BlueCross BlueShield of Alabama

Name of Policy:

Left-Atrial Appendage Closure Devices for Stroke Prevention in Atrial Fibrillation

Policy #: 490
Category: Medicine/Cardiology

Latest Review Date: May 2018
Policy Grade: B

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

Stroke prevention in atrial fibrillation (AF) is an important goal of treatment. Treatment with anticoagulant medications is the most common approach to stroke prevention. Most embolic strokes originate from the left atrial appendage; therefore, occlusion of the left atrial appendage may offer a non-pharmacologic alternative to anticoagulant medications for this purpose. Multiple percutaneously-deployed devices are being investigated for left atrial appendage closure. There is only 1 LAA occlusion device approved by the FDA for stroke prevention in patients with AF, The Watchman device.

Stroke

Stroke is the most serious complication of atrial fibrillation. The estimated incidence of stroke in non-treated patients with atrial fibrillation is 5% per year. Stroke associated with atrial fibrillation is primarily embolic in nature, tends to be more severe than the typical ischemic stroke, and causes higher rates of mortality and disability. As a result, stroke prevention is one of the main goals of atrial fibrillation treatment.

Stroke in AF occurs primarily as a result of thromboembolism from the left atrium. The lack of atrial contractions in atrial fibrillation leads to blood stasis in the left atrium, and this low flow state increases the risk for thrombosis. The area of the left atrium with the lowest blood flow in atrial fibrillation, and, therefore, the highest risk of thrombosis, is the left-atrial appendage (LAA). It has been estimated that 90% of left-atrial thrombi occur in the LAA.

Treatment

Pharmacologic

The main treatment for stroke prevention in AF is anticoagulation, which has proven efficacy. The risk for stroke among patients with AF is evaluated using several factors. Two commonly used scores, the CHADS2 score, and the CHA2DS2-VASc score are described in Table 1. Warfarin is the predominant agent in clinical use. A number of newer anticoagulant medications, including dabigatran, rivaroxaban, and apixaban, have recently received U.S. Food and Drug Administration (FDA) approval for stroke prevention in nonvalvular AF and have demonstrated non-inferiority to warfarin in clinical trials. While anticoagulation is effective for stroke prevention, there is an increased risk of bleeding. Also, warfarin requires frequent monitoring and adjustments, as well as lifestyle changes. Dabigatran does not require monitoring. However, unlike warfarin, the antithrombotic effects of dabigatran are not reversible with any currently available hemostatic drugs. Guidelines from the American College of Chest Physicians recommend the use of oral anticoagulation for patients with AF who are at high risk of stroke (i.e., CHADS2 score of 2 or greater), with more individualized choice of antithrombotic therapy in patients with lower stroke risk.

Table 1. CHADS2 and CHADS2-VASc Scores to Predict Ischemic Stroke Risk in Patients With Atrial Fibrillation

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 y	2
D	Diabetes (fasting glucose >125 mg/dL or treatment with oral hypoglycemic agent and/or insulin)	1
S	Stroke or transient ischemic attack (includes any history of cerebral ischemia)	2
V	Vascular disease (prior myocardial infarction, peripheral arterial disease, or aortic plaque)	1
A	Age 65-74 y	1
Sc	Sex category of female (female sex confers higher risk)	1

Bleeding is the primary risk associated with systemic anticoagulation. Risk scores have been developed to estimate the risk of significant bleeding in patients treated with systemic anticoagulation. An example is the HAS-BLED score, which has validated to assess the annual risk of significant bleeding in patients with AF treated with warfarin. The score ranges from zero to nine, based on a number of clinical characteristics, including the presence of hypertension, renal and liver function, history of stroke, bleeding, labile international normalized ratios (INRs), age, and drug/alcohol use. Scores of three or greater are considered to be associated with high risk of bleeding, potentially signaling the need for closer monitoring of the patient for adverse risks, closer monitoring of INRs, or differential dose selections of oral anticoagulants or aspirin.

Surgery

Surgical removal, or exclusion, of the LAA is often performed in patients with atrial fibrillation who are undergoing open heart surgery for other reasons. Percutaneous LAA closure devices have been developed as a nonpharmacologic alternative to anticoagulation for stroke prevention in atrial fibrillation. The devices may prevent stroke by occluding the LAA, thus preventing thrombus formation.

Several versions of the devices have been developed. The WATCHMAN® left atrial appendage system (Boston Scientific, Maple Grove, MN) is a self-expanding nickel titanium device. It has a polyester covering and fixation barbs for attachment to the endocardium. Implantation is performed percutaneously through a catheter delivery system, utilizing venous access and transseptal puncture to enter the left atrium. Following implantation, patients are anticoagulated with warfarin or alternate agents for approximately one-two months. After this period, patients are maintained on antiplatelet agents (i.e., aspirin and/or clopidogrel) indefinitely. The Lariat® Loop Applicator is a suture delivery device that is intended to close a variety of surgical wounds in addition to left atrial appendage closure. The Cardioblate® closure device developed by Medtronic Corp. is currently being tested in clinical studies. The Amplatzer cardiac plug (St. Jude Medical, Minneapolis, MN), is FDA-approved for closure of atrial septal defects but not for LAA closure. A second-generation device, the Amplatzer Amulet, has been developed. The Percutaneous LAA Transcatheter Occlusion (PLATTO) device (eV_3, Plymouth MN) has also

been studied for this purpose but has not received FDA approval. The Occlutech® (Occlutech, Sweden) Left Atrial Appendage Occluder (has received a CE mark for coverage in Europe.

Outcome Measures
The optimal study design for evaluating the efficacy of percutaneous LAAC for the prevention of stroke in AF is a randomized controlled trial that includes clinically relevant measures of health outcomes. The rate of ischemic stroke during follow-up is the primary outcome of interest, along with rates of systemic embolization, cardiac events, bleeding complications, and death. For the LAAC devices, the appropriate comparison group could be oral anticoagulation, no therapy (for patients who have prohibitive risk for oral anticoagulation), or open surgical repair.

Policy:

The use of percutaneous left-atrial appendage closure devices for the prevention of stroke in atrial fibrillation **does not meet** Blue Cross and Blue Shield of Alabama's criteria for coverage and is considered **investigational**.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the members' contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The most recent update with literature review covers the period of through March 5, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is

preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

The evidence on the efficacy of left atrial appendage (LAA) closure devices consists of numerous case series of various occlusion devices, two published randomized controlled trial (RCT) of the Watchman™ device, the PROTECT AF and PREVAIL trials, that compared LAA closure with warfarin anticoagulation. Evidence on each different device will be reviewed separately, because the devices are not similar in design, and each may have its own unique considerations.

WATCHMAN® Device

The Watchman device is intended as an alternative to anticoagulation for patients with atrial fibrillation (AF) who are at increased risk for embolic stroke.

Systematic Reviews

A TEC Assessment in 2014, evaluated the use of the Watchman device for patients who were eligible and ineligible for anticoagulation therapy and determined that it does not meet Technology Evaluation Criteria. The assessment determined that the device did not meet TEC criteria. The Assessment made the following conclusions about the use of LAA closure in patients without contraindications to anticoagulation:

> "We identified two randomized controlled trials (RCTs) and one case series evaluating the Watchman™ device. The RCTs were noninferiority trials and compared LAAC with anticoagulation. The first trial showed a lower rate of a composite outcome (stroke, death, and embolism) in patients receiving LAAC [left atrial appendage closure] and met noninferiority criteria compared with anticoagulation, but FDA [Food and Drug Administration] review noted problems with patient selection, potential confounding with other treatments, and losses to follow-up. The second trial, which incorporated the first trial's results as a discounted informative prior in a Bayesian analysis, showed similar rates of the same composite outcome but did not meet noninferiority criteria. The second trial met its second principal outcome noninferiority criteria in one of two analyses and a performance goal for short-term complication rate. When assessing the results of both trials, the relative performance of LAAC and anticoagulation is uncertain."

Although the Watchman device and other LAA closure devices would ideally represent an alternative to oral anticoagulation for the prevention of stroke in patients with AF, during the postimplantation period, the device may be associated with increased thrombogenicity and, therefore, anticoagulation is used during the periprocedural period. Most studies that have evaluated the Watchman device have included patients who are eligible for anticoagulation.

Meta-Analyses

A number of systematic reviews published after the TEC Assessment have combined the results of the available RCTs. Others have included RCTs and observational studies.

The most rigorous meta-analysis is a patient-level meta-analysis by Holmes et al (2015). This study reported results of a patient-level data from the industry-sponsored PROTECT AF and PREVAIL trials, described below, together with both studies' continued access registries. The PROTECT AF and PREVAIL registries were designed to include patients with similar baseline characteristics as their respective RCTs. The meta-analysis included a total of 2406 patients, 1877 treated with the Watchman device and 382 treated with warfarin alone. Mean patient follow-up durations were 0.58 years and 3.7 years, respectively, for the PREVAIL continued access registry and the PROTECT AF continued access registry. In a meta-analysis of 1114 patients treated in the RCTs, compared with warfarin, LAA closure met the study's noninferiority criteria for the primary composite efficacy end point of all-cause stroke, systemic embolization, and cardiovascular death (hazard ratio [HR], 0.79, 95% confidence interval [CI], 0.52 to 1.2; p=0.22). All-cause stroke rates did not differ significantly between groups (1.75 per 100 patient-years for LAA closure vs 1.87 per 100 patient-years for warfarin; HR=1.02; 95% CI, 0.62 to 1.7; p=0.94). However, LAA closure–treated patients had higher rates of ischemic stroke (1.6 events/100 patient-years vs 0.9 events/100 patient-years; HR=1.95, p=0.05) when procedure-related strokes were included, but had lower rates of hemorrhagic stroke (0.15 events/100 patient-years vs 0.96 events/100 patient-years; HR=0.22; 95% CI, 0.08 to 0.61; p=0.004).

A second patient-level meta-analysis of the 2 RCTs, reported by Price (2015), evaluated bleeding outcomes. There were a total of 54 episodes of major bleeding, with the most common types being gastrointestinal (GI) bleed (31/54 [57%]) and hemorrhagic stroke (9/54 [17%]). On combined analysis, the rate of major bleeding episodes over the entire study period did not differ between groups. There were 3.5 events per 100 patient-years in the Watchman group compared with 3.6 events per 100 patient-years in the anticoagulation group, for a rate ratio (RR) of 0.96 (95% CI, 0.66 to 1.40; p=0.84). However, there was a reduction in bleeding risk for the Watchman group past the initial periprocedural period. For bleeding events occurring more than 7 days postprocedure, the event rates were 1.8 per 100 patient-years in the Watchman group compared with 3.6 per 100 patient-years in the anticoagulation group (RR=0.49; 95% CI, 0.32 to 0.75; p=0.01). For bleeding events occurring more than 6 months postprocedure (the time at which antiplatelet therapy is discontinued for patients receiving the Watchman device), the event rates were 1.0 per 100 patient-years in the Watchman group compared with 3.5 per 100 patient-years in the anticoagulation group (RR=0.28; 95% CI, 0.16 to 0.49; p<0.001).

Reddy et al (2017) presented final results of the PROTECT AF trial and PREVAIL AF trial and conducted a meta-analysis of 5-year outcomes using data from both trials. Meta-analytic results are summarized in Table 2, showing that the Watchman device is noninferior to warfarin alone in stroke prevention among patients with nonvalvular AF. In addition, patients treated with the Watchman device experienced significantly lower bleeding and mortality; however, the incidence of ischemic stroke trended up in the Watchman group.

Table 2. Five-Year Meta-Analytics Results for the PROTECT AF and PREVAIL AF Trials

Outcomes	Watchman, n (Rate per 100 PY)	Warfarin Alone, n (Rate per 100 PY)	HR (95% CI)	p
Composite stroke/SE/CV death	79 (2.8%)	50 (3.4%)	0.8 (0.6 to 1.2)	0.3
All stroke or SE	49 (1.7%)	27 (1.8%)	1.0 (0.6 to 1.5)	0.9
CV/unexplained death	39 (1.3%)	33 (2.2%)	0.6 (0.4 to 0.9)	0.03
All cause death	106 (3.0%)	73 (4.9%)	0.7 (0.5 to 1.0)	0.03
Major bleeding, all	85 (3.1%)	50 (3.5%)	0.9 (0.6 to 1.3)	0.6
Major bleeding, non-LAAC-related	48 (1.7%)	51 (3.6%)	0.5 (0.3 to 0.7)	<0.001

Adapted from Reddy et al (2017). CI: confidence interval; CV: cardiovascular; HR: hazard ratio; LAAC: left atrial appendage closure; PY: patient-years;
SE: systemic embolism.

Additional systematic reviews have used network meta-analyses to compare Watchman with novel oral anticoagulants and vitamin K antagonists (6 RCTs, n=59,627 subjects), and have compared percutaneous LAA occlusion (5 RCTs, N=1285 subject) with standard anticoagulant or antiplatelet therapy with device-based surgical or percutaneous LAA exclusion.

Randomized Controlled Trials

PROTECT-AF

The first RCT published is the PROTECT-AF study, which was a randomized, unblinded trial that evaluated the non-inferiority of an LAA closure device compared with warfarin for stroke prevention in AF. The trial randomized 707 patients from 59 centers in the U.S. and Europe to the Watchman device or warfarin treatment in a 2:1 ratio. Mean follow-up was 18 +/- 10 months. The primary efficacy outcome was a composite end point of stroke (ischemic or hemorrhagic), cardiovascular or unexplained death, or systemic embolism. There was also a primary safety outcome, which was a composite end point of excessive bleeding (intracranial or gastrointestinal [GI] bleeding) and procedure-related complications (pericardial effusion, device embolization, procedure-related stroke).

The primary efficacy outcome occurred at a rate of 3.0 per 100 patient years in the LAA closure group compared with 4.9 per 100 patient years in the warfarin group (rate ratio [RR]=0.62; 95% credible interval [CrI], 0.35 to 1.25). Based on these outcomes, the probability of non-inferiority was greater than 99.9%. For the individual components of the primary outcome, cardiovascular/unexplained death and hemorrhagic stroke were higher in the warfarin group. In contrast, ischemic stroke was higher in the LAA closure group at 2.2 per 100 patient years compared with 1.6 per 100 patient years in the warfarin group (RR=1.34; 95% CI, 0.60 to 4.29).

The primary safety outcome occurred more commonly in the LAA closure group, at a rate of 7.4 per 100 patient years compared with 4.4 per 100 patient years in the warfarin group (RR=1.69; 95% CrI, 1.01 to 3.19). The excess in adverse event rates for the LAA closure group were primarily the result of early adverse events associated with placement of the device. The most frequent type of complication related to LAA closure device placement was pericardial effusion requiring intervention, which occurred in 4.8% of patients (22/463).

Longer term follow-up from the PROTECT AF study was reported by Reddy et al in 2013. At a mean follow-up of 2.3 years, the results were similar to the initial report. The relative risk for the composite primary outcome in the Watchman group compared with anticoagulation was 0.71, and this met non-inferiority criteria with a confidence of greater than 99%. Complications were more common in the Watchman group, with an estimated rate of 5.6%/year in the Watchman group compared with 3.6%/year in the warfarin group.

Outcomes through four years of follow-up were reported by Reddy et al in 2014. Mean follow-up was 3.9 years in the LAA closure group and 3.7 years in the warfarin group. In the LAA closure group, warfarin was discontinued in 345 of 370 patients (93.2%) by the 12 month follow-up evaluation. During the follow-up period, the relative risk for the composite primary outcome in the Watchman group compared with anticoagulation was 0.60 (8.4% in the device group vs 13.9% in the anticoagulation group; 95% CrI, 0.41 to 1.05), which met the noninferiority criteria with a confidence of greater than 99.9%. Fewer hemorrhagic strokes occurred in the Watchman group (0.6% vs 4.0%; RR=0.15; 95% CrI, 0.03 to 0.49), and fewer cardiovascular events occurred in the Watchman group (3.7% vs 0.95%; RR=0.40; 95% CrI, 0.23 to 0.82). Rates of ischemic stroke did not differ significantly between groups, but Watchman group patients had lower all-cause mortality than anticoagulation group patients (12.3% vs 18.0%; HR=0.66; 95% CI, 0.45 to 0.98; p=0.04).

Alli et al reported quality-of-life parameters, as measured by change in scores on the Short-Form 12 Health Survey from baseline to 12 months of follow up, for a subset of 547 subjects in the PROTECT AF study. For the subset of PROTECT AF subjects included in the present analysis, at baseline, control group subjects had a higher mean CHADS2 score (2.4 vs 2.2; p=0.0517) and were more likely to have a history of coronary artery disease (49.5% vs 39.6%; p=0.0275). For subjects in the Watchman group, the total physical score improved in 34.9% and was unchanged in 29.9%; for those in the warfarin group, the total physical score improved in 24.7% and was unchanged in 31.7% (p=0.01).

Five-year follow-up results, published by Reddy et al (2017), indicated that the LAAC group had a higher ischemic stroke rate than the warfarin only group (1.35 vs 1.07 respectively). The composite efficacy end point (stroke, systemic embolism, cardiovascular death) in the LAAC group was lower when compared with the warfarin-only group (p=0.04).

PREVAIL

A second RCT, the PREVAIL trial, was conducted after the 2009 FDA decision on the Watchman device to address some of the limitations of the PROTECT AF study, including its inclusion of patients with low stroke risk (CHADS2 scores of 1), high rates of adjunctive antiplatelet therapy use in both groups, and generally poor compliance with warfarin therapy in the control group. Results from the PREVAIL trial were published by Holmes et al in 2014. In the PREVAIL trial, 461 subjects enrolled at 41 sites were randomized in a 2:1 fashion to either the Watchman™ device or control, which consisted of either initiation or continuation of warfarin therapy with a target international normalized ratio (INR) of 2.0-3.0. Subjects had nonvalvular AF and required treatment for prevention of thromboembolism based on a CHADS2 score of two or higher (or one or higher with other indications for warfarin therapy based on

American College of Cardiology/American Heart Association/European Society of Cardiology guidelines) and were eligible for warfarin therapy. In the device group, warfarin and low-dose aspirin were continued until 45 days postprocedure; if a follow-up echocardiogram at 45 days showed occlusion of the LAA, warfarin therapy could be discontinued. Subjects who discontinued warfarin were treated with aspirin and clopidogrel for six months post-device implantation and with 325 mg aspirin indefinitely after that.

Three non-inferiority primary efficacy end points were specified: 1) occurrence of ischemic or hemorrhagic stroke, cardiovascular or unexplained death, and systemic embolism (18 month rates); 2) occurrence of late ischemic stroke and systemic embolization (beyond seven days post-randomization, 18-month rates); and 3) occurrence of all-cause death, ischemic stroke, systemic embolism, or device- or procedure-related events requiring open cardiac surgery or major endovascular intervention (e.g., pseudoaneurysm repair, arteriovenous fistula repair, or other major endovascular repair) occurring within seven days of the procedure or by hospital discharge, whichever was later. The 18-month event rates were determined using Bayesian statistical methods to integrate data from the PROTECT-AF study. All patients had a minimum follow-up of six months. For randomized subjects, the mean follow-up was 11.8 months and the median follow-up was 12.0 months (range 0.03-25.9 months).

The first primary end point, the 18-month modeled RR between the device and control groups was 1.07 (95% Crl, 0.57 to 1.89). Because the upper bound of the 95% credible interval was above the preset non-inferiority margin of 1.75, the non-inferiority criteria were not met. For the second primary end point of late ischemic stroke and systemic embolization, the 18-month RR between the device and control groups was 1.6 (95% Crl, 0.5 to 4.2), with an upper bound of the 95% credible interval above the preset non-inferiority margin of 2.0. The rate difference between the device and control groups was 0.0053 (95% Crl, -0.0190 to 0.0273). The upper bound of the 95% credible interval was lower than the non-inferiority margin of 0.0275, so the non-inferiority criterion was met for the rate difference. For the third primary end point, major safety issues, the non-inferiority criterion was met. At the time of the FDA decision, only 28% of PREVAIL subjects had actually reached 18-month follow-up.

Five-year follow-up results, published by Reddy et al (2017), indicated that the Watchman device was noninferior to warfarin alone in the composite efficacy end point (stroke, systemic embolism, cardiovascular death) (p=0.47).

Nonrandomized Studies

Numerous case series and nonrandomized studies have been published. Several are notable in that they were conducted in patients not eligible for anticoagulation, a population not included in PROTECT AF and PREVAIL. Reddy et al conducted a multicenter, prospective, nonrandomized trial to evaluate the safety and efficacy of LAAC with the Watchman device in patients with nonvalvular AF with a CHADS2 score 1 or higher who were considered ineligible for warfarin. Postimplantation, patients received 6 months of clopidogrel or ticlopidine and lifelong aspirin therapy. Thirteen (8.7%) patients had a procedure- or device-related serious adverse event, most commonly pericardial effusion (3 patients). Over a mean 14.4 months of follow-up, all-cause stroke or systemic embolism occurred in 4 patients.

Chun et al (2013) compared the Watchman device to the Amplatzer cardiac plug among patients with nonvalvular AF, who were at high risk for stroke and had a contraindication to or were not willing to accept oral anticoagulants. Eighty patients were randomized to left atrial appendage occlusion with the Watchman or the Amplatzer device. After device implantation, either preexisting oral anticoagulation therapy or dual platelet inhibition with aspirin and clopidogrel was continued for 6 weeks. There were no statistically significant differences in procedure time, fluoroscopy time, or major safety events between the 2 groups. At a median 364 days of follow-up, there were no cases of stroke/transient ischemic attack or other bleeding complications.

The EWOLUTION Watchman registry is intended to evaluate procedural success, long-term outcomes, and adverse events in real-world settings. This registry compiles data from patients receiving the Watchman device at 47 centers in 13 countries. A publication from the EWOLUTION registry in 2016 reported on 30-day outcomes of device implantation in 1021 patients. The overall population had a risk of bleeding that was substantially higher than that for patients in the RCTs. Over 62% of patients included in the registry were deemed ineligible for anticoagulation by their physicians. Approximately one-third of patients had a history of major bleeding, and 40% had HAS-BLED scores of 3 or greater, indicating moderate-to-high risk of bleeding. Procedural success was achieved in 98.5% of patients, and 99.3% of implants demonstrated no blood flow or minimal residual blood flow postprocedure. Serious adverse events due to the device or procedure occurred at an overall rate of 2.8% (95% CI, 1.9% to 4.0%) at 7 days and 3.6% (95% CI, 2.5% to 4.9%) at 30 days. The most common serious adverse event was major bleeding.

Fauchier et al, in 2017, retrospectively evaluated the incidence, predictors, and prognosis of thrombus formation on 469 patients who received either the Watchman device (n=272) or Amplatzer device (n=197). The data was reviewed from 8 centers in France from 2012 – 2017. Patients were followed up for 13 +/- 13 months. A total of 98 major adverse events were reported, including 26 thrombi on devices, 19 ischemic strokes, 2 TIAs, 18 major hemorrhages, and 33 deaths. The authors stated that older age and history of stroke were predictors of thrombus formation on the devices, whereas dual antiplatelet therapy and oral anticoagulation at discharge were protective factors. Independent predictors of ischemic strokes and TIAs included thrombus on the device and vascular disease during follow-up. There were no clear differences between the devices. The authors conclude by stating that "thrombus formation on the device is not uncommon in patients with atrial fibrillation who are treated by LAA closure. Such events are strongly associated with a higher risk of ischemic stroke during follow-up."

Section Summary: Watchman Device

The most relevant evidence on use of the Watchman device for LAAC in patients eligible for anticoagulation is from 2 industry-sponsored RCTs and a patient-level meta-analysis of those studies. This evidence suggests that the Watchman is associated with an increased periprocedural ischemic stroke risk, which is balanced against a decreased hemorrhagic stroke risk. While neither trial individually demonstrates definitive improvement in outcomes, the patient-level meta-analysis reported improvement for a range of clinical outcomes for patients treated with the Watchman device. The overall bleeding risk is greater for the Watchman device in the periprocedural period, but decreased after the initial periprocedural period. A retrospective study

on 469 patients, who received an LAAC device, showed that thrombus formation is not uncommon and is strongly associated with a higher risk of ischemic stroke.

Other Closure Devices

Lariat® Device

A systematic review of published studies on the Lariat device was published in 2016. No RCTs were identified. Five case series were selected, with a total of 309 patients (range, 4-154 patients) treated. The combined estimate of procedural success was 90.3%. One (0.3%) death was reported and 7 (2.3%) patients required urgent cardiac surgery. The MAUDE database was searched for adverse events, and found 35 unique reports. Among the 35 reported complications, there were 5 deaths and 23 cases of emergency cardiac surgery.

Individual case series published since the systematic review, include a large 2016 case series of 712 consecutive patients from 18 U.S. hospitals. This series reported a procedural (suture deployment) success rate of 95% and complete closure in 98%. The high success rate was attributed to the appropriate selection of patients for the procedure, which was determined by a screening computed tomography scan showing if the LAA anatomy was suitable for LARIAT deployment. There was 1 death and emergent cardiac surgery was required in 1.4%. Cardiac perforations (overall and those needing surgery) and number of patients needing blood transfusions decreased when providers altered the procedure from using large bore needles to micropuncture needles. Other individual case series are smaller, reporting success rates and complication rates in the same range.

Section Summary: Lariat Device

There are no RCTs of the Lariat device for this indication. The available case series are not sufficient to determine treatment efficacy.

Amplatzer® Cardiac Plug Device

The available evidence on use of the Amplatzer® device for left atrial occlusion consists of a number of case series. The largest series identified was by Nietlispach et al, which included 152 patients from a single institution in Europe. Short-term complications occurred in 9.8% (15/152). Longer-term adverse outcomes occurred in 7% of patients, including two strokes, one peripheral embolization, and four episodes of major bleeding. Device embolization occurred in 4.6% (7/152) of patients.

Other smaller series of patients treated with the Amplatzer® device include a series of 90 patients from Belgium (2013), 86 patients from Portugal (2012), 37 patients from Italy, 35 patients from Spain (2013), 21 patients from Poland (2012), and 20 patients from China (2012). All series reported high procedural success rates, as well as various complications such as vascular complications, air embolism, esophageal injury, cardiac tamponade, and device embolization.

Several studies have reported the use of the Amplatzer device in patients with a contraindication to oral anticoagulation therapy. The largest study, by Santoro et al (2016), reported outcomes, up to four years postprocedure, for 134 patients with nonvalvular AF and a long-term contraindication to oral anticoagulation treated with the Amplatzer device. Patients had a median

CHA2DS2-VASc score of four and were generally considered at high risk for bleeding complications. Procedural success occurred in 93.3%, and three major procedure-related complications (two cases of cardiac tamponade, one case of pericardial effusion requiring drainage or surgery) occurred. Over a mean follow-up of 680 days, observed annual rates of ischemic strokes and any thromboembolic events were 0.8% and 2.5%, respectively.

Other case series have been published in this population, ranging from 37 to 100 patients. They also reported high success rates and low procedural complications.

Section Summary: Amplatzer Cardiac Plug Device
There are no RCTs of the Amplatzer device for LAAC. The available case series are not sufficient to determine treatment efficacy.

PLAATO Device
The available evidence on outcomes following use of the PLAATO device for stroke prevention in AF comes from case series and cohort studies. Bayard et al reported on 180 patients with non-rheumatic AF and a contraindication to warfarin and who were treated with the Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO) device. Placement was successful in 90% of patients. Two patients died within 24 hours of the procedure (1.1%), and six patients had cardiac tamponade (3.3%), with two requiring surgical drainage. Other case reports and small case series report complications, including multiple reports of thrombus formation at the site of device placement.

Section Summary: PLAATO Device
There are no RCTs of the PLAATO device for this indication. Future trials seem unlikely because the PLAATO device is no longer manufactured.

Summary
For individuals who have atrial fibrillation (AF) who are at increased risk for embolic stroke who receive the Watchman percutaneous left atrial appendage closure (LAAC) device, the evidence includes 2 randomized controlled trials (RCTs) and meta-analyses of these trials. Relevant outcomes are overall survival, morbid events, and treatment-related morbidity. The most relevant evidence comes from 2 industry-sponsored RCTs that compared the Watchman device with anticoagulation alone. One trial reported noninferiority on a composite outcome of stroke, cardiovascular/unexplained death, or systemic embolism after 2 years of follow-up, with continued benefits with the Watchman device after 4 years of follow-up. The second trial did not demonstrate noninferiority for the same composite outcome, but did demonstrate noninferiority of the Watchman device to warfarin for late ischemic stroke and systemic embolization. Patient-level meta-analyses at 5 year follow-up of the 2 trials reported that the Watchman device is noninferior to warfarin on the composite outcome of stroke, systemic embolism, and cardiovascular death, but the ischemic stroke rate was higher in the Watchman group. Also, the Watchman was associated with a higher periprocedural risk of bleeding but a lower risk of hemorrhagic stroke over the long term. Case series have demonstrated that these devices can be successfully implanted percutaneously in most patients. Complications such as pericardial effusion and tamponade are reported in available studies at a rate of 2-5%. A retrospective study on 469 patients who received an LAAC device, showed that thrombus formation is not

uncommon and is strongly associated with a higher risk of ischemic stroke. The evidence is insufficient to determine net health outcomes.

For individuals who have AF who are at increased risk for embolic stroke who receive a percutaneous LAAC device other than the Watchman device (e.g., the Lariat or Amplatzer), the evidence includes uncontrolled case series. Relevant outcomes are overall survival, morbid events, and treatment-related morbidity. Case series of these devices have reported high procedural success, but also numerous complications. In addition, these devices do not have the U.S. Food and Drug Administration approval for LAAC. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

American College of Cardiology, Heart Rhythm Society, et al

In 2015, the American College of Cardiology (ACC), Heart Rhythm Society (HRS), and Society for Cardiovascular Angiography and Interventions published an overview of the integration of percutaneous LAA closure devices into the clinical practice of patients with AF. The overview was organized around questions related to the sites of care delivery for LAA closure devices, training for proceduralists, necessary follow-up data collection, identification of appropriate patient cohorts, and reimbursement. The statement provides general guidelines for facility and operator requirements, including the presence of a multidisciplinary heart team, for centers performing percutaneous LAA closures. The statement does not provide specific recommendations about the indications and patient populations appropriate for percutaneous LAA closure.

American College of Cardiology, American Heart Association, et al

In 2014, the American College of Cardiology, the American Heart Association, and the Heart Rhythm Society issued guidelines on the management of patients with AF. These guidelines recommend that surgical excision of the LAA may be considered in patients undergoing cardiac surgery (Class IIB recommendation; Level of evidence: C), but make no specific recommendations regarding percutaneous LAA closure.

American College of Chest Physicians

In 2012, the American College of Chest Physicians has evidence-based clinical best practice guidelines on the use of antithrombotic therapy for prevention of stroke in AF. In relation to the use of LAA closure devices, the guidelines state: “At this time, we make no formal recommendations regarding LAA closure devices, pending more definitive research in this field.”

European Society of Cardiologists et al

In 2016, the European Society of Cardiology (ESC) and the European Society for Cardiothoracic Surgery (EACTS) issued guidelines on the management of AF. The guidelines included the following recommendations about exclusion of the left atrial appendage in AF (see Table 1).

Table 1. ESC Recommendations about LAA Occlusion55

Recommendation	COR	LOE
"After surgical occlusion or exclusion of the LAA, it is recommended to continue anticoagulation in at risk patients with AF for stroke prevention"	I	B
"LAA occlusion may be considered for stroke prevention in patients with AF and contraindications for long-term anticoagulant treatment (e.g., those with a previous life-threatening bleed without a reversible cause)."	IIb	B

AF: atrial fibrillation; COR: class of recommendation; LAA: left atrial appendage; LOE: level of evidence

They go on to state that "Adequately powered controlled trials are urgently needed to inform the best use of these devices, including LAA occluders in patients who are truly unsuitable for OAC or in patients who suffer a stroke on OAC, randomized comparisons of LAA occluders with NOACs, and assessment of the minimal antiplatelet therapy acceptable after LAA occlusion."

U.S. Preventive Services Task Force Recommendations
LAA closure devices are not preventive services and are therefore not included in the U.S. Preventive Task Force Recommendations for preventive services.

Key Words:

Left Atrial Appendage Closure Device, WATCHMAN®, LARIAT®, AMPLATZER®, PLATTO, LAA, AtriClip

Approved by Governing Bodies:

In 2002, the PLAATO system (ev3 Endovascular) was the first device to be approved by the U.S. Food and Drug Administration (FDA) for LAA occlusion. The device was discontinued in 2007 for commercial reasons and intellectual property was sold to manufacturers of the Watchman system.

In 2009, the Watchman Left Atrial Appendage Closure Technology (Boston Scientific, Marlborough, MA) was originally considered by the U.S. Food and Drug Administration (FDA) for approval based on the results the results of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients with Atrial Fibrillation (PROTECT-AF) randomized controlled trial (RCT). The device underwent three panel reviews before it was approved by FDA through the premarket approval process on March 13, 2015.

This device is indicated to reduce the risk of thromboembolism from the left atrial appendage (LAA) in patients with nonvalvular atrial fibrillation who:

- Are at increased risk for stroke and systemic embolism based on CHADS2 or CHA2DS2-VASc scores and are recommended for anticoagulation therapy;
- Are deemed by their physicians to be suitable for warfarin; and
- Have an appropriate rationale to seek a nonpharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.

Other devices are being evaluated for LAA occlusion, but are not approved in the U.S. for percutaneous closure of the LAA. The Lariat® Loop Applicator device (SentreHEART, Inc, Redwood City, CA) is a suture delivery system that received 510(k) marketing clearance from FDA in 2006. The intended use is to facilitate suture placement and knot tying in surgical applications where soft tissues are being approximated or ligated with a pre-tied polyester suture. The Amplatzer Amulet® device (St. Jude Medical, Plymouth, MN) and WaveCrest® (Coherex Medical) have CE approval in Europe for left atrial appendage closure, but are not currently approved in the U.S. for this indication.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply.
FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity

Current Coding:

CPT Codes:

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. **(Effective 01/01/17)**

Previous Coding:

CPT Codes:

0281T	Percutaneous transcatheter closure of the left atrial appendage with implant, including fluoroscopy, transseptal **(Deleted 12/31/16)**

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Policy History:

Medical Policy Group, December 2011 **(3)**
Medical Policy Administration Committee, December 2011
Available for comment December 14, 2011 through January 27, 2012
Medical Policy Group, March 2012 **(3):** 2012 Updates to Description, Key Points & References
Medical Policy Panel, March 2013
Medical Policy Group, June 2013 **(4):** 2013 Updates to Description, Key Points, Key Words & References; no change in policy statement
Medical Policy Panel, July 2014
Medical Policy Panel, July 2014 **(4):** Updated Description, updated Key Points to include Practice Guidelines, updated Approved Governing Bodies and References. There were no changes to the policy at this time.
Medical Policy Group, May 2015 **(4):** Update to Approved Governing Bodies
Medical Policy Panel, October 2015
Medical Policy Group, December 2015 **(4):** Updates to Description, Key Points, Approved Governing Bodies, and References. No change to policy statement.
Medical Policy Panel, May 2016
Medical Policy Group, June 2016 **(4):** Updates to Key Points and References. No change to policy statement.
Medical Policy Group, December 2016: 2017 Annual Coding Update. Created Previous Coding section and moved deleted code 0281T to this section. Added new CPT code 33340 to Current Coding.
Medical Policy Panel, May 2017
Medical Policy Group, May 2017 **(4):** Updates to Description, Key Points, Key Words and References. No change to policy statement.
Medical Policy Panel, 2018
Medical Policy Group, May 2018 **(4):** Updates to Description, Key Points, Key Words, Approved by Governing Bodies, and References. No change to policy statement.
