

## Medical Policy



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

- Related Policies:*
- *Catheter Ablation as Treatment for Atrial Fibrillation*
  - *Open and Thoracoscopic Approaches to Treat Atrial Fibrillation and Atrial Flutter (Maze and Related Procedures)*

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

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> <li>• With atrial fibrillation who are at increased risk for embolic stroke</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Percutaneous left atrial appendage closure device other than the Watchman device</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Anticoagulation</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Morbid events</li> <li>• Treatment-related morbidity</li> </ul>

**DESCRIPTION**

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

**OBJECTIVE**

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

**BACKGROUND**

**Atrial Fibrillation and Stroke**

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

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

**TREATMENT**

**Pharmacologic**

The main treatment for stroke prevention in AF is anticoagulation, which has proven efficacy. The risk for stroke among patients with AF is evaluated using several factors. Two commonly used scores, the CHADS<sub>2</sub> score and the CHA<sub>2</sub>DS<sub>2</sub>-VASc score are described below in Table 1. Warfarin is the predominant agent in clinical use. A number of newer anticoagulant medications, including dabigatran, rivaroxaban apixaban, and edoxaban have received U.S. Food and Drug Administration (FDA) approval for stroke prevention in nonvalvular AF and have demonstrated noninferiority to warfarin in clinical trials. While anticoagulation is effective for stroke prevention, it carries an increased risk of bleeding. Also, warfarin requires frequent monitoring and adjustments as well as lifestyle changes. Newer agents do not require the frequent monitoring seen with warfarin therapy; however, specific reversal agents do not exist for all of these agents. The 2018 American College of Chest Physicians guidelines (updated from 2012) recommend that

CHA<sub>2</sub>DS<sub>2</sub>VASc be used to evaluate stroke risk, and patients initially identified as having a low stroke risk should not be given antithrombotic therapy. In addition, they recommend bleeding risk assessments be given to every patient at every patient contact and that “potentially modifiable bleeding risk factors” should be the initial focus.

**Table 1. CHA DS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc Scores to Predict Ischemic Stroke Risk in Patients With Atrial Fibrillation**

Letter	Clinical Characteristics	Points Awarded
C	Congestive heart failure (signs/symptoms of heart failure confirmed with objective evidence of cardiac dysfunction)	1
H	Hypertension (resting blood pressure >140/90 mmHg on at least 2 occasions or current antihypertensive pharmacologic treatment)	1
A	Age ≥75 y	1 (CHADS <sub>2</sub> ) 2 (CHA <sub>2</sub> DS <sub>2</sub> -VASc)
D	Diabetes (fasting glucose >125 mg/dL or treatment with oral hypoglycemic agent and/or insulin)	1
S	Stroke or transient ischemic attack (includes any history of cerebral ischemia)	2
V	Vascular disease (prior myocardial infarction, peripheral arterial disease, or aortic plaque)	1
A	Age 65-74 y	1
Sc	Sex category of female (female sex confers higher risk)	1

Adapted from Lip et al (2018)<sup>3</sup>, and January et al (2014).<sup>2</sup>

Bleeding is the primary risk associated with systemic anticoagulation. Risk scores have been developed to estimate the risk of significant bleeding in patients treated with systemic anticoagulation, such as the HAS-BLED score, which has been validated to assess the annual risk of significant bleeding in patients with AF treated with warfarin.<sup>4</sup> The score ranges from 0 to 9, based on clinical characteristics, including the presence of hypertension, renal and liver function, history of stroke, bleeding, labile international normalized ratios, age, and drug/alcohol use. Scores of 3 or greater are considered to be associated with a high risk of bleeding, potentially signaling the need for closer monitoring of patients for adverse risks, closer monitoring of international normalized ratios, or differential dose selections of oral anticoagulants or aspirin.<sup>2</sup>

### **Surgery**

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

Several versions of LAA occlusion devices have been developed. The PLAATO system (ev3 Endovascular) was the first device to be approved by the FDA for LAA occlusion. The device was discontinued in 2007 for commercial reasons, and intellectual property was sold to manufacturers

of the Watchman system. The Watchman Left Atrial Appendage System (Boston Scientific) is a self-expanding nickel titanium device. It has a polyester covering and fixation barbs for attachment to the endocardium. Implantation is performed percutaneously through a catheter delivery system, using venous access and transseptal puncture to enter the left atrium. Transesophageal echocardiography and fluoroscopy are used to guide the procedure. Following implantation, patients receive anticoagulation with warfarin or alternative agents for approximately 1 to 2 months. After this period, patients are maintained on antiplatelet agents (i.e., aspirin and/or clopidogrel) indefinitely. The Watchman FLX device is a next-generation Watchman device that is also FDA-approved for LAAC. This device is based on the design of the Watchman device, is fully recapturable and repositionable, and was made to occlude a wider size range of LAA than the original Watchman device.<sup>5</sup> The Amplatzer cardiac plug (St. Jude Medical), is FDA-approved for closure of atrial septal defects but not for LAAC. A second-generation device, the Amplatzer Amulet, has been developed for the specific indication of LAAC but currently does not have FDA approval. The Amplatzer Amulet consists of a nitinol mesh disc to seal the ostium of the LAA and a nitinol mesh distal lobe, to be positioned within the LAA. The device is preloaded within a delivery sheath. The Percutaneous LAA Transcatheter Occlusion device (ev3) has also been evaluated in research studies but has not received the FDA approval. The Occlutech® (Occlutech) Left Atrial Appendage Occluder has received a CE mark for coverage in Europe. The Cardioblade® closure device (Medtronic) is currently being tested in clinical studies.

The Lariat Loop Applicator is a suture delivery device approved by the FDA, intended to close a variety of surgical wounds. It is not specifically approved for LAAC. While the Watchman and other devices are implanted in the endocardium, the Lariat is a non-implant epicardial device.

### **Outcome Measures**

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

Although the Watchman device and other LAAC devices would ideally represent an alternative to oral anticoagulation for the prevention of stroke in patients with AF, during the post-implantation period, the device may be associated with increased thrombogenicity, therefore, anticoagulation is used during the periprocedural period. Most studies evaluating the Watchman device have included patients who are eligible for anticoagulation.

### **REGULATORY STATUS**

In 2002, the PLAATO system (ev3 Endovascular) was the first device to be approved by the FDA for LAA occlusion. The device was discontinued in 2007 for commercial reasons, and intellectual property was sold to manufacturers of the Watchman system.

In 2015, the Watchman™ Left Atrial Appendage Closure Technology (Boston Scientific) was approved by the FDA through the premarket approval process by the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients with Atrial Fibrillation randomized controlled trial.<sup>6</sup>In 2020, the Watchman FLX device (Boston Scientific) was approved by the FDA

based on the single-arm, nonrandomized PINNACLE FLX study.<sup>5</sup> These devices are indicated to reduce the risk of thromboembolism from the LAA in patients with nonvalvular AF who:

- Are at increased risk for stroke and systemic embolism based on CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>-VASc scores and are recommended for anticoagulation therapy;
- Are deemed by their physicians to be suitable for anticoagulation therapy ; and
- Have an appropriate rationale to seek a nonpharmacologic alternative to anticoagulation therapy , taking into account the safety and effectiveness of the device compared to anticoagulation therapy.

FDA product code: NGV.

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

**POLICY**

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

1. There is an increased risk of stroke and systemic embolism based on CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>-VASc score and systemic anticoagulation therapy is recommended

Guidelines from the American College of Chest Physicians recommend the use of oral anticoagulation for patients with AF who are at high risk of stroke (ie, CHADS<sub>2</sub> score ≥2), with more individualized choice of antithrombotic therapy in patients with lower stroke risk.<sup>1</sup>

**Table P1. CHADS<sub>2</sub> and CHADS<sub>2</sub>-VASc Scores to Predict Ischemic Stroke Risk in Patients With Atrial Fibrillation**

Letter	Clinical Characteristics	Points Awarded
C	Congestive heart failure (signs/symptoms of heart failure confirmed with objective evidence of cardiac dysfunction)	1
H	Hypertension (resting blood pressure >140/90 mmHg on at least 2 occasions or current antihypertensive pharmacologic treatment)	1
A	Age ≥75 y	1 (CHADS <sub>2</sub> ) 2 (CHA <sub>2</sub> DS <sub>2</sub> -VASc)
D	Diabetes (fasting glucose >125 mg/dL or treatment with oral hypoglycemic agent and/or insulin)	1
S	Stroke or transient ischemic attack (includes any history of cerebral ischemia)	2
V	Vascular disease (prior myocardial infarction, peripheral arterial disease, or aortic plaque)	1
A	Age 65-74 y	1
Sc	Sex category of female (female sex confers higher risk)	1

Adapted from You et al (2012)<sup>1</sup> and January et al (2014).<sup>2</sup>

**AND**

2. 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 (Pisters et al, 2010). The score ranges from 0 to 9, based on a number of clinical characteristics (see Table P2).

**Table P2. Clinical Components of the HAS-BLED Bleeding Risk Score**

Letter	Clinical Characteristics	Points Awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile international normalized ratios	1
E	Elderly (>65 y)	1
D	Drugs or alcohol (1 point each)	1 or 2

Adapted from Pisters et al (2010)<sup>1</sup>.

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

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.

- B. The use of a device with FDA approval for percutaneous left atrial appendage closure (eg, the Watchman) for stroke prevention in patients who do not meet the above criteria is considered **experimental / investigational**.
- C. The use of other percutaneous left atrial appendage closure devices, including, but not limited, to the Lariat and Amplatzer devices, for stroke prevention in patients with atrial fibrillation is considered **experimental / investigational**.

### Policy Guidelines

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

### RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through March 18, 2021.

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant,

studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

The evidence on the efficacy of left atrial appendage closure (LAAC) devices consists of numerous observational studies of various occlusion devices, and 2 published RCTs of the Watchman device, the Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation (PROTECT AF) and Prospective Randomized Evaluation of the Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy (PREVAIL) trials, 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 unique considerations.

## **WATCHMAN DEVICE**

### **Clinical Context and Therapy Purpose**

The purpose of the Watchman device in patients who have atrial fibrillation (AF) and are at increased risk for embolic stroke is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of the Watchman device improve the net health outcome compared with systemic anticoagulation treatment in patients with AF who are at increased risk for embolic stroke?

The following PICO was used to select literature to inform this review.

### ***Populations***

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

### ***Interventions***

The therapy being considered is use of the Watchman percutaneous LAAC device and the Watchman FLX device (a next generation device based on the design of the original Watchman device).<sup>5</sup> The devices are made of nickel titanium and are implanted percutaneously through a catheter, into the left atrium. The Watchman devices come in 5 sizes and self-expand to occlude the LAA. By occluding the LAA, thrombus formation is prevented, potentially preventing stroke. Following implantation of the device, the patient receives anticoagulation for 1 to 2 months. Once it is established that there is no peridevice leak or thrombus development, the patient is then placed on antiplatelet agents indefinitely.



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

### **Comparators**

The current treatment for stroke prevention in patients with AF is systemic anticoagulation. While anticoagulants are effective in preventing stroke, the increased risk of bleeding is a potential harm. Warfarin, which is the most common anticoagulant in use, requires frequent monitoring and lifestyle changes. Other anticoagulants found to be noninferior to warfarin include dabigatran, rivaroxaban apixaban, and edoxaban.

Patients with AF are actively managed by a cardiologist.

### **Outcomes**

The general outcomes of interest are rates of ischemic or hemorrhagic stroke, cardiovascular or unexplained death, and systemic embolism, measured between 6 to 12 months of follow-up, although some studies show follow-up of up to 5 years.<sup>7</sup> Additional outcomes of interest include device- or procedure-related events that may occur within 1 week of the procedure. In particular, events requiring open cardiac surgery or major endovascular intervention (e.g., pseudoaneurysm repair, arteriovenous fistula repair, or other major endovascular repair) should be noted.

### **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess longer term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

## **REVIEW OF EVIDENCE**

### **Systematic Reviews**

A TEC Assessment (2014) evaluated the use of the Watchman device for patients eligible and ineligible for anticoagulation therapy.<sup>8</sup> The Assessment determined that the device did not meet TEC criteria. The Assessment made the following conclusions about the use of LAAC in patients without contraindications to anticoagulation:

"We identified 2 randomized controlled trials [RCTs] and 1 case series evaluating the Watchman™ device. The RCTs were noninferiority trials and compared LAAC with anticoagulation. The first trial showed a lower rate of a composite outcome (stroke, death, and embolism) in patients receiving LAAC and met noninferiority criteria compared with anticoagulation, but FDA [Food and Drug Administration] review noted problems with patient selection, potential confounding with other treatments, and losses to follow-up. The second trial, which incorporated the first trial's results as a discounted informative prior in a Bayesian analysis, showed similar rates of the same composite outcome but did not meet noninferiority criteria. The second trial met its second principal outcome noninferiority criteria in 1 of 2 analyses and a performance goal for short-term complication rate. When assessing the results of both trials, the relative performance of LAAC and anticoagulation is uncertain."

A number of systematic reviews published after the TEC Assessment have combined the results of the available RCTs.<sup>9,10,11,12,13,14,15,16</sup> Others have included RCTs and observational studies.<sup>12,17,18</sup>

Holmes et al (2015) published the most rigorous meta-analysis.<sup>11</sup> This analysis included patient-level data from the industry-sponsored PROTECT AF and PREVAIL trials (described below), together with both studies' continued access registries. The PROTECT AF and PREVAIL registries were designed to include patients with similar baseline characteristics as their respective RCTs. The meta-analysis included 2406 patients, 1877 treated with the Watchman device and 382 treated with warfarin alone. Mean patient follow-up durations were 0.58 years and 3.7 years, respectively, for the PREVAIL continued access registry, and the PROTECT AF continued access registry. In a meta-analysis of 1114 patients treated in the RCTs, compared with warfarin, LAAC met the trial's noninferiority criteria for the primary composite efficacy endpoint of all-cause stroke, systemic embolization, and cardiovascular death (hazard ratio [HR], 0.79, 95% confidence interval [CI], 0.52 to 1.2;  $p=.22$ ). All-cause stroke rates did not differ significantly between groups (1.75 per 100 patient-years for LAAC vs 1.87 per 100 patient-years for warfarin; HR, 1.02; 95% CI, 0.62 to 1.7;  $p=.94$ ). LAAC-treated patients had higher rates of ischemic stroke (1.6 events per 100 patient-years vs. 0.9 events per 100 patient-years; HR, 1.95,  $p=.05$ ) when procedure-related strokes were included but had lower rates of hemorrhagic stroke (0.15 events per 100 patient-years vs 0.96 events per 100 patient-years; HR, 0.22; 95% CI, 0.08 to 0.61;  $p=.004$ ).

Price et al (2015) reported on a second patient-level meta-analysis of the 2 RCTs that focused on bleeding outcomes.<sup>14</sup> There were 54 episodes of major bleeding, with the most common types being gastrointestinal bleed (31/54 [57%]) and hemorrhagic stroke (9/54 [17%]). On combined analysis, the rate of major bleeding episodes over the entire study period did not differ between groups. There were 3.5 events per 100 patient-years in the Watchman group compared with 3.6 events per 100 patient-years in the anticoagulation group, for a rate ratio of 0.96 (95% CI, 0.66 to 1.40;  $p=.84$ ). However, there was a reduction in bleeding risk for the Watchman group past the initial periprocedural period. For bleeding events occurring more than 7 days post procedure, the event rates were 1.8 per 100 patient-years in the Watchman group compared with 3.6 per 100 patient-years in the anticoagulation group (rate ratio, 0.49; 95% CI, 0.32 to 0.75;  $p=.01$ ). For bleeding events occurring more than 6 months post procedure (the time at which antiplatelet therapy is discontinued for patients receiving the Watchman device), the event rates were 1.0 per 100 patient-years in the Watchman group compared with 3.5 per 100 patient-years in the anticoagulation group (rate ratio, 0.28; 95% CI, 0.16 to 0.49;  $p<.001$ ).

Additional systematic reviews have used network meta-analyses to compare vitamin K antagonists with the Watchman device and with novel oral anticoagulants (6 RCTs,  $N=59,627$  subjects),<sup>19</sup> and have compared percutaneous LAA occlusion (5 RCTs,  $N=1285$  subject) with standard anticoagulant or antiplatelet therapy with device-based surgical or percutaneous LAA exclusion.<sup>20</sup> Bajaj et al (2016) published a network meta-analysis comparing vitamin K antagonists with novel oral anticoagulants and with the Watchman device.<sup>19</sup> They reported that all the treatment strategies had comparable ischemic stroke rates. However, the cluster analyses showed the novel oral anticoagulants ranked best in safety and efficacy, followed by vitamin K antagonists, and then the Watchman device. Interpretation of these results is limited by the small sample sizes and population heterogeneity in the RCTs comparing the Watchman with vitamin K antagonists. The network meta-analysis comparing LAAC with oral anticoagulants, antiplatelets,

and placebo, reported a trend in stroke and mortality favoring LAAC, but the differences were not statistically significant.<sup>20</sup> The authors noted that overall quality of the evidence was low.

Baman et al (2018) conducted a systematic review of LAAC devices, including Watchman, Amplatzer cardiac plug, Amplatzer Amulet, and Lariat devices.<sup>21</sup> The literature search, conducted through April 2017, identified 2 RCTs and 15 registry studies. No meta-analyses were conducted. The authors concluded that the Watchman may be noninferior to warfarin and that long-term efficacy outcomes are promising. For the remaining devices included in the review, the authors note that high-quality prospective studies comparing the devices to each other and with anticoagulants are needed.

## **RANDOMIZED CONTROLLED TRIALS**

### **PROTECT AF Trial**

The first RCT published was PROTECT AF, an unblinded randomized trial evaluating the noninferiority of an LAAC device compared with warfarin for stroke prevention in AF.<sup>22</sup> The trial randomized 707 patients from 59 centers in the U.S. and Europe to the Watchman device or warfarin treatment in a 2:1 ratio. Mean follow-up was 18 months. The primary efficacy outcome was a composite endpoint of stroke (ischemic or hemorrhagic), cardiovascular or unexplained death, or systemic embolism. There was also a primary safety outcome, a composite endpoint of excessive bleeding (intracranial or gastrointestinal bleeding) and procedure-related complications (pericardial effusion, device embolization, procedure-related stroke).

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

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

Reddy et al (2013) reported on longer-term follow-up from the PROTECT AF trial.<sup>23</sup> At a mean follow-up of 2.3 years, the results were similar to the initial report. The relative risk for the composite primary outcome in the Watchman group compared with anticoagulation was 0.71, and this met noninferiority criteria with a confidence greater than 99%. Complications were more common in the Watchman group, with an estimated rate of 5.6% per year, compared with 3.6% per year in the warfarin group.

Reddy et al (2014) also reported outcomes through 4 years of follow-up.<sup>24</sup> Mean follow-up was 3.9 years in the LAAC group and 3.7 years in the warfarin group. In the LAAC group, warfarin was discontinued in 345 (93.2%) of 370 patients by the 12-month follow-up evaluation. During the follow-up period, the relative risk for the composite primary outcome in the Watchman group

compared with anticoagulation was 0.60 (8.4% in the device group vs 13.9% in the anticoagulation group; 95% CrI, 0.41 to 1.05), which met the noninferiority criteria with a confidence greater than 99.9%. Fewer hemorrhagic strokes (0.6% vs 4.0%; rate ratio, 0.15; 95% CrI, 0.03 to 0.49) and fewer cardiovascular events (3.7% vs 0.95%; rate ratio, 0.40; 95% CrI, 0.23 to 0.82) occurred in the Watchman group. Rates of ischemic stroke did not differ significantly between groups, but Watchman patients had lower all-cause mortality rates than anticoagulation patients (12.3% vs 18.0%; HR, 0.66; 95% CI, 0.45 to 0.98;  $p=.04$ ).

Alli et al (2013) reported on quality-of-life parameters, as measured by change in the 12-Item Short-Form Health Survey scores from baseline to 12-month follow-up, for a subset of 547 subjects in the PROTECT AF trial.<sup>25</sup> For the subset of PROTECT AF subjects included in the Alli et al (2013) analysis, at baseline, control group subjects had a higher mean CHADS<sub>2</sub> score (2.4 vs 2.2;  $p=.052$ ) and were more likely to have a history of coronary artery disease (49.5% vs 39.6%;  $p=.028$ ). For subjects in the Watchman group, the 12-Item Short-Form Health Survey total physical score improved in 34.9% and was unchanged in 29.9%; for those in the warfarin group, the total physical score improved in 24.7% and was unchanged in 31.7% ( $p=.01$ ).

Reddy et al (2017) published 5-year follow-up results indicating that the LAAC group had significantly lower rates of the composite efficacy endpoint (stroke, systemic embolism, cardiovascular death) compared with the warfarin-only group ( $p=.04$ ).<sup>7</sup>

### **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<sub>2</sub> scores of 1), high rates of adjunctive antiplatelet therapy use in both groups, and generally poor compliance with warfarin therapy in the control group. Holmes et al (2014) published results from the PREVAIL trial.<sup>26</sup> 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  $\geq 1$  with other indications for warfarin therapy based on American College of Cardiology, American Heart Association, and European Society of Cardiology joint guidelines) and were eligible for warfarin therapy. In the device group, warfarin and low-dose aspirin were continued until 45 days post procedure; if a follow-up echocardiogram at 45 days showed occlusion of the LAA, warfarin therapy could be discontinued. Subjects who discontinued warfarin were treated with aspirin and clopidogrel for 6 months after device implantation and with aspirin 325 mg indefinitely after that.

Three noninferiority primary efficacy endpoints were specified: (1) occurrence of ischemic or hemorrhagic stroke, cardiovascular or unexplained death, and systemic embolism (18-month rates); (2) occurrence of late ischemic stroke and systemic embolization (beyond 7 days 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 (e.g., pseudoaneurysm repair, arteriovenous fistula repair, or other major endovascular repair) occurring within 7 days of the procedure or by hospital discharge, whichever was later. The 18-month event rates were determined using Bayesian statistical methods to integrate data from the PROTECT AF trial. All patients had a minimum

follow-up of 6 months. For randomized subjects, mean follow-up was 11.8 months, and median follow-up was 12.0 months (range, 0.03 to 25.9 months).

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

Reddy et al (2017), in their 5-year follow-up results, indicated that the Watchman device was noninferior to warfarin alone in the composite efficacy endpoint (stroke, systemic embolism, cardiovascular death) ( $p=.5$ ).<sup>7</sup>

Reddy et al (2017) , in addition to providing 5-year final results for the individual trials, also conducted a meta-analysis of the 5-year outcomes using data from both trials.<sup>7</sup> Meta-analytic results are summarized in Table 2, showing that the Watchman device is noninferior to warfarin alone in stroke prevention among patients with nonvalvular AF. Also, patients treated with the Watchman device experienced significantly lower bleeding and mortality compared with patients receiving warfarin.

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

<b>Outcomes</b>	<b>Watchman, n (Rate per 100 PY), %</b>	<b>Warfarin Alone, n (Rate per 100 PY), %</b>	<b>HR (95% CI)</b>	<b>p-value</b>
Composite stroke/SE/CV death	79 (2.8)	50 (3.4)	0.8 (0.6 to 1.2)	.3
All stroke or SE	49 (1.7)	27 (1.8)	1.0 (0.6 to 1.5)	.9
CV/unexplained death	39 (1.3)	33 (2.2)	0.6 (0.4 to 0.9)	.03
All cause death	106 (3.0)	73 (4.9)	0.7 (0.5 to 1.0)	.03
Major bleeding, all	85 (3.1)	50 (3.5)	0.9 (0.6 to 1.3)	.6
Major bleeding, non-LAAC-related	48 (1.7)	51 (3.6)	0.5 (0.3 to 0.7)	<.001

Adapted from Reddy et al (2017).<sup>7</sup>

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

### **PRAGUE-17 Trial**

Osmanic et al (2020) published the LAAC versus Novel Anticoagulation Agents in AF (PRAGUE-17) study, a multicenter, randomized, noninferiority study that compared use of LAAC to direct oral anticoagulants in high risk patients with nonvalvular AF.<sup>27</sup> Patients were included if they had a history of bleeding requiring intervention or hospitalization, history of cardioembolic event while taking an anticoagulant, or CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 3$  with a HAS-BLED score  $\geq 2$ . Patients either received LAAC (n=181) with either the Amulet or Watchman/Watchman FLX devices based on discretion of the implanting center, or a direct oral anticoagulant (rivaroxaban, apixaban, or dabigatran) (n=201).

The primary endpoint was a composite of ischemic or hemorrhagic stroke or transient ischemic attack (TIA), systemic embolism, clinically significant bleeding, cardiovascular death, or significant peri-procedural or device-related complications. At baseline, the mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score was 4.7 and HAS-BLED score was 3.1. Follow-up was 20.8 months. Of the LAAC group, 61.3% received an Amulet, 35.9% received a Watchman device, and 2.8% received a Watchman-FLX device. The primary endpoint occurred in 41 patients (47 events) in the direct oral anticoagulant group (13.42 event rate per year) compared to 35 patients (38 events) in the LAAC group (10.99 event rate per year) (subdistribution HR, 0.84; 95% CI, 0.53 to 1.21; p-value for noninferiority, p=.004). All stroke/TIA events occurred in 9 patients (9 events) in each group, subdistribution HR, 1.0 (95% CI, 0.40 to 2.51). Results were not divided by type of LAAC device received. Significant procedure- or device-related complications occurred in 9 patients in the LAAC group. Early complications ( $\leq 7$  days) included device embolization (n=1), procedure-related death (n=1), and vascular complications (n=2), while late complications ( $>7$  days) included pericardial effusion (n=2), device-related death (n=1), and other complications (n=2). The procedure-related death was due to a femoral vascular access bleed and myocardial infarction. The device-related death occurred with the Amulet device due to a pericardial effusion approximately 6 weeks after the procedure.

Chun et al (2013) compared the Watchman device with the Amplatzer cardiac plug among patients who had nonvalvular AF, were at high risk for stroke, and had a contraindication to or were unwilling to take oral anticoagulants.<sup>28</sup> 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, TIA, or other bleeding complications.

### **Nonrandomized Studies**

Numerous case series and nonrandomized studies of the Watchman have been published.<sup>29,30,31,32,33</sup> Several are notable in that they were conducted in patients not eligible for anticoagulation, a population not included in PROTECT AF and PREVAIL. Reddy et al (2013) conducted a multicenter, prospective, nonrandomized trial to evaluate the safety and efficacy of LAAC with the Watchman device in patients who had nonvalvular AF, with a CHADS<sub>2</sub> score 1 or higher, and were considered ineligible for warfarin.<sup>34</sup> Post implantation, patients received 6 months of clopidogrel or ticlopidine and lifelong aspirin therapy. Thirteen (8.7%) patients had a procedure- or device-related serious adverse event, most commonly pericardial effusion (3 patients). Over a mean follow-up of 14.4 months, all-cause stroke or systemic embolism occurred in 4 patients.

The EWOLUTION Watchman registry tracks procedural success, long-term outcomes, and adverse events in real-world settings. This registry compiles data from patients receiving the Watchman device at 47 centers in 13 countries. Boersma et al (2016) conducted an analysis of the EWOLUTION registry data reporting 30-day outcomes after device implantation in 1021 patients.<sup>35</sup> The overall population had a risk of bleeding that was substantially higher than that for patients in the RCTs. Over 62% of patients included in the registry were deemed ineligible for anticoagulation by their physicians. Approximately one-third of patients had a history of major bleeding, and 40% had HAS-BLED scores of 3 or greater, indicating moderate- to high-risk of bleeding. Procedural success was achieved in 98.5% of patients, and 99.3% of implants demonstrated no blood flow or minimal residual blood flow post procedure. Serious adverse events due to the device or procedure occurred at an overall rate of 2.8% (95% CI, 1.9% to 4.0%) at 7 days and 3.6% (95% CI, 2.5% to 4.9%) at 30 days. The most common serious adverse event was major bleeding.

Dukkipati et al (2018) studied the incidence, predictors, and clinical outcomes of device-related thrombus (DRT) among the following patients receiving the Watchman in the following trials and registries: PROTECT AF, PREVAIL, Continued Access to PROTECT AF registry, and Continued Access to PREVAIL registry.<sup>36</sup> Surveillance transesophageal electrocardiograms were conducted in all patients at 45 days and 12 months. Patients in the RCTs also received the electrocardiograms at 6 months. A total of 1739 patients were followed for a total of 7159 patient-years. Mean age of the population was 74 years and 34% were women. DRT was detected in 65 (3.7%) of the patients. Stroke or systemic embolism rates were 7.5 and 1.8 per 100 patient-years for patients with and without DRT, respectively. A multivariable modeling analysis found the following predictors of DRT: history of transient ischemic attack or stroke, permanent AF, vascular disease, LAA diameter, and left ventricular ejection fraction.

Jazayeri et al (2018) evaluated the safety profiles of the Watchman and the Lariat devices, using the FDA's Manufacturer and User Facility Device Experience (MAUDE) database from 2009 to 2016.<sup>37</sup> MAUDE consists of mandatory reports from manufacturers and voluntary reports from healthcare professionals and patients. Outcomes assessed included: a composite of stroke/TIA, pericardiocentesis, cardiac surgery, and death; DRT; cardiac surgery; and myocardial infarction. A total of 5849 Watchman devices were implanted, with 472 events reported during the study period. The most common events in patients receiving the Watchman, were device malfunction (97 [1.7%]), pericardial effusion (84 [1.4%]), need for pericardiocentesis (57 [0.97%]), and intracardiac thrombus (47 [0.84%]). Twenty deaths were reported in the Watchman group, with 1 likely related to DRT. Compared with the Lariat device, the composite outcome occurred significantly more in the group receiving the Watchman than within the group receiving the Lariat, 1.9% vs. 1.1%,  $p=.001$ ). Analysis results for the Lariat device will be discussed in the next section, "Other Closure Devices".

### **Section Summary: Watchman Device**

The most relevant evidence on the use of the Watchman device for LAAC in patients eligible for anticoagulation derives from 2 industry-sponsored RCTs comparing Watchman and systemic anticoagulants and a patient-level meta-analysis of those studies. After 5 years of follow-up, meta-analytic results showed that the ischemic stroke risk beyond 7 days did not differ between groups and that the hemorrhagic stroke risk remained significantly lower in the LAAC group. The results showed that the Watchman device is noninferior to warfarin alone in stroke prevention among patients with nonvalvular AF. Also, patients treated with the Watchman device

experienced significantly lower bleeding and mortality. A large study of patients receiving the Watchman device (combining patients from the 2 RCTs and 2 registries) reported that patients who developed DRT were 4 times more likely to experience a stroke or systemic embolism. The authors suggest a surveillance strategy for patients at high risk of DRT following Watchman implantation. One RCT found use of LAAC with either the Watchman device or Amplatzer Amulet device noninferior to direct oral anticoagulants for high-risk patients with AF; however, subgroup analyses by type of LAAC device were not performed, limiting interpretation.

## **OTHER CLOSURE DEVICES**

### **Clinical Context and Therapy Purpose**

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

The question addressed in this evidence review is: Does the use of other LAAC devices improve the net health outcome compared with systemic anticoagulation treatment in patients with AF who are at increased risk for embolic stroke?

The following PICO was used to select literature to inform this review.

### ***Populations***

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

### ***Interventions***

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

- The Lariat Loop Applicator is a suture delivery device approved by the FDA to facilitate suture placement and knot tying for use in surgical applications where soft tissues are being approximated or ligated with a pretied polyester suture. The approved use does not specify LAA occlusion. While the Watchman and other devices are implanted in the endocardium, the Lariat is a non-implant epicardial device. The Lariat is contraindicated in patients with active pericarditis; prior sternotomy or other mediastinal surgery or known pericardial adhesions; appendage width >45 mm; superiorly oriented appendage lying near or behind the pulmonary arterial trunk; or appendage thrombus.
- The Amplatzer Amulet device comes in 8 sizes to accommodate various patient anatomies. The mechanism of action is similar to the Watchman. Following implantation of the Amulet, patients are placed on antiplatelet agents and do not need warfarin. There is an ongoing trial comparing the Amplatzer Amulet with the Watchman (NCT03399851).

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



### **Comparators**

The current treatment for stroke prevention in patients with AF is systemic anticoagulation. While anticoagulants are effective in preventing stroke, the increased risk of bleeding is a potential harm. Warfarin, which is the most common anticoagulant in use, requires frequent monitoring and lifestyle changes. Other anticoagulants found to be noninferior to warfarin include dabigatran, rivaroxaban, apixaban, and edoxaban.

Patients with AF are actively managed by a cardiologist.

### **Outcomes**

The general outcomes of interest are rates of ischemic or hemorrhagic stroke, cardiovascular or unexplained death, and systemic embolism, measured between 6 to 12 months of follow-up, although some studies show follow-up of up to 5 years. Additional outcomes of interest include device- or procedure-related events that may occur within 1 week of the procedure, in particular, events requiring open cardiac surgery or major endovascular intervention (e.g., pseudoaneurysm repair, arteriovenous fistula repair, or other major endovascular repair).

### **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess longer term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

## **REVIEW OF EVIDENCE**

### **LARIAT DEVICE**

#### **Systematic Review**

Chatterjee et al (2015) published a systematic review of studies on the Lariat device.<sup>38</sup> No RCTs were identified. Five case series or observational studies were included, with a total of 309 patients (range, 4 to 154 patients).<sup>39,40,41,42,43</sup> The combined estimate of procedural success was 90.3%. One (0.3%) death was reported and 7 (2.3%) patients required urgent cardiac surgery. Reviewers also searched the MAUDE database for adverse events and found 35 unique reports. Among the 35 reported complications, there were 5 deaths and 23 cases of emergency cardiac surgery.

#### **Observational Studies**

Individual observational studies published since the systematic review included a large 2016 observational study of 712 consecutive patients from 18 U.S. hospitals.<sup>44</sup> This study reported a procedural (suture deployment) success rate of 95% and complete closure rate in 98%. The high success rate was attributed to the appropriate selection of patients for the procedure, which was determined by a screening computed tomography scan showing if the LAA anatomy was suitable for Lariat deployment. There was 1 death, and emergent cardiac surgery was required in 1.4%. Cardiac perforations (overall and those needing surgery) and the number of patients needing blood transfusions decreased when providers altered the procedure from using large bore

needles to micropuncture needles. Other individual observational studies are smaller, reporting success rates and complication rates in the same range.<sup>45,46,47,48,</sup>

Litwinowicz et al (2018) presented an observational study of 139 patients from a single-center undergoing LAAC with the Lariat device, with a longer follow-up than the other observational studies.<sup>49</sup> After a follow-up of 5 years (428 patient-years), the thromboembolism rate was 0.8%, with a calculated bleeding risk reduction of 78%. The overall mortality rate was 1.6%.

Litwinowicz et al (2019) reported on the same set of patients, dividing them into 2 groups: patients with prior stroke (n=37) and those without prior stroke (control group; n=102).<sup>50</sup> Results showed that patients in the stroke group had significantly higher CHADS<sub>2</sub>, CHA<sub>2</sub>-DS<sub>2</sub>-VASc, and HAS-BLED scores than the control group (all p<.0001). Thromboembolic event rate, bleeding event rate, and mortality rate were not significantly different between groups. The investigators concluded that patients with prior stroke may be preferred for LAAC, regardless of whether a contraindication for anticoagulant therapy exists.

### **Nonrandomized Comparative Study**

Jazayeri et al (2018) evaluated the safety profiles of the Watchman and the Lariat devices, using the FDA's MAUDE database from 2009 to 2016, as described in the Watchman section above.<sup>37</sup> A total of 4889 Lariat devices were implanted, with 136 events reported during the study period. The most common events in the Lariat group were pericardial effusion (46 [0.94%]), need for cardiac surgery (38 [0.78%]), and pericardiocentesis (23 [0.47%]). Ten deaths were reported in the Lariat group, with 6 involving tightening of the suture around the LAA. Compared to the Watchman device, the composite outcome occurred significantly more in the group receiving the Watchman than in the group receiving the Lariat, 1.9% vs. 1.1%, p=.001.

Litwinowicz et al (2019) compared outcomes of patients undergoing LAAC with the Lariat device (n=57) with patients receiving either warfarin or clopidogrel (n=31).<sup>51</sup> Age, sex, and comorbidities were similar between the 2 groups. Treatment prior to the study differed significantly. The Lariat group received warfarin (93%), aspirin (4%), aspirin plus clopidogrel (2%) and no anticoagulation (1%). The control group received warfarin (87%) or clopidogrel (13%). However, there was no significant difference in CHA<sub>2</sub>DS<sub>2</sub>-VAS scores between the groups at baseline. Average follow-up in the Lariat group was 59 months and average follow-up in the control group was 60 months. There were no thromboembolic events in the Lariat group, while 9.6% of the control group experienced thromboembolic events (p=0.02). The bleeding risk reduction in the Lariat group was estimated at 53%.

### **Section Summary: Lariat Device**

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

## **AMPLATZER CARDIAC PLUG DEVICE AND AMPLATZER AMULET DEVICE**

### **Amplatzer Cardiac Plug (first generation)**

The available evidence on the use of the Amplatzer device for left atrial occlusion consists of a number of observational studies. Nietlispach et al (2013) published the largest cohort, which included 152 patients from a single institution in Europe.<sup>52</sup> Short-term complications occurred in 9.8% (15/152) of patients. The longer-term adverse outcomes occurred in 7% of patients, including 2 strokes, 1 peripheral embolization, and 4 episodes of major bleeding. Device embolization occurred in 4.6% (7/152) of patients. Other reports of patients treated with the Amplatzer device include a study of 90 patients from Belgium (2013),<sup>53</sup> 86 patients from Portugal (2012),<sup>54</sup> 37 patients from Italy (2013),<sup>55</sup> 35 patients from Spain (2013),<sup>56</sup> 21 patients from Poland (2013),<sup>57</sup> and 20 patients from China (2012).<sup>29</sup> All studies reported high procedural success rates, as well as complications such as vascular events, air embolism, esophageal injury, cardiac tamponade, and device embolization.

Cruz-Gonzales et al (2020), in their retrospective registry study, aimed to evaluate the safety and efficacy of LAA occlusion for patients with nonvalvular AF with prior stroke or TIA despite anticoagulant therapy (resistant stroke).<sup>58</sup> They assessed data from the Amplatzer Cardiac Plug multicenter registry on 1047 consecutive patients with nonvalvular AF undergoing LAA occlusion. Out of the 1047, 115 had resistant stroke and 932 had other indications. There were no significant differences in baseline characteristics between the 2 groups. The resistant stroke group had a significantly higher mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score (5.5±1.5 in the resistant stroke group vs 4.6±1.6 in the non-stroke group; p<.001) and HAS-BLED score (3.9±1.3 vs 3.1±1.2; p<.001). There were no significant differences between groups in procedural success or periprocedural major safety events (7.8% vs 4.5%; p=.1). All patients completed at least 1 year of follow-up. At follow-up, the observed annual rate of stroke or TIA was 2.6% (65% relative reduction of thromboembolism based on the CHA<sub>2</sub>DS<sub>2</sub>-VASc score) in the resistant stroke group and 1.2% (78% relative risk reduction) for the non-stroke group. In addition, the observed annual major bleeding rate was 0% (100% relative reduction based on the HAS-BLED score) for resistant stroke patients and 1.2% (79% relative reduction) for those without prior stroke/TIA. Although larger controlled trials are needed, LAA occlusion showed significant benefit to patients who had had a previous stroke or TIA.

Several other observational studies have reported on the use of the Amplatzer device in patients with a contraindication to oral anticoagulation therapy. Santoro et al (2016), in the largest observational study, reported on outcomes up to 4 years post procedure for 134 patients with nonvalvular AF and a long-term contraindication to oral anticoagulation treated with the Amplatzer device.<sup>59</sup> Patients had a median CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 4 and were generally considered at high risk for bleeding complications. Procedural success occurred in 93.3%, and 3 major procedure-related complications (2 cases of cardiac tamponade, 1 case of pericardial effusion requiring drainage or surgery) occurred. Over a mean follow-up of 680 days, observed annual rates of ischemic strokes and any thromboembolic events were 0.8% and 2.5%, respectively. Other observational studies have been published in this population, evaluating between 37 and 100 patients.<sup>55,60,61,62,63</sup> These studies also reported high success rates and low procedural complications.

### **Amplatzer Amulet (second generation)**

A second generation device, the Amplatzer Amulet was developed to potentially lower device embolization rates, simplify the technical implantation procedure, and lower severe complication

rates. The Amulet first became available in Europe in January 2013. Below are descriptions of studies comparing the amulet with the first generation cardiac plug. There is currently an ongoing trial comparing the Amplatzer Amulet with the Watchman (NCT03399851).

## **RANDOMIZED CONTROLLED TRIALS**

### **PRAGUE-17 Trial**

As described above, the PRAGUE-17 RCT found use of LAAC (Watchman device or the Amplatzer Amulet) noninferior to direct oral anticoagulants for the primary composite endpoint in high-risk patients with AF.<sup>27</sup> The primary endpoint was a composite of ischemic or hemorrhagic stroke or TIA, systemic embolism, clinically significant bleeding, cardiovascular death, or significant periprocedural or device-related complications. Although 61.3% of patient received an Amplatzer Amulet device, subgroup analyses by device type were not presented which limits interpretation. One device-related death occurred with the Amulet device due to a pericardial effusion approximately 6 weeks after the procedure.

### **Observational Studies**

Landmesser et al (2017) presented periprocedural (within 7 days of procedure) and early clinical outcomes (1 to 3 months post procedure) from a multicenter registry of 1088 patients receiving the Amplatzer Amulet between June 2015 and September 2016.<sup>64</sup> Technical success was defined as implantation of the device in the correct position, which was reported for 1078 (99%) of the patients. A composite of ischemic stroke, systemic embolism, and cardiovascular death occurred in 7 (0.6%) patients during the periprocedural period and in 15 (1.4%) patients between 7 days post procedure and 3 months follow-up.

Landmesser et al (2018) and Hildick-Smith et al (2020) provided updated analyses on 950 patients and 864 patients from the registry series described above who had 1-year and 2-year follow-up data.<sup>65,66</sup> Oral anticoagulants were used by 6% of the patients at 3, 6, and 12 months post procedure and 6.6% of patients at 2 years. At year 1, there were 29 ischemic strokes (27 patients), 9 patients experiencing a TIA, and no systemic embolisms reported. At year 2, there were 42 ischemic strokes (39 patients), 20 TIA events (16 patients; 9 events over the first year and 11 over the second year) and no systemic embolisms reported. The annualized bleeding rate was 10.1% per year in year 1 (103 events per 1016 patient-years) and 4.0% per year in year 2 (37 events per 917 patient-years). The proportion of patients experiencing a major bleeding event was 8.0% over the first year (87 of 1088 patients) and 3.2% over the second year (31 of 958 patients). The DRT rate was 1.6% at 2 years, with 19 events in 17 patients. There were 91 and 70 deaths reported in the first and second years, respectively, with 55 deaths considered cardiovascular-related, 71 non-cardiovascular-related, and 35 with unknown causes.

Nielsen-Kudsk et al (2021) compared patients from the Amulet Observational Registry described above (n=1088) with a successful LAAC (n=1078) compared with a control cohort of patients with AF treated with direct oral anticoagulants (n=1184).<sup>67</sup> The direct oral anticoagulant cohort consisted of patients selected by propensity score matching based on CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED covariates among patients from Danish registries. The primary outcome was a composite of ischemic stroke, major bleeding, or all-cause mortality at 2 years. At baseline, the CHA<sub>2</sub>DS<sub>2</sub>-VASc scores were 4.2 and 4.3 and the HAS-BLED scores were 3.3 and 3.4 in the LAAC and direct oral anticoagulant groups, respectively. At 2 years follow-up, 58% of patients had discontinued the direct oral anticoagulant. The primary outcome of ischemic stroke, major bleeding, and mortality was lower with LAAC (256 events; 14.5 event rate per 100 patient-years) compared with the

direct oral anticoagulant group (461 events; 25.7 event rate per 100 patient-years) (HR, 0.57; 95% CI, 0.49 to 0.67). Ischemic stroke was not significantly different between groups (HR, 1.11; 95% CI, 0.71 to 1.75). Major bleeding (HR, 0.62; 95% CI, 0.49 to 0.79), all-cause mortality (HR, 0.53; 95% CI, 0.43 to 0.64), and cardiovascular mortality (HR, 0.51; 95% CI, 0.37 to 0.70) were reduced with LAAC compared to direct oral anticoagulants.

### **Nonrandomized Comparative Studies**

Gloekler et al (2015) reviewed records from 2 university hospitals' occlusion registries and conducted a retrospective analysis comparing the last 50 consecutive patients receiving the cardiac plug with the first 50 consecutive patients receiving the Amulet.<sup>63</sup> Follow-up examinations were performed between 4 to 6 months post-procedure. No significant differences between the 2 devices were detected in mortality, neurologic events, late pericardial effusions, major bleeding, device leaks, or device thrombi. Interpretation of these results is limited by the small sample size and short follow-up period.

Al-Kassou et al (2017) presented periprocedural and 2 to 3 month follow-up data for patients undergoing LAA occlusion with the Amplatzer cardiac plug and the Amplatzer Amulet.<sup>68</sup> Periprocedural data was available for 99 patients receiving the cardiac plug and for 97 patients receiving the Amulet. Use of the Amulet was associated with significantly lower fluoroscopy time, lower radiation dose, and reduced amount of contrast dye. Occurrence of adverse events during the periprocedural period were comparable. Transesophageal echocardiographic follow-up data at 2 to 3 months was available for 81 patients receiving the cardiac plug and for 82 patients receiving the Amulet. None of the patients experienced DRT during this follow-up. Minor leaks were detected in 12 (15%) patients receiving the cardiac plug and in 4 (5%) patients receiving the Amulet (p=0.03).

### **Section Summary: Amplatzer Cardiac Plug Device and Amplatzer Amulet**

One RCT has evaluated use of LAAC with either the Amplatzer Amulet or Watchman device; however, subgroup analyses were not performed, limiting study interpretation. There are no RCTs of the Amplatzer device alone for LAAC. There are 2 nonrandomized studies comparing the first generation Amplatzer cardiac plug with the second generation Amplatzer Amulet, 1 of which reported procedural advantages of the Amulet over the cardiac plug. Both nonrandomized comparator studies reported no difference in clinical outcomes at first follow-up, 2 to 6 months. The remaining evidence consists of observational studies. One cohort study based on registry data found that the Amulet device reduced the composite of ischemic stroke, major bleeding, and all-cause mortality compared to direct oral anticoagulants. The nonrandomized comparator studies and the observational studies are insufficient to draw conclusions about treatment efficacy. There is an ongoing trial comparing the Amplatzer Amulet with the Watchman (NCT03399851).

### **Summary of Evidence**

For individuals who have AF who are at increased risk for embolic stroke who receive the Watchman percutaneous LAAC device, the evidence includes 2 RCTs and meta-analyses of these trials. Relevant outcomes are overall survival, morbid events, and treatment-related morbidity. The most relevant evidence comes from 2 industry-sponsored RCTs that compared the Watchman device with anticoagulation alone. One trial reported noninferiority on a composite outcome of stroke, cardiovascular/unexplained death, or systemic embolism after 2 years of follow-up, with continued benefits with the Watchman device after 4 years of follow-up. The

second trial did not demonstrate noninferiority for the same composite outcome but did demonstrate noninferiority of the Watchman device to warfarin for late ischemic stroke and systemic embolization. Patient-level meta-analyses at 5-year follow-up for the 2 trials reported that the Watchman device is noninferior to warfarin on the composite outcome of stroke, systemic embolism, and cardiovascular death. Also, the Watchman was associated with lower rates in major bleeding, particularly hemorrhagic stroke, and mortality over the long term. The evidence also indicates that the Watchman device is efficacious in preventing stroke in the subset of patients with AF who are at increased risk for embolic stroke. Among patients in which the long-term risk of systemic anticoagulation exceeds the procedural risk of device implantation, the net health outcome will be improved. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have AF who are at increased risk for embolic stroke who receive a percutaneous LAAC device other than the Watchman device (e.g., Lariat or Amplatzer), the evidence includes several nonrandomized comparator studies and uncontrolled observational studies. Relevant outcomes are overall survival, morbid events, and treatment-related morbidity. One nonrandomized study that compared outcomes among patients undergoing LAAC with the Lariat device with patients receiving anticoagulant or antiplatelet therapy reported fewer thromboembolic events in the group receiving the Lariat device. Although a RCT evaluated use of LAAC with either the Amplatzer Amulet or Watchman device, subgroup analyses were not performed, limiting study interpretation. One cohort study based on registry data found that the Amulet device reduced the composite of ischemic stroke, major bleeding, and all-cause mortality compared to direct oral anticoagulants. Two nonrandomized studies compared the Amplatzer cardiac plug with the Amplatzer A mullet. While the A mullet may be technically easier to implant, clinical outcomes were similar between the 2 groups. The remaining evidence consists of observational studies of these devices which report high procedural success but also numerous complications. In addition, these devices do not have U.S. Food and Drug Administration approval for LAAC. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome

### **SUPPLEMENTAL INFORMATION**

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

### **Clinical Input 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, 1 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 U.S. Food and Drug Administration for patients with an increased risk of stroke and systemic embolism, based on CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>-VASc score. Systemic anticoagulation therapy was recommended, but the long-term risks of systemic anticoagulation outweigh the risks of the device implantation.

### Practice Guidelines and Position Statements

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

#### American Heart Association

In 2019, the American Heart Association, in collaboration with the American College of Cardiology and the Heart Rhythm Society, published an update of their guideline for the management of patients with atrial fibrillation (AF).<sup>69</sup> A new recommendation in the guideline states: "Percutaneous LAA [left atrial appendage] occlusion may be considered in patients with AF at increased risk of stroke who have contraindications to long-term anticoagulation." The class of recommendation is IIB and the level of evidence is B<sub>NR</sub> (moderate quality of evidence, nonrandomized). No other LAA closure (LAAC) devices are mentioned in the guideline.

#### American College of Chest Physicians

In 2018, the American College of Chest Physicians (CHEST) guideline made the following recommendation regarding LAA occlusion and oral anticoagulation: "In patients with AF at high risk of ischemic stroke who have absolute contraindications for OAC [oral anticoagulation], we suggest using LAA occlusion (Weak recommendation, low quality evidence)."<sup>3</sup>

#### Guideline Comparison

In 2017, Andrade et al provided the following summary ( Table 3) comparing guidelines by American, Canadian, and European societies on left atrial appendage exclusion and closure for the management of AF.<sup>70</sup>

**Table 3. Comparison of American, Canadian, and European Guidelines on LAA Exclusion/Closure**

Procedure	AHA/ACC/HRS	CCS	ESC
Surgical LAA closure (excision or obliteration of LAA)	May be considered in patients undergoing cardiac surgery (IIB)	Should be considered as part of surgical ablation of AF associated with mitral, aortic valve, or coronary artery bypass surgery	May be considered in patients undergoing cardiac surgery (IIB), more data needed to confirm safety and efficacy of thoroscopic exclusion
Percutaneous LAA exclusion	No recommendation	Not be used, except in research or in systematically documented use protocols in patients at high risk of stroke (CHADS <sub>2</sub> ≥2) and antithrombotic therapy precluded	May be considered in patients with contraindications for long term anticoagulant treatment (IIB)

Adapted from Andrade et al (2017).<sup>70</sup>

ACC: American College of Cardiology; AF: atrial fibrillation; AHA: American Heart Association; CCS: Canadian Cardiovascular Society; CHADS<sub>2</sub>: Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke/Transient Ischemic Attack; ESC: European Society of Cardiology; HRS: Heart Rhythm Society; LAA: left atrial appendage.

#### U.S. Preventive Services Task Force Recommendations

Not applicable.

### Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 4.

**Table 4. Summary of Key Trials**

<b>NCT No.</b>	<b>Trial Name</b>	<b>Planned Enrollment</b>	<b>Completion Date</b>
<i>Ongoing</i>			
NCT03276169	Left Atrial Function Changes after Left Atrial Appendage Closure in Patients with Persistent Atrial Fibrillation	105	Nov 2020
NCT02513797 <sup>a</sup>	aMAZE Study: LAA Ligation with the LARIAT Suture Delivery System as Adjunctive to Pulmonary Vein Isolation for Persistent Atrial Fibrillation (aMAZE)	600	Dec 2021
NCT03204695 <sup>a</sup>	A Prospective, Multicenter, Non-Randomized, Post-market Clinical Follow-up Study to Confirm Safety and Performance of the Coherex WaveCrest Left Atrial Appendage Occlusion System in Patients with Non-valvular Atrial Fibrillation	65	Mar 2022
NCT03463317	Left Atrial Appendage CLOSURE in Patients With Atrial Fibrillation at High Risk of Stroke and Bleeding Compared to Medical Therapy: a Prospective Randomized Clinical Trial	1512	Feb 2023
NCT02964208 <sup>a</sup>	AMPLATZER LAA Occluder Post Approval Study (PAS)	1000	Oct 2023
NCT02879448	AMPLATZER™ Amulet™ Left Atrial Appendage Occluder Randomized Controlled Trial	1878	Aug 2024
NCT03399851	Comparison of Amplatzer Amulet vs. Watchman Device in Patients Undergoing Left Atrial Appendage Closure: the SWISS-APER0 Randomized Clinical Trial	2000	Dec 2025
NCT03302494 <sup>a</sup>	WAVECrest Vs. Watchman TransscEptal LAA Closure to REduce AF-Mediated STroke 2 (WAVECREST2)	1250	Dec 2028
NCT03309332 <sup>a</sup>	OSB Lead-AMPLATZER PFO Occluder New Enrollment PAS	1214	Dec 2027
NCT03795298	Comparison of Anticoagulation with Left Atrial Appendage Closure After AF Ablation (OPTION)	1600	Nov 2024
NCT04394546	WATCHMAN FLX Versus NOAC for Embolic ProtectIOn in in the Management of Patients With Non-Valvular Atrial Fibrillation	3000	Dec 2027
NCT04226547	Clinical Trial of Atrial Fibrillation Patients Comparing Left Atrial Appendage Occlusion Therapy to Non-vitamin K Antagonist Oral Anticoagulants	2650	April 2029
<i>Unpublished</i>			
NCT01118299	AMPLATZER Cardiac Plug Clinical Trial	3000	Dec 2018 (updated 02/01/19)



NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT02681042	Left Atrial Appendage Closure with SentreHeart Lariat Device	9	May 2018 (updated 02/21/21)

NCT: national clinical trial.

<sup>a</sup> indicates industry-sponsored study.

## **CODING**

**The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.**

**Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.**

**The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.**

### CPT/HCPCS

- 33267 Open exclusion of left atrial appendage any method (01-01-22)
- 33268 Open exclusion of left atrial appendage performed at the time of other sternotomy or thoracotomy procedure (01-01-22)
- 33269 Thoracoscopic exclusion of left atrial appendage
- 33340 Percutaneous transcatheter closure of the left atrial appendage with endocardial implant, including fluoroscopy, transeptal puncture, catheter placement(s), left atrial angiography, left atrial appendage angiography, when performed, and radiological supervision and interpretation (01-01-22)

### ICD-10 Diagnoses

- I48.0 Paroxysmal atrial fibrillation
- I48.11 Longstanding persistent atrial fibrillation
- I48.19 Other persistent atrial fibrillation
- I48.20 Chronic atrial fibrillation, unspecified
- I48.21 Permanent atrial fibrillation
- I48.91 Unspecified atrial fibrillation
- I63.30 Cerebral infarction due to thrombosis of unspecified cerebral artery
- I63.311 Cerebral infarction due to thrombosis of right middle cerebral artery
- I63.312 Cerebral infarction due to thrombosis of left middle cerebral artery
- I63.313 Cerebral infarction due to thrombosis of bilateral middle cerebral arteries
- I63.319 Cerebral infarction due to thrombosis of unspecified middle cerebral artery
- I63.321 Cerebral infarction due to thrombosis of right anterior cerebral artery
- I63.322 Cerebral infarction due to thrombosis of left anterior cerebral artery
- I63.323 Cerebral infarction due to thrombosis of bilateral anterior cerebral arteries
- I63.329 Cerebral infarction due to thrombosis of unspecified anterior cerebral artery
- I63.331 Cerebral infarction due to thrombosis of right posterior cerebral artery

- I63.332 Cerebral infarction due to thrombosis of left posterior cerebral artery
- I63.333 Cerebral infarction due to thrombosis of bilateral posterior cerebral arteries
- I63.339 Cerebral infarction due to thrombosis of unspecified posterior cerebral artery
- I63.341 Cerebral infarction due to thrombosis of right cerebellar artery
- I63.342 Cerebral infarction due to thrombosis of left cerebellar artery
- I63.343 Cerebral infarction due to thrombosis of bilateral cerebellar arteries
- I63.349 Cerebral infarction due to thrombosis of unspecified cerebellar artery
- I63.39 Cerebral infarction due to thrombosis of other cerebral artery
- I63.40 Cerebral infarction due to embolism of unspecified cerebral artery
- I63.411 Cerebral infarction due to embolism of right middle cerebral artery
- I63.412 Cerebral infarction due to embolism of left middle cerebral artery
- I63.413 Cerebral infarction due to embolism of bilateral middle cerebral arteries
- I63.419 Cerebral infarction due to embolism of unspecified middle cerebral artery
- I63.421 Cerebral infarction due to embolism of right anterior cerebral artery
- I63.422 Cerebral infarction due to embolism of left anterior cerebral artery
- I63.423 Cerebral infarction due to embolism of bilateral anterior cerebral arteries
- I63.429 Cerebral infarction due to embolism of unspecified anterior cerebral artery
- I63.431 Cerebral infarction due to embolism of right posterior cerebral artery
- I63.432 Cerebral infarction due to embolism of left posterior cerebral artery
- I63.433 Cerebral infarction due to embolism of bilateral posterior cerebral arteries
- I63.439 Cerebral infarction due to embolism of unspecified posterior cerebral artery
- I63.441 Cerebral infarction due to embolism of right cerebellar artery
- I63.442 Cerebral infarction due to embolism of left cerebellar artery
- I63.443 Cerebral infarction due to embolism of bilateral cerebellar arteries
- I63.449 Cerebral infarction due to embolism of unspecified cerebellar artery
- I63.49 Cerebral infarction due to embolism of other cerebral artery
- I63.50 Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebral artery
- I63.511 Cerebral infarction due to unspecified occlusion or stenosis of right middle cerebral artery
- I63.512 Cerebral infarction due to unspecified occlusion or stenosis of left middle cerebral artery
- I63.513 Cerebral infarction due to unspecified occlusion or stenosis of bilateral middle cerebral arteries
- I63.519 Cerebral infarction due to unspecified occlusion or stenosis of unspecified middle cerebral artery
- I63.521 Cerebral infarction due to unspecified occlusion or stenosis of right anterior cerebral artery
- I63.522 Cerebral infarction due to unspecified occlusion or stenosis of left anterior cerebral artery
- I63.523 Cerebral infarction due to unspecified occlusion or stenosis of bilateral anterior cerebral arteries
- I63.529 Cerebral infarction due to unspecified occlusion or stenosis of unspecified anterior cerebral artery
- I63.531 Cerebral infarction due to unspecified occlusion or stenosis of right posterior cerebral artery
- I63.532 Cerebral infarction due to unspecified occlusion or stenosis of left posterior cerebral artery

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

**REVISIONS**

12-20-2013	Policy added to the bcbsks.com web site.
07-01-2016	<p>Updated Description section.</p> <p>In Policy section:</p> <ul style="list-style-type: none"> <li>▪ Removed "The use of percutaneous left-atrial appendage closure devices for the prevention of stroke in atrial fibrillation is considered experimental / investigational."</li> <li>▪ Added the following: <ul style="list-style-type: none"> <li>A. The use of a device with U.S. Food and Drug Administration (FDA) approval for percutaneous left atrial appendage closure (e.g., the Watchman) may be considered medically necessary for the prevention of stroke in patients with atrial fibrillation when the following criteria are met: <ol style="list-style-type: none"> <li>1. There is an increased risk of stroke and systemic embolism based on CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>-VASc score and systemic anticoagulation therapy is recommended; AND</li> </ol> </li> </ul> </li> </ul>

	<p>2. The long-term risks of systemic anticoagulation outweigh the risks of the device implantation (see Policy Guidelines).</p> <p>B. The use of a device with FDA approval for percutaneous left atrial appendage closure (e.g., the Watchman) for stroke prevention in patients who do not meet the above criteria is considered experimental / investigational.</p> <p>C. The use of other percutaneous left atrial appendage closure devices, including but not limited to the Lariat, PLAATO, and Amplatzer devices, for stroke prevention in patients with atrial fibrillation is considered experimental / investigational.</p> <ul style="list-style-type: none"> <li>▪ Added Policy Guidelines.</li> </ul>
	Updated Rationale section.
	<p>In Coding section:</p> <ul style="list-style-type: none"> <li>▪ Updated CPT code 0281T nomenclature.</li> <li>▪ Added ICD-10 codes.</li> </ul>
	Updated References section.
07-07-2016	Updated Description section.
	Updated Rationale section.
	Updated References section.
10-01-2016	<p>In Coding section:</p> <ul style="list-style-type: none"> <li>▪ Added ICD-10 codes effective 10-01-2016: I63.313, I63.323, I63.333, I63.343, I63.413, 863.423, I63.433, I63.443, I63.513, I63.523, I63.533, I63.543</li> </ul>
01-01-2017	<p>In Coding section:</p> <ul style="list-style-type: none"> <li>▪ Added CPT code: 33340 (<i>New code, effective January 1, 2017</i>).</li> <li>▪ Removed CPT code: 0281T (<i>Termed code, effective December 31, 2016</i>).</li> </ul>
07-11-2017	Updated Description section.
	Updated Rationale section.
	Updated References section.
10-01-2017	<p>In Coding section:</p> <ul style="list-style-type: none"> <li>▪ Revised nomenclature to ICD-10 codes: I63.323, I63.333, I63.513, I63.523, I63.533.</li> </ul>
08-08-2018	Updated Description section.
	<p>In Policy section:</p> <ul style="list-style-type: none"> <li>▪ In Item A, added "nonvalvular" to read, "The use of a device with U.S. Food and Drug Administration (FDA) approval for percutaneous left atrial appendage closure (eg, the Watchman) may be considered medically necessary for the prevention of stroke in patients with nonvalvular atrial fibrillation when the following criteria are met:"</li> <li>▪ In Item C, removed "PLAATO" to read, "The use of other percutaneous left atrial appendage closure devices, including, but not limited, to the Lariat and Amplatzer devices, for stroke prevention in patients with atrial fibrillation is considered experimental / investigational."</li> <li>▪ Updated Policy Guidelines.</li> </ul>
	Updated Rationale section.
	Updated References section.
10-01-2018	<p>In Coding section:</p> <ul style="list-style-type: none"> <li>▪ Added ICD-10 codes: I63.81, I63.89.</li> <li>▪ Removed ICD-10 code: I63.8.</li> <li>▪ Revised ICD-10 codes: I63.333, I63.343.</li> </ul>
06-19-2019	Updated Description section.
	Updated Rationale section.
	Updated References section.
10-01-2019	In Coding section:

	<ul style="list-style-type: none"> <li>▪ Added ICD-10 codes: I48.11, I48.19, I48.20, I48.21</li> <li>▪ Removed ICD-10 code: I48.2</li> </ul>
07-02-2021	Updated Description section.
	Policy guidelines #2 and #3 were moved up into the policy position statement for clarification.
	Updated Rationale section.
	Updated References section.
01-03-2022	In Coding Section <ul style="list-style-type: none"> <li>▪ Added: CPT 33267, 33268, 33269</li> </ul>

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