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

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DESCRIPTION

Stroke prevention in patients with atrial fibrillation (AF) is an important goal of treatment. Treatment with anticoagulant medications is the most common approach to stroke prevention. Because most embolic strokes originate from the left atrial appendage, occlusion of the left atrial appendage may offer a nonpharmacologic alternative to anticoagulant medications to lower the risk of stroke. Multiple percutaneously deployed devices are being investigated for left atrial appendage closure (LAAC) the Watchman Left Atrial Appendage System (Boston Scientific), AMPLATZER™ (Amulet) Left Atrial Appendage Occluder (Abbot Medical) and LARIAT® Suture Delivery Device and Accessories.

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

Stroke in AF occurs primarily because 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.

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 in the below in Table. Warfarin is the predominant agent in clinical use. A number of newer anticoagulant medications, including dabigatran, rivaroxaban, and apixaban, have received U.S.FDA approval for stroke prevention in nonvalvular AF and have demonstrated noninferiority to warfarin in clinical trials. While anticoagulation is effective for stroke prevention, it carries an increased risk of bleeding. Also, warfarin requires frequent monitoring and adjustments as well as lifestyle changes. Dabigatran does not require monitoring. However, unlike warfarin, the antithrombotic effects of dabigatran are not reversible with any currently available hemostatic drugs. 2018 American College of Chest Physicians guidelines (updated from 2012) recommend that CHA_2DS_2VASc be used to evaluate stroke risk, and patients initially identified as having a low stroke risk should not be given antithrombotic therapy. In addition, they recommend bleeding risk assessments be given to every patient at every patient contact and that “potentially modifiable bleeding risk factors” should be the initial focus.

CHA2DS$_2$ and CHA$_2$DS$_2$-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

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. 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 associated with high risk of bleeding, potentially signaling the need for closer monitoring of patients for adverse risks, closer monitoring of international normalized ratios, or differential dose selections of oral anticoagulants or aspirin.
Surgical removal, or exclusion, of the LAA is often performed in patients with AF who are undergoing open heart surgery for other reasons. Percutaneous left atrial appendage closure (LAAC) devices have been developed as a nonpharmacologic alternative to anticoagulation for stroke prevention in AF. The devices may prevent stroke by occluding the LAA, thus preventing thrombus formation.

Several versions of LAA occlusion devices have been developed. The PLAATO system (ev3 Endovascular) was the first device to be approved by the FDA for LAA occlusion. The device was discontinued in 2007 for commercial reasons, and intellectual property was sold to manufacturers of the Watchman system. The Watchman Left Atrial Appendage System (Boston Scientific) is a self-expanding nickel titanium device. It has a polyester covering and fixation barbs for attachment to the endocardium. Implantation is performed percutaneously through a catheter delivery system, using venous access and transseptal puncture to enter the left atrium. Transesophageal echocardiography and fluoroscopy are used to guide the procedure. Following implantation, patients receive anticoagulation with warfarin or alternative agents for approximately 1 to 2 months. After this period, patients are maintained on antiplatelet agents (i.e., aspirin and/or clopidogrel) indefinitely. The Amplatzer cardiac plug (St. Jude Medical), is FDA-approved for closure of atrial septal defects but not for LAAC. A second-generation device, the Amplatzer Amulet Left Atrial Appendage Occluder, has been developed for the specific indication of LAAC and was approved by the FDA April 2021. The Amplatzer Amulet Left Atrial Appendage Occluder consists of a nitinol mesh disc to seal the ostium of the LAA and a nitinol mesh distal lobe, to be positioned within the LAA. The device is preloaded within a delivery sheath. The Percutaneous LAA Transcatheter Occlusion device (ev3) has also been evaluated in research studies but has not received the FDA approval. The Occlutech® (Occlutech) Left Atrial Appendage Occluder has received a CE mark for coverage in Europe. The Cardioblate® closure device (Medtronic) is currently being tested in clinical studies. The Lariat Loop Applicator is a suture delivery device approved by the FDA, intended to close a variety of surgical wounds. It is not specifically approved for LAAC. While the Watchman and other devices are implanted in the endocardium, the Lariat is a non-implant epicardial device.

Watchman Left Atrial Appendage System

Clinical Context and Therapy Purpose
The purpose of the Watchman Left Atrial Appendage System 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.

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

Interventions
The therapy being considered is use of the Watchman percutaneous left atrial appendage (LAA) closure device. The device is made of nickel titanium and is implanted percutaneously through a catheter, into the left atrium. The Watchman comes in 5 sizes and self-expands to occlude the LAA. By occluding the LAA, thrombus formation is prevented, potentially preventing stroke. Following implantation of the device, the patient receives warfarin for 1 to 2 months. Once it is established that there is no peri device leak or thrombus development, the patient is then placed on antiplatelet agents indefinitely.

LAAC is performed by a cardiac surgeon under general anesthesia (although it is not invasive surgery) in an outpatient surgical setting.

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.

Patients with AF are actively managed by a cardiologist.

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 (e.g., pseudoaneurysm repair, arteriovenous fistula repair, or another major endovascular repair) should be noted.

Systemic Reviews

In 2018, Baman et. al. conducted a systematic review of LAA closure devices, including Watchman, Amplatzer cardiac plug, Amplatzer Amulet, and Lariat devices. 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.

Bajaj et. al. (2016) published the network meta-analysis comparing vitamin K antagonists with novel oral anticoagulants and with the Watchman device. 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. The authors noted that overall quality of the evidence was low.

In 2015, Holmes et. al. published a meta-analysis. This analysis included patient-level data from the industry-sponsored PROTECT AF and PREVAIL trials together with both studies' continued access registries. The PROTECT AF and PREVAIL registries were designed to include patients with similar baseline characteristics as their respective RCTs. The meta-analysis included 2406 patients, 1877 treated with the Watchman device and 382 treated with warfarin alone. Mean patient follow-up durations were 0.58 years and 3.7 years, respectively, for the PREVAIL continued access registry, and the PROTECT AF continued access registry. In a meta-analysis of 1114 patients treated in the RCTs, compared with warfarin, LAAC met the trial's noninferiority criteria for the primary composite efficacy endpoint of all-cause stroke, systemic embolization, and cardiovascular death (hazard ratio [HR], 0.79, 95% confidence interval [CI], 0.52 to 1.2; p=.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. 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=.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 post procedure, 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 post procedure (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).

Randomized Controlled Trials

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. The trial randomized 707 patients from 59 centers in the U. S. and Europe to the Watchman device or warfarin treatment in a 2:1 ratio. Mean follow-up was 18 months. The primary efficacy outcome was a composite endpoint of stroke (ischemic or hemorrhagic), cardiovascular or unexplained death, or systemic embolism. There was also a primary safety outcome, a composite endpoint of excessive bleeding (intracranial or gastrointestinal bleeding) and procedure-related complications (pericardial effusion, device embolization, procedure-related stroke).

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

The primary safety outcome occurred more commonly in the LAAC group, at a rate of 7.4 per 100 patient-years compared with 4.4 per 100 patient-years in the warfarin group (rate ratio, 1.69; 95% CrI, 1.01 to 3.19). The excess in adverse event rates for the LAAC group was primarily the result of early adverse events associated with device placement. The most frequent type of complication related to LAAC device placement was pericardial effusion requiring intervention, which occurred in 4.8% (22/463) of patients. Reddy et. al. (2013) reported on longer-term follow-up from the PROTECT AF trial. 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. 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=.04).
Alli et al (2013) reported on quality-of-life parameters, as measured by change in the 12-Item Short-Form Health Survey scores from baseline to 12-month follow-up, for a subset of 547 subjects in the PROTECT AF trial. 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 endpoint (stroke, systemic embolism, cardiovascular death) compared with the warfarin-only group (p=.04).

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 (2014). 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 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 endpoints were specified: (1) occurrence of ischemic or hemorrhagic stroke, cardiovascular or unexplained death, and systemic embolism (18-month rates); (2) occurrence of late ischemic stroke and systemic embolization (beyond 7 days post randomization, 18-month rates); and (3) occurrence of all-cause death, ischemic stroke, systemic embolism, or device- or procedure-related events requiring open cardiac surgery or major endovascular intervention (e.g., pseudoaneurysm repair, arteriovenous fistula repair, or other major endovascular repair) occurring within 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 composite primary endpoint, the 18-month modeled rate ratio between the device and control groups was 1.07 (95% CrI, 0.57 to 1.89). Because the upper bound of the 95% CrI was above the preset noninferiority margin of 1.75, the noninferiority criteria were not met. For the second primary endpoint of late ischemic stroke and systemic embolization, the 18-month relative risk between the device and control groups was 1.6 (95% CrI, 0.5 to 4.2), with an upper bound of the 95% CrI above the preset noninferiority margin of 2.0. The rate difference between the device and control groups was 0.005 (95% CrI, -0.019 to 0.027). The upper bound of the 95% CrI was lower than the noninferiority margin of 0.0275, so the noninferiority criterion was met for the rate difference. For the third primary endpoint (major safety issues), the noninferiority criterion was met.

Reddy et al (2017), in their-5-year follow-up results, (2017), indicated that the Watchman device was noninferior to warfarin alone in the composite efficacy endpoint (stroke, systemic embolism, cardiovascular death) (p=.5)
Reddy et. al. (2017) also, in addition to providing 5-year final results for the individual trials, (2017) conducted a meta-analysis of the 5-year outcomes using data from both trials. Meta-analytic results are summarized in the below table, 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.

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)*	*.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*

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.

Nonrandomized Studies

Numerous case series and nonrandomized studies of the Watchman have been published. Several are notable in that they were conducted in patients not eligible for anticoagulation, a population not included in PROTECT AF and PREVAIL.

In 2018, Jazayeri et.al. (2018) evaluated the safety profiles of the Watchman and the Lariat devices, using the FDA's Manufacturer and User Facility Device Experience (MAUDE) database from 2009 to 2016. 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 device, the composite outcome occurred significantly more in the group receiving the Watchman than within the group receiving the Lariat, 1.9% vs. 1.1%, p=.001). Analysis results for the Lariat device will be discussed in the next section, "Other Closure Devices".

In 2018, Dukkipati et. al. 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.[34,] Surveillance transesophageal electrocardiograms were conducted in all patients at 45 days and 12 months. Patients in the RCTs also received the electrocardiograms at 6 months. A total of 1739 patients were followed for a total of 7159 patient-years. Mean age of the population was 74 years and 34% were women. DRT was detected in 65 (3.7%) of the patients. Stroke or systemic embolism rates were 7.5 and 1.8 per 100 patient-years for patients with and without DRT, respectively. A multivariable modeling analysis found the following predictors of DRT: history of transient ischemic attack or stroke, permanent AF, vascular disease, LAA diameter, and left ventricular ejection fraction.

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. Post implantation, 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 1,021 patients. The overall population had a risk of bleeding that was substantially higher than that for patients in the RCTs. Over 62% of patients included in the registry were deemed ineligible for anticoagulation by their physicians. Approximately one-third of patients had a history of major bleeding, and 40% had HAS-BLED scores of 3 or greater, indicating moderate- to high-risk of bleeding. Procedural success was achieved in 98.5% of patients, and 99.3% of implants demonstrated no blood flow or minimal residual blood flow post procedure. 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
The most relevant evidence on the use of the Watchman device for LAAC in patients eligible for anticoagulation derives from 2 industry-sponsored RCTs comparing Watchman and systemic anticoagulants and a patient-level meta-analysis of those studies. After five years of follow-up, meta-analytic results showed that the ischemic stroke risk beyond 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. 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.

Other Closure Devices

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

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

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

- The Lariat Loop Applicator is a suture delivery device approved by the FDA to facilitate suture placement and knot tying for use in surgical applications where soft tissues are being approximated or ligated with a pretied polyester suture. The approved use does not specify LAA occlusion. While the Watchman and other devices are implanted in the endocardium, the Lariat is a non-implant epicardial device. The Lariat is contraindicated in patients with active pericarditis; prior sternotomy or other mediastinal surgery or known pericardial adhesions; appendage width >45 mm; superiorly oriented appendage lying near or behind the pulmonary arterial trunk; or appendage thrombus.

- The Amplatzer Amulet device comes in 8 sizes to accommodate various patient anatomies. The mechanism of action is similar to the Watchman. Following implantation of the Amulet, patients are placed on antiplatelet agents and do not need warfarin. There is an ongoing trial comparing the Amplatzer Amulet with the Watchman (NCT03399851).

LAAC is performed by a cardiac surgeon under general anesthesia (although it is not invasive surgery) in an outpatient surgical setting.

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.

Patients with AF are actively managed by a cardiologist.

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 (e.g., pseudoaneurysm repair, arteriovenous fistula repair, or other major endovascular repair).

Lariat Device

Systematic Review

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

Case Series

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). 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.

In 2018, Litwinowicz et. al. presented a case series of 139 patients from a single-center undergoing LAA closure with the Lariat device, with a longer follow-up than the other case series. 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%.

Nonrandomized Studies

In 2019, Litwinowicz et. al. compared outcomes of patients undergoing LAA closure with the Lariat device (n=57) with patients receiving either warfarin or clopidogrel (n=31). 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. Average follow-up in the Lariat group was 59 months and average follow-up in the control group was 60 months. There were no thromboembolic events in the Lariat group, while 9.6% of the control group experienced thromboembolic events (p=.02). The bleeding risk reduction in the Lariat group was estimated at 53%.

Jazayeri et. al. (2018) evaluated the safety profiles of the Watchman and the Lariat devices, using the FDA's MAUDE database from 2009 to 2016, as described in the Watchman section above. 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 tightening of the suture around the LAA. Compared to the Watchman device, the composite outcome occurred significantly more in the group receiving the Watchman than in the group receiving the Lariat, 1.9% vs. 1.1%, p=.001.

Section Summary
There are no randomized controlled trials (RCTs) of the Lariat device for LAAC. There was 1 nonrandomized study comparing patients undergoing LAA closure with the Lariat device with patients receiving either anticoagulant or antiplatelet therapy. Results showed significantly fewer thromboembolic events in the group undergoing LAA closure with the Lariat device compared with the group receiving medication alone. The remaining evidence consisted of case series.

Amplatzer

Amplatzer Cardiac Plug (First Generation)
The available evidence on the use of the Amplatzer device for left atrial occlusion consists of several case series.

In 2020, Cruz-Gonzales et.al. in their retrospective registry study, aimed to evaluate the safety and efficacy of LAA occlusion for patients with nonvalvular AF with prior stroke or TIA despite anticoagulant therapy (resistant stroke [RS]). They assessed data from the Amplatzer Cardiac Plug multicenter registry on 1047 consecutive patients with nonvalvular AF undergoing LAA occlusion. Out of the 1047, 115 had RS and 932 had other indications. There were no significant differences in baseline characteristics between the 2 groups. The RS group had a significantly higher mean CHA_2-DS_2-VASc score (5.5±1.5 in the RS 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=.1). 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 RS 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 RS patients and 1.2% (79% relative reduction) for those without prior stroke/TIA. Although larger controlled trials are needed, LAA occlusion showed significant benefit to patients who had had a previous stroke or TIA.

In 2016, Santoro et. al. in the largest case series, 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 Amplatzer device. 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. These studies also reported high success rates and low procedural complications.

In 2013, Nietlispach et. al. *p*ublished the largest series, which included 152 patients from a single institution in Europe. 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.

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

Nonrandomized Controlled Studies
In 2017, Al-Kassou et. al. *p*resented periprocedural and 2-to-3-month follow-up data for patients undergoing LAA occlusion with the Amplatzer cardiac plug and the Amplatzer Amulet. Periprocedural data was available for 99 patients receiving the cardiac plug and for 97 patients receiving the Amulet. Use of the Amulet was associated with significantly lower fluoroscopy time, lower radiation dose, and reduced amount of contrast dye. Occurrence of adverse events during the 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=0.03).

Gloekler et. al. (2015) reviewed records from 2 university hospitals' occlusion registries and conducted a retrospective analysis comparing the last 50 consecutive patients receiving the cardiac plug with the first 50 consecutive patients receiving the amulet. 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.

Case Series
In 2018, Landmesser et. al. provided updated analyses on 950 patients from the registry series described above who had 1-year follow-up data. Oral anticoagulants were used by 6% of the patients at 3-, 6-, and 12-months post procedure. There were 29 ischemic strokes (27 patients), 9 patients experiencing a transient ischemic attack, and no systemic embolisms reported. The annualized bleeding rate was 10.3% per year, with 103 events in 87 patients, majority occurring within the first 7 days post procedure. The DRT rate was

1.7% per year, with 18 events in 17 patients. A total of 88 patients died within the first-year post procedure, 53 were cardiovascular-related and 35 non cardiovascular. Two of the cardiovascular-related deaths were attributed to the device.

In 2017, Landmesser et. al. (2017) presented periprocedural (within 7 days of procedure) and early clinical outcomes (1 to 3 months post procedure) from a multicenter registry of 1088 patients receiving the Amplatzer Amulet between June 2015 and September 2016.[62,] 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 post procedure and 3 months follow-up.

Section Summary
There are no randomized controlled trials (RCTs) of the Amplatzer device for LAAC. There are 2 nonrandomized studies comparing the first generation Amplatzer cardiac plug with the second generation Amplatzer Amulet, 1 of which reported procedural advantages of the Amulet over the cardiac plug. Both nonrandomized comparator studies reported no difference in clinical outcomes at first follow-up, 2 to 6 months. The remaining evidence consists of case series. The nonrandomized comparator studies and the case series are insufficient to draw conclusions about treatment efficacy. There is an ongoing trial comparing the Amplatzer Amulet with the Watchman (NCT03399851).

Summary of Evidence
For individuals who have atrial fibrillation (AF) who are at increased risk for embolic stroke who receive the Watchman percutaneous left atrial appendage closure (LACC) device, the evidence includes 2 randomized controlled trials (RCTs) and meta-analyses of these trials. 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. Among patients in which the long-term risk of systemic anticoagulation exceeds the procedural risk of device implantation, the net health outcome will be improved. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have atrial fibrillation (AF) who are at increased risk for embolic stroke who receive a percutaneous left atrial appendage closure (LACC) device other than the Watchman percutaneous left atrial appendage closure (LACC) device (e.g., the Lariat or Amplatzer, Amplatzer Amulet), the evidence includes several nonrandomized comparator studies and uncontrolled case series. One nonrandomized study that compared outcomes among patients undergoing LAAC with the Lariat device with patients receiving anticoagulant or antiplatelet therapy reported fewer thromboembolic events in the group receiving the Lariat device. Two nonrandomized studies compared the Amplatzer cardiac plug with the Amplatzer Amulet. While the Amulet may be technically easier to implant, clinical outcomes were similar between the 2 groups. The remaining evidence consists of case series of these devices which report high procedural success but also numerous complications. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

American Heart Association (AHA)/ American College of Cardiology (ACC)/ Heart Rhythm Society (HRS)
In 2019, the American Heart Association (AHA)/ American College of Cardiology (ACC)/ Heart Rhythm Society (HRS) focused update of the 2014 AHA/ACC/HRS guidelines for the management of atrial fibrillation issued a category IIb (weak) recommendation, indicating "percutaneous LLA occlusion may be considered in patients with AF at increased risk of stroke who have contraindications to long-term anticoagulation"

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

The FDA granted PMA approval March 2015 for the WATCHMAN LAA Closure Device in individuals with non-valvular AF in facilities equipped for heart surgery as an alternative option to long-term warfarin therapy. According to the manufacturer, Boston Scientific Corporation:

- WATCHMAN is indicated to reduce the risk of thromboembolism from the left atrial appendage in patients with non-valvular atrial fibrillation who are at increased risk for stroke and systemic embolism based on $CHADS_2$ or CHA_2DS_2-VASc scores, are deemed by their physicians to be suitable for warfarin; and have an appropriate rationale to seek a non-pharmacologic alternative to warfarin,

taking into account the safety and effectiveness of the device compared to warfarin.

In June 2020, the FDA approved the next generation WATCHMAN FLX Left Atrial Appendage Closure Device, which is the first device to be fully recapturable for repositioning and redeployment. The device has more sizes which can accommodate a variety of LAA anatomy. The FDA approval was based on unpublished 12-month results from the PINNACLE FLX US IDE Clinical Study (NCT02702271), an ongoing single arm, non-randomized trial, evaluating WATCHMAN FLX for non-inferiority to safety and efficacy performance goals based on the WATCHMAN LAAC device. The inclusion and exclusion criteria were consistent with the WATCHMAN clinical study criteria. The safety, effectiveness and benefit-risk profile of the WATCHMAN FLX Device has not been established in individuals in whom anticoagulation is determined to be contraindicated. Estimated enrollment is 458 participants and estimated study completion is February 2021.

In August 2021, the FDA approved the Amplatzer Amulet Left Atrial Appendage Occluder (Abbott Medical). This device is a percutaneous transcatheter device intended to reduce the risk of thrombus embolization from the left atrial appendage (LAA) in patients who have nonvalvular atrial fibrillation and who are at increased risk for stroke and systemic embolism based on CHADS2 or CHA2DS2-VASc scores, are suitable for short term anticoagulation therapy, and have appropriate rationale to seek a nonpharmacologic alternative to oral anticoagulation

PRIOR APPROVAL

Not applicable.

POLICY

See Related Medical Policies

- 02.02.20 Intracardiac Ischemia Monitoring
- 02.02.22 Non-invasive Heart Failure and Arrhythmia Management and Monitoring System

Watchman Device

The use of the Watchman percutaneous left atrial appendage closure (LACC) device or Watchman FLX Left Atrial Appendage Closure Device may be considered **medically necessary** for the prevention of stroke in members with atrial fibrillation (AF) when **ALL** the following criteria are met:

- There is an increased risk of stroke and system embolism based on $CHADS_2$ (score $\geq$ 2) or CHA_2DS_2-VASc (score $\geq$ 3) and systemic anticoagulation therapy is recommended; **and**
- The long-term risks of systemic anticoagulation outweigh the risk of the device implantation (see Policy Guidelines).

CHA2DS2-VASc Calculator for Atrial Fibrillation **Criteria**		**Points**
Age	<65 years old	0
	65-74 years old	+1
	≥75 years old	+2
Sex	Male	0
	Female	+1
Congestive heart failure history		+1
Hypertension history		+1
Stroke/TIA/thromboembolism history		+2
Vascular disease history (prior MI, peripheral artery disease, or aortic plaque)		+1
Diabetes mellitus history		+1

The use of the Watchman percutaneous left atrial appendage closure (LACC) device or Watchman FLX Left Atrial Appendage Closure Device for stroke prevention in an individual who does not meet the above criteria is considered **investigational,** because the evidence is insufficient to determine the effects of the technology on health outcomes.

Other Percutaneous Left Atrial Appendage Closure (LACC) Device
The use of other percutaneous left atrial appendage closure (LACC) devices, including but not limited to the following, is considered **investigational**, because the evidence is insufficient to determine the effects of the technology on health outcomes.

- Amplatzer Amulet Left Atrial Appendage Occluder
- Lariat Loop Applicator device (SentreHEART)
- WaveCrest

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

Bleeding is the primary risk associated with systemic anticoagulation. A number of risk scores have been developed to estimate the risk of significant bleeding in patients treated with systemic anticoagulation. An example is the HAS-BLED score, which is validated to assess the annual risk of significant bleeding in patients with atrial fibrillation treated with warfarin. Scores range from 0 to 9, based on a number of clinical characteristics.

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

HAS-BLED: Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR (international normalized ratio), Elderly, Drugs/alcohol concomitantly.

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

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 33340 Percutaneous transcatheter closure of the left atrial appendage with endocardial implant, including fluoroscopy, transseptal puncture, catheter placement(s), left atrial angiography, left atrial appendage angiography, when performed, and radiological supervision and interpretation
- 93799 Unlisted cardiovascular service or procedure (May be utilized for one of the following: Watchman percutaneous left atrial appendage closure (LACC) device, Watchman FLX Left Atrial Appendage Closure Device, Lariat or Lariat Loop Applicator device , Amplatzer Amulet Left Atrial Appendage Occluder or WaveCrest devices)

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    - FDA Approval of Abbot Amplatzer Amulet Left Atrial Appendage Occluder.

POLICY HISTORY		
Date	**Reason**	**Action**
January 2022	Annual Review	Policy Revised, New Medical Policy Created

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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