Percutaneous Patent Foramen Ovale (PFO) Closure (for Louisiana Only)

Policy Number: CS329LA.B
Effective Date: June 1, 2023

Instructions for Use

Table of Contents Page

Application

This Medical Policy only applies to the state of Louisiana.

Coverage Rationale

Note: This policy does not apply to individuals < 18 years of age.

Percutaneous patent foramen ovale closure for the prevention of recurrent ischemic stroke is proven and medically necessary when used according to U.S. Food and Drug Administration (FDA) labeled indications, contraindications, warnings and precautions and all of the following criteria are met:

- History of cryptogenic stroke confirmed by imaging; and
- A cardiologist and a neurologist agree that the stroke is likely embolic in nature; and
- Other causes of ischemic stroke have been ruled out including, but not limited to, carotid disease, hypercoagulable states or atrial fibrillation; and
- Individual is 18–60 years of age

Due to insufficient evidence of efficacy, percutaneous patent foramen ovale closure is unproven and not medically necessary for all other stroke or related neurological indications including, but not limited to, primary prevention of stroke, transient ischemic attacks, and migraine prevention.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
93580	Percutaneous transcatheter closure of congenital interatrial communication (i.e., Fontan fenestration, atrial septal defect) with implant

CPT® is a registered trademark of the American Medical Association

Description of Services

A stroke occurs when there is a loss of blood flow to the brain causing damage and tissue death. There are two types of strokes: ischemic and hemorrhagic. An ischemic stroke is caused by a blood clot that blocks a blood vessel in the brain. A hemorrhagic stroke is caused by a blood vessel that breaks and bleeds into the brain. A cryptogenic stroke is a type of ischemic stroke in which a specific cause is not found. In some individuals, the cause of a cryptogenic stroke may be due to a patent foramen ovale (PFO). A transient ischemic attack (TIA) occurs when the blood supply to the brain is blocked or interrupted for a short period of time but causes no permanent damage.

A PFO is a normal opening in the heart that is present in all people during fetal development. The opening is in the septal wall separating the left and right atria of the heart. Typically, this opening closes on its own after birth, but in some cases, the opening remains opened throughout adulthood. For the majority of people with a PFO, the condition does not cause any problems and requires no treatment. However, in some people with a PFO, small blood clots that form in the peripheral venous system may cross from the right to the left circulation and cause ischemic stroke if they reach the cerebral arterial circulation. Prevention of recurrent cryptogenic stroke in people with a PFO may be achieved through antithrombotic/anticoagulation therapy, surgery or percutaneous closure. While surgery is theoretically one treatment option, it is rarely used for this indication due to the inherent risks of surgery. Additionally, surgery has not been studied in comparison to percutaneous closure (American Heart Association, 2017).

Percutaneous or transcatheter PFO closure devices use catheter technology to access the heart and close the PFO without the need for open-heart surgery and cardiopulmonary bypass. Once in place, the device prevents blood, and potentially blood clots, from flowing between the heart's right and left atria.

Clinical Evidence

Stroke

A systematic review and meta-analysis of randomized controlled trials compared the safety and efficacy of percutaneous PFO closure (with medical therapy) versus medical therapy alone in patients with cryptogenic stroke or TIA. Among 3627 patients, 1829 were allocated to PFO closure and 1798 to medical treatment. The mean follow-up was 3.7 years. Results showed a significant reduction in ischemic stroke recurrence using the two currently FDA approved PFO closure devices. One study using the older STARFlex device showed no improvement. Combined data across all studies showed no significant reduction in all-cause mortality or TIA. New-onset atrial fibrillation occurred more frequently (five-fold) in the PFO group but resolved in 72% of cases within 45 days (Ntaios et al., 2018).

The following studies were included in the review:

- CLOSE (Mas et al., 2017) – used several PFO closure devices including the two currently FDA approved devices.
- REDUCE (Søndergaard et al., 2017) – Gore® Helex® (product discontinued) or Gore® Cardioform Septal Occluder.
- RESPECT (Carroll et al., 2013; Saver et al., 2017) – Amplatzer™ PFO Occluder.
- PC Trial (Meier et al., 2013) – Amplatzer™ PFO Occluder.
- CLOSURE I (Furlan et al., 2012) – STARFlex (no longer on the market).

Two other meta-analyses reached similar conclusions (Garg et al., 2018; Turc et al., 2018).

In a small randomized controlled trial (DEFENSE-PFO) published after the Ntaois et al. (2018) meta-analysis, Lee et al. (2018) reported that device closure in addition to medical therapy prevented secondary stroke events following cryptogenic stroke in patients with high-risk PFO. High-risk PFO was defined as PFO with atrial septal aneurysm, hypermobility or PFO size ≥ 2 mm. ClinicalTrials.gov. number NCT01550588.

A Hayes report concluded that there is some evidence that PFO closure is a relatively safe procedure with a very low incidence of serious complications and is associated with a lower risk of recurrent stroke or other cerebrovascular events than that seen with medical therapy alone. Cross study comparison is limited by the use of different devices (some that are no longer available), follow-up durations, and heterogeneous treatment parameters for adjunctive treatment with antiplatelet therapies. (Hayes, 2018; updated July 2022).

Migraine Prevention

The evidence is insufficient to support the use of PFO closure for treating migraines. Several randomized trials have failed to reach their primary endpoint of cessation or reduction in migraine days.

In a 2022 meta-analysis, Zhang et al. conducted a systematic review and meta-analysis to assess the utility and safety of migraine with and without aura. In total, three RCTs (MIST, PRIMA, and PREMIUM outlined below), one pooled study, and eight retrospective case series including 1,165 participants met the inclusion criteria. The results showed that compared to control intervention, PFO closure reduced monthly migraine attacks and days. A subgroup analysis showed complete resolution of migraine of those with aura, particularly those with frequent aura. In patients with migraines without aura, PFO closure did not significantly reduce migraine days or result in complete headache cessation. A low incident of adverse events occurred in all three RCTs, and included pericardial effusion, retroperitoneal bleed, access-site bleeding and device related events that resulted in atrial fibrillation. These were transient and recoverable, and some are routine following occlusion surgery. The authors concluded that PFO closure is safe and effective, especially for migraine with aura. This study is limited by the retrospective nature of the majority of the included studies, heterogenous post-surgical therapy and protocols for assessing outcome, and different devices used.

Mojadidi et al. (2021) conducted a pooled analysis of individual patient level data from 2 randomized migraine trials, (the PRIMA and PREMIUM trials outlined below), to assess the efficacy and safety of percutaneous device closure as a therapy for episodic migraine with or without aura at 12 months. 337 total participants were randomized, 176 to device PFO closure, and 161 to medical management only. Since the two trials used different endpoints, all were selected for the efficacy endpoints of this pooled analysis, and included responder rate, mean reduction in monthly migraine days, defined as ≥ 50% reduction in monthly migraine attacks, mean reduction in monthly migraine attacks, and the percentage of patients who experienced complete cessation of migraine. Additionally, a subgroup analysis was done on participants who have migraine with aura, particularly frequent aura (defined as aura occurring in 50% or more of the migraine attacks). The safety endpoint was major procedure and device-related adverse events. The results showed in the PFO closure group, a significant reduction in monthly migraine days at 12 months with the mean reduction of monthly migraine days 1.2 greater than the control group, no statistical difference in responder rate, and a significant mean reduction in migraine attacks, and a higher rate of complete migraine cessation when compared to medical therapy. In participants with migraine with aura and frequent aura compared to controls, there was a significant reduction in migraine days, and the responder rate was not significantly greater. Complete headache cessation occurred in 12 of 114 (11%) in the PFO closure group compared with 1 of 111 (0.9%) in the control group. In subjects without aura, complete headache cessation occurred in 2 of 43 (5%) in the PFO closure group compared with none in the control group. There was a total of 9 procedure related, and 4 device related adverse events. Procedure related adverse events were those that would be expected with any right heart catheterization including hematoma and transient hypotension. The most common device related adverse event was paroxysmal atrial fibrillation. All of the events were transient. The authors concluded that despite the clinical trials failing to reach primary endpoints, individual patient data supports PFO as reducing migraine burden in select patients at 12 months, and it is not known if the benefit extends beyond this time. This pooled analysis increases the power of the 2 trials assessed and PFO closure for treating migraine, especially with frequent aura, warrants further evaluation. The findings are limited by inclusion of selected studies.

In the CLOSE-MIG study, Mas et al. (2021) conducted a planned sub study of patients with migraines enrolled in the CLOSE randomized controlled trial. Of 473 patients randomized to PFO closure or antiplatelet therapy, 145 had migraines (75 with aura and 70 without aura). Sixty-seven patients were randomized to PFO closure and antiplatelet therapy and 78 to antiplatelet therapy alone. The primary outcome was the mean annual number of migraine attacks. Secondary outcomes were the proportion of patients with cessation of migraine attacks during the follow-up period, the proportion of patients who used migraine-preventive treatment during follow-up and the proportion of patients with substantial to severe migraine-related disability at 2 years. During a mean follow-up of about 5 years, PFO closure plus antiplatelet therapy did not significantly reduce the mean annual number of migraine attacks compared to antiplatelet therapy alone in migraine patients both with and without aura. There were also no statistically significant differences between treatment groups regarding cessation of migraine attacks, migraine-related disability at 2 years and use of migraine-preventive drugs.

In the PREMIUM study, Tobis et al. (2017) randomly assigned patients who had a PFO and medically intractable migraine with or without aura to undergo closure with the Amplatzer PFO Occluder (n = 123) or a sham procedure (n = 107). Both groups also received medical therapy. The procedure was generally safe, with only one device-related serious adverse event occurring during 1 year of follow-up. There was no difference between the groups in the percentage of responders (primary efficacy endpoint), defined as those having at least a 50% reduction in migraine attacks per month in months 10 through 12 after randomization. However, the PFO closure group had a lower mean number of headache days per month.

In the multicenter, prospective, randomized, open-label, international PRIMA trial, Mattle et al. (2016) investigated the effect of percutaneous PFO closure in patients with migraines refractory to medical treatment. Participants were randomized to PFO closure using the Amplatzer PFO Occluder (n = 53) or medical treatment (n = 54). The primary endpoint was reduction in monthly migraine days during months 9-12 after randomization compared with a 3-month baseline phase. The trial was terminated prematurely because of slow enrollment. Eighty-three patients (40 occluder, 43 control) completed 12-month follow-up. Mean migraine days at baseline were 8 (±4.7 SD) in the closure group and 8.3 (±2.4) in controls. Findings on the primary endpoint were inconclusive with -2.9 days after PFO closure versus -1.7 days in control group. In patients with refractory migraine with aura and PFO, closure did not reduce overall monthly migraine days.

In the MIST study, Dowson et al. (2009) evaluated the effectiveness of PFO closure to resolve refractory migraine headache. One hundred forty-seven patients were randomized to transcatheter PFO closure with the STARFlex implant (n = 74) or to a sham procedure (n = 73). Patients were followed up for 6 months. The primary efficacy end point was cessation of migraine headache 91 to 180 days after the procedure. No significant difference was observed in the primary end point of migraine headache cessation between implant and sham groups (3 of 74 versus 3 of 73, respectively). Secondary end points also were not achieved.

Clinical Practice Guidelines

Society for Cardiovascular Angiography and Interventions (SCAI)

The evidence based 2022 SCAI Guidelines for the Management of Patent Foramen Ovale make key recommendations for PFO closure to prevent PFO-associated stroke. Thirteen recommendations are made, based on five clinical scenarios, including recommendations for patients with and without a history of stroke, combined antiplatelet and anticoagulant therapy, as well as other less common conditions such as platypnea-orthodeoxia syndrome, thrombophilia and diving related decompression illness. SCAI also states that the decision to perform PFO closure on any patient for any clinical scenario should be highly individualized and nuanced in the context of a multi-disciplinary team. Furthermore, the following recommendations are made:

- PFO closure is recommended for prevention of recurrent PFO-associated stroke (strong recommendation).
- In persons experiencing migraines without a prior PFO-associated stroke, the guidelines suggest against the routine use of PFO closure for the treatment of migraine (conditional recommendation, moderate certainty of evidence).
- In persons with systemic embolism and without a prior PFO associated stroke, in whom other embolic etiologies have been excluded, the SCAI guideline panel suggests PFO closure rather than medical therapy alone (conditional recommendation, very low certainty of evidence).
- In persons with a history of transient ischemic attack (TIA) and without a prior PFO-associated stroke, the SCAI guideline panel suggests against PFO closure (conditional recommendation, very low certainty of evidence).

American Academy of Neurology (AAN)

An AAN practice advisory (Messé et al., 2020) makes the following recommendations for transcatheter PFO closure:

- In patients younger than 60 years with a PFO and an embolic-appearing infarct and no other mechanism of stroke identified, clinicians may recommend closure following a discussion of potential benefits (reduction of stroke recurrence) and risks (procedural complication and atrial fibrillation). Level C
- Clinicians may inform patients that presence of a large shunt probably is associated with benefit from closure. Conversely, there probably is less likelihood of benefit in patients with a small shunt or a non−embolic-appearing single, small, deep infarct, and it is uncertain whether atrial septal aneurysm in the absence of a large shunt influences the likelihood of benefitting from PFO closure. Level C
- PFO closure may be offered in other populations, such as for a patient who is 60−65 years old with a very limited degree of traditional vascular risk factors (i.e., hypertension, diabetes, hyperlipidemia, or smoking) and no other mechanism of stroke detected following a thorough evaluation, including prolonged monitoring for atrial fibrillation. Level C

- PFO closure may be offered to younger patients (e.g., < 30 years) with a single, small, deep stroke (< 1.5 cm), a large shunt, and absence of any vascular risk factors that would lead to intrinsic small vessel disease such as hypertension, diabetes, or hyperlipidemia. Level C
- In a patient for whom PFO closure is being considered, a shared decision-making approach between clinicians and the patient should be used, exploring how well the patient's attributes match those included in the positive PFO closure trials and the patient's preferences and concerns regarding risk of stroke recurrence and risk of adverse events. Level B

Level B indicates a recommendation that should be done. In most circumstances, adherence to the recommendation will likely improve health-related outcomes.

Level C represents a recommendation that may be done. In some circumstances, adherence to the recommendation might improve health-related outcomes.

American Heart Association/American Stroke Association (AHA/ASA)

The AHA/ASA guidelines for the secondary prevention of stroke state that it is reasonable to percutaneously close a PFO in individuals who meet each of the following criteria: age 18–60 years of age, nonlacunar stroke, no other identified cause and high-risk PFO features (Kleindorfer et al., 2021).

The AHA/ASA guidelines for the primary prevention of stroke state that given the uncertainties and relatively low risk of initial stroke caused by PFO and the potential risk of antithrombotic therapy or invasive treatments, no treatment is recommended for the primary prevention of stroke in people with PFO (Meschia et al., 2014).

National Institute for Health and Care Excellence (NICE)

A NICE report concluded that evidence on the efficacy of percutaneous PFO closure for recurrent migraine is inadequate in quality and quantity. The evidence on safety shows a small incidence of well-recognized but sometimes serious adverse events, including device embolization and device prolapse (each reported in less than 1% of patients) (NICE, 2010).

A NICE report concluded that evidence on the safety of percutaneous PFO closure to prevent recurrent cerebral embolic events shows serious but infrequent complications. Evidence on its efficacy is adequate (NICE, 2013).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Transcatheter PFO closure is a procedure and, therefore, is not subject to FDA regulation. However, the devices designed for PFO occlusion are subject to FDA regulation. These devices are regulated by the premarket approval process and are classified as transcatheter septal occluders (product code MLV).

The Amplatzer™ PFO Occluder (Abbott) received FDA premarket approval (P120021) on October 28, 2016. The device is indicated for percutaneous transcatheter closure of a patent foramen ovale (PFO) to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P120021. (Accessed October 7, 2022)

As a supplement to the original PMA, the Amplatzer™ Talisman™ PFO Occluder received FDA premarket approval (P120021, S020) on September 27, 2021. The device is a line extension of the current Amplatzer™ PFO Occluder product family.

The Gore® Cardioform Septal Occluder (W.L. Gore) received FDA premarket approval (P050006/S060) on July 31, 2017. The device is indicated for the percutaneous, transcatheter closure of the following defects of the atrial septum:
- Ostium secundum atrial septal defects
- PFO to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke.

Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P050006S060. (Accessed October 7, 2022)

References

American Heart Association (AHA). Patent foramen ovale (PFO). Last reviewed March 31, 2017. Available at: https://www.heart.org/en/health-topics/congenital-heart-defects/about-congenital-heart-defects/patent-foramen-ovale-pfo. Accessed October 7, 2022.

Carroll JD, Saver JL, Thaler DE, et al.; RESPECT Investigators. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. N Engl J Med. 2013 Mar 21;368(12):1092-100.

Dowson A, Mullen MJ, Peatfield R, et al. Migraine Intervention With STARFlex Technology (MIST) trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache. Circulation. 2008 Mar 18;117(11):1397-404. Erratum in: Circulation. 2009 Sep 1;120(9):e71-2.

Furlan AJ, Reisman M, Massaro J, et al.; CLOSURE I Investigators. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. N Engl J Med. 2012 Mar 15;366(11):991-9.

Garg L, Haleem A, Varade S, et al. Patent foramen ovale closure in the setting of cryptogenic stroke: a meta-analysis of five randomized trials. J Stroke Cerebrovasc Dis. 2018 Sep;27(9):2484-2493.

Hayes, Inc. Comparative Effectiveness Review. Transcatheter closure of patent foramen ovale for prevention of recurrent cryptogenic stroke. Lansdale, PA: Hayes, Inc.; May 2018. Updated July 2022.

Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 Guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. Stroke. 2021 Jul;52(7):e364-e467. Erratum in: Stroke. 2021 Jul;52(7):e483-e484.

Kuijpers T, Spencer FA, Siemieniuk RAC, et al. Patent foramen ovale closure, antiplatelet therapy or anticoagulation therapy alone for management of cryptogenic stroke? A clinical practice guideline. BMJ. 2018 Jul 25;362:k2515.

Lee PH, Song JK, Kim JS, et al. Cryptogenic stroke and high-risk patent foramen ovale: the DEFENSE-PFO trial. J Am Coll Cardiol. 2018 May 22;71(20):2335-2342.

Mas JL, Guillon B, Charles-Nelson A, et al.; CLOSE investigators. Patent foramen ovale closure in stroke patients with migraine in the CLOSE trial. The CLOSE-MIG study. Eur J Neurol. 2021 Aug;28(8):2700-2707.

Mas JL, Derumeaux G, Guillon B, et al.; CLOSE Investigators. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. N Engl J Med. 2017 Sep 14;377(11):1011-1021.

Mattle HP, Evers S, Hildick-Smith D, et al. Percutaneous closure of patent foramen ovale in migraine with aura, a randomized controlled trial. Eur Heart J. 2016 Jul 7;37(26):2029-36.

Meier B, Kalesan B, Mattle HP, et al.; PC Trial Investigators. Percutaneous closure of patent foramen ovale in cryptogenic embolism. N Engl J Med. 2013 Mar 21;368(12):1083-91.

Meschia JF, Bushnell C, Boden-Albala B, et al.; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Functional Genomics and Translational Biology; Council on Hypertension. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014 Dec;45(12):3754-832.

Messé SR, Gronseth GS, Kent DM, et al. Practice advisory update summary: Patent foramen ovale and secondary stroke prevention: Report of the Guideline Subcommittee of the American Academy of Neurology. Neurology. 2020 May 19;94(20):876-885.

Mojadidi MK, Kumar P, Mahmoud AN, et al. Pooled analysis of PFO occluder device trials in patients with PFO and migraine. J Am Coll Cardiol. 2021 Feb 16;77(6):667-676.

National Institute for Health and Care Excellence (NICE). Percutaneous closure of patent foramen ovale to prevent recurrent cerebral embolic events. IPG 472. December 2013.

National Institute for Health and Care Excellence (NICE). Percutaneous closure of patent foramen ovale for recurrent migraine. IPG 370. December 2010.

Ntaios G, Papavasileiou V, Sagris D, et al. Closure of patent foramen ovale versus medical therapy in patients with cryptogenic stroke or transient ischemic attack: updated systematic review and meta-analysis. Stroke. 2018 Feb;49(2):412-418.

Saver JL, Carroll JD, Thaler DE, et al.; RESPECT Investigators. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. N Engl J Med. 2017 Sep 14;377(11):1022-1032.

Society for Cardiovascular Angiography and Interventions (SCAI). Guidelines for the Management of Patent Foramen Ovale. May 2022.

Søndergaard L, Kasner SE, Rhodes JF, et al.; Gore REDUCE Clinical Study Investigators. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. N Engl J Med. 2017 Sep 14;377(11):1033-1042.

Tobis JM, Charles A, Silberstein SD, et al. Percutaneous closure of patent foramen ovale in patients with migraine: the PREMIUM trial. J Am Coll Cardiol. 2017 Dec 5;70(22):2766-2774.

Turc G, Calvet D, Guérin P, et al.; CLOSE Investigators. Closure, anticoagulation, or antiplatelet therapy for cryptogenic stroke with patent foramen ovale: systematic review of randomized trials, sequential meta-analysis, and new insights from the CLOSE study. J Am Heart Assoc. 2018 Jun 17;7(12). pii: e008356.

Zhang Y, Wang H, Liu L. Patent foramen ovale closure for treating migraine: a meta-analysis. J Interv Cardiol. 2022 Feb 2;2022:6456272.

Policy History/Revision Information

Date	Summary of Changes
06/01/2023	Supporting Information • Updated *Clinical Evidence*, *FDA*, and *References* sections to reflect the most current information • Archived previous policy version CS329LA.A

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.