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

I. Description

Summary

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

The evidence for the use of the Watchman device for stroke prevention in patients with AF who are candidates for oral anticoagulation includes 2 randomized controlled trials (RCTs) and a patient-level meta-analysis 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 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. A patient-level meta-analysis of the 2 trials suggested that the Watchman is associated with a periprocedural risk of ischemic stroke but a lower risk of hemorrhagic stroke over the long term. The published evidence is sufficient to determine that the Watchman device is efficacious in preventing stroke for patients with AF who are eligible to receive systemic anticoagulation. 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.
The evidence for the use of LAA closure devices other than the Watchman (eg, the Lariat, PLAATO, and Amplatzer devices) for stroke prevention in patients with AF includes uncontrolled case series. Relevant outcomes are overall survival, morbid events, and treatment-related morbidity. Case series of these devices report high procedural success but also numerous complications. In addition, these devices do not have FDA approval for LAA closure. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical input was obtained to identify specific criteria for determining when the Watchman would be associated with clinical benefit. Results of clinical input generally supported the use of the Watchman device in patients who have an increased risk of stroke or systemic embolization but have long-term risks associated with oral anticoagulation that are determined, on an individual basis, to outweigh the short-term risk of Watchman device implantation.

II. Criteria/Guidelines

The use of a device with U.S. Food and Drug Administration (FDA) approval for percutaneous left atrial appendage closure (eg, the Watchman) is covered (subject to Limitations and Administrative Guidelines) for the prevention of stroke in patients with atrial fibrillation when all of the following criteria are met:

A. Patient has a CHADS2 score of score ≥ 2 or CHA2DS2-VASc score ≥ 3 (see Appendix Table 1 and 2) and systemic anticoagulation therapy is recommended.

B. The long-term risks of systemic anticoagulation outweigh the risks of the device implantation. 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. The score ranges from 0 to 9, based on a number of clinical characteristics (see Appendix Table 3).

III. Limitations

The use of other percutaneous left atrial appendage closure devices, that are not FDA approved for stroke prevention in patients with atrial fibrillation, including but not limited to the Lariat, PLAATO, and Amplatzer devices, are not covered.

IV. Administrative Guidelines

A. Precertification is required. Complete HMSA’s precertification request and fax or mail the form as indicated. Include the clinical notes with documentation of:

1. Atrial Fibrillation.
2. An increased risk of stroke and systemic embolism based on CHADS2 or CHA2DS2-VASc score or recommendation for long term systemic anticoagulation therapy.
3. The rationale for the long-term risks of systemic anticoagulation outweighing the risks of the device implantation.

B. Applicable Code:
V. Background

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

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

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. The CHADS₂-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 ≥2), with more individualized choice of antithrombotic therapy in patients with lower stroke risk.

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. The score ranges from 0 to 9, based on a number of clinical characteristics, including the presence of hypertension, renal and liver function, history of stroke, bleeding, labile international normalized ratios (INRs), age, and drug/alcohol use. Scores of 3 or greater are considered to be associated with high risk of bleeding,

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<td>Percutaneous transcatheter closure of the left atrial appendage with implant, including fluoroscopy, trans-septal puncture, catheter placement(s), left atrial angiography, left atrial appendage angiography, radiological supervision and interpretation.</td>
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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.

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

Several versions of LAA occlusion devices have been developed. The Watchman left atrial appendage system (Boston Scientific, Maple Grove, MN) is a self-expanding nickel titanium device. It has a polyester covering and fixation barbs for attachment to the endocardium. Implantation is performed percutaneously through a catheter delivery system, using venous access and transseptal puncture to enter the left atrium. Following implantation, patients are anticoagulated with warfarin or alternative agents for approximately 1 to 2 months. After this period, patients are maintained on antiplatelet agents (ie, aspirin and/or clopidogrel) indefinitely. The Lariat Loop Applicator is a suture delivery device that is intended to close a variety of surgical wounds in addition to left atrial appendage closure. The Cardioblate closure device developed by Medtronic is currently being tested in clinical studies. The Amplatzer cardiac plug (St. Jude Medical, Minneapolis, MN), is FDA-approved for closure of atrial septal defects but not LAA closure device. A second-generation device, the Amplatzer Amulet, has been developed. The Percutaneous LAA Transcatheter Occlusion device (eV3, Plymouth, MN) has also been evaluated in research studies but has not received FDA approval.

**Regulatory Status**

In 2009, the Watchman Left Atrial Appendage Closure Technology (Boston Scientific, Marlborough, MA) was originally considered by the U.S. Food and Drug Administration (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 left atrial appendage (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 2 other devices have been studied for LAA occlusion, but are not approved in the United States for percutaneous closure of the LAA. In 2006, the Lariat Loop Applicator device (SentreHEART, Redwood City, CA), 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 4randomiz
polyester suture. The Amplatzer Amulet device (St. Jude Medical, Plymouth, MN) has a CE approval in Europe for LAA closure, but is not currently approved in the United States for any indication.

VI. Rationale

This evidence review was created in 2011 and has been updated periodically with literature review. The most recent update with literature review covers the period of through May 29, 2015.

Assessment of efficacy for therapeutic interventions such as the left atrial appendage (LAA) closure devices involves a determination of whether the intervention improves health outcomes. The optimal study design for this purpose is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may also be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health outcomes, but are prone to biases. For the use of LAA closure 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 LAA closure devices consists of numerous case series of various occlusion devices, and 2 published RCTs of the Watchman device that compared LAA closure with warfarin anticoagulation. Evidence on each different device will be reviewed separately, because the devices are not similar in design, and each may have its own unique considerations.

Watchman Device

The review of the evidence related to the efficacy of the Watchman device is based, in part, on a Blue Cross Blue Shield Association TEC Assessment developed in June 2014, which evaluated use of the Watchman device for patients who were eligible and ineligible for anticoagulation therapy and determined that it does not meet Technology Evaluation Criteria. The TEC assessment made the following conclusions about the use of LAA closure 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 [left atrial appendage closure] 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 LAA closure 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.

**Patients Who Are Eligible for Anticoagulation**

Two RCTs, the PROTECTAF and PREVAIL trials, have evaluated the Watchman device for stroke prevention in patients with atrial fibrillation (AF).

**Meta-Analyses**

In 2015, Holmes et al reported results of a patient-level meta-analysis that included 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 a total of 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, LAA closure 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 LAA closure vs 1.87 per 100 patient-years for warfarin; HR=1.02; 95% CI, 0.62 to 1.7; p=0.94). However, LAA closure–treated patients had higher rates of ischemic stroke (1.6 events/100 patient-years vs 0.9 events/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/100 patient-years vs 0.96 events/100 patient-years; HR=0.22; 95% CI, 0.08 to 0.61; p=0.004).

**PROTECT-AF**

The first RCT published was the PROTECT AF study, which was a randomized, 6randomize trial that evaluated the noninferiority of an LAA closure device compared with 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 warfarin treatment in a 2:1 ratio. Mean follow-up was 18±10 months. The primary efficacy outcome was a composite end point of stroke (ischemic or hemorrhagic), cardiovascular or unexplained death, or systemic embolism. There was also a primary safety outcome, a composite end point of excessive bleeding (intracranial or gastrointestinal [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 LAA closure group compared with 4.9 per 100 patient years in the warfarin group (rate ratio [RR], 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. In
contrast, ischemic stroke was higher in the LAA closure group at 2.2 per 100 patient years compared with 1.6 per 100 patient years in the warfarin group (RR=1.34; 95% CI, 0.60 to 4.29).

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

Longer term follow-up from the PROTECT AF study 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 of greater than 99%. Complications were more common in the Watchman group, with an estimated rate of 5.6%/year in the Watchman group compared with 3.6%/year in the warfarin group. Outcomes through 4 years of follow-up were reported by Reddy et al in 2014.18 Mean follow-up was 3.9 years in the LAA closure group and 3.7 years in the warfarin group. In the LAA closure group, warfarin was discontinued in 345 of 370 patients (93.2%) by the 12 month follow-up evaluation. During the follow-up period, the relative risk for the composite primary outcome in the Watchman group compared with anticoagulation was 0.60 (8.4% in the device group vs 13.9% in the anticoagulation group; 95% CI, 0.41 to 1.05), which met the noninferiority criteria with a confidence of greater than 99.9%. Fewer hemorrhagic strokes occurred in the Watchman group (0.6% vs 4.0%; RR=0.15; 95% CI, 0.03 to 0.49), and fewer cardiovascular events occurred in the Watchman group (3.7% vs 0.95%; RR=0.40; 95% CI, 0.23 to 0.82). Rates of ischemic stroke did not differ significantly between groups, but Watchman group patients had lower all-cause mortality than anticoagulation group patients (12.3% vs 18.0%; HR=0.66; 95% CI, 0.45 to 0.98; p=0.04).

Alli et al reported quality-of-life parameters, as measured by change in scores on the Short-Form 12-Item Health Survey from baseline to 12-month follow-up, for a subset of 547 subjects in the PROTECT AF study. For the subset of PROTECT AF subjects included in the present analysis, at baseline, control group subjects had a higher mean CHADS2 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**

A second RCT, the PREVAIL trial, was conducted after the 2009 FDA decision on the Watchman device to address some of the limitations of the PROTECT AF study, including its inclusion of patients with low stroke risk (CHADS2 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 either the Watchman™ device or control, which consisted of either initiation or continuation of warfarin therapy with a target international normalized ratio (INR) of 2.0 to 3.0. Subjects had nonvalvular AF and required treatment for prevention of thromboembolism based on a CHADS2 score of 2 or higher (or ≥1 with other indications for warfarin therapy based on American College of Cardiology/American Heart Association/European Society of Cardiology 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 postdevice implantation and with 325 mg aspirin 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 study. 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).

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

**Noncomparative Studies**

In addition to these RCTs, a number of case series have reported on outcomes for the Watchman device. A number of small published case series are primarily intended to establish safety and feasibility of the device. A larger case series of 143 patients from Europe was published in 2011.15 This series reported successful implantation in 96% (137/143) of patients and serious complications in 7.0% (10/143). Complications included stroke (n=3), device embolization (n=2), and pericardial effusion (n=5). Another larger series was reported by Reddy et al,16 primarily focusing on the adverse event rate from a registry of 460 patients who received the Watchman device. Serious pericardial effusion occurred in 2.2% of patients, and there were no deaths or periprocedural strokes reported. Matsuo et al reported results from a case series of 179 patients who underwent
LAA closure at a single center, most (n=172) of whom received a Watchman device.18 Device deployment was successful in 98.9% of patients. The overall complication rate was 11.2%; major complications occurred in 3.3% (tamponade in 2 cases; possible transient ischemic attack [TIA] in 1 case; device dislocation in 3 cases). At 45-day follow-up, 99.4% of patients (164/166) had closure of the LAA.

**Section Summary: Watchman Device in Patients Eligible for Anticoagulation**

The most relevant evidence related to the use of the Watchman device for LAA closure in patients who are eligible for anticoagulation is from 2 industry-sponsored RCTs and a patient-level meta-analysis of those studies. These studies suggest that the Watchman is associated with an increased periprocedural ischemic stroke risk, which is balanced against a decreased hemorrhagic stroke risk.

**Patients with Contraindications to Anticoagulation**

The PROTECT AF and PREVAIL studies included only patients who were candidates for oral anticoagulation therapy based on stroke risk and were able to receive oral anticoagulation. As such, uncertainty remains about the role of the Watchman device in patients with AF who have absolute contraindications to oral anticoagulants. Reddy et al conducted a multicenter, prospective, nonrandomized trial to evaluate the safety and efficacy of LAA closure with the Watchman device in patients with nonvalvular AF with a CHADS2 score 1 or higher who were considered ineligible for warfarin. Postimplantation, patients received 6 months of clopidogrel or ticagrelor and lifelong aspirin therapy. Thirteen patients (8.7%) had a procedure- or device-related serious adverse event, most commonly pericardial effusion (3 patients). Over a mean 14.4 months of follow-up, all-cause stroke or systemic embolism occurred in 4 patients.

Chun et al compared the Watchman device with the Amplatzer cardiac plug among patients with nonvalvular AF, who were at high risk for stroke and had a contraindication to or were not willing 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. A follow-up transesophageal echocardiogram was performed at 6 weeks postprocedure; if a device-related thrombus had formed, patients received intensive antithrombotic therapy for 6 weeks. Aspirin was continued indefinitely for all patients. The primary end point of successful device implantation occurred in 98% of patients. There were no statistically significant differences in procedure time, fluoroscopy time, or major safety events between the 2 groups. At a median 364 days of follow-up, there were no cases of stroke/TIA or other bleeding complications.

**Lariat Device**

The available evidence on the efficacy of the Lariat device for LAA closure consists of a number of small case series. The largest case series was reported by Price et al in 2014 in retrospective multicenter study of early outcomes after use of the Lariat device. This study included 154 patients with a median CHADS2 score of 3. Device success, defined as suture deployment and a residual shunt less than 5 mm, was achieved in 94% of patients. Procedural success, defined as device success and no major complication (death, MI, stroke, major bleeding, or emergency surgery) at hospital discharge, was achieved in 86% of patients. Fifteen patients (10%) had at least 1 major
periprocedural complication, and 10% had significant pericardial effusion. Of the 134 patients (87%) who had out-of-hospital outcome data available, the composite out-of-hospital outcome of death, MI, or stroke occurred in 4 patients (2.9%).

In 2013, Bartus et al reported results of a case series that enrolled 89 patients with AF and either a contraindication to warfarin or previous warfarin failure. A total of 85 of 89 (96%) had successful left atrial ligation, and 81 of 89 (91%) had complete closure immediately. There were 3 access-related complications, 2 cases of severe pericarditis postoperatively, 1 late pericardial effusion, and 2 cases of unexplained sudden death. There were 2 late strokes, which the authors did not attribute to an embolic source. At 1-year follow-up, complete closure was documented by echocardiography in 98% of available patients (n=65). In a smaller, earlier series from the same research group, 13 patients were treated with the Lariat device, 11 of whom were treated as part of percutaneous radiofrequency ablation for AF. One of the 11 procedures was terminated due to unsuccessful placement, and the other 10 procedures were successful, with complete closure verified on echocardiography. There was 1 procedural complication in which the snare could not be removed and were retrieved by thoracoscopy.

In 2015, Stone et al reported outcomes for 27 patients with AF, a high stroke risk (CHADS2 score ≥2), and contraindications or intolerance to anticoagulation who underwent percutaneous LAA ligation with the Lariat device. Acute procedural success was 92.6%; periprocedural complications included 3 cases of pericarditis and 1 periprocedural stroke associated with no long-term disability. A follow-up transesophageal echo was performed in 22 patients at an average of 45 days postprocedure, which demonstrated successful LAA exclusion in all 22. Follow-up was for an average of 4 months, during which time 1 stroke and no deaths occurred.

Massumi et al reported on 21 patients with AF and contraindications to anticoagulation. Twenty of 21 patients had successful atrial closure, which was documented by echocardiography to be intact at a mean follow-up of 96 days. No patients had a stroke during a mean follow-up of approximately 1 year. Complications were reported in 5 of 21 patients. One patient had right ventricular perforation and tamponade requiring surgical intervention. One patient developed pleuropericarditis that required multiple drainage procedures. Three additional patients developed pericarditis within 30 days of the procedure.

**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, which included 152 patients from a single institution in Europe. Short-term complications occurred in 9.8% (15/152). 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 series of patients treated with the Amplatzer device include a series of 90 patients from Belgium, 86 patients from Portugal, 37 patients from Italy, 35 patients from Spain, 21 patients from Poland, and 20 patients from China. All series reported high procedural success, as well as various complications such as vascular complications, air embolism, esophageal injury, cardiac tamponade, and device embolization.
Several studies have reported the use of the Amplatzer device in patients with a contraindication to oral anticoagulation therapy. The largest study 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. Postprocedural antithrombotic therapy was tailored to the patient’s individual risk profile, but the authors described that, generally, short-term dual antiplatelet therapy (1-2 months) and subsequent indefinite single antiplatelet therapy were prescribed after successful device implantation. 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.

Meerkin et al reported outcomes for 100 patients with AF, a CHADS2 score of 2 or higher, and a contraindication to oral warfarin who were treated with the Amplatzer device at a single institution. All patients were treated with heparin during the procedure; they were maintained on clopidogrel for 1 month postprocedure and daily aspirin indefinitely. Successful deployment occurred in all patients. There were 2 significant periprocedural complications, including 1 pericardial effusion with tamponade and 1 case of acute respiratory distress with pulmonary edema.

Wiebe et al reported results of a retrospective cohort of 60 patients with nonvalvular AF who had a CHADS2-VASc score of at least 1 and contraindications to warfarin anticoagulation who underwent percutaneous LAA closure with the Amplatzer device. Contraindications to warfarin included contraindications as defined in the warfarin product label, a history of severe bleeding while receiving anticoagulant therapy, as well as a history of bleeding tendencies in the absence of anticoagulation or blood dyscrasia, along with patients who were unable to maintain a stable INR and those with a known hypersensitivity to warfarin or a high-risk of falling who were also included. Patients received heparin during the closure procedure; they were maintained on clopidogrel for 3 months postprocedure and daily aspirin indefinitely. Device implantation was successful in 95% of patients. Over a median follow-up of 1.8 years, no patients experienced a stroke. The rate of major bleeding complications was 1.9%/year of follow-up.

Urena et al reported results from a similar cohort of 52 patients with nonvalvular AF who had a CHADS2-VASc score of at least 2 and contraindication to oral anticoagulation therapy who underwent percutaneous LAA closure with the Amplatzer device. Device implantation was successful in all but 1 patient. There were no periprocedural strokes or death. Over the follow-up period (mean, 20 months), rates of death, stroke, and systemic embolism were 5.8 (3/52), 1.9% (1/52), and 0%, respectively.

Other smaller case series of patients with contraindication to oral anticoagulation include studies by Danna et al, which included 37 patients and reported a 1-year stroke rate of 2.94%, and Horstmann et al, which included 20 patients and reported no episodes of strokes over a mean follow-up of 13.6 months.
Gloekler et al compared outcomes for nonvalvular AF patients treated with the first-generation Amplatzer cardiac plug (n=50) and those treated with the second-generation Amulet device (n=50) in a retrospective analysis of prospectively collected data. There were no significant differences between devices in terms of safety outcomes.

**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 reported on 180 patients with nonrheumatic AF and a contraindication to warfarin and who were treated with the Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO) device. Placement was successful in 90% of patients. Two patients died within 24 hours of the procedure (1.1%), and 6 patients had cardiac tamponade (3.3%), with 2 requiring surgical drainage. Other case reports and small case series report complications, including multiple reports of thrombus formation at the site of device placement.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this policy are listed in Table 1.

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<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>Unpublished</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01363895</td>
<td>Interventional Strategies in Treatment of Atrial Fibrillation: Percutaneous Closure of the Left Atrial Appendage Versus Catheter Ablation</td>
<td>120</td>
<td>Nov 2013</td>
</tr>
<tr>
<td>NCT01628068</td>
<td>Efficacy of Left Atrial Appendage Closure After Gastrointestinal Bleeding</td>
<td>120</td>
<td>Jul 2014</td>
</tr>
<tr>
<td>NCT01118299</td>
<td>AMPLATZER Cardiac Plug Clinical Trial</td>
<td>3000</td>
<td>Not approved/cleared</td>
</tr>
</tbody>
</table>

**Summary of Evidence**

The evidence for the use of the Watchman device for stroke prevention in patients with atrial fibrillation (AF) who are candidates for oral anticoagulation includes 2 randomized controlled trials (RCTs) and a patient-level meta-analysis 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 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. A patient-level meta-analysis of the 2 trials suggested that the Watchman is associated with a periprocedural risk of ischemic stroke but a lower risk of hemorrhagic stroke over the long term. The published evidence is sufficient to determine that the Watchman device is efficacious in preventing stroke for patients with AF who are eligible to receive systemic anticoagulation. 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.

The evidence for the use of left atrial appendage (LAA) closure devices other than the Watchman (eg, the Lariat, PLAATO, and Amplatzer devices) for stroke prevention in patients with AF includes uncontrolled case series. Relevant outcomes are overall survival, morbid events, and treatment-related morbidity. Case series of these devices report high procedural success but also numerous complications. In addition, these devices do not have the U.S. Food and Drug Administration (FDA) approval for LAA closure. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Clinical Input Received From Physician Specialty Societies and Academic Medical Centers

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

2015 Input

In response to requests, input was received from 1 physician specialty society (2 responses) and 4 academic medical centers, one of which provided 4 responses, for a total of 8 responses, while this policy was under review in 2015. The input generally supported the use of an FDA-approved LAA closure device for patients with an increased risk of stroke and systemic embolism based on CHADS2 or CHA2DS2-VASc score and systemic anticoagulation therapy is recommended but the long-term risks of systemic anticoagulation outweigh the risks of the device implantation.

Practice Guidelines and Position Statements

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 LAA closure devices into the clinical practice of patients with AF. The overview was organized around questions related to the sites of care delivery for LAA closure devices, training for proceduralists, necessary follow-up data collection, identification of appropriate patient cohorts, and reimbursement. The statement provides general guidelines for facility and operator
requirements, including the presence of a multidisciplinary heart team, for centers performing percutaneous LAA closures. The statement does not provide specific recommendations about the indications and patient populations appropriate for percutaneous LAA closure.

American College of Cardiology, American Heart Association, et al

In 2014, the ACC, American Heart Association, and HRS issued guidelines on the management of patients with AF. These guidelines recommend that surgical excision of the LAA may be considered in patients undergoing cardiac surgery (class IIB recommendation; level of evidence: C), but make no specific recommendations regarding percutaneous LAA closure.

American College of Chest Physicians

In 2012, the American College of Chest Physicians published evidence-based clinical best practice guidelines on the use of antithrombotic therapy for prevention of stroke in AF. In relation to the use of LAA closure devices, the guidelines state: “At this time, we make no formal recommendations regarding LAA closure devices, pending more definitive research in this field.”

VII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §43E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VIII. References


5. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Percutaneous left atrial appendage closure therapy for prevention of stroke. TEC Assessments 2014; 29; Tab 5.


IX. Appendix

Table 1. CHADS2

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Prior stroke or TIA or thromboembolism</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 2. CHA2DS2-VASc

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure (or Left ventricular systolic dysfunction)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Hypertension</strong>: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Prior <strong>Stroke</strong> or <strong>TIA</strong> or thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td>Age 65–74 years</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (i.e. female sex)</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 3. HAS-BLED Bleeding Risk Score

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal renal and liver function (1 point each)</td>
<td>1 or 2</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td>1</td>
</tr>
<tr>
<td>Labile INRs</td>
<td>1</td>
</tr>
<tr>
<td>Elderly (&gt;65)</td>
<td>1</td>
</tr>
<tr>
<td>Drugs or alcohol (1 point each)</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

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