Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 3/1/25**
(See policy history boxes for previous effective dates)

Title: Closure Devices for Patent Foramen Ovale and Atrial Septal Defects

Description/Background

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 a course of months after birth, an increase in left atrial pressure and a decrease in right atrial pressure result in the 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, a type of stroke defined as an ischemic stroke occurring in the absence of potential cardiac, pulmonary, vascular, or neurologic sources. Studies also show an association of PFO and migraine headache.

ATRIAL SEPTAL DEFECT

Unlike PFO, which represents the postnatal persistence of normal fetal cardiovascular physiology, atrial septal defects (ASDs) represent an abnormality in the development of the

heart that results in free communication between the atria. ASDs are categorized by their anatomy. Ostium secundum describes defects located 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 one of 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 operative 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 device so that smaller catheters can be used, developing techniques to properly center the device across the ASD, and ensuring that the device can be easily retrieved or repositioned, if necessary.

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

Transcatheter Closure Devices

Transcatheter PFO and ASD occluders consist of a single or paired wire mesh disc, covered or filled with polyester or polymer fabric, which are placed over the septal defect. Over time, the occlusion system is epithelialized. ASD occluder devices consist of flexible mesh disks 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, 2 transcatheter devices were cleared for marketing by the FDA through a humanitarian device exemption (HDE) as a treatment for patients with cryptogenic stroke and patent foramen ovale (PFO): the CardioSEAL® Septal Occlusion System (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 HDE,(2) prompting the FDA to withdraw the HDE 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. PFO 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 patent foramen ovale (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.
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 5 devices for ASD closure through the premarket approval process or a premarket approval supplement: the Amplatzer Septal Occluder, the GORE HELEX Septal Occluder (discontinued), GORE CARDIOFORM ASD Occluder, the GORE CARDIOFORM Septal Occluder, and Occlutech® ASD Occluder . (see Table 2)

FDA product code: 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 (Abbott Medical)	Dec 2001	• Occlusion of ASDs in the secundum position • Use in patients who have had a fenestrated Fontan procedure who require closure of the fenestration • Patients indicated for ASD closure have echocardiographic evidence of ostium secundum ASD and clinical evidence of right ventricular volume overload.

GORE HELEX Septal Occluder	W.L. Gore & Associates	Aug 2006 (discontinued)	• Percutaneous, transcatheter closure of ostium secundum ASDs
GORE CARDIOFORM ASD Occluder	W.L. Gore & Associates	May 2019 (supplement)	• Percutaneous, transcatheter closure of ostium secundum ASDs
GORE CARDIOFORM Septal Occluder	WL. Gore & Associates	Apr 2015 (supplement)	• Percutaneous, transcatheter closure of ostium secundum ASDs
Occlutech ASD Occluder	Occlutech	Dec 2023	• Percutaneous, transcatheter closure of ostium secundum ASDs

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

Medical Policy Statement

Closure of patent foramen ovale, using a FDA approved device according to the labeled instructions, for a percutaneous transcatheter approach may be considered established when specified criteria are met.

Transcatheter closure of secundum atrial septal defects may be considered established when using a device that has been FDA approved for that purpose and used according to the labeled indications.

Inclusionary and Exclusionary Guidelines

Inclusions:

Closure of patent foramen ovale (PFO) using a percutaneous transcatheter approach, with an FDA approved device per labeled instructions, when ALL of the following are met:

- Used to reduce the risk of recurrent ischemic stroke
- Patient is predominantly between 18 and 60 years of age
- Echocardiography confirms diagnosis of patent foramen ovale with a right-to-left interatrial shunt
- Documented history of cryptogenic ischemic stroke or TIA due to presumed paradoxical embolism as determined by a Neurologist *AND* Cardiologist:
  - Any other identifiable cause of stroke has been excluded including:
    - Large vessel atherosclerotic disease
    - Small vessel occlusive disease
- None of the following are present:
  - Uncontrolled vascular risk factors including:
    - Uncontrolled diabetes mellitus
    - Uncontrolled hypertension
  - Other sources of right-to-left shunts including:
    - Atrial septal defect
    - Fenestrated septum
  - Active endocarditis or other untreated infections
  - Inferior vena cava filter

Transcatheter closure of atrial septal defects with an FDA approved device, per labeled instructions, when BOTH of the following are met:

- There is echocardiographic evidence of ostium secundum atrial septal defect **AND**
- There is evidence of right ventricular volume overload or paradoxical embolism

Exclusions:
- Patent foramen ovale with recurrent cryptogenic migraine
- Closure of a septal defect when performed using the transmyocardial approach
- Open surgery is needed to repair multiple congenital defects or other cardiac defects
- Multiple cardiac defects that cannot be covered by the device

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CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

93580

Other codes (investigational, not medically necessary, etc.):

33999 93799

Rationale

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 PICOs were used to select literature to inform this review.

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

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

Comparators
The following therapies are currently being used to manage PFO closure in individuals with cryptogenic stroke: conventional therapy for cryptogenic stroke 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 closure.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

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

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

Alushi et al (2018) included all 5 trials and reported outcomes as pooled hazard ratios (HRs) or odds ratios (ORs) in a third meta-analysis (Tables 3 and 4).(12) Results were similar to previous systematic reviews: there was a 48% reduction in the composite primary outcome of TIA or stroke but no significant reduction in risk of TIA (Table 4). There was an increased risk of atrial fibrillation but no difference between groups in the risk of major bleeding.

Table 3. Systematic Review & Meta-Analysis Characteristics

Study	Dates	Trials	Participants	N (Range)	Designs	Duration
Shah et al (2018)[7,]	1966-2017	4	Adults with PFO and cryptogenic stroke	4866 (NR)	RCTs	No restrictions
De Rosa et al (2018)[8,]	2004-2017	4	Adults with PFO and cryptogenic stroke	2932 (67-622)	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 Review & Meta-Analysis Results

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

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

Randomized Controlled Trials

Transcatheter Patent Foramen Ovale Closure with Device versus Medical Management

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

In the PC trial (2013), the primary 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 two notable differences from to 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 three publications (13-15), 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.

Carroll et al (2013), reported in the first publication a median follow-up of 2.3 years and no difference in the primary end point 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 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 who 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 (hazard ration [HR]=0.37; 95% confidence interval [CI], 0.14 to 0.96; p=0.03 and 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 9-fold increased use of warfarin in the medical group.

Rogers et al (2017) published an overview of the U.S. Food and Drug Administration (FDA) assessment of the Amplatzer PFO Occluder that included analysis of data with approximately five years of follow-up.(15) The FDA conducted ITT, per-protocol, as-treated, and device-in-place analyses and results are summarized in Table 6. Although the FDA panel had some disagreements about using non-ITT analysis because excluding patients compromises randomization, the panel agreed that a 50% relative risk reduction in stroke-especially in a younger patient population-is clinically significant. All 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, FDA concluded that it might be reasonable for conclusions drawn from RESPECT to

be limited to the select subgroup of at-risk patients with stroke and PFO in whom other causes of ischemic stroke have been excluded by a neurologist.

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

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

Table 5. Summary of Key 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	2003-2001	With PFO 18-60 y and cryptogenic ischemic stroke	Amplatzer PFO Occluder	Medical treatment[b]	5.9
Lee et al (2018) DEFENSE-PFO	South Korea	2	2011-2017	With cryptogenic stroke and high-risk PFO.	Amplatzer PFO Occluder with medical treatment	Medical treatment[b]	2.8

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

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

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

Table 6. Summary of Key RCT Results for 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 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); 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% I); 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); 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) 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) 0.013	Not applicable	(NR) 0.023

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

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

[b] Composite of stroke, TIA, or peripheral embolism.

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

[d] Intention-to-treat analysis.

[e] Kaplan-Meier estimates.

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

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

Analysis Population	Definitions	RRR %	p-value
Intention to Treat	Primary analysis population, which included all randomized patients regardless of whether the Amplatz was implanted	50	0.089
Per-Protocol	All patients adhering to protocol requirements[a] regardless of whether Amplatz was implanted	63	0.034[b]
As-Treated	All patients adhering to protocol requirements[1] but who actually had the Amplatz implanted	72	0.008[b]
Device-in-place	All randomized patients but who actually had the Amplatz implanted	70	0.007[b]

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

FDA: Food and Drug Administration; RESPECT: Patent Foramen Ovale Closure or Medical Therapy After Stroke; RRR: relative risk reduction.

[a] Adherence to guideline-directed medical therapy defined as ≥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 versus Medical Management Alone

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

In the REDUCE trial (2017), the blinded adjudicated coprimary 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 9).(9) The number of patients who needed to be treated (NNT) to prevent one stroke in 24 months was approximately 28.

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).

Anderson et al (2021) described the occurrence of post-procedural atrial fibrillation in the REDUCE trial.(17) In this trial, a total of 408/441 patients had successful PFO closure with either the HELEX device (39%) or the Gore Cardioform Septal Occluder (61%). During a median follow-up of 5 years, 30/408 (7.4%) patients had a diagnosis of atrial fibrillation after PFO closure, whereas only 1/223 (0.4%) patients who received antiplatelet therapy alone had atrial fibrillation (p<.001). The majority of cases of atrial fibrillation (79.4%) occurred within 45 days after PFO closure and most episodes (62.5%) were less than 2 weeks in duration. In the REDUCE clinical study, postprocedural atrial fibrillation was mostly transient, early onset and did not recur at a later time. Postprocedural atrial fibrillation (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 versus antiplatelet-only group in ITT analysis as well as per-protocol analysis (see Table 9). The five-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 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	
Sondergaard 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]	Median 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]	Mean 5.3

CLOSE: Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence; DOF: duration of follow-up; PFO: patent foramen ovale; REDUCE: GORE Septal Occluder Device for Patent Foramen Ovale (PFO) Closure in Stroke Patients.
[a] Antiplatelet therapy could consist of aspirin alone (75-325 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]
Sondergaard (2017); REDUCE	664	664	N/A
Helex or Cardioform plus antiplatelet therapy	6/441 (1.4)	22/383 (5.7)	N/A
Antiplatelet therapy alone	12/223 (5.4)	20/177 (11.3)	N/A
HR (95%CI); p-value	0.23 (0.09 to 0.62); 0.002	0.51 (0.29 to 0.91); 0.04	N/A
NNT (95% CI)	20 (17 to 25)	Not reported	N/A
Mas et al (2017); CLOSE	473		Not reported
Multiple closure devices plus Antiplatelet therapy, n/N (%)	0/238 (0)	N/A	Not reported (3.4)
Antiplatelet therapy alone, n/N (%)	14/235 (6.0)	N/A	Not reported (8.9)
HR (95% CI); p-value	0.03 (0.00 to 0.26); <0.001	N/A	0.39 (0.16 to 0.82); 0.01

CI: confidence interval; CLOSE: Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence; HR: hazard ratio; NA: not applicable; NNT: number needed to treat; NR: not reported; REDUCE: GORE® Septal Occluder Device for Patent Foramen Ovale (PFO) Closure in Stroke Patients;
[a] Freedom from ischemic stroke (reported as the percentage of patients who had a recurrence of stroke) 2 years post randomization
[b] Incidence of new brain infarction (clinical ischemic stroke or silent brain infarction on imaging) 2 years post 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% and recurrent cerebral ischemic events occurred in 0.8% of patients. The occlusion rate was 93.8%. No aortic or atrial free wall erosion was reported.

Wintzer-Wehekind et al (2019) reported on long-term outcomes for 201 consecutive patients who had had a cryptogenic embolism (stroke, 76%; TIA, 32%; systemic embolism, 1%) and underwent PFO closure.(19) Median follow-up, completed by 96% of the patients, was 12 years (range, 10 to 17 years). Patients also had follow-up at between one and six 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, six patients had a residual shunt, one 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 one TIA or stroke. At the time of final follow-up, 20.9% (42/201) had been off antithrombotic therapy for a mean of 10 years (±4 y). There

were no significant differences in rates of ischemic events or death between the group that went off antithrombotic medication and those who continued medication.

Section Summary: Transcatheter Device Closure of Patent Foramen Ovale for Stroke
The results of RCTs of PFO closure compared with medical management have reported point estimates of 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 (PC-TRIAL and RESPECT) but were significant in later trials (RESPECT extended follow-up, REDUCE, CLOSE). Initially, inadequate power was blamed for demonstrating the lack of superiority of PFO closure in the early RCTs, but the reasons are probably multifactorial. The RESPECT, REDUCE, and CLOSE trials enrolled patients when off-label PFO closure had decreased, allowing for inclusion for patients with vascular anatomic features (e.g., large intra-arterial shunt size) associated with a relatively higher risk of stroke among those with PFO. In addition, other factors such as the requirement of neuroimaging confirmation of stroke prior to enrollment, exclusion of lacunar infarcts, longer follow-up, and selection of patients with an associated atrial septal aneurysm in RESPECT, REDUCE, and CLOSE possibly contributed to selection of a trial population that adequately excluded other causes of cryptogenic stroke, yielding a sample at higher risk of cryptogenic stroke and therefore amenable to risk modification by PFO closure. It is important to acknowledge that higher rates of atrial fibrillation have been reported in a few of the individual trials and meta-analyses that incorporate evidence from RESPECT, REDUCE, and CLOSE trials. Thus, patient selection is crucial when assessing the risks and benefits of PFO closure over medical management.

Transcatheter Patent Foramen Ovale Closure for Migraine

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

The purpose of PFO closure with a transcatheter device in 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 PICOs were used to select literature to inform this review.

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

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

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

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

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

Review of Evidence

Systematic Reviews

Lip and Lip (2014) published a descriptive, systematic review that assessed 20 studies evaluating the prevalence of PFO in patients with migraines and 21 studies on the effects of PFO closure.(20) In case series and cohort studies of patients with migraines, the prevalence of PFO in patients with migraines ranged from 14.6% to 66.5%. In the case-control studies, the prevalence of PFO in control patients ranged from 16.0% to 25.7%, while the prevalence of PFO in patients who had a migraine with and without aura ranged from 26.8% to 96.0% and 22.6% to 72.4%, respectively. In the 18 case series that reported migraine outcomes after PFO closure, rates of resolution for migraine with and without aura ranged from 28.6% to 92.3% and 13.6% to 82.9%, respectively. In 2 case-control studies that compared PFO closure with no medical intervention or preventive migraine medication, improvement in migraine symptoms occurred in 83% to 87% of those who underwent PFO closure compared with 0% to21% of those who received no intervention or who were managed medically. The single RCT included (Dowson et al [2008](21) did not identify significant improvements in migraine symptoms in the PFO closure group (3/74 in the implant group vs. 3/73 in the sham group; p=.51).

Wang et al (2022) conducted a meta-analysis to investigate the impact of PFO transcatheter closure on migraine burden.(22) Studies were eligible if they compared transcatheter closure with drug or sham therapy in adults with migraine and PFO, with at least 6 months of follow-up. Overall, 12 studies were included: 3 RCTs and 9 case-control studies. Table 10 lists the studies included and Table 11 describes characteristics of the meta-analysis. Compared with medical or sham therapy, PFO closure significantly increased the rate of adults who were completely migraine-free at end of follow-up (see Table 12 for results). Additionally, PFO closure showed a statistically significant reduction in monthly migraine days and monthly migraine attacks compared to comparator groups. In the measurement of activities of daily living (ADLs), 2 scores were used: the Headache Impact Test-6 (HIT-6) and the Migraine Disability Assessment Survey (MIDAS). In the transcatheter closure group, HIT-6 was significantly decreased, implying improved ADLs, but there was no difference in MIDAS score between groups. Among the included trials, 3 articles were considered to be of moderate quality and 9 were of high quality. The studies that examined ADLs had high heterogeneity (I^2=93%). The meta-analysis is limited by the retrospective nature of many of the included studies, since recall and reporting biases cannot be ruled out. There was heterogeneity among included studies, especially the case-control studies. Due to the limited number of included

studies, further subgroup analysis stratifying patients with aura was not possible. Additionally, differences in outcomes across trials limits interpretability. The RCTs included in the trial, Dowson et al (2008),(21), Mattle et al (2016),(23) and Tobis et al (2017),(24) did not individually find any significant improvements in migraine symptoms, migraine-free days, or migraine attacks in the PFO closure group compared to sham or drug therapy, so all significant data in favor of PFO closure came from case-control studies.

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

Study	Wang (2022)[22,]
Anzola et al (2006) - case-control	

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 end point of migraine headache cessation (3/74 in the implant group, 3 /73 in the sham group, p=0.51). The results of this trial cast some doubt on the causal relationship 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 right-to-left shunt, who were randomized to PFO closure with the Amplatzer PFO Occluder (n=53) or medical management (n=54). The trials power calculations required an enrollment of 72 in each group. The trial was stopped prematurely due to slow enrollment, and there was relatively high loss to follow up (22%). In the device group, 45/53 patients agreed to have the PFO occluder implanted, and of those 41 underwent implantation. This suggests that the trial may have been underpowered to detect differences between groups. For the primary endpoint, reduction in mean migraine days at 1-year post-randomization, there were not 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 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. Enrolled patients had failed at least 3 migraine preventive medications, and had significant right-to-left shunt identified by transcranial Doppler.(24) 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.

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 which evaluated the association between migraine with aura and PFO among patients who underwent an agitated saline transesophageal echocardiogram over a 4 year period at a single outpatient cardiology clinic and completed a validated headache questionnaire (n=889).(26) In this sample, a PFO with atrial septal aneurysm was associated significantly with migraine with aura (odds ratio [OR] 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, one sham-controlled RCT 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 PICOs were used to select literature to inform this review.

Populations

The relevant population 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 individuals 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.

Review of Evidence

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

Mojadidi et al (2015) reported on a series of 17 patients who underwent transcatheter PFO closure for platypnea-orthodeoxia syndrome at a single institution, among whom 11 (65%) were classified as having improved oxygen saturation post procedure.(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 that are typically near the fossa ovalis. Ostium primum defects lie immediately adjacent to the atrioventricular valves and are within the spectrum of atrioventricular septal defects. Primum defects occur commonly in patients with Down syndrome. Sinus venous defects occur high in the atrial septum and are frequently associated with anomalies of the pulmonary veins.

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

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

The following PICOs were used to select literature to inform this review.

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

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: 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.

Review of Evidence

The evidence supporting the efficacy of devices for 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 (total N=3082). The rate of procedural complications was higher in the surgical group (31%; 95% CI, 21% to 41%) than in the percutaneous group (6.6%; 95% CI, 3.9% to 9.2%), with an 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 that, for ASD closure, the pooled rate of major complications was 1.6% (95% CI, 1.4% to 1.8%).(33)

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

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

Study	Butera (2011)[32,]	Rigatelli (2021)[31,]	Chambault (2022)[30,]
Berger et al (1999)			

Schneeberger et al (2017)

significant differences in closure rates between groups (91% for deficient rims vs 94% for sufficient rims) along with no major complications at 24 hours and 6-month follow-up. 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 one patient complication (second-degree atrioventricular block) noted.(44) Brochu et al (2002) evaluated 37 patients with New York Heart Association (NYHA) functional class I or II physical capacity who underwent transcatheter closure of ASD.(45) At 6-month follow-up, maximal oxygen uptake improved significantly, and the dimensions of the right ventricle decreased significantly. Twenty patients moved from NYHA class II to class I and improved exercise capacity. Numerous other small, single-arm studies have reported similar results, with procedural success approaching 100% and successful closure rates on follow-up reported in the 90% to 100% range.(11,41)

Single-Arm Studies in Pediatrics

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

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

Section Summary: Transcatheter Device Closure of Atrial Septal Defects

For individuals 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. 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. 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 individuals 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. 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 RCTs 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 was likely 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 ASD and evidence of left-to-right shunt or right ventricular overload who receive ASD closure with a transcatheter device, the evidence includes systemic 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.

Supplemental Information:

Clinical Input Received From Physician Specialty Societies and Academic Medical Centers

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

2016 Input

In response to requests, input was received, by BCBSA, from 2 academic medical centers (1 of which provided 2 responses) and no specialty societies while this policy was under review in 2016. Input was mixed about the medical necessity of closure devices for patent foramen ovale (PFO) in patients with cryptogenic stroke or transient ischemic attack due to presumed paradoxical embolism through the PFO. There was consensus that closure devices for PFO in patients with other conditions (e.g., migraine, platypnea-orthodeoxia syndrome) is not medically necessary.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American College of Chest Physicians

The American College of Chest Physicians (2012) updated its guidelines on antithrombotic therapy and the prevention of thrombosis, which made the following recommendations related to patent foramen ovale (PFO) and cryptogenic stroke:(46)

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

American Academy of Neurology

The American Academy of Neurology (2020) 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.(52) This update to the practice advisory published in 2016 was completed due to the approval of the Amplatzer PFO Occluder and the GORE CARDIOFORM Septal Occluder. Following a systematic review of the literature and structured formulation of recommendations, the Academy developed the following conclusions

addressing percutaneous PFO closure as compared to medical therapy alone. For patients with cryptogenic stroke and PFO, percutaneous PFO closure:

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

The guidelines recommended :

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

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

American Heart Association and American Stroke Association

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

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

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

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

Condition	Recommendation	COR[a]/LOE[b]
Symptomatic isolated secundum ASD, right atrial and/or RV enlargement, and net left-to-right shunt sufficiency large enough to cause physiological sequelae, without cyanosis at rest or during exercise	Transcatheter or surgical closure	I1/B-NR2
Symptomatic primum ASD, sinus venosus defect, or coronary sinus defect, right atrial and/or RV enlargement, and net left-to-right shunt sufficiency large enough to cause physiological sequelae, without cyanosis at rest or during exercise	Surgical closure unless precluded by comorbidities	I1/B-NR2
Asymptomatic isolated secundum ASD, right atrial and RV enlargement, and net left-to-right shunt sufficiency large enough to cause physiological sequelae, without cyanosis at rest or during exercise	Transcatheter or surgical closure	IIa1/C-LD2
Secundum ASD when a concomitant surgical procedure is being performed and there is a net left-to-right shunt sufficiently large enough to cause physiological sequelae, and right atrial and RV enlargement without cyanosis at rest or during exercise	Surgical closure	IIa1/C-LD2
ASD when net left-to-right shunt is ≥1.5:1, PA systolic pressure and/or pulmonary vascular resistance is greater than of one-third of systemic resistance	Percutaneous or surgical closure	IIb1/B-NR2
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)
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.
[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 US-based experts were listed as authors on part II of the position paper.(50)

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

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

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

Ongoing and Unpublished Clinical Trials

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

Table 15. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03309332[a]	OBS Lead-AMPLATZER PFO New Enrollment Study	1214	Apr 2030
NCT04100135[a]	GORE® CARDIOFORM Septal Occluder Migraine Clinical Study: A Study to Evaluate the Safety and Efficacy of Transcatheter Closure of Patent Foramen Ovale for Relief of Migraine Headaches	150	Aug 2027
NCT05561660	Comparison of the Effect of Device Closure in Alleviating Migraine With Patent Foramen Oval (COMPETE-2)	460	Oct 2025
NCT04029233[a]	Prospective, Open-label, Multicenter, Non-randomized Investigation on Percutaneous Patent Foramen Ovale (PFO) Closure Using the Occlutech PFO Occluder to Prevent Recurrence of Stroke in Patients With Cryptogenic Stroke and High Risk PFO	570	May 2024 (Active; no results posted)
Unpublished			
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 (Completed; results posted)

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

Government Regulations

National:

There is no national coverage determination (NCD) on this topic.

Local:

There is no local coverage determination (LCD) on this topic.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Percutaneous Left-Atrial Appendage Closure Devices for Stroke Prevention in Atrial Fibrillation

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through September 19, 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/1/13	12/11/12	12/31/12	Replaces JUMP policy Transcatheter Closure of Cardiac Defects and/or Occlusion of Left Atrial Appendage
5/1/15	2/17/15	2/27/15	Routine maintenance
7/15/16	4/19/16	4/19/16	Routine approval
11/1/16	8/16/16	8/16/16	• Routine maintenance • Per prior versions, MPS Exclusions align with BCBSA, but information has been included that is reflective of FDA guidelines and Rationale
11/1/17	-	-	Tabled
7/1/19	6/20/19		• Updated MPS • Added language to BCBSA exclusion bullet regarding stroke dt presumed paradoxical embolism
3/1/20	12/17/19		• Routine maintenance
3/1/21	12/15/20		• Routine maintenance
3/1/22	12/14/21		• Routine maintenance
3/1/23	12/20/22		• Routine maintenance (slp)
3/1/24	12/19/23		• Routine maintenance (slp) • Vendor managed: N/A
3/1/25	12/17/24		• Routine maintenance (slp) • Vendor managed: N/A

Next Review Date: 4th Qtr, 2025

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN: N/A	Revised: N/A
BCBSM: 2/16/01	Revised: N/A

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: CLOSURE DEVICES FOR PATENT FORAMEN OVALE AND ATRIAL SEPTAL DEFECTS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.