Medical Coverage Policy

Effective Date **11/15/2021**
Next Review Date **11/15/2022**
Coverage Policy Number **0469**

Nonpharmacological Treatments for Atrial Fibrillation

Table of Contents

Related Coverage Resources

Cardiac Electrophysiological (EP) Studies
EviCore Adult Cardiac Imaging Guideline
Ambulatory External and Implantable Electrocardiographic Monitoring
Implantable Cardioverter Defibrillator (ICD)
Transcatheter Ablation for the Treatment of Supraventricular Tachycardia in Adults
Transthoracic Echocardiography in Adults
Wearable Cardioverter Defibrillator and Automatic External Defibrillator

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) is considered medically necessary when EITHER of the following criteria are met:

- Individual with a 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).
- Individual with 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 closure of the left atrial appendage (CPT code 33340) for non-valvular atrial fibrillation using a U.S. Food and Drug Administration (FDA) approved device is considered medically necessary for the prevention of stroke when ALL of the following criteria are met:

- Individual has an increased risk of stroke and systemic embolism based on $CHADS_2$* ≥ 2 or CHA_2DS_2-VASc** score ≥ 3 and systemic anticoagulation therapy is recommended.
- Attestation that for this individual the long-term risk of systemic anticoagulation outweighs the risk of the device implantation.

* $CHADS_2$ score: Congestive heart failure, hypertension, age greater than 75, diabetes, stroke/transient ischemia attack/thromboembolism.
** CHA_2DS_2-VASc score: Congestive heart failure, hypertension, age greater than or equal to 65, diabetes, stroke/transient ischemia attack/thromboembolism, vascular disease, sex category.

Percutaneous transcatheter closure of the left atrial appendage for ANY other indication is considered experimental, investigational or unproven.

Surgical closure of the left atrial appendage, including use of a clip, (CPT code 33268) in conjunction with other cardiac surgical procedures using a U.S. Food and Drug Administration (FDA) approved device is considered medically necessary for the prevention of stroke when ALL of the following criteria are met:

- Individual has an increased risk of stroke and systemic embolism based on $CHADS_2$* ≥ 2 or CHA_2DS_2-VASc** score ≥ 3 and systemic anticoagulation therapy is recommended.
- Individual has a documented diagnosis of paroxysmal or persistent atrial fibrillation

* $CHADS_2$ score: Congestive heart failure, hypertension, age greater than 75, diabetes, stroke/transient ischemia attack/thromboembolism.
** CHA_2DS_2-VASc score: Congestive heart failure, hypertension, age greater than or equal to 65, diabetes, stroke/transient ischemia attack/thromboembolism, vascular disease, sex category.

Surgical closure of the left atrial appendage for ANY other indication 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).

Ugowe et al. (2018) conducted a systematic review that aimed to assess the racial and ethnic differences in the epidemiology, management, and outcomes of patients with AF. The authors reported that underrepresented racial and ethnic groups have a higher prevalence of established risk factors associated with the development of AF but an overall lower incidence and prevalence of AF as compared with non-Hispanic whites. There are racial and ethnic differences in detection, awareness and AF-associated symptoms. Nonwhite populations also have decreased use of rhythm control modalities and anticoagulation for stroke prevention. Additionally, underrepresented racial and ethnic groups had increased morbidity and mortality relative to white groups. The study concluded that racial and ethnic differences in AF warrant further analysis to understand the factors contributing to the differences in prevalence and management to ensure the delivery of high quality care that prevents stroke, reduces deaths, and decreases expenses associated with caring for underrepresented population.

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 (Spragg, et al., 2021; Passman, et al., 2020; Morady, et al, 2019; 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 $CHADS_2$ (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 $CHADS_2$ score and the annual risk of stroke in the absence of aspirin or warfarin therapy. The $CHADS_2$ score has been superseded by the CHA_2DS_2-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 nine, 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, cryothermy (cryoballoon ablation) or infrared laser. Access to the left atrium is typically obtained using a special trans-septal-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 (trans-septal 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; Jahangiri, et al., 2006).

Yao et al. (2020) conducted a study that evaluated sex-specific differences in AF presentation, symptom severity and health-related quality of life, symptomatic and asymptomatic arrhythmia recurrence, AF burden, and health care utilization. The results reported that freedom from any atrial tachyarrhythmia and symptomatic atrial tachyarrhythmia were similar between male and female patients. Post-ablation, the median AF burden was 0.00% in male and female with no difference observed between the sexes. Periprocedural complications occurred twice as frequently in female patients. In comparison to male patients, female patients also reported a significantly worse symptom score and quality of life at baseline and all follow-up intervals, but they derived similar magnitude of improvement post-ablation. There was no difference between male and female patients with respect to emergency department visits, hospitalization, cardioversion, or repeat ablation. The authors concluded that when compared with male patients, female patients have significantly worse symptom scores and quality of life at baseline. Despite this, they have similar benefit in freedom from recurrent arrhythmia and similar improvements in quality of life following AF ablation.

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; Calkins, et al., 2009; Oral, et al., 2006; Stabile, et al., 2006; Pappone, et al., 2006). 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 (Luik, et al., 2015; Aryana, et al., 2015; Jourda, et al., 2015; Skelly, et al., 2015; Straube, et al., 2014; DeVille, et al., 2014; Mugnai, et al., 2014; Andrade, et al., 2014; Xu, et al., 2014; Packer, et al., 2013; Malmborg, et al., 2013; Vogt, et al., 2013; Andrade, et al., 2011; Kojodjojo, et al., 2010; Kühne, et al., 2010; Tang, et al., 2010; Linhart, et al., 2009; 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; Dukkipati, 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. 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).

U.S. Food and Drug Administration (FDA): 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.

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.

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 - Transcatheter ablation of the pulmonary veins: 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 randomized studies. The randomized controlled trials have demonstrated that cryoballoon catheter ablation as an initial, first-line rhythm control strategy is an effective first-line treatment strategy in recurrent symptomatic paroxysmal atrial fibrillation (Andrade, et al., 2021; Kuniss, et al., 2021; Wazni, et al., 2021). 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., 2021; Calkins, et al., 2017; Kirchhof, et al., 2016, January, et al., 2014).

Randomized Controlled Trials: Andrade et al. (2021) conducted the randomized Early Aggressive Invasive Intervention for Atrial Fibrillation (EARLY-AF) trial of initial rhythm control in patients with symptomatic, untreated atrial fibrillation. The study compared the catheter cryoballoon ablation to antiarrhythmic drugs to prevent the recurrence of atrial tachyarrhythmia, as assessed by an implantable continuous rhythm monitor. The study included patients (n=303) aged 18 years or older with symptomatic, paroxysmal atrial fibrillation (AF) and at least one episode of atrial fibrillation detected on electrocardiography within 24 months before randomization. Patients were randomized into two groups: catheter cryoballoon ablation group (n=154) or antiarrhythmic drug therapy group (n=149). Patients in the catheter ablation group underwent pulmonary-vein isolation using a 23-mm or 28-mm cryoballoon (Arctic Front Advance, Medtronic). The antiarrhythmic drug therapy group were prescribed daily therapy within one week after randomization. In the event of inefficacy or unacceptable side effects during the first 90 days, patients were switched to a prespecified second or third agent. Follow-up occurred telephonically at seven days and at visits at three, six, and 12 months. The implantable cardiac monitor automatically transmitted on a daily basis and manual transmissions were obtained at least weekly. The primary outcome measured the first recurrence of any atrial tachyarrhythmia (atrial fibrillation, atrial flutter, or atrial tachycardia) lasting 30 seconds or longer between 91 and 365 days after the initiation of an antiarrhythmic drug or the catheter ablation procedure. The secondary outcomes measured the first recurrence of symptomatic atrial tachyarrhythmia between 91 and 365 days after the initiation of treatment, the arrhythmia burden, the success of multiple ablation procedures, quality of life, health care utilization, and serious adverse events. At 1 year, a clinically significant recurrence of atrial tachyarrhythmia had occurred in 101 of the 149 patients assigned to receive antiarrhythmic drugs (67.8%) (p<0.001) compared to 66 of the 154 patients assigned to undergo cryoablation (42.9%). Symptomatic atrial tachyarrhythmia recurred in 11.0% of the patients in the ablation group and in 26.2% of those who received antiarrhythmic drugs. Serious adverse events were noted in five patients (3.2%) who underwent ablation and in six patients (4.0%) who received antiarrhythmic drugs. The authors concluded that catheter cryoballoon ablation resulted in a significantly lower rate of recurrence of atrial tachyarrhythmia, as assessed by continuous cardiac rhythm monitoring, than antiarrhythmic drug therapy.

Dukkipati 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 × 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%; non-inferiority (p=0.003), suggesting non-inferiority. Patients experiencing ≥ 1 AEs (number [%]): 20/170 (11.8%); 25/172 (14.5%); non-inferiority (p=0.002), suggesting non-inferiority. 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 ± SD): 236.0 ± 52.8; 193.0 ± 63.6; (p<0.0001), favoring RFA. Fluoroscopy time (mean minutes ± SD): 35.6 ± 18.2; 29.7 ± 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.

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 ± SD): 149 ± 34; 129 ± 29; 103 ± 33; (p≤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 pre-procedural cerebral magnetic resonance imaging (MRI) scans in 20 patients; thus, the existence of pre-procedural ACLs in the remaining 79 patients was unknown.

Nonrandomized Controlled Trials: 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.

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 ± SD): 195 ± 47; 164 ± 29; 208 ± 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.

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 ± 30 minutes for the CB group and 144 ± 33 minutes for the LB group (p=0.13). Mean fluoroscopy time was longer in the CB group (21 ± 9 minutes vs 15 ± 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.

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 ± SD): 234 ± 62; 185 ± 28; (p=0.0014), favoring RFA. Fluoroscopy time (mean minutes ± SD): 28 ± 16; 26 ± 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.

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 verses 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 trails 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 ≥ 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 stated 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 verses 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 (January, et al., 2019; Packer, et al., 2018).

Use Outside of the US
The updated 2020 European Society of Cardiology (ESC)/European Association of Cardio-Thoracic Surgery (EACTS) guidelines for the diagnosis and management of atrial fibrillation (AF) addressed the following recommendations for catheter ablation of AF (Hindricks, et al., 2021):

- Repeated pulmonary vein isolation (PVI) procedures should be considered in patients with AF recurrence provided the patient's symptoms were improved after the initial PVI (Class IIa Level of evidence B).
- AF catheter ablation for PVI is recommended for rhythm control after one failed or intolerant class I or III antiarrhythmic drug (AAD), to improve symptoms of AF recurrences in patients with
    - Paroxysmal AF, or (Class I Level of evidence A)
    - Persistent AF without major risk factors for AF recurrence, or (Class I Level of evidence A)
    - Persistent AF with major risk factors for AF recurrence (Class I Level of evidence B)
- AF catheter ablation for PVI should be considered for rhythm control after one failed or intolerant to beta-blocker treatment to improve symptoms of AF recurrences in patients with paroxysmal and persistent AF (Class IIa Level of evidence B).
- AF catheter ablation for PVI should/may be considered as first-line rhythm control therapy to improve symptoms in selected patients with symptomatic as an alternative to AAD class I or III, considering patient choice, benefit, and risk:
    - Paroxysmal AF episodes, (Class IIa Level of evidence B).
    - Persistent AF without major risk factors for AF recurrence. (Class IIb Level of evidence C).
- AF catheter ablation for PVI should be considered as a strategy to avoid pacemaker implantation in patients with AF-related bradycardia or symptomatic pre-automaticity pause after AF conversion considering the clinical situation. (Class IIa Level of evidence C).
- Complete electrical isolation of the pulmonary veins is recommended during all AF catheter-ablation procedures (Class I Level of evidence A).

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 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation has recommended the following for catheter ablation of AF (Andrade, et al., 2020):

- Recommended 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, High Quality Evidence).

- Suggested catheter ablation to maintain sinus rhythm as first-line therapy for relief of symptoms in select patients with symptomatic, AF (Weak Recommendation, Moderate Quality Evidence).
- Suggested that catheter ablation of AF should be performed by electrophysiologists with a high degree of expertise and high annual procedural volumes (Weak Recommendation, Low-Quality Evidence).

The 2020 Comprehensive Guidelines for the Management of Atrial Fibrillation replaces the previous published guidelines, recommendations, and practical tips. The primary indication for AF ablation is to achieve rhythm control in patients in whom antiarrhythmic drug therapy has already failed. However, early intervention for AF can prevent progression to persistent AF and avoid some of the long-term risks of the arrhythmia including stroke and HF (Andrade, et al., 2020).

An updated Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation was published in 2017 by the Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA)/European Cardiac Arrhythmia Society (ECAS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Society of Cardiac Stimulation and Electrophysiology (SOLAECE) that replaced 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 (Calkins, et al., 2017).

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 stated 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 addressed techniques for obtaining permanent PVI with balloon technologies. The authors stated 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 provided an update on examples on many of the technologies and tools that are employed for AF ablation procedures. The authors stated 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 discussed 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.

The 2016 Guidelines of the Taiwan Heart Rhythm Society and the Taiwan Society of Cardiology for the management of atrial fibrillation stated 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 stated 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 stated 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).

The 2013 National Heart Foundation of Australia consensus statement on catheter ablation as a therapy for atrial fibrillation recommended the following catheter ablation therapy for atrial fibrillation (AF):

- 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).

In 2021, the National Institute for Health and Clinical Excellence (NICE) (United Kingdom) released a clinical guideline on the diagnosis and management of AF. NICE recommended the following when drug treatment is not tolerated or ineffective in patients with symptomatic paroxysmal or persistent atrial fibrillation:

- considering radiofrequency point-by-point ablation or if radiofrequency point-by-point ablation is assessed as being unsuitable, cryoballoon ablation or laser balloon ablation can be considered
- when offering left atrial catheter ablation, explain that the resolution of symptoms might not be long-lasting
- considering left atrial surgical ablation at the same time as other cardiothoracic surgery for people with symptomatic atrial fibrillation
- Discussing the benefits and risks of treatment with the individual.

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 stated 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., 2015; Bordignon, et al., 2013; Metzner, et al., 2011), two case series and two case reports.

NICE Interventional Procedures Guidance issued in 2012 addressed percutaneous balloon cryoablation for pulmonary vein isolation in atrial fibrillation (AF). NICE Guidance stated 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 encouraged 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 (Gaita, et al., 2011; Kojodjojo, et al., 2010; Chierchia, et al., 2010; Sorgente, et al., 2010;), one case-control study (Linhart, et al., 2009) and three case series (Ahmed, et al., 2009; Neumann, et al., 2008, Van Belle, et al., 2008). 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.

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 non-valvular 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 and Saw, 2021; Morady, et al., 2019; Whitlock, et al., 2014).

Several studies have reported that women had higher rates of in-hospital adverse events following LAAC than men did. It is recommended that further research is warranted to identify sex-specific, racial/ethnic, and socioeconomic pathways during the patient selection process to minimize complications in patients undergoing LAAC (Darden, et al., 2021; Sanjoy, et al., 2020).

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.

The Amplatzer™ Cardiac Plug (St. Jude Medical, Minneapolis, MN) 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 Amulet has more stabilizing wires, up to 10 pairs, for improved device stability and larger lobe size to occlude larger appendages.

U.S. Food and Drug Administration (FDA): The Watchman LAA Closure Technology received FDA premarket approval on 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 $CHADS_2$ (cardiac failure, hypertension, age ≥ 75 years, diabetes, stroke) or CHA_2DS_2-VASc[1] (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

On July 2020, a premarket approval application (PMA) supplement (P130013/S035) was approved for a modified version of the Watchman LAA Closure Device with Delivery System, referred to as the Watchman FLX Left Atrial Appendage Closure Device with Delivery System, to expand the indications to include anticoagulation therapy. These devices are indicated to reduce the risk of thromboembolism from the left atrial appendage in patients with non-valvular atrial fibrillation who:

- are at increased risk for stroke and systemic embolism based on $CHADS_2$ or CHA_2DS_2-VASc scores and are recommended for anticoagulation therapy;

- are deemed by their physicians to be suitable for anticoagulation therapy; and
- have an appropriate rationale to seek a non-pharmacologic alternative to anticoagulation therapy, taking into account the safety and effectiveness of the device compared to anticoagulation therapy

In September 2021, the FDA informed health care providers of the potential for differences in procedural outcomes between women and men undergoing implant of a left atrial appendage occlusion (LAAO) device. The letter explained that the FDA would be working with manufacturers to evaluate information from several sources and included recommendations for the providers. The letter was prompted by the data reported in the National Cardiovascular Data Registry LAAO Registry.

The Amplatzer™ Amulet™ Left Atrial Appendage Occluder received FDA premarket approval on August 14, 2021 (P200049). 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 $CHADS_2$ or CHA_2DS_2-VASc scores;
- are suitable for short term anticoagulation therapy; and
- have appropriate rationale to seek a non-pharmacologic alternative to oral anticoagulation, taking into consideration the safety and effectiveness of the device

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

- 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.
- LAmbre™ LAA Closure System (Lifetech Scientific, Shenzhen, China) is a self-expanding LAA occluder constructed from a nitinol mesh and polyester membranes and consists of an umbrella and a cover connected by a short central waist. The device is delivered by an 8-10 French sheath and has full recapture and repositioning capabilities. LAmbreTM LAA Closure System received the CE mark in June 2016.

Literature Review - Percutaneous transcatheter closure of the LAA: The Watchman device received FDA approval based upon the results of PROTECT AF and PREVAIL randomized controlled trials (RCT).

The Amplatzer™ Amulet™ Left Atrial Appendage Occluder received FDA approval based upon the results of The Prospective Amulet Observational Study.

Randomized Controlled Trials - Amulet IDE: Lakkireddy et al. (2021) conducted the randomized controlled Amulet IDE trial that evaluated the safety and effectiveness of the Amulet occluder to the Watchman device. Patients (n=1878) were included in the study if they were age ≥ 18 years with documented paroxysmal, persistent, or permanent non-valvular atrial fibrillation and were at increased risk of stroke or systemic embolism defined as CHADS2 score ≥ 2 or a CHA2DS2-VASc score of ≥ 3. Patients were randomized to receive the Amulet occluder (n=934) or Watchman device (n=944). The primary outcomes measured safety (composite of procedure-related complications, all-cause death, or major bleeding at 12 months), effectiveness (composite of ischemic stroke or systemic embolism at 18 months) and the rate of LAA occlusion at 45 days. Secondary outcome measurements included a composite of all stroke, systemic embolism, or cardiovascular/unexplained death at 18 months, major bleeding at 18 months and superiority test of the three primary endpoints. Patients implanted with the Amulet occluder were discharged on either aspirin plus clopidogrel or aspirin plus OAC at the discretion of the investigator, while patients assigned to and implanted with the Watchman device received aspirin plus warfarin per the device instructions. When LAA occlusion was confirmed by TEE at the 45-day visit, cessation of OAC was required for all patients. Patients were then instructed to take aspirin and clopidogrel until the six month visit when clopidogrel was discontinued and aspirin continued indefinitely. The Amulet occluder was non-inferior to the Watchman device for the primary safety endpoint, the primary effectiveness endpoint and the composite of stroke, systemic embolism or cardiovascular/unexplained death (All: p<0.001 for non-inferiority). Major bleeding and all-cause death were similar between groups. Procedure-related complications were higher for the Amulet occluder (4.5% vs. 2.5%), largely related to more frequent pericardial effusion and device embolization. LAA occlusion was significantly higher for the Amulet occluder compared with the Watchman device (p<0.001 for non-inferiority; p=0.003 for superiority). Author noted limitations included: a high number of excluded patients which may limit the generalizability of the findings; echocardiographic core lab was not blinded; the Amulet device was compared to the first-generation Watchman device, not the newer generation; and it is unknown which antithrombotic regimen provides the best outcomes. The authors concluded that the Amulet occluder was non-inferior for safety and effectiveness of stroke prevention for NVAF compared with the Watchman device, and superior for LAA occlusion. However, additional studies are needed to better understand the higher occurrence of late pericardial effusion in Amulet patients receiving post-procedure OAC. No health disparities were identified by the investigators.

PRAGUE-17: Osmancik et al. (2020) conducted a multicenter, randomized, noninferiority trial (PRAGUE-17) comparing Percutaneous left atrial appendage closure (LAAC) with direct oral anticoagulant (DOACs). Patients were eligible to be enrolled if they had non-valvular AF; were indicated for oral anticoagulation (OAC); had a history of bleeding requiring intervention or hospitalization, had a history of a cardioembolic event while taking an OAC, and/or a CHA2DS2-VASc of ≥ 3 and HAS-BLED of > 2. Patients (n=402) were randomized to receive LAAC or DOAC. Patients randomized to the DOAC group could receive rivaroxaban, apixaban, or dabigatran at the manufacturer-recommended dose. Medication compliance was monitored by querying patients about regular medication use during each visit. Patients randomized to LAAC underwent implantation with a commercially available Amulet (Abbott Inc., St. Paul, Minnesota) or Watchman/Watchman-FLX (Boston Scientific Inc., St. Paul, Minnesota) device. Following LAAC, the recommended antithrombotic regimen was aspirin 100 mg/day plus clopidogrel 75 mg/day for 3 months. If a TEE then showed no device-related thrombus or leak of ≥ 5mm, clopidogrel was withdrawn; aspirin was continued indefinitely. The primary outcome measured safety, efficacy, stroke, transient ischemic attack, systemic embolism, cardiovascular death, major or non-major clinically relevant bleeding, or procedure/device related complications. For both groups, outpatient follow-up occurred at six weeks and three, six, nine, and 12 months and every six months thereafter. The minimum follow-up for the last enrolled patient was the six month visit. During each visit, patients were asked about the endpoint occurrence, all other changes in clinical status, hospitalization or other health care utilization, and medication changes. LAAC was successful in 181 of 201 (90.0%) patients. The implanted devices were either Amulet, Watchman, or Watchman-FLX in 61.3%, 35.9%, or 2.8%, respectively. In the DOAC group, apixaban was most frequently used (192 of 201; 95.5%). At a median 19.9 months of follow-up, the annual rates of the primary outcome were 10.99% with LAAC and 13.42%with DOAC (p=0.44; p=0.004 for noninferiority). There were no significant differences between groups for the components of the composite endpoint: all-stroke/TIA, clinically significant bleeding and cardiovascular death. Major LAAC-related complications occurred in nine (4.5%) patients. Limitations included that the study was underpowered to evaluate the relative differences in the individual components of the primary endpoint. The high event rate allowed sufficient power to assess the primary endpoint. Although the mean follow-up is substantial, additional follow-up is needed to determine the relative long-term differences between groups. In the DOAC group, no medication logs were kept; however, the observed ischemic stroke rate suggests reasonable DOAC compliance. The authors concluded that among patients at high risk for stroke and increased risk of bleeding, LAAC was non-inferior to DOAC in preventing major AF-related cardiovascular, neurological, and bleeding events.

PROTECT AF: A non-inferiority RCT compared LAA closure with Watchman device to warfarin treatment in patients with non-valvular atrial fibrillation (NVAF), the PROTECT AF trial (Reddy, et al. 2014; Reddy, et al., 2013a; Holmes, et al., 2009). 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, $CHADS_2$ 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/yrs), compared with 34 events in 244 patients (13.9%) for primary event rate of 3.8 in 100 pt/yrs in warfarin group. In the primary efficacy outcome, there was a non-inferiority > 99%, and in the primary safety endpoint a non-inferiority > 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 non-inferiority 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 non-inferiority 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; $CHADS_2$ ≥2 or 1 $CHADS_2$ 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 non-inferiority. The rate for the second coprimary efficacy endpoint (stroke or SE >7 days' post-randomization) was 0.0253 vs 0.0200 achieving non-inferiority. 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%). Non-inferiority 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 non-inferiority (posterior probability for non-inferiority = 88.4%), whereas the second coprimary endpoint of post-procedure ischemic stroke/SE did achieve non-inferiority (posterior probability for non-inferiority=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.

Nonrandomized Controlled Trials: Kar et al. (2021) reported the results of the prospective, nonrandomized, multicenter US Food and Drug Administration PINNACLE FLX study (Protection Against Embolism for Non-valvular AF Patients: Investigational Device Evaluation of the Watchman FLX LAA Closure Technology) that evaluated the safety and effectiveness of the next-generation WATCHMAN FLX LAA closure device in patients with non-valvular atrial fibrillation in whom oral anticoagulation is indicated and who have an appropriate rationale to seek a nonpharmacological alternative. Patients (n=400) were included in the study if they met the following criteria: non-valvular atrial fibrillation (NVAF) and a CHA2DS2-VASc score of ≥ 2 for men or ≥ 3 for women, were able to take the prescribed post-implant antithrombotic medication regimen, had a rationale for a nonpharmacological approach to stroke prevention, and had no other diagnoses that would require long-term anticoagulation. The primary safety outcome measured the occurrence of one of the following events within seven days after the procedure or by hospital discharge, whichever was later: death, ischemic stroke, systemic embolism, or device- or procedure-related events requiring cardiac surgery. The primary effectiveness outcome measured the incidence of effective LAA closure (peri-device flow ≤ 5 mm), which was assessed by the echocardiography core laboratory at 12-month follow-up. After device placement, treatment with a direct oral anticoagulant (DOAC) was required through at least the 45-day follow-up, with apixaban or rivaroxaban strongly recommended. Patients were also prescribed concomitant low-dose (81–100 mg) aspirin. On evidence of adequate LAA seal (leak ≤ 5 mm) at the 45-day TEE evaluation, patients were directed to discontinue DOAC therapy and begin a dual antiplatelet therapy regimen of clopidogrel (75 mg) plus low-dose aspirin until six months postimplant, followed by low-dose aspirin indefinitely. If a leak > 5 mm was measured at the 45-day follow-up, patients continued DOAC plus aspirin and were reevaluated at six months post-implant. If there were no leaks >5 mm at the subsequent follow-up visit, patients could forego dual antiplatelet therapy and proceed straight to lifelong low-dose aspirin. Post-implant follow-up visits were required at 45 days, six, 12, 18, and 24 months. The primary safety and efficacy outcomes were met (both: p<0.0001). Device-related thrombus was reported in seven patients, no patients experienced pericardial effusion requiring open cardiac surgery, and there were no device embolizations. Author reported study limitations included the lack of a control group, the procedural safety and efficacy of closure of the next-generation LAA closure device was not directly compared with that of the predicate device and clinical event incidence with the first-generation device cannot be directly compared with a similar population treated with oral anticoagulation. Secondly, the incidence of anatomic and effective closure that are surrogates for the clinical outcomes of stroke and systemic embolism outcomes will be reported when the prespecified two year follow-up is complete. Thirdly, the results should not be generalized to patients who have absolute contraindications to oral anticoagulant therapy. Lastly, the study sample size was not large enough to provide robust estimates of the incidence of rare events, such as device embolization. The authors concluded that LAA closure with the next-generation LAA closure device was associated with a low incidence of adverse events and a high incidence of anatomic closure.

Hildick-Smith et al. (2020) conducted The Amulet Observational Study prospectively that evaluated the safety and efficacy of left atrial appendage occlusion (LAAO) with the Amplatzer™ Amulet™ occluder. Patients (n=1088) were age 18 years and older with history of paroxysmal, persistent or permanent non-valvular atrial fibrillation eligible for an Amulet LAA Occluder device. Left atrial appendage occlusion was performed by 93 implanters at 61 centers in 17 countries. Primary outcomes measured: the rate of ischemic stroke, systemic embolism and cardiovascular (CV) death at two years; the rate of major bleeding events at two years; the assessment of acute (0–7 days) serious adverse events; and the assessment of late (> 7 days–2 years) serious adverse events. Secondary outcomes measured the rates of technical and procedural success along with the rate of patients taking OAC and antiplatelet drugs through two years. Patient follow-up occurred at discharge, 1–3 months, six months, one year, and two years (±3months) post-procedure. A transesophageal echocardiography (TOE) was required per protocol at the 1–3 month visit. Patients not implanted were followed for seven days and then withdrawn per protocol. Antithrombotic medication and adverse events were assessed at each visit. The follow-up rate at two years was 94.2%, with 864 of the 917 expected two year visits performed. The 40 patients who withdrew consent were followed for an average of 167± 210 days, while the 15 patients lost to follow-up were followed for an average of 743± 227 days. Major adverse events (≥ 7 days post-procedure) occurred in 4.0%, including death (0.3%), stroke (0.4%), major vascular (1.3%), and device embolization (0.2%). A total of 80.2%

of patients were discharged on antiplatelet therapy alone. Peridevice flow was < 3mm in 98.4% at follow-up TOE. Device-related thrombus (DRT) was seen in 1.6% of cases. Cardiovascular death or ischemic stroke occurred in 8.7% of patients at two years. The ischemic stroke rate was 2.2% year, a 67% reduction compared to the CHA2DS2-VASc predicted rate. Major bleeding occurred at rates of 10.1% during the first year and 4.0% during the second year. Author noted limitations included that the study enrolled an all-comer population (not consecutive) and the lack of a control group. Additionally, although using CHA2DS2-VASc and HAS-BLED scores to compare observed to predicted event rates standard clinical practice, the methodology is imperfect. Finally, the current study only evaluated a single LAAO device, and results may not be applicable to other devices, in other patient populations, or with other post-implant antithrombotic medication regimens. Authors concluded that using the Amplatzer Amulet device during LAAO resulted in a reduction of the ischemic stroke rate by 67% compared to the predicted risk. Closure was complete in 98.4% of cases and DRT seen in only 1.6%. The Amulet occluder allows for prevention of AF-related thromboembolic events without the need for long-term OAC. No health disparities were identified by the investigators.

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 non-valvular 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.

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 non-valvular 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 non-valvular 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.

Registry Studies: Freeman et al. (2020) described the National Cardiovascular Data Registry (NCDR) left atrial appendage occlusion (LAAO) registry and present patient, hospital, and physician characteristics and in-hospital adverse event rates for Watchman procedures in the United States during its first three years. The LAAO Registry is the largest registry of patients undergoing percutaneous LAAO procedures in the world. To better understand the utilization, safety, and effectiveness of LAAO devices in real-world clinical practice, the American College of Cardiology (ACC) and the Society for Coronary Angiography and Interventions (SCAI) collaborated with the FDA, the Centers for Medicare and Medicaid Services (CMS), and Boston Scientific to develop the National Cardiovascular Data Registry (NCDR) LAAO Registry. The LAAO Registry will include active follow-up at 45 days, six months, one year, and two years, and linkage to Medicare data to capture adverse events that occur during follow-up years three and four after implant. A total of 38,158 procedures from 495 hospitals performed by 1,318 physicians in the United States were included between January 2016 and December 2018. The mean patient age was 76.1± 8.1 years, the mean CHA_2DS_2–VASc (congestive heart failure, hypertension, 65 years of age and older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, 65 to 74 years of age, female) score was 4.6± 1.5, and the mean HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly) score was 3.0± 1.1. Most patients in the LAAO Registry had relative or absolute contraindications to long-term anticoagulation, including a 69% rate of prior bleeding and a 12% rate of intracranial bleeding. In comparison, only 13.3% of the patients enrolled in the PROTECT AF and PREVAIL randomized clinical trials had a prior bleeding event. The median annual number of LAAO procedures performed for hospitals was 30 and for physicians was 12. .Procedures were canceled or aborted in 7% of cases; among cases in which a device was deployed, 98.1% were implanted with < 5-mm leak. Major in-hospital adverse events occurred in 2.16% of patients; the most common complications were pericardial effusion requiring intervention (1.39%) and major bleeding (1.25%), whereas stroke (0.17%) and death (0.19%) were rare. This study is limited by lack of a control group. Information about post-Watchman antithrombotic therapy is not reported. The study does not report if LAAO is effective in minimizing thromboembolization and bleeding complications in comparison to cohorts. The LAAO Registry relies on site-reported data, which may result in over- or under-reporting of hospital, patient, or physician data.

Holmes et al. (2019) reported long-term follow-up data from two U.S. FDA left atrial appendage closure (LAAC) mandated registries (CAP [continued access PROTECT-AF] and CAP2 [continued access PREVAIL]) for safety and efficacy of LAAC for stroke prevention in participants with non-valvular AF. The CAP registry included 566 participants (average follow-up 50.1 months) and CAP2 registry included 578 participants (average follow-up 50.3 months). These registries represent the longest follow-up for participants that have been implanted with the WATCHMAN LAAC Device. The CAP registry enrolled participants who met identical inclusion/exclusion criteria as the original PROTECT-AF RCT; similarly, the CAP2 registry used identical inclusion/exclusion criteria as PREVAIL. Notably, both registries excluded warfarin-contraindicated individuals. Participants enrolled in CAP2 were significantly older (≥ 75 years of age) and had higher CHA_2DS_2-VASc scores (4.51 vs. 3.88). In both the CAP and CAP2 the procedural success was similar (94%). In the CAP registry, full 5-year follow-up was completed in 68% of participants; inability to obtain full follow-up was related to mortality, which occurred in 17.8% of participants; initial failure to implant the device, which occurred in 5.7%, loss to follow-up, which occurred in 5.1%, and another 3.5% of participants withdrew permission and consent. At 60 months, 94.8% of participants remained off warfarin. Similar results were reported in the CAP2 registry, although a higher percent of participants died before follow-up completion (21.8%). The primary composite endpoint – stroke (ischemic and hemorrhagic), cardiovascular death, and systemic embolism – occurred in 12.4% of CAP and 17.6% of CAP2 participants; events contributing to the composite endpoint included mostly cardiovascular death and ischemic stroke. The most frequent adverse event in the CAP registry was gastrointestinal bleeding (5.8%), followed by pericardial effusion with cardiac tamponade (1.2%); device-related thrombus occurred in 2.6% of CAP and 3.9% of CAP2 participants. Due to a lack of a comparator arm, it is difficult to assess the long-term effectiveness and safety of the WATCHMAN LAAC device versus standard of care, particularly direct oral anticoagulant therapy. Furthermore, the CAP and CAP2 registries provide no additional data for participants unable to tolerate long-term anticoagulation. Both registries were subject to high rates of loss to follow-up which was mostly related to mortality, which complicates attempts to compare relative ischemic stroke reductions with expected rates (based on CHA_2DS_2-VASc scores estimated in the absence of therapy). Long-term, prospective comparison to standard of care is required to establish the relative benefits and harms of the WATCHMAN LAAC device in individuals without contraindications to anticoagulation.

Boersma et al. (2016) reported on peri-procedural outcomes of up to 30-days from the prospective, multicenter registry Evaluating Real-Life Clinical Outcomes in Atrial Fibrillation Patients Receiving the WATCHMAN Left Atrial Appendage Closure Technology (EWOLUTION). EWOLUTION was designed to obtain periprocedural and outcome data over a 2-year time frame from >1000 patients with non-valvular AF at high risk for stroke in everyday clinical practice outside of controlled trials. Baseline/implant data were available for 1021 subjects with high risk of stroke and moderate-to-high risk of bleeding. The objective of the study was to obtain data on procedural success and complications, and long-term patient outcomes, including bleeding and incidence of stroke/transient ischemic attack (TIA)/systemic embolism (SE). Baseline CHA_2DS_2-VASc was 4.5±1.6 (historic stroke risk of 7.2% per patient-years in the absence of anticoagulation therapy) and HAS-BLED 2.3±1.2 (historic bleeding risk of 5.0% per patient-years in the presence of VKA therapy). A HAS-BLED score ≥3 was present in 40% of patients. Mean age was 73.4±8.9 years, prior ischemic stroke/TIA was present in 30.5%, 15.1% had previous hemorrhagic stroke, and 31.3% had a history of major bleeding; 72.2% of patients were deemed contraindicated for oral anticoagulation. Data were not always provided on the reasons for a contraindication. It is possible that some of these patients may have had relative versus absolute contraindications to the drugs, but nevertheless, they were deemed unsuitable for short- or long-term oral anticoagulation treatment at the time of implant. 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). At the final follow-up of two years, 8% of active patients were still on oral anticoagulation, 7% were on dual antiplatelet therapy, 71% were on single antiplatelet therapy, while 14% were not using any anticoagulant. 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. A high number of participants enrolled in EWOLUTION died during the two-years of follow-up. A majority of individuals remained on some form of anticoagulation therapy despite being deemed unsuitable for short- or long-term oral anticoagulation at the time of implant. The lack of a control arm limits the full assessment of therapy benefit in this patient 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 non-valvular 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 (LAAO). The authors evaluated the procedural safety and complications of all transcatheter LAAO 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. LAAO 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 LAAO devices to warfarin showed lower mortality (p=0.03) with similar bleeding risk (p=0.20) with LAAO. The author concluded that LAAO 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 LAAO. 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 non-valvular 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.

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 included 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 included 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 ≥ 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 stated 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 stated 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 stated 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 (ASAP study [ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology] Reddy, et al., 2013b; EWOLUTION study Boersma, et al., 2017); and this is the focus of an ongoing RCT The Assessment of the Watchman Device in Patients Unsuitable for Oral Anticoagulation (ASAP-TOO) (Holmes, et al., 2017).

Surgical closure of the LAA (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. Surgical ligation or amputation of the LAA is feasible without significant morbidity or mortality in patients with AF who are undergoing cardiac surgery for other indications. Surgical LAA occlusion is most commonly performed in patients undergoing mitral valve or Maze surgery (Hijazi and Saw, 2021; Sarraf, et al., 2018; Price, et al., 2016; Masoudi, et al., 2015).

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 - Surgical closure of the LAA (CPT Code 33268): 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).

Randomized Controlled Trial: Whitlock et al. (2021) conducted the Left Atrial Appendage Occlusion Study (LAAOS III) which is a multicenter, randomized controlled trial that evaluated the efficacy and safety of concomitant left atrial appendage occlusion in participants with a history of atrial fibrillation undergoing cardiac surgery for another indication. The aim of the study was to determine whether concomitant occlusion would prevent ischemic stroke or systemic embolism in participants who continued to receive usual care, including anticoagulation. Included patients were aged 18 years or older who were scheduled to undergo cardiac surgery with cardiopulmonary bypass and had a history of atrial fibrillation and a score of at least 2 on the CHA2DS2-VASc scale. Patients were excluded if they were undergoing off-pump surgery, mechanical-valve implantation, heart transplantation, surgery for complex congenital heart disease, or isolated implantation of a left ventricular assist device. Additionally, patients with a previous surgery that involved opening the pericardium; and those who had previously undergone implantation of a left atrial appendage closure device were excluded. Patients were randomized to the occlusion group (n=2379) or the no-occlusion group (n=2391) left atrial appendage occlusion at the time of cardiac surgery for another indication. The primary outcome measured the first occurrence of ischemic stroke (including transient ischemic attack with positive neuroimaging) or noncerebral systemic embolism during follow-up. Strokes of undetermined cause were included as ischemic strokes in the primary analysis. Secondary outcomes measured any stroke or noncerebral systemic embolism; ischemic stroke, noncerebral systemic embolism, or death from any cause; 30-day mortality; the volume of chest-tube drainage in the first 24 hours after surgery; re-exploration for bleeding within the first 48 hours after surgery; hospitalization for heart failure; myocardial infarction; and major bleeding. The mean duration of follow-up was 3.8 years, and follow-up was completed by 97.9% of the participants; 50 participants (1.1%) had withdrawn consent and 49 (1.0%) had been lost to follow-up.

Ischemic stroke or systemic embolism occurred in 114 participants (4.8%) in the occlusion group and in 168 (7.0%) in the no-occlusion group, which was clinically significant in favor of the occlusion group (p=0.001). There were no significant differences found between the groups in perioperative bleeding, heart failure or death. The cause of death was attributed to stroke in 1.3% of the trial participants. At hospital discharge, 83.4% of the participants in the occlusion group and 81.0% of those in the no-occlusion group were receiving oral anticoagulation, and the corresponding values were 79.6% and 78.9% at the 1-year visit and 75.3% and 78.2% at the 3-year visit, respectively. Death occurred in 538 participants in the occlusion group (22.6%) and in 537 (22.5%) in the no-occlusion group. Author noted limitations included the lack of information about the relative efficacy of left atrial appendage occlusion as compared with oral anticoagulation. Furthermore, the findings from LAAOS III apply primarily to surgical occlusion of the appendage performed as a concomitant procedure and not to stand-alone surgical or endovascular occlusion. Additionally, the study was unable to discern whether all surgical closure methods are comparable or examine whether occlusion was sustained over follow-up. The authors concluded that among patients with atrial fibrillation who had undergone cardiac surgery, most of whom continued to receive ongoing antithrombotic therapy, the risk of stroke or systemic embolism was lower with concomitant left atrial appendage occlusion performed during the surgery than without it.

Nonrandomized Controlled Trials: Mahmood et al. (2020) reported the short-term outcomes of left atrial appendage (LAA) exclusion in patients with atrial fibrillation undergoing isolated coronary artery bypass graft surgery. The National Readmissions Database was queried for patients who underwent coronary artery bypass graft repair with and without LAA ligation. Only patients with a history of atrial fibrillation were included in the analysis. The primary outcome of the study was 30-day readmissions following discharge. Secondary outcomes were in-hospital mortality and stroke. Of a total of 253,287 patients undergoing coronary artery bypass graft surgery, 7.0% received LAA closure. LAA exclusion was associated with a greater risk of postoperative respiratory failure (8.2% versus 6.2%) and acute kidney injury (21.8% versus 18.5%), but it did not significantly change the rate of blood transfusions or occurrence of cardiac tamponade. LAA exclusion was associated with a nonsignificant reduction in stroke (7.9% versus 8.6%), no difference in in-hospital mortality (2.2% versus 2.2%), and a greater risk of 30-day readmission (16.0% versus 9.6%).

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 five 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.

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.

Systematic Reviews: In a systematic review, Toale et al., (2019) assessed the safety and efficacy of the AtriClip device in patients with AF. Data including demographics, medical history intervention(s) performed, periprocedural outcomes and follow-up were assessed and analyzed. A total of 922 patients were identified in eleven studies. LAA occlusion was achieved in 902 out of 922 patients (97.8%). No device-related adverse events were reported across the studies. The reported incidence of stroke or transient ischemic attack post-clip placement ranged from 0.2 to 1.5/100 patient-years. Four hundred and seventy-seven of 798 patients (59.7%) had ceased anticoagulation on follow-up. Reported limitation of this study are that this review assesses data from a number of heterogeneous studies of differing design and methodology. Epicardial clipping was performed via a number of different approaches including open placement via sternotomy/minithoracotomy and thoracoscopic techniques. The approach to combined ablative procedures varied both within and across studies. Though some patients underwent epicardial clipping as part of a stand-alone procedure, others underwent ablation, epicardial maze or other operations for the management of AF. Postoperatively, the approach to anticoagulation was inconsistent across studies. Data regarding postprocedural stroke rates should be interpreted with caution, particularly as other potential embolic factors such as carotid stenosis were not recorded or adjusted for many included patients. Studies with long-term outcomes data comparing the safety and efficacy of epicardial clipping with established surgical and percutaneous methods of LAA closure are needed. Clear guidelines are needed regarding the need for postoperative anticoagulation in patient's postepicardial clipping.

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.

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 ≥ 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.

Society of Thoracic Surgeons (STS): The STS published clinical practice guidelines for the surgical treatment of atrial fibrillation (Badhwar, et al., 2017) addressing left atrial appendage excision or exclusion in the section on additional considerations for surgical ablation therapy. The STS recommendation stated that it is reasonable to perform left atrial appendage excision or exclusion in conjunction with surgical ablation for AF for longitudinal thromboembolic morbidity prevention (Class IIA, Level C limited data).

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

Use Outside of the US
The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial has recommended the following for catheter ablation of AF (Andrade, et al., 2020):

- Suggested that percutaneous LAAO can be considered for stroke prevention in patients with NVAF who are at moderate to high risk of stroke and have absolute contraindications to OAC (Weak Recommendation; Low-Quality Evidence).
- Recommended that surgical LAAO can be considered for stroke prevention in patients with NVAF who are not suitable for percutaneous LAAO and have moderate to high risk of stroke and have contraindications to OAC (Weak Recommendation; Low-Quality Evidence).
- Suggested that concomitant surgical LAAO can be considered in patients with AF who are undergoing an open chest cardiac surgical procedure and who are ineligible for long-term OAC (Weak Recommendation; Low-Quality Evidence).

The updated 2020 European Society of Cardiology (ESC) and European Association of Cardio-Thoracic Surgery (EACTS) guidelines for the diagnosis and management of atrial fibrillation (AF) listed the following recommendations for occlusion or exclusion of the left atrial appendage (Hindricks, et al., 2021):

- After surgical occlusion or exclusion of the LAA, it is recommended to continue anticoagulation in at-risk patients with AF for stroke prevention (Class I Level of evidence B).
- LAA occlusion may be considered for stroke prevention in patients with AF and contraindications for long-term anticoagulant treatment (e.g. intracranial bleeding without a reversible cause) (Class IIb Level of evidence B).
- Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery (Class IIb Level of evidence C).

The 2020 European Heart Rhythm Association (EHRA) and European Association of Percutaneous Cardiovascular Interventions (EAPCI) expert consensus statement on catheter-based left atrial appendage occlusion-an update included the following consensus statements for LAAO device implantation and LAA closure by cardiac surgery. The guideline addressed the consensus statements as “should do this”, “may do this” and “should not do this”: (Glikson, et al., 2020):

- AF patients with CHA2DS2-VASc score > 2 (3 in females) who have absolute contraindications for long-term OAC may be considered for LAAO if a minimum period (2-4 weeks) of a single antiaggregant can be given (should do this)
- In patients with an elevated bleeding risk during long-term oral anticoagulation (e.g., post intracranial bleeding) an individual risk-benefit assessment needs to be carried out between oral anticoagulation and LAA occlusion (should do this)
- In patients with an elevated bleeding risk during long-term OAC, LAA occlusion may be considered (may do this)
- Patients who are eligible for long-term OAC and who also require prevention of stroke and embolism may receive an LAAO instead of long-term OAC only if they refuse OAC despite explanation (may do this)
- In AF patients with a high risk score for stroke and embolism who refuse OAC even after personal and detailed advice, LAA occlusion may be considered (may do this)
- In patients with documented noncompliance, LAA occlusion can be discussed as a therapeutic alternative after attempts to resolve the reasons (may do this)
- In patients who are opposed to chronic drug intake, LAA occlusion is currently not offered as a simple and equally effective treatment alternative (should not do this)
- Surgical LAA excision or occlusion in conjunction with any type of cardiac surgery in patient with AF (may do this)
- Surgical LAA excision or occlusion can be performed as an isolated or concomitant procedure by several minimally invasive techniques and devices with epicardial or hybrid (epicardial and endocardial) approaches in cases when endocardial closure cannot be done or when no antithrombotic therapy can be administered even for 2-4 weeks following the procedure (may do this)
- Surgical LAA excision or exclusion in conjunction with any type of cardiac surgery in patient with AF and significant comorbidities, when prolongation of the procedure may be dangerous, in re-do cases because of pericardial adhesions, in very thin, friable or calcified atrial walls (should not do this)

The 2017 Heart Rhythm Society (HRS); European Heart Rhythm Association (EHRA); European Cardiac Arrhythmia Society (ECAS) Asia Pacific Heart Rhythm Society (APHRS); and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (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).

The 2021 National Institute for Health and Care Excellence (NICE) clinical guideline for the diagnosis and management of atrial fibrillation included 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.

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 non-beating 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 (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; Albåge, 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).

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.

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 (Maclean, et al., 2020; Khan, et al., 2020; Luo, et al., 2019; Pearman, et al., 2017; Geršak, et al., 2014; Pison, et al., 2014; Ismail, et al., 2014; Kurfirst, et al., 2014; Lawrance, et al., 2014b; La Meir, et al., 2013a; Gehi, et al., 2013; Geršak, et al., 2012; La Meir, 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., 2011b; La Meir, 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).

Randomized Controlled Trials: DeLurgio et al. (2020) conducted a multicenter, randomized controlled trial that evaluated the effectiveness of the combined hybrid epicardial and endocardial ablation (Hybrid Convergent) for the treatment of persistent and long-standing persistent AF with endocardial catheter ablation. Adults 18–80 years, with symptomatic persistent AF that was refractory or intolerant to at least one class I/III antiarrhythmic drug (AAD) and had a left atrium size of ≤ 6.0 cm. There was no limitation on duration of AF. Patients (n=153) were randomized 2:1 to the Hybrid Convergent group (n=101) or the catheter ablation group (n=51). In-person follow-up visits were performed at seven days, one, three, six, and 12 months and included an electrogram and review of medications and adverse events. The trial also included an in-person longer-term follow-up visit at 18 months and phone follow-up at two, three, four, and five years. A total of 96% patients in the Hybrid Convergent group and 98% in the catheter ablation group completed the 12-month visit. Six- and 12-month Holter data were available for 97.1% and 96.1% patients in the Hybrid Convergent group, and 100% and 98% patients in the catheter ablation group. Hybrid Convergent had significant improvement in persistent and long standing atrial fibrillation (p=0.036) and success off antiarrhythmic drugs (p=0.0128) when compared to catheter ablation. At 18 months using 7-day Holter, 74.0% Hybrid Convergent and 55% CA patients experienced ≥ 90% AF burden reduction, which was clinically significant (p=0.0395) in favor of the Hybrid Convergent group. A total of 2.9% patients had primary safety events within seven days, and 4.9% between eight and 30 days postprocedure. No deaths, cardiac perforations, or atrioesophageal fistulas occurred. All but one primary safety event resolved. Author noted limitations included: the absence of empirical endocardial posterior wall ablation in the catheter ablation group; only using irrigated radiofrequency catheters for endocardial ablation in both groups; cryoablation was not included and electrical isolation or exclusion of LAA was not performed. Additional limitations included small patient population, unequal randomization and short term follow-up. No health disparities were identified by the investigators.

Haldar et al. (2020) conducted a randomized controlled trial that evaluated if thoracoscopic surgical ablation (SA) is superior to catheter ablation CA as a first-line procedure in long-standing persistent atrial ablation (LSPAF), refractory or intolerant to at least one AAD (CASA-AF study). Adults (n=120) with symptomatic LSPAF, European Heart Rhythm Association EHRA symptom score > 2, left ventricular ejection fraction > 40%, referred for treatment and suitable for both procedures were included in the study. Patients were randomized to SA (n=60) or CA (n= 60), five patients withdrew consent post-randomization in the SA arm and were excluded from analyses. Study treatment was received by 115 patients of whom 110 completed all follow-up visits. In the SA group, six patients crossed over to CA due to lung or cardiac adhesions precluding access for SA and two patients had incomplete lesion sets due to adverse anatomical features: one patient did not have the left pulmonary vein (PV) isolated nor the LAA excluded, and the other did not have LAA exclusion. All patients underwent predetermined lesion sets and implantable loop recorder insertion. Primary measured outcome was freedom from AF/atrial tachycardia (AT) > 30 s without anti-arrhythmic drugs at 12 months. Secondary measured outcomes included clinical success (> 75% reduction in AF/AT burden); procedure-related serious adverse events; changes in patients' symptoms and quality-of-life scores; and cost-effectiveness. The authors concluded that SA was significantly more expensive (p<0.01) and provided significantly fewer quality-adjusted life-years (QALYs) compared with CA (p=0.02). A significant reduction (p=0.3) in AF/AT burden > 75% was noted in the CA group when compared to the SA group. Procedure-related adverse events rate over the 12-month follow-up period was greater in the SA than the CA arm: 40% (22/55) vs. 15% (9/60) p=0.003]. There were not any significant differences in freedom from AF/AT (p=0.83), procedure-related serious adverse events within 30 days of intervention (p=0.46), 12-month follow-up period procedure-related serious adverse events (p=0.65). One death was reported after SA. The authors noted that the main limitation of this study was that the interventions were performed in four highly specialized centers in the UK, which may have an impact on the generalizability of results. Additionally, the study was not double-blinded and thoracoscopic AF ablation which includes LAA exclusion may reduce stroke and bleeding risks. The study also had a small patient population with short term follow-up. The authors concluded that single procedure thoracoscopic SA is not superior to CA in treating LSPAF. Catheter ablation provided greater improvements in symptoms and accrued significantly more QALYs during follow-up than SA. No health disparities were identified by the investigators.

Technology Assessment: 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 ≥ 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

Use Outside of the US
In 2021, the National Institute for Health and Care Excellence (NICE) clinical guideline for the diagnosis and management of atrial fibrillation did not provide recommendations regarding the use of minimally invasive maze procedures for treatment of AF.

The updated 2020 European Society of Cardiology (ESC) and European Association of Cardio-Thoracic Surgery (EACTS) guidelines for the diagnosis and management of atrial fibrillation (AF) addressed the following recommendations for surgical ablation of AF (Hindricks, et al., 2021):

- Concomitant AF ablation should be considered in patients undergoing cardiac surgery, balancing the benefits of freedom from atrial arrhythmias and the risk factors for recurrence (left atrial dilatation, years in AF, age, renal dysfunction, and other cardiovascular risk factors) (Class IIa Level of evidence B).
- Thoracoscopic, including hybrid surgical ablation, procedures should be considered in patients who have symptomatic paroxysmal or persistent AF refractory to AAD therapy and have failed percutaneous AF ablation, or with evident risk factors for catheter failure, to maintain long-term sinus rhythm. The decision must be supported by an experienced team of electrophysiologists and surgeons (Class IIa Level of evidence B).
- Thoracoscopic, including hybrid surgical ablation, procedures may be considered in patients with persistent AF with risk factors for recurrence, who remain symptomatic during AF despite at least one failed AAD and who prefer further rhythm control therapy (Class IIB Level of evidence C).

The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial has recommended the following for catheter surgical AF ablation (Andrade, et al., 2020):

- Surgical AF ablation procedure can be considered in association with a planned cardiac surgical procedure (e.g., mitral valve, aortic valve, or coronary artery bypass surgery) in patients with symptomatic nonpermanentAFwhen the likelihood of success is deemed to be high, the additional risk is low, and sinus rhythm is expected to achieve substantial symptomatic benefit (Weak Recommendation; Low- Quality Evidence).
- A stand-alone surgical or hybrid ablation of AF may be considered for patients with symptomatic nonpermanent AF that is refractory to attempts at percutaneous catheter ablation and whose symptoms warrant the additional risk of a surgical procedure (Weak Recommendation; Low- Quality Evidence).

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

Medicare Coverage Determinations

	Contractor	Policy Name/Number	Revision Effective Date
NCD	National	Percutaneous Left Atrial Appendage Closure (LAAC) (20.34)	2/8/2016
LCD		No LCD found	

Note: Please review the current Medicare Policy for the most up-to-date information.

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 transseptal 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)

Percutaneous Transcatheter or Surgical Closure of the Left Atrial Appendage

Considered Medically Necessary when criteria in the applicable policy statements listed above are met and when used to report percutaneous transcatheter closure of the left atrial appendage for non-valvular atrial fibrillation for the prevention of stroke:

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

Considered Medically Necessary when criteria in the applicable policy statements listed above are met and when used to report surgical closure of the left atrial appendage, including use of a clip, for the prevention of stroke in conjunction with other cardiac procedures using a U.S. Food and Drug Administration (FDA) approved device:

CPT®* Codes	Description
33268	Exclusion of left atrial appendage, open, performed at the time of other sternotomy or thoracotomy procedure(s), any method (eg, excision, isolation via stapling, oversewing, ligation, plication, clip) (List separately in addition to code for primary procedure) (Effective 01/01/2022)
33999	Unlisted procedure, cardiac surgery (Code effective for this policy until 12/31/2021)

Considered Experimental/Investigational/Unproven when used to report surgical closure of the left atrial appendage for the prevention of stroke for ANY other indication:

CPT®* Codes	**Description**
33267	Exclusion of left atrial appendage, open, any method (eg, excision, isolation via stapling, oversewing, ligation, plication, clip) (Effective 1/1/2022)
33269	Exclusion of left atrial appendage, thoracoscopic, any method (eg, excision, isolation via stapling, oversewing, ligation, plication, clip) Effective (1/1/2022)

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

Considered Experimental/Investigational/Unproven:

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

References

References-Catheter Ablation for Atrial Fibrillation

1. Ahmed H, Neuzil; P, Skoda J, D'Avila A, Donaldson DM, Laragy MC, Rdeddy VY. The permanency of pulmonary vein isolation using a balloon cryoablation catheter. J Cardiovasc Electrophysiol 2010 Jul;21(7):731-7.

2. Ahmed H, Neuzil P, d'Avila A, Cha YM, Laragy M, Mares K, et al. The esophageal effects of cryoenergy during cryoablation for atrial fibrillation. Heart Rhythm. 2009 Jul;6(7):962-9.

3. Al Halabi S, Qintar M, Hussein A, Alraies MC, Jones DG, Wong T, et al. Catheter Ablation for Atrial Fibrillation in Heart Failure Patients: A Meta-Analysis of Randomized Controlled Trials. JACC Clin Electrophysiol. 2015 Jun 1;1(3):200-209.

4. Andrade JG, Aguilar M, Atzema C, Bell A, Cairns JA, Cheung CC, et al. The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation. Can J Cardiol. 2020 Dec;36(12):1847-1948.

5. Andrade JG, Khairy P, Guerra PG, Deyell MW, Rivard L, Macle L, et al. Efficacy and safety of cryoballoon ablation for atrial fibrillation: a systematic review of published studies. Heart Rhythm. 2011 Sep;8(9):1444-51.

6. Andrade JG, Khairy P, Macle L, Packer DL, Lehmann JW, Holcomb RG, Ruskin JN, Dubuc M. Incidence and significance of early recurrences of atrial fibrillation after cryoballoon ablation: insights from the multicenter Sustained Treatment of Paroxysmal Atrial Fibrillation (STOP AF) Trial. Circ Arrhythm Electrophysiol. 2014 Feb;7(1):69-75.

7. Andrade JG, Verma A, Mitchell LB, Parkash R, Leblanc K, Atzema C, et al; CCS Atrial Fibrillation Guidelines Committee. 2018 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation. Can J Cardiol. 2018 Nov;34(11):1371-1392.

8. Andrade JG, Wells GA, Deyell MW, Bennett M, Essebag V, Champagne J, et al. Cryoablation or Drug Therapy for Initial Treatment of Atrial Fibrillation. N Engl J Med. 2021 Jan 28;384(4):305-315.

9. Aryana A, Singh SM, Kowalski M, Pujara DK, Cohen AI, Singh SK, et al. Acute and Long-Term Outcomes of Catheter Ablation of Atrial Fibrillation Using the Second-Generation Cryoballoon versus Open-Irrigated Radiofrequency: A Multicenter Experience. J Cardiovasc Electrophysiol. 2015 Aug;26(8):832-9.

10. Bordignon S, Chun KR, Gunawardene M, Fuernkranz A, Urban V, Schulte-Hahn B, et al. Comparison of balloon catheter ablation technologies for pulmonary vein isolation: the laser versus cryo study. J Cardiovasc Electrophysiol. 2013 Sep;24(9):987-94.

11. Bordignon S, Boehmer MC, Klostermann A, Fuernkranz A, Perrotta L, Dugo D, et al. Visually guided pulmonary vein isolation in patients with persistent atrial fibrillation. Europace. 2016 Apr;18(4):538-42.

12. Buch E, Boyle NG, Shivkumar K. Catheter Ablation: Technical Aspects. In: Cardiac Electrophysiology. From Cell to Bedside, 7th ed. Saunders, an imprint of Elsevier; 2018. Philadelphia, PA. Ch 123. pg 1185-93.

13. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, et al.; Heart Rhythm Society Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. 2012 HRS/EHRA/ECAS expert 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: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Developed in partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society of Thoracic

Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the Heart Rhythm Society. Heart Rhythm. 2012 Apr;9(4):632-696.e21.

14. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, et al; Document Reviewers: 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Europace. 2018 Jan 1;20(1):e1-e160.

15. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, et al; Document Reviewers. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Europace. 2017 Sep 15.

16. Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A, et al. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. Circ Arrhythm Electrophysiol. 2009 Aug;2(4):349-61.

17. CardioFocus®. HeartLight® Endoscopic Ablation System. Accessed September 13, 2021. Available at URL address: https://www.cardiofocus.com/heartlight/

18. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determinations (LCDs) alphabetical index. Accessed September 13, 2021. Available at URL address: https://www.cms.gov/medicare-coverage-database/indexes/lcd-alphabetical-index.aspx?Cntrctr=373&ContrVer=1&CntrctrSelected=373*1&DocType=Active%7cFuture&s=All&bc=AggAAAQAAAAA&

19. Centers for Medicare and Medicaid Services (CMS). National Coverage Determinations (NCDs) alphabetical index. Accessed September 13, 2021. Available at URL address: https://www.cms.gov/medicare-coverage-database/indexes/ncd-alphabetical-index.aspx

20. Chiang CE, Wu TJ, Ueng KC, Chao TF, Chang KC, Wang CC, et al. 2016 Guidelines of the Taiwan Heart Rhythm Society and the Taiwan Society of Cardiology for the management of atrial fibrillation. J Formos Med Assoc. 2016 Nov;115(11):893-952.

21. Chierchia GB, Capulzini L, Droogmans S, Sorgente A, Sarkozy A, Müller-Burri A, et al. Pericardial effusion in atrial fibrillation ablation: a comparison between cryoballoon and radiofrequency pulmonary vein isolation. Europace. 2010 Mar;12(3):337-41.

22. ClinicalTrials.gov. Accessed October 8, 2020. Available at URL address: https://clinicaltrials.gov/

23. Conte G, Chierchia GB, Sieira J, Levinstein M, Casado-Arroyo R, De Asmundis C, . Repeat procedure using radiofrequency energy for recurrence of atrial fibrillation after initial cryoballoon ablation: a 2-year follow-up. Europace. 2013 Oct;15(10):1421-5.

24. Cosedis Nielsen J, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Kongstad O, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. N Engl J Med. 2012 Oct 25;367(17):1587-95.

25. DeVille JB, Svinarich JT, Dan D, Wickliffe A, Kantipudi C, Lim HW, et al. Comparison of resource utilization of pulmonary vein isolation: cryoablation versus RF ablation with three-dimensional mapping in the Value PVI Study. J Invasive Cardiol. 2014 Jun;26(6):268-72.

26. Di Biase L, Mohanty P, Mohanty S, Santangeli P, Trivedi C, Lakkireddy D, et al. Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device: Results From the AATAC Multicenter Randomized Trial. Circulation. 2016 Apr 26;133(17):1637-44.

27. Dukkipati SR, Cuoco F, Kutinsky I, Aryana A, Bahnson TD, Lakkireddy D, et al. HeartLight Study Investigators. Pulmonary Vein Isolation Using the Visually Guided Laser Balloon: A Prospective, Multicenter, and Randomized Comparison to Standard Radiofrequency Ablation. J Am Coll Cardiol. 2015 Sep 22;66(12):1350-60.

28. Ferrero-de Loma-Osorio A, Izquierdo-de Francisco M, Martínez-Brotons A, Sánchez-Gómez JM, Mascarell-Gregori B, Ruiz-Ros V, et al. Medium-term results of cryoballoon ablation of the pulmonary veins in patients with paroxysmal and persistent atrial fibrillation. First experience of a Spanish center. J Interv Card Electrophysiol. 2013 Aug;37(2):189-96.

29. Fürnkranz A, Brugada J, Albenque JP, Tondo C, Bestehorn K, Wegscheider K, Ouyang F, Kuck KH. Rationale and Design of FIRE AND ICE: A multicenter randomized trial comparing efficacy and safety of pulmonary vein isolation using a cryoballoon versus radiofrequency ablation with 3D-reconstruction. J Cardiovasc Electrophysiol. 2014 Dec;25(12):1314-20.

30. Gaita F, Leclercq JF, Schumacher B, Scaglione M, Toso E, Halimi F, et al. Incidence of silent cerebral thromboembolic lesions after atrial fibrillation ablation may change according to technology used: comparison of irrigated radiofrequency, multipolar nonirrigated catheter and cryoballoon. J Cardiovasc Electrophysiol. 2011 Sep;22(9):961-8.

31. Gopinathannair R, Chen LY, Chung MK, Cornwell WK, Furie KL, Lakkireddy DR, et al. Managing Atrial Fibrillation in Patients With Heart Failure and Reduced Ejection Fraction: A Scientific Statement From the American Heart Association. Circ Arrhythm Electrophysiol. 2021 Jun;14(6):HAE0000000000000078.

32. Haines DE, Beheiry S, Akar JG, Baker JL, Beinborn D, Beshai JF, et al. Heart Rythm Society expert consensus statement on electrophysiology laboratory standards: process, protocols, equipment, personnel, and safety. Heart Rhythm. 2014 Aug;11(8):e9-51.

33. Hakalahti A, Biancari F, Nielsen JC, Raatikainen MJ. Radiofrequency ablation vs. antiarrhythmic drug therapy as first line treatment of symptomatic atrial fibrillation: systematic review and meta-analysis. Europace. 2015 Mar;17(3):370-8.

34. Heart Rhythm Society. Symptoms of Atrial Fibrillation (AFib). Accessed September 13, 2021. Available at URL address: http://www.hrsonline.org/Patient-Resources/Heart-Diseases-Disorders/Atrial-Fibrillation-AFib/Symptoms-of-AFib

35. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021 Feb 1;42(5):373-498. Erratum in: Eur Heart J. 2021 Feb 1;42(5):507. Erratum in: Eur Heart J. 2021 Feb 1;42(5):546-547.

36. Jahangiri M, Weir G, Mandal K, Savelieva I, Camm J. Current strategies in the management of atrial fibrillation. Ann Thorac Surg. 2006 Jul;82(1):357-64.

37. January CT, Wann LS, Alpert JS, Calkins H, Cleveland JC Jr, Cigarroa JE, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation. 2014 Apr 10.

38. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial

Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. Circulation. 2019 Jul 9;140(2):e125-e151.

39. Jourda F, Providencia R, Marijon E, Bouzeman A, Hireche H, Khoueiry Z, et al. Contact-force guided radiofrequency vs. second-generation balloon cryotherapy for pulmonary vein isolation in patients with paroxysmal atrial fibrillation-a prospective evaluation. Europace. 2015 Feb;17(2):225-31.

40. Khan Z, Hamandi M, Khan H, DiMaio JM, Evans M. Convergent epicardial-endocardial ablation for treatment of long-standing persistent atrial fibrillation: A review of literature. J Card Surg. 2020 Jun;35(6):1306-1313.

41. Kalman JM, Sanders P, Brieger DB, Aggarwal A, Zwar NA, Tatoulis J, et al; National Heart Foundation of Australia. National Heart Foundation of Australia consensus statement on catheter ablation as a therapy for atrial fibrillation. Med J Aust. 2013 Jan 21;198(1):27-8.

42. Khan MN, Jais P, Cummings J, Di Biase L, Sanders P, Martin DO, et al., for the PABA-CHF Investigators. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. N Engl J Med. 2008 Oct 23;359(17):1778-85.

43. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur J Cardiothorac Surg. 2016 Nov;50(5):e1-e88.

44. Koch L, Haeusler KG, Herm J, Safak E, Fischer R, Malzahn U, et al. Mesh ablator vs. cryoballoon pulmonary vein ablation of symptomatic paroxysmal atrial fibrillation: results of the MACPAF study. Europace. 2012 Oct;14(10):1441-9.

45. Kojodjojo P, O'Neill MD, Lim PB, Malcolm-Lawes L, Whinnett ZI, Salukhe TV, et al. Pulmonary venous isolation by antral ablation with a large cryoballoon for treatment of paroxysmal and persistent atrial fibrillation: medium-term outcomes and non-randomised comparison with pulmonary venous isolation by radiofrequency ablation. Heart. 2010 Sep;96(17):1379-84.

46. Kuck KH, Lebedev DS, Mikhaylov EN, Romanov A, Gellér L, Kalējs O, et al. Catheter ablation or medical therapy to delay progression of atrial fibrillation: the randomized controlled atrial fibrillation progression trial (ATTEST). Europace. 2021 Mar 8;23(3):362-369.

47. Kuniss M, Pavlovic N, Velagic V, Hermida JS, Healey S, Arena G, et al. Cryoballoon ablation vs. antiarrhythmic drugs: first-line therapy for patients with paroxysmal atrial fibrillation. Europace. 2021 Jul 18;23(7):1033-1041.

48. Kühne M, Suter Y, Altmann D, Ammann P, Schaer B, Osswald S, Sticherling C. Cryoballoon versus radiofrequency catheter ablation of paroxysmal atrial fibrillation: biomarkers of myocardial injury, recurrence rates, and pulmonary vein reconnection patterns. Heart Rhythm. 2010 Dec;7(12):1770-6.

49. Linhart M, Bellmann B, Mittmann-Braun E, Schrickel JW, Bitzen A, Andrié R, et al. Comparison of cryoballoon and radiofrequency ablation of pulmonary veins in 40 patients with paroxysmal atrial fibrillation: a case-control study. J Cardiovasc Electrophysiol 2009 Dec;20(12):1343-8.

50. Luik A, Radzewitz A, Kieser M, Walter M, Bramlage P, Hörmann P, et al. Cryoballoon Versus Open Irrigated Radiofrequency Ablation in Patients With Paroxysmal Atrial Fibrillation: The Prospective, Randomized, Controlled, Noninferiority FreezeAF Study. Circulation. 2015 Oct 6;132(14):1311-9.

51. Macle L, Cairns J, Leblanc K, Tsang T, Skanes A, Cox JL, et al; CCS Atrial Fibrillation Guidelines Committee. 2016 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation. Can J Cardiol. 2016 Oct;32(10):1170-1185.

52. Malmborg H, Lönnerholm S, Blomström P, Blomström-Lundqvist C. Ablation of atrial fibrillation with cryoballoon or duty-cycled radiofrequency pulmonary vein ablation catheter: a randomized controlled study comparing the clinical outcome and safety; the AF-COR study. Europace. 2013 Nov;15(11):1567-73.

53. Mao YJ, Feng WY, Huang QY, Yu FL, Chen JX, Wang H. Meta-analysis of cryoballoon ablation versus antiarrhythmic drugs as initial therapy for symptomatic atrial fibrillation. Clin Cardiol. 2021 Oct;44(10):1393-1401.

54. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, et al; CASTLE-AF Investigators. Catheter Ablation for Atrial Fibrillation with Heart Failure. N Engl J Med. 2018 Feb 1;378(5):417-427.

55. Metzner A, Schmidt B, Fuernkranz A, Wissner E, Tilz RR, Koester I, et al. Esophageal temperature change and esophageal thermal lesions after pulmonary vein isolation using the novel endoscopic ablation system. Heart Rhythm. 2011 Jun;8(6):815-20.

56. Morady F, Zipes D. Atrial Fibrillation: Clinical Features, Mechanisms and Management. Catheter Ablation of Atrial Fibrillation. In: Bonow: Braunwald's heart disease- A Textbook of Cardiovascular Medicine, 11th ed. Saunders, an imprint of Elsevier; 2019. Philadelphia, PA. Ch 38. pg 730-52.

57. Mugnai G, Chierchia GB, de Asmundis C, Sieira-Moret J, Conte G, Capulzini L, et al. Comparison of pulmonary vein isolation using cryoballoon versus conventional radiofrequency for paroxysmal atrial fibrillation. Am J Cardiol. 2014 May 1;113(9):1509-13.

58. National Institute for Health and Clinical Excellence (NICE). Percutaneous balloon cryoablation for pulmonary vein isolation in atrial fibrillation. Interventional Procedures Guidance 427. 2012 May. Accessed September 13, 2021. Available at URL address: https://www.nice.org.uk/guidance/ipg427

59. National Institute for Health and Clinical Excellence (NICE). Atrial fibrillation: diagnosis and management. Clinical Guideline 196. 2021 April. Accessed September 13, 2021. Available at URL address: https://www.nice.org.uk/guidance/ng196

60. National Institute for Health and Clinical Excellence (NICE). Percutaneous endoscopic laser balloon pulmonary vein isolation for atrial fibrillation. 2016 July. Accessed September 13, 2021. Available at URL address: https://www.nice.org.uk/guidance/ipg563

61. Neumann T, Vogt J, Schumacher B, Dorszewski A, Kuniss M, Neuser H, et al. Circumferential pulmonary vein isolation with the cryoballoon technique results from a prospective 3-center study. J Am Coll Cardiol. 2008 Jul 22;52(4):273-8.

62. Nielsen JC, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, et al; MANTRA-PAF Investigators. Long-term efficacy of catheter ablation as first-line therapy for paroxysmal atrial fibrillation: 5-year outcome in a randomised clinical trial. Heart. 2017 Mar;103(5):368-376.

63. Nyong J, Amit G, Adler AJ, Owolabi OO, Perel P, Prieto-Merino D, Lambiase P, Casas JP, Morillo CA. Efficacy and safety of ablation for people with non-paroxysmal atrial fibrillation. Cochrane Database Syst Rev. 2016 Nov 22;11:CD012088. Review.

64. Noheria A, Kumar A, Wylie JV, Josephson ME. Catheter ablation vs antiarrhythmic drug therapy for atrial fibrillation: a systematic review. Arch Intern Med. 2008 Mar 24;168(6):581-6.

65. Olshansky B. The management of atrial fibrillation in patients with heart failure. In: UpToDate, Colucci WS, Knight BP, Parikh N (Eds). UpToDate, Waltham, MA. Literature review current through: August 2021. Topic last updated: November 6, 2019. Accessed September 13, 2021.

66. Oral H, Pappone C, Chugh A, Good E, Bogun F, Pelosi FB, et al. Circumferential pulmonary-vein ablation for chronic AF. N Engl J Med. 2006 Mar 2;354(9):934-41.

67. Packer DL, Kowal RC, Wheelan KR, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. J Am Coll Cardiol. 2013; 61(16):1713-1723.

68. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Moretz K, et al; CABANA Investigators. Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) Trial: Study Rationale and Design. Am Heart J. 2018 May;199:192-199.

69. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Poole JE, et al; CABANA Investigators. Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. JAMA. 2019 Apr 2;321(13):1261-1274.

70. Pandya B, Sheikh A, Spagnola J, Bekheit S, Lafferty J, Kowalski M. Safety and efficacy of second-generation versus first-generation cryoballoons for treatment of atrial fibrillation: a meta-analysis of current evidence. J Interv Card Electrophysiol. 2015 Nov 18.

71. Pappone C, Vicedomini G, Augello G, Manguso F, Saviano M, Baldi M, et al. Radiofrequency catheter ablation and antiarrhythmic drug therapy: a prospective, randomized, 4-year follow-up trial: the APAF study. Circ Arrhythm Electrophysiol. 2011 Dec;4(6):808-14.

72. Pappone C, Augello G, Sala S, Gugliotta F, Vicedomini G, Gulletta S, et al. A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation the APAF Study J Am Coll Cardiol. 2006 Dec 5;48(11):2340-7.

73. Passman R. Maintenance of sinus rhythm in atrial fibrillation: Catheter ablation versus antiarrhythmic drug therapy. In: UpToDate, Knight BP, Estes M, Parikh N (Eds). UpToDate, Waltham, MA. Literature review current through: August 2021. Topic last updated: December 2020. Accessed on September 10, 2021.

74. Passman R. Catheter ablation to prevent recurrent atrial fibrillation: Technical considerations for non-electrophysiologists. In: UpToDate, Knight BP, Estes M, Parikh N (Eds). UpToDate, Waltham, MA. . Literature review current through: August 2021. Topic last updated: December 2019. Accessed on September 10, 2021.

75. Pokushalov E, Romanov A, Artyomenko S, Baranova V, Losik D, Bairamova S, et al. Cryoballoon versus radiofrequency for pulmonary vein re-isolation after a failed initial ablation procedure in patients with paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol. 2013 Mar;24(3):274-9.

76. Poole JE, Bahnson TD, Monahan KH, Johnson G, Rostami H, Silverstein AP, et al. Recurrence of Atrial Fibrillation After Catheter Ablation or Antiarrhythmic Drug Therapy in the CABANA Trial. J Am Coll Cardiol. 2020 Jun 30;75(25):3105-3118.

77. Prabhu S, Taylor AJ, Costello BT, Kaye DM, McLellan AJA, Voskoboinik A, et al. Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction: The CAMERA-MRI Study. J Am Coll Cardiol. 2017 Oct 17;70(16):1949-1961.

78. Sawhney N, Anousheh R, Chen WC, Narayan S, Feld GK. Five-year outcomes after segmental pulmonary vein isolation for paroxysmal atrial fibrillation. Am J Cardiol 2009:104-366-372.

79. Schmidt B, Gunawardene M, Krieg D, Bordignon S, Fürnkranz A, Kulikoglu M, et al. A prospective randomized single-center study on the risk of asymptomatic cerebral lesions comparing irrigated

radiofrequency current ablation with the cryoballoon and the laser balloon. J Cardiovasc Electrophysiol. 2013 Aug;24(8):869-74.

80. Skelly A, Hashimoto R, Al-Khatib S, Sanders-Schmidler G, Fu R, Brodt E, McDonagh M. Catheter Ablation for Treatment of Atrial Fibrillation. Technology Assessment. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. HHSA 290-2012-00014-I.) AHRQ Publication. Rockville, MD: Agency for Healthcare Research and Quality; April 2015.

81. Sorgente A, Chierchia GB, Capulzini L, Yazaki Y, Muller-Burri A, Bayrak F, et al. Atrial fibrillation ablation: a single center comparison between remote magnetic navigation, cryoballoon and conventional manual pulmonary vein isolation. Indian Pacing Electrophysiol J. 2010 Dec 26;10(11):486-95.

82. Spragg D. Paroxysmal atrial fibrillation. In: UpToDate, Knight BP, Parika N (Eds). UpToDate, Waltham, MA. Literature review current through: August 2021. Topic last updated: August 2021. Accessed September 10, 2021.

83. Stabile G, Bertaglia E, Senatore G, De Simone A, Zoppo F, Donnici G, et al. Catheter ablation treatment in patients with drug-refractory atrial fibrillation: a prospective, multi-centre, randomized, controlled study (Catheter Ablation For The Cure Of Atrial Fibrillation Study). Eur Heart J. 2006 Jan;27(2):216-21.

84. Straube F, Dorwarth U, Vogt J, Kuniss M, Heinz Kuck K, Tebbenjohanns J, et al. Differences of two cryoballoon generations: insights from the prospective multicentre, multinational FREEZE Cohort Substudy. Europace. 2014 Oct;16(10):1434-42.

85. Steinberg BA, Beckley PD, Deering TF, Clark CL, Amin AN, Bauer KA, et al; Society of Cardiovascular Patient Care. Evaluation and management of the atrial fibrillation patient: a report from the Society of Cardiovascular Patient Care. Crit Pathw Cardiol. 2013 Sep;12(3):107-15.

86. Stöckigt F, Kohlmann AT, Linhart M, Nickenig G, Andrié RP, Beiert T, Schrickel JW. Laserballoon and Cryoballoon Pulmonary Vein Isolation in Persistent and Longstanding Persistent Atrial Fibrillation. Pacing Clin Electrophysiol. 2016 Oct;39(10):1099-1107.

87. Su WW, Reddy VY, Bhasin K, Champagne J, Sangrigoli RM, Braegelmann KM, et al. Cryoballoon ablation of pulmonary veins for persistent atrial fibrillation: Results from the multicenter STOP Persistent AF trial. Heart Rhythm. 2020 Nov;17(11):1841-1847.

88. Tang M,, Kriatselis C, Nedios S, Ye G, Roser M, Fleck E, Gerds-Li JH. A novel cryoballoon technique for mapping and isolating pulmonary veins: a feasibility and efficacy study. J Cardiovasc Electrophyiol 2010 Jun 1;21(6):626-31.

89. Tsyganov A, Petru J, Skoda J, Sediva L, Hala P, Weichet J, et al. Anatomical predictors for successful pulmonary vein isolation using balloon-based technologies in atrial fibrillation. J Interv Card lectrophysiol. 2015 Dec;44(3):265-71.

90. Ugowe FE, Jackson LR 2nd, Thomas KL. Racial and ethnic differences in the prevalence, management, and outcomes in patients with atrial fibrillation: A systematic review. Heart Rhythm. 2018 Sep;15(9):1337-1345.

91. U.S. Food and Drug Administration (FDA). Center for Devices and Radiological Health. Premarket Approval (PMA). Accessed September 13, 2021. Available at URL address: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm

92. Van Belle Y, Janse P, Theuns D, Szili-Torok T, Jordaens L. One year follow-up after cryoballoon isolation of the pulmonary veins in patients with paroxysmal atrial fibrillation. Europace. 2008 Nov;10(11):1271-6.

93. Verma A, Cairns JA, Mitchell LB, Macle L, Stiell IG, Gladstone D, et al; CCS Atrial Fibrillation Guidelines Committee. 2014 focused update of the Canadian Cardiovascular Society Guidelines for the management of atrial fibrillation. Can J Cardiol. 2014 Oct;30(10):1114-30.

94. Vogt J, Heintze J, Gutleben KJ, Muntean B, Horstkotte D, Nölker G. Long-term outcomes after cryoballoon pulmonary vein isolation: results from a prospective study in 605 patients. J Am Coll Cardiol. 2013 Apr 23;61(16):1707-12.

95. Wazni OM, Dandamudi G, Sood N, Hoyt R, Tyler J, Durrani S, et al. Cryoballoon Ablation as Initial Therapy for Atrial Fibrillation. N Engl J Med. 2021 Jan 28;384(4):316-324.

96. Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, et al.; ThermoCool AF Trial Investigators. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. JAMA. 2010 Jan 27;303(4):333-40.

97. Wilber D. Electrophysiological Interventional Procedures and Surgery. In: Goldman-Cecil Medicine, 25th ed. Saunders, an imprint of Elsevier; 2016. Philadelphia, PA. Ch 66. pg 379-80.

98. Wissner E, Metzner A, Neuzil P, Petru J, Skoda J, Sediva L, et al. Asymptomatic brain lesions following laserballoon-based pulmonary vein isolation. Europace. 2014 Feb;16(2):214-9.

99. Xu J, Huang Y, Cai H, Qi Y, Jia N, Shen W, Lin J, Peng F, Niu W. Is cryoballoon ablation preferable to radiofrequency ablation for treatment of atrial fibrillation by pulmonary vein isolation? A meta-analysis. PLoS One. 2014 Feb 28;9(2):e90323.

100. Yao RJR, Macle L, Deyell MW, Tang L, Hawkins NM, Sedlak T, Nault I, Verma A, Khairy P, Andrade JG; CIRCA-DOSE Study Investigators. Impact of Female Sex on Clinical Presentation and Ablation Outcomes in the CIRCA-DOSE Study. JACC Clin Electrophysiol. 2020 Aug;6(8):945-954.

References- Left Atrial Appendage (LAA) Closure

1. Abbott Amplatzer™ Amulet LAA Occluder ©2021 Abbott. Accessed September 13, 2021. Available at URL address: https://www.cardiovascular.abbott/us/en/hcp/products/structural-heart/structural-interventions/amplatzer-amulet.html

2. Ailawadi G, Gerdisch MW, Harvey RL, Hooker RL, Damiano RJ Jr, Salamon T, Mack MJ. Exclusion of the left atrial appendage with a novel device: early results of a multicenter trial. J Thorac Cardiovasc Surg. 2011 Nov;142(5):1002-9, 1009.e1.

3. Ali M, Rigopoulos AG, Mammadov M, Torky A, Auer A, Matiakis M, et al. Systematic review on left atrial appendage closure with the LAmbre device in patients with non-valvular atrial fibrillation. BMC Cardiovasc Disord. 2020 Feb 12;20(1):78.

4. Alkhouli M, Busu T, Shah K, Osman M, Alqahtani F, Raybuck B. Incidence and Clinical Impact of Device-Related Thrombus Following Percutaneous Left Atrial Appendage Occlusion: A Meta-Analysis. JACC Clin Electrophysiol. 2018 Dec;4(12):1629-1637.

5. Andrade JG, Aguilar M, Atzema C, Bell A, Cairns JA, Cheung CC, et al. The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation. Can J Cardiol. 2020 Dec;36(12):1847-1948.

6. Andrade JG, Verma A, Mitchell LB, Parkash R, Leblanc K, Atzema C, et al; CCS Atrial Fibrillation Guidelines Committee. 2018 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation. Can J Cardiol. 2018 Nov;34(11):1371-1392.

7. Badhwar V, Rankin JS, Damiano RJ Jr, Gillinov AM, Bakaeen FG, Edgerton JR, et al. The Society of Thoracic Surgeons 2017 Clinical Practice Guidelines for the Surgical Treatment of Atrial Fibrillation. Ann Thorac Surg. 2017 Jan;103(1):329-341.

8. Betts TR, Leo M, Panikker S, Kanagaratnam P, Koa-Wing M, Davies DW, et al. Percutaneous left atrial appendage occlusion using different technologies in the United Kingdom: A multicenter registry. Catheter Cardiovasc Interv. 2017 Feb 15;89(3):484-492.

9. Boersma LV, Schmidt B, Betts TR, Sievert H, Tamburino C, Teiger E, et al.; EWOLUTION investigators. Implant success and safety of left atrial appendage closure with the WATCHMAN device: peri-procedural outcomes from the EWOLUTION registry. Eur Heart J. 2016 Aug;37(31):2465-74.

10. Boersma LV, Ince H, Kische S, Pokushalov E, Schmitz T, Schmidt B; EWOLUTION Investigators. Efficacy and safety of left atrial appendage closure with WATCHMAN in patients with or without contraindication to oral anticoagulation: 1-Year follow-up outcome data of the EWOLUTION trial. Heart Rhythm. 2017 May 31. pii: S1547-5271(17)30715-4.

11. Boersma LV, Ince H, Kische S, Pokushalov E, Schmitz T, Schmidt B, et al; following investigators and institutions participated in the EWOLUTION study. Evaluating Real-World Clinical Outcomes in Atrial Fibrillation Patients Receiving the WATCHMAN Left Atrial Appendage Closure Technology. Circ Arrhythm Electrophysiol. 2019 Apr;12(4):e006841.

12. Boston Scientific. WATCHMAN LAA Closure Technology. ©2021 Boston Scientific. Accessed September 13, 2021. Available at URL address: http://www.bostonscientific.com/en-US/products/laac-system/watchman.html

13. Caliskan E, Sahin A, Yilmaz M, Seifert B, Hinzpeter R, Alkadhi H, et al. Epicardial left atrial appendage AtriClip occlusion reduces the incidence of stroke in patients with atrial fibrillation undergoing cardiac surgery. Europace. 2018 Jul 1;20(7):e105-e114.

14. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determinations (LCDs) alphabetical index. Accessed September 13, 2021. Available at URL address: https://www.cms.gov/medicare-coverage-database/indexes/lcd-alphabetical-index.aspx

15. Centers for Medicare and Medicaid Services (CMS). National Coverage Determinations (NCDs) alphabetical index. Accessed September 13, 2021. Available at URL address: https://www.cms.gov/medicare-coverage-database/indexes/ncd-alphabetical-index.aspx

16. Chen S, Chun KRJ, Ling Z, Liu S, Zhu L, Wang J, Schratter A, Acou WJ, Kiuchi MG, Yin Y, Schmidt B. Comparison of Left Atrial Appendage Occlusion versus Non-Vitamin-K Antagonist Oral Anticoagulation in High-Risk Atrial Fibrillation: An Update. J Cardiovasc Dev Dis. 2021 Jun 11;8(6):69.

17. Chen Y, Zhang Y, Huang W, Huang K, Xu B, Su XI. Primary and Secondary Stroke Prevention Using Left Atrial Appendage Closure with Watchman Devices in Atrial Fibrillation Patients: A Single Center Experience from Mainland China. Pacing Clin Electrophysiol. 2017 Jun;40(6):607-614.

18. ClinicalTrials.gov. Left Atrial Appendage Occlusion Study III (LAAO III). Last update posted Dec 3, 2018. Accessed September 13, 2021. Available at URL address: https://clinicaltrials.gov/ct2/show/NCT01561651

19. Darden D, Duong T, Du C, Munir MB, Han FT, Reeves R, et al. Sex Differences in Procedural Outcomes Among Patients Undergoing Left Atrial Appendage Occlusion: Insights From the NCDR LAAO Registry. JAMA Cardiol. 2021 Aug 11:e213021.

20. Fauchier L, Cinaud A, Brigadeau F, Lepillier A, Pierre B, Abbey S, et al. Device-Related Thrombosis After Percutaneous Left Atrial Appendage Occlusion for Atrial Fibrillation. J Am Coll Cardiol. 2018 Apr 10;71(14):1528-1536.

21. Freeman JV, Varosy P, Price MJ, Slotwiner D, Kusumoto FM, Rammohan C, Kavinsky CJ, Turi ZG, Akar J, Koutras C, Curtis JP, Masoudi FA. The NCDR Left Atrial Appendage Occlusion Registry. J Am Coll Cardiol. 2020 Apr 7;75(13):1503-1518.

22. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2011 Mar 15;123(10):e269-367.

23. Glikson, M., Wolff, R., Hindricks, G., Mandrola, J., Camm, A. J., Lip, G., et al. (2020). EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion - an update. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology, 15(13), 1133–1180.

24. Gopinathannair R, Chen LY, Chung MK, Cornwell WK, Furie KL, Lakkireddy DR, et al. Managing Atrial Fibrillation in Patients With Heart Failure and Reduced Ejection Fraction: A Scientific Statement From the American Heart Association. Circ Arrhythm Electrophysiol. 2021 Jun;14(6):HAE0000000000000078.

25. Hayes, Inc. Hayes Evidence Analysis Research Brief. AtriClip Left Atrial Appendage (LAA) Exclusion System (AtriCure Inc.) in Patients With Atrial Fibrillation. Lansdale, PA: Hayes, Inc.; published September 19, 2019.

26. Health Quality Ontario. Left Atrial Appendage Closure Device With Delivery System: A Health Technology Assessment. Ont Health Technol Assess Ser. 2017 Jul 4;17(9):1-106. eCollection 2017.

27. Hijazi ZM, Saw J. Atrial fibrillation: Left atrial appendage occlusion. In: UpToDate, Knight BP, Yeon SB (Eds). UpToDate, Waltham, MA. Literature review current through: August 2021. Topic last updated: July 2021. Accessed September 13, 2021.

28. Hildick-Smith D, Landmesser U, Camm AJ, Diener HC, Paul V, Schmidt B, et al. Left atrial appendage occlusion with the Amplatzer™ Amulet™ device: full results of the prospective global observational study. Eur Heart J. 2020 Aug 7;41(30):2894-2901.

29. Holmes DR, Reddy VY, Turi ZG, Dosi SK, Sievert H, Buchbinder M, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomized non-inferiority trial. Lancet. 2009 Aug 15;374(9689): 534-42.

30. Holmes DR Jr, Doshi SK, Kar S, Price MJ, Sanchez JM, Sievert H, Valderrabano M, Reddy VY. Left Atrial Appendage Closure as an Alternative to Warfarin for Stroke Prevention in Atrial Fibrillation: A Patient-Level Meta-Analysis. J Am Coll Cardiol. 2015 Jun 23;65(24):2614-23.

31. Holmes DR Jr, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, Huber K, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. J Am Coll Cardiol. 2014 Jul 8;64(1):1-12.

32. Holmes DR, Reddy VY, Buchbinder M, Stein K, Elletson M, Bergmann MW, Schmidt B, Saw J. The Assessment of the Watchman Device in Patients Unsuitable for Oral Anticoagulation (ASAP-TOO) trial. Am Heart J. 2017 Jul;189:68-74.

33. Holmes DR Jr, Reddy VY, Gordon NT, Delurgio D, Doshi SK, Desai AJ, Stone JE Jr, Kar S. Long-Term Safety and Efficacy in Continued Access Left Atrial Appendage Closure Registries. J Am Coll Cardiol. 2019 Dec 10;74(23):2878-2889.

34. Huang WP, Zhang YH, He L, Su X, Yang XW, Guo ZX. Efficacy and Safety of the WATCHMAN Left Atrial Appendage System for Stroke Prevention in Chinese Patients with Nonvalvular Atrial Fibrillation: A Single-center, Prospective, Observational Study. Chin Med J (Engl). 2017 Feb 20;130(4):434-438.

35. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, ACC/AHA Task Force Members. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation. 2014 Dec 2;130(23):e199-267.

36. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. Circulation. 2019 Jul 9;140(2):e125-e151.

37. Kar S, Doshi SK, Sadhu A, Horton R, Osorio J, Ellis C, et al. Primary Outcome Evaluation of a Next-Generation Left Atrial Appendage Closure Device: Results From the PINNACLE FLX Trial. Circulation. 2021 May 4;143(18):1754-1762.

38. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al.; Authors/Task Force Members; Document Reviewers:. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS: The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC Endorsed by the European Stroke Organisation (ESO). Europace. 2016 Aug 27.

39. Labori F, Bonander C, Persson J, Svensson M. Clinical follow-up of left atrial appendage occlusion in patients with atrial fibrillation ineligible of oral anticoagulation treatment-a systematic review and meta-analysis. J Interv Card Electrophysiol. 2021 Aug;61(2):215-225.

40. Lakkireddy D, Thaler D, Ellis CR, Swarup V, Sondergaard L, Carroll J, et al. Amplatzer™ Amulet™ Left Atrial Appendage Occluder Versus Watchman™ Device For Stroke Prophylaxis (Amulet IDE): A Randomized Controlled Trial. Circulation. 2021 Aug 30.

41. Lakkireddy DR, Turagam MK. NCDR Left Atrial Appendage Occlusion Registry: The "Watch" Man Has Arrived. J Am Coll Cardiol. 2020 Apr 7;75(13):1519-1522.

42. Li X, Wen SN, Li SN, Bai R, Liu N, Feng L, et al. Over 1-year efficacy and safety of left atrial appendage occlusion versus novel oral anticoagulants for stroke prevention in atrial fibrillation: A systematic review and meta-analysis of randomized controlled trials and observational studies. Heart Rhythm. 2016 Jun;13(6):1203-14.

43. Mahmood E, Matyal R, Mahmood F, Xu X, Sharkey A, Chaudhary O, et al. Impact of Left Atrial Appendage Exclusion on Short-Term Outcomes in Isolated Coronary Artery Bypass Graft Surgery. Circulation. 2020 Jul 7;142(1):20-28.

44. Majule DN, Jing C, Rutahoile WM, Shonyela FS. The Efficacy and Safety of the WATCHMAN Device in LAA Occlusion in Patients with Non-Valvular Atrial Fibrillation Contraindicated to Oral Anticoagulation: A Focused Review. Ann Thorac Cardiovasc Surg. 2018 Dec 20;24(6):271-278.

45. Masoudi FA, Calkins H, Kavinsky CJ, Slotwiner DJ, Turi ZG, Drozda JP Jr, et al.; American College of Cardiology; Heart Rhythm Society; Society for Cardiovascular Angiography and Interventions. 2015 ACC/HRS/SCAI Left Atrial Appendage Occlusion Device Societal Overview: A professional societal overview from the American College of Cardiology, Heart Rhythm Society, and Society for Cardiovascular Angiography and Interventions. Catheter Cardiovasc Interv. 2015 Nov;86(5):791-807.

46. Masoud A, Bartoletti S, Fairbairn T, Khurana A, Velavan P, Morrison WL, et al. Outcome of left atrial appendage occlusion in high-risk patients. Heart. 2018 Apr;104(7):594-599.

47. Meier B, Blaauw Y, Khattab AA, Lewalter T, Sievert H, Tondo C, Glikson M; Document Reviewers. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion. Europace. 2014 Oct;16(10):1397-416.

48. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, et al.; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Functional Genomics and Translational Biology; Council on Hypertension. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014 Dec;45(12):3754-832.

49. Morady F, Zipes D. Atrial Fibrillation: Clinical Features, Mechanisms and Management. Catheter Ablation of Atrial Fibrillation. In: Bonow: Braunwald's heart disease- A Textbook of Cardiovascular Medicine, 11th ed. Saunders, an imprint of Elsevier; 2019. Philadelphia, PA. Ch 38. pg 730-52.

50. Morillo CA, Verma A, Connolly SJ, Kuck KH, Nair GM, Champagne J, et al; RAAFT-2 Investigators. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. JAMA. 2014 Feb 19;311(7):692-700. doi: 10.1001/jama.2014.467. Erratum in: JAMA. 2014 Jun 11;311(22):2337.

51. National Institute for Health and Clinical Excellence (NICE). Atrial fibrillation: diagnosis and management. NICE clinical guideline 196. Issued: April 2021 last updated: June 30. Accessed October 9, 2020. Available at URL address: https://www.nice.org.uk/guidance/ng196

52. National Institute for Health and Clinical Excellence (NICE). Percutaneous occlusion of the left atrial appendage in nonvalvular atrial fibrillation for the prevention of thromboembolism. NICE interventional procedure guidance 349. June 2010. Accessed October 15, 2021. Available at URL address: http://www.nice.org.uk/guidance/IPG349

53. Nielsen-Kudsk JE, Korsholm K, Damgaard D, Valentin JB, Diener HC, Camm AJ, Johnsen SP. Clinical Outcomes Associated With Left Atrial Appendage Occlusion Versus Direct Oral Anticoagulation in Atrial Fibrillation. JACC Cardiovasc Interv. 2021 Jan 11;14(1):69-78.

54. Noelck N, Papak J, Freeman M, Paynter R, Low A, Motu'apuaka M, Kondo K, et al. The Effectiveness of Procedures to Remove or Occlude the Left Atrial Appendage: A Systematic Review of the Evidence [Internet]. Washington (DC): Department of Veterans Affairs (US); 2015 Oct.

55. Osmancik P, Herman D, Neuzil P, Hala P, Taborsky M, Kala P, et al. Left Atrial Appendage Closure Versus Direct Oral Anticoagulants in High-Risk Patients With Atrial Fibrillation. J Am Coll Cardiol. 2020 Jun 30;75(25):3122-3135.

56. Panikker S, Lord J, Jarman JW, Armstrong S, Jones DG, Haldar S, et al. Outcomes and costs of left atrial appendage closure from randomized controlled trial and real-world experience relative to oral anticoagulation. Eur Heart J. 2016 Dec 7;37(46):3470-3482.

57. Park-Hansen J, Holme SJV, Irmukhamedov A, Carranza CL, Greve AM, Al-Farra G, Riis RGC, Nilsson B, Clausen JSR, Nørskov AS, Kruuse CR, Rostrup E, Dominguez H. Adding left atrial appendage closure to open heart surgery provides protection from ischemic brain injury six years after surgery independently of atrial fibrillation history: the LAACS randomized study. J Cardiothorac Surg. 2018 May 23;13(1):53.

58. Price MJ, Valderrabano M. Left Atrial Appendage Closure and Stroke. Local Device Therapy for Cardioembolic Stroke Prevention. In: Textbook of Interventional Cardiology, 7th ed. Saunders, an imprint of Elsevier; 2016. Philadelphia, PA. Ch 50. pg 771-87.

59. Reddy VY, Doshi SK, Kar S, Gibson DN, Price MJ, Huber K, Horton RP, Buchbinder M, Neuzil P, Gordon NT, Holmes DR Jr; PREVAIL and PROTECT AF Investigators. 5-Year Outcomes After Left Atrial Appendage Closure: From the PREVAIL and PROTECT AF Trials. J Am Coll Cardiol. 2017 Dec 19;70(24):2964-2975.

60. Reddy VY, Doshi SK, Sievert H, Buchbinder M, Neuzil P, Huber K, Halperin JL, et al.; PROTECT AF Investigators. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-Year Follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) Trial. Circulation. 2013a Feb 12;127(6):720-9.

61. Reddy VY, Möbius-Winkler S, Miller MA, Neuzil P, Schuler G, Wiebe J, et al. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology). J Am Coll Cardiol. 2013b Jun 25;61(25):2551-6.

62. Reddy VY, Sievert H, Halperin J, Doshi SK, Buchbinder M, Neuzil P, Huber K, et al.; PROTECT AF Steering Committee and Investigators. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. JAMA. 2014 Nov 19;312(19):1988-98.

63. Reddy VY, Holmes D, Doshi SK, Neuzil P, Kar S. Safety of percutaneous left atrial appendage closure: results from the Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF (PROTECT AF) clinical trial and the Continued Access Registry. Circulation. 2011 Feb 1;123(4):417-24.

64. Reynolds MR, Zheng Q, Doros G. Laser balloon ablation for AF: A systematic review and meta-analysis. J Cardiovasc Electrophysiol. 2018 Oct;29(10):1363-1370.

65. Sahay S, Nombela-Franco L, Rodes-Cabau J, Jimenez-Quevedo P, Salinas P,Biagioni C, et al. Efficacy and safety of left atrial appendage closure versus medical treatment in atrial fibrillation: a network meta-analysis from randomised trials. Heart. 2017 Jan 15;103(2):139-147.

66. Sanders GD, Lowenstern A, Borre E, Chatterjee R, Goode A, Sharan L, Allen LaPointe NM, Raitz G, Shah B, Yapa R, Davis JK, Lallinger K, Schmidt R, Kosinski A, Al-Khatib S. Stroke Prevention in Patients With Atrial Fibrillation: A Systematic Review Update. Comparative Effectiveness Review No. 214. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290-2015-00004-I for AHRQ and PCORI.) AHRQ Publication No. 18(19)-EHC018-EF. PCORI Publication No. 2018-SR-04. Rockville, MD: Agency for Healthcare Research and Quality; October 2018

67. Sanjoy SS, Choi YH, Sparrow RT, Baron SJ, Abbott JD, Azzalini L, et al. Sex Differences in Outcomes Following Left Atrial Appendage Closure. Mayo Clin Proc. 2021 Jul;96(7):1845-1860.

68. Sarraf M, Packer DL, Holmes DR. Left Atrial Appendage Closure. In: Cardiac Electrophysiology. From Cell to Bedside, 7th ed. Saunders, an imprint of Elsevier; 2018. Philadelphia, PA. Ch 139. pg 1337-44.

69. Saw J, Fahmy P, Azzalini L, Marquis JF, Hibbert B, Morillo C, et al. Early Canadian Multicenter Experience With WATCHMAN for Percutaneous Left Atrial Appendage Closure. J Cardiovasc Electrophysiol. 2017 Apr;28(4):396-401.

70. Schmidt B, Neuzil P, Luik A, Osca Asensi J, Schrickel JW, Deneke T, et al. Laser Balloon or Wide-Area Circumferential Irrigated Radiofrequency Ablation for Persistent Atrial Fibrillation: A Multicenter Prospective Randomized Study. Circ Arrhythm Electrophysiol. 2017 Dec;10(12).

71. Seeger J, Birkemeyer R, Rottbauer W, Wöhrle J. First experience with the Watchman FLX occluder for percutaneous left atrial appendage closure. Cardiovasc Revasc Med. 2017 Oct - Nov;18(7):512-516.

72. Søndergaard L, Wong YH, Reddy VY, Boersma LVA, Bergmann MW, Doshi S, et al. Propensity-Matched Comparison of Oral Anticoagulation Versus Antiplatelet Therapy After Left Atrial Appendage Closure With WATCHMAN. JACC Cardiovasc Interv. 2019 Jun 10;12(11):1055-1063.

73. Toale C, Fitzmaurice GJ, Eaton D, Lyne J, Redmond KC. Outcomes of left atrial appendage occlusion using the AtriClip device: a systematic review. Interact Cardiovasc Thorac Surg. 2019 Jul 10.

74. Verma A, Cairns JA, Mitchell LB, Macle L, Stiell IG, Gladstone D, et. Al.; CCS Atrial Fibrillation Guidelines Committee. 2014 focused update of the Canadian Cardiovascular Society Guidelines for the management of atrial fibrillation. Can J Cardiol. 2014 Oct;30(10):1114-30.

75. Viles-Gonzalez JF, Kars, Douglas P, Dukkipati S, Feldman T, Horton R, et al. The clinical impact of incomplete left atrial appendage closure with the Watchman device in patients with atrial fibrillation: a PROTECT AF (Peripheral to Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients with Atria Fibrillation) substudy. J Am Coll Cardiol. 2012 Mar 6;59(10):923-9.

76. U.S. Food and Drug Administration (FDA). PMS Database. P130013. Watchman LAA Closure Technology. 2015 March. September 14, 2021. Available at URL address: https://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfPMA/pma.cfm?id=P130013

77. U.S. Food and Drug Administration (FDA). 510(k) summary. AtriClip LAA Exclusion System with preloaded Gillinov-Cosgrove Clip. K093679. 2010 June. Accessed September 14, 2021. Available at URL address: http://home.healthcare.cigna.com/CHCHOME/CRUintranet/displayAttachment.asp?id=55449

78. Vainrib AF, Bamira D, Benenstein RJ, Aizer A, Chinitz LA, Saric M. Echocardiographic Guidance of the Novel WaveCrest Left Atrial Appendage Occlusion Device. CASE (Phila). 2018 Sep 27;2(6):297-300.

79. Wei Z, Zhang X, Wu H, Xie J, Dai Q, Wang L, Xu B. A meta-analysis for efficacy and safety evaluation of transcatheter left atrial appendage occlusion in patients with nonvalvular atrial fibrillation. Medicine (Baltimore). 2016 Aug;95(31):e4382.

80. Whitlock RP, Belley-Cote EP, Paparella D, Healey JS, Brady K, Sharma M, et al. Left Atrial Appendage Occlusion during Cardiac Surgery to Prevent Stroke. N Engl J Med. 2021 Jun 3;384(22):2081-2091.

81. Whitlock R, Healey J, Vincent J, Brady K, Teoh K, Royse A, Shah P, et al. Rationale and design of the Left Atrial Appendage Occlusion Study (LAAOS) III. Ann Cardiothorac Surg. 2014 Jan;3(1):45-54.

82. Xu H, Xie X, Wang B, Ma S, Wang F. Efficacy and Safety of Percutaneous Left Atrial Appendage Occlusion for Stroke Prevention in Nonvalvular Atrial Fibrillation: A Meta-analysis of Contemporary Studies. Heart Lung Circ. 2016 Nov;25(11):1107-1117.

83. Yerasi C, Lazkani M, Kolluru P, Miryala V, Kim J, Moole H, Sawant AC, Morris M, Pershad A. An updated systematic review and meta-analysis of early outcomes after left atrial appendage occlusion. J Interv Cardiol. 2018 Apr;31(2):197-206.

References- Maze and Related Procedures

1. Ad N, Cheng DCH, Martin J, Berglin EE, Chang BC, Doukas G, et al. Surgical ablation for atrial fibrillation in cardiac surgery a consensus statement of the International Society of Minimally Invasive Cardiothoracic Surgery (ISMICS) 2009. Innovations. 2010 March/April; 5(2): 74-83.

2. Ad N, Holmes SD, Massimiano PS, Pritchard G, Stone LE, Henry L. The effect of the Cox-maze procedure for atrial fibrillation concomitant to mitral and tricuspid valve surgery. J Thorac Cardiovasc Surg. 2013 Dec;146(6):1426-34; discussion 1434-5.

3. Albåge A, Jidéus L, Ståhle E, Johansson B, Berglin E. Early and long-term mortality in 536 patients after the Cox-maze III procedure: a national registry-based study. Ann Thorac Surg. 2013 May;95(5):1626-32.

4. Albrecht A, Kalil RA, Schuch L, Abrahão R, Sant'Anna JR, de Lima G, Nesralla IA. Randomized study of surgical isolation of the pulmonary veins for correction of permanent atrial fibrillation associated with mitral valve disease. J Thorac Cardiovasc Surg. 2009 Aug;138(2):454-9.

5. Andrade JG, Aguilar M, Atzema C, Bell A, Cairns JA, Cheung CC, et al. The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation. Can J Cardiol. 2020 Dec;36(12):1847-1948.

6. Bagge L, Blomström P, Nilsson L, Einarsson GM, Jidéus L, Blomström-Lundqvist C. Epicardial off-pump pulmonary vein isolation and vagal denervation improve long-term outcome and quality of life in patients with atrial fibrillation. J Thorac Cardiovasc Surg. 2009 May;137(5):1265-71.

7. Bakir I, Casselman FP, Brugada P, Geelen P, Wellens F, Degrieck I, et al. Current strategies in the surgical treatment of atrial fibrillation: review of the literature and Onze Lieve Vrouw Clinic's strategy. Ann Thorac Surg. 2007 Jan;83(1):331-40.

8. Ballaux PK, Geuzebroek GS, van Hemel NM, Kelder JC, Dossche KM, Ernst JM. Freedom from atrial arrhythmias after classic maze III surgery: a 10-year experience. J Thorac Cardiovasc Surg. 2006 Dec;132(6):1433-40.

9. Bando K, Kobayashi J, Kosakai Y, Hirata M, Sasako Y, Nakatani S, et al. Impact of Cox maze procedure on outcome in patients with atrial fibrillation and mitral valve disease. J Thorac Cardiovasc Surg. 2002 Sep;124(3):575-83.

10. Beyer E, Lee R, Lam BK. Point: Minimally invasive bipolar radiofrequency ablation of lone atrial fibrillation: early multicenter results. J Thorac Cardiovasc Surg. 2009 Mar;137(3):521-6.

11. Boersma LV, Castella M, van Boven W, Berruezo A, Yilmaz A, Nadal M, et al. Atrial fibrillation catheter ablation versus surgical ablation treatment (FAST): a 2-center randomized clinical trial. Circulation. 2012 Jan 3;125(1):23-30.

12. Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008 Sep 23;52(13):e1-142.

13. Calkins H, Brugada J, Packer DL, Cappato R, Chen SA, Crijns HJ, et al.; Heart Rhythm Society; European Heart Rhythm Association; European Cardiac Arrhythmia Society; American College of Cardiology; American Heart Association; Society of Thoracic Surgeons. HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. A report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation developed in partnership with the European Heart Rhythm Association (EHRA) and the European Cardiac Arrhythmia Society (ECAS); in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), and the Society of Thoracic Surgeons (STS). Endorsed and approved by the governing bodies of the American College of Cardiology, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, and the Heart Rhythm Society. Europace. 2007 Jun;9(6):335-79.

14. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, et al. 2012 HRS/EHRA/ECAS Expert 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: A report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Developed in partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society of Thoracic Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the Heart Rhythm Society. Europace. 2012 Apr;14(4):528-606.

15. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart Rhythm. 2017 Oct;14(10):e275-e444.

16. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al.; ESC Committee for Practice Guidelines-CPG; Document Reviewers. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation--developed with the special contribution of the European Heart Rhythm Association. Europace. 2012 Oct;14(10):1385-413.

17. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determinations (LCDs) alphabetical index. Accessed October 15, 2021. Available at URL address: https://www.cms.gov/medicare-coverage-database/reports/local-coverage-final-lcds-alphabetical-report.aspx?lcdStatus=all

18. Centers for Medicare and Medicaid Services (CMS). National Coverage Determinations (NCDs) alphabetical index. Accessed October 15, 2021. Available at URL address: https://www.cms.gov/medicare-coverage-database/indexes/ncd-alphabetical-index.aspx

19. Cheema FH, Weisberg JS, Khalid I, Roberts HG Jr. Warm beating heart, robotic endoscopic Cox-cryomaze: an approach for treating atrial fibrillation. Ann Thorac Surg. 2009 Mar;87(3):966-8.

20. Cox JL, Ad N, Palazzo T, Fitzpatrick S, Suyderhoud JP, DeGroot KW, et al. The Maze-III procedure combined with valve surgery. Semin Thorac Cardiovasc Surg. 2000 Jan;12(1):53-5.

21. DeLurgio DB, Crossen KJ, Gill J, Blauth C, Oza SR, Magnano AR, et al. Hybrid Convergent Procedure for the Treatment of Persistent and Long-Standing Persistent Atrial Fibrillation: Results of CONVERGE Clinical Trial. Circ Arrhythm Electrophysiol. 2020 Dec;13(12):e009288.

22. Deneke T, Khargi K, Grewe PH, Laczkovics A, von Dryander S, Lawo T, et al. Efficacy of an additional MAZE procedure using cooled-tip radiofrequency ablation in patients with chronic atrial fibrillation and mitral valve disease: a randomized, prospective trial. Eur Heart J. 2002 Apr;23(7):558-66.

23. Doty JR, Doty DB, Jones KW, Flores JH, Mensah M, Reid BB, et al. Comparison of standard Maze III and radiofrequency Maze operations for treatment of atrial fibrillation. J Thorac Cardiovasc Surg. 2007 Apr;133(4):1037-44.

24. Doukas G, Samani NJ, Alexiou C, Oc M, Chin DT, Stafford PG, et al. Left atrial radiofrequency ablation during mitral valve surgery for continuous atrial fibrillation: a randomized controlled trial. JAMA. 2005 Nov 9;294(18):2323-9.

25. Edgerton ZJ, Edgerton JR. A review of current surgical treatment of patients with atrial fibrillation. Proc (Bayl Univ Med Cent). 2012 Jul;25(3):218-23.

26. Edgerton JR, Brinkman WT, Weaver T, Prince SL, Culica D, Herbert MA, Mack MJ. Pulmonary vein isolation and autonomic denervation for the management of paroxysmal atrial fibrillation by a minimally invasive surgical approach. J Thorac Cardiovasc Surg. 2010 Oct;140(4):823-8.

27. Edgerton JR, McClelland JH, Duke D, Gerdisch MW, Steinberg BM, Bronleewe SH, et al. Minimally invasive surgical ablation of atrial fibrillation: six-month results. J Thorac Cardiovasc Surg. 2009 Jul;138(1):109-13; discussion 114.

28. Edgerton JR, Edgerton ZJ, Weaver T, Reed K, Prince S, Herbert MA, Mack MJ. Minimally invasive pulmonary vein isolation and partial autonomic denervation for surgical treatment of atrial fibrillation. Ann Thorac Surg. 2008 Jul;86(1):35-8; discussion 39.

29. European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery, Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace. 2010 Oct;12(10):1360-420.

30. Gaynor SL, Schuessler RB, Bailey MS, Ishii Y, Boineau JP, Gleva MJ, et al. Surgical treatment of atrial fibrillation: predictors of late recurrence. J Thorac Cardiovasc Surg. 2005 Jan;129(1):104-11.

31. Gehi AK, Mounsey JP, Pursell I, Landers M, Boyce K, Chung EH, et al. Hybrid epicardial-endocardial ablation using a pericardioscopic technique for the treatment of atrial fibrillation. Heart Rhythm. 2013 Jan;10(1):22-8.

32. Gehi AK, Adams DH, Filsoufi F. The modern surgical management of atrial fibrillation. Mt Sinai J Med. 2006 Sep;73(5):751-8.

33. Gelsomino S, Van Breugel HN, Pison L, Parise O, Crijns HJ, Wellens F, et al. Hybrid thoracoscopic and transvenous catheter ablation of atrial fibrillation. Eur J Cardiothorac Surg. 2014 Mar;45(3):401-7.

34. Geršak B, Pernat A, Robic B, Sinkovec M. Low rate of atrial fibrillation recurrence verified by implantable loop recorder monitoring following a convergent epicardial and endocardial ablation of atrial fibrillation. J Cardiovasc Electrophysiol. 2012 Oct;23(10):1059-66.

35. Geršak B, Zembala MO, Müller D, Folliguet T, Jan M, Kowalski O, et al. European experience of the convergent atrial fibrillation procedure: multicenter outcomes in consecutive patients. J Thorac Cardiovasc Surg. 2014 Apr;147(4):1411-6.

36. Gillinov AM, Bhavani S, Blackstone EH, Rajeswaran J, Svensson LG, Navia JL, et al. Surgery for permanent atrial fibrillation: impact of patient factors and lesion set. Ann Thorac Surg. 2006 Aug;82(2):502-13; discussion 513-4.

37. Haldar S, Khan HR, Boyalla V, Kralj-Hans I, Jones S, Lord J, Onyimadu O, et al. Catheter ablation vs. thoracoscopic surgical ablation in long-standing persistent atrial fibrillation: CASA-AF randomized controlled trial. Eur Heart J. 2020 Dec 14;41(47):4471-4480.

38. Gopinathannair R, Chen LY, Chung MK, Cornwell WK, Furie KL, Lakkireddy DR, et al. Managing Atrial Fibrillation in Patients With Heart Failure and Reduced Ejection Fraction: A Scientific Statement From the American Heart Association. Circ Arrhythm Electrophysiol. 2021 Jun;14(6):HAE0000000000000078.

39. Hayes, Inc. Hayes Comparative Effectiveness Review. Hybrid Maze Procedure for Atrial Fibrillation. Lansdale, PA: Hayes, Inc.; published July 15, 2019.

40. Ismail I, Fleissner F, Cebotari S, Rustum S, Haverich A. Left-sided mini-maze procedure via the left atrial appendage. Interact Cardiovasc Thorac Surg. 2014 Jun;18(6):847-9.

41. January CT, Wann LS, Alpert JS, Calkins H, Cleveland JC Jr, Cigarroa JE, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014 Mar 28.

42. Je HG, Shuman DJ, Ad N. A systematic review of minimally invasive surgical treatment for atrial fibrillation: a comparison of the Cox-Maze procedure, beating-heart epicardial ablation, and the hybrid procedure on safety and efficacy†. Eur J Cardiothorac Surg. 2015 Jan 6. pii: ezu536.

43. Jeanmart H, Casselman F, Beelen R, Wellens F, Bakir I, Van Praet F, et al. Modified maze during endoscopic mitral valve surgery: the OLV Clinic experience. Ann Thorac Surg. 2006 Nov;82(5):1765-9.

44. Johansson BI, Väärt O, Edvardsson N, Nyström B, Scherstén H, Karlsson T, Berglin E. Low mortality and low rate of perceived and documented arrhythmias after Cox maze III surgery for atrial fibrillation. Pacing Clin Electrophysiol. 2014 Feb;37(2):147-56.

45. Kasirajan V, Spradlin EA, Mormando TE, Medina AE, Ovadia P, Schwartzman DS, et al. Minimally invasive surgery using bipolar radiofrequency energy is effective treatment for refractory atrial fibrillation. Ann Thorac Surg. 2012 May;93(5):1456-61.

46. Khargi K, Hutten BA, Lemke B, Deneke T. Surgical treatment of atrial fibrillation; a systematic review. Eur J Cardiothorac Surg. 2005 Feb;27(2):258-65.

47. Khargi K, Keyhan-Falsafi A, Hutten BA, Ramanna H, Lemke B, Deneke T. Surgical treatment of atrial fibrillation : a systematic review. Herzschrittmacherther Elektrophysiol. 2007 Jun;18(2):68-76.

48. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur J Cardiothorac Surg. 2016 Nov;50(5):e1-e88.

49. Kiser AC, Mounsey JP, Landers MD. The Convergent Procedure is a Collaborative Atrial Fibrillation Treatment. May 2011. Innovations in Cardiac Rhythm Management. Accessed September 13, 2021. Available at URL address: http://www.innovationsincrm.com/cardiac-rhythm-management/2011/may/78-convergent-procedure-collaborative-effort

50. Kiser AC, Landers MD, Boyce K, Sinkovec M, Pernat A, Geršak B. Simultaneous catheter and epicardial ablations enable a comprehensive atrial fibrillation procedure. Innovations (Phila). 2011 Jul;6(4):243-7.

51. Kiser AC, Landers M, Horton R, Hume A, Natale A, Gersak B. The convergent procedure: a multidisciplinary atrial fibrillation treatment. Heart Surg Forum. 2010 Oct;13(5):E317-21.

52. Kong MH, Lopes RD, Piccini JP, Hasselblad V, Bahnson TD, Al-Khatib SM. Surgical Maze procedure as a treatment for atrial fibrillation: a meta-analysis of randomized controlled trials. Cardiovasc Ther. 2010 Oct;28(5):311-26.

53. Krul SP, Driessen AH, van Boven WJ, Linnenbank AC, Geuzebroek GS, Jackman WM, et al. Thoracoscopic video-assisted pulmonary vein antrum isolation, ganglionated plexus ablation, and periprocedural confirmation of ablation lesions: first results of a hybrid surgical-electrophysiological approach for atrial fibrillation. Circ Arrhythm Electrophysiol. 2011a Jun;4(3):262-70.

54. Krul SP, Driessen AH, Zwinderman AH, van Boven WJ, Wilde AA, de Bakker JM, de Groot JR. Navigating the mini-maze: Systematic review of the first results and progress of minimally-invasive surgery in the treatment of atrial fibrillation. Int J Cardiol. 2011b Nov 9.

55. Krul SP, Driessen AH, Zwinderman AH, van Boven WJ, Wilde AA, de Bakker JM, de Groot JR. Navigating the mini-maze: systematic review of the first results and progress of minimally-invasive surgery in the treatment of atrial fibrillation.Int J Cardiol. 2013 Jun 5;166(1):132-40.

56. Kurfirst V, Mokraček A, Bulava A, Čanadyova J, Haniš J, Pešl L. Two-staged hybrid treatment of persistent atrial fibrillation: short-term single-centre results. Interact Cardiovasc Thorac Surg. 2014 Apr;18(4):451-6.

57. La Meir M, Gelsomino S, Lucà F, Pison L, Parise O, Colella A, et al. Minimally invasive surgical treatment of lone atrial fibrillation: early results of hybrid versus standard minimally invasive approach employing radiofrequency sources. Int J Cardiol. 2013a Aug 20;167(4):1469-75.

58. La Meir M, Gelsomino S, Lucà F, Pison L, Colella A, Lorusso R, et al. Minimal invasive surgery for atrial fibrillation: an updated review. Europace. 2013b Feb;15(2):170-82.

59. La Meir M, Gelsomino S, Lorusso R, Lucà F, Pison L, Parise O, et al. The hybrid approach for the surgical treatment of lone atrial fibrillation: one-year results employing a monopolar radiofrequency source. J Cardiothorac Surg. 2012 Jul 19;7:71.

60. La Meir M, Gelsomino S, Luca F, Pison L, Chambille P, Parise O, et al. Time-related prevalence of postoperative atrial fibrillation after stand-alone minimally invasive radiofrequency ablation. J Card Surg. 2011 Jul;26(4):453-9.

61. Lawrance CP, Henn MC, Miller JR, Sinn LA, Schuessler RB, Damiano RJ Jr. Comparison of the stand-alone Cox-Maze IV procedure to the concomitant Cox-Maze IV and mitral valve procedure for atrial fibrillation. Ann Cardiothorac Surg. 2014a Jan;3(1):55-61.

62. Lawrance CP, Henn MC, Miller JR, Sinn LA, Schuessler RB, Maniar HS, Damiano RJ Jr. A minimally invasive Cox maze IV procedure is as effective as sternotomy while decreasing major morbidity and hospital stay. J Thorac Cardiovasc Surg. 2014b Sep;148(3):955-61; discussion 962-2.

63. Lee AM, Melby SJ, Damiano RJ Jr. The surgical treatment of atrial fibrillation. Surg Clin North Am. 2009 Aug;89(4):1001-20, x-xi.

64. Louagie Y, Buche M, Eucher P, Schoevaerdts JC, Gerard M, Jamart J, Blommaert D. Improved patient survival with concomitant Cox Maze III procedure compared with heart surgery alone. Ann Thorac Surg. 2009 Feb;87(2):440-6.

65. Luo X, Li B, Zhang D, Zhu J, Qi L, Tang Y. Efficacy and safety of the convergent atrial fibrillation procedure: a meta-analysis of observational studies. Interact Cardiovasc Thorac Surg. 2019 Feb 1;28(2):169-176.

66. Maclean E, Yap J, Saberwal B, Kolvekar S, Lim W, Wijesuriya N, et al. The convergent procedure versus catheter ablation alone in longstanding persistent atrial fibrillation: A single centre, propensity-matched cohort study. Int J Cardiol. 2020 Mar 15;303:49-53.

67. Mahapatra S, LaPar DJ, Kamath S, Payne J, Bilchick KC, Mangrum JM, Ailawadi G. Initial experience of sequential surgical epicardial-catheter endocardial ablation for persistent and long-standing persistent atrial fibrillation with long-term follow-up. Ann Thorac Surg. 2011 Jun;91(6):1890-8.

68. McClelland JH, Duke D, Reddy R. Preliminary results of a limited thoracotomy: new approach to treat atrial fibrillation. J Cardiovasc Electrophysiol. 2007 Dec;18(12):1289-95.

69. Melby SJ, Zierer A, Bailey MS, Cox JL, Lawton JS, Munfakh N, et al. A new era in the surgical treatment of atrial fibrillation: the impact of ablation technology and lesion set on procedural efficacy. Ann Surg. 2006 Oct;244(4):583-92.

70. Melby SJ, Schuessler RB, Damiano RJ Jr. Ablation technology for the surgical treatment of atrial fibrillation. ASAIO J. 2013 Sep-Oct;59(5):461-8.

71. Morady F, Zipes DP. Atrial Fibrillation: Clinical Features, Mechanisms, and Management. In: Zipes DP, Libby P, Bonow RO, Mann D, Zipes B, Braunwald E, editors. Braunwald's heart disease. Textbook of cardiovascular medicine. 10th ed. Philadelphia, PA: W.B. Saunders; 2015. Ch 38. pg 811.

72. Nasso G, Bonifazi R, Del Prete A, Del Prete G, Lopriore V, Bartolomucci F, et al. Long-term results of ablation for isolated atrial fibrillation through a right minithoracotomy: toward a rational revision of treatment protocols. J Thorac Cardiovasc Surg. 2011 Aug;142(2):e41-6.

73. National Institute for Health and Clinical Excellence (NICE). Atrial fibrillation: diagnosis and management. Clinical Guideline 196. 2021 April. Accessed September 13, 2021. Available at URL address: https://www.nice.org.uk/guidance/ng196

74. National Institute for Health and Clinical Excellence (NICE) Interventional Procedure Guidance #286. January 2009. Thoracoscopic epicardial radiofrequency ablation for atrial fibrillation. Accessed September 14, 2021. Available at URL address: http://www.nice.org.uk/guidance/ipg286

75. National Institute for Health and Clinical Excellence (NICE) Interventional Procedure Guidance #121. May 2005. Radiofrequency ablation for atrial fibrillation in association with other cardiac surgery. Accessed September 14, 2021. Available at URL address: http://www.nice.org.uk/guidance/ipg121

76. National Institute for Health and Clinical Excellence (NICE) Interventional Procedure Guidance #122. May 2005. Microwave ablation for atrial fibrillation in association with other cardiac surgery. Accessed September 14, 2021. Available at URL address: http://www.nice.org.uk/guidance/ipg122

77. National Institute for Health and Clinical Excellence (NICE) Interventional Procedure Guidance #123. May 2005. Cryoablation for atrial fibrillation in association with other cardiac surgery. Accessed September 14, 2021. Available at URL address: http://www.nice.org.uk/guidance/ipg123

78. Okada S, Weimar T, Moon MR, Schuessler RB, Sinn LA, Damiano RJ, Maniar HS. The impact of previous catheter-based ablation on the efficacy of the Cox-maze IV procedure. Ann Thorac Surg. 2013 Sep;96(3):786-91; discussion 791.

79. Pearman CM, Poon SS, Bonnett LJ, Haldar S, Wong T, Mediratta N, Gupta D. Minimally Invasive Epicardial Surgical Ablation Alone Versus Hybrid Ablation for Atrial Fibrillation: A Systematic Review and Meta-Analysis. Arrhythm Electrophysiol Rev. 2017 Dec;6(4):202-209.

80. Phan K, Xie A, Tian DH, Shaikhrezai K, Yan TD. Systematic review and meta-analysis of surgical ablation for atrial fibrillation during mitral valve surgery. Ann Cardiothorac Surg. 2014a Jan;3(1):3-14.

81. Phan K, Xie A, La Meir M, Black D, Yan TD. Surgical ablation for treatment of atrial fibrillation in cardiac surgery: a cumulative meta-analysis of randomised controlled trials. Heart. 2014b May;100(9):722-30.

82. Pison L, La Meir M, van Opstal J, Blaauw Y, Maessen J, Crijns HJ. Hybrid thoracoscopic surgical and transvenous catheter ablation of atrial fibrillation. J Am Coll Cardiol. 2012 Jul 3;60(1):54-61. Pison L, Gelsomino S, Lucà F, Parise O, Maessen JG, Crijns HJ, La Meir M. Effectiveness and safety of simultaneous hybrid thoracoscopic and endocardial catheter ablation of lone atrial fibrillation. Ann Cardiothorac Surg. 2014 Jan;3(1):38-44.

83. Pison L, La Meir M, van Opstal J, Blaauw Y, Maessen J, Crijns HJ. Hybrid thoracoscopic surgical and transvenous catheter ablation of atrial fibrillation. J Am Coll Cardiol. 2012 Jul 3;60(1):54-61.

84. Pruitt JC, Lazzara RR, Dworkin GH, Badhwar V, Kuma C, Ebra G. Totally endoscopic ablation of lone atrial fibrillation: initial clinical experience. Ann Thorac Surg. 2006 Apr;81(4):1325-30; discussion 1330-1.

85. Reston JT, Shuhaiber JH. Meta-analysis of clinical outcomes of maze-related surgical procedures for medically refractory atrial fibrillation. Eur J Cardiothorac Surg. 2005 Nov;28(5):724-30.

86. Robertson JO, Lawrance CP, Maniar HS, Damiano RJ Jr. Surgical techniques used for the treatment of atrial fibrillation. Circ J. 2013;77(8):1941-51.

87. Robertson JO, Lindsey LS, Damiano RT. Surgery for Atrial Fibrillation and other SVTs. In: Zipes DP, Jalife J, editors. Cardiac Electrophysiology: From Cell to Bedside. 6th ed. Philadelphia, PA: Elsevier; 2014. Ch 128. pg 1295-1305.

88. Saint LL, Damiano RJ Jr, Cuculich PS, Guthrie TJ, Moon MR, Munfakh NA, Maniar HS. Incremental risk of the Cox-maze IV procedure for patients with atrial fibrillation undergoing mitral valve surgery. J Thorac Cardiovasc Surg. 2013 Nov;146(5):1072-7.

89. Santini M, Loiaconi V, Tocco MP, Mele F, Pandozi C. Feasibility and efficacy of minimally invasive stand-alone surgical ablation of atrial fibrillation. A single-center experience. J Interv Card Electrophysiol. 2012 Jun;34(1):79-87

90. Sirak J, Jones D, Sun B, Sai-Sudhakar C, Crestanello J, Firstenberg M. Toward a definitive, totally thoracoscopic procedure for atrial fibrillation. Ann Thorac Surg. 2008 Dec;86(6):1960-4.

91. Speziale G, Bonifazi R, Nasso G, Bartolomucci F, Caldarola P, Fattouch K, et al. Minimally invasive radiofrequency ablation of lone atrial fibrillation by monolateral right minithoracotomy: operative and early follow-up results. Ann Thorac Surg. 2010 Jul;90(1):161-7.

92. Srivastava V, Kumar S, Javali S, Rajesh TR, Pai V, Khandekar J,et al. Efficacy of three different ablative procedures to treat atrial fibrillation in patients with valvular heart disease: a randomised trial. Heart Lung Circ. 2008 Jun;17(3):232-40.

93. Stulak JM, Sundt TM 3rd, Dearani JA, Daly RC, Orsulak TA, Schaff HV. Ten-year experience with the Cox-maze procedure for atrial fibrillation: how do we define success? Ann Thorac Surg. 2007a Apr;83(4):1319-24.

94. Stulak JM, Dearani JA, Sundt TM 3rd, Daly RC, McGregor CG, et al. Superiority of cut-and-sew technique for the Cox maze procedure: comparison with radiofrequency ablation. J Thorac Cardiovasc Surg. 2007b Apr;133(4):1022-7.

95. Stulak JM, Suri RM, Burkhart HM, Daly RC, Dearani JA, Greason KL, et al. Surgical ablation for atrial fibrillation for two decades: are the results of new techniques equivalent to the Cox maze III procedure? J Thorac Cardiovasc Surg. 2014 May;147(5):1478-86.

96. Unites States Food and Drug Administration (FDA). 510(k) summary. Center for Devices and Radiological Health (CDRH). K013392. Cardioblate surgical ablation pen, model 60811c; cardioblate surgical ablation generator, model 60880. 2002 January. Accessed September 14, 2021. Available at URL address: https://www.accessdata.fda.gov/SCRIPTS/cdrh/devicesatfda/index.cfm?db=pmn&id=K013392

97. Unites States Food and Drug Administration (FDA). 510(k) summary. Center for Devices and Radiological Health (CDRH). K022008. Cardima ablation system. 2003 January. Accessed September 14, 2021. Available at URL address: https://www.accessdata.fda.gov/SCRIPTS/cdrh/devicesatfda/index.cfm?db=pmn&id=K022008

98. van der Heijden CAJ, Vroomen M, Luermans JG, Vos R, Crijns HJGM, Gelsomino S, La Meir M, Pison L, Maesen B. Hybrid versus catheter ablation in patients with persistent and longstanding persistent atrial fibrillation: a systematic review and meta-analysis†. Eur J Cardiothorac Surg. 2019 Sep 1;56(3):433-443.

99. VonOppell UO, Masani N, O'Callaghan P, Wheeler R, Dimitrakakis G, Schiffelers S. Mitral valve surgery plus concomitant atrial fibrillation ablation is superior to mitral valve surgery alone with an intensive rhythm control strategy. Eur J Cardiothorac Surg. 2009 Apr;35(4):641-50.

100. Vroomen M, La Meir M, Maesen B, Luermans JGL, Vernooy K, Essers B, et al. Hybrid thoracoscopic surgical and transvenous catheter ablation versus transvenous catheter ablation in persistent and longstanding persistent atrial fibrillation (HARTCAP-AF): study protocol for a randomized trial. Trials. 2019 Jun 20;20(1):370.

101. Wang J, Meng X, Li H, Cui Y, Han J, Xu C. Prospective randomized comparison of left atrial and biatrial radiofrequency ablation in the treatment of atrial fibrillation. Eur J Cardiothorac Surg. 2009 Jan;35(1):116-22.

102. Wang J, Li Y, Shi J, Han J, Xu C, Ma C, Meng X. Minimally invasive surgical versus catheter ablation for the long-lasting persistent atrial fibrillation. PLoS One. 2011;6(7):e22122.

103. Wolf RK, Schneeberger EW, Osterday R, Miller D, Merrill W, Flege JB Jr, Gillinov AM. Video-assisted bilateral pulmonary vein isolation and left atrial appendage exclusion for atrial fibrillation. J Thorac Cardiovasc Surg. 2005 Sep;130(3):797-802.

104. Wong JW, Mak KH. Impact of maze and concomitant mitral valve surgery on clinical outcomes. Ann Thorac Surg. 2006 Nov;82(5):1938-47.

105. Wudel JH, Chaudhuri P, Hiller JJ. Video-assisted epicardial ablation and left atrial appendage exclusion for atrial fibrillation: extended follow-up. Ann Thorac Surg. 2008 Jan;85(1):34-8.

106. Yanagawa B, Holmes SD, Henry L, Hunt S, Ad N. Outcome of concomitantCox-maze III procedure using an argon-based cryosurgical system: a single-center experience with 250 patients. Ann Thorac Surg. 2013 May;95(5):1633-9.

107. Zembela M, Filipiak K, Kowalski O, Boidol J, Sokal A, Lenarczyk R. Minimally invasive hybrid ablation procedure for the treatment of persistent atrial fibrillation: one year results. Kardiol Pol. 2012;70(8):819-28.

108. Zhang D, Shi J, Quan H, Liu L, Zhang J, Guo Y. Five-year results of a modified left atrial maze IV procedure in the treatment of atrial fibrillation: a randomized study. ANZ J Surg. 2020 Apr;90(4):602-607.