Left Atrial Appendage Closure (Occlusion)

Policy Number: SURGERY 123.1 T2
Effective Date: October 1, 2022

Instructions for Use

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Related Policies

None

Coverage Rationale

See Benefit Considerations

Percutaneous endovascular closure (occlusion) of the left atrial appendage (LAA) is proven and medically necessary to reduce the risk of stroke when using a U.S. Food and Drug Administration (FDA) approved device, when all of the following criteria are met:

- Device is used according to FDA labeled indications, contraindications, warnings and precautions
- Diagnosis of nonvalvular atrial fibrillation
- Moderate to high risk of embolic stroke (CHA_2DS_2-VASc score ≥2)
- Documented medical contraindication to long-term anticoagulation

Surgical closure (occlusion) of the LAA as part of cardiac surgery with cardiopulmonary bypass for a different indication is proven and medically necessary to reduce the risk of stroke when all of the following criteria are met:

- Age 18 years or above
- History of atrial fibrillation
- CHA_2DS_2-VASc Score ≥ 2
- Device is used according to FDA labeled indications, contraindications, warnings and precautions, when applicable

Thoracoscopic closure (occlusion) of the LAA as a stand-alone procedure or as an adjunct to thoracoscopic atrial fibrillation ablation is unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Definitions

CHA_2DS_2-VASc Score: also known as the Birmingham schema, is a risk stratification score used to estimate the long-term systematic embolization risk in patients with atrial fibrillation. (Lipp 2010)

2009 Birmingham Schema Expressed as a Point-Based Scoring System, with the Acronym CHA_2DS_2-VAScRisk Factor	Points
Congestive Heart Failure Associated signs and symptoms, or left ventricular systolic dysfunction	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke, transient ischemic attack, or thromboembolism	2
Vascular Disease (prior myocardial infarction, peripheral artery disease or aortic plaque) Myocardial infarction, peripheral artery disease, or aortic plaque	1
Age 65–74 years	1
Sex category (i.e., female gender)	1

Prior Authorization Requirements

Prior authorization is required in all sites of service.

Notes:

- Participating providers in the office setting: Prior authorization is required for services performed in the office of a participating provider.
- Non-participating/out-of-network providers in the office setting: Prior authorization is not required but is encouraged for out-of-network services. If prior authorization is not obtained, Oxford will review for out-of-network benefits and medical necessity after the service is rendered.

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 the member specific benefit plan document 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 may apply.

CPT Code	Description
33267	Exclusion of left atrial appendage, open, any method (e.g., 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 (e.g., excision, isolation via stapling, oversewing, ligation, plication, clip) (List separately in addition to code for primary procedure)
33269	Exclusion of left atrial appendage, thoracoscopic, any method (e.g., excision, isolation via stapling, oversewing, ligation, plication, clip)
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
33999	Unlisted procedure, cardiac surgery

Description of Services

Atrial fibrillation is a common cause of cardioembolic ischemic strokes, many of them resulting from a thrombus that originated at the left atrial appendage (LAA). Anticoagulation is the most common approach to atrial fibrillation related cardioembolic

ischemic stroke prevention but poses a risk for bleeding complications. An alternative or in addition to chronic anticoagulation is percutaneous endovascular closure (occlusion) and surgical closure (occlusion). Percutaneous LAA closure or occlusion involves the use of a catheter-inserted, permanently implanted device to close the LAA or a temporarily inserted device to assist in the permanent ligation of the LAA. Open surgical closure is performed at the same time another open cardiac surgical procedure is being performed for a different indication with the use of any of the following techniques: amputation and closure (preferred), stapler closure, double-layer linear closure from the atrium in patients undergoing a minithoracotomy, or closure with an approved surgical occlusion device.

Stand-alone thoracoscopic closure (occlusion) of the LAA is an emerging technique that is being studied for its long-term efficacy. This minimally invasive thoracoscopic technique involves the use of an epicardial exclusion device clip to occlude the LAA.

Clinical Evidence

Percutaneous Endovascular Left Atrial Appendage Closure (Occlusion)

Labori et al. (2021) conducted a systematic review and meta-analysis of observational studies on the long-term clinical effectiveness of percutaneous endocardial left atrial occlusion (LAAO) for stroke prevention in patients with atrial fibrillation (AF), and contraindication to oral anticoagulation (OAC). The authors note that this study differs from the 2 RCT's Protect AF and PREVAIL, these studies excluded participants if they had contraindications to OACs. Authors performed a systematic review and meta-analysis, using Poisson random effect models, to estimate the incidence rate (events per 100 patient-years) of ischemic stroke, transient ischemic attack, major bleeding, and all-cause death after LAAO treatment. They also calculated the risk reduction of ischemic stroke with LAAO compared with no stroke prevention estimated through a predicted risk in an untreated population (5.5 per 100 patient-years). There were 29 observational studies in the meta-analysis, including 7 951 individuals and 12 211 patient-years. The mean CHA^2DS^2-VASc score among the patients in the included studies was 4.32. The pooled incidence rate of ischemic stroke was 1.38 per 100 patient-years (95% CI 1.08; 1.77). According to a meta-regression model, the estimated incidence rate of ischemic stroke at CHA^2DS^2-VASc 4 was 1.39 per 100 patient-years. This suggests a risk reduction of 74.7% with LAAO compared to predicated risk with no stroke prevention. . Results suggest that LAAO is effective in preventing ischemic stroke for patients with AF that are at increased risk of stroke and have contraindications to oral anticoagulation. This review is limited by inclusion of observational studies only and comparisons to historical controls.

A Hayes report compared the safety and efficacy of percutaneous LAA closure devices to reduce risk in stroke risk in patients with atrial fibrillation. and with each other, to reduce stroke risk in patients with nonvalvular AF. They conclude that studies indicate that percutaneous LAA closure may reduce the risk of stroke in some patients with AF and high risk of stroke with contraindications to OAC or unwillingness to adhere to long-term OAC therapy. However, device mediated LAA closure is associated with a measurable risk of serious and potentially life-threatening complications such as major bleeding, pericardial effusion, stroke, device embolization and cardiac perforation or tamponade. The overall quality of evidence varies amongst the devices studied. There was moderate support for the Watchman device. Randomized controlled trial (RCT) findings were offset by concerns regarding the lack of studies comparing the Watchman device relative to newer OAC medications. Also, there was uncertainty whether the benefit outweighs possible harms given the potential for device-related complications or mortality. Well-powered RCTs are needed to compare closure using the Watchman and other percutaneous LAA devices versus treatment with newer OACs and to test the use of newer OACs as an adjunct to LAA closure. Hayes concluded that there is insufficient data to evaluate the comparative effectiveness and safety of these devices. (Hayes, 2018; updated 2022)

An ECRI report comparing Watchman and Watchman FLX with other LAA closure devices or warfarin for thrombosis and stroke prevention concluded that the evidence is somewhat favorable in support of the Watchman devices. The assessment found no head-to-head RCT comparisons of Watchman to other devices. Based on two RCTs, Watchman devices reduce all-cause mortality compared to warfarin, but all-stroke or systemic embolism and major bleeding did not differ statistically between groups at 5-year follow-up. No studies were included that compared Watchman or Watchman FLX to novel oral anticoagulation methods that have less adverse events than warfarin. (ECRI, 2021a)

Watchman/Watchman Flx

The prospective, multicenter case series PINNACLE FLX study (n=400) evaluated the safety and effectiveness of the next-generation Watchman FLX LAA closure device in patients with nonvalvular atrial fibrillation in whom oral anticoagulation is not contraindicated, but who have an appropriate rationale to seek a nonpharmaceutical alternative. The primary safety end point

was the occurrence of one of the following events within 7 days after the procedure or by hospital discharge: death, ischemic stroke, systemic embolism, or device- or procedure-related events requiring cardiac surgery. The primary effectiveness end point was the incidence of effective LAA closure (peri-device flow ≤5 mm), as assessed by transesophageal echocardiography. At one-year, effective closure was seen in 100% of patients who had a Watchman FLX successfully implanted, and the incidence of the primary safety end point was 0.5%. Device-related thrombus was reported in 7 patients, no patients experienced pericardial effusion requiring open cardiac surgery, and there were no device embolization's. This study is limited by lack of comparison group, in particular, one that uses newer OACs. Additionally, the study was not designed to evaluate non-inferiority or superiority of the Watchman FLX device versus long-term anticoagulation in terms of mortality and stroke (Kar et al., 2021). NCT02702271. A clinical trial is in progress to compare the safety and efficacy of the Watchman FLX device to novel oral anticoagulants. NCT04394546

Both the PROTECT-AF and PREVAIL studies noted below had accompanying registries designed to continue accrual of data on longer-term outcomes. These registries, CAP (Continued Access to PROTECT-AF) and CAP2 (Continued Access to PREVAIL]) represent the largest number and longest follow-up of patients implanted with the Watchman device. Holmes et al. (2019) reported on the final 5-year total experience of CAP and the 4-year follow-up of CAP2. The nonrandomized CAP registry included 566 patients who continued follow-up through their 5-year visit or until study exit. The nonrandomized CAP2 registry enrolled 578 patients with follow-up data available through 4 years on all patients remaining in the trial. CAP2 patients were significantly older and had higher CHA2DS2-VASc score scores (4.51 versus 3.88; $p < 0.001$). Procedural success was similar in both (94%). The primary composite endpoint occurred at a rate of 3.05 per 100 patient-years in CAP and 4.80 per 100 patient-years in CAP2. Events contributing to this endpoint were most commonly cardiovascular/unexplained death (1.69 per 100 patient-years for CAP and 2.92 per 100 patient-years for CAP2). Hemorrhagic stroke was significantly less than ischemic stroke (0.17 per 100 patient-years in CAP and 0.09 per 100 patient-years in CAP2), and total stroke rates were significantly less than predicted by CHA2DS2-VASc score (78% reduction with CAP, 69% reduction with CAP2).

Reddy (2017a) evaluated 5-year outcomes of the PREVAIL trial, combined with the 5-year outcomes of the PROTECT AF trial. In patients with AF undergoing LAA closure using the Watchman device, protection against ischemic stroke and systemic embolism was similar to that achieved with warfarin, but LAA closure was associated with substantial reductions in hemorrhagic, disabling and fatal stroke. Additional studies may be advantageous comparing the benefit of LAA occlusion against OACs other than warfarin in patients with AF, and to assess advantages for those with contraindications to anticoagulation.

Reddy et al. (2017b) evaluated the acute procedural performance and complication rates for all Watchman implants performed in the United States since FDA approval. In 3,822 consecutive cases, implantation was successful in 3,653 patients (95.6%), with a median procedure time of 50 minutes. Implanting physicians (n=382) included 71% new, nonclinical trial implanters, who performed 50% of the procedures. Procedural complication rates included 39 pericardial tamponades (1.02%) (24 treated percutaneously, 12 surgically and 3 fatal); 3 procedure-related strokes (0.078%); 9 device embolization's (0.24%) (6 requiring surgical removal); and 3 procedure-related deaths (0.078%).

The prospective, multicenter EWOLUTION registry (Boersma et al., 2016) reported 30-day periprocedural outcomes with the Watchman device. Implant data were available for 1021 patients at high risk of stroke and moderate-to-high risk of bleeding. The device was successfully implanted in 98.5% of patients with no flow or minimal residual flow achieved in 99.3% of implanted patients. Twenty-eight patients experienced 31 serious AEs (SAEs) within 1 day of the procedure. The most common SAE occurring within 30 days of the procedure was major bleeding requiring transfusion. Incidence of SAEs within 30 days was significantly lower for subjects deemed to be ineligible for OAC therapy compared with those eligible for OAC therapy (6.5 versus 10.2%). The overall 30-day mortality rate was 0.7%. The authors reported that improvement in implantation techniques has led to a reduction of periprocedural complications previously limiting the net clinical benefit of the procedure.

Holmes et al. (2015) performed a meta-analysis on composite data from the PROTECT AF and PREVAIL trials and their respective registries comparing warfarin to the Watchman device for the prevention of stroke, systemic embolism and cardiovascular death in patients with nonvalvular AF. The analysis included 2,406 patients with 5,931 patient-years of follow-up. A total of 1,877 patients were treated with Watchman (1,145 registry patients) and 382 received warfarin. Patients receiving the Watchman device had significantly fewer hemorrhagic strokes, cardiovascular/unexplained death and nonprocedural bleeding compared with warfarin; however, there were more ischemic strokes in the device group. All-cause stroke or systemic embolism was similar between both strategies. The composite efficacy endpoint favored the Watchman patients, but did not reach statistical significance. The authors reported that further studies are needed to define risk thresholds for

thromboembolism and bleeding at which patients with AF benefit from LAA occlusion therapy for stroke prevention and to compare the safety and efficacy of this strategy with target specific OACs.

Briceno et al. (2015) conducted a systematic review and meta-analysis evaluating the safety and efficacy of different approaches for preventing stroke in patients with nonvalvular AF. The three groups investigated were novel OACs, the Watchman LAA occlusion device and warfarin. Efficacy outcomes were stroke or systemic embolism, and all-cause mortality. Safety outcome was major bleeding and procedure-related complications. Seven RCTs (n=73,978) were included in the analysis. There was a significant difference favoring novel OACs for systemic embolism, all-cause mortality and safety outcomes compared with warfarin. No difference was seen between the Watchman device and warfarin for efficacy end points; however, there were a few safety concerns. (Holmes 2009 and 2014 are included in this review)

The PREVAIL study (Holmes et al., 2014) is a multicenter, prospective RCT to further assess the safety and efficacy of LAA occlusion using the Watchman device for stroke prevention compared with long-term warfarin therapy. Patients with nonvalvular AF who had a CHADS2 (congestive heart failure, hypertension, age >75 years, diabetes mellitus and previous stroke/TIA) score ≥2 or 1 and another risk factor were eligible. Patients were randomly assigned (in a 2:1 ratio) to undergo LAA occlusion and subsequent discontinuation of warfarin (n=269) or receive chronic warfarin therapy (n=138). There were three primary endpoints (two effectiveness and one safety): 1) the composite of ischemic stroke, hemorrhagic stroke, systemic embolism and cardiovascular or unexplained death; 2) the composite of ischemic stroke and systemic embolism, excluding events occurring in the first 7 days following randomization; and 3) the occurrence of all-cause mortality, ischemic stroke, systemic embolism or device or procedure-related events requiring open cardiac surgery or major endovascular intervention between the time of randomization and 7 days of the procedure or by hospital discharge, whichever is later. Due to the low overall trial event rates, there was limited power with the planned sample size to establish noninferiority for the primary efficacy endpoint and the prespecified criteria noninferiority was not achieved for this outcome. At 18 months, LAA occlusion was noninferior to warfarin for the second primary efficacy endpoint. Event rates were low and comparable in both arms. Early safety events occurred in 2.2% of the Watchman arm, significantly lower than in PROTECT AF, satisfying the safety performance goal. Using a broader, more inclusive definition of adverse effects, these still were lower in the PREVAIL trial than in PROTECT AF (4.2% versus 8.7%). Pericardial effusions requiring surgical repair decreased from 1.6% to 0.4%, and those requiring pericardiocentesis decreased from 2.9% to 1.5%. The authors concluded that these results provide additional data that LAA occlusion is a reasonable alternative to warfarin therapy for stroke prevention in patients with nonvalvular AF who do not have an absolute contraindication to short-term warfarin therapy.

The PROTECT AF trial Holmes et al. (2009) included 707 patients with nonvalvular AF who had at least 1 risk factor for stroke. Patients were randomized to chronic warfarin treatment (n=244) or percutaneous placement of the LAA device (n=463). The clinical endpoint of the study was a composite measure of stroke, cardiovascular death and embolism. The safety assessment included serious adverse events, including major bleeding, pericardial effusion and device embolization. After 1065 patient-years of follow-up, the efficacy event rate was 3.0 per 100 patient-years in the device group compared with 4.9 in the warfarin group - a relative reduction of 38%. However, serious safety events were more common in the device group (7.4 events per 100 patient-years) compared with the warfarin group (4.4). Most of these safety events were related to the procedural implant and pericardial effusion. Statistical analysis demonstrated that the LAA was 99.9% likely to be noninferior to warfarin alone. At 2 years, both treatment groups had a similar intention-to-treat cumulative event rate. Since warfarin therapy is burdensome and carries risks of its own, the authors concluded that closure of the LAA might provide an alternative strategy to chronic warfarin therapy for stroke prophylaxis in patients with nonvalvular AF. However, these data likely do not justify routine LAA occlusion in all patients with nonvalvular AF, primarily because the trial did not demonstrate prevention of embolism and stroke in high-risk patients. In addition, the short duration of follow-up does not offer enough information regarding long-term safety and efficacy Reddy et al. (2011) reported a significant improvement in the safety of the Watchman device with increased operator experience. In a 2.3-year follow-up to the PROTECT AF trial, Reddy et al. (2013b) reported primary efficacy event rates of 3.0 per 100 patient-years in the Watchman group and 4.3 in the warfarin group which indicated the Watchman device 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. Patients in the device group had lower rates of both cardiovascular and all-cause mortality.

In the ASAP trial, Reddy et al. (2013a) conducted a multicenter case series to assess the safety and efficacy of the Watchman LAA closure device in nonvalvular AF patients (n=150) ineligible for warfarin therapy. The primary efficacy endpoint was the combined events of ischemic stroke, hemorrhagic stroke, systemic embolism and cardiovascular/unexplained death. History of hemorrhagic/bleeding tendencies (93%) was the most common reason for warfarin ineligibility. Serious procedure- or device-

related safety events occurred in 13 patients (8.7%). All-cause stroke or systemic embolism occurred in 4 patients (2.3% per year): ischemic stroke in 3 patients (1.7% per year) and hemorrhagic stroke in 1 patient (0.6% per year). The authors concluded that the Watchman device is a reasonable alternative for patients at high risk for stroke but with contraindications to systemic OAC.

Amulet

Galea et al. (2021) initiated the SWISS APERO trial which was a randomized controlled trial to assess the relative efficacy of Amulet compared with Watchman FLX for patients undergoing left atrial appendage closure (LAAC). Participants at eight European centers undergoing LAAC were randomized 1:1 to receive the Amulet or Watchman 2.5 or FLX. The main endpoint was the composite of justified crossover to a non-randomized device during LAAC procedure or residual LAA patency detected by cardiac computed tomography angiography (CCTA) at 45 days. The secondary outcomes included procedural complications, device related thrombus (DRT), peri-device leak at TEE and clinical outcomes at 45 days. Between June 2018 and May 2021, participants were randomly assigned to Amulet (111 [50.2%]) or Watchman (110 [49.8%]. In the Watchman group, 22.7 % had a procedure with an older-generation device (Watchman 2.5), and the rest had a procedure with the new Watchman FLX. The primary end point was assessable in 205 (92.8%) patients and occurred in 71 (67.6%) patients receiving Amulet and 70 (70.0%) patients receiving Watchman, respectively (risk ratio, 0.97 [95% CI, 0.80-1.16]; *P*=0.713). A single justified crossover occurred in a patient with Amulet who fulfilled LAA patency criteria at 45-day CCTA. Major procedure-related complications occurred more frequently in the Amulet group (9.0% versus 2.7%; *P*=0.047) because of more frequent bleeding (7.2% versus 1.8%). At 45 days, the peri-device leak rate at transesophageal echocardiography was higher with Watchman than with Amulet (27.5% versus 13.7%, *P*=0.020), even though none was major (i.e., >5 mm), whereas device-related thrombus was detected in 1 (0.9%) patient with Amulet and 3 (3.0%) patients with Watchman at CCTA and in 2 (2.1%) and 5 (5.5%) patients at transesophageal echocardiography, respectively. Clinical outcomes at 45 days did not differ between the groups. Study limitations included the following: during a CCTA or TEE, the devices can be easily distinguished because of their structural characteristics; the trial was not intended to show differences in the clinical endpoints; the Watchman FLX was not available to after October 2019, therefore a fair amount received the Watchman 2.5; procedural complications were higher than previous studies; and last the follow-up was limited to 45 days. The results of this trial indicate that Amulet is not overall superior to Watchman for LAA patency (assessed by CCTA) at 45 days among patients undergoing percutaneous LAAC. Peri-device leaks were higher with Watchman on CTA and TEE, while intra-device leaks were higher with Amulet on CTA, although some of these could improve with time as endothelization takes place. The Amulet device resulted in higher procedural complications, including major bleeding and pericardial effusions. A similar higher complication risk was noted in the Amulet IDE trial (Lakkireddy included below).

The multicenter Amulet IDE Trial (Lakkireddy et al., 2021) evaluated the safety and effectiveness of the dual-seal mechanism of the Amulet LAA occluder compared with the Watchman device. A total of 1878 patients with nonvalvular AF at high risk of stroke were randomly assigned (1:1) to undergo percutaneous implantation with the Amulet occluder or Watchman device. The primary endpoints included safety (composite of procedure-related complications, all-cause death, or major bleeding at 12 months) and effectiveness (composite of ischemic stroke or systemic embolism at 18 months) and the rate of LAA occlusion at 45 days. Pre-specified secondary endpoints included a composite of all strokes, systemic embolism, or cardiovascular/unexplained death at 18 months, major bleeding at 18 months, and superiority test of the three primary endpoints. The Amulet occluder was noninferior to the Watchman device for the primary safety endpoint (14.5% vs. 14.7%). Major bleeding and all-cause death were similar between groups (10.6% vs 10.0% and 3.9% vs 5.1%, respectively). Procedure-related complications were higher for the Amulet occluder (4.5% vs. 2.5%), largely related to more frequent pericardial effusion and device embolization. The rate of complications decreased with operator experience. The Amulet occluder was noninferior to the Watchman device for the primary effectiveness endpoint (2.8% vs. 2.8%), and the composite of stroke, systemic embolism or cardiovascular/unexplained death (5.6% vs 7.7%). The rate of major bleeding was similar between groups (11.6% vs. 12.3%). LAA occlusion was higher for the Amulet occluder compared with the Watchman device (98.9% vs. 96.8%). Patient follow-up will continue for up to five years. Clinicaltrial.gov NCT02879448.

In a systematic review and meta-analysis of observational studies, Basu Ray et al. (2020) compared the safety and efficacy of the Amplatzer and Watchman LAA closure devices. Six studies, with 342 patients in the Watchman group and 274 patients in the Amplatzer group, were included in the meta-analysis. Of the six studies, two were prospective nonrandomized studies and four were retrospective studies. No RCTs were identified. Overall, both devices had relatively low complication rates. No significant differences between the devices were found in safety outcomes or in the rates of all-cause mortality, cardiac death, stroke/TIA, or device-related thrombosis. The total bleeding rate was significantly lower in the Watchman group, yet no significant differences were found when the bleeding rate was categorized into major and minor bleeding. Total peridevice

leakage rate and insignificant peridevice leakage rate were significantly higher in the Watchman group. However, significant peridevice leakages were similar in both the devices. The authors noted that observations were limited by the small number of available studies.

Surgical Closure (Occlusion) of the LAA as Part of Cardiac Surgery with Cardiopulmonary Bypass for a Different Indication

Whitlock et al. (2021) conducted the Left Atrial Appendage Occlusion Study (LAAOS III) after the LAAO I (Healey 2005) and LAOOS II (Whitlock 2013) trials. The LAAOS I and LAAOS II indicated LAA was a promising approach to stroke prevention in atrial fibrillation (AF), although larger trials were needed to support its safety and efficacy. The LAAOS III is a multicenter, randomized controlled trial that evaluated the efficacy and safety of concomitant left atrial appendage occlusion in participants with a history of atrial fibrillation undergoing cardiac surgery with cardiopulmonary bypass for another indication. The authors aimed to specifically determine whether concomitant occlusion would prevent ischemic stroke or systemic embolism in participants who continued to receive usual care, including anticoagulation. This multicenter, randomized trial involved adults with atrial fibrillation who had a CHA_2DS_2-VASc score of at least 2 (on a scale from 0 to 9, with higher scores indicating greater risk of stroke) who were scheduled to undergo cardiac surgery for another indication. The participants were randomly assigned to undergo, using a range of procedures, or not undergo occlusion of the left atrial appendage during surgery; all the participants were expected to receive usual care, including oral anticoagulation, during follow-up. The primary outcome was the occurrence of ischemic stroke (including transient ischemic attack with positive neuroimaging) or systemic embolism. The participants, research personnel, and primary care physicians were unaware of the trial-group assignments. The study population included 2379 participants in the occlusion group and 2391 in the no-occlusion group, with a mean age of 71 years and a mean CHA_2DS_2-VASc score of 4.2. The participants were followed for a mean of 3.8 years. A total of 92.1% of the participants received the assigned procedure, and at 3 years, 76.8% of the participants continued to receive oral anticoagulation. Stroke or systemic embolism occurred in 114 participants (4.8%) in the occlusion group and in 168 (7.0%) in the no-occlusion group (hazard ratio, 0.67; 95% confidence interval, 0.53 to 0.85; P = 0.001). The incidence of perioperative bleeding, heart failure, or death did not differ significantly between the trial groups. Limitations included lack of comparison of the efficacy of LAAO compared with oral anticoagulation and that the findings from LAAOS III apply primarily to surgical occlusion of the appendage performed as a concomitant procedure and not to stand-alone surgical or endovascular occlusion. The study design did not allow to determine whether all surgical closure methods were comparable. The results indicated that among patients with atrial fibrillation who are scheduled to undergone cardiac surgery with cardiopulmonary bypass for another indication, most of whom continued to take ongoing antithrombotic therapy, the risk of stroke or systemic embolism was lower when left atrial appendage occlusion that was performed at the time of the cardiac surgery.

Ando et al. (2018) conducted a systematic review and meta-analysis of studies comparing patients who underwent open cardiac surgery with or without LAA closure. Seven studies were included in the analysis. There were 1,963 patients in the LAA closure group and 1,934 patients in the non-LAA closure group. Of the 7 studies, 3 were RCTs, 3 were propensity-matched studies and 1 was a case-matching study. At 30-day/in-hospital follow-up, LAA closure was significantly associated with decreased risk of mortality and cerebrovascular accident. The authors concluded that concomitant surgical LAA closure should be considered at the time of open cardiac surgery, particularly among those with preoperative AF. The benefit of LAA closure for patients without preoperative AF and for those undergoing nonvalvular surgery is still unclear. Additionally, the findings are mostly based on included observational studies, with the findings of the three RCTs being less conclusive. Atti et al. (2018) had similar findings supporting the safety of surgical LAA closure but acknowledging RCTs are needed to evaluate long-term outcomes.

Caliskan et al. (2018), in an observational study with historical controls, evaluated the safety, effectiveness, and durability of the Atriclip implanted in patients undergoing open heart surgery. A total of 291 AtriClip devices were implanted epicardially in patients (mean CHA2DS2-VASc-Score: 3.1 ± 1.5) undergoing open-heart surgery (including isolated coronary artery bypass grafting, valve, or combined procedures) comprising of forty patients from a first-in-man device trial (NCT00567515) and 251 patients from a consecutive institutional registry afterwards. In all patients (n = 291), the LAA was successfully excluded, and overall mean follow-up (FU) was 36 ± 23months (range: 1-97 months). No device-related complications were detected throughout the FU period. Long-term imaging work-up (computed tomography) in selected patients ≥5years post-implant (range: 5.1-8.1 years) displayed complete LAA occlusion with no signs of residual reperfusion or significant LAA stumps. Subgroup analysis of patients with discontinued OAC during FU (n = 166) revealed a relative risk reduction of 87.5% with an observed ischemic stroke-rate of 0.5/100 patient-years compared with what would have been expected in a group of patients with similar CHA2DS2-VASc scores (expected rate of 4.0/100 patient-years). No strokes occurred in the subgroup with OAC.

The study had several limitations, including lack of contemporary controls, wide range of follow-up, and concomitant surgical ablations performed in some patients which likely impacted outcomes. In addition, long-term data (5-year analyses) was only reported on 32 patients. While the study results support the safety and effectiveness of the AtriClip system, well-designed controlled trials are needed to evaluate the AtriClip device in regard to stroke-prevention compared with current pharmacological and interventional therapies.

Emmert et al. (2014) evaluated the AtriClip device in 40 patients with AF undergoing elective cardiac surgery with planned concomitant ablation. Early mortality was 10% due to non-device-related reasons; however, the remaining 36 patients were evaluated at 3, 12, 24 and 36 months. After imaging, clips were found to be stable, showing no secondary dislocation 36 months after surgery. No intracardial thrombi, LAA perfusion or LAA stump were detected. Apart from one unrelated TIA that occurred 2 years after surgery in a patient with carotid plaque, no other strokes and/or neurological events were reported. While the results were promising, the study is limited by lack of randomization and small sample size.

Thoracoscopic Closure of the Left Atrial Appendage as a Stand-Alone Procedure or as an Adjunct to Thoracoscopic Atrial Fibrillation Ablation

The quality of evidence is insufficient to support the long-term efficacy of thoracoscopic closure of the left atrial appendage using an occlusion device as a stand-alone procedure or as an adjunct to thoracoscopic atrial fibrillation ablation procedure.

Cartledge et al. (2022) in a retrospective case series evaluated the safety, feasibility and long-term outcomes of standalone thoracoscopic LAAE in patients at high stroke risk AF who had contraindications to oral anticoagulation and were not candidates for ablation nor other cardiac surgery. Standalone thoracoscopic LAAE was performed using 3 unilateral ports access and epicardial clip. Periprocedural adverse events, long-term observational clinical outcomes and stroke rate were evaluated. Procedural success was 99.4% (174/175 patients). Pleural effusion occurred in 4 (2.3%) patients; other periprocedural complications were <1% each. One perioperative hemorrhagic stroke occurred (0.6%). No phrenic nerve palsy or cardiac tamponade occurred. Predicted annual ischemic stroke rate of 4.8/100 patient-years (based on median CHA2DS2-VASc score of 4.0) was significantly higher than stroke risk observed in follow-up after LAAE. No ischemic strokes occurred (median follow-up: 12.5 months), resulting in observed rate of 0 (95% CI 0-2.0)/100 patient-years ($P < 0.001$ versus predicted). Six all-cause (non-device-related) deaths occurred during follow-up. Study limitations include the following: many individuals did not return for an in-person postoperative visit to report outcomes, therefore adverse effects may have been underreported; there was no control arm and the stroke rate was compared to the risk-factor predicted rate; antiplatelet and OAC use was only reported at discharge and no long term discontinuation was reported; and because this is a new and not yet standardized treatment, facilities used their own standard qualifications, anticoagulation and follow up which may have weakened feasibility and safety results. Authors indicated this new surgical option, standalone thoracoscopic LAAE, is feasible and safe and may be an option for AF patients who have contraindications and/or intolerance to OAC. Further studies are needed to confirm these findings.

Evidence assessing AtriClip Flex-V and Pro-V is limited to reported clinical experiences on five patients that may not represent typical outcomes of LAA occlusion with these devices. Large clinical studies are needed to assess AtriClip Flex-V and Pro-V safety and effectiveness. (ECRI 2021b)

A Hayes technology assessment concluded that a very low-quality body of evidence from single arm studies demonstrated a high rate of complete LAA occlusion; however, the specific impact of AtriClip on relevant clinical outcomes including stroke risk cannot be determined due to the lack of comparative studies and the confounding effect of concurrent cardiac interventions. Well-designed comparative studies with sufficient follow-up duration are needed to determine whether the AtriClip system is a safe and effective preventive measure for stroke. (Hayes, 2021)

Franciulli et al. (2020) observed 20 consecutive patients with AF , mean age 75.1 years, 16 (80%) males who underwent thoracoscopic LAA closure as a stand-alone procedure, using an epicardial clip device. These patients had high risk of bleeding and oral anticoagulants (OAC) were contraindicated. Mean CHA_2DS_2-VASc score was 3.61, and the mean HAS-BLED score was 4.42. Successful LAA closure was assessed by transesophageal echocardiography. Primary endpoints were complete LAA closure (no residual LAA flow), operative complications, and all-cause mortality; secondary endpoints were 30-day and 6-month complications (death, ischemic stroke, hemorrhagic stroke, transient ischemic attack, any bleeding). Mean follow-up was 6 ± 4 months. Complete LAA closure was accomplished in all patients. No operative clip-related complications or deaths happened. At follow-up, freedom from postoperative complications was 95% and from any cerebrovascular events was

100%. Overall survival rate was 100%. The authors concluded that, in patients with nonvalvular AF at high bleeding risk (HAS-BLED score >3), thoracoscopic LAA closure appeared to be a valid alternative to percutaneous techniques not requiring dual antiplatelet or OAC treatment. Author's note that further studies are needed to confirm thoracoscopic LAA closure as a stand-alone procedure's effectiveness and morbidity.

Toale et al. (2019) conducted a systematic review of 11 studies (n=922) evaluating the safety, efficacy and durability of LAA occlusion using the AtriClip device in the management of patients with AF. Rates of total LAA occlusion compared favorably to conventional surgical and percutaneous closure methods. No device-related adverse events were reported across the studies. The reported incidence of stroke or TIA post-procedure ranged from 0.2 to 1.5/100 patient-years. Four hundred and seventy-seven of 798 patients (59.7%) had ceased anticoagulation on follow-up. Limitations include heterogenous studies of differing design and methodology, use of various procedural approaches and inconsistent post-operative anticoagulation. Most of the included studies appeared to be case series without a comparator, limiting the conclusions that can be drawn from this review. The authors noted that future trials comparing AtriClip with established surgical and percutaneous methods of LAA closure are needed. Ellis et al. (2017) and Ailawadi et al. (2011), which were previously cited in this policy, are included in this systematic review.

Ohtsuka et al. (2013) performed a case series to evaluate the thoracoscopic standalone left atrial appendectomy for thromboembolism prevention in nonvalvular AF. Thirty patients (mean age, 74 ± 5.0 years) who had had thromboembolisms were selected. A subgroup of 21 patients (mean age, 75 years; mean CHA2DS2 VASc score, 4.5) urgently needed an alternative treatment to anticoagulation: warfarin was contraindicated due to hemorrhagic side effects in 13, the international normalized ratio was uncontrollable in 7, and transient ischemic attacks had developed immediately after the warfarin dose was reduced for oncological treatment in 1. The LAA was thoracoscopically excised with an endoscopic cutter. Thoracoscopic appendectomy (mean operating time, 32 min, switched to mini-thoracotomy in 2 cases) led to no mortality and no major complications. Three-month post-operative 3-dimensional enhanced computed tomography, performed with patients' consent, confirmed the completeness of the appendectomy. Patients have been followed for 1 to 38 months (mean, 16 ± 9.7 months [18 ± 9.4 months for the subgroup]). One patient died of breast cancer 28 months after surgery. Despite discontinued anticoagulation, no patients experienced recurrence of thromboembolism. Limitations included a small non-randomized study group without a comparison group along with a short-term follow up. The authors concluded that thoracoscopic stand-alone appendectomy was potentially safe and may allow surgeons to achieve closure fairly simply and completely. The data to date is insufficient to address possible safety concerns associated with applying the technique in a limited-access environment, additional practice may demonstrate this to be a feasible option for thromboembolism protection in patients with nonvalvular AF.

Clinical Practice Guidelines

American Heart Association, the American College of Cardiology and the Heart Rhythm Society

Joint guidelines from the American Heart Association, the American College of Cardiology and the Heart Rhythm Society made the following recommendations regarding LAA occlusion: (January et al., 2014; January et al., 2019)

- Percutaneous closure of the LAA may be considered in patients with AF at increased risk of stroke with contraindications to long-term anticoagulation. (Class IIb; Level of Evidence B-NR)
- Surgical closure of the LAA may be considered in patients with AF undergoing cardiac surgery, as a component of an overall heart team approach to the management of AF. (Class IIb; Level of Evidence B-NR). Data on LAA occlusion at the time of concomitant cardiac surgery reveal a lack of clear consensus because of the inconsistency of techniques used for surgical excision, the highly variable rates of successful LAA occlusion and the unknown impact of LAA occlusion on future thromboembolic events.

Agency for Healthcare Research and Quality

An Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review update of invasive treatments for AF, including LAA closure devices, noted the evidence remains sparse in terms of stroke prevention. Observational studies comparing different LAA closure devices have suggested no statistically significant differences in risk of stroke, thromboembolism or mortality among the different devices; however, those studies were limited by small sample sizes and short follow-up. Based on these observational studies, LAA shows a trend toward a benefit over warfarin for all strokes and all-cause mortality. Although LAA with percutaneous closure results in less frequent major bleeding than warfarin, it is also associated with a higher rate of adverse safety events such as pericardial effusion and device embolization. Further studies are

needed to determine if and how anticoagulation strategies should be modified in patients receiving these procedures. (Sanders et al., 2018)

European Society of Cardiology

The European Society of Cardiology guidelines for the management of atrial fibrillation (AF) make the following recommendations regarding LAA occlusion: (Hindricks, et al., 2021)

- LAA occlusion may be considered for stroke prevention in patients with AF and contraindications for long-term anticoagulant treatment (e.g., intracranial bleeding without a reversible cause).
- Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery. Multiple observational studies indicate the feasibility and safety of surgical LAA occlusion/exclusion, but only limited controlled trial data are available.

National Institute for Health and Care Excellence (NICE)

National Institute for Health and Care Excellence (NICE) guidelines make the following recommendations:

- Consider LAA occlusion if anticoagulation is contraindicated or not tolerated and discuss the benefits and risks with the individual. (NICE, 2021; NICE, 2014)
- Do not offer LAA as an alternative to anticoagulation unless anticoagulation is contraindicated or not tolerated. (NICE, 2014)
- Current evidence on the safety and efficacy of thoracoscopic exclusion of the LAA for nonvalvular AF for the prevention of thromboembolism as an adjunctive procedure to surgical ablative techniques is inadequate in quantity and quality; therefore, this procedure should only be used as an adjunct to surgical ablation with special arrangements for clinical governance, consent and audit or research. (NICE, 2011)
- Current evidence suggests that percutaneous occlusion of the LAA is efficacious in reducing the risk of thromboembolic complications associated with nonvalvular AF. With regard to safety, there is a risk of life-threatening complications from the procedure, but the incidence of these is low. Therefore, this procedure may be used provided that normal arrangements are in place for clinical governance, consent and audit. (NICE, 2010)

Society of Thoracic Surgeons

The Society of Thoracic Surgeons clinical practice guidelines for the surgical treatment of AF state the following: (Badhwar et el., 2017)

- It is reasonable to perform LAA excision or exclusion in conjunction with surgical ablation for AF for longitudinal thromboembolic morbidity prevention. (Class IIA, Level C limited data)
- At the time of concomitant cardiac operations in patients with AF, it is reasonable to surgically manage the LAA for longitudinal thromboembolic morbidity prevention. (Class IIA, Level C expert opinion)

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.

The Watchman™ LAA closure device (Boston Scientific) received FDA premarket approval (P130013) on March 13, 2015. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P130013. Accessed June 1, 2022.

On July 21, 2020, the FDA approved an expanded indication to include patients deemed by their physicians to be suitable for anticoagulation therapy and have an appropriate rationale to seek a non-pharmacologic alternative to anticoagulation therapy. This next-generation device (Watchman FLX) was approved with supplement S035. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P130013S035. Accessed June 1, 2022.

The Amulet™ LAA closure device (Abbott) received FDA premarket approval (P200049) on August 14, 2021. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P200049. Accessed June 1, 2022.

There are several FDA 510(k) premarket notifications for the AtriClip LAA occlusion system (AtriCure, Inc.). For additional information, search the following website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. Accessed June 1, 2022.

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The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by UnitedHealthcare Medical Technology Assessment Committee. [*2022T0637A*]

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Policy History/Revision Information

Date	Summary of Changes

10/01/2022	**Template Update**
	• Created service-specific policy version for content previously included in the Clinical Policy titled *Omnibus Codes*
	Coverage Rationale
	• Added language to indicate surgical closure (occlusion) of the LAA as part of cardiac surgery with cardiopulmonary bypass for a different indication is proven and medically necessary to reduce the risk of stroke when all of the following criteria are met:
	  ○ Age 18 years or above
	  ○ History of atrial fibrillation
	  ○ CHA_2DS_2-VASc Score ≥ 2
	  ○ Device is used according to FDA labeled indications, contraindications, warnings, and precautions, when applicable
	• Replaced language indicating:
	  ○ "*Implantable cardiac devices for* percutaneous endovascular closure (occlusion) of the left atrial appendage (LAA) are proven and medically necessary to reduce the risk of stroke when using a U.S. Food and Drug Administration (FDA) approved device, *and* all of the [listed]criteria are met" with "percutaneous endovascular closure (occlusion) of the left atrial appendage (LAA) is

Date	Summary of Changes
	proven and medically necessary to reduce the risk of stroke when using a U.S. Food and Drug Administration (FDA) approved device, *when* all of the [listed] criteria are met" ○ "*Open or* thoracoscopic closure (occlusion) of the LAA *using any method (e.g., excision, isolation via stapling, oversewing, ligation, plication, clip)* is unproven due to insufficient evidence of safety and/or efficacy" with "thoracoscopic closure (occlusion) of the LAA *as a stand-alone procedure or as an adjunct to thoracoscopic atrial fibrillation ablation* is unproven *and not medically necessary* due to insufficient evidence of safety and/or efficacy" • Revised coverage criteria for percutaneous endovascular closure (occlusion) of the left atrial appendage (LAA); replaced criterion requiring "moderate to high risk of embolic stroke (CHA_2DS_2-VASc score ≥ 2 *in men or ≥ 3 in women*)" with "moderate to high risk of embolic stroke (CHA_2DS_2-VASc score ≥ 2)" **Definitions** • Added definition of "CHA_2DS_2-VASc score" **Prior Authorization Requirements** • Added language to indicate prior authorization is required in all sites of service ○ Participating providers in the office setting: Prior authorization is required for services performed in the office of a participating provider ○ Non-participating/out-of-network providers in the office setting: Prior authorization is not required but is encouraged for out-of-network services; if prior authorization is not obtained, Oxford will review for out-of-network benefits and medical necessity after the service is rendered **Supporting Information** • Added *Description of Services* and *FDA* sections • Updated *Clinical Evidence* and *References* sections to reflect the most current information • Archived previous policy version ADMINISTRATIVE 212.59 T2

Instructions for Use

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

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UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Oxford Clinical 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.