



BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

Closure Devices for Patent Foramen Ovale and Atrial Septal Defects

Policy # 00016

Original Effective Date: 06/05/2002

Current Effective Date: 03/19/2014

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

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

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

Based on review of available data, the Company may consider transcatheter closure of secundum atrial septal defects (ASDs) to be **eligible for coverage** when patient selection criteria are met.

Patient Selection Criteria

Coverage eligibility for the use of transcatheter closure of secundum atrial septal defects (ASDs) will be considered when all of the following criteria are met:

- Device used is U.S. Food and Drug Administration (FDA) approved specifically for the transcatheter treatment of atrial septal defect; and
- Device is used according to the labeled indications; and
- 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.

When Services Are Considered Investigational

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

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

Based on review of the available data, the company considers closure of patent foramen ovale (PFO) using a transcatheter approach to be **investigational**. (There are currently no transcatheter devices with U.S. Food and Drug Administration (FDA) approval or clearance for this indication.)

Background/Overview

"Closure" devices are intended as less invasive, catheter-based approaches of repairing PFO or ASDs. These devices are alternatives to treatment with anti-platelet and/or anticoagulant medications in patients with cryptogenic stroke and a PFO.



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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 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.

Atrial Septal Defect

In contrast to PFO, which represents the persistence of normal fetal cardiovascular physiology, Atrial septal defects represent an abnormality in the development of the heart that results in free communication between the atria. Atrial septal defects 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 older than age 40 years. 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 age 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 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration

Two transcatheter devices received approval for marketing from the U.S. FDA in 2002 as a treatment for patients with cryptogenic stroke and PFO: the CardioSEAL[®] Septal Occlusion System and the Amplatzer[®] PFO 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



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safety and the probable clinical benefit. Clinical trials validating the device effectiveness are not required. The labeled indications of both limited the use of these devices to closure of PFO in patients with recurrent cryptogenic stroke due to presumed paradoxical embolism through a PFO and who have failed conventional drug therapy.

Following this limited FDA approval, the use of PFO closure devices increased by more than 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 (RCTs) 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 RCTs of these devices. Currently, all uses of closure devices to treat PFO are off-label uses.

At present, 2 devices are FDA approved for ASD closure: the AMPLATZERTM Septal Occluder, and the GORE HELEXTM Septal Occluder.

Centers for Medicare and Medicaid Services (CMS)

None

Rationale/Source

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 PFO.

Evidence on the efficacy of PFO closure devices consists of one 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 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



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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

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 HR 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 HR 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

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 HR 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 HR 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



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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. 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 HR 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. 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 HR 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.

Systematic reviews

Several systematic reviews of the observational studies have compared outcomes of PFO closure with medical therapy. 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. 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.



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Wohrle 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. 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. 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 (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. 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 4 years' 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 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, $p = \text{NS}$).

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 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%, $p =$



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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. 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 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 and colleagues 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 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. 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



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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 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. 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 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. 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 OR 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: 4-9.5%) compared to the percutaneous group (1.9%, 95% CI: 0.9-2.9%), for an OR 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. A study by Berger et al. showed identical 98% success rate in both treatment groups.

Single-arm studies show high success rates of ASD closure. The 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. In this evaluation study, closure was achieved in



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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 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. Finally, Brochu and colleagues evaluated 37 New York Heart Association (NYHA) Class I or II patients who underwent transcatheter closure of ASD. At 6-month follow-up, maximal oxygen uptake improved significantly and the dimensions of the right ventricle decreased significantly 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.

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

There have been numerous RCTs comparing PFO closure with medical therapy planned in the last two decades. However, these trials have been hampered by slow enrollment and some of the trials have been terminated due to low enrollment. A search of online site ClinicalTrials.gov using the keywords patent foramen ovale returned 38 studies. Four of these studies were RCTs that are listed as still 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.



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Summary

The evidence on the efficacy of closure devices for patients with PFO and cryptogenic stroke is insufficient to draw conclusions. One RCT of 909 patients reported that PFO closure does not reduce recurrent stroke or TIA compared to medical therapy. The results of this RCT 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 compared to medical therapy. The discrepancy in these results may arise from selection bias, since the non-randomized populations may differ on important clinical and demographic confounding variables. It is also possible that the rates of recurrent stroke following PFO closure are biased in the observational studies, since the RCT reported a rate of stroke following PFO closure that was much higher than the rates reported in the observational studies. Because the evidence does not support a benefit for percutaneous PFO closure, PFO closure devices are considered investigational for patients with cryptogenic stroke and 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.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	93580
HCPCS	C1817
ICD-9 Diagnosis	745.5, 745.61
ICD-9 Procedure	35.52, 35.71

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04/18/2002 Medical Policy Committee review
06/05/2002 Managed Care Advisory Council approval
06/24/2002 Format revision
03/31/2004 Medical Director review
04/20/2004 Medical Policy Committee review. Format revision. Coverage eligibility unchanged.
04/26/2004 Managed Care Advisory Council approval
04/05/2005 Medical Director review
04/19/2005 Medical Policy Committee review. Coverage eligibility unchanged. Investigational statement added to policy to address the use of transcatheter closure devices in situations where patient selection criteria are not met.

05/23/2005 Managed Care Advisory Council approval
04/05/2006 Medical Director review
04/19/2006 Medical Policy Committee approval. Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
07/07/2006 Format revised. Investigational statements added to clarify coverage eligibility. Coverage eligibility unchanged.

04/04/2007 Medical Director review
04/18/2007 Medical Policy Committee approval. Coverage eligibility unchanged.
04/02/2008 Medical Director review
04/16/2008 Medical Policy Committee approval. No change to coverage eligibility.
04/02/2009 Medical Director review
04/15/2009 Medical Policy Committee approval. Closure of patent foramen ovale using a transcatheter approach is now considered to be investigational.

04/08/2010 Medical Policy Committee approval.
04/21/2010 Medical Policy Implementation Committee approval. No change to coverage.
04/07/2011 Medical Policy Committee approval.
04/13/2011 Medical Policy Implementation Committee approval. No change to coverage.
04/12/2012 Medical Policy Committee review
04/25/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/04/2013 Medical Policy Committee review
04/24/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/06/2014 Medical Policy Committee review
03/19/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date: 03/2015

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***Investigational** – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
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 2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. reference to federal regulations.

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- A. in accordance with nationally accepted standards of medical practice;
- B. clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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