



BlueCross BlueShield  
of Alabama

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**Name of Policy:**

**Transcatheter Closure Devices for Septal Defects**

Policy #: 218  
Category: Medical

Latest Review Date: October 2014  
Policy Grade: B

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**Background/Definitions:**

*As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.*

*The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:*

- 1. The technology must have final approval from the appropriate government regulatory bodies;*
- 2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
- 3. The technology must improve the net health outcome;*
- 4. The technology must be as beneficial as any established alternatives;*
- 5. The improvement must be attainable outside the investigational setting.*

*Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:*

- 1. In accordance with generally accepted standards of medical practice; and*
- 2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
- 3. Not primarily for the convenience of the patient, physician or other health care provider; and*
- 4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

## **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. Over the last two decades, interventional 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), patent foramen ovale (PFO), or persistent patent ductus arteriosus (PDA). 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 procedure is done in a cardiac catheterization lab.

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 many situations.

### **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. 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 patients. However, a patent foramen ovale may be detected in up to 25% of adult patients. Although common, PFOs are typically clinically insignificant and are not associated with right-to-left shunting of blood. However, they may be associated with paradoxical embolus, in which an embolus arising in the venous circulation gains access to the arterial circulation through the PFO, resulting in a stroke or transient ischemic attack. There has been interest in either open surgery or transcatheter approaches to close the PFO in patients with a history of embolic stroke of unknown cause.

### **Atrial Septal Defect (ASD)**

In contrast to PFOs, which represent 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 ovalis. Ostium primum defects lie immediately adjacent to the atrioventricular valves and are within the spectrum of atrioventricular septal defects. Primum defects occur commonly in patients with Down syndrome. Sinus venous defects occur high in the atrial septum and are frequently associated with anomalies of the pulmonary veins. Ostium secundum ASDs are the third most common form of congenital heart disorder and one of the most common congenital cardiac malformations in adults, accounting for 30% to 40% of these patients older than age 40 years. The ASD often goes unnoticed for decades because the physical signs are subtle and the clinical sequelae are mild. However, virtually all patients who survive into their sixth decade are

symptomatic; fewer than 50% of patients survive beyond age 40 to 50 years due to heart failure or pulmonary hypertension related to the left-to-right shunt. Symptoms related to ASD depend on the size of the defect and the relative diastolic filling properties of the left and right ventricles. Reduced left ventricular compliance and mitral stenosis will increase left-to-right shunting across the defect. Conditions that reduce right ventricular compliance and tricuspid stenosis will reduce left-to-right shunting or cause a right-to-left shunt. Symptoms of an ASD include exercise intolerance and dyspnea, atrial fibrillation, and, less commonly, signs of right heart failure. Patients with ASDs are also at risk for paradoxical emboli.

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 over the past 20 years; 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.

Several devices have been developed to treat PFO via a transcatheter approach, including the CardioSEAL® STARFlex™ Septal Occlusion System (NMT Medical) and the Amplatzer® PFO Occluder (Amplatzer, Inc., now St. Jude Medical, St. Paul, MN). The STARFlex system is no longer manufactured. Transcatheter PFO 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 passed via catheter to cover the ASD.

### **Ventricular Septal Defect (VSD)**

VSD is the most common congenital heart defect at birth and presents in approximately 3.0 to 3.5 infants per 1000 live births. 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 TGA). 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.

Indications for catheter device closure of VSD include residual defects after prior attempts at surgical closure, restrictive VSDs with a significant left-to-right shunt, trauma, or iatrogenic artifacts after surgical replacement of the aortic valve.

**Policy:**

**Effective for dates of service on or after April 12, 2011:**

**Transcatheter closure of atrial septal defects (ASD) with a diameter of 5mm or greater including patent foramen ovale (PFO) in adult or pediatric patients meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage 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.

**Transcatheter closure of atrial septal defects (ASD) with a diameter of less than 5mm including patent foramen ovale (PFO) in adult or pediatric patients meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage 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.

**Transcatheter closure of ASD does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage in patients with severe irreversible PAH and no evidence of a left-to-right shunt.**

**Transcatheter closure of ventricular septal defects (VSD) meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage 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)

**Transcatheter closure of patent ductus arteriosus (PDA) meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage 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 Cross and Blue Shield of Alabama 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 Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate 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:**

### **Transcatheter Device Closure of Patent Foramen Ovale (PFO)**

Conventional therapy for cryptogenic stroke consists of either 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 patent foramen ovale (PFO).

Evidence on the efficacy of PFO closure devices consists of three randomized controlled trials (RCT), 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 of percutaneous closure versus 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 also received antiplatelet therapy. Patients in the medical therapy group were treated with aspirin, warfarin, or both at the discretion of the treating physician. The primary end point was a composite of stroke/TIA at two years, death from any cause during the first 30 days after treatment, and death from neurologic causes at two years.

Of 405 patients in the closure group, 362 (89.4%) had successful implantation without procedural complications. At six months, echocardiography revealed effective closure in 315/366 patients (86.1%). 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 two-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 versus 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 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. The RESPECT trial 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 randomly assigned to PFO closure with the Amplatzer Occluder, or to medical therapy. Medical therapy consisted of one of four 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±2.0 years.

A total of nine events occurred in 499 patients assigned to closure, and 16 events occurred in 464 patients assigned to medical therapy. All of the events were nonfatal strokes. The HR for this outcome was 0.49, but this result did not reach statistical significance in 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, with a HR of 0.37 (95% CI, 0.14 to 0.96; p=0.03). On subgroup analyses, there were no statistically significant differences in outcomes, 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 and medical therapy groups (23.0% vs 21.6%, p=0.65). Major bleeding (n=2) and cardiac tamponade (n=2) were the most frequent procedure-related adverse events.

### ***PC Trial***

The PC trial was a multicenter RCT comparing PFO closure with medical therapy in 414 patients younger than 60 years of age with a prior cryptogenic stroke or peripheral embolization and a

documented PFO. Patients were recruited from 29 centers worldwide and randomly assigned to PFO closure with the Amplatzer device or 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 one 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 nine of 204 patients (3.4%) in the closure group compared with 11 of 210 patients (5.7%) in the medical group. The HR for this outcome was 0.63 (95% CI, 0.24 to 1.62;  $p=0.34$ ) on ITT analysis. On per-protocol analysis, results were similar with a hazard ratio of 0.70 (95% CI, 0.27 to 1.85;  $p=0.48$ ). 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.

### ***Systematic Reviews***

A large number of systematic reviews with meta-analysis of the three available RCTs have been published; several representative studies are summarized here. Rengifo-Moreno et al performed a combined analysis of the three RCTs previously discussed. The analysis included a total of 1150 patients randomized to PFO closure and 1153 patients randomized to medical therapy followed for a mean of 3.5 years. Two end points were included, recurrent vascular events and a combined end point of death plus recurrent vascular events. On combined analysis, there was a statistically significant reduction in recurrent vascular events with a pooled hazard ratio of 0.59 (95% CI, 0.36 to 0.97;  $p=0.04$ ). For the composite outcome of death plus recurrent vascular events, combined analysis revealed a reduction for the closure group of borderline statistical significance (HR=0.67; 95% CI, 0.12 to 1.03;  $p=0.05$ ). On subgroup analysis, there was a trend for greater benefit in patients with a substantial right-to-left shunt, although this result did not reach statistical significance (HR=0.35; 95% CI, 0.12 to 1.03;  $p=0.06$ ).

Another meta-analysis of the same three RCTs was reported by Kitsios et al. This study used recurrent stroke as the primary outcome. The authors noted that the rates of recurrent stroke varied widely across the studies, thereby raising the possibility of ascertainment bias for this outcome. On combined analysis, the difference between groups did not reach statistical significance, with a hazard ratio of 0.55 (95% CI, 0.26 to 1.18). Combined analysis was also performed for the composite outcomes reported in the trials, even though the composite outcomes were not defined in the same way. The combined result for the composite outcome was of borderline statistical significance, with a hazard ratio of 0.67 (95% CI, 0.44 to 1.00). There were no significant differences found on combined analysis of the subgroup analyses from the trials.

Meta-analyses of the same three RCTs were reported by Chen et al, Hakeem et al, Khan et al, Kwong et al, Nagaraja et al, Ntaios et al, Pandit et al, and Pineda et al. Results from these meta-analyses generally supported findings from previous meta-analyses. For the primary outcome of recurrent stroke or TIA, Chen et al found a pooled risk ratio with PFO device closure for recurrent stroke or TIA of 0.70 (95% CI, 0.47 to 1.04;  $p=0.08$ ). Hakeem et al reported a pooled

risk ratio for a composite outcome of death or recurrent stroke or TIA of 0.71 (95% CI, 0.48 to 1.06; p=0.09). Neither the Chen et al nor the Hekeem et al meta-analyses found significant differences between PFO device closure and medical management for the risk of death or adverse events. Khan et al reported pooled analyses for the primary outcome of recurrent stroke, with a pooled effect-estimated hazard ratio for the primary outcome of recurrent stroke in patients treated with PFO device closure compared with medical management of 0.67 (95% CI, 0.44 to 1.00). In analysis of only the RESPECT and PC trials, which used the Amplatzer PFO occluder device, the hazard ratio for recurrent stroke in patients treated with PFO device closure was 0.54 (95% CI, 0.29 to 1.01). Similarly, Pandit et al reported sensitivity analyses including only the RESPECT and PC trials, and found that patients who received the Amplatzer PFO occluder device had a lower risk of recurrent strokes compared with medical therapy (HR=0.44, 95% CI, 0.21 to 0.94; p=0.03). In addition to pooled estimates for the risk of the primary outcomes of recurrent stroke, TIA, or death, Kwong et al reported pooled outcomes for risk of new-onset atrial fibrillation and found that PFO closure was associated with a significantly higher incidence of new-onset atrial fibrillation compared with medical therapy (OR=3.77, 95% CI, 1.44 to 9.87; p=0.007). In the analysis by Ntaios et al, the risk of new-onset atrial fibrillation with device closure compared with medical therapy was not higher in patients who received the Amplatzer PFO Occluder device (1.28% vs 0.72%; OR=1.81; 95% CI, 0.60 to 5.42), but was higher in patients who received the STARFlex device (5.14% vs 0.64%; OR=8.30; 95% CI, 1.44 to 9.87).

Cappodano et al published an updated systematic review and meta-analysis of studies that compared outcomes associated with medical management or PFO closure among patients with cryptogenic stroke. This analysis included the three RCTs previously described, along with eleven observational studies. In the randomized trials, PFO closure was not associated with significantly lower rates of stroke than medical therapy (HR=0.62, 95% CI, 0.34 to 1.11; p=0.10) or with lower rates of TIA (HR=0.77, 95% CI, 0.46 to 1.32; p=0.34). When the analysis was restricted to the RESPECT and PC trials, which used the Amplatzer PFO occluder device, PFO closure was significantly associated with lower recurrent stroke risk (HR=0.44, 95% CI, 0.20 to 0.95; p=0.04). In the observational studies, which included 2231 patients, PFO closure was significantly associated with lower rates of stroke than medical therapy (HR=0.23, 95% CI, 0.11 to 0.49; p<0.01).

Similarly, Wolfrum et al conducted a systematic review and meta-analysis of controlled trials that compared outcomes for PFO closure with medical management among patients with cryptogenic stroke, including three RCTs and eleven nonrandomized studies. Again, among the RCTs, there was no significant improvement in stroke risk with PFO closure compared with medical management. However, among the non-RCT studies, PFO closure was associated with a reduced risk of stroke (RR=0.37; 95% CI, 0.20 to 0.67; p<0.001). In a time-to-stroke analysis that included three RCTs and two non-RCTs that had multivariable adjustments, PFO closure was associated with a borderline significant stroke risk reduction compared with medical therapy (HR=0.58; 95% CI, 0.33 to 0.99; p=0.047).

A number of systematic reviews of the observational studies have also been published, comparing outcomes of PFO closure with medical therapy. Similar to the findings reported by

Cappodano et al. these reviews are consistent in reporting that the combined rate of recurrent stroke is lower for patients treated with a closure device compared with medical therapy.

Kitsios et al published a systematic review of observational studies and the single RCT in 2012. This review included 52 single-arm studies, seven nonrandomized comparative studies, and one RCT. The combined incident rate for recurrent stroke was lower for patients treated with PFO (0.36 events/100 patient-years; 95% CI, 0.24 to 0.56) compared with patients treated medically (2.53 events/100 patient-years; 95% CI, 1.91 to 3.35). The incident rate ratio was 0.19 (95% CI, 0.18 to 0.98), which indicated an approximately 80% reduction in the rate of strokes for the closure group. This systematic review noted that the incident rate for recurrent strokes in patients treated with closure devices was much lower in the RCT compared with the observational studies, while the incident rate for recurrent stroke in patients treated medically was only slightly lower in the RCT compared with observational studies. This finding raises the possibility that ascertainment bias in the observational studies may have led to a spuriously low rate of recurrent stroke reported for patients treated with PFO closure.

Wohrle compared the results of twelve series of PFO closure (n=2016) with eight series (n=998 patients) of medical therapy. At two-year follow-up, the range of recurrent stroke was 0% to 1.6% for PFO closure and 1.8% to 9.0% for medical therapy. The combined annual incidence of stroke or TIA was 1.3% (95% CI, 1.0% to 1.8%) following PFO closure compared with 5.2% (95% CI, 4.4 to 6.2) for medical therapy. In an earlier review, Khairy et al analyzed six series of medical therapy (n=895 patients) and ten series of PFO closure (n=1355 patients). These authors noted differences in key clinical characteristics among patients in the two treatment groups. Patients treated with medical therapy were older, had a greater proportion of men, and higher rates of smoking and diabetes. Patients treated with PFO closure were more likely to have had more than one cerebrovascular event. The recurrence rate at one year ranged from 0% to 4.9% with PFO closure, compared with 3.8% to 12.0% with medical therapy. There was an estimated major complication rate (death, hemorrhage requiring transfusion, tamponade, need for surgical intervention, pulmonary embolus) for PFO closure of 1.5%, and a minor complication rate of 7.9%.

Abaci et al conducted a systematic review and meta-analysis of studies of both PFO and ASD device closure procedures. The authors reviewed 203 articles, 111 of which reported ASD closure, 61 of which reported PFO closure, and 31 of which reported both ASD and PFO closures. 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***

A number of nonrandomized comparative studies of closure devices versus medical therapy have been published. Wahl et al performed a nonrandomized comparative study using propensity matching in 308 consecutive patients with stroke or TIA that was presumed due to a PFO. A total of 103 pairs of matched patients were compared on the primary composite outcome of stroke, TIA, or peripheral embolism. After a mean of nine years of follow-up, the primary end point was reached by 11% of patients in the closure group compared with 21% in the medical therapy group (HR=0.43; 95% CI, 0.20 to 0.94; p=0.039). The main difference in the outcome measure

seemed to be driven by differences in TIA, which occurred in 5% of closure patients compared with 14% of medical therapy patients.

Windecker et al compared 150 patients who underwent PFO closure between 1994 and 2000 with 158 medically treated patients over the same time period. The choice of therapy was based on clinician and/or patient preference. The patients who received closure differed from the medically treated patients on key clinical variables, including the percentage with more than one cerebrovascular event and the size of the PFO. At four-year follow-up, there was a trend toward lower recurrence of stroke or TIA in the PFO group that did not reach statistical significance (7.8% vs 22.2%,  $p=0.08$ ).

Harrer et al reported on 124 patients with cryptogenic stroke and PFO treated over a ten-year period. Eighty-three patients were treated with medical therapy, 34 were treated with percutaneous PFO closure, and seven were treated with surgical closure. After a mean follow-up of  $52\pm 32$  months, annual recurrence rates of stroke were not different between medical therapy and PFO closure (2.1% vs 2.9%, respectively,  $p=NS$ ).

Paciaroni et al performed a prospective observational study on 238 consecutive patients with cryptogenic stroke and PFO treated at 13 Italian centers. A total of 117 patients were treated with antithrombotic therapy, and 121 patients were treated with a closure device, with the treatment decision made according to patient and physician preference. Procedure-related adverse events were reported in eight of 121 (6.8%) patients treated with a closure device (four patients with tachycardia, two patients with allergic reaction, one patient with atrial fibrillation, and one patient with sepsis). After a follow-up of two years, ten of 117 patients (8.5%) in the medical therapy group had a recurrent neurologic event (stroke or TIA), compared with 7/121 patients (5.8%,  $p=0.28$ ) in the closure device group. For recurrent stroke, the difference between the groups was statistically significant, with 8/117 (6.8%) in the medical therapy group compared with 1/121 (0.8%,  $p=0.018$ ) in the closure device group. On multivariate analysis, treatment with a closure device was a significant predictor of a reduced stroke rate (OR=0.1; 95% CI, 0.0 to 1.0;  $p=0.05$ ) but was not a significant predictor of the combined outcome of stroke or TIA (OR=0.1; 95% CI, 0.02 to 1.5;  $p=0.10$ ).

Alushi et al 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 versus device closure was determined by the treating physician and patient. Percutaneous device closure was preferably 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.

### ***Single-Arm Case Series***

Many case series report on outcomes of PFO closure in an uncontrolled fashion; some examples of these series are as follows. Cifarelli et al reported on 202 consecutive patients treated with a closure device for secondary prevention of thromboembolism. They reported no periprocedural deaths or strokes, and one case of device migration 24 hours after placement. Recurrence-free survival was reported in 99% of patients 55 years of age or younger and 84% in patients older than age 55 years. Recurrence of thromboembolism was associated with a septal aneurysm, with all patients who experienced recurrence of thromboembolism having a septal aneurysm. Onorato et al reported on 256 patients with paradoxical embolism who received transcatheter closure of PFO. The authors reported a 98.1% full closure rate of the PFO and no neurologic events at a mean follow-up of 19 months. Martin et al also reported on a study of 110 patients with paradoxical embolism who received transcatheter closure of PFO. While the full closure rate of PFO was 71% at two years, only two patients had experienced a recurrent neurologic event. Windecker et al reported on a case series of 80 patients with a history of at least one paradoxical embolic event and who underwent closure of a PFO with a variety of transcatheter devices. Patients were followed up for a mean of 1.6 years. During five years of follow-up, the risk of an embolic event (TIA, stroke, peripheral embolism) was 3.4%, considered comparable with either medical therapy with anticoagulation or open surgical approaches. The presence of a postprocedural shunt was a predictor of recurrent thromboembolic events, emphasizing the importance of complete closure. Butera et al reported results from a registry that included 122 consecutive patients who underwent PFO closure with the Gore Septal Occluder device, 110 of whom underwent closure for previous stroke or TIA, and 12 of whom underwent closure for a history of migraines. During a median follow-up of nine months (range, 1-18 months), seven patients experienced atrial arrhythmias, four of whom required medical treatment. On chest radiograph, two patients were found to have evidence of wire fractures in the device; the devices were not removed and the patients had no evidence of further problems from the wire fractures at 12 months of follow up. Three patients experienced neurologic problems, one of which was recurrent migraines. None of these patients were found to have residual shunt or intracardiac or device thrombi.

Other single-arm studies of transcatheter PFO closure in patients presenting with stroke or TIA and PFO generally report high rates of freedom from embolic events.

No clinical trials focus specifically on patients who have failed medical therapy, as defined by recurrent stroke or TIA while on therapy. Many of the published studies include both patients with first cryptogenic stroke, as well as patients with recurrent stroke or TIA, and generally do not analyze 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.

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

The consequence of a left-to-right shunt across an ASD is right ventricular (RV) volume overload and pulmonary over-circulation. Large atrial shunts lead to symptoms from excess pulmonary blood flow and right-sided heart failure, including frequent pulmonary infections, fatigue, exercise intolerance, and palpitations. Atrial arrhythmias (atrial flutter, atrial fibrillation

and sick sinus syndrome) are a common result of long-standing right-sided heart volume and pressure over-load.

Small ASDs with a diameter of less than 5mm and no evidence of RV volume overload do not impact the natural history of the patient and thus may not require closure unless associated with paradoxical embolism. Larger defects with evidence of right ventricular overload on echocardiography usually only cause symptoms in the third decade of life and closure is indicated to prevent long-term complications.

### **Overview of the Evidence**

Evidence supporting the efficacy of devices for closure of ASD consists of nonrandomized comparison studies and case series studies. However, in contrast to the situation of PFO and cryptogenic stroke, the relationship of 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; 423 patients received 433 devices. This study was subsequently published with slightly different numbers, 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 systematic review and 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, 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 showed

identical 98% success rate in both treatment groups. A nonrandomized comparative analysis by Kotowycz et al 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). Xu et al 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. Fischer et al 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. Other smaller studies have reported favorable results for transcatheter closure of ASD. In Du et al, 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 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 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 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 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 reported improvements in echocardiographic parameters in a series of 25 pediatric patients (mean age, 9.02) who underwent successful transcatheter closure of secundum ASD.

In summary, for patients with an ASD, nonrandomized comparison studies and single arm case series show high success rates of closure using closure 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.

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

The 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<sup>®</sup> 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.

### **U.S. Preventive Services Task Force Recommendations**

Use of closure devices for PFO or ASDs is 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

**Approved by Governing Bodies:**

AMPLATZER<sup>®</sup> Septal Occluder received FDA approval via premarket application (PMA) on December 6, 2001 for the occlusion of ASD in the secundum position.

Gore HELEX<sup>®</sup> Septal Occluder received FDA approval via premarket application (PMA) on August 11, 2006, for the percutaneous, transcatheter closure of ostium secundum ASD.

CardioSEAL<sup>®</sup> Septal Occlusion System with Qwik Load received FDA approval via premarket application (PMA) on December 5, 2001 for closure of complex VSD.

AMPLATZER<sup>®</sup> Muscular VSD Occluder received FDA approval via premarket application (PMA) on September 7, 2007 for closure of complex VSD.

CardioSEAL<sup>®</sup> STARFlex Septal Occlusion System was granted FDA Humanitarian Device Exemption (HDE) on February 1, 2000. This was withdrawn August 16, 2006; effective October 31, 2006. The device may be available through an FDA approved Investigational Device Exemption (IDE) at some health care facilities.

AMPLATZER<sup>®</sup> PFO Occluder was granted FDA Humanitarian Device Exemption (HDE) on April 5, 2002. This was withdrawn August 16, 2006; effective October 31, 2006. The device may be available through an FDA approved Investigational Device Exemption (IDE) at some health care facilities.

**Benefit Application:**

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply

FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

**Current Coding:**

CPT Codes:

- 93799** Unlisted cardiovascular service or procedure
- 93533** Combined right heart catheterization and transseptal left heart catheterization through existing septal opening, with or without retrograde left heart catheterization, for congenital cardiac anomalies
- 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  
(Effective 01/01/2014)
- 93315** Transesophageal echocardiography for congenital cardiac anomalies; including probe placement, image acquisition, interpretation and report
- 93452** Left heart catheterization including intraprocedural injection(s) for left ventriculography, imaging supervision and interpretation, when performed.
- 93453** Combined right and left heart catheterization including intraprocedural injection(s) for left ventriculography, imaging supervision and interpretation, when performed.
- 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)
- \*99354** Prolonged physician service in the office or other outpatient setting requiring direct (face-to-face) patient contact beyond the usual service; first hour (List separately in addition to code for office or other outpatient evaluation and management service
- \*99355** ;each additional 30 minutes (List separately in addition to code for office or other outpatient evaluation and management service)
- \*99356** Prolonged service in the inpatient setting, unit/floor time beyond the usual service; first hour (List separately in addition to code for inpatient evaluation and management service)
- \*99357** ;each additional 30 minutes (List separately in addition to code for prolonged service)

\* May be used in addition to 93315 to reflect the extended time spent on TEE (beyond the usual 30 minutes) during insertion of **transcatheter closure device for treatment of patent foramen ovale (PFO) defects**. For example, for a 90-minute procedure in the inpatient setting, the TEE should be billed using 93315 and 99356, not 93315, 99356, and 99357.

### **References:**

1. Abaci A, Unlu S, Alsancak Y, et al. Short and long term complications of device closure of atrial septal defect and patent foramen ovale: meta-analysis of 28,142 patients from 203 studies. Catheter Cardiovasc Interv. Dec 1 2013;82(7):1123-1138.

2. Albers GW, Amarenco P, Easton D, et al. Antithrombotic and thrombolytic therapy for ischemic stroke: American College of Chest physicians evidence-based clinical practice guidelines (8<sup>th</sup> edition). *Chest* 2008; 133; 630S-669S DOI 10.1378/chest.08-0720.
3. Alushi B, Biasco L, Orzan F, et al. Patent foramen ovale treatment strategy: an Italian large prospective study. *J Cardiovasc Med (Hagerstown)*. Jun 27 2014.
4. American College of Chest Physicians. Comparing outcomes of medical management and percutaneous closure in patients with patent foramen ovale and cryptogenic stroke. *Chest* 2008; [journal.publications.chestnet.org/article.aspx?articleid=1094512&resultClick=3](http://journal.publications.chestnet.org/article.aspx?articleid=1094512&resultClick=3).
5. Berger F., Ewert P., et al. Percutaneous closure of large atrial septal defects with the Amplatzer septal occluder: technical overkill or recommendable alternative treatment? *J of Interventional Cardio*, 2001; 14:1.
6. Berger F, Vogel M, et al. Comparison of results and complications of surgical and Amplatzer device closure of atrial septal defects. *J Thorac Cardiovasc Surg* 1999; 118(4):674-8.
7. Biasco L, Infantino V, Orzan F, et al. Impact of transcatheter closure of patent foramen ovale in the evolution of migraine and role of residual shunt. *J Cardiol*. Apr 5 2014.
8. Brochu MC, Baril JF, et al. Improvement in exercise capacity in asymptomatic and mildly symptomatic adults after atrial septal defect percutaneous closure. *Circulation* 2002; 106(14):1821-6.
9. Butera G., Bini M.R., et al. Transcatheter closure of patent foramen ovale in patients with cryptogenic stroke, *Ital Heart J* 2001; 2 (2): 115-118.
10. Butera G, Biondi-Zoccai G, Sangiorgi G, et al. Percutaneous versus surgical closure of secundum atrial septal defects: a systematic review and meta-analysis of currently available clinical evidence. *EuroIntervention*. Jul 2011; 7(3):377-385.
11. Butera G, Saracino A, Danna P, et al. Transcatheter PFO closure with GORE((R)) septal occluder: early and mid-term clinical results. *Catheter Cardiovasc Interv*. Nov 15 2013; 82(6):944-949.
12. Cao Q.L., Du Z.D., et al. Immediate and six-month results of the profile of the Amplatzer septal occluder as assessed by transesophageal echocardiography, *American Journal of Cardiology*, 2001; 88:1.
13. Capodanno D, Milazzo G, Vitale L, et al. Updating the evidence on patent foramen ovale closure versus medical therapy in patients with cryptogenic stroke: a systematic review and comprehensive meta-analysis of 2,303 patients from three randomised trials and 2,231 patients from 11 observational studies. *EuroIntervention*. Mar 20 2014; 9(11):1342-1349.
14. Carroll JD, Saver JL, Thaler DE et al. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. *N Engl J Med* 2013; 368(12):1092-100.
15. Chen L, Luo S, Yan L, et al. A systematic review of closure versus medical therapy for preventing recurrent stroke in patients with patent foramen ovale and cryptogenic stroke or transient ischemic attack. *J Neurol Sci*. Feb 15 2014;337(1-2):3-7.
16. Cifarelli A, Musto C, Parma A, et al. Long-term outcome of transcatheter patent foramen ovale closure in patients with paradoxical embolism. *Int J Cardiol*. Jun 11 2010; 141(3):304-310.
17. Cotran R.S., Kumar V., and Collins T. Robbins pathologic basis of disease, W. B. Saunders Co. Philadelphia, 1999.

18. Demkow M., Ruzyllo W., et al. Transvenous closure of moderate and large secundum atrial septal defects in adults using the Amplatzer septal occluder, *Catheterization and Cardiovascular Interventions*, 2001; 52:188-193.
19. Dowson A, Mullen MJ, Peatfield R, et al. Migraine Intervention With STARFlex Technology (MIST) trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache. *Circulation*. Mar 18 2008; 117(11):1397-1404.
20. Du ZD, Hijazi ZM, et al. Comparison between transcatheter and surgical closure of secundum atrial septal defect in children and adults: results of a multicenter nonrandomized trial. *J Am Coll Cardiol* 2002; 39(11):1836-44.
21. Du ZD, Koenig P, et al. Comparison of transcatheter closure of secundum atrial septal defect using the Amplatzer septal occluder associated with deficient versus sufficient rims. *Am J Cardiol* 2002; 90(8):865-9.
22. Eeckhout E, Martin S, Delabays A, et al. Very long-term follow-up after percutaneous closure of patent foramen ovale. *EuroIntervention*. Jan 17 2014.
23. Fischer G, Stieh J, et al. Experience with transcatheter closure of secundum atrial septal defects using the Amplatzer septal occluder: a single centre study in 236 consecutive patients. *Heart* 2003; 89(2):199-204.
24. Formigari R., DiDonato R.M., et al. Minimally invasive or interventional repair of atrial septal defects in children: experience in 171 cases and comparison with conventional strategies, *Journal of American College of Cardiology*, 2001; 37:6.
25. Furlan AJ, Reisman M, Massaro J, et al. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. *N Engl J Med*. Mar 15 2012; 366(11):991-999.
26. Grohmann J, Hohn R, Fleck T, et al. Transcatheter closure of atrial septal defects in children and adolescents: Single-center experience with the GORE septal occluder. *Catheter Cardiovasc Interv*. Mar 24 2014.
27. Hakeem A, Marmagkiolis K, Hacioglu Y, et al. Safety and efficacy of device closure for patent foramen ovale for secondary prevention of neurological events: Comprehensive systematic review and meta-analysis of randomized controlled trials. *Cardiovasc Revasc Med*. Nov-Dec 2013; 14(6):349-355.
28. Handke M, Harloff A, et al. Patent foramen ovale and cryptogenic stroke in older patients. *NEJM*, November 2007; 357(22): 2262-2268.
29. Harrer JU, Wessels T, et al. Stroke recurrence and its prevention in patients with patent foramen ovale. *Can J Neurol Sci*. 2006 Feb; 33(1):39-47.
30. Homma S., Sacco R.L., et al. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study, *Circulation* 2002; 105(22): 2625-31.
31. Hung J., Ladzbert M.J., Jenkins K.J., et al. Closure of patent foramen ovale or paradoxical emboli: intermediate-term risk of recurrent neurological events following transcatheter device placement, *J Am College Cardio* 2000; 35: 1311-1316.
32. Inglessis I, Elmariah S, Rengifo-Moreno PA, et al. Long-term experience and outcomes with transcatheter closure of patent foramen ovale. *JACC Cardiovasc Interv*. Nov 2013; 6(11):1176-1183.
33. Instruction for Use: Amplatzer® Septal Occluder System. In: AGA Medical Corporation; Golden Valley M, ed.

34. Iverek H.R., Bone I., Lees K.R. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies, *Neurology* 2000; 55(8).
35. Khairy P, O'Donnell CP, Landzberg MJ. Transcatheter closure versus medical therapy of patent foramen ovale and presumed paradoxical thromboemboli: a systematic review. *Ann Intern Med.* 2003 Nov 4; 139(9):753-60.
36. Khan AR, Bin Abdulhak AA, Sheikh MA, et al. Device closure of patent foramen ovale versus medical therapy in cryptogenic stroke: a systematic review and meta-analysis. *JACC Cardiovasc Interv.* Dec 2013; 6(12):1316-1323.
37. Kitsios GD, Dahabreh IJ, Abu Dabrh AM, et al. Patent foramen ovale closure and medical treatments for secondary stroke prevention: a systematic review of observational and randomized evidence. *Stroke.* Feb 2012; 43(2):422-431.
38. Kitsios GD, Thaler DE, Kent DM. Potentially large yet uncertain benefits: a meta-analysis of patent foramen ovale closure trials. *Stroke* 2013; 44(9):2640-3.
39. Kotowycz MA, Therrien J, Ionescu-Ittu R, et al. Long-term outcomes after surgical versus transcatheter closure of atrial septal defects in adults. *JACC Cardiovasc Interv.* May 2013; 6(5):497-503.
40. Kwong JS, Lam YY, Yu CM. Percutaneous closure of patent foramen ovale for cryptogenic stroke: a meta-analysis of randomized controlled trials. *Int J Cardiol.* Oct 9 2013; 168(4):4132-4138.
41. Lip PZ, Lip GY. Patent foramen ovale and migraine attacks: a systematic review. *Am J Med.* May 2014; 127(5):411-420.
42. Marshall A.C. and Lock J.E. Valvular and congenital heart disease: structural and compliant anatomy of the patent foramen ovale in patients undergoing transcatheter closure, *American Heart Journal* 2000; 140(2).
43. Martin F, Sanchez PL, Doherty E, et al. Percutaneous transcatheter closure of patent foramen ovale in patients with paradoxical embolism. *Circulation.* 2002 Aug 27; 106(9):1121-6.
44. McDaniel N.L. Ventricular and atrial septal defects, *Pediatrics in Review* 2001; 22(8).
45. Meier B, Kalesan B, Mattle HP et al. Percutaneous closure of patent foramen ovale in cryptogenic embolism. *N Engl J Med* 2013; 368(12):1083-91.
46. Messe Sr, Silverman IE, Kizer JR, et al. Practice parameter: recurrent stroke with patent foramen ovale and atrial septal aneurysm: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2004 Apr 13; 62(7):1042-50.
47. Mohr J.P., Thompson J.L.P., et al. A comparison of Warfarin and aspirin for the prevention of recurrent ischemic stroke, *N Engl J Med* 2001; 345(20): 1444-1451.
48. Nagaraja V, Raval J, Eslick GD, et al. Is transcatheter closure better than medical therapy for cryptogenic stroke with patent foramen ovale? A meta-analysis of randomized trials. *Heart Lung Circ.* Nov 2013; 22(11):903-909.
49. Nagpal SV, Lerakis S, Flueckiger PB, et al. Long-term outcomes after percutaneous patent foramen ovale closure. *Am J Med Sci.* Sep 2013;346(3):181-186.
50. Nedeltchev K., Arnold M., et al. Outcome of patient with cryptogenic stroke and patent foramen ovale, *J Neurol Neurosurg Psychiatry* 2002; 27: 347-350.
51. Ntaios G, Papavasileiou V, Makaritsis K, et al. PFO closure vs. medical therapy in cryptogenic stroke or transient ischemic attack: a systematic review and meta-analysis. *Int J Cardiol.* Oct 30 2013; 169(2):101-105.

52. Nyboe C, Hjordtal VE, Nielsen-Kudsk JE. First experiences with the GORE((R)) Septal Occluder in children and adults with atrial septal defects. Catheter Cardiovasc Interv. Nov 15 2013; 82(6):929-934.
53. O’Gara PT, Messe SR, et al. Percutaneous device closure of patent foramen ovale for secondary stroke prevention: A call for completion of randomized clinical trials: a science advisory from the American Heart Association/American Stroke Association and the American College of Cardiology Foundation. *Circulation* 2009;119:2743-2747;originally published online May 11, 2009;DOI: 10.1161/Circulationaha.109.192272.
54. Oho S, Ishizawa A, et al. Transcatheter closure of atrial septal defects with the Amplatzer septal occluder – a Japanese clinical trial. *Circ J* 2002; 66(9):791-4.
55. Onorato E, Melzi G, et al. Patent foramen ovale with paradoxical embolism: mid-term results of transcatheter closure in 256 patients. *J Interv Cardiol.* 2003 Feb; 16(1):43-50.
56. Paciaroni M, Agnelli G, Bertolini A, et al. Risk of recurrent cerebrovascular events in patients with cryptogenic stroke or transient ischemic attack and patent foramen ovale: the FORI (Foramen Ovale Registro Italiano) study. Cerebrovasc Dis. 2011; 31(2):109-116.
57. Pandit A, Aryal MR, Pandit AA, et al. Amplatzer PFO occluder device may prevent recurrent stroke in patients with patent foramen ovale and cryptogenic stroke: a meta-analysis of randomised trials. Heart Lung Circ. Apr 2014; 23(4):303-308.
58. Pineda AM, Nascimento FO, Yang SC, et al. A meta-analysis of transcatheter closure of patent foramen ovale versus medical therapy for prevention of recurrent thromboembolic events in patients with cryptogenic cerebrovascular events. Catheter Cardiovasc Interv. Nov 15 2013; 82(6):968-975.
59. Podnar T., Martanovic P., et al. Morphological variations of secundum-type atrial septal defects: feasibility for percutaneous closure using Amplatzer septal occluders, *Catheterization and Cardiovascular Interventions*, 2001; 53:386-391.
60. Rengifo-Moreno P, Palacios IF, Junpaparp R et al. Patent foramen ovale transcatheter closure vs. medical therapy on recurrent vascular events: a systematic review and meta-analysis of randomized controlled trials. *Eur Heart J* 2013.
61. Rhodes JF, Jr., Goble J. Combined prospective United States clinical study data for the GORE((R)) HELEX((R)) septal occluder device. Catheter Cardiovasc Interv. May 1 2014; 83(6):944-952.
62. Sacco RL, Adams R, et al. Guidelines for Prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke:co-sponsored by the Council on Cardiovascular Radiology and Intervention. *Stroke* 2006; 37; 577-617.
63. Slottow TL, Steinberg DH, Waksman R. Overview of the 2007 Food and Drug Administration Circulatory System Devices Panel meeting on patent foramen ovale closure devices. Circulation. Aug 7 2007; 116(6):677-682.
64. Suchon E, Piculewicz M, et al. Transcatheter closure as an alternative and equivalent method to the surgical treatment of atrial septal defect in adults: comparison of early and late results. *Med Sci Monit* 2009; 15(12):CR612-7.
65. Taeed R., Shim D., et al. One-year follow-up of the Amplatzer device to close atrial septal defects, *American Journal of Cardiology*, 2001; 84:1.
66. The AMPLATZER® septal occluder and delivery system, AGA Medical Corporation, Golden Valley, Minnesota.

67. Thomson JD, Hildick-Smith D, Clift P, et al. Patent foramen ovale closure with the gore septal occluder: initial UK experience. Catheter Cardiovasc Interv. Feb 15 2014; 83(3):467-473.
68. Tobis J, Shenoda M. Percutaneous Treatment of Patent Foramen Ovale and Atrial Septal Defects. J Am Coll Cardiol. 2012; 60(18):1722-1732.
69. Wahl A, Juni P, Mono ML, et al. Long-term propensity score-matched comparison of percutaneous closure of patent foramen ovale with medical treatment after paradoxical embolism. Circulation. Feb 14 2012;125(6):803-812.
70. Wallenborn J, Bertog SC, Franke J, et al. Recurrent events after percutaneous closure of patent foramen ovale. Catheter Cardiovasc Interv. Oct 1 2013; 82(4):541-546.
71. Warnes CA, Williams RG, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults with Congenital Heart Disease). Circulation 2008; 118(23):e714-833.
72. Wein T.H., Bornstein N.M. Stroke prevention: cardiac and carotid-related stroke, Neurologic Clinics 2000; 18(2).
73. Whitlock RP, Sun JC, Frenes SE, et al. Antithrombotic and thrombolytic therapy for valvular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. Feb 2012; 141(2 Suppl):e576S-600S.
74. Windecker S, Wahl A, et al. Comparison of medical treatment with percutaneous closure of patent foramen ovale in patients with cryptogenic stroke. J Am Coll Cardiol. 2004 Aug 18; 44(4):750-8.
75. Windecker S., Wahl A., et al. Percutaneous closure of patent foramen ovale in patients with paradoxical embolism, Circulation 2000; 101:893-898.
76. Wohrle J. Closure of patent foramen ovale after cryptogenic stroke. Lancet. 2006 Jul 29; 368(9533):350-2.
77. Wolfrum M, Froehlich GM, Knapp G, et al. Stroke prevention by percutaneous closure of patent foramen ovale: a systematic review and meta-analysis. Heart. Mar 2014;100(5):389-395.
78. Xu XD, Liu SX, Zhao XX, et al. Comparison of Medium-term Results of Transcatheter Correction Versus Surgical Treatment for Secundum Type Atrial Septal Defect Combined With Pulmonary Valve Stenosis. Int Heart J. Jul 10 2014; 55(4):326-330.
79. Yilmazer MM, Guven B, Vupa-Cilengiroglu O, et al. Improvement in cardiac structure and functions early after transcatheter closure of secundum atrial septal defect in children and adolescents. Turk J Pediatr. Jul-Aug 2013; 55(4):401-410.

### **Policy History:**

Medical Policy Group, September 2011 (2)

Medical Policy Administration Committee, April 2011

Available for comment September 22 through November 7, 2011

Medical Policy Group, December 2011 (1): 2012 Code Updates; verbiage change on codes 99354, 99355, 99356, and 99357

Medical Policy Panel, September 2013

Medical Policy Group, October 2013 **(2)**: No change to policy statement. Key Points and References updated to reflect information from latest literature search.

Medical Policy Group, December 2013 **(3)**: 2014 Coding Update – added new code 93582 to current coding (effective 01/01/14); added key words Patent Ductus Arteriosus and PDA

Medical Policy Panel, September 2014

Medical Policy Group, October 2014 **(3)**: 2014 Updates to Description, Key Points & References; no change in policy statement

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*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.*