Name of Blue Advantage Policy:
Transcatheter Closure Devices for Septal Defects

Policy #: 218       Latest Review Date: June 2019
Category: Medical       Policy Grade: B

Background:
Blue Advantage medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:

1. Safe and effective;
2. Not experimental or investigational*;
3. Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:
   • Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient’s condition or to improve the function of a malformed body member;
   • Furnished in a setting appropriate to the patient’s medical needs and condition;
   • Ordered and furnished by qualified personnel;
   • One that meets, but does not exceed, the patient’s medical need; and
   • At least as beneficial as an existing and available medically appropriate alternative.

*Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill Original Medicare for covered services that are related to clinical trials that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).
Description of Procedure or Service:
Despite the success of standard open-heart surgery to repair cardiac defects, the risks and morbidity of open-heart surgery remain. Intervventional cardiac catheterization techniques have advanced to a point where percutaneous transcatheter devices can be offered as an alternative for carefully selected patients. Transcatheter closure devices are permanent implants designed to close defects between chambers of the heart, including atrial septal defect (ASD), ventricular septal defect (VSD), and patent foramen ovale (PFO). Devices are also used for persistent patent ductus arteriosus (PDA), which is an opening between the descending thoracic aorta and the pulmonary artery which fails close after birth. These devices are self-expandable, self-centering umbrella-like devices. They are implanted in the defect through catheters inserted into either a vein or an artery using a transcatheter or percutaneous approach.

The standard for managing clinically significant cardiac defects mentioned above has been surgical closure, which except for complex ventricular septal defects, is associated with a very low mortality. Conventional surgical closure is done through a midline sternotomy. The newer approaches utilizing the closure devices offer repair of the defect without major thoracic surgery, less post-operative pain, and decreased hospital stay without compromising outcomes in a select group of patients.

Patent Foramen Ovale (PFO)
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 un-inflated lungs. The ductus arteriosus is another feature of the fetal cardiovascular circulation, consisting of a connection between the pulmonary artery and the distal aorta. Prior to 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 arterial pressure and a decrease in right atrial pressure result in the permanent closure of the foramen ovale in most individuals. However, a patent foramen ovale may be detected in up to 25% of asymptomatic adults. In some epidemiologic studies, patent foramen ovale (PFO) has been associated with cryptogenic stroke, a type of stroke defined as an ischemic stroke occurring in the absence of potential cardiac, pulmonary, vascular, or neurologic sources. Studies also show an association of PFO and migraine headache.

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

Atrial Septal Defect (ASD)
Unlike PFOs, 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 according to their anatomy. Ostium secundum describes defects that are located mid-septally and are typically near the fossa ovaris.
Ostium primum defects lie immediately adjacent to the atroventricular valves and are within the spectrum of atroventricular septal defects. Primum defects occur commonly in patients with Down syndrome. Sinus venous defects occur high in the atrial septum and are frequently associated with anomalies of the pulmonary veins.

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

Treatment
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 operative repair, there has been interest in developing a catheter-based approach to ASD repair to avoid the risks and morbidity of open heart surgery. A variety of devices have been researched. Technical challenges include minimizing the size of device so that smaller catheters can be used, developing techniques to properly center the device across the ASD, and ensuring that the device can be easily retrieved or repositioned, if necessary.

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

Transcatheter Closure Devices
Transcatheter PFO and ASD occluders consist of a single or paired wire mesh 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.

Ventricular Septal Defect (VSD)
VSD is the most common congenital heart defect at birth and presents in approximately 42 out of every 10,000 births per year. Although VSD is most often an isolated lesion, it is a common component of complex abnormalities such as conotruncal defects (e.g., tetralogy of Fallot and Transposition of Great Arteries). VSD can also be associated with left-sided obstructive lesions such as subaortic stenosis (SubAS) and coarctation of the aorta. A subpulmonary (supracristal) VSD is often associated with progressive aortic valve regurgitation caused by prolapse of the aortic cusp (usually right) through the defect.
Ventricular septal defects (VSDs) are usually present at birth but may also occur following myocardial infarction. Small VSDs may never be detected. A large VSD can allow blood to flow from the left to the right ventricle which increases load on the heart and lungs. Septal defects may also be created during surgical repair of certain types of congenital heart defects, such as hypoplastic left ventricle syndrome. A hole is made in the septum of the repaired section of the heart (Fontan fenestration) to improve recovery from the surgery. The fenestration is intended to be closed at a later time.

**Treatment**
Small VSDs may cause no problems and close on its own. If the VSD is large, open heart surgery may be required which is usually performed in infancy or childhood. During open heart surgery, a patch is sewn over the defect or if possible, the defect is sewn shut without a patch.

**Transcatheter Closure Devices**
The Amplatzer™ Muscular VSD Occluder is a device to occlude ventricular septal defects. The device is made of a polyester material that promotes occlusion and tissue in-growth. Similarly, the CardioSEAL® Septal Occlusion System is a permanent implant made of a metal framework to occlude VSDs.

**Patent Ductal Arteriosus (PDA)**
PDA is another fairly common type of congenital heart defect (CHD) affecting approximately 8 out of every 1000 premature babies. Although it can affect full term babies, it is more common in premature babies. With this CHD, there is abnormal blood flow between the aorta and pulmonary artery. These two arteries are connected by the ductus arteriosus which is a normal and essential part of fetal blood circulation. Soon after birth, the vessel should close. When the vessel does not close, it allows oxygen rich blood from the aorta to mix with oxygen poor blood from the pulmonary artery which may strain the heart and increase blood pressure in lung arteries.

**Treatment**
A PDA may be treated with medications, catheter based procedures or open surgery. Transcatheter closure of a PDA is an established treatment and is often the treatment of choice.

**Policy:**
**Effective for dates of service on or after August 14, 2016:**
Blue Advantage will treat transcatheter closure of a patent foramen ovale (PFO) using an FDA approved closure device as a covered benefit for the following indication:
- The patient is between 18 and 60 years of age.
- Diagnosis of PFO with a right to left shunt confirmed by echocardiography
- Diagnosis of cryptogenic stroke due to a presumed paradoxical embolism

Blue Advantage will treat transcatheter closure of atrial septal defects (ASD) in adult or pediatric patients as a covered benefit for any of the following indications:
- For the occlusion of ASDs in secundum position OR patients who have undergone a fenestrated Fontan procedure who now require closure of the fenestration;
- Have echocardiographic evidence of ostium secundum ASD AND clinical evidence of right ventricular volume overload (e.g. 1.5:1 degree of left to right shunt or RV enlargement).
- Have echocardiographic evidence of ostium secundum ASD AND clinical evidence of paradoxical embolism
- Documented platypnea- orthodeoxia
- Presence of net left-to-right shunting, pulmonary artery pressure less than two thirds systemic levels, PVR less than two thirds systemic vascular resistance, or when responsive to either pulmonary vasodilator therapy or test occlusion of the defect

Blue Advantage will treat transcatheter closure of atrial septal defects (ASD,) in all other situations, including but not limited to coronary sinus ASD, ostium primum ASD and sinus venosus ASD, as a non-covered benefit and as investigational.

Blue Advantage will treat transcatheter closure of ventricular septal defects (VSD) as a covered benefit for any of the following indications:
- Complex VSD of significant size to warrant closure (e.g. large volume left to right shunt, pulmonary hypertension, and/or clinical symptoms of congestive heart failure) AND are considered to be at high risk for standard transatrial or transarterial surgical closure based on anatomical conditions and/or based on overall medical condition.**
- Iatrogenic artifacts after surgical replacement of the aortic valve

**High risk anatomical factors for transatrial or transarterial surgical closure include patients:
- Requiring left ventriculotomy or an extensive right ventriculotomy
- With a failed previous VSD closure
- With multiple apical and/or anterior muscular VSDs (Swiss Cheese Septum)
- With posterior apical VSDs covered by trabeculae

Blue Advantage will treat transcatheter closure of ventricular septal defects (VSD) as a non-covered benefit and as investigational including but not limited to, when the above criteria are not met and in patients with severe irreversible PAH.

Blue Advantage will treat transcatheter closure of patent ductus arteriosus (PDA) as a covered benefit when using an FDA approved device for this indication.

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**Effective for dates of service on or after April 12, 2011 and prior to August 14, 2016:**
Blue Advantage will treat transcatheter closure of atrial septal defects (ASD) with a diameter of 5mm or greater including patent foramen ovale (PFO) in adult or pediatric patients as a covered benefit for any of the following indications:
- Paradoxical embolism
- Documented orthodeoxia-platypnea
• Presence of net left-to-right shunting, pulmonary artery pressure less than two thirds systemic levels, PVR less than two thirds systemic vascular resistance, or when responsive to either pulmonary vasodilator therapy or test occlusion of the defect

• To prevent long-term complications such as atrial arrhythmias, reduced exercise tolerance, hemodynamically significant tricuspid regurgitation (TR), right-to-left shunting, and embolism during pregnancy, overt congestive cardiac failure, or pulmonary vascular disease.

**Blue Advantage** will treat **transcatheter closure of atrial septal defects (ASD)** with a diameter of less than 5mm including patent foramen ovale (PFO) in adult or pediatric patients as a **covered benefit** for **any** of the following indications:

- Paradoxical embolism

**Transcatheter closure of atrial septal defects** is contraindicated in the above patient population when:

- Patient is known to have extensive congenital cardiac anomaly which can only be adequately repaired by way of open cardiac surgery
- Patient is known to have sepsis within one month prior to implantation, or any systemic infection that cannot be successfully treated prior to device placement
- Patient is known to have a bleeding disorder, untreated ulcer or any other contraindications to aspirin therapy, unless another anti-platelet agent can be administered for six months
- Patient is known to have a demonstrated intracardiac thrombi on echocardiography (especially left atrial or left atrial appendage thrombi)
- Patient’s size (i.e., too small for transesophageal echocardiography (TEE) probe, catheter size, etc.) or condition (active infection, etc.) would cause the patient to be a poor candidate for cardiac catheterization
- The margins of the patient’s defect are <5mm to the coronary sinus, AV valves or right upper lobe pulmonary vein.

**Blue Advantage** will treat **transcatheter closure of ASD** as a **non-covered benefit** in patients with severe irreversible PAH and no evidence of a left-to-right shunt.

**Blue Advantage** will treat **transcatheter closure of ventricular septal defects (VSD)** as a **covered benefit** for any of the following indications:

- VSD is remote from the tricuspid valve and the aorta
- VSD is associated with severe left-sided heart chamber enlargement
- Presence of PAH
- Residual defects after prior attempts at surgical closure
- Restrictive VSDs with significant left-to-right shunt
- Trauma
- Iatrogenic artifacts after surgical replacement of the aortic valve
- History of bacterial endocarditis
- Hemodynamically significant left-to-right shunt (Qp/Qs greater than 1.5:1)
Blue Advantage will treat transcatheter closure of patent ductus arteriosus (PDA) as a covered benefit for any of the following indications:

- Left atrial and/or LV enlargement
- PAH is present
- Presence of net left-to-right shunting
- Prior endarteritis

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:
The most recent update with literature review is through March 5, 2019.

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Transcatheter Device Closure of Patent Foramen Ovale (PFO) for Stroke
The evidence for the efficacy of transcatheter patent foramen ovale (PFO) closure devices consists of 3 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 vs Medical Management

Two RCTs, the PC and RESPECT trials, have been published and reported on outcomes comparing the Amplatzer PFO Occluder with medical management. Trial characteristics and results are summarized in Tables 1 and 2.

Randomized Controlled Trials
In the PC trial (2013), the primary end point (composite of death, nonfatal stroke, transient ischemic attack [TIA], or peripheral embolism after independent adjudication) did not differ significantly between the closure and medical groups either on intention-to-treat (ITT) analysis or per-protocol analysis. There were no significant differences in the rate of the individual components of the primary outcome, and there were no significant differences in outcome on subgroup analyses. The adverse event rate was 34.8% in the closure group compared with 29.5% in the medical therapy group. This trial was designed to have 80% power to detect a reduction of 66% in primary end point (from 3% per year in the medical therapy group vs 1% per year in the closure group). However, the observed event rate in the trial was less than half of the anticipated event rate used in the power calculation and, as reported by authors, the trial had less than 40% power to detect a 66% reduction.

RESPECT (2013) also compared closure with medical management, with 2 notable differences from to the PC trial: TIA was not included as a component of the primary composite end point, and all end points were adjudicated in a blinded fashion. These protocol differences were attempts to address shortcomings observed in the PC trial where authors noted that TIA as a component in the primary end point might have diluted effects, as suggested by the difference in the estimated hazard ratios (HRs) for stroke (0.20) and TIA (0.71). Trialists had also noted the possibility of selective reporting of potential events in the PC trial owing to the open-label nature of the trial.

Results of the RESPECT trial have been reported in 3 publications with each publication reporting longer follow-up. The primary end point was a stroke or early death, 30 and 45 days after implantation or randomization, respectively.

The first publication, by Carroll et al (2013), reported a median follow-up of 2.3 years and no difference in the primary end point with ITT analysis. The ITT analysis (n=980) included 3 patients from the closure group who had recurrent ischemic stroke before device implantation. However, the per-protocol cohort (n=944; patients as randomized plus adhered to the protocol-mandated medical treatment, and did not have a major inclusion or exclusion violation) and as-treated cohort (n=958; patients with a protocol-approved treatment, adhered to the protocol-mandated medical treatment, and were classified by treatment actually received) showed statistically significant improvements in primary end point in both analyses (HR=0.37; 95% confidence interval [CI], 0.14 to 0.96; p=0.03; HR=0.27; 95% CI, 0.10 to 0.75; p=0.007, respectively). The number needed to treat (NNT) after 5 years in the ITT population was 27. The rate of serious, device- or procedure-related complications was 4.5%. There was no difference in major bleeding between arms, but there was a higher incidence of deep vein thrombosis and pulmonary thromboembolism in the device arm. This was attributed to a ninefold increased use of warfarin in the medical group.
Subsequent to this analysis, Rogers et al (2017) published an overview of the U.S. Food and Drug Administration (FDA) assessment of the Amplatzer PFO Occluder that included analysis of data with approximately 5 years of follow-up. FDA conducted ITT, per-protocol, as-treated, and device-in-place analyses and results are summarized in Table 4. Although the FDA panel had some disagreements about using non-ITT analysis because excluding patients compromises randomization, the panel agreed that a 50% relative risk reduction in stroke—especially in younger patient population—is clinically significant. All 3 analyses (i.e., per-protocol, as-treated, and device-in-place) reported statistically significant relative reductions of more than 50% in the risk of recurrent strokes. Note that with extended follow-up analyses, the event-free survival curves converged and the NNT after 5 years in the ITT population rose from 27 to 43. However, FDA concluded that it might be reasonable for conclusions drawn from RESPECT to be limited to the select subgroup of at-risk patients with stroke and PFO in whom other causes of ischemic stroke have been excluded by a neurologist.

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

Table 1. Summary of Key RCT Characteristics for the Amplatzer PFO Occluder

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
<th>Median DOF, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meier et al (2013); PC Trial</td>
<td>Europe, 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>Amplatzer PFO Occluder</td>
<td>Active Comparator</td>
</tr>
<tr>
<td>Carroll et al (2013); RESPECT</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>Amplatzer PFO Occluder</td>
<td>Medical treatmenta</td>
</tr>
<tr>
<td>Saver et al (2017); RESPECT</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>Amplatzer PFO Occluder</td>
<td>Medical treatmentb</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 2. Summary of Key RCT Results for the Amplatzer PFO Occluder

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Primary End Point</th>
<th>Secondary End Point</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meier et al (2013); 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)c</td>
<td>11/210 (5.2%)d</td>
<td>5/210 (2.4%)</td>
</tr>
<tr>
<td>HR (95% CI); p</td>
<td>0.63 (0.24 to 1.62); 0.34a</td>
<td>0.45 (0.16 to 1.29); 0.14b</td>
<td>0.20 (0.02 to 1.72); 0.14</td>
</tr>
<tr>
<td>Carroll et al (2013); RESPECT</td>
<td>980</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amplatzer, n/N (%)</td>
<td>9/499 (1.8)c</td>
<td>Not applicable</td>
<td>9/499 (1.8)</td>
</tr>
<tr>
<td>Medical treatment, n/N (%)</td>
<td>16/481 (3.3)d</td>
<td>Not applicable</td>
<td>16/481 (3.3)</td>
</tr>
</tbody>
</table>
| HR (95% CI); p       | 0.49 (0.22 to 1.11); 0.08c | Not applicable       | 0.49 (0.22 to 1.11);
Table 3. FDA Summary of Kaplan-Meier Analyses of the Primary End Point in RESPECT Trial (Amplatzer PFO Occluder)

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

FDA assessment as reported by Rogers et al (2017).7
FDA: Food and Drug Administration; RRR: relative risk reduction.
\(^a\) Adherence to guidelines-directed medical therapy defined as \(\geq 67\%\) cumulative compliance over the duration of the study.
\(^b\) \(p<0.05\) was considered statistically significant.

Transcatheter PFO Closure with Device plus Medical Management vs Medical Management Alone

Two RCTs, REDUCE and CLOSE trials, have been published and reported on outcomes comparing various closure devices plus medical management with medical management alone. They are summarized in Tables 4 and 5. Note that both the REDUCE and CLOSE trials enrolled more patients with a moderate-to-large interatrial shunt size (58.4% and 75.2%) compared with 16.7% and 19.3% of patients with a large interatrial shunt size in the PC and RESPECT trials, all respectively.

In the REDUCE trial (2017), the blinded adjudicated coprimary end points of freedom from ischemic stroke (reported as the percentage of patients who had a stroke recurrence) and incidence of new brain infarction (clinical ischemic stroke plus silent brain infarction on imaging) 2 years after randomization were significantly lower in the PFO closure plus antiplatelet therapy than the antiplatelet therapy alone group in ITT analysis, the per-protocol analysis, and the as-treated population analysis (see Table 5). The number of patients who needed to be treated to prevent 1 stroke in 24 months was approximately 28 patients. Previous trials such as RESPECT, PCI, and CLOSURE allowed discontinuation of antithrombotic therapy after PFO closure, and the use of anticoagulants in the medical therapy group was at the discretion of treating physician. Such a design may have led to the confounding of results and
bias within the medical therapy groups in favor of control because of increased protection from the risk of stroke due to causes other than PFO. Serious adverse events occurred in 23.1% of patients in the PFO closure group and 27.8% of patients in the antiplatelet-only group (p=0.22).

In the CLOSE trial (2017), 663 patients were randomized to PFO closure plus antiplatelet therapy (PFO closure group), antiplatelet therapy alone (antiplatelet-only group), or oral anticoagulation (anticoagulation group). The primary blinded adjudicated outcome of stroke was significantly lower in the PFO closure vs antiplatelet therapy in ITT analysis as well as per-protocol analysis (see Table 4). The 5-year stroke risk, using the Kaplan-Meier probability estimate, was 4.9 percentage points lower in the PFO closure group than in the antiplatelet-only group, which would result in 1 stroke avoided at 5 years for every 20 treated patients (95% CI, 17 to 25). The rate of atrial fibrillation was higher in the PFO closure group (4.6%) than in the antiplatelet-only group (0.9%; p=0.02). The number of serious adverse events did not differ significantly between treatment groups (p=0.56).

No clinical trials have focused specifically on patients who failed medical therapy, as defined by recurrent stroke or TIA while on therapy. Many published studies have included patients with first cryptogenic stroke patients with recurrent stroke or TIA and have generally not analyzed these patient populations separately. As a result, it is not possible to determine from the evidence whether PFO closure in patients who have failed medical therapy reduces the risk of subsequent recurrences.

Table 4. Summary of Key RCT Characteristics

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
<th>Median DOF, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Søndergaard et al (2017); 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&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.2</td>
</tr>
<tr>
<td>Mas et al (2017); 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&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5.4-5.2&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

DOF: duration of follow-up; PFO: patent foramen ovale; RCT: randomized controlled trial.
<sup>a</sup> 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).
<sup>b</sup> 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.
<sup>c</sup> Antiplatelet therapy (aspirin, clopidogrel, or aspirin combined with extended release dipyridamole).
<sup>d</sup> Duration of follow-up in device closure group and antiplatelet-only group.

Table 5. Summary of Key RCT Results

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Primary End Point&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Primary End Point&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Secondary End Point&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Søndergaard et al (2017); REDUCE</td>
<td>664</td>
<td>664</td>
<td>-</td>
</tr>
<tr>
<td>HELEX or CARDIOFORM plus antiplatelet therapy, n/N (%)</td>
<td>6/441 (1.4)</td>
<td>22/383 (5.7)</td>
<td>-</td>
</tr>
<tr>
<td>Antiplatelet therapy alone, n/N (%)</td>
<td>12/223 (5.4)</td>
<td>20/177 (11.3)</td>
<td>-</td>
</tr>
<tr>
<td>HR (95% CI); p</td>
<td>0.23 (0.09 to 0.62)</td>
<td>0.51 (0.29 to 0.91)</td>
<td>-</td>
</tr>
<tr>
<td>mas et al (2017); close</td>
<td>0.002</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<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></td>
</tr>
<tr>
<td>473</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>multiple closure devices plus antiplatelet therapy, n/n (%)</td>
<td>0/238 (0)</td>
<td>-</td>
<td>Not reported (3.4)</td>
</tr>
<tr>
<td>antiplatelet therapy alone, n/n (%)</td>
<td>14/235 (6.0)</td>
<td>-</td>
<td>Not reported (8.9)</td>
</tr>
<tr>
<td>hr (95% ci); p</td>
<td>0.03 (0.00 to 0.26); &lt;0.001</td>
<td>-</td>
<td>0.39 (0.16 to 0.82); 0.01</td>
</tr>
</tbody>
</table>

CI: confidence interval; HR: hazard ratio; NNT: number needed to treat; RCT: randomized controlled trial.
a Freedom from ischemic stroke (reported as percentage of patients who had a recurrence of stroke) 2 years after randomization.
b Incidence of new brain infarction (clinical ischemic stroke or silent brain infarction on imaging) 2 years after randomization.
c Composite outcome of stroke, transient ischemic attack, or systemic embolism.

Systematic Reviews

A large number of systematic reviews and meta-analyses have evaluated outcomes related to the percutaneous transcatheter closure of a PFO. Of these, 2 systematic reviews, by Kent et al (2016) and Li et al (2015), have pooled data from 3 RCTs (CLOSURE II, PC trial, RESPECT). However, the findings of analyses published prior 2018 may no longer be relevant because (1) they pooled data across multiple devices (STARFlex septal closure system is no longer available), which might differ in terms of efficacy and safety, and (2) did not incorporate results of multiple RCTs with long-term follow-up of up to 5 years published in 2017. Therefore, systematic reviews published before 2017 are not discussed further.

Two meta-analyses published in 2018 included data from PC trial, RESPECT extended follow-up, REDUCE, and CLOSE but excluded CLOSURE II trial data because it used the STARFlex PFO closure device are summarized in Tables 6 and 7. 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.

A third meta-analysis conducted by Alushi et al (2018) included all 5 trials and reported outcomes as pooled HRs or odds ratios (Tables 6 and 7). 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 6. Systematic Review Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Dates</th>
<th>Trials</th>
<th>Participants</th>
<th>N (Range)</th>
<th>Design</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>RCT</td>
<td>No restrictions</td>
</tr>
</tbody>
</table>

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

Table 7. Systematic Review 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>ARR (95% CI)</td>
<td>-3.2 (-5.0 to -1.4)</td>
<td>-0.4 (-1.7 to 1.0)</td>
<td>-2.1 (-5.1 to 0.9)</td>
<td>6.1 (NR)</td>
<td></td>
</tr>
<tr>
<td>NNT (95% CI)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>I² (p)</td>
<td>3.62 (0.38)</td>
<td>0 (0.81)</td>
<td>-</td>
<td>0 (0.92)</td>
<td>82.5 (&lt;0.001)</td>
</tr>
</tbody>
</table>

De Rosa et al (2018)

<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>N</td>
<td>2531</td>
<td>-</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>-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>
<td></td>
</tr>
<tr>
<td>NNT (95% CI)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>I² (p)</td>
<td>61 (0.003)</td>
<td>33.79 (0.29)</td>
<td>28 (0.60)</td>
<td>66 (0.002)</td>
<td></td>
</tr>
</tbody>
</table>

Alushi et al (2018)

<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>Total N</td>
<td>3440</td>
<td>2776(excludes REDUCE)</td>
<td>3440</td>
<td>3440</td>
<td>3440</td>
</tr>
<tr>
<td>HR/OR (95% CI); p</td>
<td>0.39 (0.19 to 0.83); p&lt;0.01</td>
<td>0.73 (0.49 to 1.09; p=0.12</td>
<td>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>
<tr>
<td>NNT</td>
<td>37</td>
<td>33</td>
<td>26</td>
<td>39</td>
<td>49</td>
</tr>
<tr>
<td>I² (range)</td>
<td>56 (0 to 84)</td>
<td>0</td>
<td>26</td>
<td>39</td>
<td>0</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.

Observational Studies

There is a large evidence base of observational studies. Because multiple RCTs with more than 5 years of follow-up are available, data from these observational studies are not discussed except where such studies provide longer duration of follow-up, specifically related to durability of results and adverse events (revealed by larger populations or longer length of follow-up than in trials). Rigatelli et al (2016) reported safety outcomes on a series of 1000 consecutive patients who were treated with catheter-based closure using different devices and prospectively identified, with mean follow-up of 12.3 years. Permanent atrial fibrillation occurred in 0.5%, device thrombosis occurred in 0.5%, new-onset or worsening of mitral valve regurgitation was observed in 0.2% whereas recurrent cerebral ischemic events occurred in 0.8% patients. The occlusion rate was 93.8%. No aortic or atrial free wall erosion was reported.
Section Summary: Transcatheter Device Closure Patent Foramen Ovale Closure for Stroke

The results of RCTs of PFO closure compared with medical management have reported point estimates of hazard ratios ranging from 0.03 to 0.78 suggesting that PFO closure is more effective than medical therapy for reducing event rates. These results were not statistically significant by ITT analyses in the early trials (CLOSURE I, PC, RESPECT), but were significant in later trials (RESPECT extended follow-up, REDUCE, CLOSE). Initially, inadequate power was blamed for demonstrating the lack of superiority of PFO closure in the early RCTs, but the reasons are probably multifactorial. The RESPECT, REDUCE, and CLOSE trials enrolled patients when off-label PFO closure had decreased, allowing for inclusion for patients with vascular anatomic features (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 PFO Closure for Migraine Randomized Controlled Trials

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 study, there was no significant difference observed in the primary end point of migraine headache cessation (3/74 in the implant group, 3/73 in the sham group, p=0.51). The results of this study cast some doubt on the causal relationship between PFO and migraine.

In 2016, Mattle et al published results of the PRIMA trial, a randomized, open label trial with blinded endpoint evaluation comparing transcatheter PFO closure with medical management in patients with migraine with aura. The study 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 study’s power calculations required an enrollment of 72 in each group. The study was stopped prematurely due to slow enrollment, and there was relatively high loss to follow up (22%). In the device group, 45/53 patients agreed to have the PFO occluder implanted, and of those 41 underwent implantation. This suggests that the trial may have been underpowered to detect differences between groups. For the primary endpoint, reduction in mean migraine days at 1 year postrandomization, there were not significant differences between the groups (-2.9 [95% CI -4.4 to -1.4] for PFO closure vs -1.7 [95% CI -2.5 to -1.0] for medical management, P=0.168).

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

**Systematic Reviews**
In 2014, Lip and Lip published a primarily descriptive systematic review that included 20 studies of the prevalence of PFO in patients with migraines and 21 studies of 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 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 aura or migraine 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 aura and migraine without aura ranged from 28.6% to 93.2% and 13.6% to 82.9%, respectively. In 2 case-control studies that compared PFO closure and medication for migraines with intervention, improvement in migraine symptoms occurred in 83% to 87% compared with 0% to 21% of those managed medically. The single RCT identified (Dowson et al) did not identify significant improvements in migraine symptoms in the PFO closure group.

**Observational Studies**
In a study not included in the Lip and Lip systematic review, Biasco et al (2014) retrospectively compared transcatheter PFO closure with medical therapy in terms of impact on daily activities. The study included 217 patients with migraine and echocardiographic evidence of PFO, 89 of who 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 scores on the Migraine Disability Assessment Questionnaire (MIDAS). 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.

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

**Section Summary: Transcatheter PFO Closure for Migraine**
Although observational studies have shown a possible association between PFO closure and reduction in migraine symptoms, 1 sham-controlled RCT did not demonstrate significant improvements in migraine symptoms after PFO closure. Nonrandomized studies have shown highly variable rates of migraine improvement after PFO closure.
**Transcatheter 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 about clinical outcomes related to these conditions after PFO closure is limited to case reports and case series. For example, Mojadidi et al reported on a series of 17 patients who underwent transcatheter PFO closure for platypnea-orthodeoxia syndrome at a single institution, among whom 64.8% were classified as having improved oxygen saturation postprocedure.

**Section Summary: Transcatheter PFO Closure for Other Indications**

The body of evidence on other medical conditions treated with PFO closure only consists of small case series and case reports, which is an insufficient basis on which to draw conclusions about efficacy.

**Transcatheter Device Closure for Atrial Septal Defects (ASD)**

Evidence supporting the efficacy of devices for closure of ASD consists of nonrandomized and comparative studies and case series studies. However, unlike PFO and cryptogenic stroke, the relationship between closure of the ASD and improved clinical outcomes is direct and convincing. Results generally show a high success rate in achieving closure and low complication rates. The FDA approval of the AMPLATZER Septal Occluder was based on the results of a multicenter, nonrandomized study comparing the device to surgical closure of ASDs. This study was subsequently published by Du et al (2002) with slightly different data, but similar quantitative findings. All patients had an ostium secundum atrial septal defect and clinical evidence of right ventricular volume overload. The results for the septal occluder group showed comparably high success rates to surgery; the 24-month closure success rate was 96.7% in the septal occluder group compared to 100% in the surgical group. While the pattern of adverse events was different in the two 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 two groups was significantly different; in the septal occluder group the mean age was 18 years, compared to six years in the surgically treated group.

**Systematic Reviews**

A systematic review of percutaneous closure versus surgical closure was published by Butera et al in 2011. Thirteen nonrandomized comparative studies that enrolled at least 20 patients were included, with a total of 3082 patients. The rate of procedural complications was higher in the surgical group (31%; 95% CI, 21% to 41%) compared with 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%), for 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/PFO device closures referenced earlier, for ASD closure, the pooled rate of major complications after ASD closures was 1.6% (95% CI, 1.4% to 1.8%).

Nonrandomized, Comparative Studies

Other nonrandomized studies comparing transcatheter closure to surgery show similar success rates.

Suchon et al (2009), in a study of 100 patients, had a 94% success rate in the transcatheter closure group compared to a 100% success rate in the surgical group. A study by Berger et al (1999) showed identical 98% success rate in both treatment groups. A nonrandomized comparative analysis by Kotowycz et al (2013) reported that mortality rates at five-year follow-up did not differ between transcatheter and surgical closure (5.3% vs 6.35% respectively, 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 years of follow-up, outside of the index hospitalization, transcatheter repair patients were more likely to have atrial fibrillation (1.7% vs 0, P=0.036), but other outcomes did not differ.

Xu et al (2014) reported a retrospective analysis of transcatheter (n=35) and surgical (n=43) closure of ASD in patients with ASD and pulmonary stenosis. Complication rates were not significantly different between groups, and all patients in both groups were reported to have complete correction of their ASD.

Single-Arm Studies

Single-arm studies show high success rates of ASD closure. The FDA study discussed previously was the largest series, with an enrollment of 422 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 GORE 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 including 336 patients with large secundum ASDs (balloon-stretched diameter ≥34 mm in adults or echocardiographic diameter >15 mm/m2 in children)
managed with the Amplatzer closure device, Baruteau et al (2014) reported closure rates of 92.6%.

Other smaller studies have reported favorable results for transcatheter closure of ASD. In Du et al (2002), transcatheter closure of ASD in 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 the groups (91% for deficient rims and 94% for sufficient rims) along with no major complications at 24 hours and six-month follow-up. Oho et al (2002) also reported a successful closure rate of 97% at one-year follow-up in 35 patients receiving transcatheter closure of ASD, while only one patient complication of second degree atrioventricular block was noted. Brochu et al (2002) evaluated 37 New York Heart Association (NYHA) Class I or II patients who underwent transcatheter closure of ASD. At six-month follow-up, maximal oxygen uptake improved significantly and the dimensions of the right ventricle decreased significantly while 20 patients moved from NYHA class II to Class I and improved exercise capacity. Numerous other small, single-arm studies report similar results, with procedural success approaching 100% and successful closure on follow-up reported in the 90% to 100% range.

**Single-Arm Studies in Pediatrics**
Several single-arm studies have reported outcomes from transcatheter ASD closure in children and adolescents. Grohmann et al (2014) reported outcome from a single-center series of children aged three to 17 years (median, 6) who were treated with the Gore Septal Occluder, with technical success in 41 of 45 patients in whom closure was attempted (91%). Nyboe et al (2013) reported outcomes from 22 patients with secundum ASD who underwent ASD closure with the Gore 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) 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 Closure of ASDs**
For patients with an ASD, nonrandomized comparison 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.

**Transcatheter Closure of Ventricular Septal Defects (VSD)**

VSD closure devices have been evaluated in clinical studies. The CardioSEAL high-risk study is a prospective, multicenter trial studying the use of the CardioSEAL® Septal Occlusion System to close a variety of hemodynamically significant defects. At the time the VSD data was analyzed and submitted to the FDA for approval, 74 patients with no additional anatomical lesions were enrolled in the study for closure of a VSD. The types of VSDs closed with a CardioSEAL device were: congenital muscular (n=26) and post-operative (n=31). The age of the patients ranged from 0.3 years to 70.1 years, with a median age of 3.7 years. The investigators reported that despite a high degree of comorbid illness within the treated group, 72% of the patients improved clinically at six months after implantation and 84% of the patients had a reduction in flow through the defect or reduction in the anatomical defect size. Peri-procedure events, including some serious events, occurred frequently, but all moderately serious or serious events had resolved by six months after the procedure. The investigators concluded that the CardioSEAL Septal Occlusion System is safe and effective in the intended patient population.

The AMPLATZER Muscular VSD Occluder was evaluated in a prospective, multi-center, non-randomized, controlled, investigation to evaluate muscular VSD closure. The purpose of the evaluation was to retrospectively determine if this device was reasonably safe and effective for the treatment of congenital muscular VSD in patients with complex VSD of significant size to warrant closure that are considered to be at high risk for standard transcatheter closure based on anatomical conditions and/or based on overall medical condition. There were 41 high risk patients (age range 0.1 to 49 years) who consented to participate in the study. Of these, 38 patients underwent cardiac catheterization and an attempt to place the device. In six of 38 patients, the device was not successfully implanted during any procedure.

The results showed that 38 patients underwent 47 procedures, and 83% of the procedures were a technical success. At the six month follow-up, the ECHO showed 95.2% of patients had successful closure of the muscular VSD. At the 12-month follow-up visit, 100% of patients had successful closure. Also, 43.8% of patients were classified as 12-month composite successes in that they did not experience a major adverse event, technical failure, or significant shunt within the 12 months of the implant procedure. Given the general health status of the patients in this high risk population, the FDA found these clinical outcomes to be supportive of device safety and effectiveness. Patient amendable to surgical closure were excluded from the overall analysis. It was noted that small patients (weight <5.2 kilograms) and patients with post-infarction VSDs were at increased risk for adverse outcomes and were therefore contraindicated for device use.

**Randomized Controlled Trials**

In 2014, Yang also reported a randomized controlled trial that reported the safety and efficacy of the surgical approach versus the transcatheter approach to repair perimembranous VSD. Two hundred twenty-nine children were randomly assigned between the 2 groups over an 18 month period and followed over a 2 year period. There were no major adverse events or deaths reported in either group. There was also no difference in closure rate, adverse events or
complications during the follow up period. The authors concluded that transcatheter device closure has a lower incidence of myocardial injury, less blood transfused, faster recovery, and shorter hospital stay verses the surgical approach.

Case Series
In 2010, Yang et al evaluated the safety, efficacy, and long-term results of transcatheter closure of ventricular septal defects (VSD) in a single center case series. The VSD device was placed in 832 patients. Adverse events were reported in 103 patients with most frequent minor adverse event being hematoma, junctional rhythm, and bundle branch block. Nine major adverse events reported with 2 being cases of complete atrioventricular block which needed a pacemaker. This study had strict inclusion/exclusion criteria which may show the importance of determining the proper population. The authors concluded that this procedure is an effective method for VSD treatment with a high success rate and favorable long term results.

Retrospective Studies
In 2018, Mandal et al conducted a retrospective review to evaluate procedural results and early and long term follow up outcome of transcatheter closure of pmVSD. The review was from January 2005 to December 2016. Follow up evaluation was done at 1, 3, 6, and 12 months and yearly thereafter with TTE and ECG. The device was successfully implanted in 180/186 patients. Early adverse events occurred in 16 patients (8.9%). A total of 2 events (1 complete AVB and 1 complete LBBB) were considered significant. Both recovered fully. No serious adverse events or complete AVB were reported in the median follow up period of 18.4 months. The authors conclude by stating that the incidence of serious adverse events were very low, and no late onset of complete AVB were reported. The procedure has an excellent success and closure rate.

In 2015, Ghaderian et al conducted a study to evaluate complications and mid-term follow up of VSD transcatheter closure using the Amplatzer VSD Occluder of 110 patients between April 2012 and October 2013. Follow up evaluations were completed at 1, 6, and 12 months, then yearly. The closure rate reported was 72.8% at procedure completion and then rose to 99% during the follow up. The most serious adverse events reported were 2 cases of complete atrioventricular block. The authors concluded that transcatheter closure of perimembranous VSD was safe and effective with excellent closure rates.

Section Summary: Transcatheter Closure of VSDs
For patients with a VSD, a RCT, single center case series, and clinical trials show high success rates of closure using the transcatheter approach. If the percutaneous approach is unsuccessful, VSD closure can be achieved using surgery. Because of the advantages of percutaneous closure over open surgery, this evidence is considered sufficient to determine that transcatheter VSD closure improves outcomes in selected patients with an indication for VSD closure.

Transcatheter Device Closure for Patent Ductus Arteriosus (PDA)
In 2015, Behjati-Ardakani et al investigated long term outcomes of transcatheter closure of PDA in adolescents and adults using the Amplatzer ductal occluder. Between May 2004 and October 2012, 69 adolescent and adult patients had transcatheter closure of a PDA. All patients were successfully implanted with the ADO devices. Immediately post-operatively, 16 patients
had complete occlusion and 47 patients had a residual shunt. Only 1 patient at 24 hours post-op still had a residual shunt. The patients were followed up to 46 months. There were no reports of device migration, recanalization, hemolysis observed.

In 2016, Putra et al published a case series on transcatheter closure of PDAs in Adolescents and Adults from January 2005 through December 2015. Eighteen patients were included in the series, 9 adolescents and 9 adults. PDA size ranged from 1.6 mm to 11.1 mm. Within the first 24 hours post procedure, all patients had complete closure of the PDA. At the 6 month follow up, no residual shunts were detected and no significant complications were reported. The authors conclude that the case series suggest that transcatheter closure of PDA is effective and has excellent results without significant complications.

In 2017, Gruenstein et al published a prospective study on transcatheter closure of patent ductus arterious using the Amplatzer™ duct occluder II. The study evaluated the safety and efficacy of the device in 192 patients. The device was successfully implanted in 93% of patients with complete closure in 98% of successful implantations. The authors conclude that the “ADO II was safe and effective for closure of small to moderate PDAs.”

Section Summary: Transcatheter closure of PDA
Transcatheter closure of PDA is considered standard procedure for many pediatric patients and is often the treatment of choice. Surgical closure may be indicated if the defect is too large for device closure.

Summary
PFO
For individuals who have PFO and cryptogenic stroke who receive PFO closure with a transcatheter device, the evidence includes multiple randomized controlled trials (RCTs) comparing device-based PFO closure with medical therapy, systematic reviews and meta-analyses of these studies. Relevant outcomes include overall survival, morbid events, and treatment-related morbidity and mortality. The RCTs comparing PFO closure with medical management have suggested that PFO closure is more effective than medical therapy in reducing event rates. While these results were not statistically significant by intention-to-treat analyses in the first 3 trials (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 2 randomized controlled trials of PFO closure, along with 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 RCT did not demonstrate significant
improvements in migraine symptoms after PFO closure. A second RCT with blinded endpoint
evaluation did not demonstrate improvements in migraine days after PFO closure, but was
likely 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 (e.g., 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 consists only 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.

**ASD**

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 show high success rates of closure using closure
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.

**VSD**

The evidence for transcatheter closure of VSD has shown high closure rates, low procedural
mortality and positive short term results. Low complication rates and shorter hospital stays have
made this procedure more favorable over the surgical treatment when appropriate. The evidence
is sufficient to determine qualitatively that the technology results in a meaningful improvement
in the net health outcome.

**PDA**

The evidence for transcatheter occlusion of PDA has shown that this is an established procedure
and is an efficient and safe procedure. Studies have shown excellent results for short and long
term studies. Low complication rates and shorter hospital stays have made this procedure more
favorable over the surgical treatment when appropriate. The evidence is sufficient to determine
qualitatively that the technology results in a meaningful improvement in the net health outcome.
Practice Guidelines and Position Statements
PFO
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 patent foramen ovale (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 (AAN) issued updated evidence-based guidelines about 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 AAN’s 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 -1.68%, 95% CI -3.18% to -0.19%;”
- “Possibly increases the risk of new-onset AF—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 conclude:
“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
In 2014, the American Heart Association (AHA) and American Stroke Association published updated guidelines on the prevention of stroke in patients with ischemic stroke or TIA. The guidelines list the following recommendations for device-based closure for patent foramen ovale (PFO):

- “For patients with a cryptogenic ischemic stroke or TIA and a PFO without evidence for DVT, 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).”

ASD

American College of Cardiology and American Heart Association

In 2018, the AHA and ACC published guidelines for the management of adults with congenital heart disease. They recommended:

• In adults with isolated secundum ASD causing impaired functional capacity, right atrial and/or RV enlargement, and net left to-right shunt sufficiently large to cause physiological sequelae (eg, pulmonary–systemic blood flow ratio [Qp:Qs] ≥1.5:1) without cyanosis at rest or during exercise, transcatheter or surgical closure to reduce RV volume and improve exercise tolerance is recommended, provided that systolic PA pressure is less than 50% of systolic systemic pressure and pulmonary vascular resistance is less than one third of the systemic vascular resistance. (COR I, LOE B-NR)

• In asymptomatic adults with isolated secundum ASD, right atrial and RV enlargement, and net left-to-right shunt sufficiently large to cause physiological sequelae (eg, Qp:Qs 1.5:1 or greater), without cyanosis at rest or during exercise, transcatheter or surgical closure is reasonable to reduce RV volume and/or improve functional capacity, provided that systolic PA pressure is less than 50% of systemic pressure and pulmonary vascular resistance is less than one third systemic resistance. (COR IIa, LOE C-LD)

Guidelines issued by the American College of Cardiology and AHA in 2008 on the management of congenital heart disease recommend closure of an ASD by either percutaneous or surgical methods for several indications. For sinus venosus, coronary sinus, or primum ASD, however, surgical rather than percutaneous closure is recommended.

VSD

National Institute for Health and Care Excellence

In 2010, NICE issued a guideline that stated, “Current evidence on the safety and efficacy of transcatheter endovascular closure of perimembranous ventricular septal defect (VSD) is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit.”

American College of Cardiology and American Heart Association

In 2018, the AHA and ACC published guidelines for the management of adults with congenital heart disease. They did not have a specific recommendation for transcatheter VSD closure, but stated that “Transcatheter device occlusion of muscular and perimembranous VSD is feasible, and trials have demonstrated a good safety and efficacy profile.

PDA

The ACC/AHA issued guidance in 2008 regarding closure of PDA.

“Closure of a PDA either percutaneously or surgically is indicated for the following:

a. Left atrial and/or LV enlargement or PAH is present, or in the presence of net left to right shunting. (Level of Evidence C)

b. Prior endocarditis (Level of Evidence C)
U.S. Preventive Services Task Force Recommendations
Use of closure devices are not a preventive service.

Key Words:
Atrial Septal Defect, ASD, Ventricular Septal Defect, VSD, Patent Foramen Ovale, PFO, Patent Ductus Arteriosus, PDA, AMPLATZER Septal Occluder, Gore HELEX Septal Occluder, CardioSEAL Septal Occlusion System with Qwik Load, AMPLATZER Muscular VSO Occluder, CardioSEAL STAR Flex Septal Occlusion System, AMPLATZER PFO Occluder, Monodisc Occluder

Approved by Governing Bodies:
Patent Foramen Ovale
The U.S. Food and Drug Administration (FDA) has approved three 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.

In March 2018, the FDA granted an expanded indication to the Gore® Cardioform Septal Occluder to reduce the risk of recurrent ischemic stroke. It is a permanently implanted device indicated for the percutaneous, transcatheter closure of the following defects of the atrial septum:
- Patent foramen ovale to reduce the risk of recurrent ischemic stroke in patients, predominately 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.

In November 2016, the FDA approved the Amplatzer PFO Occluder (Abbott) through the premarket approval (PMA) process for the following indication:
“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.”

In 2002, 2 transcatheter devices were cleared for marketing by the U.S. Food and Drug Administration (FDA) through a humanitarian device exemption as treatment for patients with cryptogenic stroke and PFO: the CardioSEAL® Septal Occlusion System (NMT Medical; device no longer commercially available) and the Amplatzer® PFO Occluder (Amplatzer, now Abbott). Following the limited FDA approval, use of PFO closure devices increased by more than 50-fold, well in excess of the 4000 per year threshold intended under the humanitarian device exemption, prompting FDA to withdraw the humanitarian device exemption approval for these devices in 2007.
Atrial Septal Defect
Three devices have been approved by the FDA through the premarket approval process or a premarket approval supplement for transcatheter ASD closure (see Table 8) (FDA product code: MLV).

Table 8. 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</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</td>
<td>Aug 2006 (discontinued)</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>Oct 2016 (supp.)</td>
<td>• Percutaneous, transcatheter closure of ostium secundum ASDs</td>
</tr>
</tbody>
</table>

ASD: atrial septal defect; PMA: premarket approval.

Ventricular Septal Defect
AMPLATZER® Muscular VSD Occluder received FDA approval via premarket application (PMA) on September 7, 2007 for closure of complex VSD of significant size to warrant closure on patients who are considered to be at high risk for standard transatrial or transarterial surgical closure based on anatomical conditions and/or based on overall medical condition.

CardioSEAL® Septal Occlusion System with Qwik Load (Nitinol Medical Technologies, Inc.) received FDA approval via premarket application (PMA) on December 5, 2001 for closure of complex VSD; however, NMT Medical, Inc ceased operations in 2011.

Patent Ductus Arteriosus
In May 2003, the Amplatzer Duct Occluder 180° Delivery System (AGA Medical Corporation, Golden Valley, MN) received FDA approval through the PMA process for the closure of PDA.

In August 2013, the Nit-Occlud® PDA (PFM medical) received FDA approval via PMA for closure of small to moderate size PDA

Benefit Application:
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.
Current Coding:
CPT Codes:

- **93799** Unlisted cardiovascular service or procedure
- **93580** Percutaneous transcatheter closure of congenital interatrial communication (i.e., Fontan fenestration, atrial septal defect) with implant
- **93581** Percutaneous transcatheter closure of a congenital ventricular septal defect with implant
- **93582** Percutaneous transcatheter closure of patent ductus arteriosus
- **93315** Transesophageal echocardiography for congenital cardiac anomalies; including probe placement, image acquisition, interpretation and report
- **93462** Left heart catheterization by transseptal puncture through intact septum or by transapical puncture (List separately in addition to code for primary procedure).
- **93563** Injection procedure during cardiac catheterization including imaging supervision, interpretation, and report; for selective coronary angiography during congenital heart catheterization (list separately in addition to code for primary procedure).
- **93568** Injection procedure during cardiac catheterization including imaging supervision, interpretation, and report; for pulmonary angiography (list separately in addition to code for primary procedure)

References:
7. American Heart Association. Ventricular Septal Defect. www.heart.org/HEARTORG/Conditions/CongenitalHeartDefects/AboutCongenitalHeartDe


70. McDaniel N.L. Ventricular and atrial septal defects, Pediatrics in Review 2001; 22(8).


American College of Cardiology Foundation. Circulation 2009; 119; 2743-2747; originally published online May 11, 2009; DOI: 10.1161/Circulationaha.109.192272.


114. The AMPLATZER® septal occluder and delivery system, AGA Medical Corporation, Golden Valley, Minnesota.


**Policy History:**
Adopted for Blue Advantage, September 2011
Available for comment September 22 through November 7, 2011
Medical Policy Group, December 2011
Medical Policy Group, October 2013
Medical Policy Group, December 2013
Medical Policy Group, October 2014
Medical Policy Group, July 2015
Medical Policy Group, December 2015
Medical Policy Group, June 2016
Available for comment June 29 through August 13, 2016
This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.