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**POLICY**

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

- Between 18 and 60 years of age
- Diagnosed with patent foramen ovale 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.
  - 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
Closure Devices for Patent Foramen Ovale and Atrial Septal Defects

- Inferior vena cava filter.

Transcatheter closure of secundum atrial septal defects may be considered medically necessary when using a device that has been approved by the U.S. Food and Drug Administration for that purpose and used according to the labeled indications including:

- Patients with echocardiographic evidence of ostium secundum atrial septal defect.

AND either of the following

- Clinical evidence of right ventricular volume overload (i.e., 1.5:1 degree of left-to-right shunt or right ventricular enlargement); OR
- Clinical evidence of paradoxical embolism.

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

POLICY GUIDELINES

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

Please see the Codes table for details.

BENEFIT APPLICATION

BlueCard/National Account Issues

State or federal mandates (e.g., Federal Employee Program) may dictate that certain U.S. Food and Drug Administration-approved devices, drugs, or biologics may not be considered investigational, and thus these devices may be assessed only by their medical necessity.

BACKGROUND

Patent Foramen Ovale

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

Atrial Septal Defects

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

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

**Treatment of Atrial Septal Defects**

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

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

**Transcatheter Closure Devices**

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

**Regulatory Status**

**Patent Foramen Ovale Closure Devices**

The U.S. Food and Drug Administration (FDA) has approved 3 devices for ASD closure through the premarket approval process or a premarket approval supplement: the Amplatzer Septal Occluder, the GORE HELEX Septal Occluder (discontinued), and the GORE CARDIOFORM Septal Occluder (see Table 1). FDA product code: MLV.

In 2002, 2 transcatheter devices were cleared for marketing by the FDA through a humanitarian device exemption as 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 the FDA to withdraw the humanitarian device exemption approval for these devices in 2007. The Amplatzer PFO Occluder was approved through the premarket approval process in 2016. In March 2018, the FDA granted an expanded indication to the Gore
Cardioform Septal Occluder to include closure of PFO to reduce the risk of recurrent stroke (see Table 1). The new indication was based on results of the REDUCE pivotal clinical trial.3

Table 1. PFO Closure Devices Approved by the Food and Drug Administration

<table>
<thead>
<tr>
<th>Device</th>
<th>Manufacturer</th>
<th>PMA Approval Date</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplatzer™ PFO Occluder</td>
<td>St. Jude Medical</td>
<td>Nov 2016</td>
<td>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.4</td>
</tr>
<tr>
<td>GORE HELEXSeptal Occluder</td>
<td>W.L. Gore &amp; Associates</td>
<td>Aug 2006</td>
<td>Percutaneous, transcatheter closure of ostium secundum ASDs</td>
</tr>
<tr>
<td>GORE CARDIOFORM Septal Occluder</td>
<td>W.L. Gore &amp; Associates</td>
<td>Mar 2018</td>
<td>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</td>
</tr>
</tbody>
</table>

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

Atrial Septal Defect Closure Devices

The FDA has approved 3 devices for ASD closure through the premarket approval process or a premarket approval supplement: the Amplatzer Septal Occluder, the GORE HELEX Septal Occluder (discontinued), and the GORE CARDIOFORM Septal Occluder (see Table 2) FDA product code: MLV.

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

<table>
<thead>
<tr>
<th>Device</th>
<th>Manufacturer</th>
<th>PMA Approval Date</th>
<th>Indications</th>
</tr>
</thead>
</table>
| Amplatzer™ Septal Occluder    | St. Jude 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          | • Percutaneous, transcatheter closure of ostium secundum ASDs                                                                                                                                                                                                                                                                                   |
| GORE CARDIOFORM ASD Occluder  | W.L. Gore & Associates | May 2019          | • Percutaneous, transcatheter closure of ostium secundum ASDs                                                                                                                                                                                                                                                                                   |

ASD: atrial septal defect; PMA: premarket approval.
RATIONALE

This evidence review was created in July 1999 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through March 9, 2020.

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

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

Transcatheter Device Closure of Patent Foramen Ovale for Stroke

Clinical Context and Therapy Purpose

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

The question addressed in this evidence review is: Does PFO closure with a transcatheter device improve the net health outcome in patients with cryptogenic stroke?

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

Patients

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

Interventions

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

PFO closure is performed by cardiac surgeons in a hospital setting.

Comparators

The following therapies are currently being used to manage PFO closure in patients with cryptogenic stroke: 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 without these risk factors are treated with antiplatelet agents.

Patients with PFO are managed by cardiologists in an outpatient clinical setting.

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

**Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

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

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

**Transcatheter Patent Foramen Ovale Closure with Device Versus Medical Management**

Three RCTs, the Patent Foramen Ovale and Cryptogenic Embolism (PC)-Trial\(^5\) and the Patent Foramen Ovale Closure or Medical Therapy After Stroke (RESPECT) trial\(^6\) 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 Amplatzer PFO Occluder with medical management. Trial characteristics and results are summarized in Tables 3 and 4.

In the PC-Trial (2013), the primary endpoint (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 endpoint (from 3% per year in the medical therapy group vs 1% per year in the closure group). However, the observed event rate in the trial was less than half of the anticipated event rate used in the power calculation and, as reported by authors, the trial had less than 40% power to detect a 66% reduction.

RESPECT (2013) also compared closure with medical management, with 2 notable differences from the PC-trial: TIA was not included as a component of the primary composite endpoint, and all endpoints were adjudicated in a blinded fashion. These protocol differences were attempts to address shortcomings observed in the PC-Trial where authors noted that TIA as a component in the primary endpoint might have diluted effects, as suggested by the difference in the estimated 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\(^6,7,8\) with each publication reporting longer follow-up. The primary endpoint 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 endpoint with ITT analysis.\(^6\) The ITT analysis (n = 980) included 3 patients from the closure group who had recurrent ischemic stroke before device implantation. However, the per-protocol cohort
(n = 944; patients as randomized who adhered to the protocol-mandated medical treatment, and did not have a major inclusion or exclusion violation) and as-treated cohort (n = 958; patients with a protocol approved treatment who adhered to the protocol-mandated medical treatment, and were classified by treatment actually received) showed statistically significant improvements in primary endpoint in both analyses (hazard ratio [HR] = 0.37; 95% confidence interval [CI], 0.14 to 0.96; P=.03; HR = 0.27; 95% CI, 0.10 to 0.75; P=.007, respectively). The number needed to treat (NNT) after 5 years in the ITT population was 27. The rate of serious, device- or procedure-related complications was 4.5%. There was no difference in major bleeding between arms, but there was a higher incidence of deep vein thrombosis and pulmonary thromboembolism in the device arm. This was attributed to a ninefold increased use of warfarin in the medical group.

Rogers et al (2017) published an overview of the U.S. Food and Drug Administration (FDA) assessment of the Amplatzer PFO Occluder that included analysis of data with approximately 5 years of follow-up. The FDA conducted ITT, per-protocol, as treated, and device-in-place analyses, and results are summarized in Table 5. Although the FDA panel had some disagreements about using non-ITT analysis because excluding patients compromises randomization, the panel agreed that a 50% relative risk reduction in stroke—especially in a younger patient population—is clinically significant. All 3 analyses (i.e., per-protocol, as-treated, and device-in-place) reported statistically significant relative reductions of more than 50% in the risk of recurrent strokes. Note that with extended follow-up analyses, the event-free survival curves converged, and the NNT after 5 years in the ITT population rose from 27 to 43.

However, the FDA concluded that it might be reasonable for conclusions drawn from RESPECT to be limited to the select subgroup of at-risk patients with stroke and PFO in whom other causes of ischemic stroke have been excluded by a neurologist.

Saver et al (2017) also published results from the RESPECT trial, reporting on a median of 5.9 years of follow-up. Rogers et al (2016) reported similar findings. 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. 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 3 and 4.

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meier et al (2013)</td>
<td>EU, Canada, Brazil, Australia</td>
<td>29</td>
<td>2000-2009</td>
<td>With PFO &lt;60 y and history of ischemic stroke, TIA, or a peripheral TE event</td>
<td>Active Comparator</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Amplatzer PFO Occluder</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carroll et al (2013)</td>
<td>U.S., Canada</td>
<td>69</td>
<td>2003-2011</td>
<td>With PFO 18-60 y and cryptogenic ischemic stroke</td>
<td>Active Comparator</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Amplatzer PFO Occluder</td>
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</tbody>
</table>
MP 2.02.09
Closure Devices for Patent Foramen Ovale and Atrial Septal Defects

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>U.S., Canada</th>
<th>2003-2011</th>
<th>With PFO 18-60 y and cryptogenic ischemic stroke</th>
<th>Amplatzer PFO Occluder</th>
<th>Medical treatment b</th>
<th>DOF</th>
<th>5.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saver et al (2017)[^{2}]; RESPECT</td>
<td></td>
<td>69</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee et al (2018)[^{3}]; DEFENSE-PFO</td>
<td>South Korea</td>
<td>2</td>
<td>2011-2017 With cryptogenic stroke and high-risk PFO.</td>
<td>Amplatzer PFO Occluder with medical treatment</td>
<td>Medical treatment b</td>
<td>2.8</td>
<td></td>
</tr>
</tbody>
</table>

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 4. Summary of Key RCT Results for the Amplatzer PFO Occluder

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Primary Endpoint</th>
<th>Secondary Endpoint</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meier et al (2013)[^{2}]; PC-trial</td>
<td>414</td>
<td>414</td>
<td>414</td>
</tr>
<tr>
<td>Amplatzer, n/N (%)</td>
<td>7/204 (3.4)[^{a}]</td>
<td>5/204 (2.5%)[^{b}]</td>
<td>1/204 (0.5%)</td>
</tr>
<tr>
<td>Medical treatment, n/N (%)</td>
<td>11/210 (5.2)[^{a}]</td>
<td>11/210 (5.2%)[^{b}]</td>
<td>5/210 (2.4%)</td>
</tr>
<tr>
<td>HR (95% CI); P-value</td>
<td>0.63 (0.24 to 1.62); 0.34[^{a}]</td>
<td>0.45 (0.16 to 1.29); 0.14[^{b}]</td>
<td>0.20 (0.02 to 1.72); 0.14</td>
</tr>
<tr>
<td>Carroll et al (2013)[^{4}]; RESPECT</td>
<td>980</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amplatzer, n/N (%)</td>
<td>9/499 (1.8)[^{c}]</td>
<td>NA</td>
<td>9/499 (1.8)</td>
</tr>
<tr>
<td>Medical treatment, n/N (%)</td>
<td>16/481 (3.3)[^{c}]</td>
<td>NA</td>
<td>16/481 (3.3)</td>
</tr>
<tr>
<td>HR (95% CI); p</td>
<td>0.49 (0.22 to 1.11); 0.08[^{c}]</td>
<td>NA</td>
<td>0.49 (0.22 to 1.11); 0.08</td>
</tr>
<tr>
<td>Saver et al (2017)[^{2}]; RESPECT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amplatzer, n/N (%)</td>
<td>NR</td>
<td>NA</td>
<td>18/499 (3.6)</td>
</tr>
<tr>
<td>Medical treatment, n/N (%)</td>
<td>NR</td>
<td>NA</td>
<td>28/481 (5.8)</td>
</tr>
<tr>
<td>HR (95% CI); P-value</td>
<td>NR</td>
<td>NA</td>
<td>0.55 (0.31 to 0.99); 0.04</td>
</tr>
<tr>
<td>Lee et al (2018)[^{9}]; DEFENSE-PFO</td>
<td>120</td>
<td>NA</td>
<td>120</td>
</tr>
<tr>
<td>Amplatzer, n/N (%)[^{d,e}]</td>
<td>0/60 (0.0)[^{e}]</td>
<td>NA</td>
<td>0/60 (0.0)</td>
</tr>
<tr>
<td>Medical treatment, n/N (%)[^{d,e}]</td>
<td>0/60 (0.0)[^{e}]</td>
<td>NA</td>
<td>5/60 (10.5)</td>
</tr>
<tr>
<td>95% CI; P-value</td>
<td>(3.2 to 22.6); 013</td>
<td>NA</td>
<td>(NR).023</td>
</tr>
</tbody>
</table>


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 5. U.S. Food and Drug Administration Summary of Kaplan-Meier Analyses of the Primary Endpoint in RESPECT Trial (Amplatzer PFO Occluder)

<table>
<thead>
<tr>
<th>Analysis Population</th>
<th>Definitions</th>
<th>RRR, %</th>
<th>P-value</th>
</tr>
</thead>
</table>

Original Policy Date: May 2019
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 0.034b

As treated

All patients adhering to protocol requirements who actually had the Amplatzer implanted

72 0.008b

Device-in-place

All randomized patients who had Amplatzer implanted

70 0.007b

FDA assessment as reported by Rogers et al (2017).5
FDA: Food and Drug Administration; RRR: relative risk reduction.
a Adherence to guidelines-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 6 and 7. Note that both the REDUCE and CLOSE trials enrolled more patients with a moderate-to-large interatrial shunt size (58.4% and 75.2%) compared with 16.7% and 19.3% of patients with a large interatrial shunt size in the PC-Trial and RESPECT trial, all respectively.

In the REDUCE trial (2017), the blinded adjudicated coprimary endpoints of freedom from ischemic stroke (reported as the percentage of patients who had a stroke recurrence) and incidence of new brain infarction (clinical ischemic stroke plus silent brain infarction on imaging) 2 years after randomization were significantly lower in the PFO closure plus antiplatelet therapy than the antiplatelet therapy alone group in ITT analysis, the per-protocol analysis, and the as-treated population analysis (see Table 7).10

The number of patients who needed to be treated to prevent 1 stroke in 24 months was approximately 28 patients. Previous trials such as RESPECT, PC-Trial, and CLOSURE allowed discontinuation of antithrombotic therapy after PFO closure, and the use of anticoagulants in the medical therapy group was at the discretion of the treating physician. Such a design may have led to the confounding of results and bias within the medical therapy groups in favor of control because of increased protection from the risk of stroke due to causes other than PFO. Serious adverse events occurred in 23.1% of patients in the PFO closure group and 27.8% of patients in the antiplatelet-only group (P=.22).

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).11 The primary blinded adjudicated outcome of stroke was significantly lower in the PFO closure versus 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 =.02). The number of serious adverse events did not differ significantly between treatment groups (P=.56).

No clinical trials have focused specifically on patients who failed medical therapy, as defined by recurrent stroke or TIA while on therapy. Many published studies have included patients with first cryptogenic stroke 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 6. Summary of Key RCT Characteristics
### Table 7. Summary of Key RCT Results

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
<th>Active</th>
<th>Comparator</th>
<th>Median DOF, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Søndergaard et al (2017)²; REDUCE</td>
<td>U.S., Europe</td>
<td>63</td>
<td>2008-2015</td>
<td>With PFO 18-60 y and cryptogenic ischemic stroke</td>
<td>HELEX or CARDIOFORM plus antiplatelet therapy</td>
<td>6/441 (1.4)</td>
<td>22/383 (5.7)</td>
<td>NA</td>
</tr>
<tr>
<td>Antiplatelet therapy alone, n/N (%)</td>
<td>12/223 (5.4)</td>
<td>20/177 (11.3)</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI); P-value</td>
<td>0.23 (0.09 to 0.62); 0.002</td>
<td>0.51 (0.29 to 0.91); 0.04</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNT (95% CI)</td>
<td>20 (17 to 25)</td>
<td>Not reported</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mas et al (2017)10; CLOSE</td>
<td>France, Germany</td>
<td>34</td>
<td>2008-2016</td>
<td>With PFO 16-60 y and cryptogenic ischemic stroke</td>
<td>Multiple closure devices plus antiplatelet therapy</td>
<td>0/238 (0)</td>
<td>NA</td>
<td>NR (3.4)</td>
</tr>
<tr>
<td>Antiplatelet therapy alone, n/N (%)</td>
<td>14/235 (6.0)</td>
<td>NA</td>
<td>NR (8.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI); P-value</td>
<td>0.03 (0.00 to 0.26); &lt;0.001</td>
<td>NA</td>
<td>0.39 (0.16 to 0.82); 0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

- 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).

- 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.

- Antiplatelet therapy (aspirin, clopidogrel, or aspirin combined with extended release dipyridamole).

- Duration of follow-up in device closure group and antiplatelet-only group.

### 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) in their systematic reviews.¹¹,¹² 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 (Tables 8 and 9). 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.

Alushi et al (2018) included all 5 trials and reported outcomes as pooled HRs or odds ratios (ORs) in a third meta-analysis (Tables 8 and 9, row 3). 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 5). There was an increased risk of atrial fibrillation but no difference between groups in the risk of major bleeding.

Table 8. Systematic Reviews & Meta-Analysis Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Dates</th>
<th>Trials</th>
<th>Participants</th>
<th>N (Range)</th>
<th>Designs</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alushi et al 2018</td>
<td>1990-2017</td>
<td>5</td>
<td>Adults with PFO and cryptogenic stroke</td>
<td>3440 (414-980)</td>
<td>RCTs</td>
<td>No restrictions</td>
</tr>
</tbody>
</table>

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

Table 9. Systematic Reviews & Meta-Analysis Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Stroke</th>
<th>TIA</th>
<th>Stroke or TIA</th>
<th>Major Bleeding</th>
<th>AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shah et al (2018)</td>
<td>2892</td>
<td>2892</td>
<td>NA</td>
<td>1912</td>
<td>663</td>
</tr>
<tr>
<td>ARR (95% CI)</td>
<td>-3.2 (-5.0 to -1.4)</td>
<td>-0.4 (-1.7 to 1.0)</td>
<td>NA</td>
<td>-2.1 (-5.1 to 0.9)</td>
<td>6.1 (NR)</td>
</tr>
<tr>
<td>NNT (95% CI)</td>
<td>NR</td>
<td>NR</td>
<td>NA</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>I² (p-value)</td>
<td>3.62 (0.38)</td>
<td>0 (0.81)</td>
<td>NA</td>
<td>0 (0.92)</td>
<td>82.5 (&lt;0.001)</td>
</tr>
<tr>
<td>De Rosa et al (2018)</td>
<td>2531</td>
<td>NA</td>
<td>2531</td>
<td>2531</td>
<td>2531</td>
</tr>
<tr>
<td>ARR (95% CI)</td>
<td>-3.1 (-5.1 to -1.0)</td>
<td>NA</td>
<td>-2.9 (-5.0 to -7)</td>
<td>-0.2 (-1.2 to 0.7)</td>
<td>3.3 (1.2 to 5.4)</td>
</tr>
<tr>
<td>NNT (95% CI)</td>
<td>NR</td>
<td>NA</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>I² (p-value)</td>
<td>61 (0.003)</td>
<td>NA</td>
<td>33.79 (0.29)</td>
<td>28 (0.60)</td>
<td>66 (0.002)</td>
</tr>
<tr>
<td>Alushi et al (2018)</td>
<td>3440</td>
<td>2776 (Excludes REDUCE)</td>
<td>3440</td>
<td>3440</td>
<td></td>
</tr>
<tr>
<td>HR/OR (95% CI); p-value</td>
<td>HR 0.39 (0.19 to 0.83); p&lt;0.01</td>
<td>HR 0.73 (0.49 to 1.09); P=0.12</td>
<td>HR 0.52 (0.26 to 0.77); p&lt;0.01</td>
<td>OR 0.97 (0.44 to 2.17); P=0.95</td>
<td>OR 3.75 (2.44 to 5.78); p&lt;0.01</td>
</tr>
</tbody>
</table>
Closure Devices for Patent Foramen Ovale and Atrial Septal Defects

<table>
<thead>
<tr>
<th>NNT (range)</th>
<th>NA</th>
<th>NA</th>
<th>49</th>
</tr>
</thead>
<tbody>
<tr>
<td>P (range)</td>
<td>56 (0 to 84)</td>
<td>0</td>
<td>26</td>
</tr>
</tbody>
</table>

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

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.16 Permanent atrial fibrillation occurred in 0.5%, device thrombosis occurred in 0.5%, new-onset or worsening of mitral valve regurgitation was observed in 0.2% whereas recurrent cerebral ischemic events occurred in 0.8% patients. The occlusion rate was 93.8%. No aortic or atrial free wall erosion was reported.

Wintzer-Wehekind et al (2019) reported on long-term outcomes for 201 consecutive patients who had had a cryptogenic embolism (stroke, 76%; TIA, 32%; systemic embolism, 1%) and underwent PFO closure.18 Median follow-up, completed by 96% of the patients, was 12 years (range, 10-17 years). Patients also had follow-up at between 1 and 6 months that included an echocardiographic examination with a bubble test. No cases of late device embolization, dislocation, or thrombosis, or late pericardial effusion were found; however, 6 patients had a residual shunt, 1 of which required a second closure following a recurrent TIA. Thirteen patients (6.5%) died during the follow-up period, but no deaths were caused by cardiovascular events. Seven (3.5%) had at least 1 TIA or stroke. At the time of final follow-up, 20.9% (42/201) had been off antithrombotic therapy for a mean of 10 years (±4 y). There were no significant differences in rates of ischemic events or death between the group that went off antithrombotic medication and those who stayed on it.

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

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

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

The question addressed in this evidence review is: Does PFO closure with a transcatheter device improve the net health outcome in patients with migraine?

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

**Patients**

The relevant population of interest is individuals with migraine headache. Migraine headache has been associated with PFO in epidemiologic studies, and noncontrolled observational studies have reported improvement in migraine headaches after PFO closure.

**Interventions**

The therapy being considered is PFO closure with a transcatheter device. Alternative interventions such as transcatheter device closure of PFO have been considered for patients who have persistent or recurrent migraine headaches not controlled by medical therapy.

PFO closure is performed by cardiac surgeons in a hospital setting.

**Comparators**

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

**Outcomes**

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

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

**Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.

b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

d. Studies with duplicative or overlapping populations were excluded.

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. In this trial, no significant difference was observed in the primary endpoint of migraine headache cessation (3/74 in the implant group vs 3/73 in the sham group, P=0.51). The results of this trial cast some doubt on the causal relation between PFO and migraine.
Mattle et al (2016) published results of the Percutaneous Closure of Patent Foramen Ovale in Migraine with Aura 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. The trial enrolled 107 subjects with refractory migraine and PFO with a right-to-left shunt, who were randomized to PFO closure with the Amplatzer PFO Occluder (n=53) or medical management (n=54). The trial's power calculations required enrollment of 72 in each group. The trial was stopped prematurely due to slow enrollment, and there was a relatively high loss to follow-up (22%). In the device group, 45 of 53 patients agreed to have the PFO occluder implanted, and of those 41 underwent implantation. This suggests that the trial might have been underpowered to detect differences between groups. For the primary endpoint (reduction in mean migraine days at 1 year post randomization), there were no significant differences between the groups (-2.9 [95% CI, -4.4 to -1.4] for PFO closure vs -1.7 [95% CI, -2.5 to -1.0] for medical management; P=0.168).

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

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 included (Dowson et al [2008]) did not identify significant improvements in migraine symptoms in the PFO closure group.

Observational Studies

Biasco et al (2014), which was not included in the Lip and Lip (2014) systematic review, 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 (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 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 Patent Foramen Ovale Closure for Other Indications**

**Clinical Context and Therapy Purpose**

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

The question addressed in this evidence review is: Does PFO closure with a transcatheter device improve the net health outcome in patients’ conditions associated with PFO other than cryptogenic stroke or migraine?

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

**Patients**

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 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.

**Interventions**

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

PFO closure is performed by cardiac surgeons in a hospital setting.

**Comparators**

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

**Outcomes**

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

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

**Study Selection Criteria**

Methodologically credible studies were selected using the following principles:
1. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
2. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
3. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
4. Studies with duplicative or overlapping populations were excluded.

Evidence on clinical outcomes related to these conditions after PFO closure is limited to case reports and case series. Mojadidi et al (2015) reported on a series of 17 patients who underwent transcatheter PFO closure for platypnea-orthodeoxia syndrome at a single institution, among whom 11 (65%) were classified as having improved oxygen saturation postprocedure.

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

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

The question addressed in this evidence review is: Does ASD closure with a transcatheter device improve the net health outcome in patients with ASD?

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

Patients

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

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 atrophicventricular 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.

Interventions

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

Comparators
The following therapies and practices are currently being used to make decisions about PFO closure with a transcatheater 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.

**Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

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

The evidence supporting the efficacy of devices for the closure of ASD consists of nonrandomized comparative studies and case series. However, unlike PFO and cryptogenic stroke, the relation between ASD closure and improved clinical outcomes is direct and convincing, because the accepted alternative is open surgery. Results have generally shown a high success rate in achieving closure and low complication rates. The FDA's approval of the Amplatzer Septal Occluder was based on the results of a multicenter, nonrandomized study comparing the device with surgical closure of ASDs. Du et al (2002) subsequently reported on this study (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=.03). Similarly, there was a significantly lower incidence of minor adverse events in the septal occluder group (P<.001). It should be noted that the mean age of patients of the 2 groups differed significantly; in the septal occluder group, the mean age was 18 years while in the surgically treated group it was 6 years.

**Systematic Reviews**

Butera et al (2011) published a systematic review comparing percutaneous closure with surgical closure by Butera et al (2011). Thirteen nonrandomized comparative studies that enrolled at least 20 patients were included (N = 3082 patients). The rate of procedural complications was higher in the surgical group (31%; 95% CI, 21% to 41%) than in the percutaneous group (6.6%; 95% CI, 3.9% to 9.2%), with an OR for total procedural complications of 5.4 (95% CI, 2.96 to 9.84; p<.000). There was also an increased rate of major complications for the surgical group (6.8%; 95% CI, 4% to 9.5%) compared with the percutaneous group (1.9%; 95% CI, 0.9% to 2.9%), with an OR of 3.81 (95% CI, 2.7 to 5.36; P=.006).

Abaci et al (2013) reported in their meta-analysis of periprocedural complications after ASD or PFO device closures that, for ASD closure, the pooled rate of major complications was 1.6% (95% CI, 1.4% to 1.8%).
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. Berger et al (1999) showed identical 98% success rates in both treatment groups. Kotowycz et al (2013) reported in their nonrandomized comparative analysis that mortality rates at 5-year follow-up did not differ between transcatheter (5.3%) and surgical closure (5.635%; P>.99) groups, but that reintervention rates were higher for patients undergoing transcatheter closure (7.9% vs. 0.3%, respectively, P<.004).

Chen et al (2015), in a nonrandomized comparative analysis that used national-level data from Taiwan, 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% vs. 0%, P<.001), ischemic stroke (1.9% vs. 0%, P=.002), or in-hospital death (1.3% vs. 0%, P=.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=.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 post implantation; 1 wireframe fracture associated with echocardiographic abnormalities and requiring surgical removal; and 1 unrelated death.

Baruteau et al (2014) reported closure rates of 92.6% in another relatively large series of 336 patients with large secundum ASDs (balloon-stretched diameter³ 34 mm in adults or echocardiographic diameter > 15 mm/m2 in children) managed with the Amplatzer closure device (2014) reported closure rates of 92.6%.

Other smaller studies have also reported favorable results for transcatheter closure of ASD. In Du et al (2002), compared 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.

**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. 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 one of 9 centers in France from 1998 to 2016. Follow-up was obtained through medical records and telephone calls to primary care physicians and was obtained in 91.6% of the 1158 patients who had a successful ASD closure. The procedural success rate was 95.3%. After a median follow-up duration of 3.5 years (range 6 months to 18 years), no deaths occurred and 96% of patients were asymptomatic. Major periprocedural complications occurred in 24 patients (1.8%; 95% CI: 1.1% to 2.5%). Delayed complications were observed in 12 (1.04%; 95% CI: 0.5% to 1.6%) patients. Cardiac arrhythmias were the main long-term complication, most occurring in 8 patients aged 3 to 13 years, after a median period of time of 6 months (range 1 to 108 months) from the procedure. Children weighing 15 kg or less and those with 15 kg and those with large defects 20 mm/m² were subgroups identified at risk of both periprocedural and long-term complications.

**Section Summary: Transcatheter Device Closure of Atrial Septal Defects**

For patients with an ASD, nonrandomized comparative studies and single-arm case series have reported rates of closure using catheter-based devices approaching the high success rates of surgery. The percutaneous approach has a low complication rate and avoids the morbidity and complications of open surgery. 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. The relevant outcomes are overall survival, morbidity 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 three trials (i.e., CLOSURE I, PC, and RESPECT [initial study]), they were statistically significant
in later trials (i.e., 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 two RCTs of PFO closure and multiple observational studies reporting on the association between PFO and migraine. The 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 endpoint 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.

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. The 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 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. The 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.

**SUPPLEMENTAL INFORMATION**

**Clinical Input from Physician Specialty Societies and Academic Medical Centers**

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

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

**Practice Guidelines and Position Statements**

**American College of Chest Physicians**

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

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

**American Academy of Neurology**

In 2016, the American Academy of Neurology updated its evidence-based guidelines on the management of patients with stroke and PFO to address whether percutaneous closure of PFO is superior to medical therapy alone. Following a systematic review of the literature and structured formulation of recommendations, the Academy developed conclusions for the Amplatzer PFO Occluder devices. For patients with cryptogenic stroke and PFO, percutaneous PFO closure with the Amplatzer PFO Occluder:

- "Possibly decreases the risk of recurrent stroke - RD [risk difference] -1.68%, 95% CI [confidence interval] -3.18% to -0.19%;"
- "Possibly increases the risk of new-onset AF [atrial fibrillation] - RD 1.64%, 95% CI 0.07%-3.2% (2 Class I studies; confidence downgraded to low, for risk of bias relative to magnitude of effect and imprecision);"
- "Is highly likely to be associated with a procedural complication risk of 3.4%, 95% CI 2.3%-5% (2 Class I studies)."

The guidelines concluded:

"Clinicians should not routinely offer percutaneous PFO closure to patients with cryptogenic ischemic stroke outside of a research setting (Level R). In rare circumstances, such as recurrent strokes despite adequate medical therapy with no other mechanism identified, clinicians may offer the AMPLATZER PFO Occluder if it is available (Level C)."

**American Heart Association and American Stroke Association**

The American Heart Association and American Stroke Association (2014) updated its guidelines on the prevention of stroke in patients with ischemic stroke or transient ischemic attack. The guidelines made the following recommendations for device-based closure for PFO:

- "For patients with a cryptogenic ischemic stroke or TIA [transient ischemic attack] and a PFO without evidence for DVT [deep vein thrombosis], available data do not support a benefit for PFO closure (Class III; Level of Evidence A)."
- "In the setting of PFO and DVT, PFO closure by a transcatheter device might be considered, depending on the risk of recurrent DVT (Class IIb; Level of Evidence C)."
American College of Cardiology and American Heart Association

In 2018, the American College of Cardiology and American Heart Association updated guidelines on the management of adults with congenital heart disease. The treatment recommendations are summarized in Table 10., coronary sinus, or primum atrial septal defect, however, surgery rather than percutaneous closure was recommended.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommendation</th>
<th>COR/LOE&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>Transcatheter or surgical closure</td>
<td>I1/B-NR2</td>
</tr>
<tr>
<td>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</td>
<td>Surgical closure unless precluded by comorbidities</td>
<td>I1/B-NR2</td>
</tr>
<tr>
<td>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</td>
<td>Transcatheter or surgical closure</td>
<td>IIa1/C-LD2</td>
</tr>
<tr>
<td>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</td>
<td>Surgical closure</td>
<td>IIa1/C-LD2</td>
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<tr>
<td>ASD when net left-to-right shunt is ≥1.5:1, PA systolic pressure and/or pulmonary vascular resistance is greater than one-third of systemic resistance</td>
<td>Percutaneous or surgical closure</td>
<td>IIb1/B-NR2</td>
</tr>
<tr>
<td>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</td>
<td>ASD closure should not be performed</td>
<td>III-Harm1/CLD2</td>
</tr>
</tbody>
</table>

Adapted from Stout et al (2019)<sup>49</sup>

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 11.

Table 10. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
</table>

Adapted from Stout et al (2019)<sup>49</sup>

ASD: atrial septal defect; COR: class (strength) of recommendation; LOE: level (quality) of evidence; PA: pulmonary artery; RCT: randomized controlled trial; RV: right ventricular.

<sup>a</sup> COR key: I=strong; IIa=moderate; IIb=weak; III: No Benefit=weak; III: Harm=strong.<sup>49</sup>

<sup>b</sup> LOE key: A=high quality from >1 RCT, meta-analyses of high-quality RCTs, ≥1 RCT corroborated by high-quality registry studies; B=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.<sup>49</sup>
MP 2.02.09
Closure Devices for Patent Foramen Ovale and Atrial Septal Defects

<table>
<thead>
<tr>
<th>Ongoing</th>
<th>NCT00738894*</th>
<th>GORE® HELEX® Septal Occluder / GORE® Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed TIA in Patients with Patent Foramen Ovale (PFO)</th>
<th>664</th>
<th>Feb 2020</th>
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<tr>
<td>NCT03867708</td>
<td>Outcomes of Transcatheter Closure of Secundum Atrial Septal Defect Guided by Three-dimensional Transesophageal Echocardiography</td>
<td>80</td>
<td>Jun 2021</td>
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<td>NCT03309332</td>
<td>OBS Lead-AMPLATZER PFO Occluder New Enrollment Study</td>
<td>1214</td>
<td>Dec 2027</td>
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<tr>
<td>Unpublished</td>
<td>NCT01960491</td>
<td>Prospective Single Center Pilot Clinical Study to Evaluate the Safety and Effectiveness of an Intracardiac Septal Closure Device with Biodegradable Framework in Patients with Clinically Significant Atrial Septum Defect (ASD) or Patent Foramen Ovale (PFO)</td>
<td>15</td>
<td>Jun 2018(updated 10/11/18)</td>
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</table>

NCT: national clinical trial.
* Denotes industry-sponsored or cosponsored trial.

**ESSENTIAL HEALTH BENEFITS**

The Affordable Care Act (ACA) requires fully insured non-grandfathered individual and small group benefit plans to provide coverage for ten categories of Essential Health Benefits (“EHBs”), whether the benefit plans are offered through an Exchange or not. States can define EHBs for their respective state.

States vary on how they define the term small group. In Idaho, a small group employer is defined as an employer with at least two but no more than fifty eligible employees on the first day of the plan or contract year, the majority of whom are employed in Idaho. Large group employers, whether they are self-funded or fully insured, are not required to offer EHBs, but may voluntarily offer them.

The Affordable Care Act requires any benefit plan offering EHBs to remove all dollar limits for EHBs.

**REFERENCES**


**CODES**

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<tr>
<td>CPT</td>
<td>93580</td>
<td>Percutaneous transcatheter closure of congenital interatrial communication (ie, Fontan fenestration, atrial septal defect) with implant</td>
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<td>HCPCS</td>
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<tr>
<td>ICD-10-CM</td>
<td>Q21.1</td>
<td>Atrial septal defect (includes ostium secundum defect)</td>
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<tr>
<td></td>
<td>Q21.2</td>
<td>Atrioventricular septal defect (includes ostium primum atrial septal defect)</td>
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<tr>
<td>ICD-10-PCS</td>
<td>02Q53ZZ</td>
<td>Atrial septum repair, percutaneous</td>
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<tr>
<td></td>
<td>02Q54ZZ</td>
<td>Atrial septum repair, percutaneous endoscopic</td>
</tr>
<tr>
<td></td>
<td>02U53JZ</td>
<td>Atrial septum repair, percutaneous, with device</td>
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<tr>
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MP 2.02.09
Closure Devices for Patent Foramen Ovale and Atrial Septal Defects

POLICY HISTORY

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<tr>
<td>05/16/19</td>
<td>Add to Medicine</td>
<td>Blue Cross of Idaho adopted policy effective, 08/20/2019.</td>
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<tr>
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<td>section</td>
<td></td>
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<tr>
<td>06/01/20</td>
<td>Replace policy</td>
<td>Policy updated with literature review through March 9, 2020; references added. Policy statements unchanged.</td>
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Original Policy Date: May 2019