2.02.26	Percutaneous Left Atrial Appendage Closure Devices for Stroke Prevention in Atrial Fibrillation		
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Section:	2.0 Medicine	**Page:**	Page 1 of 23

Policy Statement

The use of a device with U.S. Food and Drug Administration (FDA) approval for percutaneous left atrial appendage closure (e.g., the Watchman) may be considered **medically necessary** for the prevention of stroke in patients with atrial fibrillation when **both** of the following criteria are met:

- There is an increased risk of stroke and systemic embolism based on $CHADS_2$ or CHA_2DS_2-VASc score and systemic anticoagulation therapy is recommended
- The long-term risks of systemic anticoagulation outweigh the risks of the device implantation (see Policy Guidelines section)

The use of a device with FDA approval for percutaneous left atrial appendage closure (e.g., the Watchman) for stroke prevention in patients who do not meet the above criteria is considered **investigational**.

The use of other percutaneous left atrial appendage closure devices, including but not limited to the Lariat and Amplatzer devices, for stroke prevention in patients with atrial fibrillation is considered **investigational**.

Policy Guidelines

The balance of risks and benefits associated with implantation of the Watchman device for stroke prevention, as an alternative to systemic anticoagulation with warfarin, must be made on an individual basis.

Bleeding is the primary risk associated with systemic anticoagulation. A number of 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 is validated to assess the annual risk of significant bleeding in patients with atrial fibrillation (AF) treated with warfarin (Pisters et al, 2010). Scores range from 0 to 9, based on a number of clinical characteristics (see Table PG1).

Table PG1. Clinical Components of the HAS-BLED Bleeding Risk Score

Letter	Clinical Characteristics	Points Awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile international normalized ratios	1
E	Elderly (>65 y)	1
D	Drugs or alcohol (1 point each)	1 or 2

Adapted from Pisters et al (2010).

Risk of major bleeding in patients with scores of 3, 4, and 5 has been reported at 3.74 per 100 patient-years, 8.70 per 100 patient-years, and 12.5 per 100 patient-years, respectively. Scores of 3 or greater are considered to be associated with high risk of bleeding, potentially signaling the need for closer monitoring of patients for adverse risks, closer monitoring of international normalized ratio, or differential dose selections of oral anticoagulants or aspirin (January et al, 2014).

Coding

The following category I CPT code is specific for this procedure:

- **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

Description

Stroke prevention in patients with atrial fibrillation (AF) is an important goal of treatment. Treatment with anticoagulant medications is the most common approach to stroke prevention. Because most embolic strokes originate from the left atrial appendage, occlusion of the left atrial appendage may offer a nonpharmacologic alternative to anticoagulant medications to lower the risk of stroke. Multiple percutaneously deployed devices are being investigated for left atrial appendage closure (LAAC). One left atrial appendage device (the Watchman device) has approval from the U.S. Food and Drug Administration for stroke prevention in patients with AF.

Related Policies

- Catheter Ablation as Treatment for Atrial Fibrillation
- Open and Thoracoscopic Approaches to Treat Atrial Fibrillation and Atrial Flutter (Maze and Related Procedures)

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

In 2002, the PLAATO system (ev3 Endovascular) was the first device to be approved by the 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 2015, the Watchman™ Left Atrial Appendage Closure Technology (Boston Scientific) was approved by the FDA through the premarket approval process by the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients with Atrial Fibrillation randomized controlled trial.[3,] This device is indicated to reduce the risk of thromboembolism from the LAA in patients with nonvalvular AF who:

- Are at increased risk for stroke and systemic embolism based on $CHADS_2$ or CHA_2DS_2-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 with warfarin.

FDA product code: NGV.

Several other devices are being evaluated for LAA occlusion but are not approved in the U.S. for percutaneous LAAC. In 2006, the Lariat® Loop Applicator device (SentreHEART), a suture delivery system, was cleared for marketing by the FDA through the 510(k) process. The intended use is to facilitate suture placement and knot tying in surgical applications where soft tissues are being approximated or ligated with a pretied polyester suture. The Amplatzer Amulet® device (St. Jude Medical) and WaveCrest® (Johnson & Johnson Biosense Webster) have CE approval in Europe for LAAC but are not currently approved in the U. S. for this indication.

Rationale

Background

Atrial Fibrillation and Stroke

AF is the most common type of irregular heartbeat, affecting at least 2.7 million people in the U.S. Stroke is the most serious complication of AF. The estimated incidence of stroke in nontreated patients with AF is 5% per year. Stroke associated with AF is primarily embolic, tends to be more severe than the typical ischemic stroke, and causes higher rates of mortality and disability. As a result, stroke prevention is a main goal of AF treatment.

Stroke in AF occurs primarily as a result of thromboembolism from the left atrium. The lack of atrial contractions in AF 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 AF, 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 $CHADS_2$ score and the $CHADS_2$-VASc score are described below in Table 1. Warfarin is the predominant agent in clinical use. A number of newer anticoagulant medications, including dabigatran, rivaroxaban, and apixaban, have received U.S. Food and Drug Administration (FDA) approval for stroke prevention in nonvalvular AF and have demonstrated noninferiority to warfarin in clinical trials. While anticoagulation is effective for stroke prevention, it carries 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 (2012) have recommended the use of oral anticoagulation for patients with AF who are at high-risk of stroke (i.e., $CHADS_2$ score ≥2), with more individualized choice of antithrombotic therapy in patients with lower stroke risk.[1,]

Table 1. $CHADS_2$ and $CHADS_2$-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

Adapted from You et al (2012)[1,] and January et al (2014).[2,]

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, such as the HAS-BLED score, which has been validated to assess the annual risk of significant bleeding in patients with AF treated with warfarin.[3] The score ranges from 0 to 9, based on clinical characteristics, including the presence of hypertension, renal and liver function, history of stroke, bleeding, labile international normalized ratios, age, and drug/alcohol use. Scores of three or greater are considered to be associated with high-risk of bleeding, potentially signaling the need for closer monitoring of patients for adverse risks, closer monitoring of international normalized ratios, or differential dose selections of oral anticoagulants or aspirin.[2,

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

Several versions of LAA occlusion devices have been developed. The PLAATO system (ev3 Endovascular) was the first device to be approved by the FDA for LAA occlusion. The device was discontinued in 2007 for commercial reasons, and intellectual property was sold to manufacturers of the Watchman system. The Watchman Left Atrial Appendage System (Boston Scientific) 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, using venous access and transseptal puncture to enter the left atrium. Transesophageal echocardiography and fluoroscopy are used to guide the procedure. Following implantation, patients receive anticoagulation with warfarin or alternative agents for approximately one to two months. After this period, patients are maintained on antiplatelet agents (i.e., aspirin and/or clopidogrel) indefinitely. The Amplatzer cardiac plug (St. Jude Medical), is FDA-approved for closure of atrial septal defects but not for LAAC. A second-generation device, the Amplatzer Amulet®, has been developed for the specific indication of LAAC, but currently does not have the FDA approval. The Amplatzer Amulet® consists of a nitinol mesh disc to seal the ostium of the LAA and a nitinol mesh distal lobe, to be positioned within the LAA. The device is preloaded within a delivery sheath. The Percutaneous LAA Transcatheter Occlusion device (ev3) has also been evaluated in research studies but has not received the FDA approval. The Occlutech® (Occlutech) Left Atrial Appendage Occluder has received a CE mark for coverage in Europe. The Cardioblate® closure device (Medtronic) is currently being tested in clinical studies.

The Lariat® Loop Applicator is a suture delivery device approved by the FDA, intended to close a variety of surgical wounds. It is not specifically approved for LAAC. While the Watchman and other devices are implanted in the endocardium, the Lariat is a non-implant epicardial device.

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 a prohibitive risk for oral anticoagulation), or open surgical repair.

Although the Watchman device and other LAAC 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 evaluating the Watchman device have included patients who are eligible for anticoagulation.

Literature Review
Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the 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 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 technology, two domains are examined: the relevance, and 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 closure (LAAC) devices consists of numerous case series of various occlusion devices, and two published RCTs of the Watchman device, the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients with Atrial Fibrillation (PROTECT AF) and Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy (PREVAIL) trials, that have compared LAAC with warfarin anticoagulation. Evidence on each device will be reviewed separately because the devices are not similar in design, and each may have its unique considerations.

Watchman Device
Clinical Context and Therapy Purpose
The purpose of the Watchman device in patients who have atrial fibrillation (AF) and are at increased risk for embolic stroke is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of the Watchman device improve net health outcomes compared with systemic anticoagulation treatment in patients with AF who are at increased risk for embolic stroke?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest are patients with AF. AF causes a low flow state in the left atrium which increases the risk of thromboembolism. Strokes in patients with AF occur primarily due to thromboembolism from the left atrium. Patients with AF who are not treated have a 5% estimated incidence of stroke.

Interventions
The therapy being considered is use of the Watchman percutaneous left atrial appendage (LAA) closure device. The device is made of nickel titanium and is implanted percutaneously through a catheter, into the left atrium. The Watchman comes in five sizes and self-expands to occlude the LAA. By occluding the LAA, thrombus formation is prevented, potentially preventing stroke. Following implantation of the device, the patient receives warfarin

for one to two months. Once it is established that there is no peridevice leak or thrombus development, the patient is then placed on antiplatelet agents indefinitely.

Comparators
The current treatment for stroke prevention in patients with AF is systemic anticoagulation. While anticoagulants are effective in preventing stroke, the increased risk of bleeding is a potential harm. Warfarin, which is the most common anticoagulant in use, requires frequent monitoring and lifestyle changes. Other anticoagulants, found to be noninferior to warfarin, include dabigatran, rivaroxaban, and apixaban.

Outcomes
The general outcomes of interest are rates of ischemic or hemorrhagic stroke, cardiovascular or unexplained death, and systemic embolism, measured between 6 to 12 months of follow-up. Additional outcomes of interest include device- or procedure-related events that may occur within one week of the procedure. In particular, events requiring open cardiac surgery or major endovascular intervention (e.g., pseudoaneurysm repair, arteriovenous fistula repair, or other major endovascular repair) should be noted.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews
A Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessment (2014) evaluated the use of the Watchman device for patients eligible and ineligible for anticoagulation therapy.[4] The Assessment determined that the device did not meet TEC criteria. The Assessment made the following conclusions about the use of LAAC in patients without contraindications to anticoagulation:

> "We identified 2 randomized controlled trials (RCTs) and 1 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 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 1 of 2 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."

A number of systematic reviews published after the TEC Assessment have combined the results of the available RCTs.[5-12] Others have included RCTs and observational studies.[8,13,14]

The most rigorous meta-analysis is the patient-level meta-analysis by Holmes et al (2015).[7] This analysis included 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 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, LAAC met the trial's noninferiority criteria for the primary composite efficacy endpoint 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 LAAC vs 1.87 per 100 patient-years for warfarin; HR=1.02; 95% CI, 0.62 to 1.7; p=0.94). LAAC-treated patients had higher rates of ischemic stroke (1.6 events per 100 patient-years vs 0.9 events per 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 per 100 patient-years vs 0.96 events per 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 et al (2015), focused on bleeding outcomes.[10] There were 54 episodes of major bleeding, with the most common types being gastrointestinal 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 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 (rate ratio, 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 (rate ratio, 0.28; 95% CI, 0.16 to 0.49; p<0.001).

Additional systematic reviews have used network meta-analyses to compare vitamin K antagonists with the Watchman devise and with novel oral anticoagulants (6 RCTs, total n=59627 subjects),[15] and have compared percutaneous LAA occlusion (5 RCTs, total n=1285 subject) with standard anticoagulant or antiplatelet therapy with device-based surgical or percutaneous LAA exclusion.[16] In the network meta-analysis comparing vitamin K antagonists with novel oral anticoagulants and with the Watchman device, Bajaj et al (2016) report that all the treatment strategies had comparable ischemic stroke rates. However, the cluster analyses showed the novel oral anticoagulants ranked best in safety and efficacy, followed by vitamin K antagonists, and then the Watchman device. Interpretation of these results is limited by the small sample sizes and population heterogeneity in the RCTs comparing the Watchman with vitamin K antagonists.[15] The network meta-analysis comparing LAAC with oral anticoagulants, antiplatelets, and placebo, reported a trend in stroke and mortality favoring LAAC, but the differences were not statistically significant. The authors noted that overall quality of the evidence was low.

Baman et al (2018) conducted a systematic review of LAA closure devices, including Watchman, Amplatzer cardiac plug, Amplatzer Amulet®, and Lariat devices.[17] The literature search, conducted through April 2017, identified 2 RCTs and 15 registry studies. No meta-analyses were conducted. The authors concluded that the Watchman may be noninferior to warfarin and that long-term efficacy outcomes are promising. For the remaining devices included in the review, the authors note that high-quality prospective studies comparing the devices to each other and with anticoagulants are needed.

Randomized Controlled Trials

Described below are two RCTs comparing the Watchman with oral anticoagulants and one RCT comparing the Watchman to the AMPLATZER cardiac plug.

PROTECT AF Trial

The first RCT published was PROTECT AF, an unblinded randomized trial evaluating the noninferiority of an LAAC device compared with warfarin for stroke prevention in AF.[18] 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 months. The primary efficacy outcome was a composite endpoint of stroke (ischemic or hemorrhagic), cardiovascular or unexplained death, or systemic embolism. There was also a primary safety outcome, a composite endpoint of excessive bleeding (intracranial or gastrointestinal bleeding) and procedure-related complications (pericardial effusion, device embolization, procedure-related stroke).

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

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

Longer term follow-up from the PROTECT AF trial was reported by Reddy et al (2013).[19,] 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 noninferiority criteria with a confidence greater than 99%. Complications were more common in the Watchman group, with an estimated rate of 5.6% per year, compared with 3.6% per year in the warfarin group.

Outcomes through 4 years of follow-up were reported by Reddy et al (2014).[20,] Mean follow-up was 3.9 years in the LAAC group and 3.7 years in the warfarin group. In the LAAC group, warfarin was discontinued in 345 (93.2%) of 370 patients 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 greater than 99.9%. Fewer hemorrhagic strokes (0.6% vs 4.0%; rate ratio, 0.15; 95% CrI, 0.03 to 0.49) and fewer cardiovascular events (3.7% vs 0.95%; rate ratio, 0.40; 95% CrI, 0.23 to 0.82) occurred in the Watchman group. Rates of ischemic stroke did not differ significantly between groups, but Watchman patients had lower all-cause mortality rates than anticoagulation patients (12.3% vs 18.0%; HR=0.66; 95% CI, 0.45 to 0.98; p=0.04).

Alli et al (2013) reported on quality-of-life parameters, as measured by change in the 12-Item Short-Form Health Survey scores from baseline to 12-month follow-up, for a subset of 547 subjects in the PROTECT AF trial.[21,] For the subset of PROTECT AF subjects included in the Alli et al (2013) analysis, at baseline, control group subjects had a higher mean $CHADS_2$ score (2.4 vs 2.2; p=0.052) and were more likely to have a history of coronary artery disease (49.5% vs 39.6%; p=0.028). For subjects in the Watchman group, the12-Item Short-Form Health Survey 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 significantly lower rates of the composite efficacy endpoint (stroke, systemic embolism, cardiovascular death) compared with the warfarin-only group (p=0.04).[22,]

PREVAIL Trial

A second RCT, the PREVAIL trial, was conducted after the 2009 FDA decision on the Watchman device to address some limitations of the PROTECT AF trial, including its inclusion of patients with low-stroke risk ($CHADS_2$ 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 (2014).[23] In the PREVAIL trial, 461 subjects enrolled at 41 sites were randomized in a 2:1 fashion to the Watchman device or control, which consisted of either initiation or continuation of warfarin therapy with a target international normalized ratio of 2.0 to 3.0. Subjects had nonvalvular AF and required treatment for prevention of thromboembolism based on a $CHADS_2$ score of 2 or higher (or ≥1 with other indications for warfarin therapy based on American College of Cardiology, American Heart Association, and European Society of Cardiology joint 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 6 months after device implantation and with aspirin 325 mg indefinitely after that.

Three noninferiority primary efficacy endpoints 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 7 days postrandomization, 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 7 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 trial. All patients had a minimum follow-up of six months. For randomized subjects, mean follow-up was 11.8 months, and median follow-up was 12.0 months (range, 0.03-25.9 months).

For the first composite primary endpoint, the 18-month modeled rate ratio between the device and control groups was 1.07 (95% CrI, 0.57 to 1.89). Because the upper bound of the 95% CrI was above the preset noninferiority margin of 1.75, the noninferiority criteria were not met. For the second primary endpoint of late ischemic stroke and systemic embolization, the 18-month relative risk between the device and control groups was 1.6 (95% CrI, 0.5 to 4.2), with an upper bound of the 95% CrI above the preset noninferiority margin of 2.0. The rate difference between the device and control groups was 0.005 (95% CrI, -0.019 to 0.027). The upper bound of the 95% CrI was lower than the noninferiority margin of 0.0275, so the noninferiority criterion was met for the rate difference. For the third primary endpoint (major safety issues), the noninferiority criterion was met.

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 endpoint (stroke, systemic embolism, cardiovascular death) (p=0.5).[22]

In addition to providing 5-year final results for the individual trials, Reddy et al (2017) conducted a meta-analysis of the 5-year outcomes using data from both trials.[22] 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. Also, patients treated with the Watchman device experienced significantly lower bleeding and mortality compared with patients receiving warfarin.

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

Outcomes	Watchman, n (Rate per 100 PY), %	Warfarin Alone, n (Rate per 100 PY),%	HR (95% CI)	p
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).[22,]
CI: confidence interval; CV: cardiovascular; HR: hazard ratio; LAAC: left atrial appendage closure; PY: patient-years; SE: systemic embolism.

Chun et al (2013) compared the Watchman device with the Amplatzer cardiac plug among patients who had nonvalvular AF, were at high-risk for stroke, and had a contraindication to or were unwilling to take oral anticoagulants.[24,] Eighty patients were randomized to LAA 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 six weeks. There were no statistically significant differences in procedure time, fluoroscopy time, or major safety events between the two groups. At a median follow-up of 364 days, there were no cases of stroke, transient ischemic attack, or other bleeding complications.

Nonrandomized Studies
Numerous case series and nonrandomized studies of the Watchman have been published.[25-29,] 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 (2013) conducted a multicenter, prospective, nonrandomized trial to evaluate the safety and efficacy of LAAC with the Watchman device in patients who had nonvalvular AF, with a $CHADS_2$ score 1 or higher, and were considered ineligible for warfarin.[30,] Postimplantation, patients received six 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 (three patients). Over a mean follow-up of 14.4 months, all-cause stroke or systemic embolism occurred in 4 patients.

The EWOLUTION Watchman registry tracks 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. Analysis of the EWOLUTION registry data by Boersma et al (2016) reported 30-day outcomes after device implantation in 1021 patients.[31,] 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 7days and 3.6% (95% CI, 2.5% to 4.9%) at 30 days. The most common serious adverse event was major bleeding.

Dukkipati et al (2018) studied the incidence, predictors, and clinical outcomes of device-related thrombus (DRT) among the following patients receiving the Watchman in the following trials and registries: PROTECT-AF, PREVAIL, Continued Access to PROTECT-AF registry, and Continued Access to PREVAIL registry.[32,] Surveillance transesophageal electrocardiograms were conducted in all patients at 45 days and 12 months. Patients in the RCTs also received the electrocardiograms at six months. A total of 1739 patients were followed for a total of 7159 patient-years. Mean age of the population was 74 years and 34% were women. DRT was detected in 65 (3.7%) of the patients. Stroke or systemic embolism rates were 7.5 and 1.8 per 100 patient-years for patients with and without DRT, respectively. A multivariable modeling analysis found the following predictors of DRT: history of transient ischemic attack or stroke, permanent AF, vascular disease, LAA diameter, and left ventricular ejection fraction.

Jazayeri et al (2018) evaluated the safety profiles of the Watchman and the Lariat devices, using the FDA's Manufacturer and User Facility Device Experience (MAUDE) database from 2009 to 2016.[33] MAUDE consists of mandatory reports from manufacturers and voluntary reports from healthcare professionals and patients. Outcomes assessed included: a composite of stroke/TIA, pericardiocentesis, cardiac surgery, and death; DRT; cardiac surgery; and myocardial infarction. A total of 5849 Watchman devices were implanted, with 472 events reported during the study period. The most common events in patients receiving the Watchman, were device malfunction (97 [1.7%]), pericardial effusion (84 [1.4%]), need for pericardiocentesis (57 [0.97%]), and intracardiac thrombus (47 [0.84%]). Twenty deaths were reported in the Watchman group, with one likely related to DRT. Compared to the Lariat device, the composite outcome occurred significantly more in the group receiving the Watchman than within the group receiving the Lariat, 1.9% vs 1.1%, p=0.001). Analysis results for the Lariat device will be discussed in the next section, "Other Closure Devices".

Section Summary: Watchman Device
The most relevant evidence on the use of the Watchman device for LAAC in patients eligible for anticoagulation derives from two industry-sponsored RCTs comparing Watchman and systemic anticoagulants and a patient-level meta-analysis of those studies. After five years of follow-up, meta-analytic results showed that the ischemic stroke risk beyond seven days did not differ between groups and that the hemorrhagic stroke risk remained significantly lower in the LAAC group. The results showed that the Watchman device is noninferior to warfarin alone in stroke prevention among patients with nonvalvular AF. Also, patients treated with the Watchman device experienced significantly lower bleeding and mortality. A large study of patients receiving the Watchman device (combining patients from the two RCTs and two registries) reported that patients who developed DRT were four times more likely to experience a stroke or systemic embolism. The authors suggest a surveillance strategy for patients at high-risk of DRT following Watchman implantation.

Other Closure Devices
Clinical Context and Therapy Purpose
The purpose of other LAA closure devices in patients who have AF and are at increased risk for embolic stroke is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of other LAA closure devices improve net health outcomes compared with systemic anticoagulation treatment in patients with AF who are at increased risk for embolic stroke?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is patients with AF. AF causes a low flow state in the left atrium which increases the risk of thromboembolism. Strokes in patients with AF occur primarily due to thromboembolism from the left atrium. Patients with AF who are not treated have a 5% estimated incidence of stroke.

Interventions
The interventions of interest are other LAA occlusion devices. By occluding the LAA, thrombus formation is prevented, potentially preventing stroke. Other devices currently being evaluated for the use of LAA occlusion include:

- The Lariat Loop Applicator is a suture delivery device approved by the FDA to facilitate suture placement and knot tying for use in surgical applications where soft tissues are being approximated or ligated with a pretied polyester suture. The approved use does not specify LAA occlusion. While the Watchman and other devices are implanted in the endocardium, the Lariat is a non-implant epicardial device. The Lariat is contraindicated in patients with active pericarditis; prior sternotomy or other mediastinal surgery or known

pericardial adhesions; appendage width >45 mm; superiorly oriented appendage lying near or behind the pulmonary arterial trunk; or appendage thrombus.

- The Amplatzer Amulet® device comes in eight sizes to accommodate various patient anatomies. The mechanism of action is similar to the Watchman. Following implantation of the Amulet, patients are placed on antiplatelet agents and do not need warfarin. There is an ongoing trial comparing the Amplatzer Amulet® with the Watchman (NCT03399851).

Comparators

The current treatment for stroke prevention in patients with AF is systemic anticoagulation. While anticoagulants are effective in preventing stroke, the increased risk of bleeding is a potential harm. Warfarin, which is the most common anticoagulant in use, requires frequent monitoring and lifestyle changes. Other anticoagulants, found to be noninferior to warfarin include dabigatran, rivaroxaban, and apixaban.

Outcomes

The general outcomes of interest are rates of ischemic or hemorrhagic stroke, cardiovascular or unexplained death, and systemic embolism, measured between 6 to 12 months of follow-up. Additional outcomes of interest include device- or procedure-related events that may occur within one week of the procedure, in particular, events requiring open cardiac surgery or major endovascular intervention (e.g., pseudoaneurysm repair, arteriovenous fistula repair, or other major endovascular repair).

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

Lariat Device

Systematic Review

A systematic review of studies on the Lariat device was published by Chatterjee et al (2015).[34] No RCTs were identified. Five case series were included, with a total of 309 patients (range, 4-154 patients).[35-39] The combined estimate of procedural success was 90.3%. One (0.3%) death was reported and 7 (2.3%) patients required urgent cardiac surgery. Reviewers also searched the MAUDE database for adverse events and found 35 unique reports. Among the 35 reported complications, there were 5 deaths and 23 cases of emergency cardiac surgery.

Case Series

Individual case series published since the systematic review included a large 2016 case series of 712 consecutive patients from 18 U.S. hospitals.[40] This series reported a procedural (suture deployment) success rate of 95% and complete closure rate 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 one death, and emergent cardiac surgery was required in 1.4%. Cardiac perforations (overall and those needing surgery) and the 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.[41-44]

Litwinowicz et al (2018) presented a case series of 139 patients from a single-center undergoing LAA closure with the Lariat device, with a longer follow-up than the other case series.[45] After a

follow-up of 5-years (428 patient-years), the thromboembolism rate was 0.8%, with a calculated bleeding risk reduction of 78%. The overall mortality rate was 1.6%.

Non-randomized Comparative Study
As described above in the Watchman section, Jazayeri et al (2018) evaluated the safety profiles of the Watchman and the Lariat devices, using the FDA's MAUDE database from 2009 to 2016.[33] A total of 4889 Lariat devices were implanted, with 136 events reported during the study period. The most common events in the Lariat group were pericardial effusion (46 [0.94%]), need for cardiac surgery (38 [0.78%]), and pericardiocentesis (23 [0.47%]). Ten deaths were reported in the Lariat group, with six involving tightening of the suture around the LAA. Compared to the Watchman device, the composite outcome occurred significantly more in the group receiving the Watchman than in the group receiving the Lariat, 1.9% vs 1.1%, p=0.001.

Litwinowicz et al (2019) compared outcomes of patients undergoing LAA closure with the Lariat device (n=57) with patients receiving either warfarin or clopidogrel (n=31).[46] Age, sex, and comorbidities were similar between the two groups. Treatment prior to the study differed significantly. The Lariat group received warfarin (93%), aspirin (4%), aspirin plus clopidogrel (2%) and no anticoagulation (1%). The control group received warfarin (87%) or clodipogrel (13%). However, there was no significant difference in CHA_2DS_2-VAS scores between the groups at baseline. Average follow-up in the Lariat group was 59 months and average follow-up in the control group was 60 months. There were no thromboembolic events in the Lariat group, while 9.6% of the control group experienced thromboembolic events (p=0.02). The bleeding risk reduction in the Lariat group was estimated at 53%.

Section Summary: Lariat Device
There are no RCTs of the Lariat device for LAAC. There was one non-randomized study comparing patients undergoing LAA closure with the Lariat device with patients receiving either anticoagulant or antiplatelet therapy. Results showed significantly fewer thromboembolic events in the group undergoing LAA closure with the Lariat device compared with the group receiving medication alone. The remaining evidence consisted of case series. The evidence is insufficient to draw conclusions about treatment efficacy.

Amplatzer Cardiac Plug Device and Amplatzer Amulet® Device
Amplatzer Cardiac Plug (First Generation)
The available evidence on the 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 (2013), which included 152 patients from a single institution in Europe.[47] Short-term complications occurred in 9.8% (15/152) of patients. The 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 reports of patients treated with the Amplatzer device include a series of 90 patients from Belgium (2013),[48] 86 patients from Portugal (2012),[49] 37 patients from Italy (2013),[50] 35 patients from Spain (2013),[51] 21 patients from Poland (2013),[52] and 20 patients from China (2012).[25] All series reported high procedural success rates, as well as complications such as vascular events, air embolism, esophageal injury, cardiac tamponade, and device embolization.

Several other case series have reported on the use of the Amplatzer device in patients with a contraindication to oral anticoagulation therapy. The largest, by Santoro et al (2016), reported on outcomes up to 4 years postprocedure, for 134 patients with nonvalvular AF and a long-term contraindication to oral anticoagulation treated with the Amplatzer device.[53] Patients had a median CHA_2DS_2-VASc score of four and were generally considered at high-risk for bleeding complications. Procedural success occurred in 93.3%, and 3 major procedure-related complications (2 cases of cardiac tamponade, 1 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, evaluating between 37 and 100 patients.[50,54-57,]These studies also reported high success rates and low procedural complications.

Amplatzer Amulet® (Second Generation)
A second generation device, the Amplatzer Amulet® was developed to potentially lower device embolization rates, simplify the technical implantation procedure, and lower severe complication rates. The Amulet first became available in Europe in January 2013. Below are descriptions of studies comparing the amulet with the first generation cardiac plug. There is currently an ongoing trial comparing the Amplatzer Amulet® with the Watchman (NCT03399851).

Case Series
Landmesser et al (2017) presented periprocedural (within 7 days of procedure) and early clinical outcomes (1 to 3 months postprocedure) from a multicenter registry of 1088 patients receiving the Amplatzer Amulet® between June 2015 and September 2016.[58,] Technical success was defined as implantation of the device in the correct position, which was reported for 1078 (99%) of the patients. A composite of ischemic stroke, systemic embolism, and cardiovascular death occurred in 7 (0.6%) patients during the periprocedural period and in 15 (1.4%) patients between 7 days postprocedure and 3 months follow-up.

Landmesser et al (2018) provided updated analyses on 950 patients from the registry series described above who had 1-year follow-up data.[59,] Oral anticoagulants were used by 6% of the patients at 3, 6, and 12 months postprocedure. There were 29 ischemic strokes (27 patients), 9 patients experiencing a transient ischemic attack, and no systemic embolisms reported. The annualized bleeding rate was 10.3% per year, with 103 events in 87 patients, majority occurring within the first 7 days postprocedure. The DRT rate was 1.7% per year, with 18 events in 17 patients. A total of 88 patients died within the first year postprocedure, 53 were cardiovascular-related and 35 noncardiovascular. Two of the cardiovascular-related deaths were attributed to the device.

Non-randomized Comparative Studies
Gloekler et al (2015) reviewed records from 2 university hospitals' occlusion registries and conducted a retrospective analysis comparing the last 50 consecutive patients receiving the cardiac plug with the first 50 consecutive patients receiving the amulet.[57,] Follow-up examinations were performed between four to six months post-procedure. No significant differences between the two devices were detected in mortality, neurologic events, late pericardial effusions, major bleeding, device leaks, or device thrombi. Interpretation of these results is limited by the small sample size and short follow-up period.

Al-Kassou et al (2017) presented periprocedural and 2 to 3 month follow-up data for patients undergoing LAA occlusion with the Amplatzer cardiac plug and the Amplatzer Amulet®.[60,] Periprocedural data was available for 99 patients receiving the cardiac plug and for 97 patients receiving the Amulet. Use of the Amulet was associated with significantly lower fluoroscopy time, lower radiation dose, and reduced amount of contrast dye. Occurrence of adverse events during the perioprocedural period were comparable. Transesophageal echocardiographic follow-up data at 2 to 3 months was available for 81 patients receiving the cardiac plug and for 82 patients receiving the Amulet. None of the patients experienced DRT during this follow-up. Minor leaks were detected in 12 (15%) patients receiving the cardiac plug and in 4 (5%) patients receiving the Amulet (p=0.03).

Section Summary: Amplatzer Cardiac Plug Device and Amplatzer Amulet®
There are no RCTs of the Amplatzer device for LAAC. There are two non-randomized studies comparing the first generation Amplatzer cardiac plug with the second generation Amplatzer Amulet®, one of which reported procedural advantages of the Amulet over the cardiac plug. Both nonrandomized comparator studies reported no difference in clinical outcomes at first follow-up, two to six months. The remaining evidence consists of case series. The non-randomized comparator studies and the case series are insufficient to draw conclusions

about treatment efficacy. There is an ongoing trial comparing the Amplatzer Amulet® with the Watchman (NCT03399851).

Summary of Evidence

For individuals who have AF who are at increased risk for embolic stroke who receive the Watchman percutaneous LAAC device, the evidence includes two RCTs and meta-analyses of these trials. The relevant outcomes are overall survival, morbid events, and treatment-related morbidity. The most relevant evidence comes from two 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 two years of follow-up, with continued benefits with the Watchman device after four 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 five-year follow-up for the two trials reported that the Watchman device is noninferior to warfarin on the composite outcome of stroke, systemic embolism, and cardiovascular death. Also, the Watchman was associated with lower rates in major bleeding, particularly hemorrhagic stroke, and mortality over the long-term. The evidence also indicates that the Watchman device is efficacious in preventing stroke in the subset of patients with AF who are at increased risk for embolic stroke. Among patients in which the long-term risk of systemic anticoagulation exceeds the procedural risk of device implantation, the net health outcome will be improved. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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 Lariator Amplatzer), the evidence includes several nonrandomized comparator studies and uncontrolled case series. The relevant outcomes are overall survival, morbid events, and treatment-related morbidity. One nonrandomized study which compared outcomes among patients undergoing LAAC with the Lariat device with patients receiving anticoagulant or antiplatelet therapy, reported fewer thromboembolic events in the group receiving the Lariat device. Two nonrandomized studies compared the Amplatzer cardiac plug with the Amplatzer amulet. While the amulet may be technically easier to implant, clinical outcomes were similar between the two groups. The remaining evidence consists of case series of these devices which report high procedural success but also numerous complications. In addition, these devices do not have the FDA approval for LAAC. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests from Blue Cross Blue Shield Association, input was received from 1 physician specialty society (2 responses) and 4 academic medical centers, one of which provided 4 responses, for a total of 8 responses, in 2015. Input generally supported the use of a left atrial appendage closure device approved by the Food and Drug Administration for patients with an increased risk of stroke and systemic embolism, based on $CHADS_2$ or CHA_2DS_2-VASc score. Systemic anticoagulation therapy was recommended, but the long-term risks of systemic anticoagulation outweigh the risks of the device implantation.

Practice Guidelines and Position Statements
American Heart Association
The American Heart Association, in collaboration with the American College of Cardiology and the Hearth Rhythm Society (2019) published an update of their guideline for the management of patients with atrial fibrillation.[61,] A new recommendation in the guideline states: "Percutaneous LAA occlusion may be considered in patients with AF at increased risk of stroke who have contraindications to long-term anticoagulation." The class of recommendation is IIb and the level of evidence is B_NR (moderate quality of evidence, non-randomized). No other LAA closure devices are mentioned in the guideline.

Guideline Comparison
Andrade et al (2017) provided the following summary (see Table 3) comparing guidelines by American, Canadian, and European societies on left atrial appendage exclusion and closure for the management of atrial fibrillation.[62,]

Table 3. Comparison of American, Canadian, and European Guidelines on LAA Exclusion/Closure

Procedure	AHA/ACC/HRS	CCS	ESC
Surgical LAA closure (excision or obliteration of LAA)	May be considered in patients undergoing cardiac surgery (IIb)	Should be considered as part of surgical ablation of AF associated with mitral, aortic valve, or coronary artery bypass surgery	• May be considered in patients undergoing cardiac surgery (IIb) • More data needed to confirm safety and efficacy of thoracoscopic exclusion
Percutaneous LAA exclusion	No recommendation	Not be used, except in research or in systematically documented use protocols in patients at high risk of stroke ($CHADS_2$ ≥2) and antithrombotic therapy precluded	May be considered in patients with contraindications for long term anticoagulant treatment (IIb)

Adapted from Andrade et al (2017).[62,]
ACC: American College of Cardiology; AF: atrial fibrillation; AHA: American Heart Association; CCS: Canadian Cardiovascular Society; $CHADS_2$: Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke/Transient Ischemic Attack; ESC: European Society of Cardiology; HRS: Heart Rhythm Society; LAA: left atrial appendage.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
The Centers for Medicare & Medicaid Services (2016) has a national coverage determination under coverage with evidence development for percutaneous left atrial appendage closure in atrial fibrillation, as follows[63,]:

> "LAAC devices are covered when the device has received Food and Drug Administration (FDA) Premarket Approval (PMA) for that device's FDA-approved indication and meet all of the conditions specified below:

The patient must have:

- A CHADS2 score ≥2 (Congestive heart failure, Hypertension, Age > 75, Diabetes, Stroke/transient ischemia attack/thromboembolism) or CHA2DS2-VASc score ≥ 3 (Congestive heart failure, Hypertension, Age ≥ 65, Diabetes, Stroke/transient ischemia attack/thromboembolism, Vascular disease, Sex category).
- A formal shared decision making interaction with an independent non-interventional physician using an evidence-based decision tool on oral anticoagulation in patients with NVAF [nonvalvular atrial fibrillation] prior to LAAC. Additionally, the shared decision making interaction must be documented in the medical record.

- A suitability for short-term warfarin but deemed unable to take long-term oral anticoagulation following the conclusion of shared decision making, as LAAC is only covered as a second line therapy to oral anticoagulants. The patient (preoperatively and postoperatively) is under the care of a cohesive, multidisciplinary team (MDT) of medical professionals. The procedure must be furnished in a hospital with an established structural heart disease (SHD) and/or electrophysiology (EP) program.

The procedure must be performed by an interventional cardiologist(s), electrophysiologist(s), or cardiovascular surgeon(s) that meet the following criteria:

- Has received training prescribed by the manufacturer on the safe and effective use of the device prior to performing LAAC; and,
- Has performed ≥ 25 interventional cardiac procedures that involve transseptal puncture through an intact septum; and,
- Continues to perform ≥ 25 interventional cardiac procedures that involve transseptal puncture through an intact septum, of which at least 12 are LAAC, over a 2-year period."

Patients must be enrolled in approved registries that track outcomes for procedures and devices.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 4.

Table 4. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02681042	Left Atrial Appendage Closure with SentreHeart Lariat Device	50	Mar 2019
NCT03276169	Left Atrial Function Changes after Left Atrial Appendage Closure in Patients with Persistent Atrial Fibrillation	105	Nov 2019
NCT02513797[a]	aMAZE Study: LAA Ligation with the LARIAT Suture Delivery System as Adjunctive to Pulmonary Vein Isolation for Persistent Atrial Fibrillation (aMAZE)	600	Dec 2019
NCT03204695[a]	A Prospective, Multicenter, Non-Randomized, Post-market Clinical Follow-up Study to Confirm Safety and Performance of the Coherex WaveCrest Left Atrial Appendage Occlusion System in Patients with Non-valvular Atrial Fibrillation	65	Mar 2020
NCT02426944	Left Atrial Appendage Closure vs Novel Anticoagulation Agents in Atrial Fibrillation	400	May 2020
NCT02964208[a]	AMPLATZER LAA Occluder Post Approval Study (PAS)	1000	Oct 2023
NCT02879448	AMPLATZER™ Amulet™ Left Atrial Appendage Occluder Randomized Controlled Trial	1878	Dec 2023
NCT03399851	Comparison of Amplatzer Amulet vs. Watchman Device in Patients Undergoing Left Atrial Appendage Closure: the SWISS-APERO Randomized Clinical Trial	200	Feb 2025
NCT03302494[a]	WAveCrest Vs. Watchman TranssEptal LAA Closure to REduce AF-Mediated STroke 2 (WAVECREST2)	1250	Dec 2025
NCT03309332[a]	OSB Lead-AMPLATZER PFO Occluder New Enrollment PAS	1214	Dec 2025
Unpublished			
NCT01118299	AMPLATZER Cardiac Plug Clinical Trial	3000	Not approved/ cleared

NCT: national clinical trial.
[a] indicates industry-sponsored study.

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Documentation for Clinical Review

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
  - Documentation of atrial fibrillation
  - Documented $CHADS_2$ or CHA_2DS_2-VASc score
- Name of the FDA approved device

Post Service

- Procedure report

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

MN/IE

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

Type	Code	Description
CPT®	33340	Percutaneous transcatheter closure of the left atrial appendage with endocardial implant, including fluoroscopy, transseptal puncture, catheter placement(s), left atrial angiography, left atrial appendage angiography, when performed, and radiological supervision and interpretation
HCPCS	None	
ICD-10 Procedure	02L73DK	Occlusion of Left Atrial Appendage with Intraluminal Device, Percutaneous Approach

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
07/06/2012	BCBSA Medical Policy adoption	Medical Policy Committee
08/29/2014	Policy title change from Left Atrial Appendage Closure Devices for Stroke Prevention in Atrial Fibrillation Policy revision with position change	Medical Policy Committee
12/04/2015	Policy revision with position change	Medical Policy Committee
07/01/2016	Policy revision without position change	Medical Policy Committee
02/01/2017	Coding update	Administrative Review
07/01/2017	Policy revision without position change	Medical Policy Committee
07/01/2018	Policy revision without position change	Medical Policy Committee

Effective Date	Action	Reason
08/01/2019	Policy revision without position change	Medical Policy Committee

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.