



Medical Coverage Policy

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Nonpharmacological Treatments for Atrial Fibrillation

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Overview

This Coverage Policy addresses nonpharmacological treatments for atrial fibrillation including transcatheter ablation of the pulmonary veins (pulmonary vein isolation), surgical and percutaneous transcatheter closure of the left atrial appendage and surgical and minimally invasive maze procedures.

Coverage Policy

Transcatheter ablation of the pulmonary veins (pulmonary vein isolation) (Current Procedural Terminology [CPT®] codes 93656, 93657, 93662) is considered medically necessary when EITHER of the following criteria are met:

- **Diagnosis of symptomatic (e.g., palpitations, fatigue, or effort intolerance) paroxysmal or persistent atrial fibrillation AND refractory or intolerant to at least one Class I or Class III antiarrhythmic medication (e.g., amiodarone, dronedarone, flecainide, propafenone, sotalol).**

- **Recurrent symptomatic paroxysmal atrial fibrillation, as an initial rhythm control strategy prior to therapeutic trials of antiarrhythmic drug therapy**

Transcatheter ablation of the pulmonary veins for any other indication is considered experimental, investigational or unproven.

Percutaneous transcatheter or surgical closure of the left atrial appendage (CPT codes 33340, 33999) is considered experimental, investigational or unproven.

Cigna covers the surgical Maze or modified Maze procedure ([CPT codes 33256, 33257, 33259), performed during cardiopulmonary bypass with or without concomitant cardiac surgery, as medically necessary for medically refractory, intermittent (i.e., paroxysmal or persistent) or continuous (i.e., permanent), symptomatic atrial fibrillation when rhythm control is considered essential.

Cigna does not cover a minimally invasive off-pump Maze procedure including a hybrid or convergent ablation procedure (CPT codes 33254, 33255, 33258, 33265, 33266) for any indication including the treatment of atrial fibrillation because each is considered experimental, investigational or unproven.

General Background

Atrial fibrillation (AF) is a heart condition that causes an irregular and often abnormally fast heart rate (tachycardia). A normal heart rate should be regular and between 60 and 100 beats a minute when resting. In AF, the heart rate is irregular and can sometimes be very fast possibly higher than 100 beats a minute. This can cause symptoms such as dizziness, shortness of breath, and tiredness that affect quality of life. AF may increase the risk of suffering a stroke and/or peripheral thromboembolism owing to the formation of atrial thrombi, usually in the left atrial appendage (LAA). The mechanisms causing and sustaining AF are multifactorial, and AF can be complex and difficult to manage. AF symptoms range from non-existent to severe. The appearance of AF is often associated with exacerbation of underlying heart disease, either because AF is a cause or consequence of deterioration, or because it contributes directly to deterioration. Other atrial arrhythmias are often encountered in patients with AF. Atrial tachycardias are characterized by an atrial rate of ≥ 100 bpm with discrete P waves and atrial activation sequences. Many potentially reversible causes of AF have been reported, including binge drinking, cardiothoracic and noncardiac surgery, pericarditis, myocardial infarction (MI), myocarditis, hyperthyroidism, electrocution, pneumonia, and pulmonary embolism. AF is the most common arrhythmia treated in clinical practice and the most common arrhythmia for which patients are hospitalized. Approximately 33% of arrhythmia-related hospitalizations are for AF (Morady, et al, 2019; Nyong, et al., 2016; January, et al., 2014).

In the majority of people, AF is recurrent and progresses from paroxysmal, to persistent with the need for cardioversion into normal heart rhythm, or it can progress into permanent forms. AF may be described in terms of the duration of episodes as follows (Morady, et al, 2019; Spragg, et al., 2019; Passman, et al., 2019a; Nyong, et al., 2016; January, et al., 2014):

- **Paroxysmal (i.e., self-terminating or intermittent) AF:** Recurrent AF (≥ 2 episodes) that terminates spontaneously or with intervention within 7 days of onset, usually less than 24 hours. Episodes may recur with variable frequency.
- **Persistent AF:** Continuous AF that fails to self-terminate within 7 days.
- **Longstanding persistent AF:** Continuous AF > 12 months duration
- **Permanent AF:** Used when there is a joint decision by the patient and the clinician to cease further attempts to restore and/or maintain sinus rhythm.
- **Nonvalvular AF:** AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair
- **Lone AF:** occurs in patients younger than 60 years who do not have hypertension or any evidence of structural heart disease

Treatment for AF focuses on the management of underlying causes, reducing the risk of stroke with antithrombotic agents (i.e., anticoagulant [e.g., warfarin] and antiplatelet drugs [e.g., aspirin]), pharmacologically

controlling the heart rate and or rhythm, and resetting the heart rhythm to sinus rhythm through the use of direct current cardioversion. If AF episodes continue despite these approaches, implantable pacemakers, or thermal energy ablation or surgical techniques, have been proposed. These treatment objectives are not mutually exclusive. Treatment strategies can be broadly subdivided into rate control (the ventricular rate is controlled and the atria are allowed to fibrillate) or rhythm control (there is an attempt to reestablish and maintain normal sinus rhythm). Several randomized trials have compared a rate-control strategy with a rhythm control strategy. In the largest such study (Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) AFFIRM Investigators, 2002), the prevalence of sinus rhythm was 35% in the rate control arm and 63% in the rhythm control arm at five years, but there was no significant difference in total mortality, stroke rate, or quality of life. Patients in the rate control arm required hospitalization at a significantly lower rate (73%) compared to patients in the rhythm-control arm (80%), and the incidence of adverse drug effects was also significantly lower in the rate-control arm than in the rhythm control arm. This study demonstrated that a rate control strategy is preferable in patients age 65 or older who are asymptomatic or minimally symptomatic. This trial did not address AF in younger, symptomatic patients without significant underlying heart disease, however. Restoration of sinus rhythm still must be considered a useful therapeutic approach in these patients. The decision of which strategy to pursue is individualized, and is based on the nature, frequency and severity of symptoms, length of duration of AF, comorbidities, response to prior cardioversions, age, side effects and efficacy of antiarrhythmic drugs, and patient preference. Left atrial size is also a consideration. Left atrial enlargement is associated with AF and is a strong predictor of recurrence. AF can be more easily induced and maintained in an enlarged atrium, and conversion to sinus rhythm is less likely to be maintained in the presence of left atrial enlargement (January et al., 2014).

A major goal of therapy in patients with AF is to prevent thromboembolic complications such as stroke. Because of the risk of hemorrhage from anticoagulants, their use is limited to patients whose risk of thromboembolic complications is greater than the risk of hemorrhage. It is useful to risk stratify patients with AF to identify appropriate candidates for anticoagulation. The strongest predictors of ischemic stroke and systemic thromboembolism are a history of stroke or transient ischemic episode and mitral stenosis.

A simple clinical scheme to risk stratify patients on the basis of the major risk factors is the CHADS₂ (cardiac failure, hypertension, age, diabetes, stroke) score. Each of the first four risk factors counts as 1 point, and a prior stroke or transient ischemic event is 2 points. There is a direct relationship between the CHADS₂ score and the annual risk of stroke in the absence of aspirin or warfarin therapy. The CHADS₂ score has been superseded by the CHA₂DS₂-VASc score because it more accurately discriminates low-risk from intermediate-risk patients. In this risk-scoring system, cardiac failure, hypertension, diabetes, vascular disease, age 65-74 years, and female gender are 1 point each, and age 75 or older and prior stroke or transient ischemic event are 2 points. (Morady, et al, 2019).

A consideration in patients treated with an oral anticoagulant is the risk of bleeding. Several risk-scoring systems have been developed to assess a patient's susceptibility to hemorrhagic complications. The scoring system with a balance of simplicity and accuracy is the HAS-BLED score. The components of this score are hypertension, abnormal renal or liver function, stroke, bleeding history or predisposition, labile international normalized ratio (INR), elderly (>75 years), and concomitant drug (antiplatelet agent or nonsteroidal anti-inflammatory drug) or alcohol use. Each of these components is 1 point. As the score increases from 0 to the maximum of 9, there is a stepwise increase in the risk of bleeding in patients treated with warfarin (Morady, et al, 2019).

Catheter Ablation of Atrial Fibrillation (AF)

Catheter ablation targeting the pulmonary veins has been considered an intermediate step prior to surgical intervention. Catheter ablation is used to destroy myocardial tissue by delivering energy over electrodes on a catheter placed next to an area of the endocardium determined to be integral to the onset and/or maintenance of the arrhythmia. A high percentage of patients with paroxysmal AF have excitatory foci in the superior aspect of the left atrium, in close proximity to the pulmonary veins. Specifically, the small area of cardiac muscle extending across the ostium of each pulmonary vein is notable for the frequent presence of excitatory foci. Transcatheter ablation of arrhythmogenic foci in the pulmonary veins is also referred to as pulmonary vein isolation (PVI), because the ablation is intended to interrupt conduction of the abnormal excitatory foci from the pulmonary veins to other areas of the atria. Several catheters with specialized tips are used to perform ablation. The majority of

ablations performed use radiofrequency energy, cryotherapy (cryoballoon ablation) or infrared laser. Access to the left atrium is typically obtained using a special transseptal-sheath-dilator combination inserted into the femoral vein and advanced over a guidewire into the right atrium. Using this system, the intra-atrial septum is punctured (transseptal puncture), allowing access by ablation catheters to the pulmonary veins. PVI has been proven effective in a subset of patients as an intermediate step prior to surgical intervention. Cardiac ablation is typically performed by an interventional cardiologist (Morady, et al., 2019; Hayes, 2016; Jahangiri, et al., 2006).

U.S. Food and Drug Administration (FDA)

Radiofrequency Ablation

Numerous radiofrequency ablation catheters have received FDA approval through the premarket application (PMA) process for treatment of arrhythmias. Devices initially were submitted for treatment of specific arrhythmias (e.g. supraventricular tachycardia, atrial flutter, ventricular tachycardia). A 2002 FDA guidance document encouraged manufacturers of approved RFA catheters to submit a PMA supplement to revise their indication statements from an arrhythmia-specific indication to a generic arrhythmia indication. This recommendation was based on the fact that the safety and effectiveness of these devices for treating many common arrhythmias had been reported and was well characterized in the medical literature.

Cryoablation

The Arctic Front® CryoCatheter System (Medtronic CryoCath, Quebec Canada) received FDA approval through the PMA process on December 17, 2010. According to the approval letter, the device is indicated for the treatment of drug refractory recurrent symptomatic paroxysmal atrial fibrillation. The system is comprised of the Arctic Front CryoAblation Catheters (models 2AT232 and 2AF282), Freezor® MAX CryoAblation Catheter, CryoConsole Gen V Model, Manual Retraction Kit and Accessories. The Freezor MAX catheter is used as an adjunctive device in the endocardial treatment of paroxysmal atrial fibrillation, in conjunction with Arctic Front CryoCatheter for the following uses:

- gap cryoablation to complete electrical isolation of the pulmonary veins
- cryoablation of focal trigger sites
- creation of ablation line between the inferior vena cava and the tricuspid valve

The Arctic Front is the first cryoballoon approved for the treatment of paroxysmal atrial fibrillation. Several cryoablation catheters had previously received PMA approval for the treatment of various cardiac arrhythmias, including ventricular tachycardia, atrial flutter, and AV nodal reentrant tachycardia.

Laser

The HeartLight® Endoscopic Ablation System (CardioFocus, Inc., Marlborough, MA) received FDA approval through the PMA process on April 1, 2016 (P150026). According to the approval letter, the device is indicated for the treatment of drug refractory recurrent symptomatic paroxysmal atrial fibrillation. The HeartLight System consists of the HeartLight Catheter, Endoscope and Balloon Fill Media, and a console. The HeartLight Catheter is a sterile, single-use, disposable device that delivers infrared laser energy to create a rise in tissue temperature resulting in thermal ablation of the target tissue.

The FDA Summary of Safety and Effectiveness Data (SSED) states that the CardioFocus HeartLight Endoscopic Ablation System has been marketed in Germany, The Czech Republic, The United Kingdom, The Netherlands, Belgium, Switzerland, Spain, Italy, Sweden and Australia. A clinical study named HeartLight (Dukkipati, et al., 2015) was performed to establish a reasonable assurance of safety and effectiveness of the HeartLight System to treat drug refractory recurrent symptomatic paroxysmal atrial fibrillation (AF) in the US under IDE G090080. Data from this clinical study were the basis for the PMA approval decision.

Literature Review

A number of studies in the peer-reviewed literature have demonstrated that transcatheter ablation of the pulmonary veins (pulmonary vein isolation) may be a secondary treatment option for patients with recurrent symptomatic paroxysmal or persistent AF when antiarrhythmic drug therapy (ADT) has failed to restore sinus rhythm. It has been increasingly used for prevention of paroxysmal AF episodes. Whether it should be considered first-line therapy has been a subject of debate and evaluated in several small randomized studies. On the basis of these findings, current professional society guidelines have classified pulmonary vein isolation as

first-line therapy for recurrent symptomatic paroxysmal atrial fibrillation, as an initial rhythm control strategy prior to therapeutic trials of antiarrhythmic drug therapy paroxysmal AF as a Class IIa recommendation. Catheter-based pulmonary vein isolation is most commonly performed with radiofrequency. Alternative energy sources have also been developed, including cryoballoon and balloon-based laser ablation (Spragg, et al., 2019; Calkins, et al., 2017; Kirchhof, et al., 2016, January, et al., 2014).

Radiofrequency Ablation: A wide range of success rates for radiofrequency catheter ablation of atrial fibrillation (AF) has been reported in the literature (Wilber, et al., 2010; Oral, et al., 2006; Stabile, et al., 2006; Pappone, et al., 2006; Calkins, et al., 2009). A meta-analysis of 63 studies in which radiofrequency catheter ablation of paroxysmal or persistent AF was performed reported an overall single-procedure success rate of 57% at a mean follow-up of 14 months and a multiple-procedure success rate of 71% (Calkins, et al., 2009).

Cryoballoon Ablation: Evidence in the peer-reviewed literature suggests that transcatheter cryoablation/CB ablation of the pulmonary veins is technically feasible and an effective alternative for the treatment of a subset of patients with paroxysmal or persistent AF. The evidence suggests that cryoablation reduces volume of contrast used, decreases the fluoroscopy and total procedure time, without compromising the success of PVI (Luke, et al., 2015; Straube, et al., 2014; Aryana, et al., 2015; Jourda, et al., 2014; DeVille, et al., 2014; Andrade, et al., 2014; Packer, et al., 2013; Malmborg, et al., 2013; Mugnai, et al., 2014; Vogt, et al., 2013; Kojodjojo, et al., 2010; Kuhne, et al., 2010; Linhart, et al., 2009; Tang, et al., 2010; Xu, et al., 2014; Andrade, et al., 2011; Skelly, et al., 2015; Noheria, et al., 2008).

Laser Balloon Ablation: The literature search identified nine clinical studies (n=60-353) that compared the efficacy and safety of laser balloon ablation (LBA) with cryoballoon ablation (CBA) or radiofrequency ablation (RFA) for the treatment of paroxysmal or persistent AF. Study designs included randomized controlled trials (Schmidt, et al., 2017; Dukkupati, et al., 2015; Schmidt, et al., 2013), nonrandomized controlled trials (Bordignon, et al., 2013), observational comparative study (Stöckigt, et al., 2016), prospective cohort studies (Wissner, et al., 2014; Metzner, et al., 2011), a trial with historical controls (Bordignon, et al., 2016), and a retrospective cohort study (Tsyganov, et al., 2015). Follow-up ranged from immediately post-ablation to 12 months. There is a moderate-quality body of evidence in the peer-reviewed literature suggesting that at 12 month follow-up LBA is comparable to radiofrequency ablation (RFA) or cryoballoon ablation (CBA) in efficacy and safety for the treatment of drug-refractory recurrent symptomatic paroxysmal atrial fibrillation (PAF). (Hayes, 2016, 2017, 2018). The HeartLight Endoscopic Ablation System is the only FDA-approved LBA system for AF and has been approved for the treatment of drug-refractory recurrent symptomatic PAF. Ongoing studies assessing laser balloon ablation for AF can be found at ClinicalTrials.gov.

Several additional types of ablation catheters have been developed including, a high-intensity focused ultrasound balloon catheter, microwave catheter, and a high-density mesh ablator catheter. These devices are being evaluated in clinical trials but have not yet received FDA approval. Additional well-designed trials with long-term follow-up are needed before a definitive assessment can be made of the safety and efficacy of these methods compared to the established ablation methods (Morady, et al., 2019; Buch, et al., 2018; Koch, et al., 2012).

Literature Review

Paroxysmal Atrial Fibrillation Studies: Dukkupati et al. (2015) conducted a multicenter (n=19) randomized controlled trial (n=353, 334 analyzed) comparing the efficacy and safety of visually guided laser ablation (VGLB) ablation with standard irrigated radiofrequency ablation (RFA) during PV isolation (PVI) catheter ablation of drug refractory paroxysmal atrial fibrillation (PAF). Patients were randomized 1:1 to either LBA or RFA and assessed at 1, 3, 6, and 12 months follow-up. Inclusion criteria: ≥ 2 symptomatic AF episodes (≥ 1 minutes) within the previous 6 months; refractory intolerance to an antiarrhythmic drug (class I, II, or III). Exclusion criteria: PV size > 35 mm; left atrial thrombus; left atrial diameter > 55 mm; LVEF $< 30\%$; previous left atrial ablation for AF or atrial flutter (AFL); New York Heart Association class III or IV symptoms; myocardial infarction within the previous 60 days; unstable angina; cardiac surgery within the previous 3 months; coronary artery bypass grafting within the previous 6 months; any history of cardiac valve surgery; a thromboembolic event within the previous 3 months; uncontrolled bleeding; active infection; atrial myxoma; severe pulmonary disease or gastrointestinal bleeding; previous valvular cardiac surgery procedure; presence of an implantable cardioverter-defibrillator; women of childbearing potential who were pregnant, lactating, or not using adequate birth control; inability to be removed

from antiarrhythmic drug therapy. The HeartLight (CardioFocus) LBA system was used to perform VGLB ablation with the typical laser energy dose of 8.5 W x 20 seconds per lesion. The ThermoCool Navistar (Biosense Webster) irrigated RFA catheter was used to perform RFA. Primary efficacy endpoint: Freedom from protocol-defined treatment failure, defined as: (1) documented symptomatic AF (≥ 1 minutes); (2) ablation-induced left AFL or atrial tachycardia (AT) or AT of unknown origin; (3) failure to acutely isolate all PVs; (4) use of any antiarrhythmic drug (class I, II, or III); or (5) left heart ablation/surgery or implantable cardioverter-defibrillator placement for AF. Primary safety endpoint: Primary adverse events (AEs), defined as: transient ischemic attack (within 1 month of treatment) or stroke; cardiac perforation; tamponade; significant effusion; PV stenosis; diaphragmatic paralysis (persisting beyond blanking period); atrio-esophageal fistula; death; major bleeding requiring transfusion; myocardial infarction (Q-wave only [within 1 week of treatment]); and AF/AFL requiring cardioversion. Secondary endpoints: 12-month drug-free rate of freedom from symptomatic AF or atypical AFL/AT; AEs; procedural data.

Primary endpoints outcomes (LBA; RFA): Freedom from treatment failure (% patients): 61.1%; 61.7%; noninferiority ($p=0.003$), suggesting noninferiority. Patients experiencing ≥ 1 AEs (number [%]): 20/170 (11.8%); 25/172 (14.5%); noninferiority ($p=0.002$), suggesting noninferiority. Clinical outcomes (LBA; CBA): 12-month drug-free rate of freedom from symptomatic AF or atypical AFL/AT (number [%] patients): 106/167 (63.5%); 106/166 (63.9%); ($p=0.94$). Total AEs: 24/170 (14.1%); 27/172 (15.7%); p value not statistically significant (NS). There was a 3.5% rate of phrenic nerve injury, but no pulmonary valve stenosis; both complications are frequently reported with other balloon technologies. Procedural data (LBA; RFA): Procedure time (mean minutes \pm SD): 236.0 \pm 52.8; 193.0 \pm 63.6; ($p<0.0001$), favoring RFA. Fluoroscopy time (mean minutes \pm SD): 35.6 \pm 18.2; 29.7 \pm 21.0; $p=0.006$, favoring RFA. Acute PVI success: 649/664 (97.7%); 658/664 (99.1%); ($p=0.05$). Study limitations include lack of blinded assessment, allocation concealment and power analysis not reported, and use of ≥ 1 -minutes definition for documenting symptomatic AF compared with the 30-second standard duration (Dukkipati, et al., 2015).

Schmidt et al. (2013) conducted a single center randomized controlled trial ($n=99$) to compare the asymptomatic cerebral lesions (ACL) incidence between irrigated radiofrequency current (RFC), the single big cryoballoon (CB), and the endoscopic laser-balloon (LB). No follow-up was noted. Inclusion criteria: adults with drug-refractory paroxysmal PAF. Exclusion criteria: Left atrial size > 50 mm; LVEF $< 45\%$; any contraindications for MRI scanning; stage III renal failure; presence of intracardiac thrombus; CHADS (congestive heart failure [C], high blood pressure [H], age ≥ 75 years [A], diabetes [D], stroke or transient ischemic attack [S]) score > 3 . Patients were randomized 1:1:1 to either LBA, CBA, or RFA. One- to 2-days post ablation, all patients underwent cerebral MRI scans. LBA group: A point-by-point method was used to apply laser energy. CBA group: A 28 mm balloon was used for all procedures. RFA group: A maximum power of 40 W, a cutoff temperature of 43° Celsius (C), and a flushing rate of 17 to 25 milliliters per minute (mL/min) was used for irrigated ablations. Outcome measures: ACL incidence; procedure time; PVI isolation rate. Outcome measure results: AEs (LBA; CBA; RFA): ACL incidence: 8/33 (24.2%); 6/33 (18.2%); 8/33 (24.2%); ($p=0.8$). No major procedural complications were reported. Procedural data (LBA; CBA; RFA): Procedure time (mean minutes \pm SD): 149 \pm 34; 129 \pm 29; 103 \pm 33; ($p\leq 0.05$), favoring CBA and RFA over LBA. PVI rate: 100%; 100%; 100%. Study limitations include small sample size, lack of power analysis, lack of blinding of outcome assessors, no follow-up, and only obtaining preprocedural cerebral magnetic resonance imaging (MRI) scans in 20 patients; thus, the existence of preprocedural ACLs in the remaining 79 patients was unknown.

Bordignon et al. (2013) conducted a nonrandomized controlled study ($n=140$) to compare the safety and efficacy of the cryoballoon (CB) and the laser balloon (LB). Patients with drug-refractory paroxysmal atrial fibrillation (PAF) were prospectively allocated in a 1:1 fashion to undergo a PVI procedure with the 28 mm CB or the LB and were followed for 12 months using 3-day Holter ECG recording. Inclusion criteria was PAF refractory to ≥ 1 membrane active antiarrhythmic drug; age 18 to 75 years; no prior PVI attempt; left atrial size < 50 millimeters (mm); left ventricular ejection fraction (LVEF) $> 45\%$; ability to receive therapeutic oral anticoagulation. Exclusion criteria was not reported. The primary efficacy endpoint was a documented AF recurrence ≥ 30 seconds between 90 and 365 days after the index ablation. Secondary endpoints: Procedural data. In total, 269 of 270 PVs (99.6%) and 270 of 273 PVs (98.9%) were acutely isolated in the CB and LB group, respectively. Mean procedural time was 136 \pm 30 minutes for the CB group and 144 \pm 33 minutes for the LB group ($p=0.13$). Mean fluoroscopy time was longer in the CB group (21 \pm 9 minutes vs 15 \pm 6 minutes; $p< 0.001$). During 12 months

follow-up, 37% of patients in the CB group and 27% in the LB group experienced an AF recurrence ($p=0.18$). Phrenic nerve palsies occurred in 5.7% (CB) and 4.2% (LB) of patients, respectively.

Wissner et al. (2014) conducted a multicenter, prospective cohort study ($n=86$) comparing laser balloon ablation (LBA) ($n=44$), cryoballoon ablation (CBA) ($n=20$), and radiofrequency ablation (RFA) ($n=22$) in adults undergoing pulmonary vein isolation (PVI) for highly symptomatic, drug-refractory paroxysmal AF (PAF) or short-standing, persistent AF. The study excluded individuals with previous left atrial ablation procedure; long-standing, persistent AF; left atrial diameter > 60 mm; severe valvular heart disease; contraindications to post-interventional oral anticoagulation. All patients underwent pre- and post-procedural cerebral MRI to detect true incidence of new ACLs. Radiologists interpreting the MRI were blinded to ablation technique. Outcome measures included ACL incidence; adverse events; acute PVI success; procedural data. Adverse events (LBA; CBA; RFA): new asymptomatic embolic lesions (number [%] patients): 5/44 (11.4%); 1/20 (5.0%); 4/22 (18.2%); $p=0.4148$. New embolic lesions (number [%] patients): 6/44 (13.6%); 1/20 (5.0%); 4/22 (18.2%); $p=0.4870$. Phrenic nerve palsy (PNP): 1/44 (2.3%); 0/20 (0%); 0/22 (0%); $p=NR$. Procedural data (LBA; CBA; RFA): procedure time (mean minutes \pm SD): 195 \pm 47; 164 \pm 29; 208 \pm 69; $P=0.0021$, favoring CBA over LBA; $p=NR$ for LBA versus RFA. Acute PVI success: 41/44 (93.2%); 20/20 (100%); 22/22 (100%); $p=NR$. Study limitations include nonrandomized design, small sample size, method of group allocation not reported, and statistically significant differences between groups at baseline.

Metzner et al (2011) conducted a prospective cohort study ($n=60$) evaluating the incidence of esophageal thermal lesions comparing LBA ($n=40$) with RFA ($n=20$) in adults undergoing PVI for drug-refractory PAF at a single German center. Inclusion criteria: Symptomatic, drug-refractory PAF; eligible for PVI. Exclusion criteria: Persistent AF; previous PVI; left atrial diameter > 50 mm; PV diameter > 32 mm; severe valvular heart disease; contraindications to post-interventional oral anticoagulation. Esophagogastroduodenoscopy was performed 1 to 3 days postablation procedure. Outcome measures: Incidence and severity of esophageal thermal lesions; procedural data. Outcome results incidence of esophageal thermal lesions (number [%] patients) (LBA; RFA): Total esophageal thermal lesion: 7/40 (18%); 3/20 (15%); ($p>0.05$). Minimal thermal lesion: 3/40 (8%); 3/20 (15%); ($p>0.05$). Ulceration: 4/40 (10%); 0/20 (0%); ($p>0.05$). Atrio-esophageal fistula: No patient experienced perforation. Procedural data (LBA; RFA): Procedure time (mean minutes \pm SD): 234 \pm 62; 185 \pm 28; ($p=0.0014$), favoring RFA. Fluoroscopy time (mean minutes \pm SD): 28 \pm 16; 26 \pm 8; ($p=0.71$). PVI rate: 100%; 100%. A majority of patients in both groups did not experience thermal lesions (LBA group 82% versus RFA 85%). Although not statistically significant, more patients undergoing LBA experienced an ulceration at follow-up compared with patients receiving RFA (10% versus 0%, respectively). No perforations occurred in either group. Study limitations include nonrandomized design, small sample size, lack of blinded assessment, limited follow-up, no report of attrition and statistically significant group differences at baseline.

Tsyganov et al. 2015 conducted a single center retrospective cohort study ($n=100$) comparing LBA ($n=50$) with CBA ($n=50$) adults undergoing PVI for documented symptomatic PAF. Follow-up was 12 months. Inclusion criteria: Inclusion criteria: documented symptomatic PAF; no left ventricular dysfunction. Exclusion criteria was not reported. The HeartLight (CardioFocus) system was used to perform LBA ablations. A 28 mm Arctic Front (Medtronic) cryoballoon was used for all RFA procedures. Outcome measures primary endpoints: Acute PVI success. Secondary endpoints: AF recurrence; AEs; procedural data. Outcome results: Procedural data (LBA; CBA): Acute PVI success: 194/206 (94%); 193/199 (97%); ($p=0.83$). Procedure time (mean minutes \pm SD): 201.2 \pm 53.2; 147.0 \pm 37.4; ($p<0.001$), favoring CBA. Fluoroscopy time (mean minutes \pm SD): 20.4 \pm 7.7; 17.8 \pm 5.2; ($p=0.082$). Clinical outcomes (LBA; CBA): AF recurrence: 7/43 (16%); 11/45 (24%); ($p=0.21$). AEs (LBA; CBA): phrenic nerve palsy: 1/50 (2%); 2/50 (4%); ($p=NR$). Study limitations include retrospective design, small sample size, no description of inclusion or exclusion criteria, and no discussion of loss to follow-up.

Persistent Atrial Fibrillation Studies: In a matched historical controls study, Bordignon et al. 2016 compared LBA with RFA in 80 patients undergoing PVI for persistent AF at a single German center. Follow-up was 12 months. Results suggest that the use of LBA for PVI in patients with drug-refractory persistent AF of short duration produces similar clinical outcomes when compared with RFA. Study limitations include nonrandomized design, potential selection bias due to retrospective matching of LBA and RFA groups, and small sample size.

In an observational study ($n=70$), Stöckigt, et al. 2016 analyzed efficacy and safety results of LBA ($n=35$) compared to CBA ($n=35$) in patients with persistent and longstanding persistent AF. Follow-up was 12 months.

No significant differences were found for AF-free survival after 12 months in the complete cohort of all patients (LB: 53.3% vs CB: 70.4%) and after excluding patients without complete PVI (LB: 57.8% vs CB: 72.5%). LB ablation resulted in longer procedure (158.5 ± 37.9 minutes vs 110.9 ± 26.5 minutes) and fluoroscopy durations (28.4 ± 11.1 minutes vs 23.5 ± 9.4 minutes), and a trend toward more major complications (14.3% vs 2.9%). Study limitations were retrospective design and small sample size.

Professional Societies/Organizations

American Heart Association (AHA), American College of Cardiology (ACC), and Heart Rhythm Society (HRS): An updated guideline on the Management of Patients with Atrial Fibrillation (AF) was published by the AHA, ACC, and HRS in 2014 (January, et al, 2014). The authors noted that the decision whether to pursue catheter ablation depends on a large number of variables, including the type of AF (paroxysmal versus persistent versus longstanding persistent), degree of symptoms, presence of structural heart disease, candidacy for alternative options such as rate control or antiarrhythmic drug therapy, likelihood of complications, and patient preference. Efficacy of radiofrequency catheter ablation for maintaining sinus rhythm is superior to current antiarrhythmic drug therapy for maintenance of sinus rhythm in selected patient populations. Cryoballoon ablation is identified as an alternative to point-by-point radiofrequency ablation to achieve pulmonary vein isolation. The evidence supporting the efficacy of catheter ablation is strongest for paroxysmal AF in younger patients with little to no structural heart disease and in procedures performed in experienced centers. Evidence is insufficient to determine whether AF catheter ablation reduces all-cause mortality, stroke, and heart failure. Recurrences of AF after catheter ablation are common during the first three months and do not preclude long-term success, although they are associated with an increased risk of procedural failure and rehospitalization. A number of centers have reported late AF recurrences >1 year after catheter ablation. Complications of radiofrequency catheter ablation for AF noted in the AHA/ACC/ESC guideline include, but are not limited to, pulmonary vein stenosis, thromboembolism, atrioesophageal fistula and left atrial flutter, in addition to potential complications inherent in any cardiac catheterization procedure. Laser balloon ablation is not addressed in the guideline.

Recommendations for catheter ablation to maintain sinus rhythm include the following:

Symptomatic Paroxysmal AF:

- AF catheter ablation is useful for symptomatic paroxysmal AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication when a rhythm control strategy is desired (Class I: Level of Evidence A).

A Class I, Level of Evidence A indicates that the procedure or treatment should be performed, and the benefit outweighs the risk. The procedure is useful and effective, with sufficient evidence from multiple randomized trials or meta-analyses.

- In patients with recurrent symptomatic paroxysmal AF, catheter ablation is a reasonable initial rhythm control strategy prior to therapeutic trials of antiarrhythmic drug therapy, after weighing risks and outcomes of drug and ablation therapy (Class IIa: Level of Evidence B).

A Class IIa, Level of Evidence B indicates it is reasonable to perform the procedure/administer the treatment. The benefit outweighs the risk, but additional studies with focused objectives are needed. The recommendation is in favor of the treatment or procedure being useful/effective, with some conflicting evidence from single randomized trial or nonrandomized studies.

Symptomatic Persistent AF:

- AF catheter ablation is reasonable for selected patients with symptomatic persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication (Class IIa: Level of Evidence A).

A Class IIa, Level of Evidence A recommendation indicates it is reasonable to perform the procedure/administer the treatment. The benefit outweighs the risk, but additional studies with focused objectives are needed. The recommendation is in favor of the treatment or procedure being useful/effective, with some conflicting evidence from multiple randomized trials or meta-analyses.

- AF catheter ablation may be considered before initiation of antiarrhythmic drug therapy with a class I or III antiarrhythmic medication for symptomatic persistent AF when a rhythm-control strategy is desired (Class IIb: Level of Evidence C).

A Class IIb, Level of Evidence C recommends the procedure/treatment may be considered. The usefulness/efficacy less well established. Very limited patient populations. Only diverging expert opinion, case studies or standard of care.

In the 2019 focused update to the 2014 AHA/ACC/HRS guideline on the Management of Patients with AF no updated recommendations were made to the existing recommendations for catheter ablation to maintain sinus rhythm as stated above. The authors have addressed a new recommendation for catheter ablation in patients with symptomatic AF and heart failure (HF) with reduced left ventricular (LV) ejection fraction (HFrEF). The guideline addresses new evidence in the peer-reviewed literature that includes data on improved mortality rate for AF catheter ablation compared with medical therapy in patients with HF.

Recommendation for catheter ablation in HF:

- AF catheter ablation may be reasonable in selected patients with symptomatic AF and HF with reduced left ventricular (LV) ejection fraction (HFrEF) to potentially lower mortality rate and reduce hospitalization for HF (Class IIb: Level of Evidence N-R).

A Class IIb, Level of Evidence N-R recommendation is a weak class of recommendation. The benefits is \geq the risk. Moderate quality evidence from one or more well-designed, well-executed, nonrandomized studies, observations studies or registry studies or meta-analysis of such studies.

The supportive text for the recommendation states that in a randomized controlled trial (CASTLE-AF [Catheter Ablation vs. Standard Conventional Treatment in Patients With LV Dysfunction and AF]), selected patients with HFrEF with paroxysmal or persistent AF and an implanted cardioverter-defibrillator or cardiac resynchronization therapy defibrillator device who did not respond to or could not take antiarrhythmic drugs were randomized to receive AF catheter ablation versus medical therapy (rate or rhythm control) in addition to guideline-directed management and therapy for HFrEF (Marrouche, et al., 2018). Patients in the AF catheter ablation group had significantly reduced overall mortality rate, reduced rate of hospitalization for worsening HF, and improved LV ejection fraction as compared with the medical therapy group, and according to device interrogation, more patients in the AF catheter ablation group were in sinus rhythm. An additional RCT in a population of patients with persistent AF, HFrEF, and an implanted cardioverter defibrillator or cardiac resynchronization therapy defibrillator device demonstrated that AF catheter ablation was superior to amiodarone for maintenance of sinus rhythm, with secondary endpoint analyses suggesting a lower rate of unplanned hospitalization and death (Di Base, et al., 2016). Both studies have limitations, including relatively small and highly selected patient populations. Further, larger studies are needed to validate these findings. Other small studies conducted in patients with AF and HFrEF have shown the superiority of AF ablation over antiarrhythmic drugs in the maintenance of sinus rhythm and in outcomes such as improved LV ejection fraction, performance in a 6-minute walk test, and quality of life (Prabhu, et al., 2017; Al Halabi, et al., 2015). However, the recent CABANA (Catheter Ablation versus Anti-arrhythmic Drug Therapy for Atrial Fibrillation) trial (n=2,204 patients randomized to either catheter ablation or drug therapy) showed that AF ablation was not superior to drug therapy for the primary cardiovascular outcomes of death, disabling stroke, serious bleeding, or cardiac arrest at 5 years among patients with new onset or untreated AF that required therapy (Packer, et al., 2018) (January, et al., 2019).

Centers for Medicare & Medicaid Services (CMS)

- National Coverage Determinations (NCDs): No NCDs found
- Local Coverage Determinations (LCDs): No LCDs found

Use Outside of the US

Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA)/European Cardiac Arrhythmia Society (ECAS)/APHRS (Asia Pacific Heart Rhythm Society)/SOLAECE (Latin American Society of Cardiac Stimulation and Electrophysiology): An updated Expert Consensus Statement on Catheter and

Surgical Ablation of Atrial Fibrillation was published in 2017 by the HRS/EHRA/ECAS/APHRS/SOLAECE. This update replaces the 2012 HRS/EHRA/ECAS Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow-up, Definitions, Endpoints, and Research Trial Design.

The indications for catheter ablation of AF include:

Symptomatic AF refractory or intolerant to at least one Class I or III antiarrhythmic medication:

- Paroxysmal: Catheter ablation is recommended I A
- Persistent: Catheter ablation is reasonable IIa B-NR
- Longstanding Persistent: Catheter ablation may be considered IIb C-LD

Symptomatic AF prior to initiation of antiarrhythmic drug therapy with a Class I or III antiarrhythmic agent:

- Paroxysmal: Catheter ablation is reasonable IIa B-R
- Persistent: Catheter ablation may be considered II C-EO
- Longstanding Persistent: Catheter ablation may be considered IIb C

The indications for catheter AF ablation in populations of patients not well represented in clinical trials include:

Asymptomatic AF**

- Paroxysmal: Catheter ablation may be considered in select patients** IIb C-EO
- Persistent: Catheter ablation may be considered in select patients IIb C-EO

**A decision to perform AF ablation in an asymptomatic patient requires additional discussion with the patient because the potential benefits of the procedure for the patient without symptoms are uncertain.

The indications for catheter ablation of AF are presented with a class and grade of recommendation as follows:

Class:

Class I recommendation means that the benefits of the AF ablation procedure markedly exceed the risks, and that AF ablation should be performed.

Class IIa recommendation means that the benefits of an AF ablation procedure exceed the risks, and that it is reasonable to perform AF ablation.

Class IIb recommendation means that the benefit of AF ablation is greater or equal to the risks, and that AF ablation may be considered.

Class III recommendation means that AF ablation is of no proven benefit and is not recommended.

Level of Evidence:

Level A if the data were derived from high-quality evidence from more than one randomized clinical trial, meta-analyses of high-quality randomized clinical trials, or one or more randomized clinical trials corroborated by high-quality registry studies.

Level B-R when data were derived from moderate quality evidence from one or more randomized clinical trials, or meta-analyses of moderate-quality randomized clinical trials.

Level B-NR was used to denote moderate-quality evidence from one or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies. This designation was also used to denote moderate-quality evidence from meta-analyses of such studies.

Level C-LD when the primary source of the recommendation was randomized or nonrandomized observational or registry studies with limitations of design or execution, meta-analyses of such studies, or physiological or mechanistic studies of human subjects.

Level C-EO was defined as expert opinion based on the clinical experience of the writing group.

In the section of the guideline addressing the relationship between presence and type of AF and symptoms the authors state that the primary indication for catheter ablation is to reduce patient symptoms and improve quality of life. Prior to undergoing catheter ablation, it is important to confirm that the patient's symptoms (palpitations, fatigue, or effort intolerance) result from AF and to assess their severity. In some patients with paroxysmal AF

arrhythmia-monitoring tools (e.g., transtelephonic monitoring, Holter) are useful to establish the correlation between symptoms and rhythm.

The guideline addresses techniques for obtaining permanent PVI with balloon technologies. The authors state that PVI is the cornerstone of all ablation strategies in AF. PVI is challenging, and there exists a considerable learning curve to develop the skills needed to safely and effectively perform RF AF under 3D electroanatomical guidance. Therefore, novel catheter designs with alternative energy sources have been developed. These catheter technologies are balloon-based ablation systems using various energy modalities, such as cryoenergy, laser and radiofrequency catheter.

In the section on technology and tools the authors provide an update on examples on many of the technologies and tools that are employed for AF ablation procedures. The authors state that in recent years, cryoballoon ablation has become the most efficient alternative to RF catheter ablation for the treatment of AF. Other energy sources and tools are in various stages of development and/or clinical investigation. The authors discuss laser and ultrasound ablation systems. The laser balloon has been used commercially in Europe and has received FDA approval for use in the United States to treat patients with drug refractory recurrent symptomatic PAF. A novel automated low-intensity collimated ultrasound ablation system is in development. The clinical availability of the ultrasound ablation system technology is limited at the present time (Calkins, et al., 2017).

European Society of Cardiology (ESC): The updated 2016 ESC Guidelines for the Management of Atrial Fibrillation (AF) list the following recommendations for catheter ablation of AF (Kirchhof et al., 2016):

- Catheter ablation of symptomatic paroxysmal AF is recommended to improve AF symptoms in patients who have symptomatic recurrences of AF on antiarrhythmic drug therapy (amiodarone, dronedarone, flecainide, propafenone, sotalol) and who prefer further rhythm control therapy, when performed by an electrophysiologist who has received appropriate training and is performing the procedure in an experienced center. Class I Level of evidence A
- Ablation of common atrial flutter should be considered to prevent recurrent flutter as part of an AF ablation procedure if documented or occurring during the AF ablation. Class IIa Level of evidence B
- Catheter ablation of AF should be considered as first-line therapy to prevent recurrent AF and to improve symptoms in selected patients with symptomatic paroxysmal AF as an alternative to antiarrhythmic drug therapy, considering patient choice, benefit, and risk. Class IIa Level of evidence B
- Catheter ablation should target isolation of the pulmonary veins using radiofrequency ablation or cryotherapy balloon catheters. Class IIa Level of evidence B
- Catheter or surgical ablation should be considered in patients with symptomatic persistent or long-standing persistent AF refractory to AAD therapy to improve symptoms, considering patient choice, benefit and risk, supported by an AF Heart Team. Class IIa Level of evidence C

Class of recommendations definitions:

Class I: Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.

Class II: divergence of opinion about the usefulness/efficacy of the given Conflicting evidence and/or a treatment or procedure.

Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.

Class IIb: Usefulness/efficacy is less well established by evidence/opinion.

Class III: Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

Level of evidence definitions:

Level A: Data derived from multiple randomized clinical trials or meta-analyses.

Level B: Data derived from a single randomized clinical trial or large non-randomized studies

Level C: Consensus of opinion of the experts and/ or small studies, retrospective studies, registries.

The guideline addresses techniques and technologies for catheter ablation. The authors discuss that complete pulmonary vein isolation (PVI) on an atrial level is the best documented target for catheter ablation, achievable by point-by-point radiofrequency ablation, linear lesions encircling the pulmonary veins, or cryoballoon ablation, with similar outcomes. Laser ablation is not addressed in the guideline (Kirchhof et al., 2016).

Canadian Cardiovascular Society (CCS): The 2014 focused update of the CCS Guidelines for the Management of Atrial Fibrillation has the following recommendations for catheter ablation of AF:

- Recommend catheter ablation of AF in patients who remain symptomatic after an adequate trial of AAD therapy and in whom a rhythm control strategy remains desired (Strong Recommendation, Moderate Quality Evidence).
- Suggest catheter ablation to maintain sinus rhythm as first-line therapy for relief of symptoms in highly selected patients with symptomatic, paroxysmal AF (Conditional Recommendation, Moderate Quality Evidence).
- Suggest that catheter ablation of AF should be performed by electrophysiologists with a high degree of expertise and high annual procedural volumes (Conditional Recommendation, Low-Quality Evidence).

The authors state that for patients with asymptomatic persistent AF, rate control is usually the therapy of choice. However, AF symptoms might be difficult to ascertain because they can be quite nonspecific. Fatigue, declining exercise tolerance, decreased motivation, and exertional dyspnea might all be attributed to aging or other conditions, but might actually be due to AF. When it is difficult to establish whether symptoms are due to AF, a trial of cardioversion might be helpful. Clear symptom relief after restoration of sinus rhythm would encourage a rhythm control approach.

The 2018 focused update of the CCS Guidelines for the Management of Atrial Fibrillation states that the Guideline Committee has not changed its recommendation that AF ablation should be second-line therapy for most patients and first-line therapy only for highly selected patients. The committee decided not to add a new recommendation for ablation in heart failure (HF) patients. The existing recommendation to pursue catheter ablation as a second-line treatment for symptomatic patients applies to this group. The guideline states that despite the lack of a new recommendation specifically for patients with HF and a reduced LVEF, it is important to recognize that the consideration of patients with structural heart disease as an appropriate ablation candidate does represent a philosophical shift in practice because these patients were previously discouraged from ablation because of concerns regarding potential inefficacy and harm (Andrade, et al., 2018).

Taiwan Heart Rhythm Society and the Taiwan Society of Cardiology: The 2016 Guidelines of the Taiwan Heart Rhythm Society and the Taiwan Society of Cardiology for the management of atrial fibrillation state that during the past decade, catheter ablation of AF has developed from an experimental unproven procedure to a commonly performed ablation procedure in the majority of electrophysiological laboratories throughout the world. The authors state that the primary justification for an AF ablation is the presence of symptomatic AF with a goal to improve the quality of life of patients. Thus, the primary selection criterion for catheter ablation should be the presence of symptomatic AF. The benefit of AF ablation has not been demonstrated in asymptomatic patients. The ablative therapy recommendations state that catheter ablation is usually performed in patients with symptomatic paroxysmal or persistent AF that is resistant to at least one antiarrhythmic drug, irrespective of the presence of structural heart disease (Chiang, et al., 2016).

National Heart Foundation of Australia: The 2013 National Heart Foundation of Australia consensus statement on catheter ablation as a therapy for atrial fibrillation recommendations on catheter ablation therapy for atrial fibrillation (AF) and levels of evidence and grades for recommendations:

- The primary indication for catheter ablation of AF is the presence of symptomatic AF that is refractory or intolerant to at least one Class 1 or Class 3 antiarrhythmic medication. (Level I, grade A*)
- In selecting patients for catheter ablation of AF, consideration should be given to the patient's age, duration of AF, left atrial size and the presence of significant structural heart disease. Best results are obtained in younger patients with paroxysmal AF and without structural heart disease or marked atrial enlargement. (Consensus†)

- Discontinuation of warfarin or equivalent therapies is not considered a sole indication for this procedure. (Consensus†)
- After ablation of AF, anticoagulation therapy is generally recommended for all patients for at least 1–3 months. Discontinuation of warfarin or equivalent therapies after ablation is generally not recommended in patients who have a CHADS2 score of 2. (Consensus†)

*Levels of evidence and grades for recommendations as defined by the National Health and Medical Research Council (NHMRC) in NHMRC levels of evidence and grades for recommendations for developers of clinical practice guidelines.

†Due to the limited number of randomized clinical trials in this area, these consensus recommendations are largely based on expert opinion, and will likely evolve as the evidence base informing the practice of AF ablation grows. As a result, only one recommendation was graded according to NHMRC guidelines (Kalman, et al., 2013).

National Institute for Health and Clinical Excellence (NICE) (United Kingdom): In 2016, NICE Interventional Procedures Guidance issued an update to the 2011 Guidance document addressing percutaneous endoscopic laser balloon pulmonary vein isolation for atrial fibrillation. NICE Guidance recommendations state that the current evidence on the safety of percutaneous endoscopic laser balloon pulmonary vein isolation for atrial fibrillation shows there are serious but well-recognized complications. Evidence on efficacy is adequate in quantity and quality to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent and audit. NICE encourages that clinicians should ensure that patients fully understand the potential complications, the uncertainty about the success of the procedure in the short term and the risk of recurrent atrial fibrillation. Patient selection and treatment should be carried out only by interventional cardiologists with expertise in electrophysiology and experience of doing complex ablation procedures. This procedure should be done only in units with arrangements for emergency cardiac surgical support. The overview is based on about 1128 patients from two randomized controlled trials (Dukkipati, et al., 2015; Schmidt, et al., 2013), three non-randomized comparative studies (Bordignon, et al., 2013; Metzner, et al., 2011; Bordignon, et al., 2015), two case series and two case reports.

NICE Interventional Procedures Guidance issued in 2012 addresses percutaneous balloon cryoablation for pulmonary vein isolation in atrial fibrillation (AF). NICE Guidance states that the current evidence on the efficacy and safety of percutaneous balloon cryoablation for pulmonary vein isolation in AF is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit. NICE encourages clinicians to enter patients into research studies with the particular aims of guiding selection of patients and of defining the place of percutaneous balloon cryoablation in relation to other procedures for treating AF. Further research should define patient selection criteria clearly and should document adverse events and long-term control of AF. The overview is based on about 1748 patients from one systematic review (Andrade, et al., 2011), four comparative case series (Kojodjojo, et al., 2010; Chierchia, et al., 2010; Sorgente, et al., 2010; Gaita, et al., 2011), one case-control study (Linhart, et al., 2009) and three case series (Neumann, et al., 2008, VanBelle, et al., 2008; Ahmed, et al., 2009). The Committee noted the advances in the understanding of the causes of AF and acknowledged that this procedure is likely to be more effective in paroxysmal than persistent AF. The overview discusses the validity and generalizability of the studies stating that a 28-mm and 23-mm cryoballoon is available. Some of the published articles commented that the smaller sized balloon may be associated with a higher incidence of phrenic nerve palsy than the large balloon. There is limited comparative data on this procedure compared with current practice. Patient follow-up is relatively short term in the published literature. The published literature reports that there is a learning curve associated with this technology.

In 2014, the NICE released a clinical guideline update on the management of AF. NICE recommends the following when drug treatment is not tolerated or ineffective at controlling AF symptoms:

- Offering left atrial catheter ablation for individuals with paroxysmal AF (PAF).
- Considering left atrial catheter or surgical ablation in individuals with persistent AF.
- Discussing the benefits and risks of treatment with the individual.

Left Atrial Appendage (LAA) Closure

Three main approaches to stroke prevention in AF are: elimination of AF; prevention of clot formation with antiplatelet or anticoagulant agents; and physical elimination of the left atrial appendage (LAA) which excludes the site of clot formation. Among patients with nonvalvular AF, the vast majority of thrombus material is located within or involves the LAA. Approximately 90% of left atrial thrombi form in the LAA. Most patients with AF receive anticoagulant therapy to reduce the risk of systemic embolization. There are varying degrees of bleeding risk associated with anticoagulation and not all individuals are candidates for this therapy. The optimal approach to reducing the risk of embolization in patients for whom long-term anticoagulation is indicated, but who are unable to take it, is unclear. Percutaneous approaches, often referred to as LAA exclusion procedures, that mechanically prevent embolization of LAA thrombi have been developed. At present, there are two categories of percutaneous LAA occlusion devices: endocardially and epicardially delivered. In addition, LAA exclusion at the time of surgery has been proposed for some patients undergoing cardiac surgery for reasons such as valve replacement or repair or coronary artery bypass graft surgery (Hijazi, et al., 2019; Morady, et al., 2019; Whitlock, et al., 2014).

Percutaneous transcatheter closure of the LAA (CPT® Code 33340)

The Watchman™ Left Atrial Appendage Closure Device (Boston Scientific, Maple Grove, MN) is a self-expanding nickel-titanium system. Implantation is performed percutaneously with a catheter delivery system, with venous access and trans-septal puncture to enter the left atrium. After implantation of device, patients receive anticoagulation with warfarin or other agents for approximately one to two months. During this acute period of time, anticoagulation may be necessary due to risk of thrombus formation related to altered blood flow around the implant. Patients are monitored with transesophageal echocardiography to assess blood flow and complete LAA closure (LAAC). After this period, patients will receive antiplatelet agents (e.g., aspirin and/or clopidogrel) indefinitely.

Other devices that have not received FDA approval for the use of LAA closure include, but are not limited to, the following:

- The Amplatzer™ Cardiac Plug (St. Jude Medical, Minneapolis, MN) received CE Mark approval in Europe in 2008. The device closes off the LAA in a manner similar to the Watchman. The technique for implanting this device is also similar to that of the Watchman system. The Amplatzer Cardiac Plug is shorter than the Watchman device and may be more advantageous in individuals with short appendages. The second generation Amplatzer Cardiac Plug device (Amulet) received CE Mark approval in 2013. The Amulet has more stabilizing wires, up to 10 pairs, for improved device stability and larger lobe size to occlude larger appendages.
- The Lariat® Loop Applicator (Sentreheart, Palo Alto, CA) is a suture delivery device that is designed to close a variety of surgical wounds in addition to LAAC. The Lariat Loop Applicator device did receive 510(k) marketing clearance from FDA in 2006 as suture delivery device, but does not have FDA approval as a LAA closure device. Its 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 technical approach differs from that of the Watchman system. The Lariat suture loop ligates the LAA from the epicardial space, with assistance of catheters and balloons in the left atrium.
- The WaveCrest® Device (Biosense Webster, Irvine, CA) device consists of a single-lobe, nitinol-based design for occluding the LAA. Unlike the Watchman device, the WaveCrest device is covered by a foam layer on the LAA side and polytetrafluoroethylene on the side facing the left atrium. It has several anchors along the LAA side and is designed to be separately deployed from the lobe. This device is meant to be deployed quite proximally in the LAA, rather than deep within the structure. This device is proposed as another alternative to the Watchman device if the LAA is too small to accommodate deeper devices. The device has CE Mark approval and is available in Europe in 2013. A prospective, multicenter, RCT of the WaveCrest® Left Atrial Appendage Occlusion System compared to an existing FDA-approved LAA Closure Device for the reduction in risk of embolic stroke in subjects with non-valvular atrial fibrillation is ongoing. The trial will enroll 1,250 patients at approximately 90 hospitals, and follow them for five years.
- PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) device (Appriva Medical, Inc., Sunnyvale, CA, USA) is no longer in production.

U.S. Food and Drug Administration (FDA)

The Watchman LAA Closure Technology received FDA premarket approval March 2015 (P130013). The approval notes that the device is indicated to reduce the risk of thromboembolism from the left atrial appendage (LAA) in patients with non-valvular atrial fibrillation who:

- are at increased risk for stroke and systemic embolism based on CHADS₂ (cardiac failure, hypertension, age ≥ 75 years, diabetes, stroke) or CHA₂DS₂-VASc¹ (congestive heart failure, hypertension, age ≥ 75 years, diabetes, stroke/transient ischemic attack/thromboembolism, vascular disease, aged 65 to 74 years, sex category [female]) scores and are recommended for anticoagulation therapy
- are deemed by their physicians to be suitable for warfarin
- have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin

Literature Review

Randomized Controlled Trials

The Watchman device received FDA approval based upon the results of PROTECT AF and PREVAIL randomized controlled trials (RCT).

PROTECT AF: A noninferiority RCT compared LAA closure with Watchman device to warfarin treatment in patients with non-valvular atrial fibrillation (NVAf), the PROTECT AF trial (Holmes, et al., 2009; Reddy, et al., 2013a; Reddy, et al. 2014). The trial included 707 patients, randomized 2:1, with the device group n=463 and warfarin group n=244 and a follow-up time was 3.8±1.7 years (Reddy et al., 2014). Inclusion criteria: age ≥18 years; paroxysmal, persistent, or permanent NVAf and eligible for warfarin treatment; and, CHADS₂ score ≥1. In the Watchman group the device implanted under transesophageal echocardiography (TEE) guidance with concomitant warfarin and Aspirin (ASA) (81-325 mg/day) for 45 days, on day 45, warfarin stopped, clopidogrel (75 mg/day) started until six month visit and then only ASA continued. In the warfarin group warfarin treatment was provided with a target INR 2-3. The primary efficacy outcome was stroke, systemic embolization, or cardiovascular death. The primary safety outcome was a composite of major bleeding events and procedure-related complications. At mean follow-up of 3.8 years, there were 39 events in 463 pts (8.4%) in the device group for primary event per 100 patient/years (pt/yr), compared with 34 events in 244 patients (13.9%) for primary event rate of 3.8 in 100 pt/yr in warfarin group. In the primary efficacy outcome, there was a noninferiority >99%, and in the primary safety endpoint a noninferiority >98%. Complications included in the Watchman group: serious pericardial effusion (4.8%); major bleeding (4.8%); procedure related ischemic stroke (1.3%); device embolization (0.6%); and hemorrhagic stroke (0.6%). In the warfarin group: major bleeding (7.4%); and, hemorrhagic stroke (3.7%). This study demonstrated the noninferiority of LAA closure compared to warfarin treatment. The study was limited in that it included warfarin, but did not include a comparison with the newer anticoagulants. The study included patients with warfarin, but does not address the patients who are unable to take anticoagulants.

PREVAIL: A noninferiority RCT of that compared LAA closure with Watchman device and long-term warfarin treatment in patients with NVAf, the PREVAIL study (Holmes, et al., 2014). The study included 407 patients (randomized 2:1); with 68 patients enrolled through roll-in process with the Watchman group, n=269 and warfarin group, n=138. The follow-up time was a median of 12 months. The inclusion criteria included: NVAf; CHADS₂ ≥2 or 1 CHADS₂ plus 1 high-risk characteristic. In the Watchman group, the device was implanted guided by fluoroscopy and TEE; post-implant patients were treated with warfarin and ASA for 45 days; TEE performed at 45 days, 6 months, and 12 months. Warfarin was discontinued if the day 45 TEE documented closure of LAA or residual peri-device flow <5 mm and no definite visible large thrombus on device; then clopidogrel 75 mg/day and ASA 81-325 mg/day was prescribed until six months when clopidogrel discontinued. In the warfarin group warfarin treatment was given with target INR 2.0-3.0. At 18 months, the rate of the first coprimary efficacy endpoint (composite of stroke, systemic embolism [SE], and cardiovascular/unexplained death) was 0.064 in the device group versus 0.063 in the control group and did not achieve the prespecified criteria noninferiority. The rate for the second coprimary efficacy endpoint (stroke or SE >7 days' post-randomization) was 0.0253 vs 0.0200 achieving noninferiority. Early safety events occurred in 2.2% of the Watchman arm. Complications (reported for Watchman-group only) (% of patients): device embolization (0.7%); arteriovenous fistula (0.4%); cardiac perforation (0.4%); pericardial effusion with cardiac tamponade (0.4%); major bleed requiring transfusion (0.4%). Noninferiority was not achieved for overall efficacy in this study. The patients in this study were required

to be candidates for long-term anticoagulation to facilitate randomization against a control group treated with warfarin. The trial does not address the safety and efficacy of LAA occlusion when anticoagulation is contraindicated. In addition, the study does not include comparison with new oral anticoagulants.

Reddy et al (2017) reported final five year results of the PREVAIL trial, both alone and as part of a patient-level meta-analysis with the PROTECT AF trial. For the PREVAIL trial, the first composite coprimary endpoint of stroke, systemic embolism (SE), or cardiovascular/unexplained death did not achieve noninferiority (posterior probability for noninferiority=88.4%), whereas the second coprimary endpoint of post-procedure ischemic stroke/SE did achieve noninferiority (posterior probability for noninferiority=97.5%); the warfarin arm maintained an unusually low ischemic stroke rate (0.73%). In the meta-analysis, the composite endpoint was similar between groups (hazard ratio [HR]: 0.820; p=0.27), as were all-stroke/SE (HR: 0.961; p=0.87). The ischemic stroke/SE rate was numerically higher with LAA closure, but this difference did not reach statistical significance (HR: 1.71; p=0.080). However, differences in hemorrhagic stroke, disabling/fatal stroke, cardiovascular/unexplained death, all-cause death, and post-procedure bleeding favored LAA closure (HR: 0.20; p=0.0022; HR: 0.45; p=0.03; HR: 0.59; p=0.027; HR: 0.73; p=0.035; HR: 0.48; p=0.0003, respectively). The author transitional outlook states that further studies are needed to compare the benefit of LAA occlusion against oral anticoagulants other than warfarin in patients with AF, and to assess advantages for those with contraindications to anticoagulation.

Registry Studies

Boersma et al. (2016) reported on peri-procedural outcomes of up to 30-days from the prospective, multicenter registry (EWOLUTION). Baseline/implant data were available for 1021 subjects with high risk of stroke and moderate-to-high risk of bleeding. The Watchman device was successfully deployed in 98.5% of patients with no flow or minimal residual flow achieved in 99.3% of the implanted patients. Thirty-one serious adverse events (SAEs) were noted in 28 subjects within 1 day of the procedure. The overall 30-day mortality rate was 0.7%. The most common SAE that occurred within 30 days of the procedure was major bleeding requiring transfusion. The incidence of SAEs within 30 days was lower for subjects deemed to be ineligible for oral anticoagulation therapy (OAT) compared with those eligible for OAT (6.5 vs. 10.2%, p=0.042). The study is limited by lack of randomization, and short term follow-up. Boersma et al. (2017) reported on one-year follow-up of the EWOLUTION trial. At one year, mortality was 9.8%, noted by the author that is reflected the advanced age and comorbidities in the population. Device thrombus was observed in 28 patients at routine TEE (3.7%) and was not correlated with the drug regimen (p=0.14). Ischemic stroke rate was 1.1% (relative risk 84% vs estimated historical data); the major bleeding rate was 2.6% and was predominantly (2.3%) nonprocedure/device related.

Boersma et al. (2019) reported two year outcomes of the prospective EWOLUTION registry described above. A total of 161 patients (16.4%) died, 22 strokes were observed, and 47 major nonprocedural bleeding events. Stroke and bleeding rates were consistently lower than historic data in those with prior ischemic (-76% and -41%) or hemorrhagic (-81% and 67%) stroke and prior bleeding (-85% and -30%). Lowest bleeding rates were seen in patients with early discontinuation of dual antiplatelet therapy. Patients with early discontinuation of antithrombotic therapy showed lower bleeding rates, while they were highest for those with prior bleeding. Device thrombus was observed in 34 patients (4.1%) and was not correlated to drug regimen during follow-up (p=0.28). The Watchman left atrial appendage occlusion device had consistently low rates of stroke and nonprocedural bleeding, although most were contraindicated to oral anticoagulation and used only single antiplatelet therapy or nothing. The lack of a control arm limits the full assessment of therapy benefit in this patient population.

Nonrandomized Controlled Trials

Fauchier et al. (2018) reported on a retrospective study to determine the incidence, predictors, and prognosis of thrombus formation on devices in patients with AF who were treated with LAA closure. The study retrospectively analyzed data from patients treated with 2 LAA closure devices seen in 8 centers in France from February 2012 to January 2017. The study included total of 469 consecutive patients with AF that underwent LAA closure (272 Watchman devices and 197 Amplatzer devices). The mean follow-up was 13 ± 13 months, during which 339 (72.3%) patients underwent LAA imaging at least once. There were 98 major adverse events (26 thrombi on devices, 19 ischemic strokes, 2 transient ischemic attacks, 18 major hemorrhages, 33 deaths) recorded in 89 patients. The incidence of device-related thrombus in patients with LAA imaging was 7.2% per year. Older age (hazard ratio [HR]: 1.07 per 1-year increase; 95% confidence interval [CI]: 1.01 to 1.14; p=0.02) and history of

stroke (HR: 3.68; 95% CI: 1.17 to 11.62; p=0.03) were predictors of thrombus formation on the devices, whereas dual antiplatelet therapy (HR: 0.10; 95% CI: 0.01 to 0.76; p=0.03) and oral anticoagulation at discharge (HR: 0.26; 95% CI: 0.09 to 0.77; p=0.02) were protective factors. Thrombus on the device (HR: 4.39; 95% CI: 1.05 to 18.43; p=0.04) and vascular disease (HR: 5.03; 95% CI: 1.39 to 18.23; p=0.01) were independent predictors of ischemic strokes and transient ischemic attacks during follow-up. The authors concluded that thrombus formation on the device is not uncommon in patients with AF who are treated with LAA closure and such events are strongly associated with a higher risk of ischemic stroke during follow-up. The authors noted that association between thrombus formation on the device and later strokes, and an optimal antithrombotic regimen that considers individual risks of device-related thrombus after LAA closure, needs to be evaluated in larger, prospective, randomized studies.

Huang et al. (2017) reported on a single center, prospective, observational study to evaluate the procedural feasibility, safety and 12-month outcomes of the WATCHMAN LAA Occlusion Device in 106 nonvalvular atrial fibrillation (NVAf) patients with high risk for stroke. There was follow-up at one, three, six and 12 months after discharge. A transesophageal echocardiograph was performed at 45 days after implantation. The procedural success rate was 94.3% (100/106), and the occlusion rate was 100.0% (100/100). There were one tamponade, one ischemic stroke, and eight minor pericardial effusions during hospitalization. In the 12-month follow-up period, two patients developed a thrombus layer on the device that resolved with additional anticoagulation: one with visible device-thrombus experienced transient ischemic stroke, and one had a hemorrhagic stroke with no deaths in the study. The overall survival rate was 100.0%, and non-major adverse event rate of 95.0% (95/100). In this study, the expected annual rate of ischemic stroke risk in these patients according to the CHA2DS2-VASc score was 4.0%, while the observed ischemic stroke rate was 2.0% per year. The authors note that large multi-center trials and long-term follow-up are needed to evaluate the safety and efficacy of this application.

Betts et al. (2017) reported on a retrospective study assessing the feasibility and long-term efficacy of left atrial appendage occlusion (LAAO) in 371 patients in eight centers in the United Kingdom. The device choice was Watchman in 63% of cases, Amplatzer Cardiac Plug in 34.7%, Lariat in 1.7%, and Coherex WaveCrest in 0.6%. The 343 patients who received an LAAO device were followed up for 24.7 ± 16.07 months. The overall procedure success was 92.5%, with major events in 3.5% of cases. A significant improvement in procedure success (from 89.2% to 95.7%; p=0.018) and reduction of acute major complications (from 6.5% to 0.5%; p=0.001) were observed between procedures in the first and the second half of the recruitment time. 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. The study was limited by retrospective nature and lack of randomization.

Chen et al. (2017) reported on a retrospective study was designed to compare the feasibility and safety of left atrial appendage closure (LAAC) in primary and secondary stroke preventions. The study included 122 non-valvular atrial fibrillation (AF) patients with CHA2DS2-VASc ≥ 1 selected for percutaneous LAAC operations. Outcome observations of primary and secondary stroke preventions with Watchman devices were analyzed and compared with 68 for primary stroke prevention and 47 for secondary prevention (included in the secondary prevention group when they had previous histories of stroke/TIA or infarct foci identified by head CT/MRI scan). Trans-esophageal echocardiography (TEE) was performed at 45 days. Both the CHA2DS2-VASc score and the HASBLED score were significantly higher in the secondary prevention group (4.09 ± 1.06 vs. 1.93 ± 1.09 for CHA2DS2-VASc and 1.83 ± 1.03 vs. 1.26 ± 0.87 for HASBLED, p<0.01). In both groups LAAC were achieved with high successful rate (98.53% in the primary prevention group and 100% in the secondary prevention group, p>0.05) and low complication rates. In median follow-up of 12 months, stroke rates were found to be at low level in both groups (1.47% in primary prevention group vs. 2.13% in secondary prevention group, p>0.05). Limitations of the study include the lack of comparator group, and that it is a retrospective study. The authors note that prospective clinical trials with larger sample size and longer follow-up period are needed to study the efficacy and safety of LAAC in secondary stroke preventions.

Saw et al. (2017) reported on a study to evaluate the safety and efficacy of WATCHMAN device for left atrial appendage (LAA) closure in 106 patients with nonvalvular atrial fibrillation (AF) and contraindications to anticoagulation. Indications for LAA closure were CHADS2 ≥ 1 or CHA2 DS2 -VASc ≥ 2 , and a contraindication/intolerance to or failure on anticoagulation. Follow-up imaging was performed one to six months post-procedure. The mean age of patients was 74.8 ± 7.7 , mean CHADS2 score was 2.8 ± 1.2 , CHA2 DS2 -

VASc score was 4.3 ± 1.5 , and HASBLED score was 3.2 ± 1.2 . Indications for LAA closure were prior bleeding 89.6% (87 major bleeding and 8 minor bleeding), 9.4% were deemed high risk for bleeding, and 0.9% with recurrent strokes on warfarin. Procedural success was 97.2% (103 of 106), with one device embolization, one implant failure due to inadequate LAA depth, and one cardiac perforation requiring surgical repair before WATCHMAN implantation. The composite major safety event-rate was 1.9% (1 death and 1 device embolization). Antithrombotic therapy post-implant included dual antiplatelet therapy in 76 of 103 (73.8%). Mean follow-up was 210 ± 182 days; there were two transient ischemic attacks, with estimated 66% reduction in thromboembolic events relative to CHADS2 predicted risk. The authors note that LAA closure with the WATCHMAN device for patients with nonvalvular AF and contraindications to oral anticoagulants (OAC) is safe and effective, and the results should be confirmed in larger prospective registries and randomized trials in this population.

Systematic Review and Meta-Analysis

Sanders et al. (2018) published an updated Agency for Healthcare and Quality (AHRQ) systematic review on stroke prevention in patients with AF. The review addressed the comparative safety (in terms of bleeding risk) and effectiveness (in terms of stroke prevention) of various procedural interventions used to prevent stroke and blood clots in patients with nonvalvular AF. Procedural interventions included: surgeries (i.e., LAA occlusion, resection/removal); minimally invasive (i.e., Atriclip, Lariat); transcatheter (i.e., Watchman, Amplatzer, PLATTO). The authors reported on key findings for percutaneous left atrial appendage (LAA) closure versus warfarin stating: "LAA shows a trend toward a benefit over warfarin for all strokes, including ischemic or hemorrhagic, and all-cause mortality (low strength of evidence for both outcomes). Although LAA with percutaneous closure results in less frequent major bleeding than warfarin (low strength of evidence), it is also associated with a higher rate of adverse safety events such as pericardial effusion and device embolization (moderate strength of evidence). These findings are based on one good-quality RCT (Holmes, et al., 2009) involving 707 patients and four observational studies involved 1,430 patients". The observational studies compared different LAA closure devices.

The AHRQ definition of strength of evidence states:

- Moderate: are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains
- Low: have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.

Yerasi et al. (2018) reported in a systematic review and meta-analysis a summary of the early outcomes of left atrial appendage occlusion (LAO). The authors evaluated the procedural safety and complications of all transcatheter LAO devices and compared procedural events across different LAA closure devices. This meta-analysis included 49 studies involving 12,415 patients. The median age was 73.5 years and 43% were males. Hypertension and diabetes were present in 36% and 15% of the population, respectively. There was a prior history of stroke and congestive heart failure in 14% and 18% of the population, respectively. The median CHADS2 score was 2.9 and the median HASBLED score was 3.3. LAO implantation was successful in 96.3% of patients. The pooled proportion of all-cause mortality was 0.28%. The pooled proportion of all-cause stroke was 0.31%, major bleeding requiring transfusion was 1.71%, and pericardial effusion was 3.25%. Sub-analysis of randomized clinical trials comparing LAO devices to warfarin showed lower mortality ($p=0.03$) with similar bleeding risk ($p=0.20$) with LAO. The author concluded that LAO occlusion is a safe and effective stroke prevention strategy in patients with non-valvular atrial fibrillation. This analysis was performed at study level and does not have individual patient-level data. The pooling of positive studies has the potential to overestimate the safety of LAO. Due to the retrospective nature of some studies included in this analysis, there is potential for recall bias.

Sahay et al. (2017) reported on a network meta-analysis to assess the efficacy and safety of LAAC compared with other strategies for stroke prevention in patients with AF. The review included randomized controlled trials comparing warfarin with placebo, antiplatelet therapy (APT) or non-vitamin K antagonist oral anticoagulants (NOAC) in patients with AF using meta-analysis guidelines. Two major trials of LAAC were also included and a network meta-analysis with indirect comparison was performed to compare the impact of LAAC on mortality,

stroke/systemic embolism (SE) and major bleeding in relation to medical treatment. The network meta-analysis included 19 RCTs (87,831 patients) with AF receiving anticoagulants, APT, placebo or LAAC. Indirect comparison with network meta-analysis using warfarin as the common comparator revealed efficacy benefit that favored 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, $p = 0.969$). LAAC showed comparable rates of major bleeding when compared with placebo (HR 2.33, 95% CI 0.67 to 8.09, $p = 0.183$), APT (HR 0.75, 95% CI 0.30 to 1.88, $p = 0.542$) and NOAC (HR 0.80, 95% CI 0.33 to 1.94, $p = 0.615$). The authors note that the findings of this meta-analysis suggest that LAAC is superior to placebo and APT, and comparable to NOAC for preventing mortality and stroke or SE, with similar bleeding risk in patients with nonvalvular AF. In addition, they note that these results should be interpreted with caution and more studies are needed to further substantiate this advantage, in view of the wide CIs with some variables in the current meta-analysis.

Noelck et al. (2015) reported on a systematic review benefits and harms of surgical or percutaneous LAA exclusion procedures. The review included controlled clinical trials that assessed the effectiveness of percutaneous LAA exclusion procedures and to assess the harms of percutaneous LAA procedures. Cohort and registry studies with 50 or more patients were included. For percutaneous interventions, the review included two randomized controlled studies and 11 registry studies. The findings note that there is low-strength evidence that percutaneous LAA exclusion is associated with a similar risk of long-term stroke and mortality as continued oral anticoagulation therapy. The finding is based on trials of one device (Watchman) studied in patients without contraindications to oral anticoagulant therapy. Most patients who received the Watchman device were able to discontinue oral anticoagulant therapy after undergoing follow-up transesophageal echocardiography (TEE) showing persistent closure of the LAA at three to six months. The review found that there is moderate strength evidence that a substantial proportion of patients undergoing various percutaneous LAA exclusion procedures experienced serious periprocedural harms with insufficient evidence to determine whether factors such as operator experience, patient selection criteria, or choice of device can modify these risks. In addition, it was noted that there is insufficient data to assess the balance of benefits and harms of percutaneous LAA exclusion procedures in patients who are ineligible for long-term oral anticoagulation therapy.

Technology Assessment

Hayes published a technology assessment for the use of percutaneous LAA closure devices to reduce risk of stroke in patient with atrial fibrillation (AF) (Hayes 2015; 2018; 2019). The review included: two randomized controlled trials (RCTs), two nonrandomized comparative prospective registries, three comparative registry studies, five comparative retrospective studies, and seven noncomparative studies. The review included adults with AF or nonvalvular atrial fibrillation (NVAf) and risk of stroke and interventions that included: percutaneous LAA closure or occlusion with Watchman, Amplatzer Cardiac Plug (ACP), Amulet, or Lariat. The comparison included: oral anticoagulants (OAC) with warfarin (two studies); medical treatment (two studies); different LAA closure devices (eight studies); none (seven studies) and the outcomes included: periprocedural and postprocedural complications; procedural and technical success; LAA leaks; stroke; systemic embolism; thrombus; major bleeding; adverse events (AEs); and death. Follow-up was periprocedural to four years.

Regarding LAA closure with Watchman the report included four studies:

- The two RCTs that compared LAA closure with Watchman versus OAC with warfarin for stroke prevention in patients with NVAf and high risk of stroke found LAA closure to be noninferior in almost all primary efficacy and safety measures.
- Two registry database studies that evaluated observed versus expected rates of stroke and major bleeding in patients who underwent LAA closure with Watchman reported that patients who underwent LAA closure had lower observed versus expected rates of stroke, stroke/transient ischemic attack (TIA)/thromboembolism (TE), and major bleeds.
- One of the registry studies pooled data from patients who had undergone LAA closure with either Watchman or Amplatzer devices; neither of these studies provided statistics to support their analyses.
- Of four studies comparing procedural success and/or safety outcomes of LAA closure with Watchman versus ACP or Amulet, two studies found no statistically significant differences in any procedural outcomes and safety outcomes; one study found similar rates of procedural outcomes and acute major adverse events (MAEs) but a significantly lower rate of acute minor AEs with Watchman versus ACP;

one study found that patients implanted with Amplatzer devices versus Watchman had lower rates of periprocedural total MAEs and major bleeding but no differences in other outcomes or at follow-up.

The report concludes that percutaneous LAA closure is associated with a measurable risk of serious procedure-/device related complications (e.g., major bleeding, pericardial effusion, stroke, device embolization, cardiac perforation or tamponade) with reported mortality rates ranging from 0% to 4%. The available evidence suggests there may be a potential benefit for use of the Watchman device for stroke prevention in adult patients with NVAf at increased risk of stroke and systemic embolism. However, there is uncertainty whether the benefit outweighs possible harms given the potential for device-related complications or mortality. The report notes that:

- Following implantation of the Watchman device, patients must continue on warfarin therapy for approximately 45 days. However, there are very limited data on if and how to use the Watchman device in patients with absolute contraindications to warfarin.
- Well-powered RCTs are needed to compare closure using the Watchman and other percutaneous LAA devices versus treatment with the newer OACs and to test the use of the newer OACs as an adjunct to LAA closure.
- More data are needed to assess the clinical applications of Watchman in patients at very high risk of bleeding and to optimize postprocedural medication regimens for patients who are intolerant to OAC.
- Trials are also needed to help identify the patient subgroups that would most benefit from LAA closure.

Professional Societies/Organizations

American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS):

The ACC/AHA/HRS published a joint guideline for the management of patients with atrial fibrillation (AF) (January, et al., 2014). The 2014 guideline includes a discussion of percutaneous occlusion of the LAA but does not provide specific recommendations regarding the use of these devices. The 2019 focused update to the 2014 guideline section on nonpharmacological stroke prevention includes the following new recommendation for percutaneous LAA occlusion (January, et al., 2019):

- Percutaneous LAA occlusion may be considered in patients with AF at increased risk of stroke who have contraindications to long-term anticoagulation (Class IIb: Level of Evidence B-NR).

Class IIb (weak): benefits \geq risk; usefulness/effectiveness is unknown/unclear/uncertain/or not well established. Level of evidence B-NR: moderate quality evidence from one or more well-designed, well-executed nonrandomized RCTs, observational studies or registry studies. Meta-analyses of such studies.

The guideline states that oral anticoagulation remains the preferred therapy for stroke prevention for most patients with AF and elevated stroke risk. However, for patients who are poor candidates for long-term oral anticoagulation (because of the propensity for bleeding or poor drug tolerance or adherence), the Watchman device provides an alternative. A number of unresolved issues remain, including the optimal patient selection and periprocedural antithrombotic regimen.

The guideline states that percutaneous LAA occlusion with the Watchman device has been compared with warfarin in patients with AF (in the absence of moderate to severe mitral stenosis or a mechanical heart valve) at increased risk of stroke in two RCTs: the PROTECT AF (Reddy, et al., 2014) and the PREVAIL (Holmes, et al., 2014) trials. A meta-analysis combining data from these two trials and their registries demonstrated that patients receiving the device had significantly fewer hemorrhagic strokes than did those receiving warfarin, but there was an increase in ischemic strokes in the device group (Holmes, et al., 2015). However, when periprocedural events were excluded, the difference in ischemic strokes was not significant.

The guideline states that the current FDA labeling specifies that patients should be deemed suitable for anticoagulation and, in particular, a period of periprocedural anticoagulation. Patients unable to take oral anticoagulation were excluded from the Watchman RCTs. There is increasing experience outside the United States with LAA closure in oral anticoagulation–ineligible patients using an antiplatelet regimen only (Reddy, et al., 2013b; Boersma, et al., 2017), and this is the focus of an ongoing RCT (Holmes, et al., 2017).

Surgical LAA Closure (CPT Code 33999)

Surgical resection of the LAA was first proposed for patients with AF as a potential therapy to reduce mortality. For decades there was heterogeneity of surgical techniques for LAA closure with few well-conducted clinical studies. The two general approaches to surgical LAA closure are exclusion and excision. Exclusion can be performed with sutures from the endocardial or epicardial surface or with a stapler. Excision can be performed by stapled excision or removal and oversewing. The results of surgical LAA closure have remained controversial. Surgical closure of the LAA was often incomplete as detected by transesophageal echocardiography. This raised concerns about the discontinuation of pharmacological anticoagulation. These issues contributed to the premature abandonment of the only randomized surgical trial undertaken to objectively evaluate the effectiveness and safety of surgical LAA ligation. There are limited data suggesting that this approach can reduce the risk of stroke. A larger study with a target enrollment of 4,700 patients (LAAOS [Left Atrial Appendage Occlusion Study] III) undergoing cardiac surgery, to either LAA excision or exclusion versus conventional medical therapy is in progress (Whitlock, et al., 2014). All patients will continue to receive usual antithrombotic therapy. The primary outcome will be the composite of stroke or non-CNS embolization. The specific surgical LAA occlusion technique will be at the individual operator's discretion (Hijazi, et al., 2019; Sarrf, et al., 2018; Price, et al., 2016; Masoudi, et al., 2015).

Epicardial LAA clipping has been approved by the U.S. Food and Drug Administration (FDA) and is increasingly being used to exclude the LAA in patients with AF undergoing cardiac surgery. The AtriClip™ device (AtriCure, Inc., West Chester, OH) is used during both open and thoracoscopic surgery, either as a stand-alone procedure or as part of a combined approach with other procedures, thoracoscopic ablation or staged catheter ablation. The AtriClip LAA Exclusion System consists of a single use, sterile, self-closing, implantable Clip preloaded on a Single Use Clip Applier, and a Selection Guide to aid in appropriate Clip size selection. The frame assembly of the implantable Clip consists of two springs connecting two opposing tubes which are covered with pressure pads. When closed, the Clip applies uniform pressure over the length of the Clip to ensure consistent, reproducible, and secure occlusion of the LAA (Toale, et al., 2019; FDA 2010).

U.S. Food and Drug Administration (FDA)

The AtriClip LAA Exclusion System (AtriCure, Inc., West Chester, OH) received 510(k) approval in June 2010 (K093679). The indications for use state the AtriClip LAA Exclusion System is indicated for the occlusion of the left atrial appendage, under direct visualization, in conjunction with other open cardiac surgical procedures. The FDA 510(k) approval lists numerous predicate devices. The FDA 510(k) approval was based on the Exclusion of the Left Atrial Appendage with the AtriClip LAA Exclusion Device in Patients Undergoing Concomitant Cardiac Surgery (EXCLUDE) clinical trial (ClinicalTrials.gov Identifier: NCT00779857). Additional modification approvals have been granted however the indicated use remains unchanged.

Literature Review

Ailawadi et al. (2011) reported results of the multicenter Exclusion of Left Atrial Appendage with AtriClip Exclusion Device in Patients Undergoing Concomitant Cardiac Surgery (EXCLUDE) clinical trial (n=70). This nonrandomized, prospective multicenter trial was designed to assess the safety and efficacy of the AtriClip. Patients undergoing elective cardiac surgery via median sternotomy with AF or a Congestive Heart Failure, Hypertension, Age >75 Years, Diabetes Mellitus, Stroke score greater than 2 were eligible for concomitant AtriClip. Safety was assessed at 30 days, and efficacy of LAA exclusion was assessed at operation (by transesophageal echocardiography) and 3-month follow-up (by computed tomography angiography or transesophageal echocardiography). Patients (mean age, 73 years) undergoing open cardiac surgery were enrolled in the study. Intraprocedural successful LAA exclusion was confirmed in 67 of 70 patients (95.7%). Significant adverse events occurred in 34 of 70 patients (48.6%). There were no adverse events related to the device and no perioperative mortality. At 3-month follow-up, one patient died and 65 of 70 patients (92.9%) were available for assessment. Of the patients who underwent imaging, 60 of 61 patients (98.4%) had successful LAA exclusion by computed tomography angiography or transesophageal echocardiography imaging. This study was limited by small sample size and short-term follow-up.

A case series (n=291) by Caliskan et al. (2018) evaluated the safety, effectiveness, and durability of the AtriClip implanted in patients undergoing open heart surgery. Of these patients, 40 were included in the initial device trial and the remaining 251 were from a consecutive institutional registry. At a mean follow-up of 36 months (range 1-97 months), there were no device-related complications. Selected patients followed 5 years post-implant

demonstrated complete LAA occlusion. Subgroup analysis of patients with discontinued anticoagulation revealed a relative risk reduction of 87.5% with an observed ischemic stroke-rate of 0.5/100 patient-years versus an expected rate of 4.0/100 patient-years in similar patients. Although study results support the safety and effectiveness of the AtriClip system, well-designed controlled trials are needed to validate these findings.

Systematic Review

In the systematic review discussed above for percutaneous LAA exclusion, Noelck et al. (2015), the summary of evidence for surgical LAA exclusion procedures is addressed. Three randomized controlled trials were found (n=33-77). These were small pilot studies conducted to assess the safety and feasibility of larger trials and therefore were not powered and did not have adequate follow-up to detect clinically significant outcomes. Two observational studies used propensity score matching to create comparator groups. One study reviewed 119 pairs of patients who underwent surgical ablation of AF over a mean follow-up of 3.1 +/- 2.8 years and found no significant differences in stroke-free survival (p=0 .88) and freedom from AF while off antiarrhythmic drugs (p= 0.46) between the 2 groups. The other study reviewed 631 pairs of patients who had undergone a variety of cardiac surgical procedures and found that while the rate of postoperative atrial fibrillation was higher in the LAA exclusion group (23% vs 18%, p=0.037), fewer of these patients had stroke through postoperative day 30 (0.0% vs 6.1%, p=0 .003). However, there were more strokes in the LAA ligation group among patients without postoperative atrial fibrillation, so the overall rate of cerebrovascular accident (CVA) was not significantly different between the two groups (p= 0.44). All patients in this study underwent surgery by the same cardiothoracic surgeon, whose practices changed over the course of 10 years from performing no LAA exclusion to routine LAA exclusion during cardiac surgery. Other concurrent changes over time, such as changes in anticoagulation strategy in patients developing AF, may confound the findings of this study. The summary of evidence states that there is insufficient evidence to determine the efficacy of surgical LAA exclusion in reducing stroke. Results from low-strength evidence found that surgical LAA exclusion in the context of heart surgery done for another indication is unlikely to be associated with significant incremental harm. In two studies, successful closure of the LAA was demonstrated in follow-up in only 40-66% of patients. There is insufficient evidence to assess the benefits of surgical LAA exclusion. Although surgical LAA exclusion does not appear to be associated with a significant increase in harms over the heart surgery during which the procedures are typically performed, rates of procedural success may be low. Overall, there is insufficient evidence to support the routine use of surgical LAA exclusion to reduce stroke risk or future need for anticoagulant therapy.

An UpToDate review (2018) notes: "Surgical ligation or amputation of the left atrial appendage (LAA) can be, and often is, performed without significant morbidity (or mortality) in AF patients who are undergoing cardiac surgery for other indications. In most instances, it is performed in patients undergoing mitral valve or Maze surgery. One limitation to surgical LAA ligation is that it may be incomplete, as detected by transesophageal echocardiography. Such patients continue to be at risk for LAA thrombus and thromboembolic events. There are limited data suggesting that this approach can reduce the risk of stroke" (Hijazi, et al., 2019).

Professional Societies/Organizations

American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS):

The ACC/AHA/HRS published a joint guideline for the management of patients with atrial fibrillation (AF) (January, et al., 2014). In the nonpharmacological stroke prevention section of the guideline addressing cardiac surgery LAA occlusion/excision, the authors stated that the current data on LA occlusion at the time of concomitant cardiac surgery reveal a lack of clear consensus because of the inconsistency of techniques used for surgical excision, the highly variable rates of successful LAA occlusion, and the unknown impact of LAA occlusion on future thromboembolic events. The guideline recommendation states that surgical excision of the LAA may be considered in patients undergoing cardiac surgery (Class IIb Level of Evidence C).

The 2019 focused update to the 2014 guideline includes the following updated recommendation for cardiac surgery LAA occlusion/excision. The Level of Evidence was updated from C to B-NR because of new evidence (January, et al., 2019):

- Surgical occlusion of the LAA may be considered in patients with AF undergoing cardiac surgery, as a component of an overall heart team approach to the management of AF (Class IIB: Level of Evidence B-NR).

Class IIb (weak): benefits \geq risk; usefulness/effectiveness is unknown/unclear/uncertain/or not well established. Level of evidence B-NR: moderate quality evidence from one or more well-designed, well-executed nonrandomized RCTs, observational studies or registry studies. Meta-analyses of such studies.

American Heart Association (AHA)/American Stroke Association (ASA): Joint guidelines from these organizations for the primary prevention of stroke include the following recommendations regarding LAA closure (Meschia, et al., 2014):

Class IIb; Level of Evidence B

- closure of the LAA may be considered for high-risk patients with AF who are deemed unsuitable for anticoagulation
- performed at a center with low rates of periprocedural complications
- the patient can tolerate the risk of at least 45 days of post-procedural anticoagulation

Level of evidence B: limited populations evaluated. Data derived from a single randomized trial or nonrandomized studies.

Class IIb: recommendation's usefulness/efficacy less well established; greater conflicting evidence from single randomized trial or nonrandomized studies

Centers for Medicare & Medicaid Services (CMS)

- National Coverage Determinations (NCDs): NCD for Percutaneous Left Atrial Appendage Closure (LAAC) (20.34) is broader in scope than this Coverage Policy. The NCD was last updated on October 2, 2016. Refer to the CMS NCD table of contents link in the reference section.
- Local Coverage Determinations (LCDs): No LCDs found

Use Outside of the US

Canadian Cardiovascular Society (CCS): In 2014, the CCS published a focused update to the 2010 guidelines for the management of atrial fibrillation (Verma, et al., 2014). The guidelines recommend the following regarding LAA closure devices which are not currently approved for use in Canada:

- It is suggested that these non-approved LAA closure devices not be used, except in research protocols or in systematically documented use protocols in patients at high risk of stroke (CHADS₂ score \geq 2) for whom antithrombotic therapy is precluded (Conditional Recommendation, Low-Quality Evidence).

The 2018 focused update to the CCS guidelines do not address LAA closure devices (Andrade, et al., 2018).

European Society of Cardiology (ESC): The ESC published updated guidelines for management of atrial fibrillation (Kirchhof, et al., 2016). The guidelines noted:

Recommendations for occlusion or exclusion of the left atrial appendage:

Class I* Level B

- After surgical occlusion or exclusion of the LAA, it is recommended to continue anticoagulation in at-risk patients with AF for stroke prevention.

Class IIb* Level B

- LAA occlusion may be considered for stroke prevention in patients with AF and contra-indications for long-term anticoagulant treatment (e.g. those with a previous life-threatening bleed without a reversible cause).
- Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery.
- Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients undergoing thoracoscopic AF surgery.

*Class of recommendations:

Class I - Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.

Class IIb - established by evidence/opinion. Usefulness/efficacy is less well established by evidence/opinion.

Level of evidence:

B - Data derived from a single randomized clinical trial or large non-randomized studies.

European Heart Rhythm Association (EHRA)/European Association of Percutaneous Cardiovascular Interventions (EAPCI): EHRA/EAPCI published expert consensus statement on catheter-based left atrial appendage occlusion (Meier, et al., 2014). The statement includes the following:

- The main indication for LAA occlusion is AF with a CHADS₂ score \geq 1 or CHA₂-DS₂-VASc score \geq 2 and a relative or absolute contraindication to prolonged oral anticoagulation.
- Tolerance for at minimum several weeks of dual antiplatelet therapy, usually followed by lifelong single antiplatelet drug therapy.

Heart Rhythm Society (HRS); European Heart Rhythm Association (EHRA); European Cardiac Arrhythmia Society (ECAS) Asia Pacific Heart Rhythm Society (APHRS); Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLAECE): The 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation does not provide recommendations regarding LAA occlusion, resection, or ligation for treatment of AF (Calkins, et al., 2017).

National Institute for Health and Care Excellence (NICE): 2014 NICE clinical guidelines for the management of atrial fibrillation include the following recommendations regarding LAA closure:

- Consider left atrial appendage occlusion (LAAO) if anticoagulation is contraindicated or not tolerated and discuss the benefits and risks of LAAO with the person.
- Do not offer LAAO as an alternative to anticoagulation unless anticoagulation is contraindicated or not tolerated.

In summary, oral anticoagulation therapy remains the standard of care for stroke prevention for most individuals with AF and elevated risk for stroke. Individuals who are not candidates for long-term oral anticoagulation have been proposed as eligible candidates for LAA occlusion with transcatheter closure of the LAA using the only FDA-approved device, the Watchman device. The current FDA labeling for the Watchman device specifies that individuals should be deemed suitable for anticoagulation and, in particular, a period of periprocedural anticoagulation. Individuals unable to take oral anticoagulation were excluded from the Watchman RCTs. Observational data suggests that most participants remain on anticoagulant therapy after LAA device implantation. The benefit versus harms of LAA occlusion with the Watchman device versus standard care remains unclear. A number of unresolved issues remain, including the optimal patient selection and periprocedural antithrombotic regimen. Long-term follow-up is needed to determine the safety of percutaneous closure of the LAA. The ASAP-TOO (assessment of the WATCHMAN device in patients unsuitable for oral anticoagulation) trial is a multicenter prospective randomized trial designed to establish the safety and effectiveness of the WATCHMAN LAA closure device in individuals with nonvalvular AF that are considered ineligible for oral anticoagulants (NCT02928497); the estimated study completion date is December 2023.

In summary, there is insufficient robust evidence in the peer-reviewed published literature regarding the long-term outcomes, safety and efficacy of surgical occlusion of the LAA in individuals with AF undergoing cardiac surgery. The current data on surgical LAA occlusion at the time of concomitant cardiac surgery reveals a lack of clear consensus because of the inconsistency of techniques used for surgical excision, the highly variable rates of successful LAA occlusion, and the unknown impact of LAA occlusion on future thromboembolic events.

Maze and Related Procedures

Surgical techniques for the treatment of AF can be broadly categorized into open heart procedures such as the “cut-and-sew” and/or the Cox-Maze procedure performed on a nonbeating heart and the minimally invasive procedures that use epicardial radiofrequency ablation, a thoracoscopic or mediastinal approach, and hybrid/convergent catheter ablations/open surgical procedures which are generally performed on the beating heart. In the open heart approach, access to the chest is made via a large incision down the sternum. The Cox-Maze procedure is generally performed in conjunction with valvular or coronary artery bypass graft surgery. Minimally invasive surgical procedures are sometimes referred to as “mini-Maze” procedures, but the 2012

consensus statement from the Heart Rhythm Society recommends that the phrase “maze” procedure only be used to describe the biatrial lesion set of the Cox-Maze procedure. The statement recommends that less extensive lesion sets be referred to as a surgical AF ablation procedure. The minimally invasive approach involves several small keyhole incisions in the intercostal spaces on either side of the chest cavity to allow entry of several devices, including a surgical camera used to guide the procedure and an energy source for ablation (Hayes, 2016; Je, et al., 2015; Stulak, et al., 2014; Calkins et al., 2012).

Surgical Maze Procedure: The surgical maze procedure was introduced in 1987. The initial two iterations were associated with high rates of pacemaker implantation and are no longer performed. The third version (Cox maze III) became the standard surgical procedure to restore sinus rhythm in patients with AF but is not widely performed because of surgeons' reluctance to perform this complicated “cut and sew” atrial lines of ablation operation approach in association with valve or coronary artery bypass procedures or as a stand-alone procedure. The Cox maze IV operation is less invasive, using radiofrequency or cryoablation to replicate surgical lines of ablation (January, et al., 2014).

U.S. Food and Drug Administration (FDA): The Maze procedures are not subject to regulation by the FDA. Any medical devices, drugs, biologics, or tests used as a part of this procedure may be subject to FDA regulation.

Literature Review: The peer-reviewed medical literature includes both relatively large retrospective and prospective studies documenting the safety and efficacy of the surgical Maze procedure performed during cardiopulmonary bypass with or without concomitant cardiac surgery. Study results suggest that the Maze procedure adds little or no additional risk when performed simultaneously with other open heart surgeries such as valvular repair or replacement. The Maze III procedure was used most commonly; however, several studies reported modifications to this procedure, such as use of cryoprobes or thermal probes for creation of ablation lines. Outcome measures in the studies vary. Some studies measure atrial function, primarily using echocardiography. Duration of follow-up in the studies is highly variable; some studies report outcomes after several months, while others follow patients for a number of years. Most studies do not describe ongoing medical therapies; thus, it is not possible to determine whether patients were still receiving antiarrhythmic medications or anticoagulants postoperatively (Phan, et al., 2014a; Phan et al., 2014b; Stulak, et al., 2014; Johansson, et al., 2014; Yanagawa, et al., 2013; Ad, et al., 2013; Albage, et al., 2013; Saint, et al., 2013; Melby, et al., 2013; Okada, et al., 2013; Kong, et al., 2010; VonOppell, et al., 2009; Lee, et al., 2009; Albrecht, et al., 2009; Wang, et al., 2009; Louagie, et al., 2009; Lönnerholm, et al., 2008; Srivastava, et al., 2008; Khargi, et al., 2007; Doty, et al., 2007; Stulak, et al., 2007a; Stulak, et al., 2007b; Wong, et al., 2006; Gillinov, et al., 2006; Melby, et al., 2006; Gaynor, et al., 2005; Reston and Shuhaiber, 2005; Khargi, et al., 2005; Bando, et al., 2002; Cox, et al., 2000).

In 2013, the Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review of treatment of atrial fibrillation. The key point under procedural therapies states " Based on seven RCTs (one good, six fair quality) involving 361 patients, surgical Maze at the time of other cardiac surgery (specifically mitral valve surgery) is superior to mitral valve surgery alone for maintenance of sinus rhythm over at least 12 months of follow-up in patients with persistent AF" (AHRQ, 2013).

There is evidence from a number of prospective and retrospective studies that the surgical Maze procedure, performed during cardiopulmonary bypass with or without concomitant cardiac surgery, is safe and effective in restoring sinus rhythm (SR) in patients with medically refractory, intermittent (i.e., paroxysmal or persistent) or continuous (i.e., permanent), symptomatic AF in whom rhythm control is considered essential. In addition, there is some evidence that, when performed in conjunction with valve repair or replacement, the Maze procedure may reduce the risk of stroke, compared with valve replacement alone.

Minimally Invasive Maze Procedures: Despite its high success rate, the surgical Maze procedure has not been widely adopted other than for patients undergoing cardiac surgery because of the need for cardiopulmonary bypass. Surgical techniques for treating AF have evolved over the past 20 years, with the introduction of minimally invasive approaches. Numerous minimally invasive off-pump Maze procedures including hybrid or convergent ablation procedures are being investigated to treat atrial fibrillation (AF). While minimally invasive surgical procedures have the advantage of minimal surgical dissection and accelerated recovery, limitations include the inability to map and isolate the source of AF and the necessity of transmural ablation lines, which can

be difficult to achieve due to varying thickness of cardiac tissue. Any approach to surgical ablation carries risk of serious complications, including phrenic nerve palsy, coronary artery injury, and esophageal perforation (Hayes, 2016).

Literature Review

Evidence in the peer-reviewed, published scientific literature is insufficient to allow strong conclusions in terms of safety and long term efficacy of minimally invasive approaches for the treatment of AF including hybrid or convergent ablation procedures. Published evidence evaluating these minimally invasive procedures is primarily in the form of single center retrospective or prospective case series with few controlled clinical trials. Generally, the outcomes of the studies demonstrate improvement in AF following ablation. However, comparison between clinical studies is difficult and limited by heterogeneous study populations, use of different lesion sets and energy sources, differences in type of designs and lack of standardized outcome measures and definitions of success. Follow-up time varies across studies as well as definition of procedure success used to assess clinical outcomes. Furthermore, there is no clear consensus among authors regarding patient selection criteria. Further scientific research, involving well-designed controlled clinical trials with long-term net health outcome data, are still needed to clearly define and establish a role for minimally invasive off-pump Maze procedures for the treatment of AF. The data are insufficient to reach conclusions about the relative effectiveness of these procedures compared to the classic surgical Maze procedure for the treatment of AF or to catheter-based ablation (Haye, et al., 2016, 2017, 2018, 2019; Gersak, et al., 2014; Pison, et al., 2014; Ismail, et al., 2014; Kurfirst, et al., 2014; Lawrance, et al., 2014b; LaMeir, et al., 2013a; Gehi, et al., 2013; Gersak, et al., 2012; LaMeir, et al., 2012; Zembela, et al., 2012; Pison, et al., 2012; Boersma, et al., 2012; Santini, et al., 2012; Kasirajan, et al., 2012; Kiser, et al., 2011; Krul, et al., 2011; LaMeir, et al., 2011; Wang, et al., 2011; Mahapatra, et al., 2011; Nasso, et al., 2011; Speziale, et al., 2010; Edgerton, et al., 2009, 2010; Kiser, et al., 2010; Wudell, et al., 2008; Sirak, et al., 2008; McClelland, et al., 2007; Pruitt, et al., 2006; Jeanmart, et al., 2006; Wolf, et al., 2005).

In a Hayes Technology Assessment on Minimally Invasive Surgical (MIS) Procedures for Treatment of Atrial Fibrillation the authors addressed if MIS ablation procedures are effective, safe and if definite patient selection criteria has been established for use of MIS procedures for treatment of AF. The conclusion state that although the evidence regarding MIS ablation for treatment of AF is large, the evidence pertaining to the effectiveness of MIS ablation is of low quality. This low-quality evidence suggests that MIS ablation may offer benefit for treatment of adult patients with AF refractory to medical therapy. Although MIS ablation procedures appear to have an acceptable safety profile during follow-up, there may be a potential for higher rates of significant postoperative complications relative to catheter ablation for AF. Finally, there is considerable variation in the instrumentation and lesion sets used in MIS ablation procedures as well as the characteristics of patients enrolled in studies evaluating MIS ablation, which results in uncertainty regarding optimal treatment parameters and patient selection criteria. Rates of freedom from AA following MIS ablation ranged from 42-100% (10 studies), with MIS ablation resulting in higher rates of freedom from AA than catheter ablation (3 of 3 studies). There are few long-term studies of good quality that compare MIS ablation with other relevant therapies. Rates of major/significant post-procedural complications were significantly greater in MIS ablation groups (21-23%) than in catheter ablation groups (3.2-5%) (2 studies). Definitions of treatment success/failure and types of instrumentation, surgical approaches, and lesions sets used in the studies varied widely and limit the ability to generalize outcomes (Hayes, 2016; annual review 2017, 2018).

In July 2019 Hayes published a comparative effectiveness review of the hybrid maze (HM) procedure for atrial fibrillation. The evidence search identified 12 comparative studies (two randomized controlled trials [RCTs], 10 comparative cohort studies) that met the inclusion criteria, enrolling 45-243 patients undergoing the HM procedure with follow-up durations ranging from the in-hospital period to 30.5 months after the procedure. The main outcome measures were freedom from atrial arrhythmia (AA), recurrence of AA, repeat ablation or reintervention, and adverse events (AEs). The conclusions state that "Findings from an overall low-quality body of evidence suggest that for adult patients undergoing treatment for AF, the HM procedure appears to have at least comparable effectiveness when compared with catheter ablation (CA), the Cox Maze (CM) procedure, or surgical ablation (SA) in studies with mainly intermediate-term follow-up (e.g., two years or less). However, it is uncertain whether HM offers additional benefit relative to the comparator treatments. Data from systematic reviews with meta-analyses suggest that HM may be associated with a greater rate of adverse events (AEs) than CA or SA. Large, well-designed, randomized studies with long-term follow-up are needed to confirm findings

described in this health technology assessment. Gaps in the current evidence include optimal procedural approaches and techniques in patients undergoing the HM procedure; the long-term safety and effectiveness of the HM procedure; and determination of which patients the HM procedure may provide optimal benefit” (Hayes, 2019).

Professional Societies/Organizations

The American College of Cardiology (ACC)/American Heart Association (AHA) and Heart Rhythm Society (HRS): In 2014, the American College of Cardiology (ACC)/American Heart Association (AHA) and Heart Rhythm Society (HRS) published an updated guideline which supersede the 2011 focused updates and the 2006 guidelines for the management of patients with atrial fibrillation (January, et al., 2014). The ACC/AHA/HRS published a focused update of the 2014 guideline. These guidelines do not provide recommendations regarding the use of minimally invasive maze procedures for treatment of AF. The surgical or minimally invasive maze procedures were not included in the 2019 focused update (January, et al., 2019).

The following recommendations for surgical maze procedures are included in the 2014 guideline:

- An AF surgical ablation procedure is reasonable for selected patients with AF undergoing cardiac surgery for other indications (Class IIa; Level of Evidence C).

Class IIa; Level of Evidence C states that the benefit is greater than the risk; Additional studies with focused objectives needed. It is reasonable to perform procedure/administer treatment. Very limited populations evaluated. Only consensus opinion of experts, case studies, or standard of care.

- A stand-alone AF surgical ablation procedure may be reasonable for selected patients with highly symptomatic AF not well managed with other approaches (Class IIb: Level of Evidence B).

Class IIb: Level of Evidence B states that benefit is \geq risk; Additional studies with broad objectives needed; additional registry data would be helpful. Procedure/treatment may be considered. Limited populations evaluated. Data derived from a single randomized trial or nonrandomized studies

Centers for Medicare & Medicaid Services (CMS)

- National Coverage Determinations (NCDs): No NCDs found
- Local Coverage Determinations (LCDs): No LCDs found

Use Outside of the US

National Institute for Health and Care Excellence (NICE): In 2014, the NICE released a guideline update on the management of AF. These guidelines do not provide recommendations regarding the use of minimally invasive maze procedures for treatment of AF.

Heart Rhythm Society (HRS); European Heart Rhythm Association (EHRA); European Cardiac Arrhythmia Society (ECAS) Asia Pacific Heart Rhythm Society (APHRS); Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLAECE): The 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation does not provide recommendations regarding the use of minimally invasive maze procedures for treatment of AF (Calkins, et al., 2017).

European Society of Cardiology (ESC): The updated 2016 guidelines for the management of atrial fibrillation addresses gaps in evidence for thoracoscopic stand alone AF surgery. The guidelines state that randomized trials using a standardized procedure are urgently needed to clearly define the benefits and risks of thoracoscopic AF ablation, and to further support decisions of the AF Heart Team (Kirchhof, et al., 2016).

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible

for reimbursement.

Transcatheter Ablation of the Pulmonary Veins

Considered Medically Necessary when criteria in the applicable policy statements listed above are met and when used to report ablation of the pulmonary veins for the treatment of symptomatic paroxysmal or persistent atrial fibrillation:

CPT®* Codes	Description
93656	Comprehensive electrophysiologic evaluation including transeptal catheterizations, insertion and repositioning of multiple electrode catheters with induction or attempted induction of an arrhythmia including left or right atrial pacing/recording when necessary, right ventricular pacing/recording when necessary, and His bundle recording when necessary with intracardiac catheter ablation of atrial fibrillation by pulmonary vein isolation
93657	Additional linear or focal intracardiac catheter ablation of the left or right atrium for treatment of atrial fibrillation remaining after completion of pulmonary vein isolation (List separately in addition to code for primary procedure)
93662	Intracardiac echocardiography during therapeutic/diagnostic intervention, including imaging supervision and interpretation (List separately in addition to code for primary procedure)

Percutaneous Transcatheter or Surgical Closure of the Left Atrial Appendage

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
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
33999	Unlisted procedure, cardiac surgery

Surgical On-Pump Maze Procedure

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
33256	Operative tissue ablation and reconstruction of atria, extensive (eg, maze procedure); with cardiopulmonary bypass
33257	Operative tissue ablation and reconstruction of atria, performed at the time of other cardiac procedure(s), limited (eg, modified maze procedure) (List separately in addition to code for primary procedure)
33259	Operative tissue ablation and reconstruction of atria, performed at the time of other cardiac procedure(s), extensive (eg, maze procedure), with cardiopulmonary bypass (List separately in addition to code for primary procedure)

Minimally Invasive Off-Pump Maze Procedure

Experimental/Investigational/Unproven/Not Covered:

CPT®* Codes	Description
33254	Operative tissue ablation and reconstruction of atria, limited (eg, modified maze procedure)
33255	Operative tissue ablation and reconstruction of atria, extensive (eg, maze procedure); without cardiopulmonary bypass

33258	Operative tissue ablation and reconstruction of atria, performed at the time of other cardiac procedure(s), extensive (eg, maze procedure), without cardiopulmonary bypass (List separately in addition to code for primary procedure)
33265	Endoscopy, surgical; operative tissue ablation and reconstruction of atria, limited (eg, modified maze procedure), without cardiopulmonary bypass
33266	Endoscopy, surgical; operative tissue ablation and reconstruction of atria, extensive (eg, maze procedure), without cardiopulmonary bypass

***Current Procedural Terminology (CPT®) ©2018 American Medical Association: Chicago, IL.**

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