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

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IMPORTANT REMINDER

DESCRIPTION

Left atrial appendage (LAA) closure devices have been developed as a nonpharmacologic alternative to anticoagulation for stroke prevention in atrial fibrillation.

MEDICAL POLICY CRITERIA

The use of left atrial appendage closure devices is considered **investigational** for all indications, including but not limited to the prevention of stroke in patients with atrial fibrillation.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

None

BACKGROUND

Stroke is the most serious complication of atrial fibrillation (AF). The estimated incidence of stroke in untreated 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). The LAA is the region responsible for an estimated 90% of left atrial thrombi.

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. Other anticoagulants e.g. apixaban and dabigatran do not require monitoring. However, unlike warfarin, the antithrombotic effects of these anticoagulants are not always reversible with 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.[1]

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

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 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 three panel reviews before it was approved by FDA through the premarket approval process in March 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.

The Atriclip™ LAA Exclusion System was cleared for marketing by the FDA through the 510(k) process. The FDA indicates the device is indicated for the occlusion of the heart’s left atrial appendage, under direct visualization, in conjunction with other open cardiac surgical procedures. Direct visualization, in this context requires that the surgeon is able to see the heart directly, without assistance from a camera, endoscope, etc., or any other viewing technology. This includes procedures performed by sternotomy (full or partial as well as thoracotomy (single or multiple).[4]

At least two other devices have been studied for LAA occlusion, but are not approved in the US 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 pretied polyester suture. The Amplatzer Amulet® device (St. Jude Medical, Plymouth, MN) has a CE approval in Europe for LAA closure, but is not currently approved in the US for any indication.

EVIDENCE SUMMARY

The standard treatment for stroke prevention in atrial fibrillation is anticoagulation, which has proven effectiveness. In order to determine the safety and effectiveness of left atrial appendage (LAA) closure devices for the prevention of stroke in atrial fibrillation, large, well-designed randomized controlled trials (RCTs) that compare LAA to no therapy (patients with a prohibitive risk for oral anticoagulation), oral anticoagulation, or open surgical repair are needed. For chronic conditions such as atrial fibrillation, RCTs with long-term follow-up are necessary in order to determine the durability of any beneficial treatment effects.

The evidence on the efficacy of LAA closure devices consists of numerous nonrandomized studies of various occlusion devices, and two published RCTs of the WATCHMAN™ device that compared LAA closure with warfarin anticoagulation. The evidence for each device is summarized separately since the devices are not similar in design and may have 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 (BCBSA) 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.[5] In addition, the PROTECT-AF and the PREVAIL RCTs evaluated the WATCHMAN™ device. The PROTECT-AF study by Holmes reported outcomes for 18 months of follow-up.[6] Noninferiority criteria were met and then the results of the final analysis were published by Reddy at a mean follow-up of 2.3 years.[7] The FDA reviewed the trial data in 2009 but the data was at a slightly earlier time point than the Holmes analyses. The FDA revealed several concerns during their review that were not reported by the peer reviewed published evidence.[8] As a result, the FDA in coordination with the trial sponsors, developed the PREVAIL trial which had different entry criteria. Study participants from the PROTECT-AF trial were included in the analysis of the PREVAIL trial if they met inclusion criteria. The quality of the two RCTs were assessed as fair by the BCBSA TEC report indicating important methodological limitations in both studies. BCBSA TEC assessment reports the following regarding the quality of the PROTECT-AF and PREVAIL trials:

> “Subject characteristics were balanced between groups. Losses to follow-up in the PROTECT-AF trial were not reported in peer-reviewed publications, and, according to FDA documents, appear to be unbalanced between treatment groups. Losses to follow-up are not clearly reported in FDA documents on the PREVAIL trial, but also appear to be unbalanced between treatment groups. Patients receiving the WATCHMAN™ device underwent more intensive surveillance for thrombosis after device implantation, and continued anticoagulation if concerns about thrombosis arose. Although this was part of the treatment protocol, it makes determinations of efficacy less certain, because there could be a benefit to imaging surveillance alone.”

SYSTEMATIC REVIEWS AND TECHNOLOGY ASSESSMENTS

Blue Cross Blue Shield Association (BCBSA) TEC Assessment developed in June 2014 evaluated the use of the WATCHMAN™ device for patients who were eligible and ineligible for anticoagulation therapy and determined that the WATCHMAN™ device did not meet Technology Evaluation Criteria. 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. There are two main RCTs for the WATCHMAN™ device and the quality of the two RCTs were assessed as fair by the BCBSA TEC report indicating important methodological limitations in both studies. The TEC assessment made the following conclusions about the use of LAA closure in patients without contraindications to anticoagulation:

> "We identified two randomized controlled trials (RCTs) and one 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 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 one of two 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."[5]

In addition, the BCBSA TEC concluded that the evidence is insufficient to make conclusions about improvement in net health outcomes compared to established alternatives.

There are several meta-analyses but the most rigorous is a patient level meta-analysis by Holmes. Holmes (2015) reported results of a patient-level meta-analysis that included data from the industry-sponsored PROTECT AF and PREVAIL trials.[9] 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 2,406 patients, 1,877 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 1,114 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).

A second patient-level meta-analysis of the two RCTs evaluated bleeding outcomes.[10] There were a total of 54 episodes of major bleeding, with the most common types being gastrointestinal (GI) bleed (31/54 [57%]) and hemorrhagic stroke (9/54 [17%]). On combined analysis, the rate of major bleeding episodes over the entire study period did not differ between groups. There were 3.5 events per 100 patient-years in the WATCHMAN™ group compared with 3.6 events per 100 patient-years in the anticoagulation group, for a rate ratio (RR) of 0.96 (95% CI, 0.66 to 1.40; p=0.84). However, there was a reduction in bleeding risk for the WATCHMAN™ group past the initial periprocedural period. For bleeding events occurring more than seven days postprocedure, the event rates were 1.8 per 100 patient-years in the WATCHMAN™ group compared with 3.6 per 100 patient-years in the anticoagulation group (RR=0.49; 95% CI, 0.32 to 0.75; p=0.01). For bleeding events occurring more than six 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 (RR=0.28; 95% CI, 0.16 to 0.49; p<0.001).

Randomized Controlled Trials

The first RCT published was the PROTECT AF study,[6] which was a randomized, unblinded 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, and procedure-related stroke). There were noted limitations to this study including 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.

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% CrI, 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% CrI, 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 (2013).[11] 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 four years of follow-up were reported by Reddy et al in 2014.[12] 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% CrI, 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% CrI, 0.03 to 0.49), and fewer cardiovascular events occurred in the WATCHMAN™ group (3.7% vs 0.95%; RR=0.40; 95% CrI, 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 (2013) 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.[13] 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).

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) 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.[9] 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 two 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 six months post device 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 seven 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 seven 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 six 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.

Reddy (2017) published a study on the five-year outcomes after left atrial appendage closure, for patients who participated in the PREVAIL and/or PROTECT AF trials.[14] When evaluating the five-year findings the authors stated that if procedure related strokes are excluded, ischemic stroke and systemic embolism differences did not vary significantly (HR: 1.40; 95% CI: 0.76 to 2.59; p = 0.28). But, hemorrhagic stroke was significantly reduced with left atrial appendage closure (HR: 0.20; 95% CI: 0.07 to 0.56; p = 0.0022). The authors go on to state patients enrolled in the studies had to be able to take oral anticoagulants; thus, the results do not tell you anything about patients unable to take oral anticoagulants. Since the PREVAIL and/or PROTECT AF trials, novel oral anticoagulants have become routinely prescribed and have not been compared to left atrial appendage closure. They stated additional studies are needed to compare left atrial appendage closure to other oral anticoagulants and to determine outcomes for patients unable to take oral anticoagulants. There are studies underway. It is important to note that there is potential conflict of interest with several authors.

Nonrandomized Studies

Saw (2017) evaluated safety and effectiveness of the WATCHMAN™ for 106 patients who cannot take anticoagulants and who had nonvalvular atrial fibrillation.[15] 97.2% of the patients had successful LAA closure, with one device embolization, one implant being placed too deep, and one cardiac perforation requiring repair prior to device implantation. The major combined safety event rate was 1.9% (one death and one device embolization). Follow-up occurred 210 ± 182 days, noting two transient ischemic events. The authors stated that their early experience is that the WATCHMAN™ is safe and effective for patients who cannot be on anticoagulation therapy, but that there were study limitations including a small sample size, varied antithrombotic therapy and device surveillance, and both the device and events were not adjudicated. Additional studies must evaluate how the Watchman™ device impacts healthcare outcomes.

Main (2016) evaluated follow-up transesophageal (TEE) studies for how often device related thrombus (DRT) occurred in patients in the PROTECT-AF trial.[16] In all, 93 follow-up TEEs in 35 patients (33 at 45-day follow-up, 33 at six-month follow-up, and 27 at one-year follow-up) were assessed. The assessment process included a three-phase adjudication (an interactive training program, an interpretation process, development of DRT criteria, and a final determination of DRTs related to the Watchman™ device). This assessment found device related DRTs in 5.7% of the patients, with DRTs not as common at 45 days, when patients continued on Warfarin. The authors noted study limitations, including but not limited the fact that event adjudication studies tend to underestimate events that occur, the TEE studies varied in clinical quality, and anticoagulant routine data was not completely documented. In addition, there is potential conflict of interest identified in the article.

A number of small published case series are primarily intended to establish safety and feasibility of the device.[17-21] A larger case series of 143 patients from Europe was published in 2011.[19] The case series reported successful implantation in 96% (137/143) of patients and serious complications in 7.0% of patients (10/143). Complications included stroke (n=3), device embolization (n=2), and pericardial effusion (n=5). Another larger case series was reported by Reddy et al[20], 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.[22] Device deployment was successful in 98.9% of patients. The overall complication rate was 11.2%; major complications occurred in 3.3% (tamponade in two cases; possible transient ischemic attack [TIA] in one case; device dislocation in three cases). At 45-day follow-up, 99.4% of patients (164/166) had closure of the LAA.

Reddy (2016) evaluated adverse events for the WATCHMAN™ since it was FDA approved.[23] Adverse events were identified by procedural data collected by the manufacturer clinical specialist present during surgery. Implantation was deemed successful in 95% of consecutive cases (3,653 out of 3,822 total). The complications included 39 pericardial tamponades (1.02%; 24 treated percutaneously, 12 surgically and 3 fatal), three procedure-related strokes (0.078%), nine device embolizations (0.24%; 6 requiring surgical removal), and three procedure-related deaths (0.078%).

Bonnet published safety and efficacy data for the WATCHMAN™ device from a small single center registry study.[24] There were 23 total patients (mean CHA2DS2-VASc score: 5). The procedural success rate was 95.7% (95% confidence interval: 77.3-100.0) and the reported efficacy was 90.9% (95% confidence interval: 71.0-98.7). No adverse events were reported during or after hospitalization.

Figini (2016) published retrospective results from a single center in Italy between 2009 and 2015.[25] The study included 165 patients in which 99 received the Amplatzer Cardiac Plug (ACP) and 66 the WATCHMAN™ system. The mean follow-up was 15 months. A total of five patients died and one patient had an ischemic attach. There were no episodes of definitive stroke recorded or reported. However, there were twenty-six leaks ≥1 mm detected (23%) and were not found to correlate with clinical events. The authors noted that further investigation is warranted for the small peri-device flow.

There is uncertainty about the role of the WATCHMAN™ device in patients with AF who have absolute contraindications to oral anticoagulants. Reddy et al[7] 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 ticlopidine and lifelong aspirin therapy. Thirteen patients (8.7%) had a procedure- or device-related serious adverse event, most commonly pericardial effusion (three patients). Over a mean 14.4 months of follow-up, all-cause stroke or systemic embolism occurred in four patients.

Chun (2013) compared the WATCHMAN™ device with the Amplatzer cardiac plug among patients with nonvalvular AF in a prospective cohort study, who were at high risk for stroke and had a contraindication to or were not willing to accept oral anticoagulants.[26] Eighty patients were assigned 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 six weeks. A follow-up transesophageal echocardiogram was performed at six weeks postprocedure; if a device-related thrombus had formed, patients received intensive antithrombotic therapy for six 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 two groups. At a median 364 days of follow-up, there were no cases of stroke/TIA or other bleeding complications.

The EWOLUTION WATCHMAN™ registry is intended to evaluate procedural success, long-term outcomes, and adverse events in real-world settings. This registry compiles data from patients receiving the WATCHMAN™ device at 47 centers in 13 countries. A publication from the EWOLUTION registry in 2016 reported on 30-day outcomes of device implantation in 1,021 patients.[27] The overall population had a risk of bleeding that was substantially higher than that for patients in the RCTs. Over 62% of patients included in the registry were deemed ineligible for anticoagulation by their physicians. Approximately one-third of patients had a history of major bleeding, and 40% had HAS-BLED scores of 3 or greater, indicating moderate-to-high risk of bleeding. Procedural success was achieved in 98.5% of patients, and 99.3% of implants demonstrated no blood flow or minimal residual blood flow postprocedure. Serious adverse events due to the device or procedure occurred at an overall rate of 2.8% (95% CI, 1.9% to 4.0%) at 7 days and 3.6% (95% CI, 2.5% to 4.9%) at 30 days. The most common serious adverse event was major bleeding.

Network Analyses

Sahay (2017) performed a network meta-analysis to evaluate the safety and effectiveness of LAAC versus other strategies to prevent stroke in AF patients.[28] Nineteen RCTs with 87,831 patients were evaluated. The authors stated that although LAAC was found to be better than anticoagulant therapy and similar to novel anticoagulants, the results should be carefully analyzed.

Bajaj (2016) conducted a network meta-analysis of published RCTs evaluating multiple novel oral anticoagulants and left atrial appendage closure devices (WATCHMAN™) which have been tested against dose-adjusted vitamin K antagonists for stroke prophylaxis in non-valvular atrial fibrillation.[29] At the time of the analysis, there were no direct comparisons of these strategies from RCTs. Six RCTs were included in the analysis (N=59,627). Safety and efficacy outcomes were evaluated for six treatment strategies. The analysis showed that all prophylaxis strategies had similar rates of ischemic stroke. The authors also reported that in a cluster analyses, assessing safety and efficacy, apixaban, edoxaban and dabigatran ranked best followed by vitamin K antagonists and rivaroxaban, whereas the WATCHMAN™ left atrial appendage closure device ranked last. All of these strategies had different safety outcomes. The authors concluded that more RCTs are needed that directly compare treatment strategies.

Tereshchenko (2016) published a network meta-analysis that included 21 RCTs (96,017 nonvalvular AF patients; median age, 72 years; 65% males; median follow-up, 1.7 years) in which the safety and efficacy of novel oral anticoagulants (NOACs) (apixaban, dabigatran, edoxaban, and rivaroxaban); vitamin K antagonists (VKA); aspirin; and the WATCHMAN™ device were evaluated.[30] The primary efficacy outcome was the combination of stroke and systemic embolism and the primary safety outcome was the combination of major extracranial bleeding and intracranial hemorrhage. The authors concluded that “in comparison to placebo/control, use of aspirin (odds ratio [OR], 0.75 [95% CI, 0.60-0.95]), VKA (0.38 [0.29-0.49]), apixaban (0.31 [0.22-0.45]), dabigatran (0.29 [0.20-0.43]), edoxaban (0.38 [0.26-0.54]), rivaroxaban (0.27 [0.18-0.42]), and the WATCHMAN™ device (0.36 [0.16-0.80]) significantly reduced the risk of any stroke or systemic embolism in nonvalvular AF patients, as well as all-cause mortality (aspirin: OR, 0.82 [0.68-0.99]; VKA: 0.69 [0.57-0.85]; apixaban: 0.62 [0.50-

0.78]; dabigatran: 0.62 [0.50-0.78]; edoxaban: 0.62 [0.50-0.77]; rivaroxaban: 0.58 [0.44-0.77]; and the WATCHMAN™ device: 0.47 [0.25-0.88])."

Section Summary

The evidence for the use of the WATCHMAN™ device for stroke prevention in patients with nonvalvular atrial fibrillation who are candidates for oral anticoagulation mainly includes two noninferiority RCTs (PROTECT-AF and PREVAIL) and patient-level meta-analysis of these trials. Both RCTs compare the WATCHMAN™ device to anticoagulation and report on composite outcomes. The first RCT reported noninferiority between the two groups for a composite outcome of stroke, cardiovascular/unexplained death, or systemic embolism up to four years of follow-up. However, there are documented issues with patient selection criteria (i.e. population low risk for stroke), losses to follow-up, and inconsistency between the two groups in the use of other treatments that may have impacted the findings. The second RCT did not demonstrate noninferiority for the same composite outcome as the first trial (stroke, cardiovascular/unexplained death, or systemic embolism). However, the trial reported noninferiority of the WATCHMAN™ device to warfarin for late ischemic stroke and systemic embolization. The meta-analysis of the two trials reported a periprocedural risk of ischemic stroke with the WATCHMAN™ device and a lower risk of hemorrhagic stroke over the long term.

The published RCTs and meta-analysis report mixed results for the primary composite outcome and risk of safety events. In addition, the two RCTs have methodological limitations that may impact not only the RCT but also the meta-analysis findings which includes unblinding, differing stroke risk among study participants, loss of patients to follow-up, and poor compliance to Warfarin in the comparison groups. The current evidence base does not consistently demonstrate a net improvement in health outcomes (balance of benefit and harms) compared with established treatments for preventing stroke in patients with AF who are eligible to receive systemic anticoagulation.

The evidence for patients where the use of oral anticoagulants is not feasible consists of small nonrandomized studies with methodological limitations. These studies report on the placement of the device but many of them do not report on the *comparative* efficacy and safety of LAA closure in preventing strokes in this population. More high quality, comparative evidence is needed.

LARIAT® DEVICE

The available evidence on the efficacy of the Lariat device for LAA closure consists of a number of small case series.

Litwinowicz (2018) published a non-randomized, non-comparative single-center study of 139 patients undergoing LAAC with the LARIAT® device.[31] The study's primary outcomes were risk of thromboembolism, severe bleeding, and mortality with an average follow-up time of 4.2 years. The results of the study indicated that the rate of thromboembolisms is 0.6% and the severe bleeding rate was 0.8%. The reported mortality rate was 1.6%. The authors concluded that LAAC using this device is a safe and effective treatment for stroke prevention and bleed risk reduction in this population. The authors also noted the significant limitations with this study including the lack of control group, variability in post-procedure anticoagulation, and relying on calculated stroke or bleeding risks for analyses.

Gianni (2016) published a retrospective multicenter study of 98 patients who underwent LAA ligation with the LARIAT® device.[32] How many times and what the clinical implications of a leak were assessed. A transesophageal echocardiography assessed leaks during the procedure, at six and 12 months and after thromboembolic events. Leaks were detected in 5%, 15%, and 20% respectfully in patients at the three evaluation periods. The authors stated that because incomplete occlusion can occur, appropriate long-term surveillance should be performed, along with the addition of anticoagulant therapy or percutaneous transcatheter closure as needed.

A SR of published studies on the Lariat device was published in 2016.[33] No RCTs were identified. Five case series were selected, with a total of 309 patients (range, 4-154 patients) treated. The combined estimate of procedural success was 90.3%. One (0.3%) death was reported and seven (2.3%) patients required urgent cardiac surgery. The reviewers also searched the MAUDE database for adverse events and found 35 unique reports. Among the 35 reported complications, there were five deaths and 23 cases of emergency cardiac surgery.

Individual case series continue to be published, including a large case series of 712 consecutive patients from 18 U.S. hospitals.[34] This series reported a procedural success rate of 95% and complete closure in 98%. There was one death and emergent cardiac surgery was required in 1.4%.

A large case series was reported by Price (2014) in a retrospective multicenter study of early outcomes after use of the Lariat device.[35] 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 one 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 four patients (2.9%).

Gianni (2016) published a retrospective, multicenter study including 98 consecutive patients which evaluated the incidence and clinical implications of leaks (acute incomplete occlusion, early and late reopening) following LAA ligation with the LARIAT device.[32] Leaks were detected in 5 (5%), 14 (15%), and 19 (20%) patients at the three time points. A total of five patients developed neurological events (four strokes and one transient ischemic attack). Three occurred late and were associated with small leaks (< 5mm). The authors concluded that "incomplete occlusion of the LAA after LARIAT ligation is relatively common and may be associated with thromboembolic events.

Bartus (2013) reported results of a case series that enrolled 89 patients with AF and either a contraindication to warfarin or previous warfarin failure.[36] A total of 85 of 89 (96%) had successful left atrial ligation, and 81 of 89 (91%) had complete closure immediately. There were three access-related complications, two cases of severe pericarditis postoperatively, one late pericardial effusion, and two cases of unexplained sudden death. There were two 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,[37] 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 one procedural complication in which the snare could not be removed and were retrieved by thoracoscopy.

Stone (2013) 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.[38] 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 four months, during which time one stroke and no deaths occurred.

Massumi (2013)[39] reported on 21 patients with AF and contraindications to anticoagulation. A total of 20 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 one year. Complications were reported in 5 of 21 patients. One patient had right ventricular perforation and tamponade requiring surgical intervention. One patient developed pleuroperidicarditis that required multiple drainage procedures. Three additional patients developed pericarditis within 30 days of the procedure.

Section Summary

The current studies on the Lariat device are limited to small nonrandomized studies. While these studies report high procedural success, interpretation is limited due to methodological limitations such as small sample size, lack of randomized treatment allocation, and lack of a control group for comparison. Larger-scaled trials are needed to confirm the efficacy and safety of the Lariat device.

AMPLATZER® CARDIAC PLUG DEVICE

The available evidence on use of the Amplatzer device for left atrial occlusion consists of a number of case series, most of which included less than 40 patients.[17,40-44] The largest case series, Nietlispach et al., attempted LAA occlusion in 152 patients from a single institution.[45] Amplatzer Cardiac Plugs were used in 120 patients and nondedicated devices were used in 32 patients. Short-term complications occurred in 9.8% of patients (15/152). Longer-term adverse outcomes occurred in 7% of patients including two strokes, one peripheral embolization, and four episodes of major bleeding. Device embolization occurred in 4.6% (7/152) of patients.

Berti (2016) evaluated consecutive, high-risk patients (n=110) with non-valvular atrial fibrillation and contraindications to oral anticoagulants.[46] There was a mean follow-up of 30±12 months. Procedures were performed using the Amplatzer Cardiac Plug or Amulet. Berti reports procedural success (technical success without major procedure-related complications) was achieved in 96.4%. The rate of major procedural complications was 3.6% (three cases of pericardial tamponade requiring drainage and one case of major bleeding). The annual rate of ischemic stroke and other thromboembolic events were 2.2% and 0%, respectively. The annual rate for major bleeding was 1.1%.

Additional case series of patients treated with the Amplatzer device were published including patients from different countries.[17,25,40,47-50] Many of the case 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 four years postprocedure, for 134 patients with nonvalvular AF and a long-term contraindication to oral anticoagulation treated with the Amplatzer device.[51] 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 three major procedure-related complications (two cases of cardiac tamponade, one 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 (2013) 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.[52] All patients were treated with heparin during the procedure; they were maintained on clopidogrel for one month postprocedure and daily aspirin indefinitely. Successful deployment occurred in all patients. There were two significant periprocedural complications, including one pericardial effusion with tamponade and one case of acute respiratory distress with pulmonary edema.

Wiebe (2014) 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.[43] 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 (2013) 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.[44] Device implantation was successful in all but one 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.

Figini (2016) published retrospective results from a single center in Italy between 2009 and 2015.[25] The study included 165 patients in which 99 received the Amplatzer Cardiac Plug (ACP) and 66 the WATCHMAN™ system. The mean follow-up was 15 months. A total of five patients died and one patient had an ischemic attach. There were no episodes of definitive stroke recorded or reported. However, there were twenty-six leaks ≥1 mm detected (23%) and were not found to correlate with clinical events. The authors noted that further investigation is warranted for the small peri-device flow.

Other smaller case series of patients with contraindication to oral anticoagulation include studies by Danna et al,[40] which included 37 patients and reported a 1-year stroke rate of 2.94%, and Horstmann et al,[53] which included 20 patients and reported no episodes of strokes over a mean follow-up of 13.6 months.

Gloekler (2015)l[54] 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.

Section Summary

All of the nonrandomized studies report high procedural success, but also report various complications such as vascular complications, air embolism, esophageal injury, cardiac tamponade, and device embolization. Well designed, large RCTs are needed to confirm the efficacy and safety of this device.

PLAATO DEVICE

Bayard (2010) reported on 180 patients with nonrheumatic atrial fibrillation and a contraindication to warfarin and who were treated with the PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) device.[55] Placement was successful in 90% of patients. Two patients died within 24 hours of the procedure (1.1%), and six patients had cardiac tamponade (3.3%), with two required surgical drainage. During a follow-up of 129 patient-years, three strokes were reported for a rate of 2.3% per year. Other case reports and small case series report complications, including multiple reports of thrombus formation at the site of device placement.[55,56]

Section Summary

The nonrandomized studies report high procedural success, but also report various complications. Well designed, large RCTs are needed to confirm the efficacy and safety of this device.

ATRICLIP DEVICE

Ad (2015) reported on 24 patients that received the Atriclip PRO. Ninety five percent of patients had nonparoxysmal AF.[57] The clip did not deploy in one patient but the procedural success was 95%. Another study reported on 30 procedures for the Atriclip.[58] The device was successfully placed in 28 of the 30 patients and the study didn’t report any adverse events at follow-up. A multicenter study reported on a total of 71 patients receiving the Atriclip device.[59] Safety of the device was assessed at 30 days and there was a three month follow-up for efficacy. One patient was not able to receive the Atriclip device but procedural success was confirmed in 67 of 70 patients. Significant adverse events were reported in 34 of 70 patients. There was no adverse events from the device itself and no perioperative mortality. At the three month follow-up, one patient passed away and 60 of 61 patients still had successful occlusion.

Section Summary

Nonrandomized studies report high procedural success, but also report various complications. Well designed, large RCTs are needed to confirm the efficacy and safety of this device.

EVALUATIONS OF MULTIPLE DEVICES

Hanif (2017) published a SR of RCTs to compare the risk of stroke in patients with left atrial appendage occlusion (LAAO) versus anticoagulant, antiplatelet, or placebo therapy.[60] The impact on operative time, major bleeding, and mortality were assessed. Although LAAO was found to be better than anticoagulant therapy for stroke and mortality, the authors stated the evidence had methodological limitations.

Health Quality Ontario (2017) performed a SR evaluating both clinical and cost effectiveness of left atrial appendage closure devices versus novel anticoagulants e.g. dabigatran or versus Warfarin.[61] .Five studies compared novel anticoagulants to Warfarin and two compared left atrial appendage closure to Warfarin. The authors concluded that moderate quality evidence indicates left atrial appendage closure is as effective as novel oral anticoagulants for patients with nonvalvular AF, but is cost effective only for patients who cannot take anticoagulants.

Lempereur (2017) published a SR evaluating device associated thrombosis (DAT) for the Watchman™, Amplatzer™ Cardiac Plug (ACP), and Amulet devices from 2008-2015.[62] Thirty studies were included. The mean frequency of DAT after LAAO was 3.9% for all devices (82/2118). The reported frequency of DAT six weeks after implant was similar for WM and ACP/Amulet (2.0 versus 2.6%, respectively, $P = 0.60$). The reported frequency of events did not appear to change over time. The conclusion was that DAT was an infrequent complication of LAAO as it occurs mostly in the early post procedure, and there is a low rate of neurological complications. But, the authors stated their review had limitations including lack of a standard definition for DAT amongst studies and that the review was based only on published data. Therefore unpublished, underreported and/or underdiagnosed DATs would impact the review outcomes. Additional larger multicenter studies are needed to determine risks, complications, and treatment efficacy of LAAO.

Wei (2016) published a SR evaluating two RCTs (PROTECT AF and PREVAIL) and 36 observational studies on the safety and effectiveness of left atrial appendage occlusion (LAAO) devices.[63] The systems mainly involved in the studies included PLAATO, the Amplatzer® Cardiac Plug device, and WATCHMAN™. Other devices such as nondedicated Amplatzer® occluders, and WaveCrest® were also reviewed. Procedure failure was 0.02 (95% CI: 0:02-0.03), with no heterogeneity amongst studies. All-cause mortality was 0.03 (95% CI: 0.02-0.03) and cardiac/neurological mortality was 0 (95% CI: 0.00-0.01), with low pooled results and no heterogeneity amongst studies. The frequency of stroke/transient ischemic attack was 0.01 (95% CI: 0.01-0.01), with no heterogeneity amongst studies. The frequency of thrombus on devices was 0.01 (95% CI: 0.01-0.02), with no heterogeneity amongst studies. Major hemorrhagic event complications were 0.01 (95% CI: 0.00-0.01), with no heterogeneity amongst studies. Of the devices, most did not differ in the frequency of events except all-cause mortality and cardiac/neurological mortality was higher for the PLAATO group and thrombus occurred more often in the ACP group and less often in the PLATTO group. The authors stated LAAO is safe and effective and there is a low rate of failure, for patients not able to be on long-term anticoagulant therapy. However, the authors stated their study had limitations, including but not limited to the definition of safety and effectiveness varied amongst studies, there were only two RCTs, two large studies did not report cardiac or neurological death frequencies, and the data on specific devices was not always easy to assess.

Li (2016) published a SR to report how effective and safe LAAO devices were for greater than one year, when compared to novel oral anticoagulants (NOACs).[64] They evaluated six RCTs and 27 observational studies. The authors stated the RCTs showed that LAAO was not better than NOACs for stroke prevention (odds ratio 0.86), but did show LAAO patients had less hemorrhagic events at follow-up. An analysis of the observational studies showed that LAAO patients had a lower rate of both thromboembolic events (1.8 per 100 patient-years versus 2.4 events per 100 patient-years) and major bleeding (2.2 events per 100 patient-years versus 2.5 events per 100 patient-years). During longer follow-up periods patients with LAAO had less thromboembolic events (2.1, 1.8, and1.0 events per 100 person-years for 1, 1-2, and > 2 years respectively). The authors stated the SR had limitations, including but not limited to different follow-up durations between LAAO and NOAC groups and number of patients who received LAAO was less than those receiving NOACs. They stated additional studies with consistent homogeneity could assess healthcare outcomes and assist in confirming this study's findings.

Xu conducted a comprehensive literature search for studies evaluating patients after receiving an occlusion device.[23] Studies were included if they had at least 10 patients followed for at least six months. Twenty five total studies were included with only two RCTs and the rest were cohort studies (N= 2,779). Xu performed a meta-analysis of stroke events and adverse events after patients received an occlusion device. Xu reported that the adjusted incidence rate of stroke was 1.2/100 person-years (PY) (95% confidence interval [CI], 0.9-1.6/100 PY) and the ischemic and hemorrhagic stroke rates were 1.1/100 PY (95% CI, 0.8-1.4/100 PY) and 0.2/100 PY (95% CI, 0.1-0.3/100 PY), respectively. Additionally, the combined efficacy outcomes (stroke or transient ischemic attacks [TIAs], systemic embolism, or cardiovascular death) was 2.7/100 PY (95% CI, 1.9- 3.4/100 PY). The most common adverse events were major bleeding and pericardial effusions at a rate of 2.6% (95% CI, 1.5%-3.6%) and 2.5% (95% CI, 1.8%-3.2%), respectively.

Sahay conducted a SR of the evidence with a network meta-analysis of all RCTs (N=19) with a total of 87,831 patients.[65] The network analysis evaluated the safety and efficacy of left atrial appendage closure compared to other strategies for stroke prevention in atrial fibrillation.[65] The network meta-analysis includes direct and indirect comparisons for these various treatment strategies. The analysis compared treatment strategies to warfarin as a common comparator group. The authors reported that "…using warfarin as the common comparator revealed efficacy benefit favoring LAAC as compared with placebo (mortality: HR 0.38, 95% CI 0.22 to 0.67, p<0.001; stroke/SE: HR 0.24, 95% CI 0.11 to 0.52, p<0.001) and APT (mortality: HR 0.58, 95% CI 0.37 to 0.91, p=0.0018; stroke/SE: HR 0.44, 95% CI 0.23 to 0.86, p=0.017) and similar to NOAC (mortality: HR 0.76,= 95% CI 0.50 to 1.16, p=0.211; stroke/SE: HR 1.01, 95% CI 0.53 to 1.92, p=0.969)." The rates for major bleeding were comparable. The authors further note that caution should be taken in interpreting these results as more studies are needed to further substantiate the findings especially in light of the wide confidence intervals.

Betts (2016) evaluated the feasibility and long term efficacy of LAAO using a retrospective multicenter registry (July 2009-November 2014).[66] The devices included the WATCHMAN™ (63%), Amplatzer™ Cardiac Plug (34.7%), Lariat (1.7%) and Coherex WaveCrest (0.6%). A total of 371 patients were included and the overall procedure success was 92.5% with major adverse events in 3.5% of patients. The authors reported "an annual 90.1% relative risk reduction (RRR) for ischemic stroke, an 87.2% thromboembolic events RRR, and a 92.9% major bleeding RRR were observed, if compared with the predicted annual risks based on CHADS2, CHA2DS2-Vasc, and HAS-BLED scores, respectively, over a follow-up period of

24.7 ± 16.07 months. In addition, the authors reported higher success rates and a reduction in acute major complications in the second half of recruitment.

PRACTICE GUIDELINE SUMMARY

AMERICAN COLLEGE OF CARDIOLOGY, HEART RHYTHM SOCIETY, AND SOCIETY FOR CARDIOVASCULAR ANGIOGRAPHY AND INTERVENTIONS

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.[67] 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, THE AMERICAN HEART ASSOCIATION, AND HEART RHYTHM SOCIETY[3]

The 2014 ACC/AHA/HRS guidelines on the management of patients with AF 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 the use of LAA closure devices.

AMERICAN COLLEGE OF CHEST PHYSICIANS (ACCP)

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.[1] In relation to the use of LAA closure devices, the guidelines states “At this time, we make no formal recommendations regarding LAA closure devices, pending more definitive research in this field.”

SUMMARY

There is not enough research to show that the WATCHMAN™ device results in consistent improved health outcomes. The current research is mixed with some research reporting improved net health outcomes (balance of benefit and harms) and other research not reporting improved outcomes compared to current standards of care. There is not enough research for the use of other left atrial appendage closure devices (e.g., PLAATO, Lariate, Amplatzer, Atriclip) to conclude improved health outcomes and there have been some safety concerns reported. No evidence-based practice guidelines recommend the use of any of these devices. Therefore, the use of left atrial appendage closure devices is investigational for all indications including but not limited to the prevention of stroke in patients with atrial fibrillation.

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CODES

Codes	Number	Description
CPT	33340	Percutaneous transcatheter closure of the left atrial appendage with endocardial implant, including fluoroscopy, transseptal puncture, catheter placement(s), left atrial angiography, left atrial appendage angiography, when performed, and radiological supervision and interpretation
	93799	Unlisted cardiovascular service or procedure
HCPCS	None	

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