I. POLICY

Patent Foramen Ovale

Closure of patent foramen ovale (PFO) using a transcatheter approach is considered investigative. (There are currently no transcatheter devices with FDA approval or clearance for this indication.) There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Atrial Septal Defects

Transcatheter closure of secundum atrial septal defects (ASD) may be considered medically necessary when using a device that has been FDA approved for that purpose and used according to the labeled indications.

Note: There are 2 FDA-approved devices for ASD closure: the AMPLATZER™ Septal Occluder, and the GORE HELEX™ Septal Occluder.

The labeled indications for these devices are similar and include:

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

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

Policy Guidelines

At present, no PFO closure devices are FDA approved for patients with cryptogenic stroke. All uses of these PFO closure devices are currently off-label.

There are 2 FDA-approved devices for ASD closure: the AMPLATZER™ Septal Occluder and the GORE HELEX™ Septal Occluder.

The labeled indications for these devices are similar and include:
Those with echocardiographic evidence of ostium secundum atrial septal defect; AND
Clinical evidence of right ventricular volume overload (i.e., 1.5:1 degree of left-to-right shunt or right ventricular enlargement).

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

Cross-reference
MP-2.103: Off-Label Use of Prescription Drug and Medical Devices

II. PRODUCT VARIATIONS
[N] = No product variation, policy applies as stated
[Y] = Standard product coverage varies from application of this policy, see below

[N] Capital Cares 4 Kids  [N] Indemnity
[N] PPO                            [N] SpecialCare
[N] HMO                            [N] POS
[Y] SeniorBlue HMO*               [Y] FEP PPO**
[Y] SeniorBlue PPO*

* The CardioSEAL® Septal Occlusion System and Amplatzer® Patent Foramen Ovale Occluder are classified by the FDA under an investigational device exemption (IDE) as Category B devices. The Centers for Medicare and Medicaid Services (CMS) may cover Category B devices if they are considered reasonable and necessary. Refer to the Medicare Benefit Policy Manual (IOM 100-02), Chapter 14, Medical Devices.

** Refer to FEP Medical Policy Manual MP-2.02.09 Closure Devices for Patient Foramen Ovale and Atrial Septal Defects. The FEP Medical Policy manual can be found at: www.fepblue.org

III. DESCRIPTION/BACKGROUND

“Closure” devices are intended as less-invasive, catheter-based approaches to repairing patent foramen ovale or atrial septal defects.
**Patent Foramen Ovale**

The foramen ovale, a component of fetal cardiovascular circulation, consists of a communication between the right and left atrium that functions as a vascular bypass of the uninflated lungs. The ductus arteriosus is another feature of the fetal cardiovascular circulation, consisting of a connection between the pulmonary artery and the distal aorta. 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 atrial pressure and a decrease in right atrial pressure result in the permanent closure of the foramen ovale in most individuals. However, a patent foramen ovale (PFO) is a common finding in normal adults, detected in up to 25% of adults. In some epidemiologic studies, PFO has been associated with cryptogenic stroke, a type of stroke defined as an ischemic stroke occurring in the absence of potential cardiac, pulmonary, vascular, or neurological sources. Studies also show an association of PFO and migraine headache.

There has been interest in either open surgery or transcatheter approaches to close the PFO in patients with a history of cryptogenic stroke in order to prevent recurrent stroke.

Two transcatheter devices received approval for marketing from the U.S. Food and Drug Administration (FDA) in 2002 as a treatment for patients with cryptogenic stroke and patent foramen ovale: the CardioSeal Septal Occlusion System and the Amplatzer Patent Foramen Ovale occluder. Both received approval by the FDA through a Humanitarian Device Exemption (HDE), a category of FDA approval that is applicable to devices that are designed to treat a patient population of fewer than 4,000 patients per year. This approval process requires the manufacturer to submit data on the safety and the probable clinical benefit. Clinical trials validating the device effectiveness are not required. The labeled indications of both limited the use of these devices to closure of PFO in patients with recurrent cryptogenic stroke due to presumed paradoxical embolism through a patent foramen ovale and who have failed conventional drug therapy.

Following this limited FDA approval, the use of PFO closure devices increased by over 50-fold, well in excess of the 4,000 per year threshold intended under the HDE. As a result, in 2006, the FDA withdrew the HDE approval for these devices. At this time, the FDA also reiterated the importance of randomized, controlled trials of PFO closure devices versus medical therapy, but noted that ongoing trials were hampered by slow enrollment. Withdrawal of the HDE approval was, in part, intended to spur greater enrollment in ongoing randomized, controlled trials of these devices.

Currently, all uses of closure devices to treat PFO are off-label uses.

**Atrial Septal Defect**

In contrast to patent foramen ovale, which represents the persistence of normal fetal cardiovascular physiology, atrial septal defects (ASDs) represent an abnormality in the development of the heart that results in free communication between the atria. ASDs are
categorized according to their anatomy. For example, 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 30–40% of these patients over the age of 40. Ostium secundum describes defects that are located midseptally and are typically near the fossa ovalis.

Ostium primum defects lie immediately adjacent to the atrioventricular valves and occur commonly in patients with Down’s syndrome. Sinus venous defects occur high in the atrial septum and are frequently associated with anomalies of the pulmonary veins. 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 40 to 50 years due to heart failure or pulmonary hypertension related to the left-to-right shunt. Patients with ASDs are also at risk for paradoxical emboli.

Repair of ASDs is recommended for those with pulmonary systemic flows 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 has 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. At present, 2 devices are FDA approved for ASD closure: the AMPLATZER™ Septal Occluder, and the GORE HELEX™ Septal Occluder.

IV. RATIONALE

Patent Foramen Ovale

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 pre-existing thromboembolism are treated with warfarin, and patients without these risk factors are treated with antiplatelet agents. Closure devices are non-pharmacologic 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 3 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.** (3) 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 anti-platelet therapy. Patients in the medical therapy group were treated with aspirin, warfarin, or both at the discretion of the treating physician. The primary endpoint was a composite of stroke/TIA at 2 years, death from any cause during the first 30 days after treatment, and death from neurologic causes at 2 years.

Of 405 patients in the closure group, 362 (89.4%) had successful implantation without procedural complications. At 6 months, echocardiography revealed effective closure in 315/366 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]: 0.45-1.35, p=0.37). Kaplan-Meier estimates of the 2-year rate of stroke were 2.9% in the closure group and 3.1% in the medical therapy group (adjusted HR: 0.90, 95% CI: 0.41-1.98). 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.** (4) 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 1 of 4 regimens prescribed at the discretion of the treating physician: aspirin, aspirin plus dipyridamole, clopidogrel, or warfarin. The primary endpoint 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 9 events occurred in 499 patients assigned to closure, and 16 events occurred in 464 patients assigned to medical therapy. All of the events were non-fatal strokes. The hazard ratio for this outcome was 0.49, but this result did not reach statistical significance in the intent-to-treat analysis (95% CI: 0.22-1.11, p=0.08). On per-protocol analysis, there was a statistically significant effect, with a hazard ratio of 0.37 (95% CI: 0.14-0.96, 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. (5) 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 endpoint was a composite of death, nonfatal stroke, TIA, or peripheral embolism. The median duration of follow-up was 4.1 years in the closure group and 4.0 years in the medical therapy group.

The primary outcome, after independent adjudication, occurred in 9 of 204 patients (3.4%) in the closure group compared to 11 of 210 patients (5.7%) in the medical group. The hazard ratio for this outcome was 0.63 (95% CI: 0.24-1.62, p=0.34) on intent-to-treat analysis. On per-protocol analysis, results were similar with a hazard ratio of 0.70 (95% CI: 0.27-1.85, 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 to 29.5% in the medical therapy group.

Systematic reviews. Several systematic reviews with meta-analysis of the 3 available RCTs have been published; 2 representative studies are summarized here. Rengifo-Moreno et al. (6) performed a combined analysis of the 3 RCTs previously discussed. The analysis included a total of 1,150 patients randomized to PFO closure and 1,153 patients randomized to medical therapy followed for a mean of 3.5 years. Two endpoints were included, recurrent vascular events and a combined endpoint 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: 0.36-0.97, 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: 0.12-1.03, 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: 0.12-1.03, p=0.06).

Another meta-analysis of the same 3 RCTs was reported by Kitsios et al. (7) 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: 0.26-1.18). 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 HR of 0.67 (95% CI: 0.44-1.00). There were no significant differences found on combined analysis of the subgroup analyses from the trials.

A number of systematic reviews of the observational studies have also been published, comparing outcomes of PFO closure with medical therapy. (8-10) These reviews are consistent in reporting that the combined rate of recurrent stroke is lower for patients treated with a closure device compared to medical therapy.

Kitsios et al. published a systematic review of observational studies and the single RCT in 2012. (9) This review included 52 single-arm studies, 7 non-randomized comparative studies, and 1 RCT. The combined incident rate for recurrent stroke was lower for patients treated with PFO (0.36 events/100 patient-years, 95% CI: 0.24-0.56) compared to patients treated medically (2.53 events/100 patient-years, 95% CI: 1.91-3.35). The incident rate ratio was 0.19 (95% CI: 0.18-0.98), 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 to the observational studies, while the incident rate for recurrent stroke in patients treated medically was only slightly lower in the RCT compared to 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 (10) compared the results of 12 series of PFO closure (n=2,016) with 8 series (n=998 patients) of medical therapy. At 2 years of follow-up, the range of recurrent stroke was 0–1.6% for PFO closure and 1.8–9.0% for medical therapy. The combined annual incidence of stroke or TIA was 1.3% (95% CI: 1.0–1.8%) following PFO closure compared with 5.2% (95% CI: 4.4–6.2) for medical therapy. In an earlier review, Khairy et al. (8) analyzed 6 series of medical therapy (n=895 patients) and 10 series of PFO closure (n=1,355 patients). These authors noted differences in key clinical characteristics among patients in the 2 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 1 year ranged from 0–4.9% with PFO closure, compared with 3.8–12.0% with medical therapy. There was an estimated major complication rate (death, hemorrhage requiring transfusion, tamponade, need for surgical intervention, and pulmonary embolus) for PFO closure of 1.5%, and a minor complication rate of 7.9%.
Non-randomized, comparative studies. A number of nonrandomized comparative studies of closure devices versus medical therapy have been published. Wahl et al. performed a non-randomized comparative study using propensity matching in 308 consecutive patients with stroke or TIA that was presumed due to a PFO. (11) 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 9 years’ follow-up, the primary endpoint was reached by 11% of patients in the closure group compared to 21% in the medical therapy group (hazard ratio [HR]: 0.43, 95% CI: 0.20-0.94, 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 to 14% of medical therapy patients.

Windecker et al. (12) compared 150 patients who underwent patent foramen ovale (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 4 years’ follow-up, there was a trend toward lower recurrence of stroke or transient ischemic attack (TIA) in the PFO group that did not reach statistical significance (7.8% vs. 22.2%, p=0.08).

Harrer et al. (13) reported on 124 patients with cryptogenic stroke and PFO treated over a 10-year period. Eighty-three patients were treated with medical therapy, 34 were treated with percutaneous PFO closure, and 7 were treated with surgical closure. After a mean follow-up of 52 +/- 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. (14) 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 anti-thrombotic 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 8/121 (6.8%) patients treated with a closure device (4 patients with tachycardia, 2 patients with allergic reaction, 1 patient with atrial fibrillation, 1 patient with sepsis). After a follow-up of 2 years, 10/117 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 (odds ratio [OR]: 0.1, 95% CI: 0.0-1.0, p=0.05) but was not a significant predictor of the combined outcome of stroke or TIA (OR: 0.1, 95% CI: 0.02-1.5, p=0.10).
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. (15) 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. (16) 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 and colleagues (17) 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 2 years, only 2 patients had experienced a recurrent neurologic event. Windecker and colleagues (18) reported on a case series of 80 patients with a history of at least 1 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 5 years of follow-up, the risk of an embolic event (either TIA, stroke, or peripheral embolism) was 3.4%, considered comparable to 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.

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.

A sham-controlled randomized clinical trial of PFO closure for the indication of refractory migraine headache was published in 2008. (19) Migraine headache is another condition that has been associated with PFO in epidemiologic studies. In this study, there was no significant difference observed in the primary endpoint of migraine headache cessation (3 of 74 in the implant group, 3 of 73 in the sham group, p=0.51). The results of this study cast some doubt on the causal relationship between PFO and migraine.

Conclusions. The results of one RCT do not support the conclusion that closure devices improve outcomes for patients with cryptogenic stroke and PFO. This trial of 909 patients reported that there was no significant difference at 2 years in the rate of stroke, or in the combined rate of stroke/TIA, between patients receiving closure devices and medical therapy. These results contrast with the results of nonrandomized, comparative studies and systematic reviews of observational studies, which report lower rates of recurrent events.
following closure of PFO. The discrepancy in these results may arise from selection bias, since selection for either closure devices or medical therapy may vary, resulting in populations that may have unequal distribution of confounders. Also, the rate of recurrent stroke for patients treated with closure devices in the RCT was much higher than combined estimates from observational studies. This raises the possibility that ascertainment bias in the observational studies may have resulted in a spuriously low stroke rate for patients treated with a closure device.

Atrial Septal Defect

At present there are 2 FDA-approved devices for atrial septal defects (ASD) closure: the AMPLATZER™ Septal Occluder, and the GORE HELEX™ Septal Occluder.

Evidence supporting the efficacy of devices for closure of ASD consists of nonrandomized comparative studies and case series. 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, since the alternative treatment is open surgery. 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. (20) This study was subsequently published with slightly different numbers but similar quantitative findings. (21) 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 2 groups, overall, those receiving a septal occluder had a significantly lower incidence of major adverse events (p=0.03). Similarly, there was a significantly lower incidence of minor adverse events in the septal occluder group (p<0.001). It should be noted that the mean age of patients of the 2 groups was significantly different; in the septal occluder group, the mean age was 18 years, compared to 6 years in the surgically treated group.

A systematic review of percutaneous closure versus surgical closure was published by Butera et al. in 2011. (22) Thirteen non-randomized comparative studies that enrolled at least 20 patients were included, with a total of 3,082 patients. The rate of procedural complications was higher in the surgical group (31%, 95% CI: 21-41%) compared to the percutaneous group (6.6%, 95% CI: 3.9-9.2%), with an odds ratio for total procedural complications of 5.4 (95% CI: 2.96-9.84, p<0.0001). There was also an increased rate of major complications for
the surgical group (6.8%, 95% CI: 4.9-9.5%) compared to the percutaneous group (1.9%, 95% CI: 0.9-2.9%), for an odds ratio of 3.81 (95% CI: 2.7-5.36, p=0.006).

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. (23) A study by Berger et al. showed identical 98% success rate in both treatment groups. (24) A non-randomized comparative analysis by Kotowycz et al. (25) reported that mortality rates at 5-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).

Single-arm studies show high success rates of ASD closure. The U.S Food and Drug Administration (FDA) study discussed previously was the largest series, with an enrollment of 423 patients. Fischer and colleagues reported on use of the AMPLATZER device in 236 patients with secundum ASD. (26) 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. (27) 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 6-month follow-up. Oho and colleagues also reported a successful closure rate of 97% at 1-year follow-up in 35 patients receiving transcatheter closure of ASD, while only 1 patient complication of second-degree atrioventricular block was noted. (28) Finally, Brochu and colleagues evaluated 37 New York Heart Association (NYHA) Class I or II patients who underwent transcatheter closure of ASD. (29) At 6-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 90-100% range. (3, 5)

Conclusions. For patients with an ASD, nonrandomized comparative 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. Because of the advantages of percutaneous closure over open surgery, the use of percutaneous ASD closure devices can be considered medically necessary.
Ongoing Clinical Trials

A search of online site ClinicalTrials.gov using the keywords patent foramen ovale returned 34 studies. Three of these studies are RCTs that are ongoing:

- NCT00562289 Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence. This is an RCT comparing PFO closure with medical therapy in patients with PFO and cryptogenic stroke. The primary endpoints are fatal and nonfatal stroke, all-cause mortality, and vascular death. Planned enrollment is for 900 patients with completion date estimated to be December 2012. As of July 2013, the status of this trial is listed as “Unknown.”
- NCT01550588 Defense-PFO study. Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients with High-Risk Patent Foramen Ovale. This is an RCT comparing PFO closure with medical therapy. Primary endpoints are non-fatal stroke, vascular death, and major bleeding. Planned enrollment is for 210 patients with an estimated completion date of February 2017.
- NCT00738894 Gore REDUCE study. GORE HELEX™ Septal Occluder for Patent Foramen Ovale (PFO) Closure in Stroke Patients. This is an RCT of PFO closure compared to medical therapy in patients with cryptogenic stroke. The primary endpoint is freedom from recurrent stroke/TIA at 2 years. Planned enrollment is for 664 patients, with an estimated completion date of January 2018.

Summary

The evidence on the efficacy of closure devices for patients with patent foramen ovale (PFO) and cryptogenic stroke does not permit conclusions on whether health outcomes are improved. Three RCTs have been completed that compare closure devices to medical therapy in patients with cryptogenic stroke and PFO. None of the 3 trials reported statistically significant improvements on their main outcome using intent-to-treat analysis. In all 3 trials, low numbers of outcome events in both groups limited the power to detect differences between groups. One trial showed a significant benefit for the closure group on per-protocol analysis and another showed significant benefit on secondary outcomes. Meta-analyses of these trials have also come to different conclusions, with some reporting a statistically significant reduction in recurrent events on pooled analysis and others reporting a trend for benefit that does not reach statistical significance. While these results suggest that a benefit might be present, the evidence is not definitive and the risk/benefit ratio is not well-defined. In addition, there are no PFO closure devices that are currently FDA-approved for use in the U.S. Therefore closure devices are considered investigational as a treatment for patients with PFO.
For patients with ASD that require closure, nonrandomized comparative 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. Since the main alternative to percutaneous closure is open surgery, this evidence is sufficient to conclude that percutaneous closure achieves similar outcomes with less risk compared to the alternative. If the percutaneous approach is unsuccessful, ASD closure can be achieved using surgery. Because of the advantages of percutaneous closure over open surgery, the use of percutaneous ASD closure devices can be considered medically necessary for this purpose.

**Practice Guidelines and Position Statements**

The American College of Chest Physicians published guidelines on antiplatelet and antithrombotic therapy in 2012, (30) which were an update to previous guidelines published in 2008. (31) These guidelines contained the following statements about the treatment of patients with a PFO:

- In patients with asymptomatic patent foramen ovale (PFO) or atrial septal aneurysm, we suggest against antithrombotic therapy (Grade 2C)
- In patients with cryptogenic stroke and PFO or atrial septal aneurysm, we recommend aspirin (50-100 mg/d) over no aspirin (Grade 1A).
- In patients with cryptogenic stroke and PFO or atrial septal aneurysm, who experience recurrent events despite aspirin therapy, we suggest treatment with (VKA [vitamin K antagonists] therapy (target INR, 2.5; range, 2.0-3.0) and consideration of device closure over aspirin therapy (Grade 2C).
- In patients with cryptogenic stroke and PFO, with evidence of DVT [deep vein thrombosis], we recommend VKA therapy for 3 months (target INR, 2.5; range, 2.0-3.0) (Grade 1B) and consideration of device closure over no VKA therapy or aspirin therapy (Grade 2C).

Guidelines from the American College of Chest Physicians (32) and the American Academy of Neurology, (33) both published in 2004, state that the evidence is inconclusive regarding the comparative efficacy of PFO closure devices and medical therapy. Neither of these guidelines offers specific recommendations as to when PFO closure devices should be used.

The American Heart Association (AHA)/American Stroke Association guidelines (34) published in 2006 offer somewhat more specific recommendations. These guidelines do not recommend PFO closure as initial therapy for patients with a first ischemic stroke and PFO, stating that, “Insufficient data exist to make a recommendation about PFO closure in patients with a first stroke and a PFO.” They also state that “…aspirin (50-325mg/d), aspirin and extended-release dipyridamole in combination, and clopidrogel are all acceptable options for
initial therapy (class IIa, level of evidence A),” and that “Warfarin is reasonable for high-risk patients who have other indications for oral anticoagulation, such as underlying hypercoagulable state or evidence of venous thrombosis (class IIa, level of evidence C).” For patients with stroke or TIA while on medical therapy, they state that, “PFO closure may be considered for patients with recurrent cryptogenic stroke despite optimal medical therapy (class IIB, level of evidence C).”

Guidelines issued by the ACC/AHA in 2008 on the management of congenital heart disease recommend closure of an ASD by either percutaneous or surgical methods for several indications. (35) For sinus venosus, coronary sinus, or primum ASD, however, surgical rather than percutaneous closure is recommended.

V. DEFINITIONS

ANTICOAGULANT is an agent that delays or prevents blood coagulation.

ATRIA are the upper chambers of the heart.

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member’s contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. REFERENCES


IX. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

<table>
<thead>
<tr>
<th>CPT Codes®</th>
<th>Description</th>
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<tbody>
<tr>
<td>93580</td>
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<tr>
<td>93799</td>
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<table>
<thead>
<tr>
<th>ICD-9-Procedure Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>35.52</td>
<td>Repair of atrial septal defect with prosthesis, closed technique</td>
</tr>
<tr>
<td>35.71</td>
<td>Other and unspecified repair of atrial septal defect (i.e., patent foramen ovale)</td>
</tr>
</tbody>
</table>
ICD-9-CM Diagnosis Code* | Description
---|---
429.71 | ACQUIRED CARDIAC SEPTAL DEFECT
745.5 | OSTIUM SECUNDUM TYPE ATRIAL SEPTAL DEFECT
745.61 | OSTIUM PRIMUM TYPE DEFECT
747.0 | PATENT DUCTUS ARTERIOSUS

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

The following ICD-10 diagnosis codes will be effective October 1, 2015:

| ICD-10-CM Diagnosis Code* | Description |
---|---|
I23.1 | Atrial septal defect as current complication following acute myocardial infarction
I23.2 | Ventricular septal defect as current complication following acute myocardial infarction
I51.0 | Cardiac septal defect, acquired
Q21.1 | Atrial septal defect
Q25.0 | Patent ductus arteriosus

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

X. POLICY HISTORY

<table>
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<th>CAC 1/28/03</th>
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<td>CAC 1/29/08 Consensus</td>
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<td>CAC 5/26/09</td>
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<td>CAC 5/25/10 Consensus</td>
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| | CAC 7/26/11 Adopted BCBA for PFO and ASD. Added list of labeled indications for Amplatzer Septal Occluder and GoreHelex Septal Occluder. Deleted information related to closure for PDA since it appears this procedure is a standard medical practice using an FDA approved device. Changed title to Closure Devices for Patent Foramen Ovale, and Atrial Septal Defects (ASD) (Formerly Closure Devices for Patent Foramen Ovale, Patent
<table>
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<tr>
<th>Policy Title</th>
<th>Closure Devices for Patent Foramen Ovale, and Atrial Septal Defects (ASD)</th>
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<tr>
<td>Policy Number</td>
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Ductus Arteriosus and Atrial Septal Defects). Minor wording changes to policy statements but intent is unchanged.

**CAC 8/28/12** Consensus review. References updated. No changes to policy statements. FEP variation added.
Codes reviewed klr

**CAC 7/30/13** Consensus review. References updated. No changes to the policy statements. Policy guidelines added. Admin code review complete.


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