Medical Policy

Subject:	Patent Foramen Ovale and Left Atrial Appendage Closure Devices for Stroke Prevention		
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Description/Scope

This document addresses the transcatheter closure of patent foramen ovale and transcatheter or open left atrial appendage (LAA) closure when performed to prevent stroke using cardiac occlusion devices.

Note: This document does not address the percutaneous transcatheter closure of atrial septal defects (ASDs).

Note: This document does not address surgical ligation or amputation of the LAA when the surgical method does not involve use of an LAA device.

Note: Please see the following related document for additional information:

- SURG.00096 Surgical and Ablative Treatments for Chronic Headaches

Position Statement

Medically Necessary:

Transcatheter closure of a patent foramen ovale (PFO) using a U.S. Food and Drug Administration (FDA) approved device approved for that indication is considered **medically necessary** for:

A. The prevention of subsequent stroke in individuals with a history of cryptogenic stroke who:
    1. have failed conventional drug therapy (for example, warfarin); **or**
    2. are not candidates for conventional drug therapy; **or**
B. Individuals 60 years old and younger with a history of cryptogenic stroke who have:
    1. an atrial septal aneurysm; **or**
    2. a large interatrial shunt (*see definition section*).

Transcatheter closure of left atrial appendage (LAA) is considered **medically necessary** in individuals with non-valvular atrial fibrillation for the prevention of stroke when the following criteria are met:

A. Individual is a candidate for long-term anticoagulation therapy based upon their estimated risk of stroke and other thromboembolic events; **and**
B. Individual is ineligible for long-term oral anticoagulation therapy (for example, a direct oral anticoagulant [apixaban, dabigatran, edoxaban, or rivaroxaban] or warfarin) due to the presence of contraindication(s) (for example, an increased risk of bleeding), but is expected to be able to tolerate short-term oral anticoagulation necessary for device implantation.

Investigational and Not Medically Necessary:

Transcatheter closure of a patent foramen ovale for the prevention of stroke is considered **investigational and not medically necessary** when the criteria above are not met.

Transcatheter closure of a left atrial appendage is considered **investigational and not medically necessary** when the criteria above are not met.

Left atrial appendage closure via surgical (non-percutaneous) implantation of a device is considered **investigational and not medically necessary** for all indications.

Rationale

Transcatheter Closure of Patent Foramen Ovale (PFO)

A transcatheter PFO occluder is a permanently implanted device that provides a non-surgical method for PFO closure, blocking clots from passing from the right atrium to the left atrium. There was limited early evidence to support the net benefit of transcatheter closure of a PFO, in individuals with a history of cryptogenic stroke who have failed, or who are not candidates for medical anticoagulation therapy, mostly in the form of case series. These studies reported that the risk of an embolic event after transcatheter closure was comparable to open surgical closure, with minimal complications. An advisory article by O'Gara and colleagues (2009) reviewed studies of participants that underwent transcatheter closure for the treatment of PFO for stroke prevention. There is no clear objective evidence to demonstrate that either medical therapy (antiplatelet agents or vitamin K antagonists), transcatheter closure, or open surgical closure are superior treatment options for the prevention of transient ischemic attack (TIA) or recurrent stroke in individuals with cryptogenic stroke. Randomized controlled trials are needed to establish the safety and efficacy, as well as to determine the benefits, of one treatment option over another.

On October 28, 2016 the FDA granted premarket approval for the AMPLATZER™ PFO Occluder (Abbott Medical, Plymouth, MN). The device is indicated for percutaneous transcatheter closure of a PFO to reduce the risk of recurrent ischemic stroke in individuals (predominantly between ages 18 to 60 years of age) 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. On September 27, 2021the FDA granted premarket approval for the AMPLATZER™ Talisman™ PFO Occluder (Abbott Medical, St. Paul, MN); a line extension of the current AMPLATZER PFO Occluder Product Family (AMPLATZER Talisman PFO Occluder Product Information, 2021).

In 2013, Carroll and colleagues conducted the RESPECT trial (NCT00465270), a prospective, multicenter, randomized study that enrolled individuals aged 18 to 60 years with a PFO and history of a cryptogenic stroke. Participants were randomized (1:1) to either the device group with PFO closure using the AMPLATZER PFO Occluder or the medical management group with four medical regimens allowed (aspirin alone, Coumadin alone, clopidogrel alone, or aspirin combined with dipyridamole). The primary efficacy endpoint was a composite outcome, which included recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization (i.e., death from any cause within 30 days after implantation or 45 days after randomization, whichever occurred later, and in the medical-therapy group, death from any cause within 45 days after randomization). Secondary efficacy endpoints included complete closure of the PFO on the 6-month follow-up transesophageal echocardiography (TEE), the absence of recurrent symptomatic nonfatal ischemic stroke or

cardiovascular death, and absence of a TIA. The investigators designed the trial to have 80% power and a 2-sided alpha level of 0.05 to detect a 75% relative risk reduction (based on the assumption that the 2-year primary endpoint rate would be 4.3% in the medical management group and 1.05% in the closure group). A total of 980 individuals participated with 499 randomly assigned to the closure group and 481 to the medical management group. In the intention-to-treat (ITT) analysis, a total of 25 primary end-point events occurred (9 in the closure group and 16 in the medical management group), all of which were nonfatal ischemic strokes (hazard ratio [HR], 0.49; 95% confidence interval [CI], 0.22 to 1.11; p=0.08). The rates of recurrent stroke differed in the per-protocol and medical management group (p=0.03) and the as-treated group and medical management group (p=0.007). There was no difference in the rate of serious adverse events between the groups. The authors concluded that:

> in patients between 18 and 60 years of age who had had a cryptogenic ischemic stroke, there was no significant benefit of closure of a patent foramen ovale over medical therapy alone in the intention-to-treat analysis. The superiority of closure with the use of the Amplatzer PFO Occluder was shown in two prespecified secondary analyses, with a low rate of associated risks.

In 2017, Saver and colleagues conducted an exploratory analysis to report long-term results from the RESPECT trial (NCT00465270) that compared PFO closure with AMPLATZER PFO Occluder (PFO closure group) to medical therapy alone (that is, aspirin, warfarin, clopidogrel, or aspirin combined with extended-release dipyridamole) for individuals at risk of recurrence of ischemic stroke who had cryptogenic stroke. Of the 980 individuals who enrolled in the original trial, 716 (73.1%) were included in the long-term analysis. Median follow-up was 5.9 years with a greater dropout rate in the medical therapy only group. In the ITT population, there were 18 participants in the PFO closure group that had recurrent ischemic stroke and in the medical therapy alone group there were 28 participants. A total of 10 participants in the PFO closure group and 23 participants in the medical therapy alone group had recurrent ischemic stroke of undetermined cause. The authors found that:

> The rate of venous thromboembolism in both groups exceeded that in healthy populations, which suggests that persons who have had a cryptogenic stroke and also have a PFO have a mildly elevated long-term risk of venous thromboemboli. In our trial, the lower intensity of antithrombotic therapy, including the less common agents, in the PFO closure group than in the medical-therapy group may have contributed to the higher rate of venous thromboembolism in the PFO closure group.
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> Among adults who had had a cryptogenic ischemic stroke, closure of a PFO was associated with a lower rate of recurrent ischemic strokes than medical therapy alone during extended follow-up…The relative difference in the rate of recurrent ischemic stroke between PFO closure and medical therapy alone was large (45% lower with PFO closure), but the absolute difference was small (0.49 fewer events per 100 patient-years with PFO closure).

In summary, the authors found that during the follow-up period, participants with a history of cryptogenic stroke due to PFO that underwent PFO closure had a lower rate of recurrent ischemic strokes than those that received medical therapy alone.

In 2017, Mas and colleagues reported results from the CLOSE study (NCT00562289), a multicenter, randomized (1:1:1), open-label study that evaluated participants who had a *recent cryptogenic stroke* (if no retinal ischemia): stroke (or retinal stroke) with no identifiable cause other than PFO with or without aspirin, based on a detailed

etiological work-up, performed under the neurologist's responsibility. Participants who enrolled had cryptogenic stroke attributed to PFO, with atrial septal aneurysm (defined as excursion of the septum primum greater than 10 mm on TEE); or large interatrial shunt (defined as presence of more than 30 microbubbles in the left atrium within three cardiac cycles after opacification of the right atrium, based on transthoracic echocardiography [TTE] or TEE). Exclusion criteria included any other cause of stroke associated with PFO, other medical indications for long-term anticoagulant or antiplatelet therapy, or increased bleeding risks. Participants (16 to 60 years of age) were assigned to either PFO closure plus long-term antiplatelet therapy (PFO group; n=238), anticoagulation alone group (n=187), or antiplatelet-only group (n=235); participants that had identified contraindication to anticoagulation therapy or PFO closure were assigned to alternative noncontraindicated treatment or to antiplatelet therapy. There were no reported strokes among the PFO group, 14 strokes occurred among the antiplatelet-only group (HR, 0.03; 95% CI, 0 to 0.26; p<0.001). Procedural complications were reported in 14 (5.9%) participants in the PFO closure group. Among the groups, adverse events did not differ significantly. The authors concluded that:

> In conclusion, among patients 16 to 60 years of age who had had a recent cryptogenic stroke attributed to PFO with an associated atrial septal aneurysm or large interatrial shunt, the rate of stroke recurrence was lower among those assigned to PFO closure plus long-term antiplatelet therapy than with antiplatelet therapy alone. The effects of oral anticoagulant therapy as compared with antiplatelet therapy on the risk of stroke recurrence could not be determined.

In April 2018, the FDA granted premarket approval for the GORE® CARDIOFORM Septal Occluder (W.L. Gore & Associates, Inc., Flagstaff, AZ), a permanently implanted device indicated in PFO to reduce the risk of recurrent ischemic stroke in individuals (predominantly between 18-60 years of age) 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. The device is contraindicated in individuals who are unable to take antiplatelet or anticoagulation therapy. The FDA approval is based on data reported by Sondergaard and colleagues (2017) from the REDUCE (NCT00738894) study, an international, prospective, randomized (2:1 ratio), controlled, open-label trial that evaluated participants who underwent PFO closure plus antiplatelet therapy (PFO group; n=441) or received antiplatelet therapy alone (antiplatelet-only group; n=223). During a median follow-up of 3.2 years, 6 participants (1.4%) in the PFO group and 12 participants (5.4%) in the antiplatelet-only group had a clinical ischemic stroke (HR, 0.23; 95% CI, 0.09 to 0.62; p=0.002). There was a lower incidence of brain infarctions reported in the PFO group (n=22; 5.7%) versus the antiplatelet group only (n=20; 11.3%). Fewer serious adverse events were reported among the PFO group than the antiplatelet-only group, 23.1% versus 27.9% respectively. The authors concluded that:

> In conclusion, among patients who had cryptogenic stroke most likely attributed to PFO, the risk of recurrent stroke and now brain infarction were significantly lower with closure of the PFO plus antiplatelet therapy than with antiplatelet therapy alone.

Lee and colleagues (2018) reported results from the DEFENSE PFO (Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients with High-Risk Patent Foramen Ovale) trial. The study enrolled 120 participants with history of cryptogenic stroke and high-risk PFO, and participants underwent randomization and were divided between PFO closure group and medication-only group. The study primary endpoint was a composition of stroke, vascular death, or thrombosis in myocardial infarction (TIMI) - defined major bleeding during a 2-year follow-up period. All participants in the PFO group had a successful PFO closure, therefore no event of primary endpoint occurred in the PFO closure group. The primary endpoint occurred in 6 of 60 participants in the medication-only

group; 2-year event rate: 12.9% (95% CI), 2-year rate of ischemic stroke: 10.5% (p=0.023). In the medication-only group, the events included ischemic stroke (n=2), and transient ischemic attack (n=1). Nonfatal procedural complications included development of atrial fibrillation (n=2), pericardial effusion (n=1), and pseudoaneurysm (n=1). In summary, the authors concluded that:

> In patients who had a recent cryptogenic stroke attributed to PFO with a large PFO, atrial septal aneurysm, or hypermobility, the rate of primary composite endpoint as well as stroke recurrence was lower with combined PFO closure in combination with medication than with medication therapy alone.

In 2020 the American Academy of Neurology (AAN) Guideline Subcommittee provided a practice advisory update summary: patent foramen ovale and secondary stroke prevention. The committee found evidence that PFO may play a role in some individuals with cryptogenic stroke older than 60 years. The subcommittee recommended that:

> PFO closure may be offered in other populations, such as for a patient who is aged 60-65 years 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.

PFO closure in individuals with only a history of a TIA (but without a prior cryptogenic stroke) has not been rigorously evaluated; studies directly investigating the effect of PFO closure in individuals with TIA are lacking. The 2022 Society for Cardiovascular Angiography and Interventions (SCAI) Guidelines for the Management of Patent Foramen Ovale provides the following recommendation:

> Recommendation 1.7 In persons with a history of TIA and without a prior PFO-associated stroke, the SCAI guideline panel suggests against PFO closure (*conditional recommendation*, very low certainty of evidence).
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> Other considerations
> By definition, TIA patients have normal neuroimaging and no persistent clinical neurologic deficits, so an ischemic etiology for any given neurologic clinical presentation cannot be proven with confidence. Therefore a suspected TIA cannot be differentiated from complex migraine nor from any other cause of transient neurological symptoms.
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> The guideline panel determined that there is very uncertain benefit from PFO closure in this population…Further research is necessary to ascertain the benefits and harms of closure in this population.

The 2021 AHA/ASA Guideline for the prevention of stroke in individuals with stroke and transient ischemic attack does not recommend PFO closure outside of individuals with a nonlacunar ischemic stroke (on neuroimaging) of undetermined cause and a PFO.

Left Atrial Appendage (LAA) (Transcatheter or Non-percutaneous) Closure

Transcatheter closure of an LAA is a new treatment strategy that prevents travel of an LAA thrombus out of the LAA in individuals with non-valvular atrial fibrillation (AF). The LAA closure system is introduced in the right atrium and then passed into the left atrium through a PFO or through a puncture hole. The Holmes and colleagues

(2009) randomized non-inferiority trial compared LAA closure using the WATCHMAN™ LAA Closure Device (Boston Scientific, Marlborough, MA) versus warfarin therapy for prevention of stroke in individuals with AF. The study evaluated efficacy between the interventional group and the warfarin group based upon the primary endpoint of reported cardiovascular death (n=5 vs. n=10), all types of stroke (n=16 vs. n=12), and systemic embolism (n=2 vs. n=0). Researchers reported a higher occurrence of primary safety events in the interventional group compared to the warfarin therapy group; serious adverse events included major bleeding, pericardial effusion and device embolization. The authors concluded:

> Thus, our strategy for closing the LAA was non-inferior to warfarin therapy in terms of primary efficacy endpoint of all stroke, cardiovascular death, and systemic embolism. Although there is a higher initial safety event rate for device implantation, adverse events were without long term sequelae for most patients. Closure of the LAA might provide an alternative strategy to chronic warfarin therapy for stroke prophylaxis in patients with non-valvular atrial fibrillation.

A study by Reddy and colleagues (2011) reported on preliminary outcomes from the Watchman LAA System for Embolic Protection in Patients with AF (PROTECT AF) trial and Continued Access PROTECT AF Registry (CAP Registry). Although with improved procedural experience there was a decline in safety events reported, there remains a higher risk of complications. The FDA granted PMA approval March 2015 for the WATCHMAN LAA Closure Device in individuals with non-valvular AF in facilities equipped for heart surgery as an alternative option to long-term warfarin therapy. According to the manufacturer, Boston Scientific Corporation:

> WATCHMAN is indicated to reduce the risk of thromboembolism from the left atrial appendage in patients with non-valvular atrial fibrillation who are at increased risk for stroke and systemic embolism based on $CHADS_2$ or CHA_2DS_2-VASc scores, are deemed by their physicians to be suitable for warfarin; and have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.

In 2014, Reddy and colleagues reported long-term outcomes of the PROTECT AF trial. The randomized, multicenter study enrolled 707 participants with nonvalvular AF (NVAF) and at least one additional stroke risk factor ($CHADS_2$ score greater than or equal to 1) who were randomized 2:1 to undergo left atrial appendage closure with the WATCHMAN LAA Closure Device (n=463, treatment group) or warfarin therapy (n=244, control group). The trial demonstrated a noninferior rate of cardiovascular death, stroke or systemic embolism, compared with warfarin alone. The authors concluded:

> After 3.8 years of follow-up among patients with nonvalvular AF at elevated risk for stroke, percutaneous LAA closure met criteria for both noninferiority and superiority, compared with warfarin, for preventing the combined outcome of stroke, systemic embolism, and cardiovascular death, as well as superiority for cardiovascular and all-cause mortality.

A multicenter, randomized, clinical trial PREVAIL assessed safety and efficacy of the WATCHMAN LAA Closure device versus long-term warfarin in individuals with NVAF who had a $CHADS_2$ score of 2 or more ($CHADS_2$ score of 1 and another risk factor were eligible) (Holmes, 2014). Exclusion criteria included contraindication to warfarin or aspirin, stroke/transient ischemic attack within the last 90 days, symptomatic carotid disease, PFO or atrial septal defect (ASD), thromboembolism or bleeding. PREVAIL enrolled 407 participants, assigned randomly (2:1 ratio) to

the device group (n=269) or control group (n=138). Unlike the PROTECT AF trial the PREVAIL did not demonstrate noninferiority in overall efficacy. The authors report that:

> At 18 months, the rate of the first co primary efficacy endpoint (composite of stroke, systemic embolism [SE], and cardiovascular/unexplained death was 0.064 in the device group versus 0.063 in the control group (rate ratio 1.07 [95% credible interval (Crl): 0.57 to 1.89]) and did not achieve the pre-specified criteria noninferiority (upper boundary of 95% Crl ≥1.75). The rate for the second co-primary efficacy endpoint (stroke or SE > 7 days' post randomization) was 0.0253 versus 0.0200 (risk difference 0.0053 [95% Crl: -0.0190 to 0.0273], achieving noninferiority. Early safety events occurring in 2.2% of the Watchman arm, significantly lower than in PROTECT AF, satisfying the pre-specified safety performance goal. Using a broader, more inclusive definition of adverse events, these still were lower in PREVAIL (Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trial than in PROTECT AF (4.2% vs. 8.7%; p=0.004). Pericardial effusions requiring surgical repair decreasing from 1.6% to 0.4% (p=0.36), although the number of events was small.
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> LAA occlusion was noninferior to warfarin for ischemic stroke prevention or SE >7 days post-procedure. Although noninferiority was not achieved for overall efficacy, event rates were low and numerically comparable in both arms. Procedural safety has significantly improved. This trial provides additional data that LAA occlusion is a reasonable alternative to warfarin therapy for stroke prevention in patients with NVAF who do not have an absolute contraindication to short-term warfarin therapy.

Two randomized controlled trials have compared use of the WATCHMAN device for LAA closure in individuals with AF eligible for anticoagulation therapy. The peer-reviewed published literature suggests that the WATCHMAN is associated with an increased periprocedural ischemic stroke risk. There is limited evidence supporting the net benefit of transcatheter closure of an LAA with the WATCHMAN LAA Closure device, in individuals with non-valvular AF who are deemed eligible for systemic anticoagulation. Further studies are needed to determine if the long-term risk of systemic anticoagulation exceeds the periprocedural risk of device implantation.

Reddy and colleagues (2017) reported final results from the PREVAIL trial and as part of a meta-analysis with PROTECT AF trial followed for 5 years. Participants underwent LAAC with the WATCHMAN or treatment with warfarin. The authors reported results:

> For the PREVAIL trial, the first composite coprimary endpoint of stroke, systemic embolism (SE), or cardiovascular/unexplained death did not achieve noninferiority (posterior probability for noninferiority = 88.4%), whereas the second coprimary endpoint of post-procedure ischemic stroke/SE did achieve noninferiority) posterior probability for noninferiority = 97.5%); the warfarin arm maintained an unusually low ischemic stroke rate (0.73%). In the meta-analysis, the composite endpoint was similar between groups (hazard ratio [HR]: 0.820; p=0.27), as were all-stroke/SE (HR: 0.961; p=0.87). The ischemic stroke/SE rate was numerically higher with LAAC, but this difference did not reach statistical significance (HR: 1.71; p=0.080). However, differences in hemorrhagic stroke, disabling/fatal stroke, cardiovascular/unexplained death, all-cause death, and

post-procedure bleeding favored LAAC (HR: 0.20; p=0.0022; HR: 0.45; p=0.03; HR: 0.59; p=0.027; HR: 0.73; p=0.0003, respectively).

The 2019 American Heart Association (AHA)/ American College of Cardiology (ACC)/ Heart Rhythm Society (HRS) focused update of the 2014 AHA/ACC/HRS guidelines for the management of atrial fibrillation issued a category IIb (weak) recommendation, indicating "percutaneous LLA occlusion may be considered in patients with AF at increased risk of stroke who have contraindications to long-term anticoagulation" (January, 2019). The HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drug/alcohol concomitantly) score is used to assess major bleeding risk factors in individuals with AF being considered for anticoagulation. The $CHADS_2$ score (congestive heart failure, hypertension, age > 75 years, diabetes mellitus, stroke/transient ischemia attack/thromboembolism) and the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism [doubled], vascular disease, age 65 to 74 years, sex category) are commonly used for stroke risk stratification in individuals with AF. The authors further concluded:

> Oral anticoagulation remains the preferred therapy for stroke prevention for most patients with AF and elevated stroke risk. However, for patients who are poor candidates for long-term oral anticoagulation (because of the propensity for bleeding or poor drug tolerance or adherence), the Watchman device provides an alternative. There are important differences in wording between the FDA approval and the Centers for Medicare & Medicaid Services (CMS) approval. In the FDA approval, the device was restricted to patients who were deemed suitable for long-term warfarin (mirroring the inclusion criteria for enrollment in the clinical trials) but had an appropriate rationale to seek a nonpharmacological alternative to warfarin. Conversely, CMS states that the device is an option for patients who are suitable for short-term warfarin but deemed unable to take long-term oral anticoagulation. CMS has specified that patients should have a $CHADS_2$ score ≥2 or a CHA_2DS_2-VASc score ≥3 to be considered for the device. A number of unresolved issues remain, including the optimal patient selection and periprocedural antithrombotic regimen.
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> The current FDA labeling specifies that patients should be deemed suitable for anticoagulation and, in particular, a period of periprocedural anticoagulation. Patients unable to take oral anticoagulation were excluded from the Watchman RCTs [randomized control trial]. However, there is increasing experience outside the United States with LAA closure in oral anticoagulation–ineligible patients using an antiplatelet regimen only, and this is the focus of an ongoing RCT.

Boersma and colleagues (2019) reported periprocedural, 2-year outcome data from the prospective, multicenter, multinational EWOLUTION registry (Evaluating Real-life Clinical Outcomes in Atrial Fibrillation Patients Receiving the WATCHMAN Left Atrial Appendage Closure Technology). Overall safety and efficacy data are presented in a subgroup of participants who are at very high-risk of stroke or bleeding, including those with a history of ischemic and hemorrhagic stroke and those with prior bleeding episodes. In total, 1020 participants (age 73.4±8.9 years) underwent implantation with the WATCHMAN device. While 72 percent of participants were deemed unsuitable for oral anticoagulation by their physicians, data was not readily provided on the reason for contraindication to anticoagulation therapy. At the time of hospital discharge, after successful WATCHMAN placement, 94% of participants were on some form of anticoagulation or antiplatelet drug, and by study-end, 86%

were using some form of anticoagulation therapy or antiplatelet drug (8% were using oral anticoagulation, 7% were on dual antiplatelet therapy and 71% were on single antiplatelet therapy). At 2-year follow-up, 16.4% (n=161) of participants that underwent a WATCHMAN LAAC had died; 4.5% (n=46) had a cardiovascular reason (most commonly reported was heart failure) and 1% (n=10) were from fatal bleeding (6 were gastrointestinal bleeds while the other 4 were cerebral; only 1 participant was not taking an anticoagulant at time of death). The composite risk of ischemic stroke/TIA/embolic event was 2.0/100 patient-years (46 thromboembolic events in 35 participants, of which 22 were ischemic stroke (5 disabling), 23 were TIA, and one was an systemic embolism), which the authors compare to a historical rate of 10.0/100 patient-years based on CHA_2DS_2-VASc (congestive heart failure, hypertension, 75 years of age and older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease 65 to 74 years of age, female; left ventricular ejection fraction) score. In 835 participants with imaging of the LAA, a total of 34 cases of device-related thrombus (4.1%) were observed, resulting in 21 participants initiating treatment, and 1 major GI bleed which resolved. By study-end, resolution occurred in all but 1 participant (6 were lost to followed-up), no subsequent reports of embolic events were reported. Stroke and bleeding rates did not appear to differ by anticoagulation treatment strata, although it is difficult to draw conclusions based on the registry nature of the study. In summary, the study is limited by its registry design; determining the absolute or relative benefit and risks of the WATCHMAN device versus standard treatment in the population studied is unclear given the lack of a randomized comparable prospective treatment arm. A high number of participants enrolled in EWOLUTION also died during the 2 years of follow-up. A majority of individuals also remained on some form of anticoagulation therapy or antiplatelet drug despite being deemed unsuitable for short- or long-term oral anticoagulation at the time of implant, thus continued use of any form of oral anticoagulation or antiplatelet drug may play a role in thromboembolic event prevention.

In June 2020, the FDA approved the next generation WATCHMAN FLX Left Atrial Appendage Closure Device, which is the first device to be fully recapturable for repositioning and redeployment. This generation of the device is available in various sizes and a reduced device length to accommodate a variety of LAA anatomy.

In 2021, Kar and colleagues published results from the Protection Against Embolism for Nonvalvular AF (NVAF) Patients: Investigational Device Evaluation of the Watchman FLX LAA Closure Technology (PINNACLE FLX) trial. This prospective, nonrandomized, multicenter trial evaluated safety and effectiveness of the WATCHMAN FLX LLA closure device. Eligible participants had NVAF, a CHA_2DS_2-VASc score of ≥ 2 for men or ≥ 3 for women, able to take the postimplant antithrombotic medication, had rationale for a nonpharmacologic stroke prevention, and no comorbid conditions that would require long-term anticoagulation therapy. After placement of the new device, follow-up visits occurred at 45 days, and 6, 12, 18 and 24 months. Participants received directly acting oral anticoagulant (DOAC) treatment and concomitant low dose aspirin through at least the 45-day follow-up appointment. With evidence of an adequate LAA seal (leak ≤ 5 mm) at the 45-day visit, participants were instructed to discontinue DOAC therapy and begin dual antiplatelet therapy with 75 mg of clopidogrel and low-dose aspirin until 6 months after implantation, followed by low-dose aspirin indefinitely. With evidence of a leak > 5 mm, participants continued DOAC therapy plus aspirin and were reevaluated at 6 months post implantation. The primary safety endpoint was the occurrence of death, ischemic stroke, systemic embolism, or device- or procedure-related events requiring cardiac surgery within 7 days after the procedure or by hospital discharge. The performance goal established for the primary safety endpoint was 4.21%. For this outcome, the investigators determined that a sample size of 400 individuals would yield 92% or 77% power (1-sided $\alpha = 0.05$ or 2-sided $\alpha = 0.05$, respectively). The primary effectiveness endpoint was incidence of effective LAA closure (peri-device flow ≤ 5 mm), as assessed by the echocardiography core laboratory at the 12-month follow-up visit. The performance goal established for the effectiveness endpoint was 97.0%, and 400 individuals would yield 92% or 81% power (1-sided $\alpha = 0.05$ or 2-sided

$\alpha = 0.05$, respectively). A total of 400 individuals were enrolled. The mean age was 73.8 ± 8.6 years, 64.5% were men, and 94% were White. A total of 395 (98.8%) achieved implant procedure success. The incidence of the primary safety end point was 0.5%, with a 2-sided 95% CI of 1.8%, which was below the performance goal of 4.21% ($p<0.0001$). The incidence of the primary effectiveness end point of LAA closure was 100%, with a 2-sided 95% CI of 98.9%, above the performance goal of 97.0% ($p<0.0001$). A total of 7 individuals experienced device-related thrombus. The investigators concluded:

> The PINNACLE FLX study results demonstrate that the next-generation LAA closure device, in combination with a 6-week postprocedural regimen of a DOAC and low-dose aspirin, is associated with a low incidence of safety events and high incidence of effective appendage closure.

In 2019, Holmes and colleagues reported long-term follow-up data from two U.S. FDA LAAC mandated registries (CAP [continued access PROTECT-AF] and CAP2 [continued access PREVAIL]) for safety and efficacy of LAAC for stroke prevention in participants with NVAF. The CAP registry included 566 participants (average follow-up 50.1 months) and CAP2 registry included 578 participants (average follow-up 50.3 months); these registries represent the longest follow-up for participants that have been implanted with the WATCHMAN LAAC Device. The CAP registry enrolled participants who met identical inclusion/exclusion criteria as the original PROTECT-AF RCT; similarly, the CAP2 registry used identical inclusion/exclusion criteria as PREVAIL. Subjects had documented paroxysmal, persistent, or permanent non-valvular AF, were eligible for long-term warfarin therapy, had $CHADS_2$ score of 2 or greater. Individuals with a $CHADS_2$ score of 1 were included but had to meet additional ACC/AHA/ESC 2006 guidelines for the management of AF for subjects requiring warfarin therapy. Notably, both registries excluded warfarin-contraindicated individuals. Participants enrolled in CAP2 were significantly older (≥ 75 years of age) and had higher CHA_2DS_2-VASc scores (4.51 vs. 3.88; $p<0.001$). In both the CAP and CAP2 the procedural success was similar (94%). In the CAP registry, full 5-year follow-up was completed in 68% of participants; inability to obtain full follow-up was related to mortality, which occurred in 17.8% of participants; initial failure to implant the device, which occurred in 5.7%, loss to follow-up, which occurred in 5.1%, and another 3.5% of participants withdrew permission and consent. At 60 months, 94.8% of participants remained off warfarin. Similar results were reported in the CAP2 registry, although a higher percent of participants died before follow-up completion (21.8%). The primary composite endpoint – stroke (ischemic and hemorrhagic), cardiovascular death, and systemic embolism – occurred in 12.4% of CAP and 17.6% of CAP2 participants; events contributing to the composite endpoint included mostly cardiovascular death and ischemic stroke. The most frequent adverse event in the CAP registry was gastrointestinal bleeding (5.8%), followed by pericardial effusion with cardiac tamponade (1.2%); device-related thrombus occurred in 2.6% of CAP and 3.9% of CAP2 participants. Given the lack of a comparator arm, it is difficult to assess the long-term effectiveness and safety of the WATCHMAN LAAC device versus standard of care, particularly direct oral anticoagulant therapy. Furthermore, for participants unable to tolerate long-term anticoagulation, the results of the CAP and CAP2 registries provide no additional data. Both registries were subject to high rates of loss to follow-up (mostly related to mortality), which complicates attempts to compare relative ischemic stroke reductions with expected rates (based on CHA_2DS_2-VASc scores estimated in the absence of therapy).

Cardiovascular outcomes may vary by gender, socioeconomic status, and ethnicity/race. A cross-sectional study by Darden and colleagues (2021) compared outcomes of males and females who underwent LAAO. Individuals in this study were enrolled in the National Cardiovascular Data LAAO Registry. Outcomes included aborted or canceled procedure (no venous access was performed), major adverse event, any in-hospital adverse event (death, cardiac

arrest, ischemic stroke, hemorrhagic stroke, undetermined stroke, TIA, intracranial hemorrhage, systemic arterial embolism, major bleeding, major vascular complication, myocardial infarction, pericardial effusion requiring drainage, and device embolization), and prolonged hospital stay (> 1 day). Multivariate logistic regression was performed to adjust for age, race/ethnicity, body mass index, congestive heart failure, hypertension, type 1 or 2 diabetes, stroke, vascular disease, coronary artery disease, left ventricular ejection fraction, glomerular filtration rate, prior P2Y12 inhibitor or oral anticoagulant prescription, and hospital region. A total of 49,357 individuals were included, of whom 20,388 (41.3%) were female. Females were more likely than males to experience any adverse and major adverse events, had lengths of stays longer than 1 day, and while a rare occurrence, in-hospital death ($p<0.001$ for all). In addition, Alkhouli and colleagues (2022) evaluated gender-specific short- and long-term outcomes by gender after LAAO in the Amulet IDE trial. A total of 1833 individuals (1099 males and 734 [40%] females) underwent attempted device implantation (917 with the Amulet and 916 with the WATCHMAN). There were no differences in the rate of implantation success, as well as rates of ischemic stroke, TIA, hemorrhagic stroke, major bleeding, cardiovascular death, or all-cause death between males and females. However, females experienced higher rates of major in-hospital adverse events compared to males ($p<0.001$) due to pericardial effusions that required intervention and major bleeding ($p<0.01$ for both). Investigators in both studies indicated that additional research is needed to reduce adverse events in women who undergo LAAO implantation.

Diverse populations have not been included in large LAAO trials. In the PROTECT-AF (Reddy 2014), PREVAIL (Homes 2014), and PINNACLE FLX (Kar 2021) trials, most of the populations were White, 91%, 94%, and 94%, respectively. A cross-sectional study by Khan and colleagues (2021) evaluated differences in clinical characteristics and in-hospital outcomes by race/ethnicity of individuals with AF who underwent WATCHMAN implantation. Data for this study was derived from the National Inpatient Sample database. The study sample was stratified into 4 groups: White, Black, Hispanic, and Other races. Multivariate logistic regression was performed to adjust for age, sex, CHA_2DS_2-VASc score, median income, and 29 Elixhauser comorbidities (Quan 2005). A total of 34,960 individuals were included. Of those, 86% were White, 5.9% Hispanic, 4.2% Black, and 3.7% Other races. Individuals who were Black and Hispanic had higher prevalence rates of heart failure, hypertension, obesity, and renal failure compared to White individuals ($p<0.01$ for all). After adjusting for confounding factors, individuals who were Black, Hispanic, and Other races, had higher likelihoods of having a major complication from the procedure, and prolonged lengths of stays (> 1 day) compared with White individuals ($p<0.01$ for both). The investigators concluded that non-white individuals with AF who underwent WATCHMAN implantation had higher rates of select comorbidities and experienced higher WATCHMAN-related adverse events. They also stated that additional research is needed to clarify why these differences exist.

In 2020, Osmancik and colleagues reported data from the Left Atrial Appendage vs. Novel Anticoagulation Agents in Atrial Fibrillation (PRAGUE-17, NCT02426944) trial. This was a multicenter, prospective, open-label, randomized, non-inferiority that compared LAAC and DOAC in high-risk cohort (CHA_2DS_2-VASc: 4.7± 1.5) with NVAF. The study randomly assigned 402 participants with NVAF to receive DOACs (n=201 or undergo LAAC (n=201). A total of 181 participants (90.0%) had a successful LAAC implantation, six participants (3.4%) experienced device-related thrombus. At a median 19.9 months of follow-up, the annual rates of primary outcomes in the LAAC group compared to the DOAC group were 10.99% and 13.42% (the HR CI spanned from 0.53 to 1.31). Between the LAAC and DOAC group there were no differences in stroke/transient ischemic attacks, clinically significant bleeding or cardiovascular death. There were nine major LAAC-related complication that occurred and two procedure and/or device related deaths reported in the LAAC group. In summary, the authors concluded that noninferiority was demonstrated, composite endpoints are challenging to interpret, and components of the composite endpoint were not powered for comparisons.

On August 14, 2021 Abbott received PMA approval for its percutaneous transcatheter device, the Amplatzer™ Amulet™ Left Atrial Appendage Occluder (Abbott Medical, St. Paul, MN) to treat individuals with AF who are at risk of ischemic stroke. The LAA occluder provides a double-seal technology for the complete and immediate sealing of the LAA. The Amulet LAA occluder is intended to reduce the risk of thrombus embolization from the LAA in individuals with NVAF and who are at increased risk for stroke and systemic embolism based on $CHADS_2$ or CHA_2DS_2-VASc scores, who are suitable for short term anticoagulation therapy, and have appropriate rationale to seek a non-pharmacologic alternative to oral anticoagulation, taking into consideration the safety and effectiveness of the device.

The FDA approval of the Amplatzer Amulet LAA Occluder is based on findings from the Amulet IDE trial (NCT02879448), a multicenter, open label, controlled trial evaluating safety and effectiveness of the Amulet occluder. Lakkireddy and colleges (2021) reported results from the Amulet IDE trial which enrolled 1878 participants who were randomized 1:1 to undergo percutaneous implantation of an LAA occluder with Amulet occluder (n=915) or with the WATCHMAN device (n=916). Eligible participants were 18 years of age or older with documented NVAF (paroxysmal, persistent or permanent) and an increased risk of stroke or systemic embolism ($CHADS_2$ score ≥ 2 or a CHA_2DS_2-VASc score of ≥ 3). In summary the authors found the Amulet occluder to be noninferior to the WATCHMAN device for the primary safety endpoint (14.5% vs. 14.7%; difference=-0.14; 95% CI, -3.42-3.13; p<0.001 for noninferiority). The Amulet occluder was also noninferior to the WATCHMAN device for primary effectiveness endpoint (2.8% vs. 2.8%; difference=0.00; 95% CI, -1.55-1.55; p<0.001 for noninferiority). "Procedure-related complications were higher with the Amulet device and decreased with operator experience."

Ongoing trials include the ASAP-TOO (assessment of the WATCHMAN device in individuals unsuitable for oral anticoagulation) trial, a multicenter prospective randomized trial designed to establish the safety and effectiveness of the WATCHMAN LAAC device in individuals with NVAF that are considered ineligible for oral anticoagulants (NCT02928497); the estimated study completion date is December 2025 (Holmes, 2017).

Sedaghat and colleagues (2021) reported findings from the multinational European-Canadian (EUROC)-DRT registry which included individuals in whom a device-related thrombus (DRT) was diagnosed after LAAC during clinical follow-up. While DRT is relatively rare, registry data assessing individuals with DRT suggests that DRT may occur long after LAAC. An analysis of 156 DRT cases from the EUROC-DRT registry found that DRT was detected after a median of 93 days (interquartile range, 54-161 days) with 17.9% being detected > 6 months after LAAC. The authors concluded that "the relevance of DRT after LAAC remains uncertain".

In conclusion, oral anticoagulation remains the standard of care therapy for stroke prevention for most individuals with AF and elevated stroke risk. Those who are poor candidates for long-term oral anticoagulation may be eligible candidates for WATCMAN LAA Closure Device placement based on observational data, including registry data suggesting improved outcomes as compared to historical controls, in accordance with generally accepted standards of medical practice.

Exclusion of the LAA may be performed at the same time as another open cardiac procedure. Examples of devices used for this procedure may include the Amplatzer Cardiac Plug, Lariat Suture Delivery Device, the AtriClip® LAA Exclusion System (AtriCure, Inc., Mason, OH), and the WATCHMAN LAA Closure Device. On August 20, 2019, the FDA granted clearance for the AtriClip LAA Exclusion System, indicated for the exclusion of the heart's left

atrial appendage, performed under direct visualization and in conjunction with other open cardiac surgical procedures. AtriClip's FDA authorization was obtained via the 510k process, based on substantial equivalence (in material composition) to predicate FDA cleared devices. The predicate devices for the AtriClip LAA Exclusion System are the Weck Hem-O-Lok® Ligating Clip and Clip Applier (K030311), Medtronic VNUS U-Clip and Applier (K031623), Tyco AutoSuture TA and GIA Staplers (K032696), Power Medical SurgASSIST® Straight Linear 4 Row No Knife DLUs with Reloads (K040398), Demetech Braided Nonabsorbable Polyester Suture and needle driver (K023030) and Gore SEAMGUARD® Bioabsorbable Staple Line Reinforcement Material (K043056). The FDA indications for use were based on animal data and preliminary clinical data reported by Ailawadi and colleagues (2011) from the EXCLUDE trial, a prospective, non-randomized study (NCT00779857) of 70 participants (mean age, 73 years), half of whom had no history of atrial fibrillation, demonstrating successful clip placement in 95.7% of participants (n=67) during concomitant cardiac surgery. In 61 participants evaluated at 3 months with a CT scan, left atrial appendage exclusion was demonstrated in all but one participant. No claims on efficacy can be made based on this limited data.

The 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guidelines for the management of atrial fibrillation; the panel offers a IIb (weak) recommendation for surgical occlusion of the LAA with AF in individuals undergoing cardiac surgery as a component of an overall heart team approach to the management of AF. Surgical occlusion involves surgical ligation or amputation of the LAA (a procedure not addressed by this document); the guideline does not mention the AtriClip device as a surgical method to exclude the LAA.

In 2021, Whitlock and colleagues conducted a multicenter, RCT which enrolled 4111 participants (mean age of 71 years) with AF and a $CHADS_2$ score ≥ 2 (mean of 4.2), scheduled for cardiac surgery for another indication. Study participants included were randomly assigned to LAAO during surgery (n=2379 in the final analysis) or not (n=2391 in the final analysis). During the follow-up period (mean of 3.8 years) participants were expected to receive usual care, including oral anticoagulation, during follow-up. The study's primary outcome was the occurrence of ischemic stroke (including transient ischemic attack with positive neuroimaging) or systemic embolism. Study participants, research personnel, and primary care physicians (other than the surgeons) were blinded to the trial-group assignments. At the time of hospital discharge, 83.4% of the participants in the occlusion group and 81.0% of those in the no-occlusion group were receiving oral anticoagulation, respectively. At year 3 of follow-up, 76.8% of the study participants continued to receive oral anticoagulation. The primary outcome, stroke or systemic embolism had occurred in 114 participants (4.8%) in the LAAO group and in 168 participants (7.0%) in the non-occlusion group (HR, 0.67; 95% CI, 0.53 to 0.85; p= 0.001). A total of 538 participants in the occlusion group (22.6%) and in 537 (22.5%) in the non-occlusion group (HR, 1.00; 95% CI, 0.89 to 1.13). Hospitalization for heart failure (either prolongation of index hospitalization or new hospitalization) occurred in 183 participants (7.7%) in the occlusion group and in 162 (6.8%) in the non-occlusion group (HR, 1.13; 95% CI, 0.92 to 1.40). The incidence of major bleeding or myocardial infarction was similar in the two groups. In this study, LAAO was performed during cardiac surgery with the use of any of the following techniques: amputation and closure (56%), stapler closure (11%), closure from within (14%), or closure with an FDA approved surgical occlusion device (e.g., AtriClip [15%]). In the current study, amputation and closure was the preferred technique (56%), whereas use of an FDA approved closure device occurred in a minority of participants (15%); outcome data stratified by closure technique was not provided.

Potential risks associated with closure device include, but are not limited to, erosion and perforation. TigerPaw II, another surgical LAA closure device, was recalled in 2017 after reports involving issues with the TIGERPAW System II resulting in possible tissue tearing on left atrial wall and bleeding during use of the device.
Currently there is insufficient clinical evidence on the safety and efficacy to support the use of surgical occlusion of the LAA with a cardiac device performed at the same time as another open cardiac procedure for the management of AF.

Background/Overview

According to the Centers for Disease Control and Prevention there are nearly 6 million people in the United States (US) with AF. In 2019 AF was the underlying cause of 26,535 deaths and contributes to about 183,000 deaths annually. It is estimated that 12.1 Americans will have the disease by 2030. AF is associated with an increased risk of stroke, reported to be the cause of 1 in 7 strokes, with a four- to fivefold increased risk of ischemic stroke (CDC, 2022).

Patent Foramen Ovale (PFO)
PFO describes the persistence of a component of the fetal circulation between the right and left atrium. Although PFOs are found in 10-15% of adults, they are typically clinically insignificant. However, they may be associated with paradoxical embolus, in which an embolus arising in the venous circulation gains access to the arterial circulation through the PFO. It is estimated that individuals with a history of PFO and paradoxical embolism have a 3.4% and 3.8% yearly risk of recurrent stroke or transient ischemic attack. Therefore, there has been interest in either open surgery or transcatheter approaches to close the PFO, in individuals with a history of embolic stroke of unknown cause. Treatment alternatives include chronic warfarin therapy, based, in part, on the theory that clotting disorders may be present in individuals with embolic stroke. To date, the AMPLATZER PFO Occluder is the only device which has received FDA approval for transcatheter closure of a PFO to reduce risk of stroke in individuals who had cryptogenic stroke due to presumed paradoxical embolism, after a comprehensive clinical evaluation (by neurologist and cardiologist) has been conducted to rule out other causes of stroke. Contraindications for the AMPLATZER PFO Occluder include: active endocarditis, untreated infection, other heart defects, or a tumor or blood clot in the vessels along the path of the heart. The GORE® HELEX® Septal Occluder/ GORE® Septal Occluder (W.L. Gore & Associates, Inc., Flagstaff, AZ) provides another potential treatment option for PFO closure in individuals who had a cryptogenic stroke.

In the CLOSE study, Mas and colleagues (2017) defined *cryptogenic stroke or retinal ischemia* as follows:

> *Cryptogenic stroke (or retinal ischemia):* with no identifiable cause other than PFO with or without ASA, based on a detailed etiological work-up, performed under the neurologist's responsibility. The following examinations, which are part of the standard etiological work-up for stroke in young adults, will be performed before randomization:
> - At least one of the following arterial investigations, performed in the 30 days following the qualifying event, as a complement to or instead of Doppler ultrasound of supra-aortic vessels and/or transcranial Doppler: (a) MRA (magnetic resonance angiography), with intracranial and extracranial investigation; (b) CT angiography, with intracranial and extracranial investigation; (c) arteriography by catheter, with extracranial and intracranial investigation.

- Biological work-up comprising blood count, ESR, CRP, fasting blood glucose, lipid survey, serum creatinine, ASAT, ALAT, PT, aPTT, antiphospholipid antibodies (at least including screening for circulating anticoagulant and anticardiolipin antibodies)
- Transthoracic and transesophageal echocardiography (see appendix)
- ECG and search for emboligenic arrhythmia: cardiac monitoring at the acute phase of stroke and/or 24h-Holter ECG
- Any other examination necessary to confirm a cause suspected on clinical data and/or the initial etiological work-up.

Ischemic stroke: Sudden onset of focal neurological symptoms with the presence of cerebral infarction in the appropriate territory on brain imaging (CT or MRI), regardless of the duration of the symptoms (less than or greater than 24 hours).

Retinal ischemia: Sudden onset of monocular visual deficit accompanied by objective signs of retinal infarction in the appropriate region of the retina. This diagnosis must be confirmed by the appropriate investigations.

Potential causes of stroke

- Atherosclerosis: presence of stenosis ≥ 30% of an artery supplying the brain or atherosclerosis of the aortic arch (plaque ≥ 4 mm). In the case of arterial occlusion in the appropriate territory, the diagnosis of atherosclerosis will be adopted if the patient presents at least two cardiovascular risk factors (hypertension, diabetes, hypercholesterolemia, smoking) OR a history of myocardial infarction or arterial disease of the lower limbs OR an atherosclerotic stenosis (≥ 30%) of another artery supplying the brain OR plaques of the aortic arch.
- Potentially emboligenic heart disease, other than PFO or ASA.
- Small artery disease, defined by the presence of a small deep infarction (< 1.5 cm in diameter) corresponding to the clinical signs, in a patient with chronic hypertension or diabetes OR at least one old small infarction or vascular leukoencephalopathy. Patients with only one small deep infarction, without hypertension or diabetes, can be included in the study.
- Other defined or probable causes of stroke (not exhaustive):
  - Non-atherosclerotic arterial disease (e.g.: dissection or arteritis)
  - Coagulopathy requiring long-term anticoagulant therapy (> 6 months).
  - Hematological malignancies (e.g.: thrombocythaemia)
  - Recent intravenous drug use (in previous 6 months).

Left Atrial Appendage

According to the Centers for Disease Control (CDC) and Prevention, in the U.S., AF is the most prevalent sustained cardiac arrhythmia, resulting in a four- to five-fold greater risk of stroke due to migration of clots that may form in the LAA (CDC, 2020). As confirmed by echocardiography and autopsy, LAA is identified as a leading source of thrombi in individuals with non-valvular AF. By closing off the LAA, the occlusion device is designed to reduce risk of stroke and other cardiovascular complications. The WATCHMAN LAA Closure Device is the first of its kind treatment giving individuals with non-valvular AF an alternative option to long-term warfarin therapy. The AMPLATZER™ Cardiac Plug (ACP) (St. Jude Medical, St. Paul, MN) and LARIAT® Suture Delivery Device and Accessories provide other potential alternatives to closure, currently being studied as alternatives to standard anticoagulation therapy.

The CHADS (cardiac failure, hypertension, age, diabetes, stroke) score is a risk assessment tool that is based on a point system, in which 2 points are assigned for a history of stroke or TIA, and 1 point each is assigned for age over 75 and a history of hypertension, diabetes or recent HF. The adjusted stroke rate can be assessed based on the CHADS score. For example, a CHADS score of 2 is associated with an adjusted stroke rate of 4% per year (Fuster, 2006).

Simple risk stratification used to predict thromboembolism in AF:
$CHADS_2$ (Congestive heart failure, Hypertension, Age >75, Diabetes, prior Stroke/transient ischemic attack)

- Low risk: Score 0
- Intermediate risk: Score 1
- High risk: Score 2-6

Current guidelines divide individuals at risk for ischemic stroke with a CHA_2DS_2-VASc scores into 3 categories:

- low-risk = 0
- intermediate = 1-2
- high risk ≥ 3

$CHADS_2$ and CHA_2DS_2-VASc scores to predict ischemic stroke risk in individuals with AF (Lip, 2011)

Letter	Clinical Characteristics	Points Awarded
C	Congestive heart failure (signs/symptoms of heart failure confirmed with objective evidence of cardiac dysfunction	1
H	Hypertension (resting blood pressure >140/90 mmHg on at least 2 occasions or current antihypertensive pharmacologic treatment)	1
A	Age ≥ 75 years	1 ($CHADS_2$) 2 (CHA_2DS_2-VASc)
D	Diabetes mellitus (fasting glucose >125 mg/dL or treatment with oral hypoglycemic agent and/or insulin	1
S	**S**troke or transient ischemic attack (includes any history of cerebral ischemia)	2
V	Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1
A	Age 65-74 years	1
Sc	Sex category of female (female sex confers higher risk)	1

In 2010, Pisters and colleagues provides the HAS-BLED bleeding risk score, a practical tool to assess individuals bleeding risk in real-world individuals with AF, supporting clinical decision making regarding antithrombotic therapy in individuals with AF.

Clinical Characteristics Composing the HAS-BLED Bleeding Risk Score

Letter	Clinical Characteristics	Points Awarded

H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly	1
D	Drugs or alcohol (1 point each)	1 or 2

Bleeding is the primary risk associated with systemic anticoagulation. The HAS-BLED bleeding risk score has been developed to estimate the risk of significant bleeding in individuals treated with systemic anticoagulation, which has been validated to assess the annual risk of significant bleeding in individuals with AF treated with warfarin. The score ranges from 0 to 9, based on clinical characteristics, including the presence of hypertension, renal and liver function, history of stroke, bleeding, labile international normalized ratios, age, and drug/alcohol use. Examples of medication usage predisposing to bleeding include clopidogrel or non-steroidal anti-inflammatory drugs. A HAS-BLED score of 3 or greater is considered to be associated with a high risk of bleeding potentially signaling the need for closer monitoring of individuals for adverse risks, closer monitoring of international normalized ratio (INR), or differential dose selections of oral anticoagulants or aspirin.

Definitions

Atrial fibrillation: A condition where there is disorganized electrical conduction in the atria, resulting in ineffective pumping of blood into the ventricle.

Atrial septal aneurysm: Redundant interatrial tissue, encompassing the fossa ovalis, with resulting hypermobility of the septum primum and excursion greater than 10 mm on TEE.

Cryptogenic stroke: Cerebral infarction that despite evaluation is not attributable to other well-established singular etiologies including cardioembolism, large artery atherosclerosis, or thromboembolism, or small vessel occlusion.

High risk of bleeding: A HAS-BLED score of 3 or greater is considered to be associated with a high risk of potential bleeding in persons requiring anticoagulation.

High risk of stroke: A $CHADS_2$ score of greater than or equal to 2 or a CHA_2DS_2-VASc score of greater than or equal to 3 are considered high risk of stroke or systemic embolism for individuals with AF.

Large interatrial shunt: Presence of more than 30 microbubbles in the left atrium within three cardiac cycles after opacification of the right atrium, based on TTE or TEE.

Left atrial appendage (LAA): A muscular pouch attached to the upper portion of the left atrium.

Patent foramen ovale (PFO): A component of the fetal circulation that consists of a communication between the left and right atria that generally closes after birth; if an opening remains after birth, the possibility of an embolus (blood clot that breaks free in the blood) getting to the brain exists, resulting in a stroke or transient ischemic attack.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Transcatheter closure of patent foramen ovale
When services may be Medically Necessary when criteria are met:

CPT

	For the following procedure codes **when specified as closure of patent foramen ovale**:
93580	Percutaneous transcatheter closure of congenital interatrial communication (ie, Fontan fenestration, atrial septal defect) with implant [*when specified as closure of patent foramen ovale*]

ICD-10 Procedure

02U53JZ	Supplement atrial septum with synthetic substitute, percutaneous approach [*when specified as closure of patent foramen ovale*]

ICD-10 Diagnosis

G45.9	Transient cerebral ischemic attack, unspecified
I25.3	Aneurysm of heart
I51.0	Cardiac septal defect, acquired
I63.81-I63.89	Other cerebral infarction
I63.9	Cerebral infarction, unspecified
Q21.12	Patent foramen ovale
Z86.73	Personal history of transient ischemic attack (TIA), and cerebral infarction without residual deficits

When services are Investigational and Not Medically Necessary:
For the procedure and diagnosis codes listed above when criteria are not met, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

Closure of left atrial appendage
When services may be Medically Necessary when criteria are met:

CPT

33340	Percutaneous transcatheter closure of the left atrial appendage with endocardial implant, including fluoroscopy, transseptal puncture, catheter placement(s), left atrial angiography, left atrial appendage angiography, when performed, and radiological supervision and interpretation

ICD-10 Procedure

02L73CK	Occlusion of left atrial appendage with extraluminal device, percutaneous approach
02L73DK	Occlusion of left atrial appendage with intraluminal device, percutaneous approach

02L74CK	Occlusion of left atrial appendage with extraluminal device, percutaneous endoscopic approach
02L74DK	Occlusion of left atrial appendage with intraluminal device, percutaneous endoscopic approach

ICD-10 Diagnosis

I48.0	Paroxysmal atrial fibrillation
I48.11-I48.19	Persistent atrial fibrillation
I48.20-I48.21	Chronic atrial fibrillation
I48.91	Unspecified atrial fibrillation

When services are Investigational and Not Medically Necessary:
For the procedure and diagnosis codes listed above when criteria are not met or for all other diagnoses not listed, for the following procedure codes, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

	For the following codes when specified as exclusion by intraluminal or extraluminal device:
33267	Exclusion of left atrial appendage, open, any method (eg, excision, isolation via stapling, oversewing, ligation, plication, clip)
33268	Exclusion of left atrial appendage, open, performed at the time of other sternotomy or thoracotomy procedure(s), any method (eg, excision, isolation via stapling, oversewing, ligation, plication, clip) [add-on code]
33269	Exclusion of left atrial appendage, thoracoscopic, any method (eg, excision, isolation via stapling, oversewing, ligation, plication, clip)

ICD-10 Procedure

02L70CK	Occlusion of left atrial appendage with extraluminal device, open approach
02L70DK	Occlusion of left atrial appendage with intraluminal device, open approach

ICD-10 Diagnosis

All diagnoses

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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Revised	08/10/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Revised hierarchy formatting. Updated Rationale, Background/Overview, Definitions and References sections.
Reviewed	08/11/2022	MPTAC review. Updated Rationale, Background, References ad Websites sections. Updated Coding section with 10/01/2022 ICD-10-CM changes, added Q21.12 effective 10/1/2022; removed Q21.1 deleted 9/30/2022.
	12/29/2021	Updated Coding section with 01/01/2022 CPT changes; added 33267, 33268, 33269 effective 01/01/2022 replacing 33999 NOC code.
	11/22/2021	Updated Rationale, Background, References and Index sections, adding the Amulet Left Atrial Appendage Occluder used for transcatheter closure of LAA

		for individuals with non-valvular atrial fibrillation for the prevention of stroke (when MN criteria are met).
Revised	08/12/2021	MPTAC review. Added MN statement for transcatheter closure of left atrial appendage (LAA) for individuals with non-valvular atrial fibrillation for the prevention of stroke when criteria are met. Revised INV/NMN statement for transcatheter closure of left atrial appendage when the criteria above are not met. Updated Rationale, Background, Definitions, Coding, References, Websites and Index sections.
Reviewed	02/11/2021	MPTAC review. Updated Rationale, Discussion, References, Websites and Index sections.
Revised	02/20/2020	MPTAC review. Added INV/NMN statement to address left atrial appendage closure via surgical (non-percutaneous) implantation of a device for all indications. Revised Title: Patent Foramen Ovale and Left Atrial Appendage Closure Devices for Stroke Prevention. Updated Description/Scope, Rationale, Background, References, Websites and Index sections. Updated Coding section; added 33999 NOC and ICD-10-PCS 02L70CK, 02L70DK, 02L73CK, 02L74CK, 02L74DK.
Revised	11/07/2019	MPTAC review. Clarified age and size of interatrial shunt in MN criteria for transcatheter closure of PFO. Updated Rationale, Definitions, References and Websites sections.
Reviewed	06/06/2019	MPTAC review. Updated Rationale, References and Websites sections. Updated Coding section; removed ICD-10-PCS 02L73CK (not applicable)
Revised	07/26/2018	MPTAC review. Revised MN statement for transcatheter closure of PFO using FDA approved device for individuals with a history of cryptogenic stroke who are under age 60 when criteria met. Updated Rationale, References and Websites sections. Updated Coding section to include 10/01/2018 ICD-10-CM changes (added I63.81-I63.89 replacing I63.8).
Revised	05/03/2018	MPTAC review. The document header wording updated from "Current Effective Date" to "Publish Date." Note added to description to clarify that the document does not address the percutaneous transcatheter closure of atrial septal defects (ASDs). Revised MN statement for transcatheter PFO closure, removing information on specific device. Updated Description, Rationale, Background, References and Websites sections.
Reviewed	08/03/2017	MPTAC review. Updated Rationale, References and Websites sections.
Revised	02/02/2017	MPTAC review. Clarified MN criteria for transcatheter closure of a PFO. Updated Rationale, Background, Index, References and Websites sections.
	01/01/2017	Updated Coding section with 01/01/2017 CPT changes; removed 0281T deleted 12/31/2016.
Reviewed	02/04/2016	MPTAC review. Updated References and Websites sections.
Reviewed	11/05/2015	MPTAC review. Updated Background, Index and Reference sections. Removed ICD-9 codes from Coding section.
Reviewed	08/06/2015	MPTAC review. Description, Rationale, Background, Index, References and Websites sections updated.
Reviewed	02/05/2015	MPTAC review. Updated Rationale, Reference, Websites and Index sections.
Reviewed	02/13/2014	MPTAC review. Updated Websites.

Reviewed	02/14/2013	MPTAC review. Description, Rationale, Background, Index, References and Websites Updated.
Reviewed	02/16/2012	MPTAC review. Updated References and Websites.
	01/01/2012	Updated Coding section with 01/01/2012 CPT changes.
Revised	02/17/2011	MPTAC review. Title change. Position statements for PFO clarified, Added investigational and not medically necessary statement for LAA. Removed position statements for patent ductus arteriosus, fenestrated Fontan procedure, atrial and ventricular defects. Transferred content addressing Transmyocardial/Perventricular transcatheter device closure of ventricular septal defects to a new medical policy, SURG.00123. Updated Description, Rationale, Definitions, Coding, Index, References and Websites.
Revised	08/19/2010	MPTAC review. Clarified medically necessary statement addressing transcatheter closure of ventricular septal defect (VSD) and secundum atrial septal defect (ASD). Updated Websites and References.
Revised	05/13/2010	MPTAC review. Changed title to "Transcatheter Closure of Cardiac Defects". Removed "complex" from ventricular septal defect (VSD) medically necessary criteria. Transcatheter closure investigational and not medically necessary position statement clarified. Definition, Websites and References updated.
Reviewed	02/25/2010	MPTAC review. Rationale, Background, Coding and References updated.
Reviewed	02/26/2009	MPTAC review. References updated.
Reviewed	02/21/2008	MPTAC review. Updated references. The phrase "investigational/not medically necessary" was clarified to read "investigational and not medically necessary." This change was approved at the November 29, 2007 MPTAC meeting.
Revised	03/08/2007	MPTAC review. A position statement was added to state that transmyocardial/perventricular device closure of VSDs is considered investigational/not medically necessary. Rationale section was also updated to include the FDA withdrawal of HDE marketing approval for the CardioSEAL STARFlex and AMPLATZER PFO occluders. Coding was also updated to add the new CPT Category III codes (0166T, 0167T) effective 01/01/2007.
Reviewed	06/08/2006	MPTAC review. References were updated, including information regarding current FDA-approved devices.
Revised	7/14/2005	MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization.

Pre-Merger Organizations	**Last Review Date**	**Document Number**	**Title**
Anthem, Inc.	01/28/2004	SURG.00032	Transcatheter Closure of Patent Ductus Arteriosus, Foramen Ovale, Closure of a Fenestrated Fontan Procedure, and Atrial and Ventricular Septal Defects
WellPoint Health Networks, Inc.	09/23/2004	3.04.04	Catheter Closure for Atrial Septal Defect and Patent Foramen Ovale
	06/24/2004	3.04.25	Transcatheter Closure for Patent Ductus Arteriosus