2.02.09	Closure Devices for Patent Foramen Ovale and Atrial Septal Defects		
Original Policy Date:	March 30, 2015	**Effective Date:**	August 1, 2023
Section:	2.0 Medicine	**Page:**	Page 1 of 31

Policy Statement

I. The percutaneous transcatheter closure of a patent foramen ovale (PFO) using a device that has been approved by the U.S. Food and Drug Administration for that purpose may be considered **medically necessary** to reduce the risk of recurrent ischemic stroke if an individual meets **all** of the following:
   A. Between 18 and 60 years of age
   B. Diagnosed with PFO with a right-to-left interatrial shunt confirmed by echocardiography with at least **one** of the following characteristics:
      1. PFO with large shunt, defined as greater than 30 microbubbles in the left atrium within 3 cardiac cycles, after opacification of the right atrium
      2. PFO associated with atrial septal aneurysm on transesophageal examination: septum primum excursion greater than 10 mm
   C. Documented history of cryptogenic ischemic stroke due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an evaluation to exclude any other identifiable cause of stroke, including large vessel atherosclerotic disease and small vessel occlusive disease
   D. **None** of the following are present:
      1. Uncontrolled vascular risk factors, including uncontrolled diabetes or uncontrolled hypertension
      2. Other sources of right-to-left shunts, including an atrial septal defect and/or fenestrated septum
      3. Active endocarditis or other untreated infections
      4. Inferior vena cava filter

II. Transcatheter closure of secundum atrial septal defects may be considered **medically necessary** when using a device that has been approved by the U.S. Food and Drug Administration for that purpose and used according to the labeled indications including **both** of the following:
   A. Individuals with echocardiographic evidence of ostium secundum atrial septal defect
   B. **Either** of the following:
      1. Clinical evidence of right ventricular volume overload (i.e., 1.5:1 degree of left-to-right shunt or right ventricular enlargement)
      2. Clinical evidence of paradoxical embolism

III. Transcatheter closure of secundum atrial septal defects is considered **investigational** for all other indications not meeting the criteria outlined above.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Two devices approved by the U.S. Food and Drug Administration for patent foramen ovale closure and atrial septal defect closure are currently marketed: the Amplatzer™ Septal Occluder and the GORE® CARDIOFORM Septal Occluder. The GORE® HELEX Septal Occluder has been discontinued.

Coding

There is a CPT code for percutaneous transcatheter closure of congenital interatrial communication (i.e., Fontan fenestration, atrial septal defect) with implant (code 93580). CPT notes that 93580

includes a right heart catheterization procedure. Other heart catheterization procedures should not be reported separately if 93580 is reported.

Description

Patent foramen ovale (PFO) and atrial septal defects (ASDs) are relatively common congenital heart defects that can be associated with a range of symptoms. PFOs may be asymptomatic but have been associated with higher rates of cryptogenic stroke. PFOs have also been investigated for a variety of other conditions, such as a migraine. Depending on their size, ASDs may lead to left-to-right shunting and signs and symptoms of pulmonary overload. Repair of ASDs is indicated for patients with a significant degree of left-to-right shunting. Transcatheter closure devices have been developed to repair PFO and ASDs. These devices are alternatives to open surgical repair for ASDs or treatment with antiplatelet and/or anticoagulant medications in patients with cryptogenic stroke and PFO.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Patent Foramen Ovale Closure Devices

The U.S. Food and Drug Administration (FDA) has approved 2 devices for PFO closure through the premarket approval process or a premarket approval supplement: the Amplatzer PFO Occluder and the GORE CARDIOFORM Septal Occluder (see Table 1).

FDA product code: MLV.

In 2002, 2 transcatheter devices were cleared for marketing by the FDA through a humanitarian device exemption as a treatment for patients with cryptogenic stroke and PFO: the CardioSEAL® Septal Occlusion System (NMT Medical; device no longer commercially available) and the Amplatzer PFO Occluder (Amplatzer, now St. Jude Medical). Following the limited FDA approval, use of PFO closure devices increased by more than 50-fold, well in excess of the 4000 per year threshold intended under the humanitarian device exemption,[2,] prompting the FDA to withdraw the humanitarian device exemption approval for these devices in 2007. The Amplatzer PFO Occluder was approved through the premarket approval process in 2016.

In March 2018, the FDA granted an expanded indication to the Gore Cardioform Septal Occluder to include the closure of PFO to reduce the risk of recurrent stroke (see Table 1). The new indication was

based on the results of the Reduction in the Use of Corticosteroids in Exacerbated COPD (REDUCE) pivotal clinical trial.[3,]

Table 1. Patent Foramen Ovale Closure Devices Approved by the U.S. Food and Drug Administration

Device	Manufacturer	PMA Approval Date	Indications
Amplatzer PFO Occluder	St. Jude Medical	Nov 2016	For percutaneous transcatheter closure of a PFO to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke.[4,]
GORE CARDIOFORM Septal Occluder	W.L. Gore & Associates	Mar 2018 (supplement)	PFO closure to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke.

PFO: patent foramen ovale; PMA: premarket approval.
FDA product code: MLV.

Atrial Septal Defect Closure Devices

The FDA has approved 4 devices for ASD closure through the premarket approval process or a premarket approval supplement: the Amplatzer Septal Occluder, the GORE HELEX Septal Occluder (discontinued), GORE CARDIOFORM ASD Occluder, and the GORE CARDIOFORM Septal Occluder (see Table 2).

FDA product code: MLV.

Table 2. Atrial Septal Defect Closure Devices Approved by the U.S. Food and Drug Administration

Device	Manufacturer	PMA Approval Date	Indications
Amplatzer Septal Occluder	St. Jude Medical (Abbott Medical)	Dec 2001	• Occlusion of ASDs in the secundum position • Use in patients who have had a fenestrated Fontan procedure who require closure of the fenestration • Patients indicated for ASD closure have echocardiographic evidence of ostium secundum ASD and clinical evidence of right ventricular volume overload.
GORE HELEX Septal Occluder	W.L. Gore & Associates	Aug 2006 (discontinued)	• Percutaneous, transcatheter closure of ostium secundum ASDs
GORE CARDIOFORM ASD Occluder	W.L. Gore & Associates	May 2019 (supplement)	• Percutaneous, transcatheter closure of ostium secundum ASDs
GORE CARDIOFORM Septal Occluder	W.L. Gore & Associates	Apr 2015 (supplement)	• Percutaneous, transcatheter closure of ostium secundum ASDs

ASD: atrial septal defect; PMA: premarket approval.
FDA product code: MLV.

Rationale

Background

Patent Foramen Ovale

The foramen ovale, a component of fetal cardiovascular circulation, consists of a communication between the right and left atrium that functions as a vascular bypass of the uninflated lungs. The ductus arteriosus is another feature of the fetal cardiovascular circulation, consisting of a connection between the pulmonary artery and the distal aorta. Before birth, the foramen ovale is held open by the large flow of blood into the left atrium from the inferior vena cava. Over the course of months after birth, an increase in left atrial pressure and a decrease in right atrial pressure result in permanent closure of the foramen ovale in most individuals. However, a patent foramen ovale (PFO) is a common finding in 25% of asymptomatic adults.[1,] In some epidemiologic studies, PFO has been associated with cryptogenic stroke, defined as an ischemic stroke occurring in the absence of potential cardiac, pulmonary, vascular, or neurologic sources. Studies have also shown an association between PFO and migraine headache.

Atrial Septal Defects

Unlike PFO, which represents the postnatal persistence of normal fetal cardiovascular physiology, atrial septal defects (ASDs) represent an abnormality in the development of the heart that results in free communication between the atria. ASDs are categorized by their anatomy. Ostium secundum describes defects located midseptally and are typically near the fossa ovalis. Ostium primum defects lie immediately adjacent to the atrioventricular valves and are within the spectrum of atrioventricular septal defects. Primum defects occur commonly in patients with Down syndrome. Sinus venous defects occur high in the atrial septum and are frequently associated with anomalies of the pulmonary veins.

Ostium secundum ASDs are the third most common form of congenital heart disorder and among the most common congenital cardiac malformations in adults, accounting for 30% to 40% of these patients older than age 40 years. The ASD often goes unnoticed for decades because the physical signs are subtle and the clinical sequelae are mild. However, virtually all patients who survive into their sixth decade are symptomatic; fewer than 50% of patients survive beyond age 40 to 50 years due to heart failure or pulmonary hypertension related to the left-to-right shunt. Symptoms related to ASD depend on the size of the defect and the relative diastolic filling properties of the left and right ventricles. Reduced left ventricular compliance, and mitral stenosis will increase left-to-right shunting across the defect. Conditions that reduce right ventricular compliance and tricuspid stenosis will reduce left-to-right shunting or cause a right-to-left shunt. Symptoms of an ASD include exercise intolerance and dyspnea, atrial fibrillation, and less commonly, signs of right heart failure. Patients with ASDs are also at risk for paradoxical emboli.

Treatment of Atrial Septal Defects

Repair of ASDs is recommended for those with a pulmonary-to-systemic flow ratio (Q_p: Q_s) exceeding 1.5:1.0. Despite the success of surgical repair, there has been interest in developing a transcatheter-based approach to ASD repair to avoid the risks and morbidity of open heart surgery. A variety of devices have been researched. Technical challenges include minimizing the size of the device so that smaller catheters can be used, developing techniques to center the device properly across the ASD, and ensuring that the device can be easily retrieved or repositioned, if necessary.

Individuals with ASDs and a history of cryptogenic stroke are typically treated with antiplatelet agents, given an absence of evidence that systemic anticoagulation is associated with outcome improvements.

Transcatheter Closure Devices

Transcatheter PFO and ASD occluders consist of a single or paired wire mesh disc covered or filled with polyester or polymer fabric that are placed over the septal defect. Over time, the occlusion system is epithelialized. ASD occluder devices consist of flexible mesh discs delivered via catheter to cover the ASD.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Transcatheter Device Closure of Patent Foramen Ovale for Stroke

Clinical Context and Therapy Purpose

The purpose of patent foramen ovale (PFO) closure with a transcatheter device in patients who have PFO and cryptogenic stroke is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with PFO and cryptogenic stroke.

Interventions

The therapy being considered is PFO closure with a transcatheter device.

Comparators

The following therapies are currently being used to manage PFO closure in patients with cryptogenic stroke: conventional therapy for cryptogenic stroke, which consists of antiplatelet therapy (aspirin, clopidogrel, or dipyridamole given alone or in combination) or oral anticoagulation with warfarin. In general, patients with a known clotting disorder or evidence of preexisting thromboembolism are treated with warfarin, and patients without these risk factors are treated with antiplatelet agents.

Outcomes
The general outcomes of interest are overall survival, morbid events, treatment-related mortality, and treatment-related morbidity.

Based on identified clinical trials, long-term follow-up of ≥10 years would be preferable to determine outcomes for patients who undergo PFO closure.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

Review of Evidence
The evidence for the efficacy of transcatheter PFO closure devices for patients with cryptogenic stroke consists of 3 RCTs, a few nonrandomized comparative studies, and numerous case series. Meta-analyses of the published RCTs have also been performed.

Systematic Reviews
A large number of systematic reviews and meta-analyses have evaluated outcomes related to the percutaneous transcatheter closure of a PFO. Systematic reviews, by Kent et al (2016) and Li et al (2015), pooled data from 3 RCTs (Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale [CLOSURE I], Patent Foramen Ovale and Cryptogenic Embolism [PC-Trial], Patent Foramen Ovale Closure or Medical Therapy After Stroke [RESPECT]) in their systematic reviews.[5,6,] However, the findings of analyses published prior to 2018 may no longer be relevant because (1) they pooled data across multiple devices (STARFlex septal closure system is no longer available), which might differ in terms of efficacy and safety, and (2) did not incorporate results of multiple RCTs with long-term follow-up of up to 5 years published in 2017. Therefore, systematic reviews published before 2017 are not discussed further.

Two meta-analyses published in 2018 included data from PC-Trial, RESPECT extended follow-up, GORE Septal Occluder Device for Patent Foramen Ovale (PFO) Closure in Stroke Patients (REDUCE), and Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE), but excluded CLOSURE I trial data because it used the STARFlex PFO closure device (Tables 3 and 4).[7,8,] Shah et al (2018) reported that PFO closure reduced the absolute risk of recurrent stroke by 3.2% (95% confidence interval [CI], 1.4% to 5.0%). De Rosa et al (2018) reported that the PFO closure reduced the absolute risk of stroke or transient ischemic attack (TIA) by 2.9% (95% CI, 1.2% to 5.4%). Shah et al (2018) concluded that the association of device therapy with new-onset atrial fibrillation was inconclusive because of marked heterogeneity between trials and extremes in CIs reported in some cases. On the other hand, De Rosa et al (2018) reported a statistically significant increase in the risk of atrial fibrillation with PFO closure devices. In the REDUCE trial, more than 80% of episodes of atrial fibrillation were observed within 45 days from randomization and resolved within 2 weeks.[9,] Similarly, in the CLOSE trial, more than 90% of atrial fibrillation cases in the PFO closure group were observed during the first month and did not recur.[10,] In the PC-Trial, new-onset atrial fibrillation was reported in 6 (2.9%) patients in the PFO closure group and was transient in 5 of these cases.[11,]

Alushi et al (2018) included all 5 trials and reported outcomes as pooled hazard ratios (HRs) or odds ratios (ORs) in a third meta-analysis (Tables 3 and 4).[12,] Results were similar to previous systematic

reviews: there was a 48% reduction in the composite primary outcome of TIA or stroke but no significant reduction in risk of TIA (Table 4). There was an increased risk of atrial fibrillation but no difference between groups in the risk of major bleeding.

Table 3. Systematic Review & Meta-Analysis Characteristics

Study	Dates	Trials	Participants	N (Range)	Designs	Duration
Shah et al (2018)[7,]	1966-2017	4	Adults with PFO and cryptogenic stroke	4866 (NR)	RCTs	No restrictions
De Rosa et al (2018)[8,]	2004-2017	4	Adults with PFO and cryptogenic stroke	2932 (67 to 622)	RCTs	No restrictions
Alushi et al (2018)[12,]	1990-2017	5	Adults with PFO and cryptogenic stroke	3440 (414 to 980)	RCTs	No restrictions

NR: not reported; PFO: patent foramen ovale; RCT: randomized controlled trial.

Table 4. Systematic Review & Meta-Analysis Results

Study	Stroke	TIA	Stroke or TIA	Major Bleeding	AF
Shah et al (2018)[7,]					
N	2892	2892	NA	1912	663
ARR (95% CI)	-3.2 (-5.0 to -1.4)	-0.4 (-1.7 to 1.0)	NA	-2.1 (-5.1 to 0.9)	6.1 (NR)
NNT (95% CI)	NR	NR	NA	NR	NR
I^2 (*P-value*)	3.62 (.38)	0 (.81)	NA	0 (.92)	82.5 (<.001)
De Rosa et al (2018)[8,]					
N	2531	NA	2531	2531	2531
ARR (95% CI)	-3.1 (-5.1 to -1.0)	NA	-2.9 (-5.0 to -0.7)	-0.2 (-1.2 to 0.7)	3.3 (1.2 to 5.4)
NNT (95% CI)	NR	NA	NR	NR	NR
I^2 (*P-value*)	61 (.003)	NA	33.79 (.29)	28 (.60)	66 (.002)
Alushi et al (2018)[12,]					
N	3440	2776 (Excludes REDUCE)	3440	3440	3440
HR/OR (95% CI); P-value	HR, 0.39 (0.19 to 0.83); <.01	HR, 0.73 (0.49 to 1.09);.12	HR, 0.52 (0.26 to 0.77); <.01	OR, 0.97 (0.44 to 2.17);.95	OR, 3.75 (2.44 to 5.78); <.01
NNT	37	NA	33	NA	49
I^2 (*range*)	56 (0 to 84)	0	26	39	0

AF: atrial fibrillation; ARR: absolute risk reduction; CI: confidence interval; HR: hazard ratio; NA: not applicable; NNT: number needed to treat; NR: not reported; OR: odds ratio; REDUCE: GORE Septal Occluder Device for Patent Foramen Ovale (PFO) Closure in Stroke Patients; TIA: transient ischemic attack.

Randomized Controlled Trials

Transcatheter Patent Foramen Ovale Closure With Device Versus Medical Management

Three RCTs, the PC-Trial [11,], the RESPECT trial[13,], and the Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale (DEFENSE-PFO) trial have been published and reported on outcomes comparing the Amplatzer PFO Occluder with medical management. Trial characteristics and results are summarized in Tables 5 and 6.

In the PC-Trial (2013), the primary endpoint (composite of death, nonfatal stroke, TIA, or peripheral embolism after independent adjudication) did not differ significantly between the closure and medical groups either on intention-to-treat (ITT) analysis or per-protocol analysis. Also, there were no significant differences in the rates of the individual components of the primary outcome or the outcomes on subgroup analyses. The adverse event rate was 34.8% in the closure group and 29.5% in the medical therapy group. This trial was designed to have 80% power to detect a reduction of 66% in primary endpoint (from 3% per year in the medical therapy group vs. 1% per year in the closure group). However, the observed event rate in the trial was less than half of the anticipated event rate used in the power calculation and, as reported by authors, the trial had less than 40% power to detect a 66% reduction.

RESPECT (2013) also compared closure with medical management, with 2 notable differences from the PC-Trial: TIA was not included as a component of the primary composite endpoint, and all endpoints were adjudicated in a blinded fashion. These protocol differences were attempts to address shortcomings observed in the PC-Trial where authors noted that TIA as a component in the primary endpoint might have diluted effects, as suggested by the difference in the estimated HRs for stroke (0.20) and TIA (0.71). Trialists had also noted the possibility of selective reporting of potential events in the PC-Trial owing to the open-label nature of the trial.

Results of the RESPECT trial have been reported in 3 publications[13,14,15,] with each publication reporting longer follow-up. The primary endpoint was stroke or early death, 30 and 45 days after implantation or randomization, respectively.

Carroll et al (2013), reported in the first publication a median follow-up of 2.3 years and no difference in the primary endpoint with ITT analysis.[13,] The ITT analysis (N=980) included 3 patients from the closure group who had recurrent ischemic stroke before device implantation. However, the per-protocol cohort (N=944; patients as randomized who adhered to the protocol-mandated medical treatment, and did not have a major inclusion or exclusion violation) and as-treated cohort (N=958; patients with a protocol-approved treatment who adhered to the protocol-mandated medical treatment, and were classified by treatment actually received) showed statistically significant improvements in primary endpoint in both analyses (HR , 0.37; 95% CI, 0.14 to 0.96; p=.03; and HR , 0.27; 95% CI, 0.10 to 0.75; p=.007, respectively). The number needed to treat (NNT) after 5 years in the ITT population was 27. The rate of serious, device- or procedure-related complications was 4.5%. There was no difference in major bleeding between arms, but there was a higher incidence of deep vein thrombosis and pulmonary thromboembolism in the device arm. This was attributed to a 9-fold increased use of warfarin in the medical group.

Rogers et al (2017) published an overview of the U.S. Food and Drug Administration (FDA) assessment of the Amplatzer PFO Occluder that included analysis of data with approximately 5 years of follow-up.[15,] The FDA conducted ITT, per-protocol, as-treated, and device-in-place analyses, and results are summarized in Table 6. Although the FDA panel had some disagreements about using non-ITT analysis because excluding patients compromises randomization, the panel agreed that a 50% relative risk reduction in stroke—especially in a younger patient population—is clinically significant. All 3 analyses (i.e., per-protocol, as-treated, and device-in-place) reported statistically significant relative reductions of more than 50% in the risk of recurrent strokes. Note that with extended follow-up analyses, the event-free survival curves converged, and the NNT after 5 years in the ITT population rose from 27 to 43. However, the FDA concluded that it might be reasonable for conclusions drawn from RESPECT to be limited to the select subgroup of at-risk patients with stroke and PFO in whom other causes of ischemic stroke have been excluded by a neurologist.

Saver et al (2017) also published results from the RESPECT trial, reporting on a median of 5.9 years of follow-up.[14,] Rogers et al (2016) reported similar findings.[15,] The relative difference in the rate of recurrent ischemic stroke between closure and medical therapy alone was large (45% lower with closure), but the absolute difference was small (0.49 fewer events per 100 patient-years with closure).

Lee et al (2018) reported on the DEFENSE-PFO randomized open-label superiority trial.[16,] The trial compared PFO closure using the Amplatzer PFO Occluder plus medical therapy with medical therapy alone. Patients included in the trial had experienced ischemic stroke within the last 6 months for no apparent cause other than a high-risk PFO with right-to-left shunting. All patients were prescribed either antiplatelet or anticoagulation medication. The trial's recruitment rate was lower than expected, and the CLOSE trial was completed and published during the course of DEFENSE-PFO. Based on the results of CLOSE, the investigators agreed to stop enrollment early for the patients' safety. The trial and its results are described in Tables 5 and 6.

Table 5. Summary of Key Randomized Controlled Trial Characteristics for the Amplatzer Patent Foramen Ovale Occluder

Trial	Countries	Sites	Dates	Participants	Interventions		Median DOF, y
					Active	*Comparator*	
Meier et al (2013)[11]; PC-Trial	European Union, Canada, Brazil, Australia	29	2000-2009	With PFO, <60 y, and history of ischemic stroke, TIA, or a peripheral TE event	Amplatzer PFO Occluder	Medical treatment[a]	4.1
Carroll et al (2013)[13]; RESPECT	United States, Canada	69	2003-2011	With PFO, 18 to 60 y, and cryptogenic ischemic stroke	Amplatzer PFO Occluder	Medical treatment[b]	2.1
Saver et al (2017)[14]; RESPECT	United States, Canada	69	2003-2011	With PFO, 18 to 60 y, and cryptogenic ischemic stroke	Amplatzer PFO Occluder	Medical treatment[b]	5.9
Lee et al (2018)[16]; DEFENSE-PFO	South Korea	2	2011-2017	With cryptogenic stroke and high-risk PFO	Amplatzer PFO Occluder with medical treatment	Medical treatment[b]	2.8

DEFENSE-PFO: Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale; DOF: duration of follow-up; PC-Trial: Patent Foramen Ovale and Cryptogenic Embolism; PFO: patent foramen ovale; RESPECT: Patent Foramen Ovale Closure or Medical Therapy After Stroke; TE: thromboembolic; TIA: transient ischemic attack.

[a] Antithrombotic as per physician discretion and could have included antiplatelet therapy or oral anticoagulation, provided that patients received at least 1 antithrombotic drug.
[b] Aspirin, warfarin, clopidogrel, or aspirin combined with extended-release dipyridamole.

Table 6. Summary of Key Randomized Controlled Trial Results for the Amplatzer Patent Foramen Ovale Occluder

Trial	Primary Endpoint	Secondary Endpoint	Stroke
Meier et al (2013)[11]; PC-Trial	414	414	414
Amplatzer, n/N (%)	7/204 (3.4)[a]	5/204 (2.5)[b]	1/204 (0.5)
Medical treatment, n/N (%)	11/210 (5.2)[a]	11/210 (5.2)[b]	5/210 (2.4)
HR (95% CI); P-value	0.63 (0.24 to 1.62);.34[a]	0.45 (0.16 to 1.29);.14[b]	0.20 (0.02 to 1.72);.14
Carroll et al (2013)[13]; RESPECT	980		
Amplatzer, n/N (%)	9/499 (1.8)[c]	NA	9/499 (1.8)
Medical treatment, n/N (%)	16/481 (3.3)[c]	NA	16/481 (3.3)
HR (95% CI); P-value	0.49 (0.22 to 1.11);.08[c]	NA	0.49 (0.22 to 1.11);.08
Saver et al (2017)[14]; RESPECT			
Amplatzer, n/N (%)	NR	NA	18/499 (3.6)
Medical treatment, n/N (%)	NR	NA	28/481 (5.8)
HR (95% CI); P-value	NR	NA	0.55 (0.31 to 0.99);.04
Lee et al (2018)[16]; DEFENSE-PFO	120		120
Amplatzer, n/N (%)[d,e]	0/60 (0.0)[e]	NA	0/60 (0.0)
Medical treatment, n/N (%)[d,e]	6/60 (12.9)[e]	NA	5/60 (10.5)
(95% CI); P-value	(3.2 to 22.6);.013	NA	(NR);.023

CI: confidence interval; DEFENSE-PFO: Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale; HR: hazard ratio; NA: not applicable; NR: not reported; PC-Trial: Patent Foramen Ovale and Cryptogenic Embolism; RESPECT: Patent Foramen Ovale Closure or Medical Therapy After Stroke; TIA: transient ischemic attack.

[a] Composite of death, nonfatal stroke, TIA, or peripheral embolism.
[b] Composite of stroke, TIA, or peripheral embolism.
[c] Composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization.
[d] Intention-to-treat analysis.

[e] Kaplan-Meier estimates.
[f] Composite of stroke, vascular death, or Thrombolysis In Myocardial Infarction (TIMI)-defined major bleeding within 2 years of procedure.

Table 7. U.S. Food and Drug Administration Summary of Kaplan-Meier Analyses of the Primary Endpoint in RESPECT Trial (Amplatzer Patent Foramen Ovale Occluder)

Analysis Population	Definitions	RRR, %	P-value
Intention to treat	Primary analysis population including all randomized patients whether or not Amplatzer implanted	50	.089
Per-protocol	All patients adhering to protocol requirements[a] whether or not Amplatzer implanted	63	.034[b]
As-treated	All patients adhering to protocol requirements[a] who actually had the Amplatzer implanted	72	.008[b]
Device-in-place	All randomized patients who had Amplatzer implanted	70	.007[b]

FDA assessment as reported by Rogers et al (2017).[15,]
FDA: Food and Drug Administration; RESPECT: Patent Foramen Ovale Closure or Medical Therapy After Stroke; RRR: relative risk reduction.
[a] Adherence to guidelines-directed medical therapy defined as ≥67% cumulative compliance over the duration of the study.
[b] p<.05 was considered statistically significant.

Transcatheter Patent Foramen Ovale Closure With Device Plus Medical Management Versus Medical Management Alone

Two RCTs —the REDUCE and CLOSE trials—have been published and reported on outcomes comparing various closure devices plus medical management with medical management alone. They are summarized in Tables 8 and 9. Note that both the REDUCE and CLOSE trials enrolled more patients with a moderate-to-large interatrial shunt size (58.4% and 75.2%) compared with 16.7% and 19.3% of patients with a large interatrial shunt size in the PC-Trial and RESPECT trial, all respectively.

In the REDUCE trial (2017), the blinded adjudicated coprimary endpoints of freedom from ischemic stroke (reported as the percentage of patients who had a stroke recurrence) and incidence of new brain infarction (clinical ischemic stroke plus silent brain infarction on imaging) 2 years after randomization were significantly lower in the PFO closure plus antiplatelet therapy than the antiplatelet therapy alone group in ITT analysis, the per-protocol analysis, and the as-treated population analysis (see Table 9).[9,] The NNT to prevent 1 stroke in 24 months was approximately 28. Previous trials such as RESPECT, PC-Trial, and CLOSURE allowed discontinuation of antithrombotic therapy after PFO closure, and the use of anticoagulants in the medical therapy group was at the discretion of the treating physician. Such a design may have led to the confounding of results and bias within the medical therapy groups in favor of control because of increased protection from the risk of stroke due to causes other than PFO. Serious adverse events occurred in 23.1% of patients in the PFO closure group and 27.8% of patients in the antiplatelet-only group (p=.22).

Anderson et al (2021) described the occurrence of post-procedural atrial fibrillation in the REDUCE trial.[17,] In this trial, a total of 408/441 patients had successful PFO closure with either the HELEX device (39%) or the Gore Cardioform Septal Occluder (61%). During a median follow-up of 5 years, 30/408 (7.4%) patients had a diagnosis of atrial fibrillation after PFO closure, whereas only 1/223 (0.4%) patients who received antiplatelet therapy alone had atrial fibrillation (p<.001). The majority of cases of atrial fibrillation (79.4%) occurred within 45 days after PFO closure and most episodes (62.5%) were less than 2 weeks in duration. In the REDUCE clinical study, postprocedural atrial fibrillation was mostly transient, early onset and did not recur at a later time. Postprocedural atrial fibrillation occurred more frequently among patients with higher age and larger devices. Male sex was the only independent predictor of postprocedural atrial fibrillation.

In the CLOSE trial (2017), 663 patients were randomized to PFO closure plus antiplatelet therapy (PFO closure group), antiplatelet therapy alone (antiplatelet-only group), or oral anticoagulation

(anticoagulation group).[10,] The primary blinded adjudicated outcome of stroke was significantly lower in the PFO closure versus antiplatelet-only group in ITT analysis as well as per-protocol analysis (see Table 9). The 5-year stroke risk, using the Kaplan-Meier probability estimate, was 4.9 percentage points lower in the PFO closure group than in the antiplatelet-only group, which would result in 1 stroke avoided at 5 years for every 20 treated patients (95% CI, 17 to 25). The rate of atrial fibrillation was higher in the PFO closure group (4.6%) than in the antiplatelet-only group (0.9%; p=.02). The number of serious adverse events did not differ significantly between treatment groups (p=.56).

No clinical trials have focused specifically on patients who failed medical therapy, as defined by recurrent stroke or TIA while on therapy. Many published studies have included patients with first cryptogenic stroke and patients with recurrent stroke or TIA and have generally not analyzed these patient populations separately. As a result, it is not possible to determine from the evidence whether PFO closure in patients who have failed medical therapy reduces the risk of subsequent recurrences.

Table 8. Summary of Key Randomized Controlled Trial Characteristics

Trial	Countries	Sites	Dates	Participants	Interventions		DOF, y
					Active	*Comparator*	
Søndergaard et al (2017)[9,]; REDUCE	US, Europe	63	2008-2015	With PFO, 18 to 60 y, and cryptogenic ischemic stroke	HELEX or CARDIOFORM plus antiplatelet therapy[a]	Antiplatelet therapy alone[a]	median, 3.2
Mas et al (2017)[10,]; CLOSE	France, Germany	34	2008-2016	With PFO, 16 to 60 y, and cryptogenic ischemic stroke	Multiple closure devices plus antiplatelet therapy[b]	Antiplatelet therapy alone[c]	mean, 5.3

CLOSE: Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence; DOF: duration of follow-up; PFO: patent foramen ovale; REDUCE: GORE Septal Occluder Device for Patent Foramen Ovale (PFO) Closure in Stroke Patients.
[a] Antiplatelet therapy could consist of aspirin alone (75 to 325 mg once daily), a combination of aspirin (50 to 100 mg daily) and dipyridamole (225 to 400 mg daily), or clopidogrel (75 mg once daily).
[b] Dual antiplatelet therapy (aspirin 75 mg plus clopidogrel 75 mg per day) for 3 months followed by single antiplatelet therapy throughout the remainder of the trial.
[c] Antiplatelet therapy (aspirin, clopidogrel, or aspirin combined with extended release dipyridamole).
[d] Duration of follow-up in device closure group and antiplatelet-only group.

Table 9. Summary of Key Randomized Controlled Trial Results

Study; Trial	Primary Endpoint[a]	Primary Endpoint[b]	Secondary Endpoint[c]
Søndergaard et al (2017)[9,]REDUCE	664	664	NA
HELEX or CARDIOFORM plus antiplatelet therapy, n/N (%)	6/441 (1.4)	22/383 (5.7)	NA
Antiplatelet therapy alone, n/N (%)	12/223 (5.4)	20/177 (11.3)	NA
HR (95% CI); P-value	0.23 (0.09 to 0.62);.002	0.51 (0.29 to 0.91);.04	NA
NNT (95% CI)	20 (17 to 25)	NR	NA
Mas et al (2017)[10,]; CLOSE	473	NA	NR
Multiple closure devices plus antiplatelet therapy, n/N (%)	0/238 (0)	NA	NR (3.4)
Antiplatelet therapy alone, n/N (%)	14/235 (6.0)	NA	NR (8.9)
HR (95% CI); P-value	0.03 (0.00 to 0.26); <.001	NA	0.39 (0.16 to 0.82);.01

CI: confidence interval; CLOSE: Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence; HR: hazard ratio; NA: not applicable; NNT: number needed to treat; NR: not reported; REDUCE: GORE Septal Occluder Device for Patent Foramen Ovale (PFO) Closure in Stroke Patients.
[a] Freedom from ischemic stroke (reported as percentage of patients who had a recurrence of stroke) 2 years after randomization.
[b] Incidence of new brain infarction (clinical ischemic stroke or silent brain infarction on imaging) 2 years after randomization.
[c] Composite outcome of stroke, transient ischemic attack, or systemic embolism.

Observational Studies

There is a large evidence base of observational studies. Because multiple RCTs with more than 5 years of follow-up are available, data from these observational studies are not discussed except where such studies provide longer duration of follow-up, specifically related to durability of results and adverse events (revealed by larger populations or longer length of follow-up than in trials). Rigatelli et al (2016) reported safety outcomes on a series of 1000 consecutive patients who were treated with catheter-based closure using different devices and prospectively identified, with mean follow-up of 12.3 years.[18,] Permanent atrial fibrillation occurred in 0.5%, device thrombosis occurred in 0.5%, new-onset or worsening of mitral valve regurgitation was observed in 0.2%, and recurrent cerebral ischemic events occurred in 0.8% of patients. The occlusion rate was 93.8%. No aortic or atrial free wall erosion was reported.

Wintzer-Wehekind et al (2019) reported on long-term outcomes for 201 consecutive patients who had had a cryptogenic embolism (stroke, 76%; TIA, 32%; systemic embolism, 1%) and underwent PFO closure.[19,] Median follow-up, completed by 96% of the patients, was 12 years (range, 10 to 17 years). Patients also had follow-up at between 1 and 6 months that included an echocardiographic examination with a bubble test. No cases of late device embolization, dislocation, or thrombosis, or late pericardial effusion were found; however, 6 patients had a residual shunt, 1 of which required a second closure following a recurrent TIA. Thirteen patients (6.5%) died during the follow-up period, but no deaths were caused by cardiovascular events. Seven (3.5%) had at least 1 TIA or stroke. At the time of final follow-up, 20.9% (42/201) had been off antithrombotic therapy for a mean of 10 years (±4 y). There were no significant differences in rates of ischemic events or death between the group that went off antithrombotic medication and those who continued medication.

Section Summary: Transcatheter Device Closure of Patent Foramen Ovale for Stroke

The results of RCTs of PFO closure compared with medical management have reported point estimates of HRs ranging from 0.03 to 0.78, suggesting that PFO closure is more effective than medical therapy for reducing event rates. These results were not statistically significant by ITT analyses in the early trials (PC-Trial and RESPECT), but were significant in later trials (RESPECT extended follow-up, REDUCE, CLOSE). Initially, inadequate power was blamed for demonstrating the lack of superiority of PFO closure in the early RCTs, but the reasons are probably multifactorial. The RESPECT, REDUCE, and CLOSE trials enrolled patients when off-label PFO closure had decreased, allowing for inclusion for patients with vascular anatomic features (e.g., large intra-arterial shunt size) associated with a relatively higher risk of stroke among those with PFO. In addition, other factors such as the requirement of neuroimaging confirmation of stroke prior to enrollment, exclusion of lacunar infarcts, longer follow-up, and selection of patients with an associated atrial septal aneurysm in RESPECT, REDUCE, and CLOSE possibly contributed to selection of a trial population that adequately excluded other causes of cryptogenic stroke, yielding a sample at higher risk of cryptogenic stroke and therefore amenable to risk modification by PFO closure. It is important to acknowledge that higher rates of atrial fibrillation have been reported in a few of the individual trials and meta-analyses that incorporate evidence from RESPECT, REDUCE, and CLOSE trials. Thus, patient selection is crucial when assessing the risks and benefits of PFO closure over medical management.

Transcatheter Patent Foramen Ovale Closure for Migraine

Clinical Context and Therapy Purpose

Migraine headache has been associated with PFO in epidemiologic studies, and noncontrolled observational studies have reported improvement in migraine headaches after PFO closure.

The purpose of PFO closure with a transcatheter device in patients who have PFO and migraine is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with migraine headache.

Interventions
The therapy being considered is PFO closure with a transcatheter device.

Comparators
The following therapies are currently being used to make decisions about PFO closure with a transcatheter device: guideline-based preventive and abortive treatment with medical therapy.

Outcomes
The general outcomes of interest are overall survival, morbid events, treatment-related mortality, and treatment-related morbidity.

Based on identified clinical trials, long-term follow-up of ≥10 years would be preferable to determine outcomes for patients who undergo PFO closure.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Systematic Reviews
Lip and Lip (2014) published a descriptive, systematic review that assessed 20 studies evaluating the prevalence of PFO in patients with migraines and 21 studies on the effects of PFO closure.[20,] In case series and cohort studies of patients with migraines, the prevalence of PFO in patients with migraines ranged from 14.6% to 66.5%. In the case-control studies, the prevalence of PFO in control patients ranged from 16.0% to 25.7%, while the prevalence of PFO in patients who had a migraine with and without aura ranged from 26.8% to 96.0% and 22.6% to 72.4%, respectively. In the 18 case series that reported migraine outcomes after PFO closure, rates of resolution for migraine with and without aura ranged from 28.6% to 92.3% and 13.6% to 82.9%, respectively. In 2 case-control studies that compared PFO closure with no medical intervention or preventive migraine medication, improvement in migraine symptoms occurred in 83% to 87% of those who underwent PFO closure compared with 0% to 21% of those who received no intervention or who were managed medically. The single RCT included (Dowson et al [2008][21,]) did not identify significant improvements in migraine symptoms in the PFO closure group (3/74 in the implant group vs. 3/73 in the sham group; p=.51).

Wang et al (2022) conducted a meta-analysis to investigate the impact of PFO transcatheter closure on migraine burden.[22,] Studies were eligible if they compared transcatheter closure with drug or sham therapy in adults with migraine and PFO, with at least 6 months of follow-up. Overall, 12 studies were included: 3 RCTs and 9 case-control studies. Table 10 lists the studies included and Table 11 describes characteristics of the meta-analysis. Compared with medical or sham therapy, PFO closure significantly increased the rate of adults who were completely migraine-free at end of follow-up (see Table 12 for results). Additionally, PFO closure showed a statistically significant reduction in monthly migraine days and monthly migraine attacks compared to comparator groups. In the measurement of activities of daily living (ADLs), 2 scores were used: the Headache Impact Test-6 (HIT-6) and the Migraine Disability Assessment Survey (MIDAS). In the transcatheter closure group, HIT-6 was significantly decreased, implying improved ADLs, but there was no difference in MIDAS score

between groups. Among the included trials, 3 articles were considered to be of moderate quality and 9 were of high quality. The studies that examined ADLs had high heterogeneity (I^2=93%). The meta-analysis is limited by the retrospective nature of many of the included studies, since recall and reporting biases cannot be ruled out. There was heterogeneity among included studies, especially the case-control studies. Due to the limited number of included studies, further subgroup analysis stratifying patients with aura was not possible. Additionally, differences in outcomes across trials limits interpretability. The RCTs included in the trial, Dowson et al (2008),[21,] Mattle et al (2016),[23,] and Tobis et al (2017)[24,] did not individually find any significant improvements in migraine symptoms, migraine-free days, or migraine attacks in the PFO closure group compared to sham or drug therapy, so all significant data in favor of PFO closure came from case-control studies.

Table 10. Comparison of Studies Included in Migraine and Patent Foramen Ovale Meta-Analysis

Study	Wang (2022)[22,]
Anzola et al (2006) - case-control	●
Dowson et al (2008) - RCT (MIST)	●
Vigna et al (2009) - case-control	●
Rigatelli et al (2010) - case-control	●
Biasco et al (2014) - case-control	●
Mattle et al (2016) - RCT (PRIMA)	●
Xing et al (2016) - non-randomized clinical trial (EASTFORM)	●
Tobis et al (2017) - RCT (PREMIUM)	●
Zhang et al (2018) - case-control	●
He et al (2019) - case-control	●
Tian et al (2019) - case-control	●
Wang et al (2019) - case-control	●

EASTFORM: Effectiveness and Safety of Transcatheter Patent Foramen Ovale Closure for Migraine; MIST: Migraine Intervention With STARFlex Technology; PREMIUM: Percutaneous Closure of Patent Foramen Ovale in Patients with Migraine; PRIMA: Percutaneous Closure of Patent Foramen Ovale in Migraine with Aura; RCT: randomized controlled trial.

Table 11. Migraine and Patent Foramen Ovale Meta-Analysis Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Wang et al (2022)[22,]	2006-2019	12	Adults (mean age, 40 y; 76.4% women) with PFO and migraine; included trials comparing PFO closure with drug treatment or sham procedure, with at least 6 months follow-up	1754 (23 to 241)	RCTs (n=3 studies) and case-control (n=9)	Range, 6 months to 1 y (retrospective looked back up to 5 y)

PFO: patent foramen ovale; RCT: randomized controlled trial.

Table 12. Migraine and Patent Foramen Ovale Meta-Analysis Results

Study	Migraine-free at end of FU	Frequency of monthly migraine attack	Monthly migraine days	ADLs: HIT-6 score	ADLs: MIDAS score
Wang et al (2022)[22,]					
Total N	1022 (7 trials)	485 (4 trials)	482 (4 trials)	694 (5 trials)	534 (4 trials)
Pooled effect (95% CI)	OR, 4.47 (2.94 to 6.80)	SMD, 0.35 (0.17 to 0.53)	SMD, 0.28 (0.10 to 0.46)	SMD, 1.23 (0.52 to 1.95)	SMD, 0.96 (-0.55 to 2.47)
I^2 (p)	*12%* (.33)	*0%* (.61)	*0%* (.53)	*93%* (<.01)	*96%* (<.01)

ADLs: activities of daily living; CI: confidence interval; FU: follow-up; HIT-6: headache impact test-6; MIDAS: migraine disability assessment survey; OR: odds ratio; SMD: standard mean difference.

Randomized Controlled Trials

Dowson et al (2008) published results of the Migraine Intervention With STARFlex Technology (MIST) trial, a sham-controlled randomized trial of PFO closure for refractory migraine headache. [21,] As noted above, this trial did not find a significant difference in the primary endpoint of migraine headache cessation (3/74 in the implant group vs. 3/73 in the sham group ; p=.51). The results of this trial cast some doubt on the causal relation between PFO and migraine.

Mattle et al (2016) published results of the Percutaneous Closure of Patent Foramen Ovale in Migraine with Aura (PRIMA) trial, a randomized, open-label trial with blinded endpoint evaluation comparing transcatheter PFO closure with medical management in patients who had a migraine with aura.[23,]The trial enrolled 107 subjects with refractory migraine and PFO with a right-to-left shunt, who were randomized to PFO closure with the Amplatzer PFO Occluder (n=53) or medical management (n=54). The trial's power calculations required enrollment of 72 in each group. The trial was stopped prematurely due to slow enrollment, and there was a relatively high loss to follow-up (22%). In the device group, 45 of 53 patients agreed to have the PFO occluder implanted, and of those 41 underwent implantation. This suggests that the trial might have been underpowered to detect differences between groups. For the primary endpoint (reduction in mean migraine days at 1-year postrandomization), there were no significant differences between the groups (-2.9; 95% CI, -4.4 to -1.4 for PFO closure vs. -1.7; 95% CI, -2.5 to -1.0 for medical management; p=.168).

Tobis et al (2017) reported on the results of the Percutaneous Closure of Patent Foramen Ovale in Patients with Migraine (PREMIUM) trial (NCT00355056), which compared PFO closure (Amplatzer PFO Occluder) with a sham procedure in 230 patients with 6 to 14 days of a migraine per month.[24,] Enrolled patients had failed at least 3 migraine preventive medications and had significant right-to-left shunt identified by transcranial Doppler. The primary endpoint (50% reduction in migraine attacks) did not differ between the PFO closure (45/117) and the control (33/103) groups. One serious adverse event (transient atrial fibrillation) occurred in the 205 subjects who underwent PFO closure.

In a subgroup analysis of patients with migraine (n=145) who were enrolled in the previously described CLOSE trial, there were no differences between antiplatelet-only and PFO closure groups with regard to the mean annual number of migraine attacks, both in patients with migraine with aura (9.2 vs. 12.0 ; p=.81) and in those without aura (12.1 vs. 11.8 ; p>.999), at a mean follow-up of 5 years.[25,] Furthermore, there were no differences between treatment groups regarding cessation of migraine attacks, migraine-related disability, and use of migraine-preventive drugs during follow-up.

Observational Studies

Snijder et al (2016) reported on an observational case-control study that evaluated the association between migraine with aura and PFO among patients who underwent an agitated saline transesophageal echocardiogram over a 4-year period at a single outpatient cardiology clinic and had completed a validated headache questionnaire (N=889).[26,] In this sample, a PFO with atrial septal aneurysm was significantly associated with migraine with aura (OR, 2.71; 95% CI, 1.23 to 5.95; p=.01), while PFO alone was not.

Section Summary: Transcatheter Patent Foramen Ovale Closure for Migraine

Although observational studies have shown a possible association between PFO closure and reduction in migraine symptoms, sham-controlled randomized trials did not demonstrate significant improvements in migraine symptoms after PFO closure. Nonrandomized studies have shown highly variable rates of migraine improvement after PFO closure.

Transcatheter Patent Foramen Ovale Closure for Other Indications

Clinical Context and Therapy Purpose

The purpose of PFO closure with a transcatheter device in patients who have PFO and conditions associated with PFO other than cryptogenic stroke or migraine is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with PFO and conditions associated with PFO other than cryptogenic stroke or migraine. Several other medical conditions have been reported to occur more frequently in patients with PFOs, including platypnea-orthodeoxia syndrome, myocardial infarction with normal coronary arteries, decompression illness in response to change in environmental pressure, high-altitude pulmonary edema, and obstructive sleep apnea.[27,]

Interventions

The therapy being considered is PFO closure with a transcatheter device.

Comparators

The following therapies and practices are currently being used to make decisions about PFO closure with a transcatheter device: condition-specific medical therapy and related interventions.

Outcomes

The general outcomes of interest are overall survival, morbid events, treatment-related mortality, and treatment-related morbidity.

Based on identified clinical trials, long-term follow-up of ≥10 years would be preferable to determine outcomes for patients who undergo PFO closure.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Case Series/Case Reports

Evidence on clinical outcomes related to these conditions after PFO closure is limited to case reports and case series.

Mojadidi et al (2015) reported on a series of 17 patients who underwent transcatheter PFO closure for platypnea-orthodeoxia syndrome at a single institution, among whom 11 (65%) were classified as having improved oxygen saturation postprocedure.[28,]

Section Summary: Transcatheter Patent Foramen Ovale Closure for Other Indications

The body of evidence on other medical conditions treated with PFO closure only consists of small case series and case reports, which is an insufficient basis on which to draw conclusions about efficacy.

Transcatheter Device Closure for Atrial Septal Defects

Clinical Context and Therapy Purpose

Atrial septal defects (ASDs) represent an abnormality in the development of the heart that results in free communication between the atria. ASDs are categorized by their anatomy. Ostium secundum describes defects located midseptally that are typically near the fossa ovalis. Ostium primum defects lie immediately adjacent to the atrioventricular valves and are within the spectrum of atrioventricular septal defects. Primum defects occur commonly in patients with Down syndrome. Sinus venous defects occur high in the atrial septum and are frequently associated with anomalies of the pulmonary veins.

Repair of ASDs is recommended for those with a pulmonary-to-systemic flow ratio (Q_p: Q_s) exceeding 1.5:1.0. Despite the success of surgical repair, there has been interest in developing a transcatheter-based approach to ASD repair to avoid the risks and morbidity of open-heart surgery. A variety of devices have been researched. Technical challenges include minimizing the size of the device so that smaller catheters can be used, developing techniques to center the device properly across the ASD, and ensuring that the device can be easily retrieved or repositioned, if necessary.

The purpose of ASD closure with a transcatheter device in patients who have ASD is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with ASD and evidence of left-to-right shunt or right ventricular overload.

Interventions

The therapy being considered is ASD closure with a transcatheter device.

Comparators

The following therapies and practices are currently being used to make decisions about ASD closure with a transcatheter device: individuals with ASDs and a history of cryptogenic stroke are typically treated with antiplatelet agents, given an absence of evidence that systemic anticoagulation is associated with outcome improvements. Depending on the size of the ASD and the left-to-right shunt or right ventricular overload, open surgical intervention to repair the defect may be performed.

Outcomes

The general outcomes of interest are overall survival, morbid events, treatment-related mortality, and treatment-related morbidity.

Based on identified clinical trials, long-term follow-up of ≥10 years would be preferable to determine outcomes for patients who undergo ASD closure.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

The evidence supporting the efficacy of devices for the closure of ASD consists of nonrandomized comparative studies and case series. However, unlike PFO and cryptogenic stroke, the relation between ASD closure and improved clinical outcomes is direct and convincing, because the accepted alternative is open surgery. Results have generally shown a high success rate in achieving closure and low complication rates. The FDA's approval of the Amplatzer Septal Occluder was based on the results of a multicenter, nonrandomized study comparing the device with surgical closure of ASDs. Du et al (2002) subsequently reported on this study with slightly different data but similar quantitative findings.[29,] All patients had an ostium secundum ASD and clinical evidence of right ventricular volume overload. The results for the septal occluder group showed comparably high success rates with surgery; the 24-month closure success rate was 96.7% in the septal occluder group and 100% in the surgical group. While the adverse event pattern differed between the 2 groups, overall, those receiving a septal occluder had a significantly lower incidence of major adverse events (p=.03). Similarly, there was a significantly lower incidence of minor adverse events in the septal occluder group (p<.001). It should be noted that the mean age of patients of the 2 groups differed significantly; in the septal occluder group, the mean age was 18 years while in the surgically treated group it was 6 years.

Systematic Reviews

Chambault et al (2022) published a systematic review of 33 studies comparing transcatheter versus surgical closure of ASDs.[30,] In adults, transcatheter closure reduced the mean length of hospital stay (difference, -4.05 days; 95% CI, -4.78 to -3.32) and the risk of complications (OR, 0.45; 95% CI, 0.28 to 0.72); similar trends were seen in pediatric patients. Furthermore, the risk of overall mortality was similar between transcatheter versus surgical methods in adults (OR, 0.76; 95% CI, 0.40 to 1.45) and pediatric patients (OR, 0.62; 95% CI, 0.21 to 1.83).

Rigatelli et al (2021) published a systematic review comparing in-hospital outcomes in patients who underwent transcatheter (n=1393) versus surgical (n=967) closure of secundum ASDs.[31,] Results demonstrated that the risk of in-hospital mortality (OR, 0.16; 95% CI, 0.66 to 0.44), perioperative stroke (OR, 0.51; 95% CI, 0.31 to 0.84), and post-procedural atrial fibrillation (OR, 0.14; 95% CI, 0.03 to 0.61) were significantly reduced with closure via a transcatheter device.

Butera et al (2011) published a systematic review comparing percutaneous closure with surgical closure.[32,] Thirteen nonrandomized comparative studies that enrolled at least 20 patients were included (N=3082). The rate of procedural complications was higher in the surgical group (31%; 95% CI, 21% to 41%) than in the percutaneous group (6.6%; 95% CI, 3.9% to 9.2%), with an OR for total procedural complications of 5.4 (95% CI, 2.96 to 9.84; p<.000). There was also an increased rate of major complications for the surgical group (6.8%; 95% CI, 4% to 9.5%) compared with the percutaneous group (1.9%; 95% CI, 0.9% to 2.9%), with an OR of 3.81 (95% CI, 2.7 to 5.36; p=.006). Abaci et al (2013) reported in their meta-analysis of periprocedural complications after ASD or PFO device closures that, for ASD closure, the pooled rate of major complications was 1.6% (95% CI, 1.4% to 1.8%).[33,]

A comparison of trials included in select meta-analyses are included in Table 13.

Table 13. Comparison of Trials Included in Systematic Reviews and Meta-Analyses on Atrial Septal Defect Closure

Study	Butera (2011)[32,]	Rigatelli (2021)[31,]	Chambault (2022)[30,]
Berger et al (1999)	●		
Cowley et al (2001)	●		
Formigari et al (2001)	●		●
Du et al (2002)	●		

Study	Butera (2011)[32],	Rigatelli (2021)[31],	Chambault (2022)[30],
Durongpisitkul et al (2002)	●		●
Hughes et al (2002)	●		●
Kim et al (2002)	●	●	
Thomson et al (2002)	●		●
Bettencourt et al (2003)	●		●
Bialkowski et al (2004)	●		●
Bové et al (2005)			●
Butera et al (2006)	●		●
Vida et al (2006)	●		
Butera et al (2007)			●
Jones et al (2007)	●		●
Rosas et al (2007)			●
Suchon et al (2009)			●
Quek et al (2010)			●
Kotowycz et al (2013)			●
Bolcal et al (2014)			●
Mylotte et al (2014)		●	
Siddiqui et al (2014)			●
Castaldi et al (2015)			●
Chen et al (2015)		●	●
Ooi et al (2016)			●
Kodaira et al (2017)		●	●
Schneeberger et al (2017)			●
Askari et al (2018)			●
Bakar et al (2018)			●
Rudzatis et al (2018)			●
Ananthakrishna et al (2019)			●
Boudiche et al (2019)			●
Mojadidi et al (2019)			●
Qiu et al (2019)			●
Tanghöj et al (2019)			●
Fujii et al (2020)		●	●
Kadirogullari et al (2020)			●
Qi et al (2020)			●
Sun et al (2020)			●

Single-Arm Studies

Single-arm studies have shown high success rates of ASD closure. The FDA study (discussed previously) was the largest series, with an enrollment of 442 patients.[29,] Fischer et al (2003) reported on the use of the Amplatzer device in 236 patients with secundum ASD.[34,] In this evaluation study, closure was achieved in 84.7% of patients, and intermediate results were reported as excellent.

Javois et al (2014) reported on outcomes up to 5 years for patients enrolled in the FDA Continued Access trial of the HELIX Septal Occluder, which included 137 patients who underwent device implantation.[35,] Of 122 patients who completed follow-up at 1 year, 96.7% were defined as having clinical success, which was a composite of safety and efficacy. During follow-up, 5 adverse events considered major were reported: 2 device embolizations, both on day 1; 1 wireframe fracture incidentally discovered at 61 days postimplantation; 1 wireframe fracture associated with echocardiographic abnormalities and requiring surgical removal; and 1 unrelated death.

Baruteau et al (2014) reported closure rates of 92.6% in another relatively large series of 336 patients with large secundum ASDs (balloon-stretched diameter 34 mm in adults or echocardiographic diameter >15 mm/m^2 in children) managed with the Amplatzer closure device (2014) reported closure rates of 92.6%.[36,]

Gillespie et al (2020) reported outcomes from a prospective cohort that evaluated the GORE CARDIOFORM Septal Occluder in pivotal and continued access participants with ostium secundum atrial septal defects.[37,] Fifty pivotal and 350 continued access patients underwent device implantation during the study period. The median age of the cohort was 6.9 years (range, 1.3 to 79.6 years). The primary endpoint (6 month composite of technical success, closure success, absence of serious adverse events within 30 days, and absence of device embolization or reintervention) was achieved by 90.2% of patients at 6 months, with a clinical closure success rate of 98.8%. Seven serious adverse events were reported, 1 of each of the following: right atrial thrombus not related to the device, left atrial thrombus related to the device, first-degree atrioventricular block, pneumonia, fever, asthma exacerbation, and small pericardial effusion. Freedom from serious adverse events at 30 days was 98.3%.

Other smaller studies have also reported favorable results for transcatheter closure of ASD. Du et al (2002) compared transcatheter closure for 23 patients with deficient ASD rims with transcatheter closure of 48 patients who had sufficient ASD rims.[38,] The authors reported no significant differences in closure rates between groups (91% for deficient rims vs. 94% for sufficient rims) along with no major complications at 24-hour and 6-month follow-ups. Oho et al (2002) also reported a closure rate of 97% at 1-year follow-up in 35 patients receiving transcatheter ASD closure, with only 1 patient complication (second-degree atrioventricular block) noted.[39,] Brochu et al (2002) evaluated 37 patients with New York Heart Association functional class I or II physical capacity who underwent transcatheter closure of ASD.[40,] At 6-month follow-up, maximal oxygen uptake improved significantly, and the dimensions of the right ventricle decreased significantly. Twenty patients moved from New York Heart Association class II to class I and improved exercise capacity. Numerous other small, single-arm studies have reported similar results, with procedural success rates approaching 100% and successful closure rates on follow-up reported in the 90% to 100% range.[11,41,]

Single-Arm Studies in Pediatric Patients

Several single-arm studies have reported on outcomes for transcatheter ASD closure in children and adolescents. Grohmann et al (2014) reported on outcome from a single-center series of children ages 3 to 17 years (median, 6 years) treated with the HELEX Septal Occluder, with technical success in 41 (91%) of 45 patients in whom closure was attempted.[42,] Nyboe et al (2013) reported on outcomes from 22 patients with secundum ASD who underwent ASD closure with the HELEX Septal Occluder, 10 of whom were children younger than age 15, with technical success in all patients.[43,] Yilmazer et al (2013) reported improvements in echocardiographic parameters in a series of 25 pediatric patients (mean age, 9.02 years) who underwent successful transcatheter closure of secundum ASD.[44,]

A retrospective cohort study conducted by Jalal et al (2018) reported outcomes in 1396 children ages 7 months to 18 years (median, 9 years) who had an attempted transcatheter closure of ASD with the Amplatzer Septal Occluder at 1 of 9 centers in France from 1998 to 2016.[45,] Follow-up was obtained through medical records and telephone calls to primary care physicians and was obtained in 91.6% of the 1158 patients who had a successful ASD closure. The procedural success rate was 95.3%. After a median follow-up duration of 3.5 years (range, 6 months to 18 years), no deaths occurred and 96% of patients were asymptomatic. Major periprocedural complications occurred in 24 patients (1.8%; 95% CI , 1.1% to 2.5%). Delayed complications were observed in 12 (1.04%; 95% CI , 0.5% to 1.6%) patients. Cardiac arrhythmias were the main long-term complication, most occurring in 8 patients aged 3 to 13 years, after a median period of time of 6 months (range, 1 to 108 months) from the procedure. Children weighing 15 kg or less and those with large defects 20 mm/m^2 were subgroups identified at risk of both periprocedural and long-term complications.

Section Summary: Transcatheter Device Closure of Atrial Septal Defects

For patients with an ASD, nonrandomized comparative studies and single-arm case series have reported rates of closure using catheter-based devices approaching the high success rates of surgery. The percutaneous approach has a low complication rate and avoids the morbidity and complications of open surgery. In systematic reviews, the risk of overall mortality was similar with transcatheter device versus surgical closure methods, whereas in-hospital death was significantly reduced with transcatheter device closure. If the percutaneous approach is unsuccessful, ASD closure can be achieved using surgery. Because of the benefits of percutaneous closure over open surgery, this evidence is considered sufficient to determine that transcatheter ASD closure improves outcomes in patients with an indication for ASD closure.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2016 Input

In response to requests, input was received from 2 academic medical centers (1 of which provided 2 responses) while this policy was under review in 2016. Input was mixed about the medical necessity of closure devices for patent foramen ovale (PFO) in patients with cryptogenic stroke or transient ischemic attack due to presumed paradoxical embolism through the PFO. There was a consensus that use of closure devices for PFO in patients with other conditions (e.g., migraine, platypnea-orthodeoxia syndrome) is not medically necessary.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Chest Physicians

In 2012, the American College of Chest Physicians updated its guidelines on antithrombotic therapy and the prevention of thrombosis, which made the following recommendations related to PFO and cryptogenic stroke[46,]:

"We suggest that patients with stroke and PFO are treated with antiplatelet therapy following the recommendations for patients with noncardioembolic stroke.... In patients with a history of noncardioembolic ischemic stroke or TIA [transient ischemic attack], we recommend long-term treatment with aspirin (75 to 100 mg once daily), clopidogrel (75 mg once daily), aspirin/extended release dipyridamole (25 mg/200 mg bid [twice daily]), or cilostazol (100 mg bid) over no antiplatelet therapy (Grade 1A), oral anticoagulants (Grade 1B), the combination of clopidogrel plus aspirin(Grade 1B), or triflusal (Grade 2B)."

American Academy of Neurology

In 2020, the American Academy of Neurology updated its evidence-based guidelines on the management of patients with stroke and PFO to address whether percutaneous closure of PFO is superior to medical therapy alone.[47,] This update to the practice advisory published in 2016 was completed due to the approval of the Amplatzer PFO Occluder and the GORE CARDIOFORM Septal Occluder. Following a systematic review of the literature and structured formulation of recommendations, the Academy developed the following conclusions addressing percutaneous PFO closure as compared to medical therapy alone. For patients with cryptogenic stroke and PFO, percutaneous PFO closure:

- "probably reduces the risk of stroke recurrence with an HR [hazard ratio] of 0.41 (95% CI [confidence interval], 0.25 to 0.67, I^2=12%) and an absolute risk reduction of 3.4% (95% CI, 2.0% to 4.5%) at 5 years,"
- "probably is associated with a periprocedural complication rate of 3.9% (95% CI, 2.3% to 5.7%), and
- "probably is associated with the development of serious non-periprocedural atrial fibrillation, with a relative risk of 2.72 (95% CI, 1.30 to 5.68, I^2=0%)."

The guidelines recommended:

"In patients being considered for PFO closure, clinicians should ensure that an appropriately thorough evaluation has been performed to rule out alternative mechanisms of stroke, as was performed in all positive PFO closure trials (level B). In patients with a PFO detected after stroke and no other etiology identified after a thorough evaluation, clinicians should counsel that having a PFO is common; that it occurs in about 1 in 4 adults in the general population; that it is difficult to determine with certainty whether their PFO caused their stroke; and that PFO closure probably reduces recurrent stroke risk in select patients (level B)."

"In patients younger than 60 years with a PFO and an embolic-appearing infarct and no other mechanism of stroke identified, clinicians may recommend closure following a discussion of potential benefits (reduction of stroke recurrence) and risks (procedural complication and atrial fibrillation) (level C). PFO closure may be offered in other populations, such as for a patient who is aged 60 to 65 years with a very limited degree of traditional vascular risk factors (i.e., hypertension, diabetes, hyperlipidemia, or smoking) and no other mechanism of stroke detected following a thorough evaluation, including prolonged monitoring for atrial fibrillation (level C). PFO closure may be offered to younger patients (e.g., <30 years) with a single, small, deep stroke (<1.5 cm), a large shunt, and absence of any vascular risk factors that would lead to intrinsic small-vessel disease such as hypertension, diabetes, or hyperlipidemia (level C)."

American Heart Association and American Stroke Association

In 2021, the American Heart Association and American Stroke Association updated their guidelines on the prevention of stroke in patients with ischemic stroke or transient ischemic attack. The guidelines made the following recommendations for device-based closure for PFO:[48,]

- "In patients 18 to 60 years of age with a nonlacunar ischemic stroke of undetermined cause despite a thorough evaluation and a PFO with high-risk anatomic features* it is reasonable to choose closure with a transcatheter device and long-term antiplatelet therapy over anti-platelet therapy alone for preventing recurrent stroke (Class IIa; Level of Evidence B-Randomized)"

- "In patients 18 to 60 years of age with a nonlacunar ischemic stroke of undetermined cause despite a thorough evaluation and a PFO without high-risk anatomic features,* the benefit of closure with a transcatheter device and long-term antiplatelet therapy over antiplatelet therapy alone for preventing recurrent stroke is not well established (Class IIb; Level of Evidence C-Limited Data)"
- "In patients 18 to 60 years of age with a nonlacunar ischemic stroke of undetermined cause despite a thorough evaluation and a PFO, the comparative benefit of closure with a transcatheter device versus warfarin is unknown (Class IIb; Level of Evidence C-Limited Data)"

*The guideline notes that high-risk anatomic features are not uniformly described throughout the literature.

The guideline also defined the following relevant terms:

- "*Cryptogenic stroke:* An imaging-confirmed stroke with unknown source despite thorough diagnostic assessment (including, at a minimum, arterial imaging, echocardiography, extended rhythm monitoring, and key laboratory studies such as a lipid profile and hemoglobin A1c [HbA1c])."
- *"Embolic stroke of undetermined source (ESUS):* A stroke that appears nonlacunar on neuroimaging without an obvious source after a minimum standard evaluation (including arterial imaging, echocardiography, extended rhythm monitoring, and key laboratory studies such as a lipid profile and HbA1c) to rule out known stroke etiologies such as cardioembolic sources and atherosclerosis proximal to the stroke. A diagnosis of ESUS implies that the stroke is embolic in origin, given the nonlacunar location; however, the source of the embolus is unknown, despite a minimal standard evaluation. Although cryptogenic stroke similarly implies that the cause of the origin is unknown, the stroke is not necessarily embolic. Individuals with ESUS have cryptogenic stroke, but the converse is not always the case."

American College of Cardiology and American Heart Association

In 2018, the American College of Cardiology and American Heart Association updated guidelines on the management of adults with congenital heart disease.[49,] The treatment recommendations are summarized in Table 14. Recommendations for surgical closure versus transcatheter closure are dependent on the underlying condition.

Table 14. American College of Cardiology and American Heart Association Recommendations for Treating Atrial Septal Defect

Condition	Recommendation	COR[a]/LOE[b]
Symptomatic isolated secundum ASD, right atrial and/or RV enlargement, and net left-to-right shunt sufficiency large enough to cause physiological sequelae, without cyanosis at rest or during exercise	Transcatheter or surgical closure	I1/B-NR2
Symptomatic primum ASD, sinus venosus defect, or coronary sinus defect, right atrial and/or RV enlargement, and net left-to-right shunt sufficiency large enough to cause physiological sequelae, without cyanosis at rest or during exercise	Surgical closure unless precluded by comorbidities	I1/B-NR2
Asymptomatic isolated secundum ASD, right atrial and RV enlargement, and net left-to-right shunt sufficiency large enough to cause physiological sequelae, without cyanosis at rest or during exercise	Transcatheter or surgical closure	IIa1/C-LD2
Secundum ASD when a concomitant surgical procedure is being performed and there is a net left-to-right shunt sufficiently large enough to cause physiological sequelae, and right atrial and RV enlargement without cyanosis at rest or during exercise	Surgical closure	IIa1/C-LD2
ASD when net left-to-right shunt is ≥1.5:1, PA systolic pressure and/or pulmonary vascular resistance is greater than of one-third of systemic resistance	Percutaneous or surgical closure	IIb1/B-NR2

Condition	Recommendation	COR[a]/LOE[b]
ASD with PA systolic pressure greater than two-thirds systemic, pulmonary vascular resistance greater than two-thirds systemic, and/or a net left-to-right shunt	ASD closure should not be performed	III-Harm1/C-LD2

Adapted from Stout et al (2019)[49].
ASD: atrial septal defect; COR: class (strength) of recommendation; LOE: level (quality) of evidence; PA: pulmonary artery; RCT: randomized controlled trial; RV: right ventricular.
[a] COR key: I=strong; IIa=moderate; IIb=weak; III: No Benefit=weak; III: Harm=strong.[49]
[b] LOE key: A=high quality from >1 RCT, meta-analyses of high-quality RCTs, ≥1 RCT corroborated by high-quality registry studies; B-R=randomized, moderate-quality evidence from ≥1 RCT or meta-analysis of moderate-quality RCTs; B-NR=nonrandomized, moderate-quality evidence from ≥1 well-designed, well-executed nonrandomized study, observational study, or registry study, or meta-analyses of such studies; C-LD: limited data, randomized or nonrandomized observational or registry studies with limitations of design or execution, meta-analyses of such studies, or physiological or mechanistic studies in human subjects; C-EO: expert opinion.[49]

European Association of Percutaneous Cardiovascular Interventions

In 2021, the European Association of Percutaneous Cardiovascular Interventions Scientific Documents and Initiatives Committee invited 8 European scientific societies and international experts to develop interdisciplinary position statements on the management of PFO; 3 US-based experts were listed as authors on part II of the position paper.[50]

For decompression sickness, authors note: *"If behavioral and technical changes are not possible or not effective, PFO closure can be proposed with shared decision making underscoring the lack of evidence"*

For migraines, authors note: *"Consider PFO closure only in clinical trials or for compassionate use in migraine with aura."*

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 15.

Table 15. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03309332[a]	OBS Lead-AMPLATZER PFO Occluder New Enrollment Study	1214	Apr 2030
NCT04100135[a]	GORE® CARDIOFORM Septal Occluder Migraine Clinical Study: A Study to Evaluate the Safety and Efficacy of Transcatheter Closure of Patent Foramen Ovale for Relief of Migraine Headaches	150	Aug 2027
NCT05561660	Comparison of the Effect of Device Closure in Alleviating Migraine With Patent Foramen Oval (COMPETE-2)	460	Oct 2025
NCT04029233[a]	Prospective, Open-label, Multicenter, Non-randomized Investigation on Percutaneous Patent Foramen Ovale (PFO) Closure Using the Occlutech PFO Occluder to Prevent Recurrence of Stroke in Patients With Cryptogenic Stroke and High Risk PFO	836	Sep 2026
Unpublished			
NCT02985684[a]	GORE® CARDIOFORM ASD Occluder Clinical Study: A Study to Evaluate Safety and Efficacy in the Treatment of	125	Sep 2022

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Transcatheter Closure of Ostium Secundum Atrial Septal Defects (ASDs) - The Gore ASSURED Clinical Study		

NCT: national clinical trial.
[a]Denotes industry sponsored or co-sponsored trial

References

1. Messé SR, Kasner SE. Is closure recommended for patent foramen ovale and cryptogenic stroke? Patent foramen ovale in cryptogenic stroke: not to close. Circulation. Nov 04 2008; 118(19): 1999-2004. PMID 18981314
2. Slottow TL, Steinberg DH, Waksman R. Overview of the 2007 Food and Drug Administration Circulatory System Devices Panel meeting on patent foramen ovale closure devices. Circulation. Aug 07 2007; 116(6): 677-82. PMID 17679629
3. U.S. Food and Drug Administration. Summary of safety and effectiveness data. Gore Cardioform Septal Occluder.March 30, 2018. https://www.accessdata.fda.gov/cdrh_docs/pdf5/P050006s060b.pdf. Accessed March 17, 2023.
4. Food and Drug Administration (FDA). Summary of Safety and Effectiveness Data (SSED): Patent Foramen Ovale (PFO) Occluder (PMA P120021). 2016; https://www.accessdata.fda.gov/cdrh_docs/pdf12/P120021B.pdf. Accessed March 17, 2023.
5. 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. Mar 01 2016; 67(8): 907-917. PMID 26916479
6. Li J, Liu J, Liu M, et al. Closure versus medical therapy for preventing recurrent stroke in patients with patent foramen ovale and a history of cryptogenic stroke or transient ischemic attack. Cochrane Database Syst Rev. Sep 08 2015; 2015(9): CD009938. PMID 26346232
7. 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. Mar 06 2018; 168(5): 335-342. PMID 29310136
8. De Rosa S, Sievert H, Sabatino J, et al. Percutaneous Closure Versus Medical Treatment in Stroke Patients With Patent Foramen Ovale: A Systematic Review and Meta-analysis. Ann Intern Med. Mar 06 2018; 168(5): 343-350. PMID 29310133
9. Søndergaard L, Kasner SE, Rhodes JF, et al. Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke. N Engl J Med. Sep 14 2017; 377(11): 1033-1042. PMID 28902580
10. Mas JL, Derumeaux G, Guillon B, et al. Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke. N Engl J Med. Sep 14 2017; 377(11): 1011-1021. PMID 28902593
11. Meier B, Kalesan B, Mattle HP, et al. Percutaneous closure of patent foramen ovale in cryptogenic embolism. N Engl J Med. Mar 21 2013; 368(12): 1083-91. PMID 23514285
12. Alushi B, Lauten A, Cassese S, et al. Patent foramen ovale closure versus medical therapy for prevention of recurrent cryptogenic embolism: updated meta-analysis of randomized clinical trials. Clin Res Cardiol. Sep 2018; 107(9): 788-798. PMID 29644412
13. Carroll JD, Saver JL, Thaler DE, et al. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. N Engl J Med. Mar 21 2013; 368(12): 1092-100. PMID 23514286
14. Saver JL, Carroll JD, Thaler DE, et al. Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke. N Engl J Med. Sep 14 2017; 377(11): 1022-1032. PMID 28902590
15. Rogers T, Slack M, Waksman R. Overview of the 2016 US Food and Drug Administration Circulatory System Devices Panel Meeting on the Amplatzer Patent Foramen Ovale Occluder. Am J Cardiol. Jan 01 2017; 119(1): 153-155. PMID 27810099
16. Lee PH, Song JK, Kim JS, et al. Cryptogenic Stroke and High-Risk Patent Foramen Ovale: The DEFENSE-PFO Trial. J Am Coll Cardiol. May 22 2018; 71(20): 2335-2342. PMID 29544871

17. Andersen A, Matzen KL, Andersen G, et al. Atrial fibrillation after closure of patent foramen ovale in the REDUCE clinical study. Catheter Cardiovasc Interv. Apr 2022; 99(5): 1551-1557. PMID 34773685
18. Rigatelli G, Pedon L, Zecchel R, et al. Long-Term Outcomes and Complications of Intracardiac Echocardiography-Assisted Patent Foramen Ovale Closure in 1,000 Consecutive Patients. J Interv Cardiol. Oct 2016; 29(5): 530-538. PMID 27500752
19. Wintzer-Wehekind J, Alperi A, Houde C, et al. Long-Term Follow-Up After Closure of Patent Foramen Ovale in Patients With Cryptogenic Embolism. J Am Coll Cardiol. Jan 29 2019; 73(3): 278-287. PMID 30678757
20. Lip PZ, Lip GY. Patent foramen ovale and migraine attacks: a systematic review. Am J Med. May 2014; 127(5): 411-20. PMID 24355354
21. Dowson A, Mullen MJ, Peatfield R, et al. Migraine Intervention With STARFlex Technology (MIST) trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache. Circulation. Mar 18 2008; 117(11): 1397-404. PMID 18316488
22. Wang YL, Wang FZ, Zhang Y, et al. Association of migraine with patent foramen ovale closure: A systematic review and meta -analysis. Int J Cardiol Heart Vasc. Apr 2022; 39: 100992. PMID 35330668
23. Mattle HP, Evers S, Hildick-Smith D, et al. Percutaneous closure of patent foramen ovale in migraine with aura, a randomized controlled trial. Eur Heart J. Jul 07 2016; 37(26): 2029-36. PMID 26908949
24. Tobis JM, Charles A, Silberstein SD, et al. Percutaneous Closure of Patent Foramen Ovale in Patients With Migraine: The PREMIUM Trial. J Am Coll Cardiol. Dec 05 2017; 70(22): 2766-2774. PMID 29191325
25. Mas JL, Guillon B, Charles-Nelson A, et al. Patent foramen ovale closure in stroke patients with migraine in the CLOSE trial. The CLOSE-MIG study. Eur J Neurol. Aug 2021; 28(8): 2700-2707. PMID 33938088
26. Snijder RJ, Luermans JG, de Heij AH, et al. Patent Foramen Ovale With Atrial Septal Aneurysm Is Strongly Associated With Migraine With Aura: A Large Observational Study. J Am Heart Assoc. Dec 01 2016; 5(12). PMID 27930349
27. Tobis J, Shenoda M. Percutaneous treatment of patent foramen ovale and atrial septal defects. J Am Coll Cardiol. Oct 30 2012; 60(18): 1722-32. PMID 23040567
28. Mojadidi MK, Gevorgyan R, Noureddin N, et al. The effect of patent foramen ovale closure in patients with platypnea-orthodeoxia syndrome. Catheter Cardiovasc Interv. Oct 2015; 86(4): 701-7. PMID 26063336
29. Du ZD, Hijazi ZM, Kleinman CS, et al. Comparison between transcatheter and surgical closure of secundum atrial septal defect in children and adults: results of a multicenter nonrandomized trial. J Am Coll Cardiol. Jun 05 2002; 39(11): 1836-44. PMID 12039500
30. Chambault AL, Olsen K, Brown LJ, et al. Transcatheter versus surgical closure of atrial septal defects: a systematic review and meta-analysis of clinical outcomes. Cardiol Young. Jan 2022; 32(1): 1-9. PMID 34819196
31. Rigatelli G, Zuin M, Roncon L, et al. Secundum atrial septal defects transcatheter closure versus surgery in adulthood: a 2000-2020 systematic review and meta-analysis of intrahospital outcomes. Cardiol Young. Apr 2021; 31(4): 541-546. PMID 33827735
32. Butera G, Biondi-Zoccai G, Sangiorgi G, et al. Percutaneous versus surgical closure of secundum atrial septal defects: a systematic review and meta-analysis of currently available clinical evidence. EuroIntervention. Jul 2011; 7(3): 377-85. PMID 21729841
33. Abaci A, Unlu S, Alsancak Y, et al. Short and long term complications of device closure of atrial septal defect and patent foramen ovale: meta-analysis of 28,142 patients from 203 studies. Catheter Cardiovasc Interv. Dec 01 2013; 82(7): 1123-38. PMID 23412921
34. Fischer G, Stieh J, Uebing A, et al. Experience with transcatheter closure of secundum atrial septal defects using the Amplatzer septal occluder: a single centre study in 236 consecutive patients. Heart. Feb 2003; 89(2): 199-204. PMID 12527678

35. Javois AJ, Rome JJ, Jones TK, et al. Results of the U.S. Food and Drug Administration continued access clinical trial of the GORE HELEX septal occluder for secundum atrial septal defect. JACC Cardiovasc Interv. Aug 2014; 7(8): 905-12. PMID 25147036
36. Baruteau AE, Petit J, Lambert V, et al. Transcatheter closure of large atrial septal defects: feasibility and safety in a large adult and pediatric population. Circ Cardiovasc Interv. Dec 2014; 7(6): 837-43. PMID 25423959
37. Gillespie MJ, Javois AJ, Moore P, et al. Use of the GORE® CARDIOFORM Septal Occluder for percutaneous closure of secundum atrial septal defects: Results of the multicenter U.S. IDE trial. Catheter Cardiovasc Interv. Jun 01 2020; 95(7): 1296-1304. PMID 32108423
38. Du ZD, Koenig P, Cao QL, et al. Comparison of transcatheter closure of secundum atrial septal defect using the Amplatzer septal occluder associated with deficient versus sufficient rims. Am J Cardiol. Oct 15 2002; 90(8): 865-9. PMID 12372575
39. Oho S, Ishizawa A, Akagi T, et al. Transcatheter closure of atrial septal defects with the Amplatzer septal occluder--a Japanese clinical trial. Circ J. Sep 2002; 66(9): 791-4. PMID 12224813
40. Brochu MC, Baril JF, Dore A, et al. Improvement in exercise capacity in asymptomatic and mildly symptomatic adults after atrial septal defect percutaneous closure. Circulation. Oct 01 2002; 106(14): 1821-6. PMID 12356636
41. Furlan AJ, Reisman M, Massaro J, et al. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. N Engl J Med. Mar 15 2012; 366(11): 991-9. PMID 22417252
42. Grohmann J, Höhn R, Fleck T, et al. Transcatheter closure of atrial septal defects in children and adolescents: single-center experience with the GORE® septal occluder. Catheter Cardiovasc Interv. Nov 15 2014; 84(6): E51-7. PMID 24664494
43. Nyboe C, Hjortdal VE, Nielsen-Kudsk JE. First experiences with the GORE(®) Septal Occluder in children and adults with atrial septal defects. Catheter Cardiovasc Interv. Nov 15 2013; 82(6): 929-34. PMID 23404677
44. Yılmazer MM, Güven B, Vupa-Çilengiroğlu Ö, et al. Improvement in cardiac structure and functions early after transcatheter closure of secundum atrial septal defect in children and adolescents. Turk J Pediatr. 2013; 55(4): 401-10. PMID 24292034
45. Jalal Z, Hascoët S, Gronier C, et al. Long-Term Outcomes After Percutaneous Closure of Ostium Secundum Atrial Septal Defect in the Young: A Nationwide Cohort Study. JACC Cardiovasc Interv. Apr 23 2018; 11(8): 795-804. PMID 29673513
46. Lansberg MG, O'Donnell MJ, Khatri P, et al. Antithrombotic and thrombolytic therapy for ischemic stroke: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. Feb 2012; 141(2 Suppl): e601S-e636S. PMID 22315273
47. 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. May 19 2020; 94(20): 876-885. PMID 32350058
48. 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. Jul 2021; 52(7): e364-e467. PMID 34024117
49. Stout KK, Daniels CJ, Aboulhosn JA, et al. 2018 AHA/ACC Guideline for the Management of Adults With Congenital Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. Apr 02 2019; 73(12): e81-e192. PMID 30121239
50. Pristipino C, Germonpré P, Toni D, et al. European position paper on the management of patients with patent foramen ovale. Part II - Decompression sickness, migraine, arterial deoxygenation syndromes and select high-risk clinical conditions. EuroIntervention. Aug 06 2021; 17(5): e367-e375. PMID 33506796

Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Prior diagnostic testing and results
  - Prior conservative treatments, duration, and response
  - Radiology report(s) and interpretation [i.e., Ultrasound, Chest X-Ray, Echocardiogram, Transcranial Doppler (TCD) bubble study, ECG]
  - Comorbidities
  - Condition to be treated
  - Type and name of device planned for use

Post Service (in addition to the above, please include the following):

- Operative report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	93580	Percutaneous transcatheter closure of congenital interatrial communication (i.e., Fontan fenestration, atrial septal defect) with implant

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
03/30/2015	BCBSA Medical Policy adoption
07/01/2016	Policy revision without position change
07/01/2017	Policy revision without position change
07/01/2018	Policy revision with position change
08/01/2019	Policy revision with position change
08/01/2023	Policy reactivated. Previously archived from 06/01/2020 to 07/31/2023.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished

primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** Blue font: Verbiage Changes/Additions
Reactivated Policy **Policy Statement:** N/A	**Closure Devices for Patent Foramen Ovale and Atrial Septal Defects 2.02.09** **Policy Statement:** I. The percutaneous transcatheter closure of a patent foramen ovale (PFO) using a device that has been approved by the U.S. Food and Drug Administration for that purpose may be considered **medically necessary** to reduce the risk of recurrent ischemic stroke if an individual meets **all** of the following: A. Between 18 and 60 years of age B. Diagnosed with PFO with a right-to-left interatrial shunt confirmed by echocardiography with at least **one** of the following characteristics: 1. PFO with large shunt, defined as greater than 30 microbubbles in the left atrium within 3 cardiac cycles, after opacification of the right atrium 2. PFO associated with atrial septal aneurysm on transesophageal examination: septum primum excursion greater than 10 mm C. Documented history of cryptogenic ischemic stroke due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an evaluation to exclude any other identifiable cause of stroke, including large vessel atherosclerotic disease and small vessel occlusive disease D. **None** of the following are present: 1. Uncontrolled vascular risk factors, including uncontrolled diabetes or uncontrolled hypertension 2. Other sources of right-to-left shunts, including an atrial septal defect and/or fenestrated septum 3. Active endocarditis or other untreated infections 4. Inferior vena cava filter II. Transcatheter closure of secundum atrial septal defects may be considered **medically necessary** when using a device that has been

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
	approved by the U.S. Food and Drug Administration for that purpose and used according to the labeled indications including **both** of the following: A. Individuals with echocardiographic evidence of ostium secundum atrial septal defect B. **Either** of the following: 1. Clinical evidence of right ventricular volume overload (i.e., 1.5:1 degree of left-to-right shunt or right ventricular enlargement) 2. Clinical evidence of paradoxical embolism III. Transcatheter closure of secundum atrial septal defects is considered **investigational** for all other indications not meeting the criteria outlined above.