Clinical Policy Bulletin:  
Transcatheter Closure of Septal Defects  

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Policy

I. Atrial Septal Defects

Aetna considers transcatheter closure of atrial septal defects (ASDs) using Food and Drug Administration (FDA)-approved closure devices (e.g., the Gore Helex Septal Occluder) medically necessary in pediatric or adult members for either of the following indications:

A. For the closure of the fenestration in individuals who have undergone a fenestrated Fontan procedure; or
B. For the occlusion of ASDs in secundum position.

Aetna considers transcatheter closure of ASDs experimental and investigational for migraine prophylaxis and for all other indications (e.g., coronary sinus atrial septal defect, ostium primum atrial septal defect, and sinus venosus atrial septal defect; not an all-inclusive list) because its effectiveness for these indications has not been established.

II. Ventricular Septal Defects

Aetna considers transcatheter closure of ventricular septal defects (VSDs) using FDA-approved closure devices medically necessary for complex VSDs in pediatric or adult members who are considered to be at high-risk for standard transatrial or transarterial surgical closure.

Aetna considers transcatheter closure of VSDs experimental and investigational for all other indications because its effectiveness for indications other than the one listed above has not been established.

III. Patent Foramen Ovale

Aetna considers transcatheter occlusion of patent foramen ovale (PFO) experimental and investigational for persons with cryptogenic stroke, transient ischemic attacks, or arterial emboli due to presumed paradoxical embolism through a PFO.

Aetna considers transcatheter closure of PFO experimental and investigational for migraine prophylaxis, stroke prevention, and for all other indications (e.g., orthodeoxia-platypnea and unexplained oxygen desaturation) because its effectiveness for these indications has not been established.
IV. **Patent Ductus Arteriosus**

Aetna considers transcatheter occlusion of patent ductus arteriosus (PDA) medically necessary using the Amplatzer duct occluder or other closure devices approved by the FDA for this indication.

Aetna considers closure devices not approved by the FDA for transcatheter occlusion of PDA experimental and investigational for this indication.

V. **Transmyocardial Transcatheter/Perventricular Closure of Septal Defects**

Aetna considers transmyocardial transcatheter/perventricular closure of ventricular septal defects with implants experimental and investigational because of an absence of published literature on the effectiveness of this approach.

**Background**

Despite the success of standard operative repair with its mortality rate of less than 1%, the risks and morbidity of open-heart surgery remain. Over the last 2 decades, interventional cardiac catheterization techniques have evolved to a point where percutaneous transcatheter devices can be offered as an alternative to their open counterparts to repair certain cardiac defects, particularly in younger patients. All of the devices require transesophageal echocardiographic guidance for optimal placement, and most procedures are performed under general anesthesia with transesophageal echocardiographic and/or fluoroscopic guidance to verify optimal placement, and to access the immediate results of the procedure.

In recent years, many different systems for transcatheter closure of an atrial septal defect (ASD) have been developed and tested. Initially, acute failures and complications were primarily due to poor selection of cases with too large a defect or selection of a defective device. Over the years, stricter implantation and patient selection criteria have lead to more successful deployment of the devices in stable positions without inducing functional abnormality or anatomical obstruction. Of utmost importance in choosing appropriate patients is the echocardiographic morphology of the ASD with reference to size, position in the interatrial septum, proximity to surrounding structures, and adequacy of septal rim. Equally essential is accurate assessment of the stretched diameter of the inter-atrial communication by balloon sizing during catheterization to determine proper size of the ASD closure device. Many of the ASD closure devices initially approved by the Food and Drug Administration (FDA) for investigational use have been withdrawn from the market due to complications (e.g., Clamshell double-umbrella device, and Angel Wing). The most frequent complications include device embolization and thrombus formation. Some ASD closure devices have been modified a number of times to improve technical feasibility, safety, and effectiveness. Devices currently under investigation for ASD closure include the Buttoned Device, CardioSEAL Septal Occluder, StarFlex, Atrial Septal Defect Occluding System (ASDOS), Guardian Angel, and the Helex.

The Amplatzer septal occluder (AGA Medical Corp., Golden Valley, MN) received FDA approval in 2001. It is a self-centering device that consists of 2 round disks made of Nitinol wire mesh and linked together by a short connecting waist. Studies have reported short-term results confirming an early high occlusion rate with no major complications when strict implantation and patient selection criteria are used. According to the FDA approval, the Amplatzer septal occluder is indicated for ASD closure in individuals who have echocardiographic evidence of ostium secundum ASD and clinical evidence of right ventricular (RV) volume overload (i.e., 1.5:1 degree to left to right shunt or RV enlargement). The device is also indicated in patients who have undergone a fenestrated Fontan procedure and who now require closure of the fenestration.
Du et al (2002) compared the safety, effectiveness and clinical utility of the Amplatzer septal occluder for closure of secundum ASD with surgical closure. A multi-center, non-randomized concurrent study was performed in 29 pediatric cardiology centers from March 1998 to March 2000. Patients were assigned to either the device or surgical closure group according to the patient’s option. Baseline physical examinations and echocardiography were performed pre-procedure and at follow-up (6 and 12 months for device group, 12 months for surgical group). A total of 442 patients were in the group undergoing device closure, whereas 154 patients were in the surgical group. The median age was 9.8 years for the device group and 4.1 years for the surgical group (p < 0.001). In the device group, 395 (89.4 %) patients had a single ASD; in the surgical group, 124 (80.5 %) (p = 0.008) had a single ASD. The size of the primary ASD was 13.3 +/- 5.4 mm for the device group and 14.2 +/- 6.3 mm for the surgery group (p = 0.099). The procedural attempt success rate was 95.7 % for the device group and 100 % for the surgical group (p = 0.006).

The CardioSEAL Septal Occlusion System (Nitinol Medical Technologies, Inc., Boston, MA) is the second generation of the Clamshell occluder. It received FDA approval for use in patients with complex ventricular septal defect (VSD) of significant size to warrant closure and who are considered to be at high risk for standard transatrial or transarterial surgical closure based on anatomical conditions and/or overall medical condition. High-risk anatomical factors for transatrial or transarterial surgical closure include the following:

- Left ventriculotomy or an extensive right ventriculotomy is required
- Multiple apical and/or anterior muscular VSDs (“Swiss Cheese Septum”)
- Posterior apical VSDs covered by trabeculae
- Previous VSD closure that failed

The CardioSEAL high-risk study is a prospective, multi-center 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 co-morbid illness within the treated group, 72 % of the patients improved clinically at 6 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 6 months after the procedure. The investigators concluded that the CardioSEAL Septal Occlusion System is safe and effective in the intended patient population.

The FDA has granted humanitarian device exemptions to two transcatheter occlusion devices for repair of patent foramen ovale (PFO): the CardioSEAL Septal Occlusion System and the Amplatzer Patent Foramen Ovale Occluder. The FDA has allowed the use of these devices for closure of PFO in persons with recurrent cryptogenic stroke due to presumed paradoxical embolism through a PFO and who have failed conventional drug therapy.

At present, it should be noted that none of these afore-mentioned technologies is widely used and few devices have undergone extensive clinical trials. Many of these devices remain investigational and large-scale studies are underway to collect sufficient long-term data to validate these various applications as viable alternatives to surgery in the initial treatment of selected patients. The FDA is requiring that both Nitinol Medical Technologies, Inc and AGA Medical Corp. continue to study their products over the next 5 years to better assess their long-term safety and effectiveness (Meadows, 2002).

A randomized controlled clinical trial funded by St. Jude Medical found that closure of a PFO for secondary prevention of cryptogenic embolism did not result in a significant reduction in
the risk of recurrent embolic events or death as compared with medical therapy. Meier et al (2013) investigated whether closure is superior to medical therapy. The investigators performed a multi-center, superiority trial in 29 centers in Europe, Canada, Brazil, and Australia in which the assessors of end-points were unaware of the study-group assignments. Patients with a PFO and ischemic stroke, transient ischemic attack (TIA), or a peripheral thrombo-embolic event were randomly assigned to undergo closure of the PFO with the Amplatzer PFO occluder or to receive medical therapy. The primary end-point was a composite of death, nonfatal stroke, TIA, or peripheral embolism. Analysis was performed on data for the intention-to-treat population. The mean duration of follow-up was 4.1 years in the closure group and 4.0 years in the medical-therapy group. The primary end-point occurred in 7 of the 204 patients (3.4 %) in the closure group and in 11 of the 210 patients (5.2 %) in the medical-therapy group (hazard ratio [HR] for closure versus medical therapy, 0.63; 95 % confidence interval [CI]: 0.24 to 1.62; p = 0.34). Non-fatal stroke occurred in 1 patient (0.5 %) in the closure group and 5 patients (2.4 %) in the medical-therapy group (HR, 0.20; 95 % CI: 0.02 to 1.72; p = 0.14), and TIA occurred in 5 patients (2.5 %) and 7 patients (3.3 %), respectively (HR, 0.71; 95 % CI: 0.23 to 2.24; p = 0.56). The authors concluded that closure of a PFO for secondary prevention of cryptogenic embolism did not result in a significant reduction in the risk of recurrent embolic events or death as compared with medical therapy.

A randomized, controlled clinical trial funded by NMT Medical (Furlan et al, 2012) found that, in patients with cryptogenic stroke or TIA who had a PFO, closure with a device did not offer a greater benefit than medical therapy alone for the prevention of recurrent stroke or TIA. The investigators conducted a multi-center, randomized, open-label trial of closure with a percutaneous device, as compared with medical therapy alone, in patients between 18 and 60 years of age who presented with a cryptogenic stroke or TIA and had a PFO. The primary end-point was a composite of stroke or TIA during 2 years of follow-up, death from any cause during the first 30 days, or death from neurologic causes between 31 days and 2 years. A total of 909 patients were enrolled in the trial. The cumulative incidence (Kaplan-Meier estimate) of the primary end-point was 5.5 % in the closure group (447 patients) as compared with 6.8 % in the medical-therapy group (462 patients) (adjusted HR, 0.78; 95 % CI: 0.45 to 1.35; p = 0.37). The respective rates were 2.9 % and 3.1 % for stroke (p = 0.79) and 3.1 % and 4.1 % for TIA (p = 0.44). No deaths occurred by 30 days in either group, and there were no deaths from neurologic causes during the 2-year follow-up period. A cause other than paradoxical embolism was usually apparent in patients with recurrent neurologic events.

In the primary intention-to-treat analysis, a randomized controlled clinical trial demonstrated no significant benefit associated with closure of a PFO in adults who had had a cryptogenic ischemic stroke. Carroll et al (2013) conducted a trial to evaluate whether closure is superior to medical therapy alone in preventing recurrent ischemic stroke or early death in patients 18 to 60 years of age. In this prospective, multi-center, randomized, event-driven trial, investigators randomly assigned patients, in a 1:1 ratio, to medical therapy alone or closure of the PFO. The primary results of the trial were analyzed when the target of 25 primary end-point events had been observed and adjudicated. The investigators enrolled 980 patients (mean age of 45.9 years) at 69 sites. The medical-therapy group received 1 or more anti-platelet medications (74.8 %) or warfarin (25.2 %). Treatment exposure between the 2 groups was unequal (1,375 patient-years in the closure group versus 1,184 patient-years in the medical-therapy group, p = 0.009) owing to a higher drop-out rate in the medical-therapy group. In the intention-to-treat cohort, 9 patients in the closure group and 16 in the medical-therapy group had a recurrence of stroke (HR with closure, 0.49; 95 % CI: 0.22 to 1.11; p = 0.08). The between-group difference in the rate of recurrent stroke was significant in the pre-specified per-protocol cohort (6 events in the closure group versus 14 events in the medical-therapy group; HR, 0.37; 95 % CI: 0.14 to 0.96; p = 0.03) and in the as-treated cohort (5 events versus 16 events; HR, 0.27; 95 % CI: 0.10 to 0.75; p = 0.007). Serious adverse events occurred in 23.0 % of the patients in the closure group and in 21.6 % in the medical-therapy group (p = 0.65). Procedure-related or device-related serious adverse events occurred in 21 of 499 patients in the closure group (4.2 %), but the rate of atrial fibrillation (AF) or device
thrombus was not increased. The authors concluded that, in the primary intention-to-treat analysis, there was no significant benefit associated with closure of a PFO in adults who had had a cryptogenic ischemic stroke. However, closure was superior to medical therapy alone in the pre-specified per-protocol and as-treated analyses, with a low rate of associated risks.

Kwong et al (2013) systematically reviewed the latest randomized data on the safety and effectiveness of percutaneous PFO closure in patients with cryptogenic stroke and PFO. MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched in April 2013 for eligible randomized controlled trials (RCTs). Primary outcome measures included: (i) stroke; (ii) TIA; and (iii) all-cause mortality. Secondary outcomes were new-onset atrial fibrillation (AF) and bleeding. These researchers included a total of 3 RCTs randomizing 2,303 participants. The intervention groups used either the STARFlex® Septal Closure System (1 trial, n = 447) or the AMPLATZER™ PFO Occluder (2 trials, n = 703). Control arms (n = 1,153) used medical treatment composing of anti-platelet or anti-coagulation therapy. There were no significant differences between groups in the analyses of stroke (OR 0.65, 95 % CI: 0.36 to 1.20, p = 0.17), TIA (HR 0.77, 95 % CI: 0.45 to 1.32, p = 0.35), all-cause mortality (OR 0.65, 95 % CI: 0.23 to 1.85, p = 0.42) or bleeding (OR 1.43, 95 % CI: 0.47 to 4.42, p = 0.53). Percutaneous PFO closure was associated with a significantly higher incidence of new-onset AF as compared to medical therapy (OR 3.77, 95 % CI: 1.44 to 9.87, p = 0.007). The authors concluded that currently available randomized data do not support the use of percutaneous PFO closure for secondary stroke prevention in patients with cryptogenic stroke and PFO. Moreover, they stated that an updated meta-analysis including further data from ongoing RCTs is needed.

Chen et al (2014) stated that the optimal treatment for secondary prevention in patients who have a PFO and history of cryptogenic stroke is still uncertain and controversial. In view of this, these researchers performed a systematic review of RCTs to investigate whether PFO closure was superior to medical therapy for prevention of recurrent stroke or TIA in patients with PFO after cryptogenic stroke. These investigators searched the Cochrane Central Register of Controlled Trials, Embase, PubMed, Web of Science, and ClinicalTrials.gov. Three RCTs with a total of 2,303 patients were included and analyzed. A fixed-effect model was used by Review Manager 5.2 (RevMan 5.2) software. The pooled risk ratio (RR) of recurrent stroke or TIA was 0.70, with 95 % CI: 0.47 to 1.04, p = 0.08. The results were similar in the incidence of death and adverse events, and the pooled RR was 0.92 (95 % CI: 0.34 to 2.45, p = 0.86) and 1.08 (95 % CI: 0.93 to 1.26, p = 0.32), respectively. The authors concluded that the data of this systematic review did not show superiority of closure over medical therapy for secondary prevention after cryptogenic stroke. Moreover, they stated that due to some limitations of the included studies, more RCTs are needed for further investigation regarding this field.

Knerr et al (2014) stated that limited data are available regarding the safety and effectiveness of the Gore septal occluder (GSO) for PFO closure. These researchers evaluated the safety and effectiveness of the GORE® Septal Occluder (GSO) at 1-, 6-, and 12-month follow-up in patients with a clinical indication for PFO closure. A total of 60 consecutive patients with an embolic event, migraine, or risk of decompression sickness were enrolled. Trans-esophageal or trans-thoracic echocardiography and clinical follow-up were performed at 1, 6 and 12 months after implantation. All patients received 100 mg aspirin and 75 mg clopidogrel for 6 months. Procedures were technically successful in 98.3 % (59/60). In 1 case, the anterior inter-atrial septal rim proved too short to allow safe GSO implantation and, instead, a different occluder was implanted. One patient developed transient neurological symptoms during the procedure without evidence for a stroke by magnetic resonance imaging. At 6-month follow-up, the closure rate was 86.6 % (52/60). The complete closure rate after 1 year was 93.3 % (56/60). Stroke, thrombus formation and atrial fibrillation (AF)/flutter occurred in 1 (1.7 %), 1 (1.7 %), and 5 (8.3 %) patients, respectively. The authors concluded that PFO closure with the GSO is accompanied by a high technical success rate and closure rates similar to other
currently used devices. The incidence of AF was higher than reported with most other devices. This may be a chance finding but warrants further investigation in larger trials.

Thomson et al (2014) reported procedural outcome and short-term follow-up data for the GSO, a new device for closure of PFO. Data from 9 centers in the United Kingdom implanting the GSO device, submitted to an electronic registry for evaluation were used for analysis. A total of 229 patients undergoing PFO closure from June 2011 to October 2012 were included. Indications for closure were secondary prevention of paradoxical cerebral emboli (83.4 %), migraine (2.1 %), platypnea orthodeoxia (3.9 %), and other (10.5 %). Median PFO size was 8 mm and 34 % and 39 %, respectively, had long tunnel anatomy or atrial septal aneurysms. A GSO was successfully implanted in all cases. A single device was used in 98 % but in 4 patients the initial device was removed and a second device required. Procedural complications occurred in 3 % and later complications (e.g., AF, atrial ectopics, and device thrombus) in 5.7 % of cases. All patients have undergone clinical and echocardiographic follow-up and all devices remain in position. Early bubble studies (median 0 months) with Valsalva maneuver in 67.2 % were negative in 89 %. The authors concluded that the GSO is an effective occlusion device for closure of PFO of all types. Moreover, they stated that longer-term follow-up particularly to document later closure rates are needed.

Percutaneous transcatheter closure of patent ductus arteriosus (PDA) is an established procedure in the pediatric field. In a multi-center clinical trial (n = 484, median age of the patients at catheterization was 1.8 years, with a range 0.2 to 70.7 years), Pass et al (2004) found that moderate to large PDAs can be effectively and safely closed using the Amplatzer ductal occluder, with excellent initial and 1-year results. These authors concluded that this device should obviate the need for multiple coils or surgical intervention for these defects. Butera et al (2004) reported that in experienced hands, percutaneous closure of moderate to large PDA in very young symptomatic children is safe, effectively closes the PDA, and solves clinical problems. An assessment of endovascular closure of PDA conducted by the National Institute for Clinical Excellence (NICE, 2004) concluded that there is adequate evidence to support the use of this procedure.

Migraine headache (MHA) is present in 12 % of adults and has been associated with inter-atrial communications. Azarbal et al (2005) examined the relationship between PFO or ASD with the incidence of MHA and evaluated if closure of the inter-atrial shunt in patients with MHA would result in improvement of MHA. A sample of 89 (66 PFO/23 ASD) adult patients underwent transcatheter closure of an inter-atrial communication using the CardioSEAL (n = 22), Amplatzer PFO (n = 43), or the Amplatzer ASD (n = 24) device. Before the procedure, MHA was present in 42 % of patients (45 % of patients with PFO and 30 % of patients with ASD). At 3 months after the procedure, MHA disappeared completely in 75 % of patients with MHA and aura and in 31 % of patients with MHA without aura. Of the remaining patients, 40 % had significant improvement (greater than or equal to 2 grades by the Migraine Disability Assessment Questionnaire) of MHA. These investigators concluded that transcatheter closure of PFO or ASD results in complete resolution of MHA in 60 % of patients (75 % of patients with migraine and aura) and improvement in symptoms in 40 % of the remaining patients. They noted that inter-atrial communications may play a role in the etiology of MHA either through paradoxical embolism or humoral factors that escape degradation in bypassing the pulmonary circulation. The authors stated that a randomized trial is needed to ascertain if transcatheter closure of inter-atrial shunts is an effective treatment for MHA compared with medical therapy.

Reisman et al (2005) examined the effects of transcatheter PFO closure on the frequency of MHA in patients with paradoxical cerebral embolism. A total of 162 consecutive patients underwent transcatheter PFO closure for prevention of recurrent cryptogenic stroke or transient ischemic attack. A 1-year retrospective analysis of migraine symptoms before and after PFO closure was performed. Active MHA was present in 35 % (57 of 162) of patients, and 68 % (39 of 57) experienced migrainous aura; 50 patients were available for analysis at 1
year. Complete resolution of migraine symptoms occurred in 56 % (28 of 50) of patients, and 14 % (7 of 50) of patients reported a significant greater than or equal to 50 %) reduction in MHA frequency. Patients reported an 80 % reduction in the mean number of MHA episodes per month after PFO closure (6.8 +/- 9.6 before closure versus 1.4 +/- 3.4 after closure, p < 0.001). Results were independent of completeness of PFO closure at 1 year. These researchers concluded that in patients with paradoxical cerebral embolism, MHA are more frequent than in the general population, and transcatheter closure of the PFO results in complete resolution or marked reduction in frequency of MHA.

In an editorial that accompanied the studies by Azarbal et al (2005) as well as Reisman et al (2005), Tsimikas (2005) stated that "before PFO closure can be proposed for migraine, a healthy skepticism should be in place, considering the high frequency of both migraine and PFO in the general population. It will be necessary to obtain definitive evidence with randomized controlled trials and to define the appropriate clinical indications".

Spies and Schrader (2006) stated that reviewed the epidemiology and pathophysiology of MHA, its association with PFO, and the impact of PFO closure on MHA. These researchers noted that primarily retrospective case-control studies demonstrated a link between PFO closure and improvement of MHA. Few prospective data confirm the initial results. However, the only randomized, controlled trial finished to date analyzing the effect of PFO closure on MHA failed to reach its primary outcome of resolution of migraine following the intervention. The authors concluded that evidence of a benefit on MHA following PFO closure is not convincing, but certainly intriguing. With currently ongoing trials, more information related to this topic can be expected.

Diener et al (2007) stated that although the results of uncontrolled observational studies suggest the PFO closure may have a beneficial effect on migraine frequency, a large randomized trial failed to support such a conclusion. Until there is more evidence from ongoing large controlled trials, PFO closure should not be performed in clinical practice for the prophylaxis of migraine.

In a prospective, multi-center, double-blind, sham-controlled study, Dowson et al (2008) examined the effectiveness of PFO closure with the STARFlex septal repair implant to resolve refractory migraine headache. Patients who suffered from migraine with aura, experienced frequent migraine attacks, had previously failed greater than or equal to 2 classes of prophylactic treatments, and had moderate or large right-to-left shunts (RLS) consistent with the presence of a PFO were randomized to transcatheter PFO closure with the STARFlex implant or to a sham procedure. Patients were followed-up for 6 months. The primary efficacy endpoint was cessation of migraine headache 91 to 180 days after the procedure. In total, 163 of 432 patients (38 %) had RLS consistent with a moderate or large PFO. A total of 147 patients were randomized. No significant difference was observed in the primary endpoint of migraine headache cessation between implant and sham groups (3 of 74 versus 3 of 73, respectively; p = 0.51). Secondary endpoints also were not achieved. On exploratory analysis, excluding 2 outliers, the implant group demonstrated a greater reduction in total migraine headache days (p = 0.027). As expected, the implant-arm experienced more procedural serious adverse events. All events were transient. The authors concluded that this trial confirmed the high prevalence of RLS in patients with migraine with aura. Although no significant effect was found for primary or secondary endpoints, the exploratory analysis supports further investigation.

Rundek et al (2008) examined the association between PFO and migraine among stroke-free individuals in an elderly, multi-ethnic cohort. As a part of the ongoing Northern Manhattan Study (NOMAS), 1,101 stroke-free subjects were assessed for self-reported history of migraine. The presence of PFO was assessed by transthoracic echocardiography. The mean age of the group was 69 +/- 10 years; 58 % were women; 48 % were Caribbean Hispanic, 24 % were white, 26 % were black, and 2 % were another race/ethnicity. The prevalence of self-reported migraine was 16 % (13 % migraine with aura). The prevalence of PFO was 15 %.
Migraine was significantly more frequent among younger subjects, women, and Hispanics. The prevalence of PFO was not significantly different between subjects who had migraine (26/178, or 14.6 %) and those who did not (138/923, or 15.0 %; p = 0.9). In an adjusted multivariate logistic regression model, the presence of PFO was not associated with increased prevalence of migraine (odds ratio 1.01, 95 % confidence interval [CI]: 0.63 to 1.61). Increasing age was associated with lower prevalence of migraine in both subjects with a PFO (odds ratio [OR] 0.94, 95 % CI: 0.90 to 0.99 per year) and those without PFO (odds ratio 0.97, 95 % CI: 0.95 to 0.99 per year). The observed lack of association between PFO and migraine (with or without aura) was not modified by diabetes mellitus, hypertension, cigarette smoking, or dyslipidemia. The authors concluded that in this multi-ethnic, elderly, population-based cohort, PFO detected with transthoracic echocardiography and agitated saline was not associated with self-reported migraine. The causal relationship between PFO and migraine remains uncertain, and the role of PFO closure among unselected patients with migraine remains questionable. In an editorial that accompanied the aforementioned article, Kurth et al (2008) stated that detection of PFO or PFO closure should not be recommended to patients who only have migraine.

In a review on dynamic optimization of chronic migraine treatment, Mathew (2009) stated that it is premature to recommend device-based treatments (e.g., occipital nerve stimulation, vagal nerve stimulation, and PFO closure) for chronic migraine because clinical trials are in the preliminary stages. Furthermore, additional studies are needed to evaluate if RLS-associated migraine can be clinically identified.

Garg and colleagues (2010) evaluated the assumption of an association between MHA and the presence of PFO. These investigators conducted a case-control study to assess the prevalence of PFO in subjects with and without migraine. Case subjects were those with a history of migraine (diagnosed by neurologists at a specialty academic headache clinic). Control subjects were healthy volunteers without migraine 1:1 matched on the basis of age and sex with case subjects. Presence of PFO was determined by transthoracic echocardiogram with second harmonic imaging and transcranial Doppler ultrasonography during a standardized procedure of infused agitated saline contrast with or without Valsalva maneuver and a review of the results by experts blinded to case-control status. Patent foramen ovale was considered present if both studies were positive. Odds ratios were calculated with conditional logistic regression in the matched cohort (n = 288). In the matched analysis, the prevalence of PFO was similar in case and control subjects (26.4 % versus 25.7 %; OR 1.04, 95 % CI: 0.62 to 1.74, p = 0.90). There was no difference in PFO prevalence in those with migraine with aura and those without (26.8 % versus 26.1 %; OR 1.03, 95 % CI: 0.48 to 2.21, p = 0.93). The authors concluded that they found no association between MHA and the presence of PFO in this large case-control study nor any association between migraine severity and PFO size.

In an editorial that accompanied the afore-mentioned study, Gersony and Gersony (2010) stated that “[a]lthough in rare instances, exceptions may be proposed, closure of PFO for migraine should not be considered standard medical practice”.

Rigatelli and Ronco (2010) provided a comprehensive review of the main concepts about PFO management. Therapy is a controversial issue, since data on these patients are variable and accepted guidelines are missing. Recurrent strokes are the most diffuse and accepted indication for transcatheter closure of PFO, but severe refractory migraine with aura, unexplained oxygen desaturation, orthodeoxia-platypnea (related to aortic elongation, allowing significant right-to-left shunt), and other conditions have been suggested to benefit from PFO closure. Different devices and techniques have been proposed for this procedure, mainly depending on operator experience and preferences. The authors concluded that PFO management is still a debated field: indications, pathophysiology and ideal closure techniques remain to be fully clarified and investigated before considering PFO closure a routine procedure.
Butera et al (2010) examined the role of transcatheter closure of PFO on the occurrence of migraine. BioMedCentral, Google Scholar, and PubMed from January 2000 to December 2008 were systematically searched for pertinent clinical studies. Secondary sources were also used. Secondary prevention studies of transcatheter closure for PFO were required to include at least more than 10 patients followed for more than 6 months. The primary endpoint was the rate of cured or significantly improved migraine after percutaneous PFO closure. After excluding 637 citations, these investigators included a total of 11 studies for a total of 1,306 patients. Forty percent of the subjects included suffered from migraine, while most had a previous history of transient ischemic attack/stroke and were investigated retrospectively. Quantitative synthesis showed that complete cure of migraine in 46% (95% CI: 25 to 67%), while resolution or significant improvement of migraine occurred in 83% (95% CI: 78 to 88%) of cases. The authors concluded that notwithstanding the limitations inherent in the primary studies, this systematic review suggested that a significant group of subjects with migraine, in particular if treated after a neurological event, may benefit from percutaneous closure of their PFO. However, the authors noted that many questions remain unsolved.

Bendaly et al (2011) reported the mid-term results of percutaneous device closure of muscular VSD (MVSD) at a single institution. Between January 2004 and December 2009, 6 patients underwent attempted percutaneous MVSD closure. Mean age was 9.8 +/- 9.1 months; mean weight was 7.2 +/- 3.7 kg. In 5 patients, closure was successful without use of bypass. In 1 patient, the device embolized to the left ventricle after release and patch closure of the MVSD was performed on cardiopulmonary bypass. The mean interval from the procedure to the most recent echocardiogram for the patients with successful percutaneous closure was 25.2 months. Three patients demonstrated no residual shunt at the last echocardiogram. Two patients had mild, hemodynamically insignificant shunting; 1 had a left ventricular pseudoaneurysm that was embolized during repeat catheterization. The authors concluded that percutaneous closure of MVSDs is attractive because it overcomes the limitations of surgery and catheterization. Additionally, it spares the need for cardiopulmonary bypass and its comorbidities. In some instances, however, successful deployment of the device is not possible. These mid-term results demonstrated overall success but identify possible complications that are not immediately identified in the short-term.

Zhang et al (2012) examined the feasibility of transthoracic echocardiographic (TTE) guidance for minimally invasive percutaneous device closure of peri-membranous VSDs. From June 2011 to September 2011, these researchers enrolled 18 young children with peri-membranous VSDs to receive minimally invasive device closure in their hospital. All of the patients were examined by TTE to determine the VSD morphology, diameter, and rims. During intra-operative device closure, real-time bedside TTE alone was used to guide device implantation. Device implantation using TTE guidance was successful in 16 patients. Symmetric devices were used in 14 patients, and asymmetric devices were used in 2 patients. Only 1 patient experienced mild aortic regurgitation, and there were no instances of residual shunt, significant arrhythmias, thromboembolism, or device displacement. Two patients were transferred to surgical closure, 1 due to residual shunting and the other as a result of unsuccessful wire penetration of the VSD gap. The authors concluded that these findings indicated that TTE-guided VSD closure is feasible in young children, although a longer follow-up may be needed to document the long-term success.

Irwin and Bay (2012) stated that migraine with aura has been linked with PFO. A recent meta-analysis suggested an association, but the one prospective population study did not. The well-publicized and controversial MIST Trial is the only randomized trial of device closure in patients with migraines yet published, and failed to demonstrate a convincing benefit from device closure. Other conditions such as platypnea-orthodeoxia syndrome and prevention of decompression sickness in divers, may justify device closure. Evidence for a role of PFO in the etiology of cryptogenic stroke and migraine is contradictory. The authors concluded that it
is possible that some patients might benefit from PFO closure, but there is scant evidence of sufficient quality to justify routine PFO closure in either group.

Rao (2013) discussed how and when to treat the most common acyanotic congenital heart defects (CHD). The indications and timing of intervention are decided by the severity of the lesion. Transcatheter closure methods are currently preferred for ostium secundum ASDs; the indications for occlusion are right ventricular volume overload by echocardiogram. Ostium primum, sinus venosus, and coronary sinus ASDs require surgical closure. For all ASDs elective closure around age 4 to 5 years is recommended or as and when detected beyond that age. For the more common peri-membranous VSDs of large size, surgical closure should be performed prior to 6 to 12 months of age. Muscular VSDs may be closed with devices. Patent ductus arteriosus may be closed with Amplatzer duct occluder if they are moderate-to-large and Gianturco coils if they are small. Surgical and video-thoracoscopic closure are the available options at some centers. In the presence of pulmonary hypertension appropriate testing to determine suitability for closure should be undertaken. An UpToDate review on “Management of atrial septal defects in adults” (Connolly, 2012) states that “Surgery is required for closure of ostium primum ASD, sinus venosus ASD, and coronary sinus septal defects.

Zhu and colleagues (2013) investigated perventricular device closure as a salvage technique in pediatric patients who had post-operative residual muscular ventricular septal defects. From February 2009 through June 2011, a total of 14 pediatric patients at the authors’ hospital had residual muscular ventricular septal defects after undergoing surgical repair of complex congenital heart defects. Ten patients met selection criteria for perventricular device closure of the residual defects: significant left-to-right shunting (Qp/Qs greater than 1.5) or substantial hemodynamic instability (a defect greater than or equal to 2 mm in size). The patients’ mean age was 20.4 ± 13.5 months, and their mean body weight was 10 ± 3.1 kg. The median diameter of the residual defects was 4.2 mm (range of 2.5 to 5.1 mm). These investigators deployed a total of 11 SQFDQ-II Muscular VSD occluders (Shanghai Shape Memory Alloy Co., Ltd.; Shanghai, China) in the 10 patients, in accord with conventional techniques of perventricular device closure. The mean procedural duration was 31.1 ± 9.1 mins. These researchers recorded the closure and complication rates peri-operatively and during a 12-month follow-up period. Complete closure was achieved in 8 patients; 2 patients had persistent trivial residual shunts. No deaths, conduction block, device embolism, or other complications occurred throughout the study period. The authors concluded that perventricular device closure is a safe, effective salvage treatment for post-operative residual muscular ventricular septal defects in pediatric patients. Moreover, they stated that long-term studies with larger cohorts might further confirm this method’s feasibility.

Furthermore, an UpToDate review on “Management of isolated ventricular septal defects in infants and children” (Dummer and Fulton, 2014) does not mention the use of perventricular closure of ventricular septal defects as a therapeutic option.

Hakeem et al (2013) stated that controversy persists regarding the management of patients with cryptogenic stroke and PFO. These researchers performed a meta-analysis of RCTs comparing PFO closure with medical therapy. A prospective protocol was developed and registered using the following data sources: PubMed, Cochrane Register of Controlled Trials, conference proceedings, and Internet-based resources of clinical trials. Primary analyses were performed using the intention-to-treat method. A total of 3 randomized trials comparing percutaneous PFO closure versus medical therapy for secondary prevention of embolic neurological events formed the data set. Baseline characteristics were similar. During long-term follow-up, the pooled incidence of the primary end-point (composite of stroke, death, or fatal stroke) was 3.4 % in the PFO closure arm and 4.8 % in the medical therapy group [RR 0.7 (0.48 to 1.06); p = 0.09]. The incidence of recurrent neurological events (secondary end-point) was 1.7 % for PFO closure and 2.7 % for medical therapy [RR 0.66 (0.35 to 1.24), p = 0.19]. There was no difference in terms of death or adverse events between the 2 groups.
The authors concluded that while this meta-analysis of RCTs demonstrated no statistical significance in comparison to medical therapy, there was a trend towards overall improvement in outcomes in the PFO closure group.

Ntaios et al (2013) examined if PFO closure is superior to medical therapy in preventing recurrence of cryptogenic ischemic stroke or TIA. These investigators searched PubMed for randomized trials that compared PFO closure with medical therapy in cryptogenic stroke/TIA using the terms: “stroke or cerebrovascular accident or TIA” and “patent foramen ovale or paradoxical embolism” and “trial or study”. Among 650 potentially eligible articles, 3 were included including 2,303 patients. There was no statistically significant difference between PFO-closure and medical therapy in ischemic stroke recurrence (1.91 % versus 2.94 %, respectively, OR: 0.64, 95 % CI: 0.37 to 1.10), TIA (2.08 % versus 2.42 %, respectively, OR: 0.87, 95 % CI: 0.50 to 1.51) and death (0.60 % versus 0.86 %, respectively, OR: 0.71, 95 % CI: 0.28 to 1.82). In subgroup analysis, there was significant reduction of ischemic strokes in the AMPLATZER PFO Occluder arm versus medical therapy (1.4 % versus 3.04 %, respectively, OR: 0.46, 95 % CI: 0.21 to 0.98, relative-risk-reduction: 53.2 %, absolute-risk-reduction: 1.6 %, number-needed-to-treat: 61.8) but not in the STARFlex device (2.7 % versus 2.8 % with medical therapy, OR: 0.93, 95 % CI: 0.45 to 2.11). Compared to medical therapy, the number of patients with new-onset AF was similar in the AMPLATZER PFO Occluder arm (0.72 % versus 1.28 % respectively, OR: 1.81, 95 % CI: 0.60 to 5.42) but higher in the STARFlex device (0.64 % versus 5.14 %, respectively, OR: 8.30, 95 % CI: 2.47 to 27.84). The authors concluded that this meta-analysis did not support PFO closure for secondary prevention with unselected devices in cryptogenic stroke/TIA. In subgroup analysis, selected closure devices may be superior to medical therapy without increasing the risk of new-onset AF. However, they stated that this observation should be confirmed in further trials using inclusion criteria for patients with high likelihood of PFO-related stroke recurrence.

Udell and colleagues (2014) noted that PFO might be a risk factor for unexplained (cryptogenic) stroke or TIA. These researchers determined the safety and effectiveness of transcatheter PFO closure compared with anti-thrombotic therapy for secondary prevention of cerebrovascular events among patients with cryptogenic stroke. These investigators performed a systematic review and meta-analysis of MedLine and Embase (from inception to March 2013) for RCTs that compared transcatheter PFO closure with medical therapy in subjects with cryptogenic stroke. Data were independently extracted on trial conduct quality, baseline characteristics, efficacy, and safety events from published articles and appendices. Risk ratios and 95 % CIs for the composite of stroke or TIA, and adverse cardiovascular events including AF/flutter were constructed. Three RCTs of 2,303 subjects with previous stroke, TIA, or systemic arterial embolism (mean age of 45.7 years; 47.3 % women; mean follow-up, 2.6 years) were included. Patent foramen ovale closure did not significantly reduce the risk of recurrent stroke/TIA (3.7 % versus 5.2 %; RR, 0.73; 95 % CI: 0.50 to 1.07; p = 0.10); however, an increased risk of incident AF/flutter was detected (3.8 % versus 1.0 %; RR, 3.67; 95 % CI: 1.95 to 6.89; p < 0.0001). No significant heterogeneity was detected for any end-point among subgroups of patients stratified according to age, sex, index cardiovascular event, device type, inter-atrial shunt size, and presence of an atrial septal aneurysm (all p interactions ≥ 0.09). The authors concluded that meta-analysis of RCTs that assessed transcatheter PFO closure for secondary prevention of cerebrovascular events in subjects with cryptogenic stroke did not demonstrate benefit compared with anti-thrombotic therapy, and suggested potential risks.

An UpToDate review on “Cryptogenic stroke” (Prabhakaran and Elkind, 2014) states that “Atrial septal abnormalities, including patent foramen ovale, atrial septal aneurysm and atrial septal defect, have been associated with cryptogenic stroke, although the strength and clinical significance of this association is uncertain … While retrospective data suggest that there is an increased prevalence of patent foramen ovale (PFO) and atrial septal aneurysm (ASA) in patients who have had a cryptogenic stroke, particularly in patients <55 years old, population-based studies suggest that PFO and large PFO are not independent risk factors for stroke. In
addition, prospective data suggest that PFO alone is not associated with a meaningfully increased risk of recurrent stroke or death in patients who have already had a cryptogenic stroke …. There is a high degree of uncertainty regarding the optimal management of patent foramen ovale (PFO), atrial septal aneurysm (ASA), and atheromatous aortic disease. The management of specific coagulation disorders and the role of hematologic testing are also unclear at the moment. Therefore, for the majority of patients with cryptogenic stroke, antiplatelet therapy is recommended. Selected patients might benefit from anticoagulant therapy”.

CPT Codes / HCPCS Codes / ICD-9 Codes

CPT codes covered if selection criteria are met:

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

Other CPT codes related to the CPB:

33615  Repair of complex cardiac anomalies (e.g., tricuspid atresia) by closure of atrial septal defect and anastomosis of atria or vena cava to pulmonary artery (simple Fontan procedure)

33617  Repair of complex cardiac anomalies (e.g., single ventricle) by modified Fontan procedure

93315  Transesophageal echocardiography for congenital cardiac anomalies; including probe placement, image acquisition, interpretation and report

93320 - 93350  Echocardiography

93353  Combined right heart catheterization and transseptal left heart catheterization through existing septal opening, with or without retrograde left heart catheterization, for congenital cardiac anomalies

HCPCS codes covered if selection criteria are met:

C1817  Septal defect implant system, intracardiac

Other HCPCS codes related to the CPB:

C1760  Closure device, vascular (implantable/insertable)

C2628  Catheter, occlusion

ICD-9 codes covered if selection criteria are met:

429.71  Acquired cardiac septal defect

745.2  Tetralogy of Fallot

745.4  Ventricular septal defect
Transcatheter Closure of Septal Defects

745.5 Ostium secundum type atrial septal defect [not covered for coronary sinus atrial septal defect or patent foramen ovale]

747.0 Patent ductus arteriosus

ICD-9 codes not covered for indications listed in the CPB: (not all-inclusive):

346.00 - 346.91 Migraine

433.00 - 435.9 Occlusion and stenosis of precerebral or cerebral arteries and transient cerebral ischemia

745.60 - 745.69 Endocardial cushion defects

784.0 Headache

786.09 Other symptoms involving respiratory system and other chest symptoms [orthodeoxia-platypnea]

790.91 Abnormal arterial blood gases [unexplained oxygen desaturation]

Other ICD-9 codes related to the CPB:

411.81 Acute coronary occlusion without myocardial infarction

745.8 Other bulbus cordis anomalies and anomalies of cardiac septal closure

799.0 Asphyxia and hypoxemia

The above policy is based on the following references:


68. Butera G, Blondi-Zoccai GG, Carminati M, et al. Systematic review and meta-analysis of currently available clinical evidence on migraine and patent foramen ovale...
73. Connolly HM. Management of atrial septal defects in adults. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed December 2012.