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Title: Percutaneous Left Atrial Appendage Closure Devices for Stroke Prevention in Atrial Fibrillation

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Description/Background

Atrial Fibrillation and Stroke
Atrial fibrillation (AF) is the most common type of irregular heartbeat, affecting at least 2.7 million people in the U.S. Risk of AF has been found to be lower in Black, Hispanic and Asian patients relative to White patients, including following adjustment for demographic and AF risk factors.[1,2] Stroke is the most serious complication of AF. The estimated incidence of stroke in nontreated patients with AF is 5% per year; despite a lower risk of AF, Black and Hispanic patients have an increased risk of stroke compared with White patients.[3.4] Stroke associated with AF 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 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. Newer agents to not require the frequent monitoring seen with warfarin therapy; however, specific reversal agents do not exist

for all of these agents. The 2018 American College of Chest Physicians guidelines (updated from 2012) recommend that CHA_2DS_2VASc be used to evaluated stroke risk, and patients initially identified as having a low risk should not be given antithrombotic therapy. In addition, they recommend bleeding risk assessments be given at every patient contact and that "potentially modifiable bleeding risk factors" should be the initial focus.

Table 1. $CHADS_2$ and CHA_2DS_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 Lip et al (2018)[5] and January et al (2014).[6]

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.[7] 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 3 or greater are considered to be associated with a 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.[6]

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 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 1 to 2 months. After this period, patients are maintained on antiplatelet agents (ie, aspirin and/or clopidogrel) indefinitely. The Watchman FLX device is a next-generation Watchman device that is also FDA-approved for LAAC. This device is based on the design of the Watchman device, is fully recapturable and repositionable, and was made to occlude a wider size range of LAA than the original Watchman device.[8] 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 (Abbott), received FDA approval in August 2021.[9] 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 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.

In September 2021, the FDA sent a letter to healthcare providers indicating that women undergoing percutaneous LAA closure may be at higher risk of adverse procedural outcomes than men.[10] This was based on an analysis of registry data from 49,357 patients who underwent LAA closure with the Watchman device.[11] When adjusted for multiple confounding factors, the study found women were more likely than men to experience any adverse event, major adverse events, and major bleeding. Women also had a significantly higher risk of death (adjusted odds ratio [OR], 2.01; 95% confidence interval [CI] 1.31 to 3.09) but absolute risk was low for both women and men (0.3% vs. 0.1%). In their letter, the FDA stated that they believe the benefits continue to outweigh the risks for approved LAA closure devices when used in accordance with their instructions for use.

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 (RCT) 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.

Ideally, percutaneous LAAC devices would represent an alternative to oral anticoagulation for the prevention of stroke in patients with AF. However, during the postimplantation period the LACC device may be associated with increased thrombogenicity and, therefore, anticoagulation is used during the periprocedural period. Most studies evaluating percutaneous LACC devices have included patients who are eligible for anticoagulation.

Regulatory Status:

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 2015, the Watchman™ Left Atrial Appendage Closure Technology (Boston Scientific, Marlborough, MA) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process on the basis of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients with Atrial Fibrillation (PROTECT-AF) randomized controlled trial.[12] In 2020, the Watchman FLX device (Boston Scientific) was approved by the FDA based on the single-arm, nonrandomized PINNACLE FLX study.[8] The Amplatzer™ Amulet™ Left Atrial Appendage Occluder (Abbott) received FDA approval in 2021 through the premarket approval process based on results from the Amplatzer Amulet Left Atrial Appendage Occluder Randomized Controlled Trial (Amulet IDE Trial).[9] The Watchman and Amplatzer Amulet devices are 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 anticoagulation therapy; and
- Have an appropriate rationale to seek a nonpharmacologic alternative to anticoagulation therapy, taking into account the safety and effectiveness of the device compared to anticoagulation therapy.

FDA product code: NGV.

Several other devices are being evaluated for LAA occlusion, but are not approved in the United States for percutaneous LAAC. In 2006, the Lariat™ Loop Applicator device (SentreHEART), a suture delivery system, was cleared for marketing by 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 Cardiac Plug device (St. Jude Medical) and WaveCrest™ (Johnson & Johnson Biosense Webster) have CE approval in Europe for LAAC, but are not currently approved in the United States for this indication.

Medical Policy Statement

The safety and effectiveness of a U.S. FDA-approved percutaneous left atrial appendage closure device (eg, Watchman™ Left Atrial Appendage Closure, Watchman FLX, Amplatzer™ Amulet™) for the prevention of stroke in individuals with atrial fibrillation have been established. It may be considered a therapeutic option when indicated.

Inclusionary and Exclusionary Guidelines

FDA approved percutaneous left atrial appendage closure devices are considered established when the following criteria are met.

Inclusions:

- 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;

AND

- The long term risks of systemic anticoagulation outweigh the risks of the device implantation.

The use of a device with FDA approval for percutaneous left atrial appendage closure (eg, the Watchman™, Watchman FLX, or Amplatzer™ Amulet™) for stroke prevention in patients who do not meet the above criteria is considered **experimental/investigational**.

The use of devices not approved by the U.S. FDA for percutaneous left atrial appendage closure (including but not limited to the Lariat Loop Applicator and Amplatzer Cardiac Plug devices) for stroke prevention in patients with atrial fibrillation is considered **experimental/investigational**.

POLICY GUIDELINES

The balance of risks and benefits associated with percutaneous implantation of a U.S. FDA approved percutaneous LAAC device for stroke prevention (eg, Watchman or Amplatzer Amulet), as an alternative to systemic anticoagulation, 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 individuals treated with systemic anticoagulation. An example is the HAS-BLED score, which is validated to assess the annual risk of significant bleeding in individuals with atrial fibrillation treated with warfarin. 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)[1]
HAS-BLED: Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR (international normalized ratio), Elderly, Drugs/alcohol concomitantly.

The risk of major bleeding in individuals 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 a high risk of bleeding, potentially signaling the need for closer monitoring of individuals for adverse events, closer monitoring of international normalized ratio, or differential dose selections of oral anticoagulants or aspirin.

CPT/HCPCS Level II Codes ***(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)***

Established codes:

33340

Other codes (investigational, not medically necessary, etc.):

N/A

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

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 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 1 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.

FDA-approved Percutaneous Left Atrial Appendage Closure Devices

Clinical Context and Therapy Purpose

The purpose of FDA-approved left atrial appendage closure (LAAC) devices (e.g., Watchman or Amplatzer Amulet 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 following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients with atrial fibrillation (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 percutaneous LAAC closure with a Watchman or Amplatzer Amulet device. Watchman devices include the Watchman percutaneous LAAC device and the Watchman FLX device (a next generation device based on the design of the original Watchman device).[9] The devices are made of nickel titanium and are implanted percutaneously through a catheter, into the left atrium. The Watchman devices come in 5 sizes and self-expand to occlude the LAA. By occluding the LAA, thrombus formation is prevented, potentially preventing stroke. Following implantation of the device, the patient receives anticoagulation for 1 to 2 months. Once it is established that there is no peridevice leak or thrombus development, he patient is then placed on antiplatelet agents indefinitely. The Amplatzer Amulet is a second-generation device based on the first-generation Amplatzer Cardiac Plug (discussed below). 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. Following device placement (confirmed by transesophageal echocardiography and fluoroscopy), patients are discharged on either dual antiplatelet therapy or aspirin plus oral anticoagulation.

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, although some studies show follow-up of up to 5 years.[13] Additional outcomes of interest include device- or procedure-related events that may occur within 1 week of the procedure. In particular, events requiring open cardiac surgery or major endovascular intervention (eg, 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 preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with preference for prospective studies;
- To assess longer 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.

REVIEW OF EVIDENCE

WATCHMAN DEVICE

Systematic Reviews

A number of systematic reviews have pooled evidence from RCTs for the Watchman device.[14,15,16,17,18,19,20,21] Others have included RCTs and observational studies.[17,22,23]

Holmes et al (2015) published the most rigorous meta-analysis.[16] 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 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=.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=.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=.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=.004).

Price et al (2015) reported on a second patient-level meta-analysis of the 2 RCTs that focused on bleeding outcomes.[19] There were 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 of 0.96 (95% CI, 0.66 to 1.40; p=.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=.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<.001).

Additional systematic reviews have used network meta-analyses to compare vitamin K antagonists with the Watchman device and with novel oral anticoagulants (6 RCTs, N=59,627),[24] and have compared percutaneous LAA occlusion (5 RCTs, N=1285 subjects) with standard anticoagulant or antiplatelet therapy with device-based surgical or percutaneous LAA exclusion.[25] Bajaj et al (2016) published a network meta-analysis comparing vitamin K antagonists with novel oral anticoagulants and with the Watchman device.[24] They reported 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. 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.[25] The authors noted that overall quality of the evidence was low.

Baman et al (2018) conducted a systematic review of LAAC devices, including Watchman, Amplatzer Cardiac Plug, Amplatzer Amulet, and Lariat Loop Applicator devices.[26] 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. A second review conducted by Takeda et al (2022) included 11 observational studies (N=24,055) comparing the Watchman and Amulet devices and direct-acting oral anticoagulants.[27] In pooled analyses of studies of the Watchman device (5 studies) and anticoagulants (3 studies) event incidence per person-years was similar for all-cause mortality (0.06; 95% CI 0.02 to 0.10 vs. 0.03; 95% CI 0.01 to 0.04), stroke (0.02; 95% CI 0.00 to 0.04 vs. 0.01; 95% CI 0.01 to 0.02) and major bleeding (0.04; 95% CI 0.02 to 0.06) vs. 0.02; 95% CI 0.01 to 0.03).

Randomized Controlled Trials

PROTECT AF Trial

The first RCT published was PROTECT AF, an unblinded randomized trial evaluating the noninferiority of a LAAC device compared with warfarin for stroke prevention in AF.[28] The trial randomized 707 patients from 59 centers in the U.S. and Europe to the Watchman device or to warfarin treatment in a 2:1 ratio. The mean follow-up was 18 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, a composite end point of excessive bleeding (intracranial or GI 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 and hemorrhagic stroke 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.

Reddy et al (2013) reported on longer term follow-up from the PROTECAF trial.[29] 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.

Reddy et al (2014) also reported outcomes through 4 years of follow-up.[30] 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% CI, 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 than anticoagulation patients (12.3% vs 18.0%; HR=0.66; 95% CI, 0.45 to 0.98; p=.04).

Alli et al (2013) reported quality-of-life parameters, as measured by the change in 12-Item Short-Form Health Survey scores from baseline to 12-month of follow-up, for a subset of 547 subjects in the PROTECT AF trial.[31] 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=.052) and were more likely to have a history of coronary artery disease (49.5% vs 39.6%; p=.028). For subjects in the Watchman group, the 12-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=.01).

Reddy et al (2017) published 5-year follow-up results, indicating that the LAAC group had significantly lower rates of the composite efficacy end point (stroke, systemic embolism, cardiovascular death) compared with the warfarin-only group (p=.04).[13]

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. Holmes et al (2014) published results from the PREVAIL trial.[32] 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 CHADS2 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 post procedure; 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 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 7 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 (eg, 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 6 months. For randomized subjects, the mean follow-up was 11.8 months and the median follow-up was 12.0 months (range, 0.03 to 25.9 months).

For the first composite primary end point, 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% credible interval was above the preset noninferiority margin of 1.75, the noninferiority criteria were not met. For the second primary end point 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% credible interval 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% credible interval was lower than the noninferiority margin of 0.0275, so the noninferiority criterion was met for the rate difference. For the third primary end point (major safety issues), the noninferiority criterion was met.

Reddy et al (2017), in their 5-year follow-up results, indicated that the Watchman device was noninferior to warfarin alone in the composite efficacy end point (stroke, systemic embolism, cardiovascular death) (p=.5).[13]

Reddy et al (2017), in addition to providing 5-year final results for the individual trials, also conducted a meta-analysis of the 5-year outcomes using data from both trials.[13] 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-value

Composite stroke/SE/CV death	79 (2.8)	50 (3.4)	0.8 (0.6 to 1.2)	.3
All stroke or SE	49 (1.7)	27 (1.8)	1.0 (0.6 to 1.5)	.9
CV/unexplained death	39 (1.3)	33 (2.2)	0.6 (0.4 to 0.9)	.03
All cause death	106 (3.0)	73 (4.9)	0.7 (0.5 to 1.0)	.03
Major bleeding, all	85 (3.1)	50 (3.5)	0.9 (0.6 to 1.3)	.6
Major bleeding, non-LAAC-related	48 (1.7)	51 (3.6)	0.5 (0.3 to 0.7)	<.001

Adapted from Reddy et al (2017).[13]
CI: confidence interval; CV: cardiovascular; HR: hazard ratio; LAAC: left atrial appendage closure; PREVAIL: Prospective Randomized Evaluation of the Watchman LAA Closure Device in Patients With Atrial Fibrillation (AF) Versus Long Term Warfarin Therapy; PROTECT AF: Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation; PY: patient-years; SE: systemic embolism.

PRAGUE-17 Trial

Osmancik et al (2020) published the LAAC versus Novel Anticoagulation Agents in AF (PRAGUE-17) study, a multicenter, randomized, noninferiority study that compared the use of LAAC to direct oral anticoagulants in high-risk patients with nonvalvular AF.[33] Patients were included if they had a history of bleeding requiring intervention or hospitalization, a history of cardioembolic event while taking an anticoagulant, or CHA2DS2-VASc score ≥3 with a HAS-BLED score ≥2. Patients received LAAC (n=181) with either the Amplatzer Amulet or Watchman/Watchman FLX devices based on the discretion of the implanting center, or a direct oral anticoagulant (rivaroxaban, apixaban, or dabigatran) (n=201). The primary endpoint was a composite of ischemic or hemorrhagic stroke or transient ischemic attack (TIA), systemic embolism, clinically significant bleeding, cardiovascular death, or significant peri-procedural or device-related complications. At baseline, the mean CHA_2DS_2-VASc score was 4.7 and HAS-BLED score was 3.1. Initial follow-up was 20.8 months. Of the LAAC group, 61.3% received an Amulet, 35.9% received a Watchman device, and 2.8% received a Watchman-FLX device. The primary endpoint occurred in 41 patients (47 events) in the direct oral anticoagulant group (13.42 event rate per year) compared to 35 patients (38 events) in the LAAC group (10.99 event rate per year) (subdistribution HR, 0.84; 95% CI, 0.53 to 1.21; p-value for noninferiority, p=.004). All stroke/TIA events occurred in 9 patients (9 events) in each group, subdistribution HR, 1.0 (95% CI, 0.40 to 2.51). Results were not divided by the type of LAAC device received. Longer-term results were subsequently published by Osmancik et al (2022).[34] After 3.5 years of follow-up, there was no significant difference in risk of the primary endpoint between the LAAC and direct oral anticoagulant groups (subdistribution HR, 0.81; 95% CI 0.56 to 1.18). Significant procedure- or device-related complications occurred in 9 patients in the LAAC group. Early complications (≤ 7 days) included device embolization (n=1), procedure-related death (n=1), and vascular complications (n=2), while late complications (> 7 days) included pericardial effusion (n=2), device-related death (n=1), and other complications (n=2). The procedure-related death was due to a femoral vascular access bleed and myocardial infarction. The device-related death occurred with the Amulet device due to a pericardial effusion approximately 6 weeks after the procedure.

Nonrandomized Studies

Numerous case series and nonrandomized studies have been published.[35],[36,37,38,39] 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 with nonvalvular AF with a $CHADS_2$ score 1 or higher who were considered ineligible for warfarin.[40] 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 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. Boersma et al (2016) conducted an analysis of the EWOLUTION registry data, reporting 30-day outcomes after device implantation in 1021 patients.[41] 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.

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.[42] Surveillance transesophageal electrocardiograms were conducted in all patients at 45 days and 12 months. Patients in the RCTs also received electrocardiograms at 6 months. A total of 1739 patients were followed for a total of 7159 patient-years. The 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 TIA or stroke, permanent atrial fibrillation, vascular disease, LAA diameter, and left ventricular ejection fraction.

Jazayeri et al (2018) evaluated the safety profiles of the Watchman and the Lariat Loop Applicator devices, using the FDA's Manufacturer and User Facility Device Experience (MAUDE) database from 2009 to 2016.[43] 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 1 likely related to DRT. Compared with the Lariat Loop Applicator device, the composite outcome occurred significantly more in the group receiving the Watchman than with in the group receiving the Lariat Loop Applicator, 1.9% versus 1.1%, p=.001). Results for the Lariat Loop Applicator device are discussed in the "Other Closure Devices" section.

Section Summary: Watchman Device

The most relevant evidence on use of the Watchman device for LAAC in patients eligible for anticoagulation derives from 2 industry-sponsored RCTs comparing Watchmen and systemic anticoagulants and a patient-level meta-analysis of those studies. After 5 years of follow-up, meta-analytic results showed that the ischemic stroke risk beyond 7 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. In addition, 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 2 RCTs and 2 registries) reported that patients who developed DRT were 4 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. One RCT found use of LAAC with either the Watchman device or Amplatzer Amulet device noninferior to direct oral anticoagulants for high-risk patients with AF.

AMPLATZER AMULET DEVICE

Randomized Controlled Trials

Two randomized noninferiority trials (SWISS-APERO and Amulet IDE, described below) have been reported comparing the Amplatzer Amulet and Watchman devices, but neither included an anticoagulant group.[44,45] A third trial (PRAGUE-17) compared either the Amulet or Watchman device with anticoagulants, but did not report subgroup analysis according to the device. The ongoing Clinical Trial of Atrial Fibrillation Patients Comparing Left Atrial Appendage Occlusion Therapy to Non-vitamin K Antagonist Oral Anticoagulants (CATALYST; NCT04226547), comparing the Amplatzer Amulet device with non-vitamin K antagonist oral anticoagulants, is expected to have primary completion in December 2024.

SWISS-APERO Trial

The Comparison of Amulet Versus Watchman/FLX Device in Patients Undergoing Left Atrial Appendage Closure (SWISS-APERO) trial conducted by Galea et al (2022) compared the Amulet and Watchman devices in 221 participants with non-valvular AF.[45] The enrolled participants were at high risk for stroke (mean CHA_2DS_2-VASc score 4.3; 39% had a history of prior stroke) and bleeding (mean HAS-BLED score 3.1; 88% had a history of bleeding requiring medical evaluation). Participants were primarily male (70%) and mean age was 77 years. Outcome assessment focused on successful closure, based on a composite outcome of either treatment group crossover during the LAAC procedure or residual LAA patency at 45 days post-intervention, based on CT angiography. The study found no difference in treatment between groups in the composite outcome (RR, 0.97; 95% CI 0.80 to 1.16). Major procedure-related complications were more common with the Amulet versus the Watchman device (9.0% vs. 2.7%; p=.047) There were 6 deaths during the trial, including 2 in the Amulet group (1.8%) and 4 in the Watchman group (3.6%; p=.409). Limitations of the study include the lack of an anticoagulant control group and the short duration of follow-up, although planned trial follow-up is ongoing. In addition, the actual Watchman device used was changed during the course of the trial due to a new device (Watchman FLX) version becoming available.

Amulet IDE Trial

Lakkireddy et al (2021) reported the results of the Amplatzer Amulet Left Atrial Appendage Occluder IDE Trial (Amulet IDE) comparing the Amulet and Watchman devices.[44] The study enrolled 1,878 patients with non-valvular AF at high-risk for stroke (mean CHA_2DS_2-VASc score 4.5 and 4.7) and bleeding (mean HAS-BLED score 3.2 and 3.3). The mean age of enrolled patients was 75 years and 59% were male; race and ethnicity were not reported. Twenty-eight percent of enrolled participants had a history of major bleeding and 19 percent had a history of stroke. The primary efficacy endpoint was a composite that included ischemic stroke or systemic embolism, while the safety analysis included a primary composite outcome of all-cause mortality, major bleeding or procedure-related complications. Duration of follow-up was 18 months for efficacy outcomes and 12 months for safety outcomes. After 18 months, there was no difference in the composite efficacy outcome between the Amulet and Watchman devices (HR, 0.00; 95% CI, -1.55 to 1.55). Results were consistent in showing no difference between groups when considering ischemic stroke and systemic embolism as individual outcomes. There was also no difference between Amulet and Watchman groups for a secondary composite outcome that included any stroke, systemic embolism or sudden cardiac death (HR, -2.12; 95% CI, -4.45 to 0.21), nor were there differences between groups when these outcomes were considered individually. In terms of safety, there was no difference between the Amulet and Watchman groups for the composite safety outcome at 12 months (HR, -0.14; 95% CI, -3.42 to 3.13). When outcomes were considered separately, there was also no difference between the Amulet and Watchman groups for all-cause mortality or major bleeding. Procedure-related complications were more likely to occur with the Amulet versus the Watchman devices (HR, 1.86; 95% CI, 1.11 to 3.12). Follow-up is planned to continue through 2024.

PRAGUE-17 Trial
As described above, the PRAGUE-17 trial found that the use of either the Watchman device or the Amplatzer Amulet was noninferior to direct oral anticoagulants for the primary composite endpoint that included ischemic or hemorrhagic stroke, TIA, systemic embolism, clinically significant bleeding, significant peri-procedural or device-related complications, or cardiovascular mortality in high-risk patients with AF.[33,34]

Observational Studies
Observational studies based on registry data provide evidence comparing the Amplatzer Amulet with anticoagulants.

Landmesser et al (2017) presented periprocedural (within 7 days of procedure) and early clinical outcomes (1 to 3 months postprocedure) from the Amulet Observational Registry of 1088 patients receiving the Amplatzer Amulet between June 2015 and September 2016.[46] 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) and Hildick-Smith et al (2020) provided updated analyses on 950 patients and 864 patients from the registry series described above who had 1-year and 2-year follow-up data.[47,48] Oral anticoagulants were used by 6% of the patients at 3, 6, and 12 months postprocedure and 6.6% of patients at 2 years. At year 1, there were 29 ischemic strokes (27 patients), 9 patients experiencing a TIA, and no systemic embolisms were reported. At year 2, there were 42 ischemic strokes (39 patients), 20 TIA events (16 patients; 9 events over the first year and 11 over the second year) and no systemic embolism were reported. The annualized bleeding rate was 10.1% per year in year 1 (103 events per 1016 patient-years) and 4.0% per year in year 2 (37 events per 917 patient-years). The proportion of patients experiencing a major bleeding event was 8.0% over the first year (87 of 1088 patients) and 3.2% over the second year (31 of 958 patients). The DRT rate was 1.6% at 2 years, with 19 events in 17 patients. There were 91 and 70 deaths reported in the first and second years, respectively, with 55 deaths considered cardiovascular-related, 71 non-cardiovascular-related, and 35 with unknown causes.

Nielsen-Kudsk et al (2021) compared Amulet Observational Registry patients with a successful LAAC using the Amulet device (n=1078) with a propensity-matched (based on CHA_2DS_2-VASc and HAS-BLED score) control cohort of patients with AF treated with direct oral anticoagulants (n=1184) identified from the Danish National Patient Registry and the Danish National Prescription Registry.[49] The primary outcome was a composite of ischemic stroke, major bleeding, or all-cause mortality at 2 years. At baseline, the CHA_2DS_2-VASc scores were 4.2 and 4.3 and the HAS-BLED scores were 3.3 and 3.4 in the LAAC and direct oral anticoagulant groups, respectively. At 2 years follow-up, 58% of patients had discontinued the direct oral anticoagulant. The primary outcome of ischemic stroke, major bleeding, and mortality was lower with LAAC (256 events; 14.5 event rate per 100 patient-years) compared with the direct oral anticoagulant group (461 events; 25.7 event rate per 100 patient-years; HR, 0.57; 95% CI, 0.49 to 0.67). Ischemic stroke was not significantly different between groups (HR, 1.11; 95% CI, 0.71 to 1.75). Major bleeding (HR, 0.62; 95% CI, 0.49 to 0.79), all-cause mortality (HR, 0.53; 95% CI, 0.43 to 0.64), and cardiovascular mortality (HR, 0.51; 95% CI, 0.37 to 0.70) were reduced with LAAC compared to direct oral anticoagulants.

Nonrandomized 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 Amplatzer Cardiac Plug (discussed below) with the first 50 consecutive patients receiving the Amulet.[51] Follow-up examinations were performed between 4 to 6 months post-procedure. No significant differences between the 2 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.[51] Periprocedural data were 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. Occurrences of adverse events during the periprocedural 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=.03).

Section Summary: Amplatzer Amulet

Two RCTs compared the Amulet and Watchman devices, one of which was a short-term trial that assessed periprocedural outcomes at 45 days. The second trial comparing the Amulet and Watchman devices found the Amulet device to be noninferior to the Watchman device after 18-months follow-up for a composite efficacy outcome that included ischemic stroke or systemic embolism and for a composite safety outcome that included all-cause mortality, major bleeding or procedure-related complications. The primary mechanism of action endpoint of device closure at 45 days was observed in 98.9% of Amulet subjects and 96.8% of Watchman subjects. The 97.5% lower confidence bound was 0.41%, which was greater than the predefined non-inferiority margin of -3% (p<.0001). Therefore, device closure with the Amulet device was non-inferior to the Watchman device.

One additional RCT evaluated the use of either the Amplatzer Amulet or Watchman device versus anticoagulants; subgroup analyses according to the device were not performed. After up to 4 years of follow-up, the study found LAA closure with either the Watchman or Amulet was noninferior to anticoagulants for a composite outcome that included stroke, TIA, systemic embolism, clinically significant bleeding, significant periprocedural or device-related complications, or cardiovascular mortality.

The summary of the clinical evidence provides a reasonable assurance that the Amulet device is effective for reducing the risk of thrombus embolization from the LAA in select patients with non-valvular atrial fibrillation.

OTHER PERCUTANEOUS Left Atrial Appendage CLOSURE DEVICES

Clinical Context and Therapy Purpose

The purpose of other percutaneous LAAC devices in patients who have atrial fibrillation 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 following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients with atrial fibrillation (AF). Atrial fibrillation 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 percutaneous LAA occlusion devices other than the Watchman or Amulet 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 pre-tied 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 Cardiac Plug is a transcatheter, self-expanding device constructed from the nitinol mesh and polyester patch. It is a precursor to the FDA-approved Amplatzer Amulet device, discussed above. The Amplatzer Cardiac Plug is not FDA-approved for LAA closure.

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, although some studies show follow up of up to 5 years. Additional outcomes of interest include device- or procedure-related events that may occur within 1 week of the procedure, in particular, events requiring open cardiac surgery or major endovascular intervention (eg, 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 preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with preference for prospective studies;
- To assess longer 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.

REVIEW OF EVIDENCE

Lariat Loop Applicator Device

Systematic Review
Chatterjee et al (2015) published a systematic review of studies on the Lariat Loop Applicator device.[53] No RCTs were identified. Five case series or observational studies were included, with a total of 309 patients (range, 4 to 154 patients).[53,54,55,56,57] 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.

Observational Studies
Individual observational studies published since the systematic review included a large 2016 observational study of 712 consecutive patients from 18 U.S. hospitals.[58] This study 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 Loop Applicator 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 observational studies are smaller, reporting success rates and complication rates in the same range.[59,60,61,62]

Litwinowicz et al (2018) presented an observational study of 139 patients from a single center undergoing LAAC with the Lariat Loop Applicator device, with a longer follow-up than the other observational studies.[63] 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%. Litwinowicz et al (2019) reported on the same set of patients, dividing them into 2 groups: patients with prior stroke (n=37) and those without prior stroke (control group; n=102).[65] Results showed that patients in the stroke group had significantly higher $CHADS_2$, CHA_2-DS_2-VASc, and HAS-BLED scores than the control group (all p<.0001). Thromboembolic event rate, bleeding event rate, and mortality rate were not significantly different between groups. The investigators concluded that patients with prior stroke may be preferred for LAAC, regardless of whether a contraindication for anticoagulant therapy exists.

Nonrandomized Comparative Study

Jazayeri et al (2018) evaluated the safety profiles of the Watchman and the Lariat Loop Applicator devices, using the FDA's MAUDE database from 2009 to 2016, as described in the Watchman section above.[43] 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 6 involving the 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% versus 1.1%, p=.001.

Litwinowicz et al (2019) compared outcomes of patients undergoing LAAC with the Lariat Loop Applicator device (n=57) with patients receiving either warfarin or clopidogrel (n=31).[65] Age, sex, and comorbidities were similar between the 2 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 clopidogrel (13%). However, there was no significant difference in CHA_2DS_2-VAS scores between the groups at baseline. The average follow-up in the Lariat group was 59 months and the 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=.02). The bleeding risk reduction in the Lariat group was estimated at 53%.

Section Summary: Lariat Loop Applicator Device

There are no RCTs of the Lariat device for LAAC. There was 1 non-randomized study comparing patients undergoing LAAC with the Lariat device with patients receiving either anticoagulant or antiplatelet therapy. Results showed significantly fewer thromboembolic events in the group undergoing LAAC with the Lariat device compared with the group receiving medication alone. The remaining evidence consisted of observational studies. The evidence is insufficient to draw conclusions about treatment efficacy.

Amplatzer Cardiac Plug Device (first generation)

The Amplatzer Cardiac Plus Clinical Trial (NCT01118299) comparing the Amplatzer Cardiac Plug device with anticoagulant therapy discontinued enrollment after enrolling 97 participants (of a planned minimum of 400 participants) and results are currently unpublished. The available evidence on use of the Amplatzer Cardiac Plug device for LAAC consists of a number of observational studies. Nietlispach et al (2013) published the largest cohort, which included 152 patients from a single institution in Europe.[66] Short-term complications occurred in 9.8% (15/152) of patients. The longer-term adverse outcomes occurred in 7% of patients, including 2 strokes, 1 peripheral embolization, and 4 episodes of major bleeding. Device embolization occurred in 4.6% (7/152) of patients. Other reports of patients treated with the Amplatzer Cardiac Plug device include a study of 90 patients from Belgium (2013),[67] 86 patients from Portugal (2012),[68] 37 patients from Italy (2013),[69] 35 patients from Spain

(2013),[70] 21 patients from Poland (2013),[71] and 20 patients from China (2012).[35] All studies reported high procedural success rates, as well as complications such as vascular complications, air embolism, esophageal injury, cardiac tamponade, and device embolization.

Cruz-Gonzales et al (2020), in their retrospective registry study, aimed to evaluate the safety and efficacy of LAAC for patients with nonvalvular AF with prior stroke or TIA despite anticoagulant therapy (resistant stroke [RS]).[72] They assessed data from the Amplatzer Cardiac Plug multicenter registry on 1047 consecutive patients with nonvalvular AF undergoing LAA occlusion. Of the 1047 patients, 115 had resistant stroke and 932 had other indications. The resistant stroke group had a significantly higher mean CHA_2-DS_2-VASc score (5.5±1.5 in the resistant stroke group vs. 4.6±1.6 in the non-stroke group; $p<.001$) and HAS-BLED score (3.9±1.3 vs. 3.1±1.2; $p<.001$). There were no significant differences between groups in procedural success or periprocedural major safety events (7.8% vs. 4.5%; $p=.10$). All patients completed at least 1 year of follow-up. At follow-up, the observed annual rate of stroke or TIA was 2.6% (65% relative reduction of thromboembolism based on the CHA_2-DS_2-VASc score) in the resistant stroke group and 1.2% (78% relative risk reduction) for the non-stroke group. In addition, the observed annual major bleeding rate was 0% (100% relative reduction based on the HAS-BLED score) for resistant stroke patients and 1.2% (79% relative reduction) for those without prior stroke/TIA. Although larger controlled trials are needed, LAAC showed significant benefit to patients who had had a previous stroke or TIA.

Several other observational studies have reported the use of the Amplatzer Cardiac Plug device in patients with a contraindication to oral anticoagulation therapy. Santoro et al (2016), in the larges observational study, reported on outcomes up to 4 years post procedure for 134 patients with nonvalvular AF and a long-term contraindication to oral anticoagulation treated with the Cardiac Plug device.[74] Patients had a median CHA_2DS_2-VASc score of 4 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 observational studies have been published in this population, evaluating between 37 to 100 patients.[69,74,,75,76,,50,] These studies also reported high success rates and low procedural complications.

Section Summary: Amplatzer Cardiac Plug Device
There are no RCTs of the Amplatzer Cardiac Plug device for LAAC. Numerous observational studies found high procedural success rates, but complication rates varied according to the AF population.

SUMMARY OF EVIDENCE

For individuals who have atrial fibrillation (AF) who are at increased risk for embolic stroke who receive an FDA-approved percutaneous left atrial appendage closure (LAAC) device (eg, the Watchman or Amulet device), the evidence includes randomized controlled trials (RCTs) and observational studies. Relevant outcomes are overall survival, morbid events, and treatment-related morbidity. The most relevant evidence for the Watchman device comes from 2 industry-sponsored RCTs comparing 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 for the 2 Watchman 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 lower rates of major bleeding, particularly hemorrhagic stroke, and mortality over the long term. Evidence for the Amplatzer Amulet device comes from 2 RCTs comparing the Amulet and Watchman devices, one of which was a short-term trial that assessed periprocedural outcomes at 45 days. The second trial comparing the Amulet and Watchman devices found the Amulet device to be noninferior to the Watchman device after 18 months of follow-up for a composite efficacy outcome that included ischemic stroke or systemic embolism and for a composite safety outcome that included all-cause mortality, major bleeding or procedure-related complications. One additional RCT evaluated the use of either the Amplatzer Amulet or Watchman device versus anticoagulants; subgroup analyses according to device were not performed. After up to 4 years of follow-up, the study found LAAC with either the Watchman or Amulet was noninferior to anticoagulants for a composite outcome that included stroke, transient ischemic attack (TIA) , systemic embolism, clinically significant bleeding, significant periprocedural or device-related complications, or cardiovascular mortality. Among patients in whom 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 an 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 FDA-approved devices (eg, Lariat Loop Applicator, Watchman, or Amplatzer Cardiac Plug), the evidence includes several nonrandomized comparator studies and uncontrolled observational studies. 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. Evidence from other observational studies of these devices report high procedural success, but also numerous complications. In addition, these devices do not have U.S. FDA approval for LAAC. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input Received From Physician Specialty Societies and Academic Medical Centers

2015 Input

In response to requests, Blue Cross Blue Shield Association received input from 1 physician specialty society (2 responses) and 4 academic medical centers, one of which provided 4 responses, for a total of 8 responses, while this policy was under their review 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

Guidelines or position statements will be considered for inclusion in 'Supplemental Information if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Chest Physicians

In 2018, the American College of Chest Physicians (CHEST) guideline made the following recommendation regarding left atrial appendage (LAA) occlusion and oral anticoagulation: "In patients with AF at high risk of ischemic stroke who have absolute contraindications for OAC [oral anticoagulation], we suggest using LAA occlusion (Weak recommendation, low-quality evidence)."[5]

American Heart Association

In 2019, the American Heart Association (AHA), in collaboration with the American College of Cardiology (ACC) and the Hearth Rhythm Society (HRS),published an update of their guideline for the management of patients with atrial fibrillation (AF).[77] A new recommendation in the guideline states: "Percutaneous LAA [left atrial appendage] 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 (LAAC) devices are mentioned in the guideline. The AHA also released a scientific statement in 2021 about managing AF in patients with heart failure and reduced ejection fraction.[78] They state that, "It is reasonable to consider LAA closure in patients with AF and heart failure with reduced ejection fraction (HFrEF) with moderate to high stroke risk and contraindications to long-term oral anticoagulation", however, they also note that the role of LAA therapies in patients with AF with HFrEF needs to be better understood, and this is an opportunity for future research.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 3.

Table 3: Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02513797[a]	aMAZE Study: LAA Ligation with the LARIAT Suture Delivery System as Adjunctive to Pulmonary Vein Isolation for Persistent Atrial Fibrillation (aMAZE)	600	Mar 2022
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 2023
NCT03463317	Left Atrial Appendage CLOSURE in Patients With Atrial Fibrillation at High Risk of Stroke and Bleeding Compared to Medical Therapy: a Prospective Randomized Clinical Trial	1512	Mar 2025
NCT02964208[a]	AMPLATZER LAA Occluder Post Approval Study (PAS)	1000	June 2023
NCT03302494[a]	WAveCrest Vs. Watchman TranssEptal LAA Closure to REduce AF-Mediated STroke 2 (WAVECREST2)	1550	Dec 2029
NCT03309332[a]	OSB Lead-AMPLATZER PFO Occluder New Enrollment PAS	1214	Apr 2030
NCT03795298	Comparison of Anticoagulation with Left Atrial Appendage Closure After AF Ablation (OPTION)	1600	Nov 2024
NCT04394546	WATCHMAN FLX Versus NOAC for Embolic ProtectION in in the Management of Patients With Non-Valvular Atrial Fibrillation	3000	Dec 2027
NCT04226547	Clinical Trial of Atrial Fibrillation Patients Comparing Left Atrial Appendage Occlusion Therapy to Non-vitamin K Antagonist Oral Anticoagulants	2650	April 2029
Unpublished			
NCT03276169	Left Atrial Function Changes after Left Atrial Appendage Closure in Patients with Persistent Atrial Fibrillation	105	Nov 2020 (updated Mar 2021)
NCT01118299	AMPLATZER Cardiac Plug Clinical Trial	3000	Dec 2018 (updated Apr 2020)
NCT02681042	Left Atrial Appendage Closure with SentreHeart Lariat Device	9	May 2018 (updated Feb 2021)

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

Government Regulations
National:

National Coverage Determination (NCD) for Percutaneous Left Atrial Appendage Closure (LAAC) (20.34)
Effective Date of the Version: 2/8/2016
Implementation Date: 10/3/2016
Indications and Limitations of Coverage

B. Nationally Covered Indications
The Centers for Medicare & Medicaid Services (CMS) covers percutaneous LAAC for non-valvular atrial fibrillation (NVAF) through Coverage with Evidence Development (CED) with the following conditions:

a. 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 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 transeptal puncture through an intact septum; and,
- Continues to perform ≥ 25 interventional cardiac procedures that involve transeptal puncture through an intact septum, of which at least 12 are LAAC, over a 2-year period.

The patient is enrolled in, and the MDT and hospital must participate in, a prospective, national, audited registry that: 1) consecutively enrolls LAAC patients, and, 2) tracks the following annual outcomes for each patient for a period of at least 4 years from the time of the LAAC:

- Operator-specific complications
- Device-specific complications including device thrombosis
- Stroke, adjudicated, by type
- Transient Ischemic Attack (TIA)
- Systemic embolism
- Death
- Major bleeding, by site and severity

[See the NCD for specific information related to registry criteria.]

C. Nationally Non-Covered Indications

LAAC is non-covered for the treatment of NVAF when not furnished under CED according to the above-noted criteria.

Local:
There is no local coverage determination. Refer to the NCD.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Medical Device Policy (retired)
- Wireless Pressure Sensors in Endovascular Aneurysm Repair (Previously titled Transcatheter Placement of Wireless Physiologic Sensor in Aneurysmal Sac During Endovascular Repair) (Retired)
- Transcatheter Closure of Patent Ductus Arteriosus (Retired)
- Closure Devices for Patent Foramen Ovale and Atrial Septal Defects

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 5/30/23, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
9/1/13	6/18/13	6/26/13	Replaces JUMP policy Transcatheter Closure of Cardiac Defects and/or Occlusion of Left Atrial Appendage
1/1/16	10/13/15	10/28/15	• New-Existing Policy Review • Updated Regulatory Status – Watchman FDA approval • MPS – position change from E/I to Established for FDA approved devices • Added Inclusionary & Exclusionary Guidelines • Updated Rationale, Practice Guidelines/Position Statements, References • Added BCBSA's 2015 Clinical Input from Physician Specialty Societies
1/1/17	10/11/16	10/11/16	• Routine maintenance • Added NCD & LCD
7/1/17	4/18/17	4/18/17	• Routine maintenance • Code update – delete 0281T; add code 33340 • Updated Medicare and Medicaid information
11/1/17	8/15/17	8/15/17	• Routine maintenance • References and rationale updated
11/1/18	8/21/18	8/21/18	Routine maintenance Removed PLAATO from criteria; device is no longer manufactured
11/1/19	8/20/19		Routine maintenance
11/1/20	8/18/20		Routine maintenance Ref added: 3,4,48,56
11/1/21	8/17/21		Routine maintenance Ref added: 5,27,66,67 MPS and Inclusion language edited; Watchman FLX added.

11/1/22	8/16/22		Amplatzer Amulet added; MPS, inclusions updated. Ref added: 3,4,5,6,10,11,12,28,35, 45,46
11/1/23	8/15/23		Routine Maintenance (jf) Vendor Managed: NA Ref 1, 2 removed; added ref 5,78

Next Review Date: 3rd Qtr, 2024

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN: N/A	Revised: N/A
BCBSM: 2/16/01	Revised: N/A

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: PERCUTANEOUS LEFT ATRIAL APPENDAGE CLOSURE DEVICES FOR STROKE PREVENTION IN ATRIAL FIBRILLATION

1. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	See Government Regulations section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

2. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.