Medical Policy

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

Professional
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Populations	Interventions	Comparators	Outcomes
Individuals: • With atrial fibrillation who are at increased risk for embolic stroke	Interventions of interest are: • Watchman percutaneous left atrial appendage closure device	Comparators of interest are: • Anticoagulation	Relevant outcomes include: • Overall survival • Morbid events • Treatment-related morbidity
Individuals: • With atrial fibrillation who are at increased risk for embolic stroke	Interventions of interest are: • Percutaneous left atrial appendage closure device other than the Watchman device	Comparators of interest are: • Anticoagulation	Relevant outcomes include: • Overall survival • Morbid events • Treatment-related morbidity

DESCRIPTION

Stroke prevention in atrial fibrillation (AF) is an important goal of treatment. Treatment with anticoagulant medications is the most common approach to stroke prevention. Most embolic strokes originate from the left atrial appendage; therefore, occlusion of the left atrial appendage may offer a nonpharmacologic alternative to anticoagulant medications for this purpose. Multiple percutaneously deployed devices are being investigated for left atrial appendage closure (LAAC). There is 1 left atrial appendage device with approval from the U.S. Food and Drug Administration (FDA) for stroke prevention in patients with AF, the Watchman device.

OBJECTIVE

The objective of this policy is to determine whether the use of percutaneous left atrial appendage closure devices improve the net health outcome in individuals with atrial fibrillation who are at increased risk for embolic stroke.

BACKGROUND

Stroke

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

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

Treatment

Pharmacologic

The main treatment for stroke prevention in AF is anticoagulation, which has proven efficacy. The risk for stroke among patients with AF is stratified on the basis of 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 recently 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, there is an increased risk of bleeding. Also, warfarin requires frequent monitoring and adjustments, as well as lifestyle changes. Dabigatran does not require monitoring. However, unlike warfarin, the antithrombotic effects of dabigatran are not reversible with any currently available

hemostatic drugs. Guidelines from the American College of Chest Physicians recommend the use of oral anticoagulation for patients with AF who are at high risk of stroke (ie, $CHADS_2$ 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. 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 has validated to assess the annual risk of significant bleeding in patients with AF treated with warfarin.[2] The score ranges from 0 to 9, based on a number of clinical characteristics, including the presence of hypertension, renal and liver function, history of stroke, bleeding, labile international normalized ratios (INRs), age, and drug/alcohol use. Scores of 3 or greater are considered to be associated with high risk of bleeding, potentially signaling the need for closer monitoring of the patient for adverse risks, closer monitoring of INRs, or differential dose selections of oral anticoagulants or aspirin.[3]

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 LAA closure 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 Watchman™ left atrial appendage system (Boston Scientific, Maple Grove, MN) is a self-expanding nickel titanium device. It has a polyester covering and fixation barbs for attachment to the endocardium. Implantation is performed percutaneously through a catheter delivery system, using venous access and transseptal puncture to enter the left atrium.

Following implantation, patients are anticoagulated with warfarin or alternative agents for approximately 1 to 2 months. After this period, patients are maintained on antiplatelet agents (i.e., aspirin and/or clopidogrel) indefinitely. The Lariat® Loop Applicator is a suture delivery device that is intended to close a variety of surgical wounds in addition to left atrial appendage closure. The Cardioblate® closure device developed by Medtronic is currently being tested in clinical studies. The Amplatzer® cardiac plug (St. Jude Medical, Minneapolis, MN), is FDA-approved for closure of atrial septal defects but not LAA closure device. A second-generation device, the Amplatzer Amulet, has been developed. The Percutaneous LAA Transcatheter Occlusion device (eV3, Plymouth, MN) has also been evaluated in research studies but has not received FDA approval. The Occlutech® (Occlutech, Sweden) Left Atrial Appendage Occluder has received a CE mark for coverage in Europe.

Outcome Measures

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

REGULATORY STATUS

In 2002, 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.

In March 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.[4] This device is indicated to reduce the risk of thromboembolism from the left atrial appendage (LAA) in patients with nonvalvular atrial fibrillation who:

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

FDA product code: NGV.

Several other devices are being evaluated for LAA occlusion but are not approved in the United States for percutaneous closure of the LAAC. In 2006, the Lariat® Loop Applicator device (SentreHEART, Redwood City, CA), 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 Amulet® device (St. Jude Medical, Plymouth, MN) has a CE approval in Europe for LAA closure, but is not currently approved in the United States for any indication.

POLICY

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

   1. 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**

   2. The long-term risks of systemic anticoagulation outweigh the risks of the device implantation (see Policy Guidelines).

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

C. 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 **experimental / investigational**.

Policy Guidelines

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

2. 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 has validated to assess the annual risk of significant bleeding in patients with AF treated with warfarin (Pisters et al, 2010). The score ranges 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 Characteristic	Points Awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (>65)	1
D	Drugs or alcohol (1 point each)	1 or 2

INR: international normalized ratio.

3. Patients with scores of 3, 4, and 5 have been reported to have a risk of major bleeding of 3.74/100 patient years, 8.70/100 patient years, and 12.5/100 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 the patient for adverse risks, closer monitoring of international normalized ratio, or differential dose selections of oral anticoagulants or aspirin (January et al, 2014).

RATIONALE

The most recent literature review was conducted through March 5, 2018.

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

The evidence on the efficacy of left atrial appendage closure (LAAC) devices consists of numerous case series of various occlusion devices, and 2 published RCTs of the Watchman device, the PROTECT AF and 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

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

Systematic Reviews

A TEC Assessment (2014) evaluated the use of the Watchman device for patients eligible and ineligible for anticoagulation therapy.[5] 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.[6-13] Others have included RCTs and observational studies.[9,14,15]

The most rigorous meta-analysis is the patient-level meta-analysis by Holmes et al (2015).[8] 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=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.[11] 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).

Reddy et al (2017) presented final results of the PROTECT AF trial and PREVAIL AF trial and conducted a meta-analysis of 5-year outcomes using data from both trials.[16] 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.

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

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

Adapted from Reddy et al (2017).[16]
CI: confidence interval; CV: cardiovascular; HR: hazard ratio; LAAC: left atrial appendage closure; PY: patient-years; SE: systemic embolism.

Additional systematic reviews have used network meta-analyses to compare Watchman with novel oral anticoagulants and vitamin K antagonists (6 RCTs, total N=59,627 subjects),[17] and have compared percutaneous left atrial appendage (LAA) occlusion (5 RCTs, total N=1285 subject) with standard anticoagulant or antiplatelet therapy with device-based surgical or percutaneous LAA exclusion.[18]

Randomized Controlled Trials

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.[19] The trial randomized 707 patients from 59 centers in the United States 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 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 gastrointestinal bleeding) and procedure-related complications (pericardial effusion, device embolization, procedure-related stroke).

The primary efficacy outcome occurred at a rate of 3.0 per 100 patient-years in the 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, cardiovascular/unexplained death) were higher in the warfarin group. By contrast, 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).[20] 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).[21] 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 (SF-12) scores from baseline to 12-month follow-up, for a subset of 547 subjects in the PROTECT AF trial.[22] For the subset of PROTECT AF subjects included in the Alli 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, the SF-12 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 end point (stroke, systemic embolism, cardiovascular death) compared with the warfarin-only group (p=0.04).[16]

PREVAIL Trial

A second RCT, the PREVAIL trial, was conducted after the 2009 Food and Drug Administration 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 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 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 (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, mean follow-up was 11.8 months, and median follow-up was 12.0 months (range, 0.03-25.9 months).

For the first 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% CrI 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% 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 end point (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 end point (stroke, systemic embolism, cardiovascular death) (p=0.5).[16]

Nonrandomized Studies

Numerous case series and nonrandomized studies of the Watchman have been published.[24-28] 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.[29] 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.

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.[30] 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 6 weeks. There were no statistically significant differences in procedure time, fluoroscopy time, or major safety events between the 2 groups. At a median follow-up of 364 days, there were no cases of stroke, transient ischemic attack, or other bleeding complications.

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 on 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 7 days and 3.6% (95% CI, 2.5% to 4.9%) at 30 days. The most common serious adverse event was major bleeding.

Section Summary: Watchman Device
The most relevant evidence on the use of the Watchman device for LAAC in patients eligible for anticoagulation derives from 2 industry-sponsored RCTs 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. Also, patients treated with the Watchman device experienced significantly lower bleeding and mortality.

Other Closure Devices

Lariat Device
A systematic review of studies on the Lariat device was published by Chatterjee et al (2016).[32] No RCTs were identified. Five case series were included, with a total of 309 patients (range, 4-154 patients) treated. The combined estimate of procedural success was 90.3%. One (0.3%) death was reported and 7 (2.3%) patients required urgent cardiac surgery. 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.

Individual case series published since the systematic review included a large 2016 case series of 712 consecutive patients from 18 U.S. hospitals.[33] 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 1 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.[34-38]

Section Summary: Lariat Device
There are no RCTs of the Lariat device for LAAC. The available case series are insufficient to draw conclusions about treatment efficacy.

Amplatzer Cardiac Plug Device
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.[39] 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 device include a series of 90 patients from Belgium (2013),[40] 86 patients from Portugal (2012),[41] 37 patients from Italy (2013),[42] 35 patients from Spain (2013),[43] 21 patients from Poland (2013),[44] and 20 patients from China (2012).[24] All series reported high procedural success rates, as well as various 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.[45] 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 case series have been published in this population, evaluating between 37 and 100 patients.[42,46-49] They also reported high success rates and low procedural complications.

Section Summary: Amplatzer Cardiac Plug Device
There are no RCTs of the Amplatzer device for LAAC. The available case series are insufficient to draw conclusions about treatment efficacy.

PLAATO Device
The available evidence on outcomes following the use of the Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO) device for stroke prevention in AF comes from case series and cohort studies. Bayard et al (2010) reported on 180 patients with nonrheumatic AF, a contraindication to warfarin, and treatment with the PLAATO device.[50] Placement was successful in 90% of patients. Two (1.1%) patients died within 24 hours of the procedure, and 6 (3.3%) patients had cardiac tamponade, with 2 requiring surgical drainage. Other case reports and small case series have found complications, including multiple reports of thrombus formation at the site of device placement.[51,52]

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

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 2 RCTs and meta-analyses of these trials. Relevant outcomes are overall survival, morbid events, and treatment-related morbidity. The most relevant evidence comes from 2 industry-sponsored RCTs that compared the Watchman device with anticoagulation alone. One trial reported noninferiority on a composite outcome of stroke, cardiovascular/unexplained death, or systemic embolism after 2 years of follow-up, with continued benefits with the Watchman device after 4 years of follow-up. The second trial did not demonstrate noninferiority for the same composite outcome but did demonstrate noninferiority of the Watchman device to warfarin for late ischemic stroke and systemic embolization. Patient-level meta-analyses at 5-year follow-up for the 2 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. When it is determined on an individualized basis that 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 (eg, the Lariat or Amplatzer), the evidence includes uncontrolled case series. Relevant outcomes are overall survival, morbid events, and treatment-related morbidity. Case series of these devices have reported high procedural success, but also numerous complications. Also, these devices do not have Food and Drug Administration approval for LAAC. The evidence is insufficient to determine the effects of the technology on health outcomes.

CLINICAL INPUT RECEIVED 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, 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, while this policy was under review in 2015. The input generally supported the use of an FDA-approved LAA closure device for patients with an increased risk of stroke and systemic embolism based on $CHADS_2$ or CHA_2DS_2-VASc score and systemic anticoagulation therapy is recommended but the long-term risks of systemic anticoagulation outweigh the risks of the device implantation.

PRACTICE GUIDELINES AND POSITION STATEMENTS

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.[53]

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).[53] 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.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently 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			
NCT02039167	WATCH Bleeding Episodes After Left Atrial Appendage Occlusion Versus Usual Care in Patients With Atrial FIBrillatIon and Severe to eNd-stage Chronic Kidney Disease (WatchAFIB in CKD)	300	Jun 2017 (ongoing)
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
NCT02426944	Left Atrial Appendage Closure vs Novel Anticoagulation Agents in Atrial Fibrillation	400	May 2020
NCT02879448	AMPLATZER™ Amulet™ Left Atrial Appendage Occluder Randomized Controlled Trial	1600	Dec 2023
NCT03302494[a]	WAveCrest Vs. Watchman TranssEptal LAA Closure to REduce AF-Mediated STroke 2 (WAVECREST2)	1250	Dec 2025
Unpublished			
NCT01118299	AMPLATZER Cardiac Plug Clinical Trial	3000	Not approved/ cleared
NCT01182441[a]	Evaluation of the Watchman LAA closure device in patients with atrial fibrillation versus long term warfarin therapy	475	Aug 2017 (unknown)

NCT: national clinical trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. 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.

CPT/HCPCS

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

ICD-10 Diagnoses

I48.0 Paroxysmal atrial fibrillation
I48.2 Chronic atrial fibrillation
I48.91 Unspecified atrial fibrillation
I63.30 Cerebral infarction due to thrombosis of unspecified cerebral artery

I63.311 Cerebral infarction due to thrombosis of right middle cerebral artery
I63.312 Cerebral infarction due to thrombosis of left middle cerebral artery
I63.313 Cerebral infarction due to thrombosis of bilateral middle cerebral arteries
I63.319 Cerebral infarction due to thrombosis of unspecified middle cerebral artery
I63.321 Cerebral infarction due to thrombosis of right anterior cerebral artery
I63.322 Cerebral infarction due to thrombosis of left anterior cerebral artery
I63.323 Cerebral infarction due to thrombosis of bilateral anterior cerebral arteries
I63.329 Cerebral infarction due to thrombosis of unspecified anterior cerebral artery
I63.331 Cerebral infarction due to thrombosis of right posterior cerebral artery
I63.332 Cerebral infarction due to thrombosis of left posterior cerebral artery
I63.333 Cerebral infarction due to thrombosis of bilateral posterior cerebral arteries
I63.339 Cerebral infarction due to thrombosis of unspecified posterior cerebral artery
I63.341 Cerebral infarction due to thrombosis of right cerebellar artery
I63.342 Cerebral infarction due to thrombosis of left cerebellar artery
I63.343 Cerebral infarction due to thrombosis of bilateral cerebellar arteries
I63.349 Cerebral infarction due to thrombosis of unspecified cerebellar artery
I63.39 Cerebral infarction due to thrombosis of other cerebral artery
I63.40 Cerebral infarction due to embolism of unspecified cerebral artery
I63.411 Cerebral infarction due to embolism of right middle cerebral artery
I63.412 Cerebral infarction due to embolism of left middle cerebral artery
I63.413 Cerebral infarction due to embolism of bilateral middle cerebral arteries
I63.419 Cerebral infarction due to embolism of unspecified middle cerebral artery
I63.421 Cerebral infarction due to embolism of right anterior cerebral artery
I63.422 Cerebral infarction due to embolism of left anterior cerebral artery
I63.423 Cerebral infarction due to embolism of bilateral anterior cerebral arteries
I63.429 Cerebral infarction due to embolism of unspecified anterior cerebral artery
I63.431 Cerebral infarction due to embolism of right posterior cerebral artery
I63.432 Cerebral infarction due to embolism of left posterior cerebral artery
I63.433 Cerebral infarction due to embolism of bilateral posterior cerebral arteries
I63.439 Cerebral infarction due to embolism of unspecified posterior cerebral artery
I63.441 Cerebral infarction due to embolism of right cerebellar artery
I63.442 Cerebral infarction due to embolism of left cerebellar artery
I63.443 Cerebral infarction due to embolism of bilateral cerebellar arteries
I63.449 Cerebral infarction due to embolism of unspecified cerebellar artery
I63.49 Cerebral infarction due to embolism of other cerebral artery
I63.50 Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebral artery
I63.511 Cerebral infarction due to unspecified occlusion or stenosis of right middle cerebral artery
I63.512 Cerebral infarction due to unspecified occlusion or stenosis of left middle cerebral artery
I63.513 Cerebral infarction due to unspecified occlusion or stenosis of bilateral middle cerebral arteries
I63.519 Cerebral infarction due to unspecified occlusion or stenosis of unspecified middle cerebral artery
I63.521 Cerebral infarction due to unspecified occlusion or stenosis of right anterior cerebral artery

I63.522	Cerebral infarction due to unspecified occlusion or stenosis of left anterior cerebral artery
I63.523	Cerebral infarction due to unspecified occlusion or stenosis of bilateral anterior cerebral arteries
I63.529	Cerebral infarction due to unspecified occlusion or stenosis of unspecified anterior cerebral artery
I63.531	Cerebral infarction due to unspecified occlusion or stenosis of right posterior cerebral artery
I63.532	Cerebral infarction due to unspecified occlusion or stenosis of left posterior cerebral artery
I63.533	Cerebral infarction due to unspecified occlusion or stenosis of bilateral posterior cerebral arteries
I63.539	Cerebral infarction due to unspecified occlusion or stenosis of unspecified posterior cerebral artery
I63.541	Cerebral infarction due to unspecified occlusion or stenosis of right cerebellar artery
I63.542	Cerebral infarction due to unspecified occlusion or stenosis of left cerebellar artery
I63.543	Cerebral infarction due to unspecified occlusion or stenosis of bilateral cerebellar arteries
I63.549	Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebellar artery
I63.59	Cerebral infarction due to unspecified occlusion or stenosis of other cerebral artery
I63.6	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
I63.81	Other cerebral infarction due to occlusion or stenosis of small artery
I63.89	Other cerebral infarction
I63.9	Cerebral infarction, unspecified
I66.01	Occlusion and stenosis of right middle cerebral artery
I66.02	Occlusion and stenosis of left middle cerebral artery
I66.03	Occlusion and stenosis of bilateral middle cerebral arteries
I66.09	Occlusion and stenosis of unspecified middle cerebral artery
I66.11	Occlusion and stenosis of right anterior cerebral artery
I66.12	Occlusion and stenosis of left anterior cerebral artery
I66.13	Occlusion and stenosis of bilateral anterior cerebral arteries
I66.19	Occlusion and stenosis of unspecified anterior cerebral artery
I66.21	Occlusion and stenosis of right posterior cerebral artery
I66.22	Occlusion and stenosis of left posterior cerebral artery
I66.23	Occlusion and stenosis of bilateral posterior cerebral arteries
I66.29	Occlusion and stenosis of unspecified posterior cerebral artery
I66.3	Occlusion and stenosis of cerebellar arteries
I66.8	Occlusion and stenosis of other cerebral arteries
I66.9	Occlusion and stenosis of unspecified cerebral artery

REVISIONS

12-20-2013	Policy added to the bcbsks.com web site.

07-01-2016	Updated Description section.
	In Policy section: ▪ Removed "The use of percutaneous left-atrial appendage closure devices for the prevention of stroke in atrial fibrillation is considered experimental / investigational." ▪ Added the following: A. 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 the following criteria are met: 1. 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 2. The long-term risks of systemic anticoagulation outweigh the risks of the device implantation (see Policy Guidelines). B. 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 experimental / investigational. C. The use of other percutaneous left atrial appendage closure devices, including but not limited to the Lariat, PLAATO, and Amplatzer devices, for stroke prevention in patients with atrial fibrillation is considered experimental / investigational. ▪ Added Policy Guidelines.
	Updated Rationale section.
	In Coding section: ▪ Updated CPT code 0281T nomenclature. ▪ Added ICD-10 codes.
	Updated References section.
07-07-2016	Updated Description section.
	Updated Rationale section.
	Updated References section.
10-01-2016	In Coding section: ▪ Added ICD-10 codes effective 10-01-2016: I63.313, I63.323, I63.333, I63.343, I63.413, 863.423, I63.433, I63.443, I63.513, I63.523, I63.533, I63.543
01-01-2017	In Coding section: ▪ Added CPT code: 33340 *(New code, effective January 1, 2017)*. ▪ Removed CPT code: 0281T *(Termed code, effective December 31, 2016)*.
07-11-2017	Updated Description section.
	Updated Rationale section.
	Updated References section.
10-01-2017	In Coding section: ▪ Revised nomenclature to ICD-10 codes: I63.323, I63.333, I63.513, I63.523, I63.533.
08-08-2018	Updated Description section.
	In Policy section: ▪ In Item A, added "nonvalvular" to read, "The use of a device with U.S. Food and Drug Administration (FDA) approval for percutaneous left atrial appendage closure (eg, the Watchman) may be considered medically necessary for the prevention of stroke in patients with nonvalvular atrial fibrillation when the following criteria are met:" ▪ In Item C, removed "PLAATO" to read, "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 experimental / investigational." ▪ Updated Policy Guidelines.
	Updated Rationale section.
	Updated References section.
10-01-2018	In Coding section: ▪ Added ICD-10 codes: I63.81, I63.89. ▪ Removed ICD-10 code: I63.8. ▪ Revised ICD-10 codes: I63.333, I63.343.

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