



Louisiana

Closure Devices for Patent Foramen Ovale and Atrial Septal Defects

Policy # 00016

Original Effective Date: 06/05/2002

Current Effective Date: 11/01/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member's contract/certificate, and
- Medical necessity criteria and guidelines are met.

Atrial Septal Defect

Based on review of available data, the Company may consider transcatheter closure of secundum atrial septal defects (ASDs) when using a device that has been approved by the U.S. Food and Drug Administration (FDA) for that purpose and used according to the labeled indications to be **eligible for coverage** when patient selection criteria are met.

Patient Selection Criteria

Three devices have been approved by the U.S. FDA for atrial septal defect closure: the Amplatzer™± Septal Occluder, the GORE HELEX Septal Occluder (discontinued), and the GORE CARDIOFORM Septal Occluder.

The labeled indications for these devices are similar and include:

- Patients with echocardiographic evidence of ostium secundum atrial septal defect; and
- Clinical evidence of right ventricular volume overload (i.e., 1.5:1 degree of left to right shunt or right ventricular enlargement).

Generally recognized indications for closure include a pulmonary-to-systemic flow ratio of greater than 1.5, right atrial and right ventricular enlargement, and paradoxical embolism.

Patent Foramen Ovale

Based on review of available data, the Company may consider the percutaneous transcatheter closure of a patent foramen ovale (PFO) using AMPLATZERPFO Occluder to be eligible for coverage to reduce the risk of recurrent ischemic stroke if patient meets all of the following criteria:

- Between 18 and 60 years of age
- Diagnosed with PFO with a right-to-left interatrial shunt confirmed by echocardiography with at least one of the following characteristics:
 - PFO with large shunt, defined as >30 microbubbles in the left atrium within 3 cardiac cycles, after opacification of the right atrium.

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- PFO associated with atrial septal aneurysm on transesophageal examination: septum primum excursion >10 mm
 - 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
- Other sources of right-to-left shunts, including an atrial septal defect and/or fenestrated septum.
- Active endocarditis or other untreated infections
- Inferior vena cava filter.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Atrial Septal Defects

Based on review of the available data, the company considers the use of transcatheter closure of secundum ASDs when patient selection criteria are not met to be **investigational**.*

Patent Foramen Ovale

Based on review of the available data, the company considers closure of PFO when patient selection criteria are not met to be **investigational**.

Background/Overview

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. 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.

Treatment

Conventional therapy for cryptogenic stroke consists of antiplatelet therapy (aspirin, clopidogrel, or dipyridamole given alone or in combination) or oral anticoagulation with warfarin. In general, patients with a known clotting disorder or evidence of preexisting thromboembolism are treated with warfarin, and patients

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without these risk factors are treated with antiplatelet agents. Closure devices are nonpharmacologic alternatives to medical therapy for cryptogenic stroke in patients with a PFO.

There has been interest in open surgery and transcatheter approaches to close the PFO in patients with a history of cryptogenic stroke to prevent recurrent stroke.

ATRIAL SEPTAL DEFECTS

Unlike PFO, which represents the postnatal 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 midseptally and are typically near the fossa ovalis. Ostium primum defects lie immediately adjacent to the atrioventricular valves and are within the spectrum of atrioventricular septal defects. Primum defects occur commonly in patients with Down syndrome. Sinus venous defects occur high in the atrial septum and are frequently associated with anomalies of the pulmonary veins.

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

Treatment

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.

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Transcatheter Closure Devices

Several devices have been developed to treat PFO and ASDs via a transcatheter approach, including the CardioSEAL STARFlex™± Septal Occlusion System, the Amplatzer PFO Occluder, the Figulla ASD Occluder (Occlutech GmbH), and the CeraFlex ASD Occluder (Lifetech Scientific).

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.

FDA or Other Governmental Regulatory Approval **U.S. Food and Drug Administration (FDA)**

PFO Closure Devices

In 2002, 2 transcatheter devices were cleared for marketing by the U.S. 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 St. Jude Medical). Following the limited FDA approval, use of PFO closure devices increased by more than 50-fold, well in excess of the 4000 per year threshold intended under the humanitarian device exemption, prompting FDA to withdraw the humanitarian device exemption approval for these devices in 2007.

In November 2016, the Amplatzer PFO Occluder was approved by FDA through the premarket approval process for the following indication:

“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.”

FDA product code: MLV.

ASD Closure Devices

Three devices have been approved by the FDA through the premarket approval process or a premarket approval supplement for transcatheter ASD closure (see Table 1) (FDA product code: MLV).

Table 1. ASD Closure Devices Approved by the 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 • Use in patients who have had a fenestrated Fontan procedure who require closure of the fenestration • Patients indicated for ASD closure have

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			echocardiographic evidence of ostium secundum ASD and clinical evidence of right ventricular volume overload.
GORE HELEX Septal Occluder	W.L. Gore & Associates	Aug 2006 (discontinued)	• Percutaneous, transcatheter closure of ostium secundum ASDs
GORE CARDIOFORM Septal Occluder	W.L. Gore & Associates	Oct 2016 (supp.)	• Percutaneous, transcatheter closure of ostium secundum ASDs

ASD: atrial septal defect; PMA: premarket approval.

Centers for Medicare and Medicaid Services (CMS)

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

Rationale/Source

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 to 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 a technology, 2 domains are examined: the relevance and the 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

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

Transcatheter PFO Closure With Device vs Medical Management

Two RCTs—the PC and RESPECT trials—have been published and reported on outcomes comparing the Amplatzer PFO Occluder with medical management. Trial characteristics and results are summarized in Tables 2 and 3.

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In the PC trial (2013), the primary end point (composite of death, nonfatal stroke, transient ischemic attack [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 end point (from 3% per year in the medical therapy group vs 1% per year in the closure group). However, the observed event rate in the trial was less than half of the anticipated event rate used in the power calculation and, as reported by authors, the trial had less than 40% power to detect a 66% reduction.

RESPECT (2013) also compared closure with medical management, with 2 notable differences from the PC trial: TIA was not included as a component of the primary composite end point, and all end points 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 end point 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 3 publications with each publication reporting longer follow-up. The primary end point was a stroke or early death, 30 and 45 days after implantation or randomization, respectively.

The first publication, by Carroll et al (2013), reported a median follow-up of 2.3 years and no difference in the primary end point with ITT analysis. The ITT analysis (n=980) included 3 patients from the closure group who had recurrent ischemic stroke before device implantation. However, the per-protocol cohort (n=944; patients as randomized plus 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, adhered to the protocol-mandated medical treatment, and were classified by treatment actually received) showed statistically significant improvements in primary end point 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 ninefold increased use of warfarin in the medical group.

Subsequent to this analysis, Rogers et al (2017) published an overview of the U.S. FDA assessment of the Amplatzer PFO Occluder that included analysis of data with approximately 5 years of follow-up. FDA conducted ITT, per-protocol, as-treated, and device-in-place analyses and results are summarized in Table 4. 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 3 analyses (ie, per-protocol, as-

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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, 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. Findings were similar to those reported by Roger et al (2016). 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).

Table 2. 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); PC Trial	Europe, Canada, Brazil, Australia	29	2000-2009	With PFO <60 y and history of ischemic stroke, TIA, or a peripheral TE event	Amplatzer PFO Occluder	Medical treatment ^a	4.1
Carroll et al (2013); RESPECT	U.S., Canada	69	2003-2011	With PFO 18-60 y and cryptogenic ischemic stroke	Amplatzer PFO Occluder	Medical treatment ^b	2.1
Saver et al (2017); RESPECT	U.S., Canada	69	2003-2011	With PFO 18-60 y and cryptogenic ischemic stroke	Amplatzer PFO Occluder	Medical treatment ^b	5.9

DOF: duration of follow-up; PFO: patent foramen ovale; TE: thromboembolic; RCT: randomized controlled trial; TIA: transient ischemic attack.

^a Antithrombotic as per physician discretion and could have included antiplatelet therapy or oral anticoagulation, provided that patients received at least 1 antithrombotic drug.

^b Aspirin, warfarin, clopidogrel, or aspirin combined with extended-release dipyridamole.

Table 3. Summary of Key RCT Results for the Amplatzer PFO Occluder

Study; Trial	Primary End Point	Secondary End Point	Stroke
Meier et al (2013); 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	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); 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	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); 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	Not reported	Not applicable	0.55 (0.31 to 0.99);

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NNT (95% CI)	-	-	0.04
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CI: confidence interval; HR: hazard ratio; NNT: number needed to treat; PFO: patent foramen ovale; RCT: randomized controlled trial; TIA: transient ischemic attack.

^a Composite of death, nonfatal stroke, TIA, or peripheral embolism.

^b Composite of stroke, TIA, or peripheral embolism.

^c Composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization.

Table 4. FDA Summary of Kaplan-Meier Analyses of the Primary End Point in RESPECT Trial (Amplatzer PFO Occluder)

Analysis Population	Definitions	RRR, %	p
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).

FDA: Food and Drug Administration; 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 PFO Closure With Device Plus Medical Management vs Medical Management Alone

Two RCTs—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 5 and 6. 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 and RESPECT trials, all respectively.

In the REDUCE trial (2017), the blinded adjudicated coprimary end points of freedom from ischemic stroke (reported as the percentage of patients who had a stroke recurrence) and incidence of new brain infarction (clinical ischemic stroke plus silent brain infarction on imaging) 2 years after randomization were significantly lower in the PFO closure plus antiplatelet therapy than the antiplatelet therapy alone group in ITT analysis, the per-protocol analysis, and the as-treated population analysis (see Table 6). 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, PCI, 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 ($p=0.22$).



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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). 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 6). The 5-year stroke risk, using the Kaplan-Meier probability estimate, was 4.9 percentage points lower in the PFO closure group than in the antiplatelet-only group, which would result in 1 stroke avoided at 5 years for every 20 treated patients (95% CI, 17 to 25). The rate of atrial fibrillation was higher in the PFO closure group (4.6%) than in the antiplatelet-only group (0.9%; $p=0.02$). 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 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 5. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions		Median DOF, y
					Active	Comparator	
Søndergaard et al (2017); 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	3.2
Mas et al (2017); 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	5.4-5.2 ^d

DOF: duration of follow-up; PFO: patent foramen ovale; RCT: randomized controlled trial.

^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 6. Summary of Key RCT Results

Study; Trial	Primary End Point ^a	Primary End Point ^b	Secondary End Point ^c
Søndergaard et al (2017); REDUCE	664	664	-
HELEX or CARDIOFORM plus antiplatelet therapy, n/N (%)	6/441 (1.4)	22/383 (5.7)	-
Antiplatelet therapy alone, n/N (%)	12/223 (5.4)	20/177 (11.3)	-
HR (95% CI); p	0.23 (0.09 to 0.62); 0.002	0.51 (0.29 to 0.91); 0.04	-
NNT (95% CI)	20 (17 to 25)	Not reported	-
Mas et al (2017) ^g ; CLOSE	473	-	-
Multiple closure devices plus antiplatelet	0/238 (0)	-	Not reported (3.4)

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therapy, n/N (%)			
Antiplatelet therapy alone, n/N (%)	14/235 (6.0)	-	Not reported (8.9)
HR (95% CI); p	0.03 (0.00 to 0.26); <0.001	-	0.39 (0.16 to 0.82); 0.01

CI: confidence interval; HR: hazard ratio; NNT: number needed to treat; RCT: randomized controlled trial.

^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.

Systematic Reviews

A large number of systematic reviews and meta-analyses have evaluated outcomes related to the percutaneous transcatheter closure of a PFO. Of these, 2 systematic reviews, by Kent et al (2016) and Li et al (2015), have pooled data from 3 RCTs (CLOSURE I, PC trial, RESPECT). However, the findings of analyses published prior 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, REDUCE, and CLOSE but excluded CLOSURE I trial data because it used the STARFlex PFO closure device are summarized in Tables 7 and 8. Shah et al (2018) reported that PFO closure reduced the absolute risk of recurrent stroke by 3.2% (95% CI, 1.4% to 5.0%) while De Rosa et al (2018) reported that the PFO closure reduced the absolute risk of stroke or 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. 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. 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.

Table 7. Systematic Review Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Shah et al (2018)	1966-2017	4	Adults with PFO and cryptogenic stroke	4866 (NR)	RCT	No restrictions
De Rosa et al (2018)	2004-2017	4	Adults with PFO and cryptogenic stroke	2932 (67-622)	RCT	No restrictions

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

Table 8. Systematic Review Results

Study	Stroke	TIA	Stroke or TIA	Major Bleeding	AF
Shah et al (2018)					
N	2892	2892	-	1912	663
ARR (95% CI)	-3.2 (-5.0 to -1.4)	-0.4 (-1.7 to 1.0)	-	-2.1 (-5.1 to 0.9)	6.1 (NR)

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NNT (95% CI)	NR	NR	-	NR	NR
\hat{r} (p)	3.62 (0.38)	0 (0.81)	-	0 (0.92)	82.5 (<0.001)
De Rosa et al (2018)					
N	2531	-	2531	2531	2531
ARR (95% CI)	-3.1 (-5.1 to -1.0)	-	-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	-	NR	NR	NR
\hat{r} (p)	61 (0.003)	-	33.79 (0.29)	28 (0.60)	66 (0.002)

AF: atrial fibrillation; ARR: absolute risk reduction; CI: confidence interval; NNT: number needed to treat; NR: not reported; TIA: transient ischemic attack.

Observational Studies

There is a large evidence base of observational studies. Because multiple RCTs with more than 5 years of follow-up are available, data from these observational studies are not discussed except where such studies provide longer duration of follow-up, specifically related to durability of results and adverse events (revealed by larger populations or longer length of follow-up than in trials). Rigatelli et al (2016) reported safety outcomes on a series of 1000 consecutive patients who were treated with catheter-based closure using different devices and prospectively identified, with mean follow-up of 12.3 years. 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.

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

The results of RCTs of PFO closure compared with medical management have reported point estimates of hazard ratios 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 (CLOSURE I, PC, 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 (eg, 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-analysis 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

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

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Randomized Controlled Trials

Dowson et al (2008) published results of the MIST trial, a sham-controlled randomized trial of PFO closure for refractory migraine headache. In this trial, no significant difference was observed in the primary end point 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 PRIMA trial, a randomized, open-label trial with blinded end point evaluation comparing transcatheter PFO closure with medical management in patients who had a migraine with aura. 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 end point (reduction in mean migraine days at 1 year postrandomization), there were no significant differences between the groups (-2.9 [95% CI, -4.4 to -1.4] for PFO closure vs -1.7 [95% CI, -2.5 to -1.0] for medical management; $p=0.168$).

Tobis et al (2017) reported on the results of 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, had failed at least 3 migraine preventive medications, and had significant right-to-left shunt identified by transcranial Doppler. The primary end point (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.

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. 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 not intervention or who were managed medically. The single RCT identified (Dowson et al [2008]) did not identify significant improvements in migraine symptoms in the PFO closure group.

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Observational Studies

In a study not included in the Lip and Lip systematic review, Biasco et al (2014) retrospectively compared transcatheter PFO closure with medical therapy to assess their impact on daily activities. The study included 217 patients with a migraine and echocardiographic evidence of PFO, 89 of whom were managed with percutaneous PFO closure and 128 medically managed. PFO device closure was recommended for patients with a migraine associated with previous suspected paradoxical embolic events, or for those without a history of suspected embolic events only in the case of severely disabling symptoms not controlled by multiple therapies. At a mean follow-up of 1299 days, both groups demonstrated significant reductions in Migraine Disability Assessment scores. However, there were no significant differences in the Migraine Disability Assessment scores between groups ($p=0.204$). The degree of residual right-to-left shunt was not associated with symptom perception.

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 ($N=889$). In this sample, a PFO with atrial septal aneurysm was significantly associated with a 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 PFO Closure for Migraine

Although observational studies have shown a possible association between PFO closure and reduction in migraine symptoms, 1 sham-controlled randomized trial 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 PFO CLOSURE FOR OTHER INDICATIONS

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

Section Summary: Transcatheter PFO 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

FDA has approved 3 devices for ASD closure: the Amplatzer Septal Occluder, the GORE HELEX Septal Occluder (discontinued), and the GORE CARDIOFORM Septal Occluder.

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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. This study was subsequently published by Du et al (2002) with slightly different data but similar quantitative findings. 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

A systematic review comparing percutaneous closure with surgical closure was published by Butera et al (2011). Thirteen nonrandomized comparative studies that enrolled at least 20 patients were included (total $N=3082$ 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; $p=0.006$).

In the Abaci et al (2013) 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%).

Nonrandomized Comparative Studies

Other nonrandomized studies comparing transcatheter closure with surgery have shown similar success rates. Suchon et al (2009), in a study of 100 patients, had a 94% success rate in the transcatheter closure group compared with a 100% success rate in the surgical group. A study by Berger et al (1999) showed identical 98% success rates in both treatment groups. A nonrandomized comparative analysis by Kotowycz et al (2013) reported that mortality rates at 5-year follow-up did not differ between transcatheter (5.3%) and surgical closure (5.635%; $p=1.00$) groups, but that reintervention rates were higher for patients undergoing transcatheter closure (7.9% vs 0.3%, respectively, $p<0.004$).

In a nonrandomized comparative analysis that used national-level data from Taiwan, Chen et al (2015) compared in-hospital and longer term (4-year) follow-up outcomes for adults who underwent secundum ASD repair by a surgical ($n=348$) or transcatheter ($n=595$) route. After propensity-score matching, during the index hospitalization, surgical repair patients were more likely to have systemic thromboembolism (4.9%

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vs 0%, $p < 0.001$), ischemic stroke (1.9% vs 0%, $p = 0.002$), or in-hospital death (1.3% vs 0%, $p = 0.013$). Over the 4-year follow-up, outside of the index hospitalization, transcatheter repair patients were more likely to have atrial fibrillation (1.7% vs 0%, $p = 0.036$), while other outcomes did not differ.

Xu et al (2014) reported on a retrospective analysis of transcatheter ($n = 35$) and surgical ($n = 43$) repair in patients with ASD and pulmonary stenosis. Complication rates did not differ significantly between groups, and all patients had a complete correction of their ASD.

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. Fischer et al (2003) reported on the use of the Amplatzer device in 236 patients with secundum ASD. 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. 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.

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, Baruteau et al (2014) reported closure rates of 92.6%.

Other smaller studies have also reported favorable results for transcatheter closure of ASD. In Du et al (2002), transcatheter closure for 23 patients with deficient ASD rims was compared with transcatheter closure of 48 patients who had sufficient ASD rims. 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. 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. 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.

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Single-Arm Studies in Pediatric Patients

Several single-arm studies have reported on outcomes for transcatheter ASD closure in children and adolescents. Grohmann et al (2014) reported on outcome from a single-center series of children ages 3 to 17 years (median, 6 years) treated with the HELEX Septal Occluder, with technical success in 41 (91%) of 45 patients in whom closure was attempted. 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. 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.

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. 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 PFO and cryptogenic stroke who receive PFO closure with a transcatheter device, the evidence includes multiple, RCTs comparing device-based PFO closure with medical therapy, systematic reviews, and meta-analyses of these studies. Relevant outcomes are 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. While these results were not statistically significant by intention-to-treat analyses in the first 3 trials (ie, CLOSURE I, PC, and RESPECT [initial study]), they were statistically significant in later trials (ie, RESPECT [extended follow-up], REDUCE, and 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 a meaningful improvement in the net health outcome.

For individuals who have PFO and migraines who receive PFO closure with a transcatheter device, the evidence includes 2 RCTs of PFO closure and multiple observational studies reporting on the association between PFO and migraine. Relevant outcomes are symptoms, quality of life, medication use, and treatment-related morbidity and mortality. The available sham-controlled randomized trial did not demonstrate significant improvements in migraine symptoms after PFO closure. A second RCT with blinded end point evaluation did not demonstrate reductions in migraine days after PFO closure but likely was underpowered. Nonrandomized studies have shown highly variable rates of migraine reduction after PFO closure. The evidence is insufficient to determine the effects of the technology on health outcomes.

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For individuals who have PFO and conditions associated with PFO other than cryptogenic stroke or migraine (eg, platypnea-orthodoxia 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. The body of evidence only consists of small case series and case reports. Comparative studies are needed to evaluate outcomes in similar patient groups treated with and without PFO closure. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have ASD and evidence of left-to-right shunt or right ventricular overload who receive ASD closure with a transcatheter device, the evidence includes 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. 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 a meaningful improvement in the net health outcome.

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Policy History

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| 04/18/2002 | Medical Policy Committee review |
| 06/05/2002 | Managed Care Advisory Council approval |
| 06/24/2002 | Format revision |
| 03/31/2004 | Medical Director review |
| 04/20/2004 | Medical Policy Committee review. Format revision. Coverage eligibility unchanged. |
| 04/26/2004 | Managed Care Advisory Council approval |
| 04/05/2005 | Medical Director review |
| 04/19/2005 | Medical Policy Committee review. Coverage eligibility unchanged. Investigational statement added to policy to address the use of transcatheter closure devices in situations where patient selection criteria are not met. |
| 05/23/2005 | Managed Care Advisory Council approval |
| 04/05/2006 | Medical Director review |

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04/19/2006	Medical Policy Committee approval. Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
07/07/2006	Format revised. Investigational statements added to clarify coverage eligibility. Coverage eligibility unchanged.
04/04/2007	Medical Director review
04/18/2007	Medical Policy Committee approval. Coverage eligibility unchanged.
04/02/2008	Medical Director review
04/16/2008	Medical Policy Committee approval. No change to coverage eligibility.
04/02/2009	Medical Director review
04/15/2009	Medical Policy Committee approval. Closure of patent foramen ovale using a transcatheter approach is now considered to be investigational.
04/08/2010	Medical Policy Committee approval.
04/21/2010	Medical Policy Implementation Committee approval. No change to coverage.
04/07/2011	Medical Policy Committee approval.
04/13/2011	Medical Policy Implementation Committee approval. No change to coverage.
04/12/2012	Medical Policy Committee review
04/25/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/04/2013	Medical Policy Committee review
04/24/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/06/2014	Medical Policy Committee review
03/19/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/07/2015	Medical Policy Committee review
05/20/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/05/2016	Medical Policy Committee review
05/18/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
07/06/2017	Medical Policy Committee review
07/19/2017	Medical Policy Implementation Committee approval. Statement, "There are currently no transcatheter devices with the U.S. Food and Drug Administration [FDA] approval or clearance for this indication," removed from investigational statement for PFO closure devices; policy statements otherwise unchanged.
08/09/2018	Medical Policy Committee review
08/15/2018	Medical Policy Implementation Committee approval. Criteria for PFO revised to track BCBSA.
Next Scheduled Review Date:	08/2019

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Code Type	Code
CPT	93580
HCPCS	C1817
ICD-10 Diagnosis	Q21.1, Q21.2

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- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
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 - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
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- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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