Cigna Medical Coverage Policy

Subject **Transcatheter Ablation of Arrhythmogenic Foci in the Pulmonary Veins for the Treatment of Atrial Fibrillation**

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Coverage Policy

Cigna covers transcatheter radiofrequency ablation of the pulmonary veins (pulmonary vein isolation) as medically necessary for the treatment of symptomatic persistent atrial fibrillation.

Cigna covers transcatheter radiofrequency ablation of the pulmonary veins as medically necessary for the treatment of symptomatic paroxysmal atrial fibrillation as an alternative to long-term antiarrhythmic drug therapy when BOTH of the following criteria are met:

- normal or mildly dilated left atria
- normal or mildly reduced left ventricular function

Cigna does not cover transcatheter radiofrequency ablation of the pulmonary veins for any other indication because it is considered experimental, investigational or unproven.

Cigna does not cover any other method of transcatheter ablation of the pulmonary veins for the treatment of atrial fibrillation, including but not limited to cryoablation/cryoballoon ablation, because it is considered experimental, investigational or unproven.

General Background

Atrial fibrillation (AF) is a frequently diagnosed cardiac arrhythmia characterized by uncoordinated atrial activation with deterioration of atrial mechanical function. AF is seen on electrocardiogram (ECG) as the

replacement of consistent P waves with rapid oscillations or fibrillatory waves that vary in size, shape, and timing, associated with an irregular, frequently rapid ventricular response when atrioventricular (AV) conduction is intact. The initial episode of AF is categorized as “first detected.” AF is considered recurrent when a patient has had two or more episodes. If the arrhythmia terminates spontaneously, recurrent AF is designated as paroxysmal, and is designated as persistent when it is sustained beyond seven days. AF is still designated as persistent even when terminated by pharmacological therapy or electrical cardioversion. Persistent AF may be the first presentation or a result of recurrent episodes of paroxysmal AF. Persistent AF also includes longstanding cases (e.g., greater than one year) usually leading to permanent AF, in which cardioversion has failed or has not been attempted. AF is associated with an increased risk of stroke, heart failure, and all-cause mortality, particularly in women. The mortality rate of patients with AF is approximately twice that of patients in normal sinus rhythm, and is linked to the severity of underlying heart disease (Fuster et al., 2011)

The management of patients with AF includes three objectives: rate control, prevention of thromboembolus, and correction of the rhythm disturbance. These treatment objectives are not mutually exclusive. With a rate-control treatment strategy, the ventricular rate is controlled with no commitment to restore or maintain sinus rhythm, while the rhythm-control strategy is intended to restore and/or maintain 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, with 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 (Fuster et al., 2011; Weigner et al., 1999; Lee et al., 2005).

Transcatheter radiofrequency 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. Early radiofrequency ablation techniques, modeled after the surgical Maze procedure, created linear scars in the atrial epicardium. Although this approach may be useful in patients who have had recurrent fibrillation after an apparently successful isolation procedure, it has largely been replaced by transcatheter ablation of arrhythmogenic foci in the pulmonary veins. 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 radiofrequency 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 radiofrequency ablation. Access to the left atrium is typically obtained using a special transseptal-sheath-dilator combination inserted into the femoral vein and advanced over a guidewire into the right atrium. Using this system, the intra-atrial septum is punctured (transseptal puncture), allowing access by ablation catheters to the pulmonary veins (Morady, et al., 2011; Jahangiri, et al., 2006).

Other Ablation Methods: Radiofrequency ablation is the most commonly used non-pharmacologic treatment for AF, and is the method used almost exclusively in early catheter ablation trials. A newer ablation method, the cryoballoon catheter, received U.S. Food and Drug Administration (FDA) approval in 2010 (Refer to U.S. FDA section below). Cryothermy causes tissue ablation when intracellular ice crystals disrupt cell membranes, leaving collagen structure intact. Based on early evidence, cryoenergy may be less likely than radiofrequency energy to cause pulmonary vein stenosis or esophageal injury. In any catheter based ablation procedure, access to the left atrium is achieved using a transseptal atrial puncture with a needle, considered to be a high-risk procedure reserved for use in select cardiac surgical centers and electrophysiology laboratories. Some

experts have expressed concern that the larger transseptal sheaths required to deliver a cryoballoon into the left atrium may be less flexible and more technically challenging, and may potentially increase the risk of pericardial tamponade (ECRI, 2011).

Several additional types of ablation catheters have been developed in addition to cryoablation, including a laser balloon catheter, a high-intensity focused ultrasound balloon catheter, and a high-density mesh ablator catheter. These devices are being evaluated in clinical trials but have not yet received FDA approval. Evidence published to date evaluating transcatheter cryoablation of the pulmonary veins is limited. 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 radiofrequency ablation. (Koch, et al., 2012; Morady, et al., 2011, 2011).

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

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

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

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

Literature Review
Radiofrequency Ablation (RFA): The most commonly used technique to eliminate paroxysmal or persistent AF is RFA using a 3.5-mm irrigated-tip catheter or an 8-mm tip catheter. A wide range of success rates for radiofrequency catheter ablation of atrial fibrillation (AF) has been reported. 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). Textbook literature reports that, “On the basis of published reports and the experience at high-volume centers, it is reasonable to expect a single-procedure 1-year success rate of 70% to 80% in patients with paroxysmal AF and approximately 50% in patients with persistent AF. After a redo procedure, a success rate of approximately 90% appears to be realistic for patients with paroxysmal AF compared with approximately 75% for patients with persistent AF. The risk of a major complication from radiofrequency catheter ablation of AF is reported to be 5% to 6%. In a large international survey, the most common major complications were cardiac tamponade (1.2%), pulmonary vein stenosis (1.3%), and cerebral thromboembolism (0.94%)” (Morady, et al., 2011).

Wilber et al. (2010) conducted a multicenter randomized controlled trial to determine the efficacy of catheter ablation compared to antiarrhythmic drug therapy (ADT) for the treatment of symptomatic paroxysmal AF. Patients who had not responded to at least one antiarrhythmic drug and who experienced at least three AF episodes within six months before randomization were assigned 2:1 to ablation (n=106) or to a previously unused antiarrhythmic drug (n=61). At nine months, 66% of patients in the ablation group remained free of

protocol-defined treatment failure, compared to 16% of patients in the ADT group. Major treatment-related adverse events occurred within 30 days in 5 of 57 patients (8.8%) in the ADT group compared to 5 of 103 patients (4.9%) in the ablation group. At three months, mean quality of life scores improved significantly in patients treated by catheter ablation compared to those treated with ADT, and improvement was maintained during the nine month evaluation period.

Oral et al. (2006) conducted a randomized controlled trial to determine the efficacy of circumferential radiofrequency pulmonary vein ablation (PVA) in maintaining sinus rhythm in the absence of antiarrhythmic drug therapy (ADT) in patients with chronic AF (n=146). Patients were randomly assigned to receive amiodarone and undergo two cardioversions during the first three months alone (n=69), or in combination with circumferential PVA (n=77). At one year, 74% of patients in the ablation group were free of recurrent AF or flutter without ADT. Of 69 patients in the control group, 53 (77%) crossed over to undergo circumferential PVA by one year. Only three (4%) of the patients in the control group were in sinus rhythm without ADT or ablation for comparison with the treatment group. The authors concluded that sinus rhythm can be maintained long-term in the majority of patients with chronic AF by means of circumferential PVA independent of the effects of ADT, cardioversion or both.

Stabile et al. (2006) conducted a randomized controlled trial (n=137) to investigate the adjunctive role of ablation therapy to ADT in preventing AF relapse in patients with paroxysmal or persistent AF in whom ADT had failed. Patients were randomized to ablation and ADT (n=68, ablation group) or ADT alone (n=69, control group). The ablation group received cavo-tricuspid and left inferior pulmonary vein mitral isthmus ablation plus circumferential pulmonary vein ablation using radiofrequency. The primary end point was the absence of recurrence of atrial arrhythmia lasting more than 30 seconds in the one-year follow-up period after a one-month blanking period. A blanking period is a time interval during which success criteria are not evaluated. Left atrial ablation procedures used to treat AF may not decrease the incidence of AF until four to six weeks following ablation. At twelve months, 63 of 69 (91.3%) patients in the control group had at least one AF recurrence, compared to 30 of 68 (44.1%) patients in the ablation group. The authors noted that most studies have used surrogate end points such as time to first symptomatic atrial arrhythmia recurrence, whereas this study chose the time to first recurrence, whether symptomatic or not, to define success. This may explain the lower success rate (56%) compared to previously published studies. The authors concluded that ablation therapy combined with ADT is superior to ADT alone in preventing atrial arrhythmia recurrences in patients with paroxysmal or persistent AF in whom antiarrhythmic drug therapy has failed.

Pappone et al. (2006) conducted a randomized controlled trial to evaluate circumferential pulmonary vein ablation compared to antiarrhythmic drug therapy (ADT) for paroxysmal AF (n=198). Patients with paroxysmal AF of six ± five years' duration were randomized to radiofrequency ablation (n=99) or to the maximum tolerable dose of another antiarrhythmic drug, A repeat ablation was performed in 9% of patients in the ablation group for recurrent AF (6%) or atrial tachycardia (3%). The primary end point was freedom from documented recurrent atrial tachyarrhythmias (AT) during a 12-month follow-up. The end point was reached with the first episode of AT, and cases with a second antiarrhythmic drug or repeat ablation procedure were considered failures. At one year, 93% of patients in the ablation group and 35% of patients in the ADT group were AT-free. One transient ischemic attack and one pericardial effusion occurred in the ablation group. Side effects of antiarrhythmics were observed in 23 patients in the ADT group. The authors concluded that, among selected patients with a long history of paroxysmal AF, a single circumferential pulmonary vein ablation is more effective than ADT with three antiarrhythmic drugs widely used as single agents or in combination.

Systematic Reviews/Technology Assessments

Radiofrequency Ablation: Calkins et al. (2009) conducted two separate systematic reviews and meta-analyses, one on radiofrequency ablation (RFA) and one on antiarrhythmic drug therapy (ADT), to evaluate the clinical efficacy and safety of both therapies in the treatment of AF. All study designs were accepted for the RFA systematic review, while the ADT therapy review was limited to prospective studies on the following drugs: amiodarone, dofetilide, sotalol, flecainide, and propafenone. Sixty-three RFA studies (n=8789) and 34 ADT studies (n=6589) were included in the reviews. Patients in the RFA studies tended to be younger than those in the ADT trials, with a mean age of 55 vs. 62 years; had a longer duration of AF (6.0 vs. 3.1 years); and had failed more previous drug trials (2.6 vs. 1.7). The single-procedure success rate of RFA was 57% and the multiple-procedure success rate was 71% for patients not on ADT therapy. The multiple-procedure success rate for patients on ADT or with unknown ADT usage was 77%. The success rate for ADT therapy was 52%. A major

complication occurred in 4.9% of catheter ablation patients. Adverse events were more common in ADT studies than in RFA studies, at 30% vs. 5%, respectively, but were less severe.

A 2009 Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review evaluated the evidence for the short-and long-term clinical effect and safety of radiofrequency catheter ablation for the management of AF. The review concluded that there is a moderate level of evidence to show that patients treated with radiofrequency ablation as a second-line therapy (i.e., patients who did not respond to medical therapy) had a higher chance of maintaining sinus rhythm than those treated with medical therapy alone. There was insufficient evidence to compare freedom from AF recurrence in patients who had radiofrequency ablation as first line therapy vs. medically treated patients. The review also states that there is a low level of evidence to show that nonparoxysmal AF is predictive of a higher rate of AF recurrence, and there is a high level of evidence demonstrating that sex, presence of structural heart disease, and duration of AF are not associated with recurrence.

Blue Cross/Blue Shield Technology Evaluation Center (TEC)
A Blue Cross/Blue Shield TEC Assessment (2008) evaluated six randomized controlled trials to determine whether radiofrequency catheter ablation improves health outcomes when used as a treatment for patients with AF. All trials reported substantial differences in favor of the ablation group on relevant outcomes, particularly in AF recurrence. The authors stated that the consistency of this finding establishes catheter ablation as more effective than medications in maintaining sinus rhythm across a wide spectrum of patients with AF, and across different variations of catheter ablation. The recurrence rate varied widely, indicating that there may be differences in absolute efficacy for different populations of patients. It cannot be concluded with confidence, however, that the lack of reported recurrence represents the elimination of AF, since AF is often intermittent and of brief duration.

The assessment concluded that radiofrequency catheter ablation of the pulmonary veins as a treatment for AF meets the TEC criteria for:

- patients with symptomatic paroxysmal or persistent atrial fibrillation who have failed antiarrhythmic medications, as an alternative to continued medical management; and
- patients with class II or III congestive heart failure and symptomatic atrial fibrillation in whom heart rate is poorly controlled by standard medications, as an alternative to AV nodal ablation and pacemaker insertion.

For other patients with atrial fibrillation, including first-line treatment for paroxysmal AF, radiofrequency catheter ablation of the pulmonary veins does not meet the TEC criteria.

Literature Review
Cryoablation: Evidence in the peer-reviewed literature suggests that transcatheter cryoablation/cryoballoon ablation of the pulmonary veins is technically feasible and may be effective for the treatment of a subset of patients with AF. Generally the studies are limited by small sample size and short-term follow-up. Additional well designed trials with long-term follow-up are needed before a definitive assessment can be made of the safety and efficacy of transcatheter cryoablation/cryoballoon ablation compared to radiofrequency ablation or antiarrhythmic drug therapies.

Packer et al. (2013) conducted a multicenter, randomized, controlled trial to compare outcomes of cryoablation (i.e., Arctic Front® cryoablation balloon catheter) and antiarrhythmic drug therapies in patients with documented symptomatic AF (i.e.,78% paroxysmal AF, 22% early persistent AF) and previously failed therapy with ≥ 1 membrane active antiarrhythmic drug. A total of 245 patients were randomized and enrolled over 21 months; 163 patients were assigned to cryoablation and 82 to antiarrhythmic drugs. The primary effectiveness endpoint for the trial was freedom from chronic treatment failure, as defined by the absence of: any detectable AF after the blanking period; use of a nonstudy, antiarrhythmic drug; or any nonprotocol intervention for AF (i.e., RF ablation). Freedom from AF after ablation while being treated with a previously ineffective antiarrhythmic drug at the same or a lower dose was considered a treatment success if patients remained in sinus rhythm. Two inferential co-primary safety endpoints were evaluated for study success: the proportion of intent-to-treat-ablated patients with more than one cryoablation procedure-related event (CPE); and an intent-to-treat comparison of the freedom from major AF events (MAFE) between groups over 12 months of follow-up. Thirty-one cryoablation patients underwent a repeat cryoablation during the 90 day blanking period when either

treatment was optimized. Sixty-five drug-treated patients crossed over to cryoablation after recurrent AF, and three drug-treated patients were lost to follow-up.

The authors reported that cryoablation produced acute isolation of three or more PVs in 98.2% and all four PVs in 97.6% of patients. PVs isolation was achieved with the balloon catheter alone in 83%. At 12 months, treatment success was 69.9% (114 of 163) of cryoblation patients compared with 7.3% of antiarrhythmic drug patients ($p<0.001$). Sixty-five (79%) drug-treated patients crossed over to cryoablation during 12 months of study follow-up due to recurrent, symptomatic AF, constituting drug treatment failure. There were seven of the resulting 228 cryoablated patients (3.1%) with a > 75% reduction in PV area during 12 months of follow-up. Twenty-nine of 259 procedures (11.2%) were associated with phrenic nerve palsy as determined by radiographic screening; 25 of these had resolved by 12 months. Pulmonary vein stenosis was reported in 3% (n=7) of the cryoablation group of which one required intervention. Cryoablation patients had significantly improved symptoms at 12 months. The freedom of major AF events rate was 96.9% in the ablation arm compared to 91.5% in the drug arm. The reported study limitations included the “frequency and timing of crossovers from drug treatment to cryoablation which makes it difficult to directly compare ablation and drug therapy beyond the median 186 days to cross-over. The number of drugs previously failed and the median doses taken were equivalent in both groups. All other demographics were also similar, suggesting the appropriateness of a comparison of these patients. The limited choice of antiarrhythmic drugs may also have contributed to the high AF recurrence rate observed in the drug-treated patients, although agents used were similar to those in other recent clinical trials. The use of dofetilide, dronedarone, or amiodarone, not permitted by the FDA in this study, might have increased the success rate of drug therapy” (Packer, et al., 2013).

In a prospective observational study, Vogt et al. (2013) investigated the long-term outcomes of freedom from AF after pulmonary vein (PV) isolation using cryoballoon ablation with balloon-size selection based on individual PV diameters. The study included 605 patients with symptomatic paroxysmal AF (n=579) or persistent AF. Cryoballoon size was based on magnetic resonance imaging and/or conventional angiograms. The primary endpoint was successful isolation of all four PVs, defined as confirmed unidirectional entrance block complete with absence of PV spikes. Secondary endpoints were the recurrence of AF during follow-up, procedural data, complications, and the time to successful PVI. Patients were followed up every three months during the first year after discharge and every six months in the second year. After 24 months, follow-up was on an outpatient basis with documented AF episodes recorded. The PV isolation was achieved without touch-up in 91.1% of patients, using the smaller balloon in 26.7%, the larger balloon in 25.6%, and both balloons in 47.7% of patients. Follow-up data for >12 months were available for 451 patients, 278 (61.6%) of whom were free of AF recurrence with no need for repeat procedures after the 3-month blanking period. Rates of freedom from AF after 1, 2, and 3 repeat procedures (using cryoballoon or radiofrequency ablation with similar success rates) were 74.9%, 76.2%, and 76.9%, respectively. Use of the smaller balloons or both balloons produced the highest rates of long-term freedom from AF. Phrenic nerve palsy occurred in 12 patients (2%), resolving within 3 to 9 months. The authors reported that rates of long-term freedom from AF after cryoballoon ablation are similar to those reported for radiofrequency ablation. A choice between balloons may improve outcomes. Reported limitations of the study are this was a single-center study with possibly smaller differences between individual operators than in multicenter studies. Follow-up became less rigorous after the first 12 months. The equipment changed during the study.

Kojodjojo et al. (2010) conducted a comparative case series study to investigate the efficacy of using a 28mm Arctic Front® cryoballoon to perform antral cryoablation with 'touch-up' ostial cryoablation for PVI in patients with paroxysmal and persistent AF (n=124). Paroxysmal and persistent AF patients undergoing their first left atrial ablation were recruited. After cryoballoon therapy, each PV was assessed for isolation and if necessary, treated with focal ostial cryoablation until PVI was achieved. Follow-up with Holter monitoring was performed. Clinical outcomes of the cryoablation protocol were compared, with consecutive patients undergoing PVI by RFA. 77% of paroxysmal and 48% of persistent AF subjects were free from AF at 12 months after a single cryoablation procedure. Over the same time period, 53 consecutive paroxysmal AF subjects underwent PVI with RFA and at 12 months, 72% were free from AF at 12 months (p=NS). There were too few persistent AF subjects (n=8) undergoing solely PVI by RFA as a comparison group. Transient phrenic nerve palsy was reported in two patients in the cryoablation group which resolved within 3 and 14 months (phrenic nerve palsy taking 14 months to resolve was caused by unmonitored cryoablation of the right lower PV). No cases reported in the RFA group. Pericardial effusion was reported in one patient in the cryoballoon group and in two patients in the RFA group. Procedural and fluoroscopic times during cryoablation were significantly shorter than RFA. Reported limitations of this study are lack of randomization of study groups, only 24 h Holter monitoring was performed to detect

asymptomatic AF and more episodes may have been detected if longer recording durations were used and limiting the total number of cryoballoon applications allowed for a shorter procedural time but did increase procedural cost, as 60% of the cryoablation cohort required a second catheter to ensure achievement of PV isolation.

In a case control study, Kuhne et al. (2010) compared pulmonary vein ablation in patients with paroxysmal AF using the Arctic Front® 28 mm cryoballoon (n=25) to traditional radiofrequency ablation (RFA) (n=20) with regard to the characteristics of myocardial injury, patterns of PV reconnection, and clinical outcomes. Myocardial injury was determined by measuring troponin T (TnT). PV reconnection patterns were studied in case of repeat procedures. Procedure duration was 166 ± 32 minutes in the cryoballoon group versus 197 ± 52 minutes in the RF group, with similar ablation times (cryoballoon: 45 minutes; RF: 47 minutes). Postprocedural TnT in the RF group was 1.29 ± 0.41 µg/L versus 0.76 ± 0.55 µg/L in the cryoballoon group. In 12 patients who underwent repeat ablation, 74% of PV reconnection sites were inferiorly located in the cryoballoon group compared to 17% in the RF group. With 1.2 ± 0.4 and 1.3 ± 0.6 procedures per patient, 88% of patients in the cryoballoon group and 92% in the RF group were in stable sinus rhythm after follow-up of 12 ± 3 months (p=ns). No periprocedural complications occurred. The authors reported that randomized comparisons between the two techniques are required.

A small case control study conducted by Linhart et al. (2009) compared pulmonary vein ablation with the Arctic Front® cryoballoon (n=20) to traditional radiofrequency ablation (RFA) (n=20). At six months, the overall success rate in the cryoballoon group was 55% (50% in the cryoballoon only group and 66% in the combination group (cryoballoon plus cryocatheter) compared to 45% in the RFA group. Three phrenic nerve palsies occurred in the cryoballoon group; all resolved spontaneously. The authors concluded that pulmonary vein ablation with the cryoballoon technique is feasible and seems to have similar success rates compared to RFA, but acknowledged study shortcomings, including small numbers of patients and relatively short follow-up, and stated that study data should be confirmed in a larger randomized trial.

Tang et al. 2010 conducted a small case series (n=23) to evaluate the feasibility and efficacy of a simplified cryoablation technique in which a microcircular catheter was introduced into a cryoballoon catheter to record PV potentials during ablation without interchanging catheters. A total of 84 pulmonary veins (84 of 92; 91.3%) were completely isolated. At a follow-up ranging from 2–18 months, 17 (73.9%) patients were free from AF. There was one instance of phrenic nerve palsy, which resolved at one month. The authors concluded that this novel technique is feasible and effective, but noted that larger and randomized studies are needed to fully compare procedure times, effectiveness, and safety between this new cryoballoon technique and conventional approaches.

Systematic Reviews

Cryoablation: Andrade et al. (2011) conducted a systematic review of 23 studies (n=1221) to define the safety and efficacy of cryoballoon ablation for paroxysmal and persistent AF. The review included twenty studies reporting cryoballoon ablation for paroxysmal AF, one reporting cryoballoon ablation for persistent AF, and two reporting cryoballoon ablation for both paroxysmal and persistent AF. A majority of the studies were case series. There was variation in study methodologies, patient characteristics, procedural characteristics, presence and composition of comparator groups and duration of follow-up. Complete isolation of all targeted pulmonary veins was achieved in 98.8% of patients. Complete pulmonary vein isolation was achieved in 98.5% of patients. One-year freedom from recurrent AF; Patients with paroxysmal AF after 3- month blanking period (time frame during which transient episodes of arrhythmia were not considered recurrences) 72.8%; patients with paroxysmal AF without a 3-month blanking period: 60.3%; patients with persistent AF after 3 month blanking period: 45.2%.The most common complication was phrenic nerve palsy (PNP), with an overall incidence of 6.38% (86/1349 procedures). The incidence of PNP persisting after the ablation procedure was 4.73% (67/1,349). Delayed recovery was the predominant outcome, with only 0.37% (5/1,349) experiencing PNP that persisted beyond one year. The authors concluded that, “this systematic review reveals that a single cryoballoon ablation procedure for paroxysmal AF results in high acute and medium-term efficacy rates, with lower success rates when used as stand-alone therapy for persistent AF. Further studies, including direct comparison to conventional RF ablation, are ongoing and will provide important insight into long-term efficacy and safety.”

Systematic Reviews

An ECRI Evidence Report evaluated pulmonary vein isolation (PVI) for atrial fibrillation (AF), based on a systematic review of 17 studies; ten controlled trials comparing interventions, and seven large case series of

PVI reporting complications. This report did not evaluate energy sources used to treat AF. The report concluded that, for the restoration of a normal heart rhythm, the evidence is sufficient to conclude that PVI is more likely to achieve this result than medications. In addition, PVI generally results in fewer hospital stays than medications alone. The authors stated that these outcomes are likely related, since hospitalization may occur because of a potentially dangerous recurrence of AF. The report also states that the possible benefits of PVI must be balanced against the possible harms. Serious rare events, including PVS, and cardiac tamponade, may occur, although the rates of these events are generally low (e.g., 1%). Antiarrhythmic medications also have adverse effects, and it is not clear whether PVI or medications have the less harmful profile, or whether the potential benefits of PVI outweigh any potential risks (ECRI, 2008).

A meta-analysis/systematic review conducted by Noheria et al. (2008) to assess whether circumferential pulmonary vein ablation is superior to antiarrhythmic drug therapy (ADT) in the treatment of AF. This report did not evaluate energy sources used to treat AF. The meta-analysis included the randomized trials by Pappone, Stabile, and Wazni, discussed above, and a trial conducted by Krittayaphong (2003). Of 214 patients in the pulmonary veins isolation group, 162 (75.7%) had atrial tachyarrhythmia recurrence-free survival at 12 months, compared to 41 of 218 patients (18.8%) in the ADT group. In addition, fewer adverse events were reported in the ablation group compared to the ADT group. Because of the limited number of studies evaluated, the authors cautioned that these conclusions must be taken as confirmation of the need for further trials and not as a guide for clinical practice.

Professional Societies/Organizations
American College of Cardiology Foundation (ACCF), American Heart Association (AHA), and Heart Rhythm Society (HRS):A focused update on the Management of Patients with Atrial Fibrillation was published by the ACCF, AHA, and HRS in 2011, and incorporated into the 2006 ACC/AHA/European Society of Cardiology (ESC) guidelines for management of patients with atrial fibrillation (AF) (Fuster et al., 2011). The authors noted that despite advances in catheter-based therapy for AF, the long-term efficacy of catheter ablation to prevent recurrent AF requires further study. Based on the available data, most carefully selected patients maintain freedom form recurrent AF for one year or more. AF may recur without symptoms and be unrecognized, however, and the risk of recurrence is uncertain. This has important implications for the duration of anticoagulation therapy in those with risk factors for stroke. In addition, little information is known about the late success of ablation in patients with heart failure and other advanced structural heart disease. Complications of PV isolation noted in the ACC/AHA/ESC guideline included pulmonary vein stenosis, thromboembolism, atrioesophageal fistula and left atrial flutter, in addition to potential complications inherent in any cardiac catheterization procedure.

Recommendations for maintenance of sinus rhythm relevant to transcatheter ablation include the following:

Class I, Level of Evidence: A
Catheter ablation performed in experienced centers is useful in maintaining sinus rhythm in selected patients with significantly symptomatic, paroxysmal AF who have failed treatment with an antiarrhythmic drug and have normal or mildly dilated left atria, normal or mildly reduced LV function, and no severe pulmonary disease.

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. This recommendation was modified from the 2006 guideline; the class of recommendation was changed from IIa to I, wording was revised, and the level of evidence was changed from C to A.

Class IIa, Level of Evidence A
Catheter ablation is reasonable to treat symptomatic persistent AF.

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. This is a new recommendation.

Class IIb, Level of Evidence A

Catheter ablation may be reasonable to treat symptomatic paroxysmal AF in patients with significant left atrial dilatation or with significant LV dysfunction.

A class IIb, level of evidence A recommendation indicates that the treatment/procedure may be considered. The benefit is equal to or greater than the risk. Additional studies with broad objectives are needed, and additional registry data would be helpful. The usefulness/efficacy are less well established, and greater conflicting evidence from multiple randomized trials or meta analyses exists. This is a new recommendation.

Use Outside of the US

Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA)/European Cardiac Arrhythmia Society (ECAS): 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 indications for catheter ablation of AF:

Symptomatic AF refractory or intolerant to at least one Class 1 or 3 antiarrhythmic medication:

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

Symptomatic AF prior to initiation of antiarrhythmic drug therapy with a Class 1 or 3 antiarrhythmic agent:

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

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

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 A if the data were derived from multiple randomized clinical trials or meta-analyses (of selected studies) or selected meta-analyses.
Level B when data were derived from a single randomized trial or nonrandomized studies.
Level C when the primary source of the recommendation was consensus opinion, case studies, or standard of care. For certain conditions for which inadequate data are available, recommendations are based on expert consensus and clinical experience and ranked as Level C.

In the section on technologies and tools the authors state that they provide an update on examples of the large number of technologies and tools that are employed for AF ablation. The authors state that it is important to recognize that RF energy is by far the dominant energy source that has been used for catheter ablation of AF. Cryoablation has more recently been developed as a tool for AF ablation procedures. Other energy sources and tools are in various stages of development and/or clinical investigation (Calkins, et al., 2012).

European Society of Cardiology (ESC): The 2012 focused update of the 2010 ESC Guidelines for the management of atrial fibrillation (AF) states that considering the results of randomized studies on catheter ablation of AF versus antiarrhythmic drug therapy and recent publications from randomized and non-randomized trials (Cosedis, et al., 2012; Boersma,et al., 2012; Pappone, et al., 2011; Tanner, et al., 2011), it is reasonable to upgrade this recommendation to class I, provided that the ablation is carried out by skilled operators. This is in line with the 2011 focused update from the ACCF/AHA and HRS, and the 2012 expert consensus statement on catheter and surgical ablation, co-authored by the EHRA. For patients with highly symptomatic paroxysmal AF with a low-risk profile for catheter ablation, primary catheter ablation should be considered. These recommendations are restricted to: (i) highly experienced centres/investigators; (ii) appropriate patient selection; (iii) careful evaluation of treatment alternatives and (iv) patient preference. For patients with drug-refractory

persistent and long-standing persistent AF, there is no change in recommendations. Currently there is no evidence to recommend catheter ablation of AF in asymptomatic patients (Camm, et al., 2012).

Canadian Cardiovascular Society (CCS): The CCS Atrial Fibrillation Guidelines 2010: Catheter Ablation for Atrial Fibrillation/Atrial Flutter states:

- Recommend catheter ablation of AF in patients who remain symptomatic following adequate trials of anti-arrhythmic drug therapy and in whom a rhythm control strategy remains desired (Strong Recommendation, Moderate-Quality Evidence).
- Suggest catheter ablation to maintain sinus rhythm in select patients with symptomatic atrial fibrillation and mild-moderate structural heart disease who are refractory or intolerant to ≥1 antiarrhythmic medication (Conditional Recommendation, Moderate-Quality Evidence).
- Suggest catheter ablation to maintain sinus rhythm as first-line therapy for relief of symptoms in highly selected patients with symptomatic, paroxysmal atrial fibrillation (Conditional Recommendation, Low-Quality Evidence).

The authors state that ablation is most commonly performed with radiofrequency energy delivered from a catheter tip. Technologies are evolving, however, to use different catheter designs and energy sources to maximize energy delivery while minimizing the risks, such as perforation (Velma, et al., 2011).

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

NICE Interventional Procedures Guidance issued in 2006 states that current evidence on the safety and efficacy of percutaneous radiofrequency ablation for atrial fibrillation (AF) appears adequate to support the use of this procedure in appropriately selected patients, provided that normal arrangements are in place for audit and clinical governance. The guidance document further states that the procedure is a treatment option for symptomatic patients with AF refractory to antiarrhythmic drug therapy, or where medical therapy is contraindicated because of comorbidity or intolerance.

Summary

A high percentage of individuals with paroxysmal atrial fibrillation (AF) have excitatory foci in the superior aspect of the left atrium, in close proximity to the pulmonary veins. Transcatheter radiofrequency ablation of arrhythmogenic foci in the pulmonary veins, also referred to as pulmonary vein isolation (PVI), interrupts conduction of the abnormal excitatory foci from the pulmonary veins to other areas of the atria. This treatment may be a reasonable treatment option for individuals with symptomatic persistent AF, and may also be considered as an alternative to long term antiarrhythmic drug therapy in carefully selected individuals with symptomatic paroxysmal AF. AF may recur without symptoms and be unrecognized, however, and the risk of recurrence is uncertain. This has important implications for the duration of anticoagulation therapy in those with risk factors for stroke. In addition, little information is known about the late success of ablation in patients with heart failure and other advanced structural heart disease. Treatment of AF should therefore be individualized, taking into account the frequency and severity of symptoms, length of duration of atrial fibrillation, left atrial size,

comorbidities, response to prior cardioversions, age, side effects and efficacy of antiarrhythmic drugs, and patient preference.

Transcatheter cryoablation/cryoballoon ablation of the pulmonary veins has been explored as an alternative to radiofrequency ablation. Cryothermy causes tissue ablation when intracellular ice crystals disrupt cell membranes, leaving collagen structure intact. Additional methods of ablation have also been proposed, including a laser balloon catheter, a high-intensity focused ultrasound balloon catheter, and a high-density mesh ablator catheter. 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 radiofrequency ablation.

Coding/Billing Information

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

Covered when medically necessary when used to report transcatheter radiofrequency ablation of the pulmonary veins for the treatment of 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 with atrial recording and pacing, when possible, right ventricular pacing and recording, His bundle recording with intracardiac catheter ablation of arrhythmogenic focus, with treatment of atrial fibrillation by ablation 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)
93799	Unlisted cardiovascular service or procedure

Experimental, investigational or unproven when used to report any other method of transcatheter ablation of the pulmonary veins, including but not limited to cryoablation/cryoballoon ablation.

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 with atrial recording and pacing, when possible, right ventricular pacing and recording, His bundle recording with intracardiac catheter ablation of arrhythmogenic focus, with treatment of atrial fibrillation by ablation 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)
93799	Unlisted cardiovascular service or procedure

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