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Closure Devices for Patent Foramen Ovale and Atrial Septal Defects

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Related Policies (if applicable)
None

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Coverage

Patent Foramen Ovale

The transcatheter closure of a patent foramen ovale (PFO) using a device that has been approved by the U.S. Food and Drug Administration (FDA) for that purpose **may be considered medically necessary** to reduce the risk of recurrent ischemic stroke if the individual meets **ALL** the following:

- Between 18 and 60 years of age; **AND**
- Diagnosed with PFO with a right-to-left interatrial shunt confirmed by echocardiography with at least 1 of the following characteristics:
 1. PFO with large shunt, defined as >30 microbubbles in the left atrium within three [3] cardiac cycles, after opacification of the right atrium;
 2. PFO associated with atrial septal aneurysm on transesophageal examination: septum primum excursion >10 mm; **AND**
- 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; **AND**

NONE of the following are present:

- Uncontrolled vascular risk factors, including uncontrolled diabetes or uncontrolled hypertension; **OR**
- Other sources of right-to-left shunts, including an atrial septal defect and/or fenestrated septum; **OR**
- Active endocarditis or other untreated infections; **OR**
- Inferior vena cava filter.

Transcatheter closure of a PFO using a device that has **NOT** been approved by the U.S. Food and Drug Administration (FDA) for that purpose (e.g., transient ischemic attacks (TIAs), migraine prevention and prevention of stroke) **is considered experimental, investigational and/or unproven.**

Atrial Septal Defects

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:

- Individuals with echocardiographic evidence of ostium secundum atrial septal defect; **AND EITHER** of the following:
- Clinical evidence of right ventricular volume overload (i.e., 1.5:1 degree of left-to-right shunt or right ventricular enlargement); **OR**
- Clinical evidence of paradoxical embolism.

Transcatheter closure of secundum atrial septal defects **is considered experimental, investigational and/or unproven** for all other indications not meeting the criteria outlined above.

Policy Guidelines

Four devices approved by the U.S. Food and Drug Administration for patent foramen ovale closure and/or atrial septal defect closure are currently marketed:

- Amplatzer™ Septal Occluder (now Amplatzer™ Talisman™ PFO Occluder),
- GORE® CARDIOFORM Septal Occluder,
- GORE® CARDIFORM ASD Occluder, and
- Occlutech® ASD Occluder.

The GORE® HELEX Septal Occluder has been discontinued.

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.

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 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 post-natal persistence of normal fetal cardiovascular physiology, 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 mid-septally 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 discs 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.

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, two transcatheter devices were cleared for marketing by the FDA through a humanitarian device exemption as 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 Abbott Cardiovascular). 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 (now Amplatzer Talisman PFO Occluder)	St. Jude Medical (now Abbott Cardiovascular)	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 multiple devices for ASD closure through the premarket approval process or a premarket approval supplement: the Amplatzer Septal Occluder, the GORE HELEX Septal Occluder (discontinued), the GORE CARDIOFORM ASD Occluder, the GORE CARDIOFORM Septal Occluder, and Occlutech® ASD Occluder (see Table 2).

FDA product codes: MLV, OZG.

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	Dec 2001	<ul style="list-style-type: none"> • Occlusion of ASDs in the secundum position.

	(Abbott Medical)		<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • Percutaneous, transcatheter closure of ostium secundum ASDs.
GORE CARDIOFORM ASD Occluder	W.L. Gore & Associates	May 2019 (supplement)	<ul style="list-style-type: none"> • Percutaneous, transcatheter closure of ostium secundum ASDs.
GORE CARDIOFORM Septal Occluder	W.L. Gore & Associates	Apr 2015 (supplement)	<ul style="list-style-type: none"> • Percutaneous, transcatheter closure of ostium secundum ASDs.
Occlutech® ASD Occluder	Occlutech	Dec 2023	<ul style="list-style-type: none"> • Percutaneous, transcatheter closure of ostium secundum ASDs.

ASD: atrial septal defect; PMA: premarket approval.

FDA product code: MLV.

Rationale

Medical policies 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, two 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.

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 individuals 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 policy.

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 individuals with cryptogenic stroke: conventional therapy for cryptogenic stroke, which consists of antiplatelet therapy or oral anticoagulation.

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 individuals who undergo PFO.

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.

The evidence for the efficacy of transcatheter PFO closure devices for patients with cryptogenic stroke consists of three 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 three 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 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 five 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 Reviews & 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 (67-622)	RCTs	No restrictions
Alushi et al. (2018) (12)	1990-2017	5	Adults with PFO and cryptogenic stroke	3440 (414-980)	RCTs	No restrictions

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

Table 4. Systematic Reviews & 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 (0.38)	0 (0.81)	NA	0 (0.92)	82.5 (<0.001)
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 (0.003)	NA	33.79 (0.29)	28 (0.60)	66 (0.002)
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); p<0.01	HR 0.73 (0.49 to 1.09); p=0.12	HR 0.52 (0.26 to 0.77); p<0.01	OR 0.97 (0.44 to 2.17); p=0.95	OR 3.75 (2.44 to 5.78); p<0.01
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; NNT: number needed to treat; NR: not reported; TIA: transient ischemic attack; HR: hazard ratio; OR: odds ratio; NA: not applicable, REDUCE: GORE Septal Occluder Device for Patent Foramen Ovale (PFO) Closure in Stroke Patients.

Randomized Controlled Trials

Transcatheter Patent Foramen Ovale Closure with Device vs Medical Management

Three RCTs – the Patent Foramen Ovale and Cryptogenic Embolism (PC)-Trial (11), the Patent Foramen Ovale Closure or Medical Therapy After Stroke (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 two 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 hazard ratios (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 three publications (13-15) 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 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 three 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% confidence interval [CI], 0.14 to 0.96; p=0.03; HR=0.27; 95% CI, 0.10 to 0.75; p=0.007, 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 nine-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 younger patient population - is clinically significant. All three 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 PRO 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 patient's safety. The trial and its results are described in Tables 5 and 6.

Table 5. Summary of Key RCT Characteristics for the Amplatzer PFO Occluder

Study; Trial	Countries	Sites	Dates	Participants	Interventions		Median DOF, y
					Active	Comparator	
Meier et al. (2013) (11); PC-Trial	Europe, Canada, Brazil, Australia	29	2000-2009	With PFO, <60 years, 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	U.S., Canada	69	2003-2011	With PFO, 18-60 years, and cryptogenic ischemic stroke	Amplatzer PFO Occluder	Medical treatment ^b	2.1
Saver et al. (2017) (14); RESPECT	U.S., Canada	69	2003-2011	With PFO, 18-60 years, and cryptogenic ischemic stroke	Amplatzer PFO Occluder	Medical treatment ^b	5.9
Lee et al. (2018)	South Korea	2	2011-2017	With cryptogenic	Amplatzer PFO	Medical treatment ^b	2.8

(16); DEFENSE- PFO				stroke and high- risk PFO	Occluder with medical treatment		
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DOF: duration of follow-up; PFO: patent foramen ovale; TE: thromboembolic; RCT: randomized controlled trial; TIA: transient ischemic attack; PC-Trial: Patent Foramen Ovale and Cryptogenic Embolism; RESPECT: Patent Foramen Ovale Closure or Medical Therapy After Stroke; DEFENSE-PFO: Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale, U.S.: United States.

^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 RCT Results for the Amplatzer PFO Occluder

Study; 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); 0.34 ^a	0.45 (0.16 to 1.29); 0.14 ^b	0.20 (0.02 to 1.72); 0.14
Carroll et al. (2013) (13); RESPECT	980		
Amplatzer, n/N (%)	9/499 (1.8) ^c	Not applicable	9/499 (1.8)
Medical treatment, n/N (%)	16/481 (3.3) ^c	Not applicable	16/481 (3.3)
HR (95% CI); P-value	0.49 (0.22 to 1.11); 0.08 ^c	Not applicable	0.49 (0.22 to 1.11); 0.08
Saver et al. (2017) (14); RESPECT			
Amplatzer, n/N (%)	Not reported	Not applicable	18/499 (3.6)
Medical treatment, n/N (%)	Not reported	Not applicable	28/481 (5.8)
HR (95% CI); P-value	Not reported	Not applicable	0.55 (0.31 to 0.99); 0.04
Lee et al. (2018) (16); DEFENSE-PFO	120		120
Amplatzer, n/N (%) ^{d,e}	0/60 (0.0) ^e	Not applicable	0/60 (0.0)
Medical treatment, n/N (%) ^{d,e}	6/60 (12.9) ^e	Not applicable	5/60 (10.5)
(95% CI); P-value	(3.2 to 22.6); 0.13	Not applicable	(NR); 0.023

CI: confidence interval; HR: hazard ratio; NNT: number needed to treat; PFO: patent foramen ovale; RCT: randomized controlled trial; TIA: transient ischemic attack; PC-Trial: Patent Foramen Ovale and Cryptogenic Embolism; RESPECT: Patent Foramen Ovale Closure or Medical Therapy After Stroke;

DEFENSE-PFO: Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale.

^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.

Table 7. FDA Summary of Kaplan-Meier Analyses of the Primary Endpoint in RESPECT Trial (Amplatzer PFO Occluder)

Analysis Population	Definitions	RRR, %	p-value
Intention to treat	Primary analysis population including all randomized patients whether or not Amplatzer implanted	50	0.089
Per-protocol	All patients adhering to protocol requirements ^a whether or not Amplatzer implanted	63	0.034 ^b
As-treated	All patients adhering to protocol requirements ^a who actually had the Amplatzer implanted	72	0.008 ^b
Device-in-place	All randomized patients who had Amplatzer implanted	70	0.007 ^b

FDA assessment as reported by Rogers et al. (2017). (15)

FDA: U.S. Food and Drug Administration; PFO: patent foramen ovale; RRR: relative risk reduction.

^a Adherence to guidelines-directed medical therapy defined as $\geq 67\%$ cumulative compliance over the duration of the study.

^b $p < 0.05$ was considered statistically significant.

Transcatheter Patent Foramen Ovale Closure With Device Plus Medical Management vs 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 trials, 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) two 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 number of patients who needed to be treated to prevent 1 stroke in 24 months was approximately 28 patients. 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 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 ($p=0.22$).

Anderson et al. (2021) described the occurrence of post-procedural atrial fibrillation (AF) 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 reoccur at a later time. Postprocedural AF occurred more frequently among patients with higher age and larger devices. Male sex was the only independent predictor of postprocedural AF.

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 vs antiplatelet therapy 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 one stroke avoided at five 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%; $p=0.02$). The number of serious adverse events did not differ significantly between treatment groups ($p=0.56$).

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 RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions		DOF, y
					Active	Comparator	
Søndergaard et al. (2017) (9); REDUCE	U.S., Europe	63	2008-2015	With PFO, 18-60 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, 16-60 y, and cryptogenic ischemic stroke	Multiple closure devices plus antiplatelet therapy ^b	Antiplatelet therapy alone ^c	Mean, 5.3 ^d
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DOF: duration of follow-up; PFO: patent foramen ovale; RCT: randomized controlled trial.

REDUCE: GORE® Septal Occluder Device for Patent Foramen Ovale (PFO) Closure in Stroke Patients;

CLOSE: Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence, U.S.: United States; Y/y: year.

^a Antiplatelet therapy could consist of aspirin alone (75-325 mg once daily), a combination of aspirin (50-100 mg daily) and dipyridamole (225-400 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 RCT 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); 0.002	0.51 (0.29 to 0.91); 0.04	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); <0.001	NA	0.39 (0.16 to 0.82); 0.01

CI: confidence interval; HR: hazard ratio; NNT: number needed to treat; NA: not applicable; NR: not reported; RCT: randomized controlled trial; REDUCE: GORE® Septal Occluder Device for Patent Foramen Ovale (PFO) Closure in Stroke Patients; CLOSE: Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence.

^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 five 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% whereas recurrent cerebral ischemic events occurred in 0.8% 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, 10-17 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 years). 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, 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 relatively higher risk of stroke among those with PFO. In addition, other factors such as requirement of neuroimaging confirmation of stroke prior to enrollment, exclusion of lacunar infarcts, longer follow-up, and selection of patients with 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 PFO 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 individuals 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 policy.

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 individuals 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.

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 a 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 identified (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; $p=0.51$).

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 et al. (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; y: year

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, 0.26 (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% (0.33)	0% (0.61)	0% (0.53)	93% (<0.01)	96% (<0.01)

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, $p=0.51$). 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 post randomization), 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; $p=0.168$).

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 a 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 (odds ratio, 2.71; 95% CI, 1.23 to 5.95; $p=0.01$), 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 individuals 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 policy.

Populations

The relevant populations of interest are 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 individuals 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.

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 mid-septally 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.

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 individuals 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 policy.

Populations

The relevant populations of interest are 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 individuals 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.

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 ($p=0.03$). Similarly, there was a significantly lower incidence of minor adverse events in the septal occluder group ($p<0.001$). 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 patients). 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 odds ratio for total procedural complications of 5.4 (95% CI, 2.96 to 9.84; p<0.000). 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 odds ratio of 3.81 (95% CI, 2.7 to 5.36; p=0.006).

Abaci et al. (2013) reported in their meta-analysis of periprocedural complications after ASD or PFO device closures, 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 et al. (2011) (32)	Rigatelli et al. (2021) (31)	Chambault et al. (2022) (30)
Berger et al. (1999)	●		
Cowley et al. (2001)	●		
Formigari et al. (2001)	●		●
Du et al. (2002)	●		
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)			●
Tanghøj 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/m² 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%.

Qureshi et al. (2024) reported long-term outcomes from a combined prospective cohort that evaluated the GORE CARDIOFORM Septal Occluder in pivotal and continued access participants with ostium secundum atrial septal defects. (38) Among 569 enrolled patients (median age: 10.4 years; range, 1.2 to 84.7 years), 526 underwent successful device implantation. The co-primary endpoints of 6-month closure success and composite clinical success were achieved in 100% and 87.6% of patients, respectively. At 36 months, composite clinical success was observed in 84.0% of patients. Technical failures were observed in 8.1% (43 out of 548) of patients, while serious adverse events occurred in 3.7% of patients within 30 days, with device embolization being the most common complication. Additionally, device-related events at 6 months were reported in 2.8% (15 out of 534) of patients.

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. (39) 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. (40) 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. (41) 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, 42)

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 outcomes 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. (43) 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. (44) 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. (45)

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. (46) 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/m² 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.

Summary of Evidence

For individuals who have patent foramen ovale (PFO) and cryptogenic stroke who receive PFO closure with a transcatheter device, the evidence includes multiple randomized controlled trials (RCTs) comparing device-based PFO closure with medical therapy, systematic reviews, meta-

analyses, and observational studies. Relevant outcomes are symptoms, change in disease status, overall survival, morbid events, and treatment-related morbidity and mortality. The RCTs comparing PFO closure with medical management have suggested that PFO closure is more effective than medical therapy in reducing event rates. Although these results were not statistically significant by intention-to-treat (ITT) analyses in earlier trials (i.e., Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism [PC-Trial], and Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment [RESPECT: initial study]), they were statistically significant in later trials (i.e., RESPECT [extended follow-up], Reduction in the Use of Corticosteroids in Exacerbated COPD [REDUCE], and Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence [CLOSE]). Use of appropriate patient selection criteria to eliminate other causes of cryptogenic stroke in RESPECT, REDUCE, and CLOSE trials contributed to findings of the superiority of PFO closure compared with medical management. Of note, higher rates of atrial fibrillation were reported in a few of the individual trials and in the meta-analysis that incorporated evidence from RESPECT, REDUCE, and CLOSE trials. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have PFO and migraines who receive PFO closure with a transcatheter device, the evidence includes 3 RCTs of PFO closure, multiple observational studies reporting on the association between PFO and migraine, and systematic reviews of these studies. Relevant outcomes are symptoms, quality of life, medication use, and treatment-related morbidity and mortality. Two sham-controlled randomized trials did not demonstrate significant improvements in migraine symptoms after PFO closure. A third RCT with blinded endpoint evaluation did not demonstrate reductions in migraine days after PFO closure compared to medical management but likely was underpowered. Nonrandomized studies have shown highly variable rates of migraine reduction after PFO closure. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have PFO and conditions associated with PFO other than cryptogenic stroke or migraine (e.g., platypnea-orthodeoxia syndrome, myocardial infarction with normal coronary arteries, decompression illness, high-altitude pulmonary edema, obstructive sleep apnea) who receive PFO closure with a transcatheter device, the evidence includes small case series and case reports. Relevant outcomes are symptoms, change in disease status, morbid events, and treatment-related morbidity and mortality. Comparative studies are needed to evaluate outcomes in similar patient groups treated with and without PFO closure. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have atrial septal defects (ASD) and evidence of left-to-right shunt or right ventricular overload who receive ASD closure with a transcatheter device, the evidence includes systematic reviews, nonrandomized comparative studies, and single-arm studies. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity and mortality. The available nonrandomized comparative studies and single-arm case series

have shown rates of closure using transcatheter-based devices approaching the high success rates of surgery, which are supported by meta-analyses of these studies. 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, whereas in-hospital mortality 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, it can be determined that transcatheter ASD closure improves outcomes in patients with an indication for ASD closure. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

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 (47):

"We suggest that patients with stroke and PFO are treated with antiplatelet therapy following the recommendations for patients with non-cardioembolic stroke.... In patients with a history of non-cardioembolic ischemic stroke or TIA, we recommend long-term treatment with aspirin (75-100 mg once daily), clopidogrel (75 mg once daily), aspirin/extended-release dipyridamole (25 mg/200 mg bid), 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. (48) 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], 0.25–0.67, $I^2 = 12\%$) and an absolute risk reduction of 3.4% (95% CI, 2.0%–4.5%) at 5 years,"
- "probably is associated with a periprocedural complication rate of 3.9% (95% CI, 2.3%–5.7%), and"
- "probably is associated with the development of serious non-periprocedural atrial fibrillation, with a relative risk of 2.72 (95% CI, 1.30–5.68, $I^2=0\%$)."

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 60–65 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: (49)

- "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 antiplatelet 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. (50) 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 ASD

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	Surgical closure	IIa1/C-LD2

enlargement without cyanosis at rest or during exercise		
ASD when net left-to-right shunt is $\geq 1.5:1$, PA systolic pressure and/or pulmonary vascular resistance is greater than of one-third of systemic resistance	Percutaneous or surgical closure	IIb1/B-NR2
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) (50).

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. (50),

^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. (50)

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 U.S.-based experts were listed as authors on part II of the position paper. (51)

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."

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 15.

Table 15 Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT03309332 ^a	OBS Lead-AMPLATZER PFO Occluder New Enrollment Study	1214	Apr 2030

NCT05561660	Comparison of the Effect of Device Closure in Alleviating Migraine With Patent Foramen Oval (COMPETE-2)	460	Oct 2025
NCT02985684 ^a	GORE® CARDIOFORM ASD Occluder Clinical Study: A Study to Evaluate Safety and Efficacy in the Treatment of Transcatheter Closure of Ostium Secundum Atrial Septal Defects (ASDs) - The Gore ASSURED Clinical Study	125	Sep 2022
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	7	Aug 2024
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	582	Apr 2024

NCT: national clinical trial.

^a Denotes industry sponsored or co-sponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	93580
HCPCS Codes	C1817

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <<https://www.cms.hhs.gov>>.

Policy History/Revision

Date	Description of Change
11/15/2025	Document updated with literature review. The following change was made to Coverage: Added "Transcatheter closure of a PFO using a device that has <u>NOT</u> been approved by the U.S. Food and Drug Administration (FDA) for that purpose (e.g., transient ischemic attacks (TIAs), migraine prevention and

	prevention of stroke) is considered experimental, investigational and/or unproven.” Added reference 38.
02/01/2025	Document updated with literature review. Coverage unchanged. Reference 22 added; some updated; others removed.
02/01/2024	Reviewed. No changes.
01/01/2023	Document updated with literature review. Coverage unchanged. References 17, 24, 30, 31, 42, 53, and 55 added; others removed.
09/01/2021	Reviewed. No changes.
08/15/2020	Document updated with literature review. Coverage unchanged. Add references 9, 18, 42, 43, and 49.
01/15/2020	Document updated with literature review. Coverage revised to state the percutaneous closure of a patent foramen ovale or transcatheter closure of secundum septal defects may be considered medically necessary when using a device approved by the U.S. Food and Drug Administration (FDA) for that purpose and used according to the labeled indications. 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. Transcatheter closure of patent ductus arteriosus and ventricular septal defects are no longer addressed in this policy. References revised and renumbered with a number being deleted; new references 7-10, 12-15, 18, 21-22, 31, 41-43 were added. Title of the policy changed from Transcatheter Closure Devices for Cardiac Defects: Atrial Septal Defects (ASD), Patent Foramen Ovale (PFO), Patent Ductus Arteriosus (PDA), and/or Ventricular Septal Defects (VSD).
05/01/2019	Reviewed. No changes.
04/01/2017	Document updated with literature review. The following conditional coverage statement was added: Transcatheter closure of patent foramen ovale (PFO) with the U.S. Food and Drug Administration (FDA) approved AMPLATZER PFO Occluder, is considered medically necessary to reduce the risk of recurrent ischemic stroke in patients with the following: 1) between the ages of 18 and 60 years and 2) documentation of known cryptogenic stroke. Note: Individual consideration may be given for those outside this age range when records document a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke and the benefits outweigh the risks associated with the procedure. Transcatheter closure of patent foramen ovale (PFO) with the U.S. Food and Drug Administration (FDA) approved AMPLATZER PFO Occluder, for all other indications including but not limited to the following, is considered experimental, investigational and/or unproven: 1) Intra-cardiac mass, vegetation, tumor or thrombus at the intended site of implant, or documented evidence of venous thrombus in the vessels through which access to the PFO is gained; 2) Vasculature,

	through which access to the PFO is gained, that is inadequate to accommodate the appropriate sheath size; 3) Anatomy in which the AMPLATZER PFO device size required would interfere with other intracardiac or intravascular structures, such as valves or pulmonary veins; 4) Other source of right-to-left shunts, including an atrial septal defect and/or a fenestrated atrial septum; and/or 5) Active endocarditis or other untreated infections. In addition, the note #1 in the coverage concerning atrial septal defects was revised to change the name of the name of U.S. Food and Drug Administration (FDA) -approved device for atrial septal defects to the GORE® CARDIOFORM Septal Occluder.
07/01/2016	Document updated with literature review. Coverage unchanged.
05/01/2015	Reviewed. No changes.
04/15/2014	Document updated with literature review. Coverage unchanged. Rationale significantly revised. CPT/HCPCS code(s) updated
09/15/2009	Revised/updated entire document; Transcatheter closure of patent foramen ovale (PFO) was added as now considered experimental, investigational and unproven.
09/15/2007	Revised/Updated Entire Document