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

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Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Percutaneous Left-Atrial Appendage Closure Devices for Stroke Prevention in Atrial Fibrillation when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
The use of an FDA-approved left atrial appendage closure device may be considered medically necessary for the prevention of stroke in patients with atrial fibrillation when the following criteria are met:
- There is an increased risk of stroke and systemic embolism based on CHADS₂ or CHA₂DS₂-VASc score and systemic anticoagulation therapy is recommended; AND
- The long term risks of systemic anticoagulation clearly outweigh the risks of the device implantation (see Considerations).

When Policy Topic is not covered
The use of the Watchman left atrial appendage closure devices for patients who do not meet the above criteria is considered investigational.

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

Considerations
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 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 Characteristics Composing the HAS-BLED Bleeding Risk Score (Pisters et al, 2010)

<table>
<thead>
<tr>
<th>Letter</th>
<th>Clinical Characteristic</th>
<th>Points Awarded</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Abnormal renal and liver function (1 point each)</td>
<td>1 or 2</td>
</tr>
<tr>
<td>S</td>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>L</td>
<td>Labile INRs</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>Elderly (&gt;65)</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>Drugs or alcohol (1 point each)</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

INR: international normalized ratio.

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

### Coding

There is a specific CPT category I code for this procedure:

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

### Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
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<tbody>
<tr>
<td>Individuals: • With atrial fibrillation who are at increased risk for embolic stroke</td>
<td>Interventions of interest are: • Watchman percutaneous left atrial appendage closure device</td>
<td>Comparators of interest are: • Anticoagulation</td>
<td>Relevant outcomes include: • Overall survival • Morbid events • Treatment-related morbidity</td>
</tr>
</tbody>
</table>

| 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 |
Stroke prevention in atrial fibrillation is an important consideration. 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 the prevention of stroke in patients with AF. Multiple percutaneously-deployed devices are being investigated for left atrial appendage closure. There is one left atrial appendage (LAA) occlusion device with approval from the U.S. Food and Drug Administration (FDA) for stroke prevention in patients with atrial fibrillation (AF), the Watchman™ device.

For individuals who have AF who are at increased risk for embolic stroke who receive the Watchman percutaneous LAA closure (LAAC) device, the evidence includes 2 randomized controlled trials (RCTs) and meta-analyses of these trials. Relevant outcomes are overall survival, morbid events, and treatment-related morbidity. The most relevant evidence comes from 2 industry-sponsored RCTs that compared the Watchman device with anticoagulation. 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 of 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 a higher periprocedural risk of bleeding and ischemic stroke but a lower risk of hemorrhagic stroke over the long term. The published evidence indicates that the Watchman device is efficacious in preventing stroke for 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 qualitatively 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, Amplatzer, and PLAATO devices), the evidence includes uncontrolled case series. Relevant outcomes are overall survival, morbid events, and treatment-related morbidity. Case series of these devices have reported high procedural success, but also numerous complications. In addition, these devices do not have FDA approval for LAAC. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Background**

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 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

Anticoagulation

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. A commonly used score, the CHADS2 score, assigns 1 point each for the presence of heart failure, hypertension, age 75 years or older, diabetes, or prior stroke or transient ischemic attack (TIA). The CHA2DS2-VASc score includes sex, more age categories, and the presence of vascular disease, in addition to the risk factors used in the CHADS2 score. 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, CHADS2 score of 2 or greater), with more individualized choice of antithrombotic therapy in patients with lower stroke risk.(1)

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 greater than or equal to 3 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 atrial fibrillation who are undergoing open heart surgery for other reasons. Percutaneous LAA closure devices have been developed as a nonpharmacologic alternative to anticoagulation for stroke prevention in atrial fibrillation. The devices may prevent stroke by occluding the LAA, thus preventing thrombus formation.

Several versions of 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, utilizing venous access and transseptal puncture to enter the left atrium. Following implantation, patients are anticoagulated with warfarin or alternate agents for approximately 1-2 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 Corp. is currently being tested in clinical studies. The Amplatzer® cardiac plug (St. Jude Medical, Minneapolis, MN), is FDA-approved for closure of atrial septal defects but has not received FDA approval for LAA closure device. A second-generation device, the Amplatzer Amulet, has been developed. The Percutaneous LAA Transcatheter Occlusion (PLAATO) device (eV3, Plymouth, MN) has also been evaluated in research studies but has not received FDA approval.

Regulatory Status
IN 2009, the Watchman Left Atrial Appendage Closure Technology (Boston Scientific, Marlborough, MA) was originally considered by FDA for approval based on the results the results of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients with Atrial Fibrillation (PROTECT-AF) randomized controlled trial (RCT). The device underwent 3 panel reviews before it was approved by FDA through the premarket approval process on March 13, 2015. This device is indicated to reduce the risk of thromboembolism from the LAA in patients with nonvalvular atrial fibrillation who:

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

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

**Rationale**

This evidence review was originally created in April 2011 and has been updated regularly with searches of the MEDLINE database. The most recent update with literature review was performed through March 23, 2017.

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

The evidence on the efficacy of LAAC devices consists of numerous case series of various occlusion devices, and 2 published RCTs of the Watchman device that 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 own unique considerations.

**Watchman Device**

The Watchman device is intended as an alternative to anticoagulation for patients with AF who are at increased risk for embolic stroke. RCTs comparing the Watchman device to anticoagulation are essential for determining efficacy of the device. Nonrandomized studies and case series may offer additional evidence on populations included in the RCTs, durability of effect, and/or adverse events. This evidence review will include RCTs and systematic reviews of RCTs for efficacy, and will review select nonrandomized studies and case series that offer additional information on different populations, durability, and/or adverse events.

This review of the evidence related to the efficacy of the Watchman device was informed by a 2014 TEC Assessment, which evaluated use of the Watchman device for patients eligible and ineligible for anticoagulation therapy. 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.”

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.

Two individual RCTs, the PROTECT AF and PREVAIL trials, have evaluated the Watchman device for stroke prevention in patients with AF who are at increased risk for embolic stroke. These trials are reviewed in depth next, along with meta-analyses of these studies.

**Systematic Reviews**

A number of meta-analyses have been performed that combine results of the available RCTs.\(^6\)\(^-\)\(^13\) Others have included RCTs and observational studies.\(^14\)\(^-\)\(^16\)

The most rigorous meta-analysis is a 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 study’s noninferiority criteria for the primary composite efficacy end point of all-cause stroke, systemic embolization, and cardiovascular death (hazard ratio [HR], 0.79, 95% confidence interval [CI], 0.52 to 1.2; p=0.22). All-cause stroke rates did not differ significantly between groups (1.75 per 100 patient-years for LAAC vs 1.87 per 100 patient-years for warfarin; HR=1.02; 95% CI, 0.62 to 1.7; p=0.94). However, 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 (2015) of the 2 RCTs evaluated bleeding outcomes. There were 54 episodes of major bleeding, with the most common types being gastrointestinal (GI) bleed (31/54 [57%]) and hemorrhagic stroke (9/54 [17%]). On combined analysis, the rate of major bleeding episodes over the entire study period did not differ between groups. There were 3.5 events per 100 patient-years in the Watchman group compared with 3.6 events per 100 patient-years in the anticoagulation group, for a rate ratio of 0.96 (95% CI, 0.66 to 1.40; p=0.84). However, there was a reduction in bleeding risk for the Watchman group past the initial periprocedural period. For bleeding events occurring more than 7 days postprocedure, the event rates were 1.8 per 100 patient-years in the Watchman group compared with 3.6 per 100 patient-years in the anticoagulation group (rate ratio, 0.49; 95% CI, 0.32 to 0.75; p=0.01). For bleeding events occurring more than 6 months postprocedure (the time at which antiplatelet therapy is discontinued for patients receiving the Watchman device), the event rates were 1.0 per 100 patient-years in the Watchman group compared with 3.5 per 100 patient-years in the anticoagulation group (rate ratio, 0.28; 95% CI, 0.16 to 0.49; p<0.001).

Additional systematic reviews have used network meta-analyses to compare Watchman with novel oral anticoagulants and vitamin K antagonists (6 RCTs, total N=59,627 subjects), 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.

**Randomized Controlled Trials**

**PROTECT-AF Trial**
The first RCT published was PROTECT AF, an unblinded randomized trial evaluating the noninferiority of a LAAC device compared to warfarin for stroke prevention in AF. The trial randomized 707 patients from 59 centers in the United States and Europe to the Watchman device or to 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 GI bleeding) and procedure-related complications (pericardial effusion, device embolization, procedure-related stroke).

The primary efficacy outcome occurred at a rate of 3.0 per 100 patient-years in the 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, cardiovascular/unexplained death and hemorrhagic stroke 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 placement of the device. 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 in 2013. At a mean follow-up of 2.3 years, the results were similar to the initial report. The relative risk for the composite primary outcome in the Watchman group compared with anticoagulation was 0.71, and this met 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 in the Watchman group compared with 3.6% per year in the warfarin group. Outcomes through 4 years of follow-up were reported by Reddy et al in 2014. 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 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 Short-Form 12-Item 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 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 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).

**PREVAIL Trial**
A second RCT, the PREVAIL trial, was conducted after the 2009 FDA decision on the Watchman device to address some limitations of the PROTECT AF trial, including its inclusion of patients with low stroke risk (CHADS\(_2\) scores of 1), high rates of adjunctive antiplatelet therapy use in both groups, and generally poor compliance with warfarin therapy in the control group. Results from the PREVAIL trial were initially presented in FDA documentation, and published in peer-reviewed form by Holmes et al in 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<sub>2</sub> 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% credible interval was above the preset noninferiority margin of 1.75, the noninferiority criteria were not met. For the second primary end point of late ischemic stroke and systemic embolization, the 18-month relative risk between the device and control groups was 1.6 (95% CrI, 0.5 to 4.2), with an upper bound of the 95% credible interval above the preset noninferiority margin of 2.0. The rate difference between the device and control groups was 0.005 (95% CrI, -0.019 to 0.027). The upper bound of the 95% credible interval was lower than the noninferiority margin of 0.0275, so the noninferiority criterion was met for the rate difference. For the third primary end point (major safety issues), the noninferiority criterion was met.

**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. Reddy et al (2013) conducted a multicenter, prospective, nonrandomized trial to evaluate the safety and efficacy of LAAC with the Watchman device in patients with nonvalvular AF with a CHADS<sub>2</sub> score 1 or higher who were considered ineligible for warfarin. Postimplantation, patients received 6 months of clopidogrel or ticlopidine and lifelong aspirin therapy. Thirteen (8.7%) patients had
a procedure- or device-related serious adverse event, most commonly pericardial effusion (3 patients). Over a mean follow-up of 14.4 months, all-cause stroke or systemic embolism occurred in 4 patients.

Chun et al (2013) compared the Watchman device to the Amplatzer cardiac plug among patients with nonvalvular AF, who were at high risk for stroke and had a contraindication to or were unwilling to accept oral anticoagulants. 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 is intended to evaluate procedural success, long-term outcomes, and adverse events in real-world settings. This registry compiles data from patients receiving the Watchman device at 47 centers in 13 countries. A publication from the EWOLUTION registry in 2016 reported on 30-day outcomes after device implantation in 1021 patients. The overall population had a risk of bleeding that was substantially higher than that for patients in the RCTs. Over 62% of patients included in the registry were deemed ineligible for anticoagulation by their physicians. Approximately one-third of patients had a history of major bleeding, and 40% had HAS-BLED scores of 3 or greater, indicating moderate-to-high risk of bleeding. Procedural success was achieved in 98.5% of patients, and 99.3% of implants demonstrated no blood flow or minimal residual blood flow postprocedure. Serious adverse events due to the device or procedure occurred at an overall rate of 2.8% (95% CI, 1.9% to 4.0%) at 7 days and 3.6% (95% CI, 2.5% to 4.9%) at 30 days. The most common serious adverse event was major bleeding.

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

**Other Closure Devices**

**Lariat Device**
A systematic review of studies on the Lariat device was published in 2016. No RCTs were identified. Five case series were selected, with a total of 309 patients
(range, 4-154 patients) treated. The combined estimate of procedural success was 90.3%. One (0.3%) death was reported and 7 (2.3%) patients required urgent cardiac surgery. 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 since include a large 2016 case series of 712 consecutive patients from 18 U.S. hospitals. This series reported a procedural success rate of 95% and complete closure in 98%. There was 1 death, and emergent cardiac surgery was required in 1.4%. Other individual case series are smaller, reporting success rates and complication rates in the same range.

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

**Amplatzer Cardiac Plug Device**
The available evidence on use of the Amplatzer device for left atrial occlusion consists of a number of case series. The largest series identified was by Nietlispach et al (2013), which included 152 patients from a single institution in Europe. Short-term complications occurred in 9.8% (15/152) of patients. 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), 86 patients from Portugal (2012), 37 patients from Italy (2013), 35 patients from Spain (2013), 21 patients from Poland (2013), and 20 patients from China (2012). 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 use of the Amplatzer device in patients with a contraindication to oral anticoagulation therapy. The largest (2016) reported 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. Patients had a median CHA₂DS₂-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, ranging from 37 to 100 patients. They also reported high success rates and low procedural complications.
**Section Summary: Amplatzer Cardiac Plug Device**
There are no RCTs of the Amplatzer device for LAAC. The available case series are not sufficient to determine treatment efficacy.

**PLAATO Device**
The available evidence on outcomes following use of the PLAATO device for stroke prevention in AF comes from case series and cohort studies. Bayard et al (2010) reported on 180 patients with nonrheumatic AF, a contraindication to warfarin, and treatment with the Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO) device. 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.

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

**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 (LAAC) device, the evidence includes 2 randomized controlled trials (RCTs) and meta-analyses of these trials. Relevant outcomes are overall survival, morbid events, and treatment-related morbidity. The most relevant evidence comes from 2 industry-sponsored RCTs that compared the Watchman device with anticoagulation. 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 of 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 a higher periprocedural risk of bleeding and ischemic stroke, but a lower risk of hemorrhagic stroke over the long term. The published evidence indicates that the Watchman device is efficacious in preventing stroke for 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, Amplatzer, and PLAATO devices), the evidence includes uncontrolled case series. Relevant outcomes are overall survival, morbid events, and treatment-
related morbidity. Case series of these devices have reported high procedural success, but also numerous complications. In addition, these devices do not have Food and Drug Administration approval for LAAC. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

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

In response to requests, 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. Input generally supported the use of a left atrial appendage closure device approved by the Food and Drug Administration for patients with an increased risk of stroke and systemic embolism, based on CHADS\textsubscript{2} or CHA\textsubscript{2}DS\textsubscript{2}-VASc score. Systemic anticoagulation therapy was recommended, but the long-term risks of systemic anticoagulation outweigh the risks of the device implantation.

Practice Guidelines and Position Statements

American College of Cardiology, Heart Rhythm Society, et al
In 2015, the American College of Cardiology (ACC), Heart Rhythm Society (HRS), and Society for Cardiovascular Angiography and Interventions published an overview of the integration of percutaneous left atrial appendage closure (LAAC) devices into the clinical practice for patients with atrial fibrillation (AF).\textsuperscript{54} The overview provided general guidelines for facility and operator requirements, including the presence of a multidisciplinary heart team, for centers performing percutaneous LAAC. It did not provide specific recommendations on indications and patient populations appropriate for percutaneous LAAC.

American College of Cardiology, American Heart Association, et al
In 2014, ACC, American Heart Association, and HRS issued guidelines on the management of patients with AF.\textsuperscript{3} The guidelines recommended that surgical excision of the left atrial appendage (LAA) be considered in patients undergoing cardiac surgery (class IIB recommendation; level of evidence: C), but made no specific recommendations on percutaneous LAAC.

European Society of Cardiology et al
In 2016, the European Society of Cardiology (ESC) and the European Society for Cardiothoracic Surgery (EACTS) issued guidelines on the management of AF.\textsuperscript{55} The guidelines included the following recommendations on exclusion of the LAA in AF (see Table 1).
Table 1. Guidelines on LAA Occlusion or Exclusion

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>CO</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>“After surgical occlusion or exclusion of the LAA, it is recommended to continue anticoagulation in at-risk patients with AF for stroke prevention”</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>“LAA occlusion may be considered for stroke prevention in patients with AF and contraindications for long-term anticoagulant treatment (e.g., those with a previous life-threatening bleed without a reversible cause).”</td>
<td>IIb</td>
<td>B</td>
</tr>
</tbody>
</table>

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

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

As of 2016, the Centers for Medicare and Medicaid Services has a national coverage determination (NCD) under coverage with evidence development for percutaneous LAAC in AF, as follows:

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

The patient must have:

- A CHADS2 score ≥2 (Congestive heart failure, Hypertension, Age > 75, Diabetes, Stroke/transient ischemia attack/thromboembolism) or CHA2DS2-VASc score ≥ 3 (Congestive heart failure, Hypertension, Age ≥ 65, Diabetes, Stroke/transient ischemia attack/thromboembolism, Vascular disease, Sex category)
- A formal shared decision making interaction with an independent non-interventional physician using an evidence-based decision tool on oral anticoagulation in patients with NVAF [nonvalvular atrial fibrillation] prior to LAAC. Additionally, the shared decision making interaction must be documented in the medical record.
- A suitability for short-term warfarin but deemed unable to take long-term oral anticoagulation following the conclusion of shared decision making, as LAAC is only covered as a second line therapy to oral anticoagulants. The patient (preoperatively and postoperatively) is under the care of a cohesive, multidisciplinary team (MDT) of medical professionals. The procedure must be furnished in a hospital with an established structural heart disease (SHD) and/or electrophysiology (EP) program.

The procedure must be performed by an interventional cardiologist(s), electrophysiologist(s), or cardiovascular surgeon (s) that meet the following criteria:
- Has received training prescribed by the manufacturer on the safe and effective use of the device prior to performing LAAC; and,
- Has performed ≥ 25 interventional cardiac procedures that involve transseptal puncture through an intact septum; and,
- Continues to perform ≥ 25 interventional cardiac procedures that involve transseptal puncture through an intact septum, of which at least 12 are LAAC, over a 2-year period.”
- Patients must be enrolled in approved registries that track outcomes for procedures and devices.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this policy are listed in Table 2.

**Table 2. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tbody>
<tr>
<td>Ongoing</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>NCT02039167</td>
<td>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)</td>
<td>300</td>
<td>Jun 2017</td>
</tr>
<tr>
<td>NCT01182441</td>
<td>EVALUATION OF THE WATCHMAN LAA CLOSURE DEVICE IN PATIENTS WITH ATRIAL FIBRILLATION VERSUS LONG TERM WARFARIN THERAPY</td>
<td>475</td>
<td>Aug 2017</td>
</tr>
<tr>
<td>NCT02426944</td>
<td>LEFT ATRIAL APPENDAGE CLOSURE VS NOVEL ANTICOAGULATION AGENTS IN ATRIAL FIBRILLATION</td>
<td>400</td>
<td>May 2020</td>
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<tr>
<td>NCT02879448</td>
<td>AMPLATZER™ AMCUL II™ LEFT ATRIAL APPENDAGE OCCLUDER RANDOMIZED CONTROLLED TRIAL</td>
<td>1600</td>
<td>Dec 2023</td>
</tr>
<tr>
<td>Unpublished</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NCT01363895</td>
<td>INTERVENTIONAL STRATEGIES IN TREATMENT OF ATRIAL FIBRILLATION: PERCUTANEOUS CLOSURE OF THE LEFT ATRIAL APPENDAGE VS CATHETER ABLATION</td>
<td>120</td>
<td>Nov 2013 (unknown)</td>
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<tr>
<td>NCT01628068</td>
<td>EFFICACY OF LEFT ATRIAL APPENDAGE CLOSURE AFTER GASTROINTESTINAL BLEEDING</td>
<td>120</td>
<td>Jul 2014 (unknown)</td>
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<tr>
<td>NCT01118299</td>
<td>AMPLATZER CARDIAC PLUG CLINICAL TRIAL</td>
<td>3000</td>
<td>Not approved/cleared</td>
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</table>

NCT: national clinical trial.

**References**


Billing Coding/Physician Documentation Information

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 (new code 1/1/2017)

Code 0281T deleted 1/1/2017

Additional Policy Key Words

N/A

Policy Implementation/Update Information

<table>
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<tr>
<th>Date</th>
<th>Description</th>
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<tbody>
<tr>
<td>1/1/12</td>
<td>New policy; considered investigational.</td>
</tr>
<tr>
<td>6/1/12</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>12/1/12</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>6/1/13</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>12/1/13</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>9/1/14</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>12/1/14</td>
<td>No policy statement changes.</td>
</tr>
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<td>12/1/15</td>
<td>The use of an FDA-approved left atrial appendage closure device is considered medically necessary with conditions.</td>
</tr>
<tr>
<td>12/1/16</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>12/1/17</td>
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