Medical Therapy (Anticoagulants and Antiplatelet Medications)

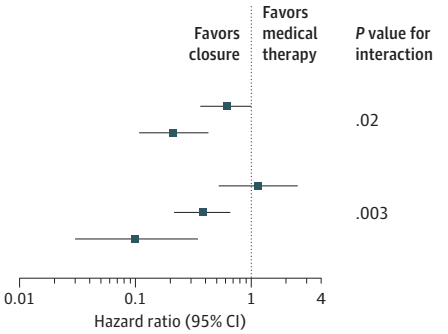
A meta-analysis of 6 RCTs (1961 patients) compared anticoagulants with antiplatelet therapies in patients with PFO-associated stroke; 2 studies assessed warfarin vs aspirin, and 4 assessed direct oral anticoagulants vs aspirin. Across these studies, anticoagulation with warfarin or direct oral anticoagulants was associated with a lower risk for recurrent ischemic stroke (3.2%) compared with antiplatelet therapy (5.5%; relative risk, 0.59 [95% CI, 0.35-0.98]; P = .04).[64]

Of the 6 randomized trials examining PFO closure vs medical therapy for prevention of recurrent stroke, 4 trials allowed investigators to select the medical therapy (antiplatelet therapy or anticoagulation with warfarin), 1 trial (REDUCE) had protocol-driven antiplatelet therapy, and 1 trial (CLOSE) randomized medically treated patients to anticoagulants or antiplatelet medications. Approximately three-fourths of medically treated patients in the 6 trials

Figure 2. Recurrent Ischemic Stroke Heterogeneity of Treatment Effect (HTE) Analyses for RoPE and PASCAL

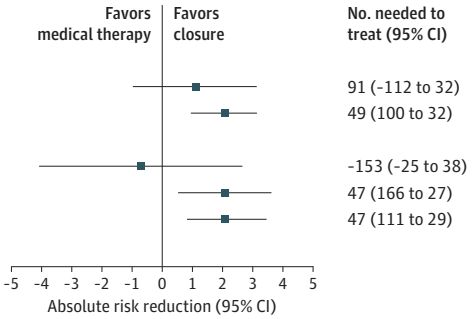
A Hazard ratios of the primary outcome of recurrent ischemic stroke

	Device, overall events/No. of patients	Medical therapy, overall events/ No. of patients	Hazard ratio (95% CI)
RoPE categories			
<7	29/700	41/704	0.61 (0.37 to 1.00)
≥7	11/1189	41/1147	0.21 (0.11 to 0.42)
PASCAL categories			
Unlikely	17/293	11/254	1.14 (0.53 to 2.46)
Possible	19/897	46/914	0.38 (0.22 to 0.65)
Probable	3/700	25/683	0.10 (0.03 to 0.35)



B Absolute risk reductions of the primary outcome of recurrent ischemic stroke

	Device, 2-y events/No. (%)	Medical therapy, 2-y events/ No. (%)	Absolute risk reduction at 2 y (95% CI)
RoPE categories			
<7	20/700 (2.9)	27/704 (4.0)	1.1 (-0.9 to 3.1)
≥7	7/1189 (0.6)	28/1147 (2.6)	2.1 (1.0 to 3.1)
PASCAL categories			
Unlikely	11/293 (4.1)	8/254 (3.4)	-0.7 (-4.0 to 2.6)
Possible	13/897 (1.5)	31/914 (3.6)	2.1 (0.6 to 3.6)
Probable	2/700 (0.3)	16/683 (2.5)	2.1 (0.9 to 3.4)



Statistically significant heterogeneous treatment effects of patent foramen ovale (PFO) closure were seen for patients subgrouped both by Risk of Paradoxical Embolism (RoPE) Score and by PFO-Associated Stroke Causal Likelihood (PASCAL). The hazard ratios observed by RoPE strata correspond very closely to anticipated relative event rate reductions shown in Table 1. Patients classified as PASCAL "unlikely" do not benefit from PFO closure. The hazard ratios in this figure are adjusted for age, sex, prior myocardial infarction, diabetes, hypertension, hyperlipidemia, prior stroke or transient ischemic attack, smoking status, index event (stroke vs transient ischemic attack), atrial septal aneurysm, shunt size, and superficial infarction on neuroimaging. Two-year absolute risk reductions are calculated as differences in Kaplan-Meier event rates at 2 years.

Republished from *JAMA*.[59]

received antiplatelet therapy. Thus, the comparative effectiveness of PFO closure vs anticoagulation alone remains uncertain and warrants further study.

Consideration of PFO Closure in Patients Older Than 60 Years

Although PFO closure in patients 60 years or younger with PFO-associated stroke is associated with decreased risk of stroke, the potential benefit in older patients is uncertain. Among the 6 randomized trials, only 1 trial enrolled patients older than 60 years, and the small sample size (34 older patients, only 13 of whom underwent PFO closure) precluded conclusive results.[65] The potential benefits of PFO closure in older patients is an area of active investigation, with at least 1 ongoing RCT.[66]

There have been 2 observational studies using propensity score approaches.[67,68] In an analysis of 130 propensity-matched pairs of patients, PFO closure was associated with a significantly lower risk of a composite outcome of ischemic stroke or TIA, with an incidence of 4.25 (95% CI, 2.77-6.53) per 100 person-years with medical therapy and 2.10 (95% CI, 1.05-4.19) per 100 patient-years with PFO closure (HR, 0.45 [95% CI, 0.24-0.84]; $P = .01$).[66] A propensity-matched cohort study including 5508 Medicare beneficiaries (device, n = 1132; control, n = 4376) with a median age of 71 years (IQR, 67-75) and a median follow-up of 2.58 years (IQR, 1.17-3.97)[68] also reported a significantly lower risk of recurrent ischemic stroke in the PFO closure group (1.65 [95% CI, 1.18-2.13] per 100 patient-years) compared with the medically treated control group (2.66 [95% CI, 2.33-3.00] per 100 patient-years) (HR, 0.62 [95% CI, 0.44-0.88]; $P = .007$). However, both of these studies had biases that may have favored the device group. The former study did not use a similarly defined time zero across study groups (so-called "immortal time bias"[69]). The latter study used "real world data" that did not permit identification of cryptogenic strokes, and there were imbalances between study groups, as reflected in mortality outcomes.

In the absence of clear evidence, some guidelines, such as those from the American Academy of Neurology, suggest that PFO closure may be reasonable for patients aged 60 to 65 years who have high-risk PFO features such as a large shunt and an atrial septal aneurysm, despite RoPE score less than 7.[55,70]

Choice of Closure Device and Future Directions

Most current PFO closure devices are double-disk occluders. There are no trials comparing US Food and Drug Administration–approved devices with respect to efficacy and safety; observational

data and meta-analyses do not provide consistent conclusions favoring one over another.[71-75]

Several new device types are under development, including bioabsorbable double-disk devices that endothelialize and biodegrade after placement.[76] Additionally, a new suture-mediated technique, which may avoid nitinol allergic reactions, as well as other device-related complications, such as dislodgement, fracture, infection, and atrial fibrillation, is under evaluation.[77] This technique may also be used to close residual defects from failed device closures.[78]

Areas of Uncertainty and Practical Considerations

First, PFO closure is associated with an increased risk of periprocedural atrial fibrillation, which is often transient and resolves spontaneously; it is unclear if these patients should receive anticoagulation.[79] Second, it is also uncertain if patients with transient ischemic attack should undergo PFO closure because these individuals have not been included in most RCTs investigating PFO closure. Third, because a PFO leads to right-to-left shunting, identification of venous thromboembolism may increase the possibility that the PFO is causally associated with stroke. In studies of patients with PFO and cryptogenic stroke who underwent workup, the frequency of deep venous thrombosis (DVT) ranged between 7% and 27%.[79] Presence of DVT is not currently included in risk stratification scores for PFO-associated stroke, and there are no high-quality data on the utility of screening for DVT in these patients. However, early evaluation for DVT, including lower extremity doppler and consideration of pelvic magnetic resonance venography, has been recommended by society guidelines.[32]

Limitations

This review has limitations. First, the quality of the included studies was not formally evaluated. Second, relevant studies may have been missed. Third, included studies had variability in the diagnostic workup of ischemic stroke, which resulted in substantial heterogeneity across studies.

Conclusions

PFO is present in approximately 25% of all adults and is a common cause of stroke in young and middle-aged patients. Percutaneous PFO closure substantially reduces the risk of stroke recurrence in younger patients after an otherwise cryptogenic stroke. The PASCAL Classification System can help guide patient selection for PFO closure to optimize benefits and minimize adverse events.

ARTICLE INFORMATION

Accepted for Publication: June 13, 2025.

Published Online: July 28, 2025. doi:10.1001/jama.2025.10946

Conflict of Interest Disclosures: None reported.

Additional Contributions: We thank Benjamin Wessler, MD (Tufts Medical Center), for contributing the video, which shows a high-risk patent foramen ovale, with both an atrial septal aneurysm and a large shunt, obtained by transesophageal echocardiography. Dr Wessler received no compensation for his contributions.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

REFERENCES

1. Saver JL, Carroll JD, Thaler DE, et al; RESPECT Investigators. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. *N Engl J Med*. 2017;377(11):1022-1032. doi:10.1056/NEJMoa1610057

2. Søndergaard L, Kasner SE, Rhodes JF, et al; Gore REDUCE Clinical Study Investigators. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. *N Engl J Med*. 2017;377(11):1033-1042. doi:10.1056/NEJMoa1707404

3. Mas JL, Derumeaux G, Guillon B, et al; CLOSE Investigators. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. *N Engl J Med*. 2017;377(11):1011-1021. doi:10.1056/NEJMoa1705915

4. Meissner I, Khandheria BK, Heit JA, et al. Patent foramen ovale: innocent or guilty? evidence from a prospective population-based study. *J Am Coll Cardiol*. 2006;47(2):440-445. doi:10.1016/j.jacc.2005.10.044

5. Tong DC, Becker KJ. Patent foramen ovale and recurrent stroke: closure is the best option: no. *Stroke*. 2004;35(3):804-805. doi:10.1161/01.STR.0000117964.10781.BA

6. Meacham RR III, Headley AS, Bronze MS, Lewis JB, Rester MM. Impending paradoxical embolism. *Arch Intern Med*. 1998;158(5):438-448. doi:10.1001/archinte.158.5.438

7. Elgendy AY, Saver JL, Amin Z, et al. Proposal for updated nomenclature and classification of potential causative mechanism in patent foramen ovale-associated stroke. *JAMA Neurol*. 2020;77(7):878-886. doi:10.1001/jamaneurol.2020.0458

8. Yan C, Li H, Wang C, et al. Frequency and size of in situ thrombus within patent foramen ovale. *Stroke*. 2023;54(5):1205-1213. doi:10.1161/STROKEAHA.122.041524

9. Zhu J, Chen A, Zhu L, et al. Right atrial septal in situ microthrombus: a potential novel cause of patent foramen ovale–associated stroke. *J Am Heart Assoc*. 2024;13(22):e035838. doi:10.1161/JAHA.124.035838

10. Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology*. 2000;55(8):1172-1179. doi:10.1212/WNL.55.8.1172

11. Alsheikh-Ali AA, Thaler DE, Kent DM. Patent foramen ovale in cryptogenic stroke: incidental or pathogenic? *Stroke*. 2009;40(7):2349-2355. doi:10.1161/STROKEAHA.109.547828

12. Saver JL, Mattle HP, Thaler D. Patent foramen ovale closure versus medical therapy for cryptogenic ischemic stroke: a topical review. *Stroke*. 2018;49(6):1541-1548. doi:10.1161/STROKEAHA.117.018153

13. Mohr JP. Cryptogenic stroke. *N Engl J Med*. 1988;318(18):1197-1198. doi:10.1056/NEJM198805053181810

14. Saver JL. Cryptogenic stroke. *N Engl J Med*. 2016;375(11):e26. doi:10.1056/NEJMc1609156

15. Prabhakaran S, Messé SR, Kleindorfer D, et al. Cryptogenic stroke: contemporary trends, treatments, and outcomes in the United States. *Neurol Clin Pract*. 2020;10(5):396-405. doi:10.1212/CPJ.0000000000000736

16. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial. *Stroke*. 1993;24(1):35-41. doi:10.1161/01.STR.24.1.35

17. Ay H, Benner T, Arsava EM, et al. A computerized algorithm for etiologic classification of ischemic stroke: the Causative Classification of Stroke System. *Stroke*. 2007;38(11):2979-2984. doi:10.1161/STROKEAHA.107.490896

18. Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Wolf ME, Hennerici MG. The ASCOD phenotyping of ischemic stroke (updated ASCO phenotyping). *Cerebrovasc Dis*. 2013;36(1):1-5. doi:10.1159/000352050

19. Hart RG, Diener HC, Coutts SB, et al; Cryptogenic Stroke/ESUS International Working Group. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol*. 2014;13(4):429-438. doi:10.1016/S1474-4422(13)70310-7

20. Ospel JM, Kappelhof M, Ganesh A, Kallmes DF, Brinjikji W, Goyal M. Symptomatic non-stenotic carotid disease: current challenges and opportunities for diagnosis and treatment. *J Neurointerv Surg*. 2024;16(4):418-424. doi:10.1136/jnis-2022-020005

21. Kamel H, Gialdini G, Baradaran H, et al. Cryptogenic stroke and nonstenosing intracranial calcified atherosclerosis. *J Stroke Cerebrovasc Dis*. 2017;26(4):863-870. doi:10.1016/j.jstrokecerebrovasdis.2016.10.035

22. Smith EE, Yaghi S, Sposato LA, Fisher M. Atrial fibrillation detection and load: knowledge gaps related to stroke prevention. *Stroke*. 2024;55(1):205-213. doi:10.1161/STROKEAHA.123.043665

23. Sanna T, Diener HC, Passman RS, et al; CRYSTAL AF Investigators. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med*. 2014;370(26):2478-2486. doi:10.1056/NEJMoa1313600

24. Gladstone DJ, Spring M, Dorian P, et al; EMBRACE Investigators and Coordinators. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med*. 2014;370(26):2467-2477. doi:10.1056/NEJMoa1311376

25. Buck BH, Hill MD, Quinn FR, et al. Effect of implantable vs prolonged external electrocardiographic monitoring on atrial fibrillation detection in patients with ischemic stroke: the PER DIEM randomized clinical trial. *JAMA*. 2021;325(21):2160-2168. doi:10.1001/jama.2021.6128

26. Bernstein RA, Kamel H, Granger CB, et al; STROKE-AF Investigators. Effect of long-term continuous cardiac monitoring vs usual care on detection of atrial fibrillation in patients with stroke attributed to large- or small-vessel disease: the STROKE-AF randomized clinical trial. *JAMA*. 2021;325(21):2169-2177. doi:10.1001/jama.2021.6470

27. Bernstein RA, Kamel H, Granger CB, et al; STROKE AF Investigators. Atrial fibrillation in patients with stroke attributed to large- or small-vessel disease: 3-year results from the STROKE AF randomized clinical trial. *JAMA Neurol*. 2023;80(12):1277-1283. doi:10.1001/jamaneurol.2023.3931

28. Chen JZ, Thijs VN. Presence of atrial fibrillation in stroke patients with patent foramen ovale: systematic review and meta-analysis. *Front Neurol*. 2021;12:613758. doi:10.3389/fneur.2021.613758

29. Sposato LA, Chaturvedi S, Hsieh CY, Morillo CA, Kamel H. Atrial fibrillation detected after stroke and transient ischemic attack: a novel clinical concept challenging current views. *Stroke*. 2022;53(3):e94-e103. doi:10.1161/STROKEAHA.121.034777

30. Sposato LA, Field TS, Schnabel RB, Wachter R, Andrade JG, Hill MD. Towards a new classification of atrial fibrillation detected after a stroke or a transient ischaemic attack. *Lancet Neurol*. 2024;23(1):110-122. doi:10.1016/S1474-4422(23)00326-5

31. Chaisinanunkul N, Khurshid S, Buck BH, et al. How often is occult atrial fibrillation in cryptogenic stroke causal vs. incidental? a meta-analysis. *Front Neurol*. 2023;14:1103664. doi:10.3389/fneur.2023.1103664

32. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 Guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. *Stroke*. 2021;52(7):e364-e467. doi:10.1161/STR.0000000000000375

33. Pristipino C, Sievert H, D'Ascenzo F, et al; Evidence Synthesis Team; Eapci Scientific Documents and Initiatives Committee; International Experts. European position paper on the management of patients with patent foramen ovale: general approach and left circulation thromboembolism. *Eur Heart J*. 2019;40(38):3182-3195. doi:10.1093/eurheartj/ehy649

34. Diener HC, Wachter R, Wong A, et al. Monitoring for atrial fibrillation prior to patent foramen ovale closure after cryptogenic stroke. *Int J Stroke*. 2023;18(4):400-407. doi:10.1177/17474930221124412

35. Caso V, Turc G, Abdul-Rahim AH, et al. European Stroke Organisation (ESO) guidelines on the diagnosis and management of patent foramen ovale (PFO) after stroke. *Eur Stroke J*. 2024;9(4):800-834. doi:10.1177/23969873241247978

36. Mojadidi MK, Bogush N, Caceres JD, Msaouel P, Tobis JM. Diagnostic accuracy of transesophageal echocardiogram for the detection of patent foramen ovale: a meta-analysis. *Echocardiography*. 2014;31(6):752-758. doi:10.1111/echo.12462

37. Dahabreh IJ, Kent DM. Index event bias as an explanation for the paradoxes of recurrence risk research. *JAMA*. 2011;305(8):822-823. doi:10.1001/jama.2011.163

38. Kent DM, Ruthazer R, Weimar C, et al. An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke. *Neurology*. 2013;81(7):619-625. doi:10.1212/WNL.0b013e3182a08d59

39. Furlan AJ, Reisman M, Massaro J, et al; CLOSURE I Investigators. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. *N Engl J Med*. 2012;366(11):991-999. doi:10.1056/NEJMoa1009639

40. Lee PH, Song JK, Kim JS, et al. Cryptogenic stroke and high-risk patent foramen ovale: the DEFENSE-PFO trial. *J Am Coll Cardiol*. 2018;71(20):2335-2342. doi:10.1016/j.jacc.2018.02.046

41. Meier B, Kalesan B, Mattle HP, et al; PC Trial Investigators. Percutaneous closure of patent foramen ovale in cryptogenic embolism. *N Engl J Med*. 2013;368(12):1083-1091. doi:10.1056/NEJMoa1211716

42. Prefasi D, Martínez-Sánchez P, Fuentes B, Díez-Tejedor E. The utility of the RoPE score in cryptogenic stroke patients ≤50 years in predicting a stroke-related patent foramen ovale. *Int J Stroke*. 2016;11(1):NP7-NP8. doi:10.1177/1747493015607505

43. Strambo D, Sirimarco G, Nannoni S, et al. Embolic stroke of undetermined source and patent foramen ovale: risk of paradoxical embolism score validation and atrial fibrillation prediction. *Stroke*. 2021;52(5):1643-1652. doi:10.1161/STROKEAHA.120.032453

44. Mas JL, Arquizan C, Lamy C, et al; Patent Foramen Ovale and Atrial Septal Aneurysm Study Group. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. *N Engl J Med*. 2001;345(24):1740-1746. doi:10.1056/NEJMoa011503

45. Belkin RN, Hurwitz BJ, Kisslo J. Atrial septal aneurysm: association with cerebrovascular and peripheral embolic events. *Stroke*. 1987;18(5):856-862. doi:10.1161/01.STR.18.5.856

46. De Castro S, Cartoni D, Fiorelli M, et al. Morphological and functional characteristics of patent foramen ovale and their embolic implications. *Stroke*. 2000;31(10):2407-2413. doi:10.1161/01.STR.31.10.2407

47. Schuchlenz HW, Saurer G, Weihs W, Rehak P. Persisting Eustachian valve in adults: relation to patent foramen ovale and cerebrovascular events. *J Am Soc Echocardiogr*. 2004;17(3):231-233. doi:10.1016/j.echo.2003.12.003

48. Kato Y, Dembo T, Takeda H, Fukuoka T, Tanahashi N. Prominent persisting Eustachian valve initiates spontaneous right-to-left shunt and paradoxical embolism in a patient with patent foramen ovale. *Neurol Sci*. 2011;32(5):925-926. doi:10.1007/s10072-011-0567-7

49. Ozdemir AO, Tamayo A, Munoz C, Dias B, Spence JD. Cryptogenic stroke and patent foramen ovale: clinical clues to paradoxical embolism. *J Neurol Sci*. 2008;275(1-2):121-127. doi:10.1016/j.jns.2008.08.018

50. Kent DM, Dahabreh IJ, Ruthazer R, et al. Device closure of patent foramen ovale after stroke: pooled analysis of completed randomized trials. *J Am Coll Cardiol*. 2016;67(8):907-917. doi:10.1016/j.jacc.2015.12.023

51. Carroll JD, Saver JL, Thaler DE, et al; RESPECT Investigators. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. *N Engl J Med*. 2013;368(12):1092-1100. doi:10.1056/NEJMoa1301440

52. Kasner SE, Lattanzi S, Fonseca AC, Elgendy AY. Uncertainties and controversies in the management of ischemic stroke and transient ischemic attack patients with patent foramen ovale. *Stroke*. 2021;52(12):e806-e819. doi:10.1161/STROKEAHA.121.034778

53. Zhang XL, Kang LN, Wang L, Xu B. Percutaneous closure versus medical therapy for stroke with patent foramen ovale: a systematic review and meta-analysis. *BMC Cardiovasc Disord*. 2018;18(1):45. doi:10.1186/s12872-018-0780-x

54. Shah R, Nayyar M, Jovin IS, et al. Device closure versus medical therapy alone for patent foramen ovale in patients with cryptogenic stroke: a systematic review and meta-analysis. *Ann Intern Med*. 2018;168(5):335-342. doi:10.7326/M17-2679

55. Messé SR, Gronseth GS, Kent DM, et al. Practice advisory update summary: patent foramen ovale and secondary stroke prevention: report of the Guideline Subcommittee of the American Academy of Neurology. *Neurology*. 2020;94(20):876-885. doi:10.1212/WNL.0000000000009443

56. Bonnesen K, Korsholm K, Andersen A, et al. Risk of ischemic stroke after patent foramen ovale closure. *J Am Coll Cardiol*. 2024;84(15):1424-1433. doi:10.1016/j.jacc.2024.07.015

57. Rudolph V, Augustin J, Hofmann T, et al. Predictors of recurrent stroke after percutaneous closure of patent foramen ovale. *EuroIntervention*. 2014;9(12):1418-1422. doi:10.4244/EIJV9I12A239

58. Merkler AE, Gialdini G, Yaghi S, et al. Safety outcomes after percutaneous transcatheter closure of patent foramen ovale. *Stroke*. 2017;48(11):3073-3077. doi:10.1161/STROKEAHA.117.018501

59. Kent DM, Saver JL, Kasner SE, et al. Heterogeneity of treatment effects in an analysis of pooled individual patient data from randomized trials of device closure of patent foramen ovale after stroke. *JAMA*. 2021;326(22):2277-2286. doi:10.1001/jama.2021.20956

60. Ntaios G, Papavasileiou V, Sagris D, et al. Closure of patent foramen ovale versus medical therapy in patients with cryptogenic stroke or transient ischemic attack: updated systematic review and meta-analysis. *Stroke*. 2018;49(2):412-418. doi:10.1161/STROKEAHA.117.020030

61. Kent DM, Saver JL, Ruthazer R, et al. Risk of Paradoxical Embolism (RoPE)–estimated attributable fraction correlates with the benefit of patent foramen ovale closure: an analysis of 3 trials.

Stroke. 2020;51(10):3119-3123. doi:10.1161/STROKEAHA.120.029350

62. Kent DM, Saver JL, Kasner SE, et al. *Evaluating Therapies to Prevent Future Stroke in Patients with Patent Foramen Ovale–Related Strokes—The SCOPE Study*. Patient-Centered Outcomes Research Institute; 2023. doi:10.25302/04.2023.RS.SCOPE2019001.

63. Mas JL, Saver JL, Kasner SE, et al. Association of atrial septal aneurysm and shunt size with stroke recurrence and benefit from patent foramen ovale closure. *JAMA Neurol*. 2022;79(11):1175-1179. doi:10.1001/jamaneurol.2022.3248

64. Ghannam M, Al-Qudah AM, Alshaer QN, et al. Anticoagulation vs antiplatelets across subgroups of embolic stroke of undetermined source: a meta-analysis of randomized controlled trials. *Neurology*. 2024;103(9):e209949. doi:10.1212/WNL.0000000000209949

65. Kwon H, Lee PH, Song JK, Kwon SU, Kang DW, Kim JS. Patent foramen ovale closure in old stroke patients: a subgroup analysis of the DEFENSE-PFO trial. *J Stroke*. 2021;23(2):289-292. doi:10.5853/jos.2021.00647

66. Mas JLCG. PFO closure, oral anticoagulants or antiplatelet therapy after PFO-associated stroke in patients aged 60 to 80 years (CLOSE-2) [NCT05387954]. ClinicalTrials.gov. Published February 1, 2025. Accessed June 16, 2025. https://clinicaltrials.gov/study/NCT05387954

67. Lee PH, Kim JS, Song JK, et al. Device closure or antithrombotic therapy after cryptogenic stroke in elderly patients with a high-risk patent foramen ovale. *J Stroke*. 2024;26(2):242-251. doi:10.5853/jos.2023.03265

68. Satpathy R, Rodes-Cabau J, Thaler D, et al. TCT 113 patent foramen ovale closure in patients >60 years: age stratified results from US Medicare beneficiaries. *J Am Coll Cardiol*. Published online October 23, 2024. doi:10.1016/j.jacc.2024.09.853

69. Suissa S. Immortal time bias in pharmaco-epidemiology. *Am J Epidemiol*. 2008;167(4):492-499. doi:10.1093/aje/kwm324

70. Farjat-Pasos JI, Chamorro A, Lanthier S, et al. Cerebrovascular events in older patients with patent foramen ovale: current status and future perspectives. *J Stroke*. 2023;25(3):338-349. doi:10.5853/jos.2023.01599

71. Gevorgyan Fleming R, Kumar P, West B, et al. Comparison of residual shunt rate and complications across 6 different closure devices for patent foramen ovale. *Catheter Cardiovasc Interv*. 2020;95(3):365-372. doi:10.1002/ccd.28527

72. Musto C, Cifarelli A, Dipasquale F, et al. A comparison between Gore Cardioform and Amplatzer septal occluder for percutaneous closure of patent foramen ovale associated with atrial septal aneurysm: clinical and echocardiographic outcomes. *J Invasive Cardiol*. 2021;33(11):E857-E862. doi:10.25270/jic/20.00655

73. Varotto L, Bregolin G, Paccanaro M, De Boni A, Bonanno C, Perini F. The closure of patent foramen ovale in preventing subsequent neurological events: a bayesian network meta-analysis to identify the best device. *Cerebrovasc Dis*. 2020;49(2):124-134. doi:10.1159/000507317

74. Gaetti G, Beneduce A, La Fauci D, et al. Suture-mediated patent foramen ovale closure using the NobleStitch EL: results from a hospital-based HTA. *Int J Environ Res Public Health*. 2022;19(13):7863. doi:10.3390/ijerph19137863

75. Hornung M, Bertog SC, Franke J, et al. Long-term results of a randomized trial comparing three different devices for percutaneous closure of a patent foramen ovale. *Eur Heart J*. 2013;34(43):3362-3369. doi:10.1093/eurheartj/eht283

76. Rigatelli G, Zuin M, Rodinò G, Marchese G, Pasquetto G. Recent advances in catheter devices for patent foramen ovale closure. *Expert Rev Med Devices*. 2023;20(1):29-34. doi:10.1080/17434440.2023.2170782

77. Gaspardone A, De Marco F, Sgueglia GA, et al. Novel percutaneous suture-mediated patent foramen ovale closure technique: early results of the NobleStitch EL Italian Registry. *EuroIntervention*. 2018;14(3):e272-e279. doi:10.4244/EIJ-D-18-00023

78. Chaudhry-Waterman N, Shapiro S, Thompson J. Use of the NobleStitch EL for the treatment of patients with residual right-to-left shunt following device closure of PFO. *Clin Case Rep*. 2021;9(4):1929-1932. doi:10.1002/ccr3.3906

79. Zietz A, Sutter R, De Marchis GM. Deep vein thrombosis and pulmonary embolism among patients with a cryptogenic stroke linked to patent foramen ovale—a review of the literature. *Front Neurol*. 2020;11:336. doi:10.3389/fneur.2020.00336