Catheter Ablation as Treatment for Atrial Fibrillation

Policy # 00267
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Percutaneous Left-Atrial Appendage Closure Devices for Stroke Prevention in Atrial Fibrillation is addressed separately in medical policy 00296.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:
- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of transcatheter radiofrequency ablation (RFA) or cryoablation to treat atrial fibrillation (AF) for certain indications to be **eligible for coverage.**

Patient Selection Criteria
The use of transcatheter RFA or cryoablation as a treatment for AF may be eligible for coverage for the following indications which have failed to respond to adequate trials of antiarrhythmic medications:
- Symptomatic paroxysmal or symptomatic persistent AF; or
- As an alternative to atrioventricular (AV) nodal ablation and pacemaker insertion in patients with class II or III congestive heart failure and symptomatic AF.

Based on review of available data, the Company may consider transcatheter RFA or cryoablation to treat AF to be **eligible for coverage** as an initial treatment for patients with recurrent symptomatic paroxysmal AF in whom a rhythm-control strategy is desired.

Based on review of available data, the Company may consider repeat RFA or cryoablation in patients with recurrence of AF and/or development of atrial flutter following the initial procedure may be considered **eligible for coverage.** (See Policy Guidelines)

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of transcatheter RFA or cryoablation as a treatment for cases of AF that do not meet the criteria outlined above, to be **investigational.***

Policy Guidelines
Transcatheter treatment of AF may include pulmonary vein isolation and/or focal ablation.

There is no single procedure for catheter ablation. Electrical isolation of the pulmonary vein musculature (pulmonary vein isolation) is the cornerstone of most AF ablation procedures, but additional ablation sites may be included during the initial ablation. Potential additional ablation procedures include: creation of linear lesions within the left atrium; ablation of focal triggers outside the pulmonary veins; ablation of areas with complex fractionated atrial electrograms; and ablation of left atrial ganglionated plexi. The specific ablation sites may be determined by electroanatomic mapping to identify additional sites of excitation. As a result, sites may vary from patient to patient, even if they are treated by the same physician. Patients with long-standing persistent AF may need more extensive ablation. Similarly, repeat ablation procedures for recurrent AF generally involve more extensive ablation than do initial procedures.

As many as 30% of patients will require a follow-up (repeat) procedure, due to recurrence of AF or to development of atrial flutter. In most published studies, success rates have been based on having as many as 3 separate procedures, although these repeat procedures may be more limited in scope than the initial procedure.

Background/Overview

ATRIAL FIBRILLATION

AF is the most common cardiac arrhythmia, with an estimated prevalence of 0.4% of the population, increasing with age. The underlying mechanism of AF involves the interplay between electrical triggering events and the myocardial substrate that permits propagation and maintenance of the aberrant electrical circuit. The most common focal trigger of AF appears to be located within the cardiac muscle that extends into the pulmonary veins.

AF accounts for approximately one-third of hospitalizations for cardiac rhythm disturbances. Symptoms of AF (e.g., palpitations, decreased exercise tolerance, dyspnea) are primarily related to poorly controlled or irregular heart rate. The loss of AV synchrony results in a decreased cardiac output, which can be significant in patients with compromised cardiac function. Also, patients with AF are at higher risk for stroke, with anticoagulation is typically recommended. AF is also associated with other cardiac conditions, such as valvular heart disease, heart failure, hypertension, and diabetes. Although episodes of AF can be converted to normal sinus rhythm using pharmacologic or electroshock conversion, the natural history of AF is that of recurrence, thought to be related to fibrillation-induced anatomic and electrical remodeling of the atria.

AF can be subdivided into 3 types:

- paroxysmal (episodes that last <7 days and are self-terminating),
- persistent (episodes that last for >7 days and can be terminated pharmacologically or by electrical cardioversion), or
- permanent.

Treatment Strategies
Treatment strategies can be broadly subdivided into rate control, in which only the ventricular rate is controlled, and the atria are allowed to fibrillate, or rhythm control, in which there is an attempt to reestablish and maintain normal sinus rhythm. Rhythm control has long been considered an important treatment goal for management of AF, although its primacy has recently been challenged by the results of several randomized trials reporting that pharmacologically maintained rhythm control offered no improvement in mortality or cardiovascular morbidity compared with rate control.

Currently, the main indications for a rhythm-control strategy are for patients with paroxysmal or persistent AF who have hemodynamic compromise associated with episodes of AF or who have bothersome symptoms, despite adequate rate control. A rhythm-control strategy involves initial pharmacologic or electronic cardioversion, followed by pharmacologic treatment to maintain normal sinus rhythm. However, antiarrhythmic medications are often not effective in maintaining sinus rhythm. As a result, episodes of recurrent AF are typical, and patients with persistent AF may require multiple episodes of cardioversion. Implantable atrial defibrillators, which are designed to detect and terminate an episode of AF, are an alternative in patients otherwise requiring serial cardioversions, but they have not yet achieved widespread use. Patients with paroxysmal AF, by definition, do not require cardioversion but may be treated pharmacologically to prevent further arrhythmic episodes.

Treatment of permanent AF focuses on rate control, using either pharmacologic therapy or ablation of the AV node, followed by ventricular pacing. Although AV nodal ablation produces symptomatic improvement, it entails lifelong anticoagulation (due to ongoing fibrillation of the atria), loss of AV synchrony, and lifelong pacemaker dependency. Implantable defibrillators are contraindicated in patients with permanent AF.

The treatment options above are not curative. A variety of ablative procedures have been investigated as potentially curative approaches, or modifying the arrhythmia so that drug therapy becomes more effective. Ablative approaches focus on interruption of the electrical pathways that contribute to AF through modifying the arrhythmia triggers and/or the myocardial substrate that maintains the aberrant rhythm. The maze procedure, an open surgical procedure often combined with other cardiac surgeries (e.g., valve repair), is an ablative treatment that involves sequential atriotomy incisions designed to create electrical barriers that prevent the maintenance of AF. Because of the highly invasive nature of this procedure, it is currently mainly reserved for patients undergoing open heart surgery for other reasons (e.g., valve repair, coronary artery bypass grafting).

Catheter Ablation for AF
RFA using a percutaneous catheter-based approach is widely used to treat a variety of supraventricular arrhythmias, in which intracardiac mapping identifies a discrete arrhythmogenic focus that is the target of ablation. The situation is more complex for AF because there is no single arrhythmogenic focus. Since the inception of ablation techniques in the early 1990s, there has been a progressive understanding of the underlying electrical pathways in the heart associated with AF. In the late 1990s, it was recognized that AF most frequently arises from an abnormal focus at or near the junction of the pulmonary veins and the left atrium, thus leading to the feasibility of more focused, percutaneous ablation techniques. Strategies that

have emerged for focal ablation within the pulmonary veins originally involved segmental ostial ablation guided by pulmonary vein potential (electrical approach) but currently more typically involve circumferential pulmonary vein ablation (anatomic approach).

The individual lesion set (in addition to the pulmonary vein isolation) and the degree to which the pulmonary vein antrum is electrically isolated vary. Research into specific ablation and pulmonary vein isolation techniques is ongoing. Evidence from a randomized controlled trial (RCT) comparing pulmonary vein isolation alone with pulmonary vein isolation plus ablation to treat patients who had electrograms showing complex fractionated activity, and to pulmonary vein isolation plus additional linear ablation across the left atrial roof and mitral valve isthmus, has suggested that the more extensive lesion sets do not reduce the AF recurrence rate. Meta-analyses have found that the addition of complex fractionated atrial electrogram ablation to pulmonary vein isolation alone has not improved rates of freedom from recurrent AF, although the RCT by Theis et al (2015) reported that patients with ablation of dormant conduction sources outside the pulmonary veins had fewer arrhythmia recurrences than those treated with pulmonary vein isolation alone.

Circumferential pulmonary vein ablation using radiofrequency energy is the most common approach at present. The procedure also can be done using cryoablation technology. Use of current radiofrequency catheters for AF has a steep learning curve because they require extensive guiding to multiple ablation points. One of the potential advantages of cryoablation is that cryoablation catheters have a circular or shaped end point, permitting a “one-shot” ablation. Other types of radiofrequency catheters, which incorporate circular or otherwise shaped end points, may also be used.

Repeat Procedures
Repeat procedures following initial RFA are commonly performed if AF recurs or if atrial flutter develops postprocedure. The need for repeat procedures may, in part, depend on the clinical characteristics of the patient (e.g., age, persistent vs paroxysmal AF, atrial dilatation), and the type of ablation initially performed. Repeat procedures are generally more limited in scope than the initial procedure. For example, in cases where electrical reconnections occur as a result of incomplete ablation lines, a ”touch up” procedure is done to correct gaps in the original ablation. In other cases when atrial flutter has developed after ablation, a "flutter ablation” is performed, which is more limited than the original AF procedure. A number of clinical and demographic factors are associated with the need for a second procedure, including age, length of AF, permanent AF, left atrial size, and left ventricular ejection fraction (LEVF).

Outcome Assessment in AF
Various outcomes for the treatment of AF may be considered. The mortality and morbidity related to AF (e.g., cardiovascular mortality, stroke, heart failure) are the most important clinical outcomes. However, they are uncommon events, and currently available trials have not been powered to detect differences in these outcomes. Quality of life (QOL) is also an important outcome because QOL measures reflect important manifestations of AF, such as symptoms and reduced exercise tolerance. AF has been shown to be associated with lower QOL scores, and maintenance of sinus rhythm has been associated with higher QOL scores for patients with paroxysmal AF.

Recurrence of AF is a more problematic outcome measure because the intermittent and often transient nature of recurrences makes accurate measurement difficult. This outcome measure has been reported in different ways. For example, the proportion of patients in sinus rhythm at the end of the study, the time to the first recurrence, and the number of recurrences within a period have been reported. Shemin et al (2007) highlighted the difficulties in measuring AF recurrence and recommended a measure of AF "burden," defined as the percentage of time an individual is in AF, as the optimal measure of treatment efficacy. However, this parameter requires continuous monitoring over a relatively long period, which is inconvenient for patients, resource intensive, and usually not pragmatic in patients who do not already have an implanted pacemaker.

Recommendations for outcome assessment in trials of AF treatment were included in the 2006 American College of Cardiology, American Heart Association, and European Society of Cardiology practice guidelines for the treatment of AF. These guidelines pointed out that the appropriate end points for evaluation of treatment efficacy in patients with paroxysmal or persistent AF have little in common. For example, in studies of persistent AF, the proportion of patients in sinus rhythm at the end of follow-up is a useful end point, but this end point is less useful in studies of paroxysmal AF. Given all these variables, ideally, controlled clinical trials would report a range of outcomes (including QOL) and complications in homogeneous patient groups and compare them with the most relevant treatment alternatives (e.g., pharmacologic therapy, defibrillator therapy, AV nodal ablation), depending on the classification of AF (paroxysmal, persistent, permanent).

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

In February 2009, the NaviStar®‡ ThermoCool®‡ Irrigated Deflectable Diagnostic/Ablation Catheter and EZ Steer ThermoCool NAV Catheter (Biosense Webster) received expanded approval by the U.S. FDA through the premarket approval process for RFA to treat drug-refractory recurrent symptomatic paroxysmal AF. FDA product code: OAD.

Devices using laser or cryoablation techniques for substrate ablation have been approved by FDA through the premarket approval process for AF (FDA product code: OAE). They include:

- Arctic Front™‡ Cardiac CryoAblation Catheter and CryoConsole (Medtronic) in 2010.
- TactiCath™‡ Quartz Catheter and TactiSysQuartz®‡ Equipment (St. Jude Medical) in 2014.
- HeartLight®‡ Endoscopic Ablation System (Cardiofocus) in 2016.
- The Freezor™‡ Xtra Catheter (Medtronic) in 2016.

Also, numerous catheter ablation systems have been approved by FDA for other ablation therapy for arrhythmias such as supraventricular tachycardia, atrial flutter, and ventricular tachycardia. FDA product code: LPB.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The RCT is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

In patients with paroxysmal or persistent AF, catheter ablation may be considered an alternative to drug therapy. In patients with permanent AF, catheter ablation may be considered an alternative to drug therapy or AV nodal ablation and pacing. For all types of AF, it is possible that catheter ablation may not be curative as a sole treatment but might alter the underlying myocardial triggers or substrate in such a way that subsequent pharmacologic therapy may become more effective.

There is an ongoing controversy about the relative benefits of rhythm vs rate control in AF, which underlies the evaluation of evidence on catheter ablation. Randomized trials of pharmacologic therapies have not demonstrated the superiority of rhythm control vs rate control. However, the apparent equivalency of these 2 strategies with pharmacologic therapy cannot be extrapolated to the rhythm control achieved with ablation. Antiarrhythmic medications used for rhythm control are only partially effective and have serious complications, including proarrhythmic properties, which can be lethal. Therefore, nonpharmacologic strategies for rhythm control have the potential to achieve outcomes superior to those seen with pharmacologic strategies.

Evidence on ablation procedures for AF was reviewed, with a focus on RCTs reporting on the AF-related outcomes of interest (see below). Also, nonrandomized studies and noncomparative studies reporting on longer term outcomes were included to evaluate for durability.

RADIOFREQUENCY ABLATION FOR AF

Radiofrequency Ablation for Symptomatic Paroxysmal or Persistent AF

Systematic Reviews

The literature review for this evidence review was informed by a TEC Assessment (2008). Six RCTs met Assessment inclusion criteria. The trials differed in patient populations, specific catheter ablation techniques used, and comparisons made. The trials addressed 3 distinct indications for catheter ablation: (1) patients with paroxysmal AF, as a first-line treatment option (1 trial); (2) patients with symptomatic paroxysmal or persistent AF who had failed treatment with antiarrhythmic drugs (4 trials); and (3) patients with symptomatic AF and heart failure who had failed treatment with standard medications for rate control and who would otherwise be considered for AV nodal ablation and pacemaker insertion (1 trial).

All 6 trials reported that maintenance of sinus rhythm was improved for the catheter ablation group. Recurrence rates of AF at 1 year ranged from 11% to 44% for the catheter ablation groups compared with 63% to 96% for the medication groups. Four of the 6 trials reported on QOL outcomes. One of these only reported within-group comparisons, as opposed to between-group comparisons. The other 3 trials reported improvements in QOL associated with catheter ablation. None of the available trials reported meaningful data on cardiovascular morbidity and mortality associated with AF. The Assessment concluded that catheter RFA is more effective than medications in maintaining sinus rhythm across a wide spectrum of patients with AF and different variations of catheter ablation. The evidence on QOL is suggestive, but not definitive, of a benefit for patients undergoing catheter ablation. For other outcomes, the evidence did not permit conclusions. Based on these findings, Technology Evaluation Centers (TEC) criteria were met for 2 indications: patients with symptomatic paroxysmal or persistent AF who have failed treatment with antiarrhythmic drugs and patients with symptomatic AF and heart failure who have failed treatment with standard medications for rate control and who would otherwise be considered for AV nodal ablation and pacemaker insertion. For the first indication, the conclusion followed from the premise that reducing episodes of recurrent AF for this population will reduce or eliminate the symptoms associated with episodes of AF. For the other indication, the single multicenter RCT available was judged sufficient to conclude that catheter ablation improved outcomes compared with the alternative, AV nodal ablation and pacemaker insertion. While this trial was relatively small, it was judged to be otherwise of high quality and reported improvements of a relatively large magnitude across a range of clinically important outcome measures, including QOL, exercise tolerance, LVEF, and maintenance of sinus rhythm.

Since the publication of the TEC Assessment, additional systematic reviews and meta-analyses of catheter ablation for AF have been reported.

Nyong et al (2016) reported on a Cochrane review of ablation for individuals with nonparoxysmal AF, which included RCTs comparing radiofrequency catheter or surgical ablation with antiarrhythmic drugs for persistent or long-standing persistent AF. Reviewers selected 3 RCTs (total N=261 subjects; Forleo et al [2009], Stabile et al [2006], and Mont et al [2014] not discussed in detail herein), all comparing catheter

RFA (n=159) to antiarrhythmic drugs (n=102) at 12 months. The trials were assessed to have a low or unclear risk of bias. Reviewers' primary outcomes are summarized in Table 1.

Table 1. Efficacy of Catheter Ablation for Nonparoxysmal Atrial Fibrillation

Outcome (Catheter vs Drug Therapy)	No. of Participants (Studies)	Evidence Quality[a]	RR	95% CI
Freedom from atrial arrhythmias or recurrence of any atrial arrhythmias	261 (3 studies)	Low	1.84	1.17 to 2.88
Need for cardioversion	261 (3 studies)	Moderate	0.62	0.47 to 0.82
Cardiac hospitalization	216 (2 studies)	Low	0.28	0.1 to 0.72

Adapted from Nyong et al (2016).
CI: confidence interval; RR: relative risk.
[a] Assessed using the GRADE assessment tool.

Overall, reviewers concluded that catheter RFA was superior to antiarrhythmic drugs for patients who had not responded to antiarrhythmic drug therapy, but there was uncertainty related to their findings.

Vaidya et al (2015) reported on results of a systematic review and meta-analysis of RCTs comparing pulmonary vein isolation, pharmacologic rate control, and AV junction ablation plus pacemaker insertion for AF. Subgroup analyses focused on patients with congestive heart failure. Reviewers identified 7 RCTs, 2 comparing AV junction ablation plus pacemaker insertion with pharmacologic rate control, 1 comparing AV junction ablation plus pacemaker insertion with pharmacologic rate control and pacemaker insertion, 1 comparing pulmonary vein isolation with AV junction ablation plus biventricular pacing, and 3 comparing pulmonary vein isolation with pharmacologic rate control. Sample sizes ranged from 36 to 99 patients, with 425 patients across the 7 studies. When pulmonary vein isolation was compared with pharmacologic rate control, based on 3 RCTs, pulmonary vein isolation–treated patients had higher increases in LVEF (weighted mean difference [WMD], +6.5; 95% confidence interval [CI], 0.6 to 12.5; p=0.03). When pulmonary vein isolation was compared with AV junction ablation plus pacemaker insertion, based on 1 RCT, pulmonary vein isolation–treated patients had higher increases in LVEF (WMD = +9.0; 95% CI, 6.3 to 11.7; p<0.01). Patients treated with pulmonary vein isolation had greater reductions in heart failure symptoms, measured by the Minnesota Living with Heart Failure Questionnaire compared with pharmacologic rate control, in 3 RCTs that included only patients with congestive heart failure (WMD = -11.0; 95% CI, -19.4 to -2.6; p=0.01). Minnesota Living with Heart Failure Questionnaire scores also improved when pulmonary vein isolation was compared with AV junction ablation plus pacemaker insertion.

Shi et al (2015) reported on the results of a meta-analysis of RCTs comparing catheter ablation with antiarrhythmic drug therapy for AF. The meta-analysis included 11 trials (total N=1763 patients), of which 4 included only patients with paroxysmal AF, 2 included only patients with persistent AF, and 5 included patients with paroxysmal or persistent AF. Eight RCTs included only patients who were drug-refractory or drug-intolerant, and the remaining three included patients treated with catheter ablation as first-line therapy. Catheter ablation–treated patients had lower rates of AF recurrence than antiarrhythmic drug therapy–treated patients (relative risk [RR], 0.47; 95% CI, 0.38 to 0.58; p<0.001; I^2=62%, p=0.003).

A Cochrane review by Chen et al (2012) evaluated catheter ablation for paroxysmal and persistent AF. It included 7 RCTs comparing catheter ablation with medical therapy. Reviewers' main conclusions were that catheter ablation was superior at reducing the recurrence of AF (RR=0.27; 95% CI, 0.18 to 0.41), but that there were no differences in mortality rates (RR=0.50; 95% CI, 0.04 to 5.65), embolic complications (RR=1.01; 95% CI, 0.18 to 5.68), or death from thromboembolism (RR=3.04; 95% CI, 0.13 to 73.4).

Ganesan et al (2013) published results of a systematic review and meta-analysis of studies reporting long-term outcomes after percutaneous catheter ablation for paroxysmal and nonparoxysmal AF. Reviewers included 19 studies (RCTs, case-control and cohort studies, case series) that reported catheter ablation outcomes at 3 years or more after the index ablation procedures. Sample sizes in these studies ranged from 39 to 1404 patients (total N=6167 patients). For a single procedure, the pooled overall success rate at 12 months postprocedure was 64.2% (95% CI, 57.5% to 70.3%). At late follow-up, the overall single-procedure success, defined as freedom from atrial arrhythmia at latest follow-up, was 53.1% (95% CI, 46.2% to 60.0%). The pooled overall multiple-procedure long-term success rate was 79.8% (95% CI, 75.0% to 83.8%). The analysis did not identify any predictors of short- or long-term recurrence. Reporting of periprocedural complications was heterogeneous across studies, but complication rates were generally low.

Earlier systematic reviews and meta-analyses (2008, 2009) comparing RFA with antiarrhythmic drug therapy for AF have reported improved rates of freedom from arrhythmias with catheter ablation.

Other systematic reviews have assessed the effect of RFA on specific AF-related outcomes. Zhuang et al (2014) conducted a meta-analysis that evaluated the effect of RFA on left atrial volume and function in patients with AF. In a summary of data from 26 studies enrolling 1821 patients, RFA was associated in improvements in left atrial volume measurements compared with preablation (e.g., for left atrial diameter); the WMD was -1.52 mm (95% CI, -2.57 to -0.47 mm). There were no significant improvements in left atrial function.

Randomized Controlled Trials

Since the TEC Assessment, additional RCTs comparing RFA with pharmacologic treatment have been identified. Wilber et al (2010) enrolled 167 patients who had failed at least 1 antiarrhythmic medication and had at least 3 AF episodes in the prior 6 months. Patients were randomized to catheter ablation or continued drug therapy and followed for 9 months. At the end of follow-up, 66% of patients in the ablation group were free of recurrent AF compared with 16% of patients in the medication group. Adverse events related to treatment occurred in 4.9% (5/103) of patients treated with ablation and in 8.8% (5/57) of patients treated with medications.

Forleo et al (2009) randomized 70 patients with type 2 diabetes and paroxysmal or persistent AF to RFA or an antiarrhythmic medication. Follow-up was for 1 year, with the primary outcome of recurrence of AF. At the end of the trial, 42.9% (15/35) of patients in the medication group were free of AF compared with 80% (28/35) of patients in the ablation group. QOL also improved significantly for patients in the ablation group. Adverse events from medications occurred more frequently (17.2% [6/35]) than complications from ablation (2.9% [1/35]).

Mont et al (2014) conducted an RCT comparing catheter RFA with antiarrhythmic drug therapy among 146 patients with symptomatic persistent AF. Patients were randomized in a 2:1 fashion to catheter RFA (n=98) or antiarrhythmic drug therapy (n=48). Although the trial was terminated before the planned sample size of 208 was enrolled (due to low enrollment), at 12 months of follow-up, the proportion of patients who were free of sustained AF episodes was higher in the catheter ablation group (70.4%) than in the antiarrhythmic drug therapy group (43.7%; p=0.002). QOL scores did not differ significantly between groups. Longer term outcomes were not reported.

Marrouche et al (2018) conducted an RCT comparing catheter ablation with medical therapy in 363 patients with systematic paroxysmal or persistent AF who had no response to, were unwilling to take, or had unacceptable side effects to antiarrhythmic drugs. Patients were randomized to catheter ablation (n=179) or medical therapy (n=184), with a median follow-up of 38 months. For patients treated with catheter ablation, there was a significantly lower rate of death from cardiac causes (20 [11.2%] vs 41 [22.3%]; hazard ratio [HR], 0.49; 95% CI, 0.29 to 0.84; p=0.009) or hospitalization for worsening heart failure (37 [20.7%] vs 66 [35.9%]; HR=0.56; 95% CI, 0.37 to 0.83; p=0.004) than found in patients treated with medical therapy alone.

RFA as First-Line Therapy for AF

Since the 2008 TEC Assessment, which found the evidence insufficient to support the use of catheter ablation as first-line therapy for individuals with paroxysmal AF, the evidence has continued to evolve.

Systematic Reviews

Hakalathi et al (2015) reported on a systematic review and meta-analysis of RCTs comparing RFA with antiarrhythmic drug therapy as first-line therapy for symptomatic AF. They selected 3 trials (total N=491 patients), including the RAAFT-2 (2014) and MANTRA-PAF (2012) trials (described below) and the earlier RAAFT-1 trial. RAAFT-2 and MANTRA-PAF were considered to be at low risk of bias. RFA was associated with lower risk of recurrence of AF (RR=0.63; 95% CI, 0.44 to 0.92; p=0.02; I^2=38%).

Randomized Controlled Trials

RAAFT-2

Morillo et al (2014) published results of the RAAFT-2 trial, an RCT comparing RFA with antiarrhythmic drug therapy as a first-line therapy for paroxysmal AF. Eligible patients had symptomatic recurrent paroxysmal AF lasting more than 30 seconds, with 4 or fewer episodes in the prior 6 months, and had had no previous antiarrhythmic drug treatment. The trial enrolled 127 patients at 16 centers; 66 were randomized to RFA and 61 to antiarrhythmic drug therapy, at the discretion of the treating physician. In the RFA group, 63 underwent ablation; during follow-up, 9 underwent reablation and 6 crossed over to receive antiarrhythmic drug therapy. In the drug therapy group, 26 crossed over to undergo ablation and 24 discontinued antiarrhythmic drug therapy but continued in the trial. Analysis was intention-to-treat (ITT). Patients were followed with biweekly scheduled transtelephonic monitor recordings and symptomatic recordings through the 24-month follow-up period. The trial's primary outcome (recurrence of any atrial tachyarrhythmia lasting >30 seconds) occurred in 72.1% (n=44) in the antiarrhythmic drug group compared with 54.5% (n=36) in the ablation group (HR=0.56; 95% CI, 0.35 to 0.90; p=0.02). Fewer patients in the RFA group had recurrence of symptomatic AF, atrial flutter, or atrial tachycardia (47% vs 59%; HR=0.56; 95% CI, 0.33 to 0.95; p=0.03) or recurrence of symptomatic AF (41% vs 57%; HR=0.52; 95% CI, 0.3 to 0.89; p=0.02). QOL measures did not differ significantly between groups.

MANTRA-PAF

An earlier RCT (MANTRA-PAF) evaluated RFA as the initial therapy for paroxysmal AF was reported by Cosedis Nielsen et al (2012). A total of 294 patients were randomized to initial treatment with catheter ablation or to pharmacologic therapy. Patients were followed to 24 months for the primary outcomes of burden of AF (percentage of time in AF on a Holter monitor) at each time point and cumulative burden of AF over all time points. For individual time points, the burden of AF was lower in the catheter RFA group only at 24 months (9% vs 18%, p=0.007). The 90th percentile cumulative burden did not differ significantly between groups (13% vs 19%; p=0.10). The secondary outcome of a percentage of patients free from AF at 24 months was greater for the catheter ablation group (85% vs 71%, p=0.004), as was the secondary outcome of freedom from symptomatic AF (93% vs 84%, p=0.01). There was 1 death in the ablation group (due to a procedural-related stroke), and 3 patients in that group developed cardiac tamponade following the procedure.

Five-year follow-up from MANTRA-PAF was reported by Nielsen et al (2017). Follow-up was available for 245 (83%) of 294 patients, of whom 227 had Holter recordings. The randomized groups did not differ significantly in terms their availability for follow-up. On ITT analysis, significantly more patients in the RFA group were free from any AF (126/146 [86%]) than those in the pharmacologic therapy group (105/148 [71%]; RR=0.82; 95% CI, 0.73 to 0.93; p=0.001). Symptomatic AF burden was also significantly lower in the RFA group, although QOL was not.

Section Summary: RFA as First-Line Therapy for AF

Multiple RCTs demonstrated lower rates of AF burden in patients with symptomatic paroxysmal AF who underwent catheter ablation as an initial treatment strategy. Rates of adverse events were relatively low.

RFA for AF in the Setting of Heart Failure

Based on 1 multicenter RCT, the 2008 TEC Assessment found the evidence was sufficient to conclude that catheter ablation improved outcomes for a patient with AF and heart failure compared with the alternative, AV nodal ablation, and pacemaker insertion. More recent RCTs and multiple observational studies have compared catheter ablation with medical therapy for AF in the setting of heart failure.

Systematic Reviews

Zhu et al (2016) reported on a systematic review and meta-analysis of RCTs comparing catheter ablation with medical rate control in patients who had persistent AF and heart failure. Three trials (total N=143 subjects; range, 41-52 subjects) met reviewers' inclusion criteria, all of which used blinded outcome assessment and were considered to have low risk of bias. For the meta-analysis's primary end point, compared with medical rate control, catheter ablation was associated with larger improvements in left ventricular end-diastolic fraction (mean difference, 6.22%; 95% CI, 0.7% to 11.74%; I^2=63%). Measures of peak oxygen capacity, New York Heart Association functional class, and QOL scores were also significantly improved in the catheter RFA-treated groups.

In that same year, Anselmino et al (2016) reported on a systematic review of available observational studies and RCTs evaluating catheter ablation for AF in patients with chronic heart failure or structural cardiomyopathies. For the population of patients with chronic heart failure, reviewers identified 17 observational studies, 4 RCTs, and 4 meta-analyses. Among the 4 RCTs, one compared catheter ablation with AV node ablation plus biventricular pacemaker insertion and the others compared catheter ablation with optimal medical therapy plus rate control. In the pooled analysis, the mean efficacy of catheter ablation in maintaining sinus rhythm was 59% after a single procedure, increasing to 77% after a repeat procedure.

Randomized Controlled Trials

Two RCTs comparing RFA with medical rate control are described next. While these trials did not directly provide evidence on the use of catheter ablation as an alternative to AV nodal ablation in patients who had failed rate control, they did support use of catheter ablation to treat AF in this population.

Hunter et al (2014) conducted an RCT comparing catheter RFA with medical rate control for patients who had persistent AF and symptomatic heart failure, with adequate rate control at the time of enrollment. There was no requirement for patients to have failed antiarrhythmic drug therapy. The trial's primary end point was the difference between groups in LVEF at 6 months postprocedure. Fifty patients were randomized, 26 to catheter ablation and 24 to medical management. At 6 months, 81% of the catheter ablation group was free from recurrent AF and antiarrhythmic drugs. LVEF at 6 months postprocedure was 40% in the catheter ablation group compared with 31% (p=0.015) in the medical management group. Catheter ablation was also associated with improvements in health-related QOL.

Jones et al (2013) reported on results from an RCT comparing catheter ablation with medical rate control for patients who had symptomatic heart failure, an LVEF of 35% or less, and persistent AF. Fifty-two patients were randomized, 26 each to catheter ablation or medical rate control. At 12 months postprocedure, sinus rhythm was maintained in 88% of the catheter ablation group, with a single-procedure success rate of 68%. For the trial's primary outcome (peak oxygen consumption at 12 months postprocedure), there was a significant increase in peak consumption in the catheter ablation group (2.13 mL/kg/min) compared with a decrease in the medical management group (-0.94 mL/kg/min; mean difference, +3.07 mL/kg/min; 95% CI, 0.56 to 5.59 mL/kg/min; p=0.018).

Observational Studies

Geng et al (2017) performed a retrospective cohort study on patients with AF, and heart failure. Patients treated with catheter ablation (n = 90) were compared with those treated with rate control therapy (n=304), with a mean follow-up of 13.5 months. Patients treated with catheter ablation had improvement in AF freedom (82.2% vs 0%). They also had a significantly lowered risk of major adverse cardiac events (13.3% vs 29.3%; HR=0.51; 95% CI, 0.26 to 0.98; p=0.044), defined as a composite score of all-cause mortality, stroke, and unplanned hospitalization. Study limitations included lack of details on selection criteria and differences in baseline criteria between groups (i.e., age, symptoms).

Joy et al (2017) retrospectively reviewed the 2013 Nationwide Readmissions Database to examine readmissions for heart failure exacerbations. Based on the 885,270 admissions for heart failure exacerbation, 90-day readmission rates were significantly higher in the 364,337 patients with heart failure with coexisting AF (41.4%) than in those without AF (37.6%; p<0.001). Treatment by catheter ablation was associated with a lower rate and length of stay for readmission due to heart failure exacerbation, compared with those without discharged without ablation (27.5% vs 41.4%, p<0.001; 5.58 days vs 6.60 days, p=0.031, respectively). The study was limited to information collected in the database, which focused on hospital data, and did not capture outcomes after discharge; also, it was not possible to compare baseline characteristics between patients who did or did not receive catheter ablation.

Section Summary: RFA for AF in the Setting of Heart Failure

Evidence from systematic reviews, RCTs, and an observational study have suggested that catheter ablation improves heart failure outcomes for patients with heart failure and coexisting AF.

Comparisons of RFA Techniques

Techniques for RFA for pulmonary vein isolation or substrate ablation have evolved. Specifying RFA techniques is not the focus of the present review, but recent large studies are described briefly.

Reddy et al (2015) reported on the results of a noninferiority RCT comparing a contact force-sensing RFA catheter with a standard (noncontact force-sensing) catheter in 300 patients with treatment-refractory paroxysmal AF. The trial's primary effectiveness end point was a composite of acute ablation success and long-term ablation success (freedom from symptomatic AF, atrial tachycardia, or atrial flutter at 12 months off antiarrhythmic drugs, after a 3-month blanking period). In the modified ITT population, patients in the contact force-sensing catheter group (n=149) were noninferior to the control catheter group (n=141; 67.8% vs 69.4%, respectively; absolute difference, -1.6%; lower limit of 1-sided 95% CI; -10.7; p=0.007 for noninferiority).

A second, smaller RCT, published by Nakamura et al (2015), compared a contact force-sensing RFA catheter with a standard catheter (N=120), and reported lower rates of pulmonary vein reconnections in those treated with a contact force-sensing catheter.

Afzal et al (2015) performed a systematic review and meta-analysis, which included 9 studies (1 RCT [but not the Reddy RCT]), comparing RFA with contact force-sensing or noncontact force-sensing catheters. At 12-month follow-up, contact force-sensing catheter-treated patients had lower AF recurrence compared with standard catheter-treated patients (RR=0.63; 95% CI, 0.44 to 0.91; p=0.01).

Longer Term Outcomes

The available RCTs have mainly reported on short-term outcomes (>1 year) and, therefore, do not provide data on the rate recurrences after 1 year. Longer term outcomes have been reported and have generally found rates of early recurrence in the range of 20% to 30%, requiring repeat ablations. Rates of longer term recurrence are lower if early recurrence does not occur, in the range of 1% to 2% per year.

Hussein et al (2011) reported on 831 patients treated in 2005 (median follow-up, 55 months). During the first year after ablation, 23.8% had a recurrence of AF. During the remaining follow-up, recurrences occurred in 8.9% additional patients. The overall rate free of arrhythmia and medications was 79.4% at 55 months. An additional 10.5% of patients were arrhythmia-free on medication, for a total clinical improvement rate of 89.9%. In a smaller study (N=509) with a follow-up to 5 years after initial ablation, Teunissen et al (2016) reported that, after a single procedure, 41.3% of patients had long-term maintenance of sinus rhythm.

Bunch et al (2013) reported on results from a prospective cohort study comparing the risk of stroke among patients with AF who had undergone catheter ablation, patients with AF who had not had ablation, and patients without a history of AF. A total of 4212 patients with AF who had had catheter ablation were age- and sex-matched at a 1:4 ratio with 16,848 subjects in each of the other groups. Mean follow-up time was 3.9 years. At 1 year postprocedure, significantly more patients with AF who had not undergone ablation had a stroke (3.5%) than those with AF who had had ablation (1.4%) or had no history of AF (1.4%; $p<0.001$ for trend). During the follow-up period, for all ages and $CHADS_2$ profiles, patients with AF who had ablation had a lower stroke risk than those with AF who had not.

Several smaller studies have also reported longer term follow-up after catheter RFA. Weerasooriya et al (2011) reported on 5-year follow-up in 100 patients treated with catheter ablation. Recurrences were most common within the first 6 months, with repeat procedures being common during that period. At 1, 2, and 5 years after ablation, arrhythmia-free survival rates were 87%, 81%, and 63%, respectively. Tzou et al (2010) reported on long-term follow-up for 123 patients who had a previous successful ablation, defined as free of AF at 1 year. At 3-year follow-up, 85% of patients were still free of AF and off all medications; at 5 years, 71% remained free of AF. The authors estimated a late recurrence rate of 7% per year for patients with an initially successful procedure. In a similar study, Bertaglia et al (2010) reported on outcomes after 6 years of follow-up for 229 patients who had had a single, successful ablation. At 1-year follow-up, 77% (177/229) of patients were free of AF and off all medications. After a mean additional follow-up of 49.7 months for these 177 patients, 58% remained free of AF. Sawhney et al (2009) reported on 5-year success rates for 71 patients who underwent ablation in 2002 or 2003. Freedom from symptomatic AF while off medications was achieved in 86% of patients at 1 year, in 79% at 2 years, and in 56% at 5 years. A substantial minority of patients (22.5%) had a recurrence at points more than 2 years after ablation. A study by Anselmino et al (2013) followed 196 patients who underwent catheter RFA for paroxysmal or persistent AF and had an LVEF of 50% or less for a mean of 46.2 months. During follow-up, 29.6% of patients required repeat ablation procedures. At the end of follow-up, 37.8% had had at least 1 episode of AF, atrial flutter, or ectopic atrial tachycardia. Takigawa et al (2014) reported on long-term follow-up for 1220 patients who underwent RFA for symptomatic paroxysmal AF. AF recurrence-free survival probabilities at 5 years were 59.4% after the initial procedure and 81.1% after the final ablation procedure (average procedures per patient, 1.3).

Section Summary: Radiofrequency Ablation for AF

Numerous RCTs of RFA for isolation of the pulmonary veins vs medical management have reported that freedom from AF at 1 year is higher with RFA than with medical management. The trials mainly included patients who failed antiarrhythmic medications. These trials have reported that most patients undergoing RFA were free of AF at 1 year. QOL was also improved in these trials for patients undergoing catheter ablation. A smaller number of studies have evaluated outcomes longer than 1 year and reported that late recurrences occur up to 5 years, but were uncommon after the first year. Complications from RFA were reported at low rates in the RCTs, but the numbers of patients in these trials are too small to accurately estimate rates of uncommon events. Two RCTs have evaluated the use of catheter ablation as an initial strategy for paroxysmal AF; 1 RCT demonstrated reduced rates of AF recurrence, while the other reported reduced cumulative overall AF burden.

CRYOABLATION FOR AF

Earlier studies assessing outcomes after cryoablation for AF were mainly case series and cohort studies reporting success rates similar to those reported for RFA. Since 2013, several RCTs have compared cryoablation with medical therapy or RFA.

Systematic Reviews

Following the publication of the large FIRE AND ICE trial in 2016 (see the Randomized Controlled Trials section below), a large number of systematic reviews comparing cryoablation with RFA for AF have been published. We identified 4 systematic reviews, which varied in inclusion criteria, primary outcomes, and designs, and are summarized in Table 2. Despite their differences, these reviews have generally reported that efficacy outcomes are comparable between the procedures, while the specific types of complications differed.

Table 2. Systematic Reviews Comparing Cryoablation With RFA for AF

Study	Population	No. of Studies Included (Participants)	Main Outcomes	Relative Effect	95% CI
Chen et al (2017)	Paroxysmal AF	9 RCTs, 29 non-RCTs (n=6218 cryoablation, n=9278 RFA)	Total complication (cryoablation vs RFA)	OR=1.37	1.19 to 1.57 (I^2=38%)
Liu et al (2016)	AF, refractory to medication	27 prospective (13 RCTs, 14 non-RCTs), 13 retrospective (N=11,395)	AF recurrence (cryoablation vs RFA)	RR=0.82	0.70 to 0.96
Cardoso et al (2016)	AF, with follow-up >12 mo	5 RCTs, 17 non-RCTs (n=3706 cryoablation, n=4962 RFA)	Freedom from recurrent atrial tachyarrhythmia at ≥12 mo (cryoablation vs RFA)	OR=1.12	0.97 to 1.29
Buiatti et al (2017)	Paroxysmal AF	3 RCTs, 2 multicenter cohort studies, 5 single-center prospective studies (n=2232 cryoablation, n=4241 RFA)	Recurrence of any atrial arrhythmia (cryoablation vs RFA)	RR=1.01	0.90 to 1.14 (I^2=0)

AF: atrial fibrillation; CI: confidence interval; OR: odds ratio; RCT: randomized controlled trial; RFA: radiofrequency ablation; RR: relative risk.

Cheng et al (2015) reported on a meta-analysis of RCTs and observational studies comparing cryoablation with RFA for AF. The meta-analysis included 11 studies (3 RCTs, 11 observational studies) with a total of 1216 patients. One RCT included only patients undergoing repeat treatment after an initially failed ablation procedure. In the pooled analysis, 66.9% of those treated with cryoablation and 65.1% of those treated with

RFA were free of AF after a mean follow-up of 16.5 months (RR=1.01; 95% CI, 0.94 to 1.07; p=0.87; I^2=5%, p=0.39).

Earlier systematic reviews comparing cryoablation with RFA included varying numbers of RCTs and observational studies and reporting findings similar to those of more recent systematic reviews.

Randomized Controlled Trials

Cryoablation vs Medical Therapy

Packer et al (2013) reported on results of the STOP AF trial, an RCT comparing cryoablation with antiarrhythmic medications. This trial enrolled 245 patients with paroxysmal AF who had failed at least 1 (median, 1.2) membrane-active antiarrhythmic medications. Patients were randomized in a 2:1 fashion to cryoablation (n=163) or drug therapy (n=82). At 1-year follow-up, 69.9% of patients in the ablation group were free of AF vs 7.3% in the medication group. The single-procedure success rate was 57.7%. There was also a significantly greater reduction in symptoms for the ablation group. Seventy-nine percent of the drug treatment group crossed over to cryoablation during the 12-month follow-up because of recurrent, persistent AF. Cryoablation procedure-related adverse events occurred in 5 (3.1%) patients; major AF events occurred in 3.1% of the cryoablation group compared with 8.5% of the drug treatment group (p<0.001 for noninferiority). Phrenic nerve injury occurred at a rate of 13.5%, of which 86% resolved at 12 months.

Andrade et al (2014) published a follow-up analysis of the STOP AF trial to evaluate the incidence and significance of early recurrence of AF after ablation. Of the 163 subjects randomized to cryoablation, 84 (51.5%) patients experienced early recurrence of AF, defined as any recurrence of AF lasting more than 30 seconds between 3 and 12 months postablation. The presence of early AF recurrence was associated with late AF recurrence: late AF recurrence occurred in 41 (25.1%) patients and was more likely in those with early recurrence (55.6% in those with early recurrence vs 12.7% in those without early recurrence; p<0.001).

Cryoablation vs RFA

Kuck et al (2016) reported on the results of the FIRE AND ICE trial, a multicenter RCT with a noninferiority design and blinded end point assessment, which compared RFA with cryoablation in individuals who had symptomatic, treatment-refractory paroxysmal AF. The trial enrolled 769 patients, of whom 750 were randomized and included in a modified ITT analysis (n=376 in the RFA group, n=374 in the cryoablation group). The trial tested the hypothesis that the cryoballoon would be noninferior to RFA regarding a prespecified efficacy end point, which was the time to the first documented clinical failure occurring more than 90 days after the index ablation period (blanking period). The trial defined clinical failure as recurrence of AF or occurrence of atrial flutter or atrial tachycardia on electrocardiographic or 24-hour Holter monitoring, prescription of class I or III antiarrhythmic drugs, or repeat ablation. After 90 days, the primary efficacy end point occurred in 138 cryoablation patients and 143 RFA patients (1-year Kaplan-Meier event rate estimates, 34.6% and 35.9%, respectively; HR=0.96; 95% CI, 0.76 to 1.22; p<0.001 for noninferiority). Cryoablation patients had shorter total procedure time (124 minutes vs 141 minutes, p<0.001) and left atrial dwell time (92 minutes vs 109 minutes, p<0.001), but longer fluoroscopy time (22 minutes vs 17 minutes, p<0.001). The trial's primary safety end point (a composite of death from any cause, stroke or transient ischemic attack (TIA) from any cause, and serious adverse events) occurred in 40 patients in the cryoablation group and 51 patients in the RFA group (1-year Kaplan-Meier event rate estimates, 10.2% and 12.8%, respectively; HR=0.78; 95% CI, 0.52 to 1.18; p=0.024). In the cryoablation group, phrenic nerve injury was the most common adverse event reported (2.7%).

Kuck et al (2016) also reported on rehospitalization, repeat ablation, and QOL outcomes during 1000 days of follow-up. The cryoablation group had fewer hospitalizations (122 patients) than the RFA group (156 patients; HR=0.72; 95% CI, 0.57 to 0.91; p=0.01). In addition, they had fewer repeat ablations (44 patients vs 66 patients; HR=0.65; 95% CI, 0.45 to 0.95; p=0.03). Patients in both groups had improvements in QOL scores from preablation through 12 months postablation, but there were no significant differences in change in QOL between groups.

Luik et al (2015) reported on results of the FreezeAF study, an RCT with a noninferiority design that compared RFA using an irrigated catheter with cryoablation in individuals who had treatment-refractory paroxysmal AF. The trial included 315 patients with paroxysmal AF refractory to treatment with at least 1 antiarrhythmic drug, who were randomized to RFA (n=159) or cryoablation (n=156). The trial tested the null hypothesis that cryoablation was noninferior to RFA regarding a coprimary end point: the absence of AF in combination with the absence of persistent complications at 6- and 12-month follow-ups. The coprimary end point was reached in 63.1% and 64.1% of the RFA and cryoablation groups, respectively, at 6 months, and in and 73.6% and 73% of the RFA and cryoablation groups, respectively, at 12 months. At 12 months postablation, the null hypothesis was rejected (null hypothesis risk difference, ≤ -0.15; risk difference, 0.029; 95% CI, -0.074 to 0.132; p<0.001).

An additional RCT by Hunter et al (2015) compared point-by-point RFA with cryoablation, but in 1 comparison group pulmonary vein isolation could be achieved with RFA if cryoablation was unsuccessful, and in the second comparison group a hybrid procedure (cryoablation following RFA) was used, which makes isolating the relative efficacy of cryoablation difficult.

The Mesh Ablator versus Cryoballoon Pulmonary Vein Ablation of Symptomatic Paroxysmal AF (MACPAF) study was a single-center RCT comparing cryoablation with RFA using the HD Mesh Ablator Catheter for AF. The HD Mesh Ablator Catheter, which is not cleared for use in the United States, is a multielectrode RFA catheter that uses a mesh electrode to deliver radiofrequency energy to multiple points of contact. Primary short-term results for MACPAF were reported by Koch et al (2012). The trial randomized symptomatic paroxysmal AF to catheter ablation with the Arctic Front cryoablation catheter or the HD Mesh Ablator Catheter. The trial's primary end point was complete isolation of the pulmonary veins at the end of the procedure. Enrollment was initially planned for 108 patients with symptomatic paroxysmal AF inadequately controlled using antiarrhythmic drug treatment. However, at interim analysis, the HD Mesh Ablator demonstrated a lack of efficacy for the primary end point and the trial's data safety monitoring board terminated the trial early. Forty-four patients with drug-resistant paroxysmal AF had been randomized at trial termination and comprised the ITT analysis cohort. The per-protocol analysis cohort included 32 patients. Three patients withdrew before the catheter procedure; 9 other patients were excluded from analysis due to use of a noncompliant catheter (n=2), identification of a trigger arrhythmia, which was subsequently ablated (n=1), failure of transseptal puncture (n=1), or ablation occurring after the interim analysis (n=5). The primary end point, by ITT analysis (complete pulmonary vein isolation), was achieved by 13 (56.5%) of 23 patients in the cryoablation group compared with 2 (9.5%) of 21 patients in the mesh ablator group (p=0.001). In the per-protocol cryoablation group, 76.5% of subjects had complete pulmonary vein isolation. Major complications included 1 case of retroperitoneal hematoma in the cryoablation group and 1 case of pericardial tamponade requiring drainage in the mesh ablator group.

Malmborg et al (2013) reported on results from an RCT comparing cryoablation using the Arctic Front cryoballoon catheter with RFA using the Pulmonary Vein Ablation Catheter. One hundred ten patients with paroxysmal or persistent AF were randomized, 54 to cryoablation and 56 to RFA. Complete pulmonary vein isolation was achieved in 98% of the cryoablation group compared with 93% of the RFA group (p=0.37). At 6-month follow-up, freedom from AF (absence of symptoms and no AF episodes on 7-day Holter monitoring or 12-lead electrocardiogram) without antiarrhythmic drug treatment was achieved in 52% of the cryoablation group and 38% of the RFA group (p=0.13).

Nonrandomized Studies
Case series of cryoablation published before the RCTs discussed above have reported success rates similar to those reported for RFA. A prospective noncomparative interventional study by Neumann et al (2008) evaluated cryoablation in 346 patients; 74% of patients with paroxysmal AF, but only 42% of those with persistent AF, were free from AF at 12-month follow-up. A small analysis by Linhart et al (2009) compared 20 patients undergoing cryoablation with 20 patients undergoing RFA, matched for age, sex, LVEF, and AF history. There were no significant differences between groups, including freedom from AF at 6 months, which was 55% in the cryoablation group and 45% in the RFA group.

Abugattas et al (2017) performed a multicenter retrospective study of patients with paroxysmal AF who underwent cryoballoon ablation. Patients who were at least 75 years old (n=53) were compared with younger patients (n=106), with a mean follow-up of 14 months. After procedure completion, 84% of all patients reported resolution of atrial arrhythmic events. There were no significant differences in the success rates between groups, but older patients had more recurrences (15%) than younger patients (5%; p=0.03). The most common complication was transient phrenic nerve palsy; there was no significant difference in its incidence between groups. This study lacked procedural complication monitoring.

In the largest nonrandomized comparative study identified, Aryana et al (2015) compared ablation using a second-generation cryoballoon with RFA in a retrospective cohort of 1196 patients with paroxysmal and persistent AF. Of the overall study population, 76% had paroxysmal AF; 773 were treated with cryoablation and 423 with RFA. Procedural success and complication rates did not differ significantly between groups. For the study’s primary end point, freedom from AF or atrial flutter or tachycardia at 12 months following a single ablation procedure without the use of antiarrhythmic medications was significantly higher for cryoablation-treated patients (76.6% vs 60.4%, p<0.001).

Another large nonrandomized study by Schmidt et al (2014) used data from a prospective German registry of catheter ablation procedures to compare RFA with cryoablation for paroxysmal AF. The cohort included 905 patients who underwent cryoablation and 2870 patients who underwent RFA, all of whom were enrolled from 2007 to 2011. The 2 groups were generally similar, with the exception that patients who had RFA were significantly more likely to have had valve disease (8.1% vs 3.0%, p<0.001) and an ejection fraction of 40% or less (2.4% vs 1.2%, p<0.05). Rates of acute success were similar for the 2 groups (97.5% for cryoablation vs 97.6% for RFA, p=0.92), as were rates of major procedure-related adverse cardiac and cerebrovascular events (0.4% for cryoablation vs 0.2% for RFA, p=0.15). Overall procedural complication rates were similar (4.6% for each group, p=1.0); the rate of postprocedural phrenic nerve palsy was significantly higher for the cryoablation group (2.1% for cryoablation vs 0% for RFA, p=0.15).

In a subsequent study, Schmidt et al (2016) compared 1-year outcomes for patients treated using RFA with cryoablation in the same German registry described above. This cohort included 2306 patients with symptomatic paroxysmal AF who underwent ablation from 2007 to 2010 (n=607 cryoablation; n=1699 RFA). The groups did not differ significantly in incidence reduction of symptomatic AF at 1 year (77.7% in RFA patients vs 79.5% in cryoablation patients; p=0.42). At 1 year, fewer cryoablation-treated patients were taking an antiarrhythmic drug (27.5% vs 32.1%, p<0.05). Rates of major clinical adverse events did not differ significantly between groups at 1 year, except phrenic nerve paralysis, which was more common in cryoablation patients (1.1% vs 0.3%, p<0.05).

Su et al (2018) performed a multicenter, retrospective study of patients with drug-refractory paroxysmal AF who underwent cryoballoon ablation. The patients (N=452) were successfully treated with pulmonary vein isolation (99%); with transient phrenic nerve injury found to be the most common complication (1.5%). After 12 months, 87% (n=393) of patients had freedom from atrial arrhythmia.

Some studies have compared newer and older generation devices, including 2 nonrandomized studies of cryoablation using a second-generation device with RFA using a contact force-sensing catheter. A smaller nonrandomized study by Julia et al (2015) reported lower rates of atrial tachycardias after cryoablation than after RFA, but with a greater magnitude of effect with cryoablation using a second-generation device. Another smaller nonrandomized study, by Wasserlauf et al (2015), reported shorter procedure times with cryoablation than with RFA, with no significant differences in resolution of AF.

Several studies have also reported on methods to reduce the risk of phrenic nerve injury with cryoballoon ablation, including fluoroscopy of spontaneous breathing and recordings of diaphragmatic electromyograms.

Longer Term Follow-Up

Similar to RFA, the available RCTs for cryoablation have reported primarily on short-term outcomes. Examples of longer term outcomes include Vogt et al (2013), who reported on 605 patients who underwent cryoablation for symptomatic, paroxysmal, or persistent AF. Follow-up data beyond 12 months were available for 451 patients (median follow-up, 30 months). Of those with follow-up available, 278 (61.6%) were free of AF recurrence with no need for repeat procedures after a 3-month blanking period. After 1, 2, and 3 repeat procedures, rates of freedom from AF were 74.9%, 76.2%, and 76.9%, respectively. Phrenic nerve palsy was the most common adverse event, occurring in 2% of patients, all of which resolved within 3 to 9 months. There were 2 periprocedural strokes (1 periprocedural pericardial tamponade, 1pericardial effusion).

Smaller studies include Neumann et al (2013), who reported on 5-year outcomes after a single cryoablation procedure among 163 patients with symptomatic, drug-refractory paroxysmal AF. Fifty-three percent of subjects were free from recurrent AF, atrial tachycardia, or atrial flutter at 5 years with no additional procedures (after a 3-month blanking period). Boho et al (2015) reported on the follow-up to a median of 3 years after cryoablation for 205 patients with symptomatic paroxysmal or early persistent AF treated at a single institution. At the 6-, 12-, 24-, and 36-month follow-ups, 88%, 71%, 49%, and 31% had no documented recurrence of AF. Davies et al (2016) reported on AF recurrence rates (median follow-up, 56 months) for 200 patients with paroxysmal or persistent AF after cryoablation. During follow-up, 46.7% and 35.6% of those with paroxysmal and persistent AF, respectively, had a recurrence of symptomatic AF after a single procedure.

Section Summary: Cryoablation for AF
The evidence on use cryoablation for AF includes RCTs and numerous nonrandomized studies. The STOP AF trial, which compared cryoablation with antiarrhythmic medication therapy, found cryoablation superior to medical management and rates of freedom from arrhythmia at 1 year in the cryoablation group were in the range reported for RFA. Interpretation of the MACPAF trial is limited by early termination due to the unexpectedly low efficacy of the RFA method used. While the Malmborg study has suggested that cryoablation is comparable to RFA, success in the RFA group was also unusually low. Two RCTs published subsequently found that cryoablation to be noninferior to RFA for pulmonary vein isolation.

OTHER ABLATION PROCEDURES
Most of the currently available research on ablation procedures for pulmonary vein isolation has focused on RFA or cryoablation—but a novel technology called visually guided laser balloon (VGLB) ablation more directly visualizes targeted atrial tissue during ablation. Other energy sources are under investigation. The CardioFocus Endoscopic Ablation System involves a visually guided balloon that uses laser energy to ablate cardiac tissue.

A prospective RCT by Dukkipati et al (2015) compared the VGLB with RFA in patients with drug-refractory paroxysmal AF. Overall, 342 (170 VGLB, 172 RFA) underwent ablation, and 334 (167 VGLB, 167 RFA) were included in the primary efficacy end point analysis after 12 months of follow-up. The trial's primary efficacy end point was freedom from treatment failure, which included documented symptomatic AF, ablation-induced or unknown origin left atrial flutter or atrial tachycardia, failure to isolate all pulmonary veins, use of any antiarrhythmic drugs, or left heart ablation surgery or implantable cardioverter defibrillator placement for AF. In a prespecified noninferiority analysis, 61.1% of those in the VGLB group met the primary efficacy end point compared with 61.7% of the RFA group (absolute difference, -9.3%; p=0.003 for noninferiority). Overall, rates of primary adverse events did not differ significantly between groups.

However, VGLB group patients had a lower rate of pulmonary valve stenosis (0% for VGLB vs 2.9% for RFA, p=0.03), but a higher rate of diaphragmatic paralysis (3.5% for VGLB vs 0.6% for RFA, p=0.05).

Schmidt et at (2017) performed a multicenter RCT comparing the efficacy and safety of the laser balloon with wide area circumferential pulmonary vein isolation using irrigated RFA and 3-dimensional mapping. In total, 134 patients with persistent AF were randomized to treatment with laser balloon catheter ablation (n=68) or RFA (n=66). Follow-up including 3-day Holter monitoring occurred at 3, 6, and 12 months. There were no significant differences in the primary efficacy end point of AF freedom between 3 and 12 months between those treated with laser balloon catheter ablation (71.2%) or those treated with RFA (69.3%).

REPEAT PROCEDURES

Repeated procedures for recurrent AF or atrial flutter were commonly performed in most clinical trials included in this evidence review. Of the 10 RCTs reviewed comparing RFA with medical management, only 2 did not include repeated procedures. In the other 5 studies, 1 or more repeated procedures were allowed, and success rates reported generally incorporated the results of up to 3 procedures. In 4 studies reporting these data, repeated procedures were performed in 8.2%, 9%, 20%, and 32% of patients randomized to ablation. In their RCT of catheter ablation of AF in patients with heart failure, Hunter et al (2014) reported that repeat procedures were required in 65.4% of the catheter ablation group. Stabile et al (2006) did not report specifics on how many patients actually underwent repeat procedures, but limited data in the publication suggested that up to 30% of treated patients were eligible for repeat procedures. In the Jais et al (2008) study, patients underwent a mean of 1.8 procedures per patient and a median of 2 procedures per patient, indicating that approximately 50% of patients in the ablation group underwent at least 1 repeated procedure.

Because of this high rate of repeat procedures, the results reported in these studies do not reflect the single-procedure success rate. Rather, they more accurately estimate the success rate of an ablation strategy that includes repeat procedures for recurrences that occur within the first year of treatment. Nonrandomized evidence has suggested that early reablation increases the success of the procedure when defined as maintenance of sinus rhythm at 1 year. There is variability in the protocol for when repeat procedures should be performed. There is also uncertainty concerning other details of repeat procedures, such as how soon after the initial procedure it should be done, the threshold for AF recurrence that should prompt a repeat, and whether medication regimens should be tried before a repeat procedure.

Pokushalov et al (2013) reported on results of an RCT comparing repeat catheter ablation with antiarrhythmic drug therapy for patients with paroxysmal AF who had failed an initial pulmonary vein isolation procedure. After an initial postablation blanking period, 154 patients with symptomatic AF recurrence were randomized to drug therapy (n=77) or repeat ablation (n=77). Patients were followed for 3 years with an implanted cardiac monitor. At the 3-year follow-up, 58% (45/77) of the repeat ablation group was free from AF or atrial tachycardia and antiarrhythmic drugs compared with 12% (9/77) of the antiarrhythmic therapy group (p<0.01). In the antiarrhythmic drug group, 43 (56%) patients crossed over to receive repeat ablation; in the repeat ablation group, 21 (27%) patients required antiarrhythmic drug therapy. By ITT analysis, 65% (50/77) of the repeat ablation group and 45% (35/77) of the drug therapy group were free from AF or atrial tachycardia (p=0.02).

COMPLICATIONS

Individual clinical trials and case series have reported relatively low rates of complications but may be limited in their ability to detect uncommon outcomes due to small sample sizes. Gupta et al (2013) conducted a systematic review evaluating periprocedural complications following catheter ablation for AF. Reviewers selected 192 studies that included at least 100 participants undergoing catheter ablation for symptomatic AF and that reported complications. The total sample size was 83,236 patients. The overall acute complication rate was 2.9% (95% CI, 2.6% to 3.2%), with significant heterogeneity across studies. The most common complications were vascular complications (1.4%), cardiac tamponade (1.0%), pericardial effusion (0.7%), stroke/TIA (0.6%), and pulmonary vein stenosis (0.5%).

In addition to the complication rates reported in clinical trials and case series, a number of database studies and postmarketing surveillance have reported complications in large numbers of patients. A representative sample of these studies is discussed next, some of which were included in the Gupta review (Shah et al [2012], Dagres et al [2009]).

Waldo et al (2012) reported on the results of a U.S. FDA–directed postmarketing safety study involving 1275 patients from 6 prospective, multicenter studies of RFA using an open-irrigated catheter. A total of 4.9% (63/1275) of patients experienced serious, acute complications within 7 days of the procedure. Vascular access complications were most common, ranging from 0.5% to 4.7% across the 6 studies. Exacerbations of heart failure occurred in 1.5% of patients, and 2 patients experienced cardiac tamponade. There were no strokes or TIAs reported after the procedure.

Shah et al (2012) used data from a California hospital database to evaluate complications in 4156 patients who underwent catheter ablation for AF. Major complications occurred in 5.1% (211/4156) patients, with approximately half (2.6% [110/4156]) consisting of hemorrhage or hematoma at the vascular entry site. The most common cardiac complication was cardiac perforation and/or tamponade, which occurred in 2.5% (104/4156) of patients. Less common rates of serious adverse events included death (0.02%), stroke/TIA (0.31%), and pneumothorax/hemothorax (0.1%). Factors predictive of complications were female sex, older age, prior hospitalizations for AF, and less hospital expertise with ablation.

In a study of Medicare beneficiaries, Ellis et al (2009) identified 6065 admissions from 168 hospitals in which RFA for AF was performed. The total rate of in-hospital complications was 9.1%, with vascular complications accounting for over half the complications (5.7%). The mortality rate was 0.4%, and 0.6% of patients suffered a stroke or TIA, respectively. Perforation or tamponade occurred in 3.1% of patients and pneumothorax in 0.4%. The presence of chronic obstructive pulmonary disease or unstable angina was associated with a higher risk of complications, while obesity and hyperlipidemia were associated with a lower risk. Age and hospital volume were not significant predictors of risk, but low hospital RFA procedure volume was a significant predictor of in-hospital death.

Complications of catheter ablation were also reported by Dagres et al (2009) in a large cohort of 1000 patients undergoing ablation at a high-volume center in Europe. No deaths were definitively attributed to the procedure, but there were 2 deaths of uncertain cause within the first 30 days following ablation. Overall, 3.9% of patients had a major complication resulting from the procedure. Tamponade was the most serious life-threatening complication (1.3%). Major vascular complications occurred in 1.1%. Thromboembolism, cerebrovascular accident or TIA, atrioesophageal fistula, and endocarditis were all reported complications that occurred at a rate of less than 1%.

Cappato et al (2009) performed a multicenter, retrospective case series to estimate the overall mortality rate following ablation. Data were collected on 32569 patients from 162 clinical centers worldwide. Thirty-two deaths were reported, for a mortality rate of 0.98 per 1000 patients. The most common causes of death were tamponade (n=8), stroke (n=5), atrioesophageal fistula (n=5), and pneumonia (n=2).

One goal of the MACPAF study was to identify adverse events, particularly cerebral thromboembolism, through the use of serial magnetic resonance imaging (MRI) and neuropsychologic testing. While there is some evidence that RFA for patients with AF reduces stroke risk, a clinically significant stroke or TIA attack occurs in 0.1% to 0.8% of patients undergoing catheter ablation, and several case series have demonstrated peridural brain lesions on diffusion-weighted MRI in up to 18% of patients undergoing catheter ablation of the left atrium. Thus, the MACPAF investigators evaluated patients pre- and postcatheter ablation with brain MRI at 3 Tesla and neurologic and neuropsychological testing. Short-term outcomes from these evaluations were reported by Haeusler et al (2013) and demonstrated that new ischemic lesions occurred in 41% of all patients. However, these brain lesions were not associated with cognitive dysfunction immediately postprocedure. Longer term follow-up was reported by Herm et al (2013). At follow-up MRI 6 months postprocedure, 31.3% of the acute brain lesions had formed a persistent glial scar. Similar to the short-term findings, there was no significant effect of either the ablation procedure or the presence of persistent brain lesions on attention or executive functions, short-term memory, or learning after 6 months.

Section Summary: Complications

Several large, database studies have estimated the adverse event rate from catheter ablation in the clinical care setting. The range of major adverse events in these studies is from 4% to 9%. Deaths have been reported and have occurred at rates less than 1%. Vascular complications at the groin site are the most common adverse events, occurring at rates of up to 5%. Serious cardiovascular adverse events such as tamponade and stroke occur uncommonly, at rates of approximately 1% or lower. There is some evidence that new ischemic lesions are commonly found using MRI after the procedure, but the clinical significance of these defects is unclear.

SUMMARY OF EVIDENCE

For individuals who have symptomatic paroxysmal or persistent AF who have failed antiarrhythmic drugs who receive RFA or cryoablation, the evidence includes multiple RCTs and systematic reviews. Relevant outcomes are overall survival, symptoms, morbid events, and QOL. RCTs comparing RFA with antiarrhythmic medications have reported that freedom from AF is more likely after ablation than after medications. Results of long-term follow-up (5-6 years) after ablation have demonstrated that late recurrences continue in patients who are free of AF at 1 year. However, most patients who are AF-free at 1 year remain AF-free at 5 to 6 years. Multiple RCTs comparing cryoablation with RFA have found that cryoablation is noninferior to RFA for AF control. RFA and cryoablation differ in their adverse event profiles. For example, cryoablation is associated with higher rates of phrenic nerve paralysis but may permit a shorter procedure time. Given current data, it would be reasonable to consider both RFA and cryoablation effective for catheter ablation of AF foci or pulmonary vein isolation, provided there is a discussion about the risks and benefits of each. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have symptomatic AF and congestive heart failure who have failed rate control and antiarrhythmic drugs who receive RFA or cryoablation, the evidence includes a TEC Assessment, supported by RCTs. Relevant outcomes are overall survival, symptoms, morbid events, and QOL. Based on a multicenter RCT, the TEC Assessment found the evidence sufficient to conclude that catheter ablation improves outcomes more than the alternative, AV nodal ablation and pacemaker insertion. Findings from this RCT have been supported by other comparative studies, which have reported improvements in AF. It is reasonable to consider both RFA and cryoablation effective for catheter ablation of AF foci or pulmonary vein isolation, provided that there is a discussion about the risks and benefits of each. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have recurrent symptomatic paroxysmal AF who receive RFA or cryoablation as an initial rhythm-control strategy, the evidence includes RCTs, nonrandomized studies, and systematic reviews. Relevant outcomes are overall survival, symptoms, morbid events, and QOL. Two RCTs with low risk of bias compared catheter ablation for pulmonary vein isolation with antiarrhythmic medications. One RCT demonstrated reduced rates of AF recurrence, while the other reported reduced cumulative overall AF burden. Together, these results suggest that, when a rhythm-control strategy is desired, catheter ablation is a reasonable alternative to antiarrhythmic drug therapy. While the RCTs comparing ablation with medical therapy were conducted using RFA, it is reasonable to consider both RFA and cryoablation effective for catheter ablation of AF foci or pulmonary vein isolation, provided that there is a discussion about the risks and benefits of each. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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Policy History

Original Effective Date:	09/15/2010
Current Effective Date:	10/17/2018
09/09/2010	Medical Policy Committee review
09/15/2010	Medical Policy Implementation Committee approval. New Policy.
09/01/2011	Medical Policy Committee review
09/14/2011	Medical Policy Implementation Committee approval. Coverage statements edited for clarity, but no change in intent of coverage statements. Note added at the end of coverage section.
10/11/2012	Medical Policy Committee review
10/31/2012	Medical Policy Implementation Committee approval. Rationale section updated. Coverage eligibility unchanged.
01/23/2013	Coding updated
10/03/2013	Medical Policy Committee review

Policy # 00267
Original Effective Date: 09/15/2010
Current Effective Date: 10/17/2018

10/16/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/04/2014	Medical Policy Committee review
12/17/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/08/2015	Medical Policy Committee review
10/21/2015	Medical Policy Implementation Committee approval. Added new policy statement for ablation as initial treatment for paroxysmal atrial fibrillation. Title change.
10/06/2016	Medical Policy Committee review
10/19/2016	Medical Policy Implementation Committee approval. The policy statement for the use of catheter ablation for initial treatment of atrial fibrillation was clarified to state that there should be greater than one episode of atrial fibrillation.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
10/05/2017	Medical Policy Committee review
10/18/2017	Medical Policy Implementation Committee approval. Added a Note, "*Transcatheter treatment of atrial fibrillation (AF) may include pulmonary vein isolation and/or focal ablation."* after the coverage section.
10/04/2018	Medical Policy Committee review
10/17/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Moved the *Notes* from the coverage section to a Policy Guidelines section.

Next Scheduled Review Date: 10/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	93656, 93657, 93799
HCPCS	No codes
ICD-10 Diagnosis	I48.0-I48.91 I50.20-I50.23 I50.30-I50.33 I50.40-I50.43 I50.9

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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