Closure Devices for Patent Foramen Ovale and Atrial Septal Defects

Policy # 00016
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

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

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

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

The labeled indications for these devices are similar and include:

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

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

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

Patient Selection Criteria
One device has been approved by the U.S. Food and Drug Administration (FDA) for transcatheter PFO closure, the Amplatzer PFO Occluder, to reduce the risk of recurrent ischemic stroke.
The labeled indications and patient selection criteria include:

- Patients are between the ages of 18 and 60 years, AND
- Documentation of known cryptogenic stroke as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke.

**When Services Are Considered Investigational**

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

**Atrial Septal Defect**

The use of transcatheter closure of secundum atrial septal defects (ASDs) when patient selection criteria are not met is considered *investigational.*

**Patent foramen ovale**

The use of transcatheter closure of patent foramen ovale (PFO) when patient selection criteria are not met is considered *investigational.*

**Background/Overview**

**PATENT FORAMEN OVALE**

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

**ATRIAL SEPTAL DEFECTS**

Unlike PFO, which represents the postnatal persistence of normal fetal cardiovascular physiology, ASDs represent an abnormality in the development of the heart that results in free communication between the atria. ASDs are categorized by their anatomy. Ostium secundum describes defects located midseptally and are typically near the fossa ovalis. Ostium primum defects lie immediately adjacent to the atrioventricular valves and are within the spectrum of atrioventricular septal defects. Primum defects occur commonly in patients with Down syndrome. Sinus venous defects occur high in the atrial septum and are frequently associated with anomalies of the pulmonary veins.
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Ostium secundum ASDs are the third most common form of congenital heart disorder and among the most common congenital cardiac malformations in adults, accounting for 30% to 40% of these patients older than age 40 years. The ASD often goes unnoticed for decades because the physical signs are subtle and the clinical sequelae are mild. However, virtually all patients who survive into their sixth decade are symptomatic; fewer than 50% of patients survive beyond age 40 to 50 years due to heart failure or pulmonary hypertension related to the left-to-right shunt. Symptoms related to ASD depend on the size of the defect and the relative diastolic filling properties of the left and right ventricles. Reduced left ventricular compliance and mitral stenosis will increase left-to-right shunting across the defect. Conditions that reduce right ventricular compliance and tricuspid stenosis will reduce left-to-right shunting or cause a right-to-left shunt. Symptoms of an ASD include exercise intolerance and dyspnea, atrial fibrillation, and, less commonly, signs of right heart failure. Patients with ASDs are also at risk for paradoxical emboli.

Treatment
Repair of ASDs is recommended for those with a pulmonary to systemic flow ratio (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 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
Several devices have been developed to treat PFO and ASDs via a transcatheter approach, including the CardioSEAL®STARFlex™ Septal Occlusion System, the Amplatzer PFO Occluder, the Figulla® ASD Occluder (Occlutech GmbH, Jena, Germany), and the CeraFlex™ ASD Occluder (Lifetech Scientific, Shenzhen, China).

Transcatheter PFO and ASD occluders consist of a single or paired wire mesh discs that are 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 disks that are delivered via catheter to cover the ASD.

FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration (FDA)
Patent Foramen Ovale Closure Devices
In 2002, 2 transcatheter devices were cleared for marketing by the U.S. FDA through a humanitarian device exemption (HDE) 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, St. Paul, MN). HDE approval is applicable to devices designed
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to treat a patient population of fewer than 4000 patients per year. This approval process requires the manufacturer to submit data on the safety and the probable clinical benefit. Clinical trials validating the device effectiveness are not required. The labeled indications of both limited the use of these devices to closure of PFO in patients with recurrent cryptogenic stroke due to presumed paradoxical embolism through a PFO and who have failed conventional drug therapy.

Following this 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. As a result, in 2006, FDA withdrew the HDE approval for these devices.

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

“For percutaneous transcatheter closure of a PFO to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke.”

The PMA was based on analysis of the RESPECT trial, initial results of which were published in 2013. We discuss the FDA’s analysis of the RESPECT trial data in the Rationale section below.

FDA product code: MLV.

Atrial Septal Defect Closure Devices

Three devices have been approved by the FDA through the PMA process or a PMA supplement for transcatheter atrial septal defect closure (see Table 1).

Table 1. ASD 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 Septal Occluder</td>
<td>St. Jude Medical (Plymouth, MN)</td>
<td>Dec 2001</td>
<td>• Occlusion of ASDs in the secundum position</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Use in patients who have had a fenestrated Fontan procedure who require closure of the fenestration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• (Patients indicated for ASD closure have echocardiographic evidence of ostium secundum ASD and clinical evidence of right ventricular volume overload.)</td>
</tr>
<tr>
<td>GORE HELEX Septal Occluder</td>
<td>W.L. Gore &amp; Associates (Flagstaff, AZ)</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 (Flagstaff, AZ)</td>
<td>Oct 2016 (supp.)</td>
<td>• Percutaneous, transcatheter closure of ostium secundum ASDs</td>
</tr>
</tbody>
</table>

ASD: atrial septal defect; PMA: premarket approval.

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

Rationale/Source
TRANSCATHETER DEVICE CLOSURE OF PATENT FORAMEN OVALE
Transcatheter Patent Foramen Ovale Closure for Stroke Prevention

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. Closure devices are nonpharmacologic alternatives to medical therapy for cryptogenic stroke in patients with a PFO.

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

Randomized Controlled Trials
CLOSURE I Trial
The 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) study was a multicenter, randomized, open-label trial (2012) comparing percutaneous closure with medical therapy. A total of 909 patients, between the ages of 18 and 60 years, with cryptogenic stroke or transient ischemic attack (TIA) and a PFO were enrolled. Patients in the closure group received treatment with the STARFlex device and antiplatelet therapy. Patients in the medical therapy group took aspirin, warfarin, or both at the discretion of the treating physician. The primary end point was a composite of stroke and TIA at 2 years, death from any cause during the first 30 days after treatment, and death from neurologic causes at 2 years. Of 405 patients in the closure group, 362 (89.4%) had successful implantation without procedural complications. At 6 months, echocardiography revealed effective closure in 315 (86.1%) of 366 patients. The composite primary outcome was reached by 5.5% of patients in the closure group and 6.8% of patients in the medical therapy group (adjusted hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.45 to 1.35; p=0.37). Kaplan-Meier estimates of the 2-year rate of stroke were 2.9% in the closure group and 3.1% in the medical therapy group (adjusted HR=0.90; 95% CI, 0.41 to 1.98). Serious adverse events were reported by 16.9% of patients in the closure group and 16.6% in the medical group. Adverse events that were increased in the closure group included vascular procedural complications (3.2% vs 0, p<0.001) and atrial fibrillation (5.7% vs 0.7%, p<0.001).
RESPECT Trial
The RESPECT trial (2013) was a multicenter RCT comparing PFO closure with medical therapy in 980 patients between the ages of 18 and 60 years with a previous cryptogenic stroke and documented PFO. Patients were randomized to PFO closure with the Amplatzer Occluder or to medical therapy. Medical therapy consisted of 1 of 4 regimens prescribed at the discretion of the treating physician: aspirin, aspirin plus dipyridamole, clopidogrel, or warfarin. The primary end point was a composite of fatal ischemic stroke, nonfatal ischemic stroke, or early death within 30 days of randomization. Mean follow-up for the entire group was 2.6 years.

A total of 9 events occurred in 499 patients assigned to closure, and 16 events occurred in 464 patients assigned to medical therapy. All events were nonfatal strokes. The hazard ratio for this outcome was 0.49, but this result was not statistically significant on the intention-to-treat (ITT) analysis (95% CI, 0.22 to 1.11; p=0.08). On per-protocol analysis, there was a statistically significant effect (HR=0.37; 95% CI, 0.14 to 0.96; p=0.03), though it was not in subgroup analyses, although there were trends for better outcomes in the closure group for patients with a substantial right-to-left shunt (p=0.07) and for patients with an atrial septal aneurysm (p=0.10). The rate of serious adverse events did not differ between the closure group (23.0%) and the medical therapy group (21.6%; p=0.65). Major bleeding (n=2) and cardiac tamponade (n=2) were the most frequent procedure-related adverse events.

Analysis of the RESPECT trial results was the basis of the FDA premarket approval of the Amplatzer Occluder in 2016. In an overview of the FDA assessment of the Amplatzer PFO Occluder, Rogers et al summarized FDA decision to consider as-treated and device-in-place analyses, with reanalysis of data after reassignment of 3 patients in the device arm who had a stroke before device implantation. In the device-in-place analysis, all randomized subjects were included, and patients were analyzed by treatment group according to whether they had received a device at the time of the end point. For the device-in-place analysis, the primary outcome occurred in 464 patients (n=6 events) in the device group and 516 patients (n=19 events) in the medical therapy group. Device therapy was associated with a significantly lower risk of the primary outcome (relative risk [RR], 0.304; 95% CI, 0.122 to 0.763; p=0.007; risk reduction, 69.6%).

PC Trial
The PC trial (2013) was a multicenter RCT comparing PFO closure with medical therapy in 414 patients under 60 years of age with a prior cryptogenic stroke or peripheral embolization and documented PFO. Patients were recruited from 29 centers worldwide and randomized to PFO closure with the Amplatzer device or to medical therapy. Recommended antiplatelet therapy in the closure group was aspirin plus ticlopidine or clopidogrel alone. Medical therapy in the control group was at the discretion of the treating physician, with the requirement that patients receive at least 1 appropriate medication. The primary end point was a composite of death, nonfatal stroke, TIA, or peripheral embolism. The median duration of follow-up was 4.1 years in the closure group and 4.0 years in the medical therapy group.

The primary outcome, after independent adjudication, occurred in 9 (3.4%) of 204 patients in the closure group compared with 11 (5.7%) of 210 patients in the medical group. The hazard ratio for this outcome was
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0.63 (95% CI, 0.24 to 1.62; p=0.34) on ITT analysis, and were similar on per-protocol analysis. There were no significant differences in rates of the individual components of the primary outcome or in outcomes on subgroup analyses. The adverse event rate was 34.8% in the closure group and 29.5% in the medical therapy group.

Systematic Reviews
Systematic Reviews Assessing Only RCTs
A large number of systematic reviews and meta-analyses have evaluated the 3 RCTs discussed above. In 2016, Kent et al reported on an individual patient data meta-analysis of the 3 RCTs (CLOSURE I, the PC trial, RESPECT) comparing transcatheter device-based PFO closure and medical therapy after stroke that are discussed above. The analysis included 2303 participants randomized to PFO closure (n=1150) or medical therapy, but, as noted in the RCT section, the various medical and device therapies differed across the 3 trials. CLOSURE I used the STARFlex septal closure system, which is not currently commercially available, while the RESPECT and PC trials used the Amplatzer PFO Occluder. In CLOSURE I, patients in the medical therapy group received warfarin, aspirin, or both, at the discretion of the principal investigator at each site. In the PC trial, antithrombotic therapy (including antiplatelet and anticoagulant therapy) was at the treating physician’s discretion. In RESPECT, 1 of 5 antithrombotic therapies was given at the discretion of each site’s principal investigator (aspirin, warfarin, clopidogrel, aspirin with dipyridamole, and aspirin with clopidogrel). The primary efficacy outcome of the meta-analysis was an ITT analysis to evaluate the association between the therapy and the composite outcome of ischemic stroke, TIA, or death from any cause. The main analysis and results, specific to trials with the Amplatzer PFO Occluder device, are shown in Table 2.

Table 2. Individual Patient Data Meta-Analysis Results for Efficacy of PFO Closure (Kent et al, 2016)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Outcome Rate, % (n/N)</th>
<th>HR(^a)</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analyses using data from all trials (N=2303)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke, TIA, or death</td>
<td>1.5% (45/3057)</td>
<td>2.3% (63/2792)</td>
<td>0.69</td>
<td>0.47 to 1.01</td>
</tr>
<tr>
<td>Recurrent ischemic stroke</td>
<td>0.7% (22/3099)</td>
<td>1.3% (36/2839)</td>
<td>0.58</td>
<td>0.34 to 0.98</td>
</tr>
<tr>
<td>Secondary composite outcome</td>
<td>1.4% (43/3057)</td>
<td>2.2% (61/2792)</td>
<td>0.68</td>
<td>0.46 to 1.00</td>
</tr>
<tr>
<td>(ischemic stroke, TIA, early death)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Analyses using data from Amplatzer PFO Occluder device trials (n=1394)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke, TIA, or death</td>
<td>1.0% (22/2274)</td>
<td>1.6% (32/2021)</td>
<td>0.63</td>
<td>0.36 to 1.08</td>
</tr>
<tr>
<td>Recurrent ischemic stroke</td>
<td>0.4% (10/2301)</td>
<td>1.1% (23/2044)</td>
<td>0.39</td>
<td>0.19 to 0.82</td>
</tr>
<tr>
<td>Secondary composite outcome</td>
<td>0.9% (20/2274)</td>
<td>1.6% (32/2021)</td>
<td>0.57</td>
<td>0.33 to 1.00</td>
</tr>
<tr>
<td>(ischemic stroke, TIA, early death)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI: confidence interval; HR: hazard ratio; TIA: transient ischemic attack.
\(^a\) Determined from Cox proportional hazards model.

After analyses were adjusted for covariates, the primary composite outcome (recurrent ischemic stroke, TIA, or death from any cause) was significantly associated with device closure (adjusted HR=0.68; 95% CI,
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0.46 to 1.0; p=0.049). In analyses of adverse events, patients who received closure devices were more likely to develop atrial fibrillation (HR=3.22; 95% CI, 1.76 to 5.90; p<0.001).

In 2015, Li et al published a Cochrane review of RCTs comparing the safety and efficacy of transcatheter device closure with medical therapy for preventing recurrent stroke or TIA in individuals with PFO and a history of stroke or TIA. The CLOSURE I, PC, and RESPECT trials were the only 3 that met reviewers’ inclusion criteria. As noted above, the medical and device therapies could differ across trials. The highest risk of bias was considered to result from high rates of participant loss to follow up and withdrawal from assigned therapy, and difference in dropout rates between groups.

The main pooled findings are summarized in Table 3. The review’s main finding was that, using ITT analysis, PFO closure was not associated with lower risks of recurrent stroke or TIA (RR=0.61; 95% CI, 0.29 to 1.27). The incidence of atrial fibrillation was higher in the closure group, but the risks of all-cause mortality and adverse events did not differ significantly between groups.

| Table 3. Meta-Analysis Results for Efficacy of PFO Closure (Li et al, 2015) |
|---------------------------------|-----------------|-------------|-----------|------------------|
| **Outcomes**                    | Intervention    | No. of Participants (Studies) | Evidence Quality | Relative ES 95% CI |
| **Primary outcomes**            |                 |                           |             |                  |
| Recurrent stroke or TIA         | Any closure device | 1323 (2 studies)   | Low       | 0.73 | 0.45 to 1.17 |
| (stratified by device)          |                 |                           |             |                  |
| Recurrent stroke or TIA         | Amplatzer PFO Occluder | 414 (1 study)   | Low       | 0.47 | 0.17 to 1.32 |
| (stratified by device)          |                 |                           |             |                  |
| Recurrent stroke (fatal or nonfatal) | Any closure device | 2303 (3 studies)   | Low       | 0.61 | 0.29 to 1.27 |
| Recurrent stroke (fatal or nonfatal) | Amplatzer PFO Occluder | 1394 (2 studies) | Low       | 0.4  | 0.14 to 1.19 |
| **Secondary outcomes**          |                 |                           |             |                  |
| All-cause mortality at end of FU | Any closure device | 2303 (3 studies)   | Low       | 0.65 | 0.23 to 1.84 |
| Total SAEs at end of FU          | Any closure device | 2303 (3 studies)   | Low       | 1.04 | 0.88 to 1.23 |
| Atrial fibrillation incidence   | Any closure device | 2303 (3 studies)   | Moderate  | 3.5  | 1.47 to 8.35 |

CI: confidence interval; ES: effect size; FU: follow-up; PFO: patent foramen ovale; SAE: serious adverse event; TIA: transient ischemic attack.

*Assessed using the GRADE tool.

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plan, earlier systematic reviews do not provide significant additional information about the efficacy of transcatheter PFO closure.

Stortecky et al (2015) reported on results of a network meta-analysis comparing percutaneous PFO closure with medical therapy among patients with cryptogenic stroke. Reviewers included 10 publications on 4 RCTs: the PC and RESPECT trials comparing the Amplatzer PFO Occluder with medical therapy, the CLOSURE I trial comparing the STARFlex PFO occluder with medical therapy, and another trial that compared head-to-head the Amplatzer, STARFlex, and Helix PFO occluder devices. Overall, patients randomized to PFO closure with the Amplatzer PFO occluder device were less likely to experience a stroke than those randomized to medical therapy (rate ratio, 0.39; 95% CI, 0.17 to 0.84). No significant differences were found between PFO closure with the STARFlex device in stroke risk or in TIA risk across treatment strategies.

Systematic Reviews Assessing RCTs and Observational Studies
In addition to the systematic reviews and meta-analyses specifically evaluating RCT data, a number of systematic reviews have included observational studies. Overall, these studies have tended to find a stronger association between percutaneous PFO closure and reduced stroke risk, but they are subject to bias.

Most recently, Patti et al (2015) published a meta-analysis of randomized and observational studies comparing outcomes across 3 management strategies for patients with cryptogenic stroke and PFO: percutaneous closure, antiplatelet therapy, and anticoagulant therapy. The meta-analysis included 21 studies (total N=3311 patients). In an evaluation of the long-term efficacy and safety of PFO closure compared with “conservative therapy” (either antiplatelet or anticoagulant therapy), 11 observational studies were included, with a mean follow-up of 36 months. The incidence of recurrent stroke and/or TIA was significantly lower in patients undergoing percutaneous PFO closure (4.3%) than in those receiving antiplatelet therapy (9.2%; OR=0.50; 95% CI, 0.35 to 0.71; p<0.001), with no increased bleeding risk. The incidence of recurrent stroke and/or TIA did not differ significantly between those undergoing percutaneous PFO closure (4.3%) and those receiving anticoagulant therapy (6.3%; OR=0.66; 95% CI, 0.42 to 1.04; p=0.07); however, patients treated with PFO closure (1%) had a lower incidence of major bleeding (7.1%; OR=0.18; 95% CI, 0.09 to 0.36; p<0.001).

Other systematic reviews published between 2006 and 2014 that assessed observational studies comparing transcatheter PFO closure with medical therapy generally reported a pooled rate of recurrent stroke that is lower for patients treated with a closure device than with medical therapy.

In addition, Abaci et al (2013) conducted a meta-analysis of studies of PFO and ASD device closure procedures. They reviewed 203 articles, 111 of which reported on ASD closure, 61 of which reported PFO closure, and 31 of which reported on both closure devices. Among patients undergoing PFO closure, the pooled rate of major complications was 1.1% (95% CI, 0.9% to 1.3%), most commonly device embolization requiring surgery.
Nonrandomized Comparative Studies

Nonrandomized comparative studies of closure devices versus medical therapy vary by patient populations and patient selection for percutaneous closure.

In the largest series identified, Pezzini et al (2016) reported results from a prospective, multicenter Italian registry evaluating outcomes for consecutive young patients (age 18-45 years) with PFO who had a first-ever ischemic stroke. The study included patients enrolled in the registry from 2000 to 2012, for a total of 521 patients with PFO and no other cause of ischemia. Of those, 315 (60.5%) were treated medically, and 206 (39.5%) with a transcatheter device. The choice of treatment was at the discretion of the treating physician and patient. The primary end point (a composite of ischemic stroke, TIA, or peripheral embolism) occurred less often in device-treated patients (7.3%) than in medically treated patients (10.5%), although the results were not significant (HR [hazard ratio] 0.72; 95% CI 0.39 to 1.32; p=0.285).

In another large prospective series, Alushi et al (2014) reported results from a prospective, single-center study comparing outcomes after PFO device closure or medical management in 418 patients presenting with PFO and cryptogenic stroke or TIA. Two hundred sixty-two patients underwent percutaneous PFO closure, while 156 were treated medically. The choice of medical intervention or device closure was determined by the treating physician and patient. Percutaneous device closure was advised for patients younger than age 55 years, with recurrent cerebrovascular events, large interatrial right-to-left shunt, and nonlacunar ischemic events on neuroimaging. Patients undergoing percutaneous closure were younger and more frequently presented with a larger interatrial right-to-left shunt, previous venous thromboembolism, and hypercoagulability state. Patients treated medically presented more frequently with multiple cerebrovascular accident risk factors. In a multivariable model to predict the composite outcome of TIA, stroke, or all-cause mortality, treatment strategy (percutaneous closure vs medical management) was not significantly associated with the outcome (adjusted OR=1.1; 95% CI, 0.44 to 2.74; p=0.81), after controlling for age, multiple prior cerebrovascular events, and the presence of aspirin.

Nonrandomized comparative studies published before the meta-analyses described above generally reported high rates of procedural success and comparable rates of stroke between device and medical therapy groups.

Single-Arm Case Series

Many case series have reported on outcomes for PFO closure. Series of transcatheter PFO closure in patients presenting with stroke or TIA and PFO has generally reported high rates of procedural success and high rates of freedom from embolic events.

More recent (ie, 2016-2017) series have reported on newer generation devices. For example, Neuser et al (2016) reported on the use of the Occlutech Figulla Flex II Occluder device in a retrospective series of 57 patients.
In a series with the longest follow-up identified, Rigatelli et al (2016) reported on a series of 1000 consecutive patients who were prospectively identified and followed for a mean of 12.3 years. Late device-related complications occurred in 2.2% of patients, most commonly recurrent stroke in 6 patients.

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.

**Section Summary: Transcatheter Patent Foramen Ovale Closure for Stroke Prevention**

The results of 3 RCTs did not support a conclusion that closure devices improve outcomes for patients with PFO and cryptogenic stroke. These trials, which included 1108 patients who underwent PFO closure and 1178 patients who received medical management, did not report significant improvement in outcomes with PFO closure. These results contrast with the results of nonrandomized, comparative studies and systematic reviews of observational studies, which have reported lower rates of recurrent events following closure of PFO. The discrepancy may arise from selection bias, because selection for closure devices or medical therapy may vary, resulting in populations that may have unequal distribution of confounders. The rate of recurrent stroke for patients treated with closure devices in the 3 RCTs was much higher than combined estimates from observational studies. This raises the possibility that ascertainment bias in the observational studies may have resulted in a spuriously low stroke rate for patients treated with a closure device. Multiple meta-analyses of the 3 RCTs, with or without the addition of nonrandomized studies, reached different conclusions, with some reporting a statistically significant reductions in recurrent events on pooled analysis and others reporting trends for benefit that were not statistically significant. While these results suggest that a benefit might be present, the evidence is inconclusive and the risk-benefit ratio not well-defined.

**Transcatheter PFO Closure for Migraine**

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

In 2008, Dowson et al published results of the MIST trial, a sham-controlled randomized trial of PFO closure for refractory migraine headache. In this trial, there was no significant difference observed in the primary end point of migraine headache cessation (3/74 in the implant group vs 3/73 in the sham group, p=0.51). The results of this trial cast some doubt on the causal relation between PFO and migraine.

In 2016, Mattle et al published results of the PRIMA trial, a randomized, open-label trial with blinded end point evaluation comparing transcatheter PFO closure to medical management in patients with migraine with aura. 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 trial’s 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 of 53
patients agreed to have the PFO occluder implanted, and of those 41 underwent implantation. This suggests that the trial might have been underpowered to detect differences between groups. For the primary end point (reduction in mean migraine days at 1 year postrandomization), there were no significant differences between the groups (-2.9 [95% CI, -4.4 to -1.4] for PFO closure vs -1.7 [95% CI, -2.5 to -1.0] for medical management; p=0.168).

A third RCT, the PREMIUM trial (NCT00355056), which compared PFO closure with a sham procedure in 230 patients with refractory migraines with or without aura was completed in 2015. The trial’s results were presented in abstract form in 2015, in which it was reported that patients in the PFO closure group did not differ from those in the sham surgery group in responder rate (50% reduction in migraine attacks per month during months 10-12 postrandomization vs presurgery; 38% in the PFO group vs 32% in the sham group; p=0.03). Results have not been published in full-length manuscript form.

In 2014, Lip and Lip published a descriptive systematic review that included 20 studies on 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 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 and no medical intervention or preventive migraine medication, improvement in migraine symptoms occurred in 83% to 87% of those who underwent PFO closure compared with 0% to 21% of those who received not intervention or who were managed medically. The single RCT identified (Dowson et al [2008]) did not identify significant improvements in migraine symptoms in the PFO closure group.

In a study not included in the Lip and Lip systematic review, Biasco et al (2014) retrospectively compared transcatheter PFO closure with medical therapy in terms of their impact on daily activities. The study included 217 patients with 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 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 improvements in Migraine Disability Assessment Questionnaire (MIDAS) scores. However, there were no significant differences in MIDAS score between groups (p=0.204). The degree of residual right-to-left shunt was not associated with symptom perception.

In 2016, Snijder et al reported on an observational case-control study that evaluated the association between migraine with aura and PFO among patients who underwent an agitated saline transesophageal echocardiogram over a 4-year period at a single outpatient cardiology clinic and had completed a validated
headache questionnaire (N=889). In this sample, a PFO with atrial septal aneurysm was significantly associated with migraine with aura (OR=2.71; 95% CI, 1.23 to 5.95; p=0.01), while PFO alone was not.

**Section Summary: Transcatheter PFO Closure for Migraine**
Although observational studies have shown a possible association between PFO closure and reduction in migraine symptoms, 1 sham-controlled randomized trial did not demonstrate significant improvements in migraine symptoms after PFO closure. Nonrandomized studies have shown highly variable rates of migraine improvement after PFO closure.

**Transcatheter PFO Closure for Other Indications**
Several other medical conditions have been reported to occur more frequently in patients with PFOs, including platypnea-orthodeoxia syndrome, myocardial infarction with normal coronary arteries, decompression illness in response to change in environmental pressure, high-altitude pulmonary edema, and obstructive sleep apnea. Evidence on clinical outcomes related to these conditions after PFO closure is limited to case reports and case series. For example, Mojadidi et al (2015) reported on a series of 17 patients who underwent transcatheter PFO closure for platypnea-orthodeoxia syndrome at a single institution, among whom 11 (65%) were classified as having improved oxygen saturation postprocedure.

**TRANSCATHETER DEVICE CLOSURE FOR ATRIAL SEPTAL DEFECTS**
The FDA has approved 3 devices for ASD closure: the Amplatzer Septal Occluder, the GORE HELEX Septal Occluder (discontinued), and the GORE CARDOFORM Septal Occluder.

**Overview of the Evidence**
The evidence supporting the efficacy of devices for the closure of ASD consists of nonrandomized comparative studies and case series. However, unlike PFO and cryptogenic stroke, the relation between ASD closure and improved clinical outcomes is direct and convincing, because the accepted alternative is open surgery. Results have generally shown a high success rate in achieving closure and low complication rates. The FDA’s approval of the Amplatzer Septal Occluder was based on the results of a multicenter, nonrandomized study comparing the device with surgical closure of ASDs in which 423 patients received 433 devices. This study was subsequently published (2002) with slightly different numbers 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 of 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.
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Systematic Reviews
A systematic review of percutaneous closure versus surgical closure was published by Butera et al (2011). Thirteen nonrandomized comparative studies that enrolled at least 20 patients were included (total N=3082 patients). The rate of procedural complications was higher in the surgical group (31%; 95% CI, 21% to 41%) than in the percutaneous group (6.6%; 95% CI, 3.9% to 9.2%), with an odds ratio for total procedural complications of 5.4 (95% CI, 2.96 to 9.84; p<0.000). There was also an increased rate of major complications for the surgical group (6.8%; 95% CI, 4% to 9.5%) compared with the percutaneous group (1.9%; 95% CI, 0.9% to 2.9%), with an odds ratio of 3.81 (95% CI, 2.7 to 5.36; p=0.006).

In the Abaci et al (2013) meta-analysis of periprocedural complications after ASD or PFO device closures (referenced earlier), for ASD closure, the pooled rate of major complications was 1.6% (95% CI, 1.4% to 1.8%).

Nonrandomized Comparative Studies
Other nonrandomized studies comparing transcatheter closure with surgery have shown similar success rates. Suchon et al (2009), in a study of 100 patients, had a 94% success rate in the transcatheter closure group compared with a 100% success rate in the surgical group. A study by Berger et al (1999) showed identical 98% success rates in both treatment groups. A nonrandomized comparative analysis by Kotowycz et al (2013) reported that mortality rates at 5-year follow-up did not differ between transcatheter (5.3%) and surgical closure (5 6.35%; p=1.00), but that reintervention rates were higher for patients undergoing transcatheter closure (7.9% vs 0.3%, respectively, p<0.004).

In a nonrandomized comparative analysis that used national-level data from Taiwan, Chen et al (2015) compared in-hospital and longer term (4-year) follow-up outcomes for adult patients 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<0.001), ischemic stroke (1.9% vs 0%, p=0.002), or in-hospital death (1.3% vs 0%, p=0.013). Over the 4-year follow-up, outside of the index hospitalization, transcatheter repair patients were more likely to have atrial fibrillation (1.7% vs 0%, p=0.036), while other outcomes did not differ.

Xu et al (2014) reported on a retrospective analysis of transcatheter (n=35) and surgical (n=43) repair in patients with ASD and pulmonary stenosis. Complication rates did not differ significantly between groups, and all patients had 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 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 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 seen: 2 device embolizations, both on day 1; 1 wire frame fracture incidentally discovered at 61 days postimplantation; 1 wire frame fracture associated with echocardiographic abnormalities and requiring surgical removal; and 1 unrelated death.

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

Other smaller studies have also reported favorable results for transcatheter closure of ASD. In Du et al (2002), transcatheter closure for 23 patients with deficient ASD rims was compared to transcatheter closure of 48 patients with 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 (NYHA) 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 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 on follow-up reported in the 90% to 100% range.

**Single-Arm Studies in Pediatric Patients**

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

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

For patients with an ASD, nonrandomized comparative studies and single-arm case series have shown 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 3 RCTs comparing device-based PFO closure with medical therapy, multiple nonrandomized comparative studies, and multiple systematic reviews and meta-analyses of these studies. Relevant outcomes are overall survival, morbid events, and treatment-related morbidity and mortality. None of the 3 trials reported statistically significant improvements on their main outcomes using intention-to-treat analysis. In all 3 trials, low numbers of outcome events in both groups limited the power to detect differences between groups. One trial showed a significant benefit for the closure group on per protocol analysis and another showed significant benefit on secondary outcomes. Meta-analyses of these trials have also come to different conclusions, with some reporting statistically significant reductions in recurrent events on pooled analysis and others reporting a trend for benefit that was not statistically significant. A high-quality meta-analysis reported a significantly lower risk of recurrent ischemic stroke with device therapy, but a higher risk of atrial fibrillation. While these results suggest that a benefit might be present, the evidence is not definitive and the risk-benefit ratio of transcatheter PFO closure as an alternative to medical therapy is not well-defined. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have PFO and migraines who receive PFO closure with a transcatheter device, the evidence includes 2 RCTs of PFO closure and multiple observational studies reporting on the association between PFO and migraine. Relevant outcomes are symptoms, quality of life, medication use, and treatment-related morbidity and mortality. The available sham-controlled randomized trial did not demonstrate significant improvements in migraine symptoms after PFO closure. A second RCT with blinded end point evaluation did not demonstrate improvements in migraine days after PFO closure, but likely it was underpowered. Nonrandomized studies have shown highly variable rates of migraine improvement 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 (eg, 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. The body of evidence only consists of small case series and case reports. Comparative studies are needed to evaluate outcomes in similar patient groups treated with and without PFO closure. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

References

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04/18/2002 Medical Policy Committee review
06/05/2002 Managed Care Advisory Council approval
06/24/2002 Format revision
03/31/2004 Medical Director review
04/26/2004 Managed Care Advisory Council approval
04/05/2005 Medical Director review

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04/19/2005 Medical Policy Committee review. Coverage eligibility unchanged. Investigational statement added to policy to address the use of transcatheter closure devices in situations where patient selection criteria are not met.
05/23/2005 Managed Care Advisory Council approval
04/05/2006 Medical Director review
04/19/2006 Medical Policy Committee approval. Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
07/07/2006 Format revised. Investigational statements added to clarify coverage eligibility. Coverage eligibility unchanged.
04/04/2007 Medical Director review
04/18/2007 Medical Policy Committee approval. Coverage eligibility unchanged.
04/05/2008 Medical Director review
04/16/2008 Medical Policy Committee approval. No change to coverage eligibility.
04/02/2009 Medical Director review
04/15/2009 Medical Policy Committee approval. Closure of patent foramen ovale using a transcatheter approach is now considered to be investigational.
04/08/2010 Medical Policy Committee approval.
04/21/2010 Medical Policy Implementation Committee approval. No change to coverage.
04/07/2011 Medical Policy Committee approval.
04/13/2011 Medical Policy Implementation Committee approval. No change to coverage.
04/12/2012 Medical Policy Committee review
04/25/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/04/2013 Medical Policy Committee review
04/24/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/06/2014 Medical Policy Committee review
03/19/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/07/2015 Medical Policy Committee review
05/20/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/05/2016 Medical Policy Committee review
05/18/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
07/06/2017 Medical Policy Committee review
07/19/2017 Medical Policy Implementation Committee approval. Statement, “There are currently no transcatheter devices with the U.S. Food and Drug Administration [FDA] approval or clearance for this indication,” removed from investigational statement for PFO closure devices; policy statements otherwise unchanged.
04/05/2018 Medical Policy Committee review
04/18/2018 Medical Policy Implementation Committee approval. Coverage for patent foramen ovale changed from investigational to eligible.

Next Scheduled Review Date: 07/2019

Coding
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