Name of Blue Advantage Policy:
Transcatheter Ablation as a Treatment of Atrial Fibrillation

Policy #: 283       Latest Review Date: July 2019
Category: Medical       Policy Grade: A

Background:
Blue Advantage medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:

1. Safe and effective;
2. Not experimental or investigational*;
3. Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:
   • Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient’s condition or to improve the function of a malformed body member;
   • Furnished in a setting appropriate to the patient’s medical needs and condition;
   • Ordered and furnished by qualified personnel;
   • One that meets, but does not exceed, the patient’s medical need; and
   • At least as beneficial as an existing and available medically appropriate alternative.

*Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill Original Medicare for covered services that are related to clinical trials that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).
Description of Procedure or Service:
Atrial fibrillation (AF) 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 ablation techniques directed at these structures. Catheter-based ablation, using radiofrequency ablation (RFA) or cryoablation, is being studied as a treatment option for various types of AF.

Atrial Fibrillation
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 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 atrioventricular (AV) synchrony results in a decreased cardiac output, which can be significant in patients with compromised cardiac function. In addition, 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 three types:
- paroxysmal (episodes that last fewer than 7 days and are self-terminating),
- persistent (episodes that last for more than 7 days and can be terminated pharmacologically or by electrical cardioversion), or
- Permanent.

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.

However, rhythm control is not curative. A variety of ablative procedures have been investigated as potentially curative approaches, or as modifiers of the arrhythmia such 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 Atrial Fibrillation
Radiofrequency ablation (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 may be no single arrhythmogenic focus. 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). Circumferential pulmonary vein ablation using radiofrequency energy is the most common approach at present. Research into specific ablation and pulmonary vein isolation techniques is ongoing.

Use of current radiofrequency catheters for AF has a steep learning curve because they require extensive guiding to multiple ablation points. The procedure also can be done using cryoablation technology. One of the potential advantages of cryoablation is that cryoablation catheters have a circular or shaped end point, permitting a “one-shot” ablation.

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. Additional clinical 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.

Policy:
Effective for dates of service on or after July 1, 2015:
Blue Advantage will treat transcatheter radiofrequency or cryoablation to treat atrial fibrillation as a covered benefit when used as a treatment for either of the following indications which have failed to respond to adequate trials of antiarrhythmic medications:

1. Symptomatic paroxysmal or symptomatic persistent atrial fibrillation; or
2. As an alternative to atrioventricular nodal ablation and pacemaker insertion in patients with class II or III congestive heart failure and symptomatic atrial fibrillation.

Blue Advantage will treat transcatheter radiofrequency ablation or cryoablation to treat atrial fibrillation as a covered benefit when used as an initial treatment for patients with symptomatic paroxysmal atrial fibrillation for patients with recurrent symptomatic
paroxysmal atrial fibrillation (>1 episode, with 4 or fewer episodes in the previous 6 months) in whom a rhythm control strategy is desired.

Blue Advantage will treat repeat radiofrequency ablation or cryoablation as a covered benefit in patients with recurrence of atrial fibrillation and/or development of atrial flutter following the initial procedure.

Blue Advantage will treat transcatheter radiofrequency ablation or cryoablation to treat atrial fibrillation as a non-covered benefit and as investigational as a treatment for all indications including, but not limited to cases of atrial fibrillation that do not meet the criteria outlined above.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:
The most recent literature search was performed through April 6, 2019.

Broadly defined, health outcomes are length of life, quality 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 randomized controlled trial (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 atrial fibrillation (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 to atrioventricular (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 ongoing controversy about the relative benefits of rhythm versus 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 versus 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.

**Catheter Ablation for Symptomatic Paroxysmal or Persistent Atrial Fibrillation who have Failed Medical Management**

**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 atrioventricular (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 radiofrequency ablation (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, 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, left ventricular ejection fraction (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>
<thead>
<tr>
<th>Outcome (Catheter vs Drug Therapy)</th>
<th>No. of Participants (Studies)</th>
<th>Evidence Quality (^a)</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freedom from atrial arrhythmias or recurrence of any atrial arrhythmias</td>
<td>261 (3 studies)</td>
<td>Low</td>
<td>1.84</td>
<td>1.17 to 2.88</td>
</tr>
<tr>
<td>Need for cardioversion</td>
<td>261 (3 studies)</td>
<td>Moderate</td>
<td>0.62</td>
<td>0.47 to 0.82</td>
</tr>
<tr>
<td>Cardiac hospitalization</td>
<td>216 (2 studies)</td>
<td>Low</td>
<td>0.28</td>
<td>0.1 to 0.72</td>
</tr>
</tbody>
</table>

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.

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; I²=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 weighted mean difference (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.

**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 CHADS2 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).

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).

**Cryoablation for AF**

**Randomized Controlled Trials**

Packer et al (2013) reported on results of the Sustained Treatment of Paroxysmal Atrial Fibrillation (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.

**Nonrandomized Studies**

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.

**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, 1 pericardial 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.

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).

Complications
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%.

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%).
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 Mesh Ablator versus Cryoballoon Pulmonary Vein Ablation of Symptomatic Paroxysmal Atrial Fibrillation (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.

Waldo et al (2012) reported on the results of a U.S. Food and Drug Administration–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 TIAIs 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.

**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).

**Section Summary: Individuals with Symptomatic Paroxysmal or Persistent AF who have Failed Antiarrhythmic Drugs**

**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
Numerous RCTs and non RCTs have reported the use of cryoablation in patients with symptomatic paroxysmal or persistent AF who have failed antiarrhythmic drugs. Longer term follow-up in these patients has also been reported.

Complications and Adverse Events
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.

Individuals with Symptomatic Atrial Fibrillation and Congestive Heart Failure who have Failed Rate Control and Antiarrhythmic Drugs
Radiofrequency Ablation
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.

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.

Randomized Controlled Trials
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).

Cryoablation
A search of the existing literature revealed no published evidence on the use of cryoablation to treat individuals with AF with heart failure.

Section Summary: Individuals with Symptomatic AF and CHF who have Failed Rate Control and Antiarrhythmic Drugs
Evidence from systematic reviews, RCTs, and an observational study are consistent in demonstrating that catheter ablation improves heart failure outcomes for patients with heart failure and coexisting AF. No literature on cryoablation was identified.
Individuals with Recurrent Symptomatic Paroxysmal Atrial Fibrillation  
Randomized Controlled Trials (Multiple Modalities)  
Packer et al (2019) published results from the Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial, an international multicenter RCT designed to determine whether catheter ablation is more effective than conventional medical therapy to prevent major cardiovascular events in AF. A total of 2204 patients were enrolled and randomized 1:1 from November 2009-April 2016. Follow-up was conducted through December 2017. Catheter ablation devices used energy sources available in the clinical trial site and with which investigators had the requisite expertise. In the catheter ablation treatment group (n=1108), the primary endpoint (a composite of death, disabling stroke, serious bleeding, and/or cardiac arrest) occurred in 8.0% of patients and in 9.2% of patients in the drug therapy group (HR: 0.86 (95% CI: 0.65-1.15) p=030) and was not superior to medical therapy. There were 13 prespecified secondary outcomes; 3 of which were reported. All-cause mortality did not differ between groups. Death or cardiovascular hospitalization and AF recurrence were statistically significantly reduced in the catheter ablation group.

Mark et al (2019) published the results of 12-month QOL outcomes (median follow-up of 48.5 months) for participants in the CABANA trial. The Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT) mean summary score in the catheter ablation group was 86.4 points vs 80.9 points in the drug therapy group (adjusted difference 5.3 points [95%CI, 3.7-6.9]: P 5 is considered a clinically meaningful difference (adjusted difference, -1.5 points [95% CI, -2.0 to 1.1]; P<0.001). The trial used a modified MAFSI questionnaire combining frequency scores range from 0 to 4 (never to always) and severity scores ranging from 0 (no AF symptoms) to 40 (most severe AF symptoms). The investigators developed a trial specific clinically meaningful change of 1.6 points for the frequency score and 1.3 points for the severity score.

Blomstrom-Lundqvist et al (2019) published the results for the Catheter Ablation compared with Pharmacological Therapy for Atrial Fibrillation (CAPTAF) trial, an RCT designed to assess the QOL after catheter ablation compared to medical therapy. The primary outcome at 12 months was the difference in the General Health subscale score. The QOL score increases in the catheter ablation group from 61.8 to 73.9 points vs 62.7 to 65.4 points in the medication group (95% CI: 3.1-14.7; p=0.003).

Radiofrequency Ablation  
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; I²=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 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 of 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: Individuals with Recurrent Symptomatic Paroxysmal AF
Numerous RCTs, including those that evaluate long-term outcomes, have evaluated RFA and cryoablation in patients with recurrent symptomatic paroxysmal AF. Most recently, the CABANA trial noted that the use of RFA did not show significant improvement over
medications.

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 quality of life. 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 quality of life. Based on a multicenter RCT, the TEC Assessment found the evidence sufficient to conclude that catheter ablation improves outcomes more than the alternative, atrioventricular 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 quality of life. The most current RCT with adequate follow-up compared pulmonary vein isolation by catheter ablation (using either cryoablation or RFA to medical therapy. Catheter ablation was not superior to medical therapy for major cardiovascular outcomes but secondary outcomes including AF recurrence favored catheter ablation. QOL measures reported in this RCT favored catheter ablation. Two other 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.
Practice Guidelines and Position Statements
Heart Rhythm Society et al
An expert consensus document on catheter and surgical catheter ablation for atrial fibrillation (AF) was developed jointly by 7 cardiac specialty societies (Heart Rhythm Society [HRS], European Heart Rhythm Association, European Cardiac Arrhythmia Society, American College of Cardiology, American Heart Association, Asia Pacific Heart Rhythm Society, Society of Thoracic Surgeons) in 2012. A related group of cardiac specialty societies (HRS, European Heart Rhythm Association, European Cardiac Arrhythmia Society, Asia Pacific Heart Rhythm Society, Latin American Society of Cardiac Stimulation and Electrophysiology) updated these guidelines in 2017, suggesting the following recommendations for catheter ablation (see Table 2).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
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<tbody>
<tr>
<td><strong>Symptomatic AF refractory or intolerant to at least 1 class 1 or 3 antiarrhythmic medication</strong></td>
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<td></td>
</tr>
<tr>
<td>Paroxysmal: Catheter ablation is recommended</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Persistent: Catheter ablation is reasonable</td>
<td>IIa</td>
<td>B-NR</td>
</tr>
<tr>
<td>Long-standing persistent: Catheter ablation may be considered</td>
<td>IIb</td>
<td>C-LD</td>
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</table>

| **Symptomatic AF prior to initiation of antiarrhythmic drug therapy with a class 1 or 3 antiarrhythmic agent** |       |      |
| Paroxysmal: Catheter ablation is reasonable                                   | IIa  | B-R  |
| Persistent: Catheter ablation may be considered                               | IIa  | C-EO |
| Longstanding Persistent: Catheter ablation may be considered                  | IIb  | C-EO |

AF: atrial fibrillation; COR: class of recommendation; LOE: level of evidence.

American College of Cardiology et al
In 2014, American College of Cardiology, American Heart Association, and HRS issued guidelines for management of patients with AF. The guidelines included the following recommendations for rate control and rhythm control (see Table 3).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
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<tbody>
<tr>
<td><strong>Rate control</strong></td>
<td></td>
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<tr>
<td>“AV nodal ablation with permanent ventricular pacing is reasonable to control heart rate when pharmacological therapy is inadequate and rhythm control is not achievable.”</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>“AV nodal ablation with permanent ventricular pacing should not be performed to improve rate control without prior attempts to achieve rate control with medications.”</td>
<td>IIIa</td>
<td>C</td>
</tr>
<tr>
<td><strong>Rhythm control</strong></td>
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<tr>
<td>“AF catheter ablation is useful for symptomatic paroxysmal AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication when a rhythm-control strategy is desired.”</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>“Before consideration of AF catheter ablation, assessment of the procedural risks and outcomes relevant to the individual patient is recommended.”</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>“AF catheter ablation is reasonable for some patients with symptomatic persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication.”</td>
<td>IIa</td>
<td>A</td>
</tr>
<tr>
<td>“In patients with recurrent symptomatic paroxysmal AF, catheter ablation is a reasonable initial rhythm-control strategy before therapeutic trials of antiarrhythmic drug therapy, after weighing the risks and outcomes of drug and ablation therapy.”</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>
“AF catheter ablation may be considered for symptomatic long-standing (>12 months) persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic medication when a rhythm-control strategy is desired.”

IIb B

“AF catheter ablation may be considered before initiation of antiarrhythmic drug therapy with a class I or III antiarrhythmic medication for symptomatic persistent AF when a rhythm-control strategy is desired.”

IIb C

“AF catheter ablation should not be performed in patients who cannot be treated with anticoagulant therapy during and after the procedure.”

IIIa C

“AF catheter ablation to restore sinus rhythm should not be performed with the sole intent of obviating the need for anticoagulation.”

IIIa C

AF: atrial fibrillation; AV: arteriovenous; COR: class of recommendation; LOE: level of evidence.

a Not recommended

Although the guidelines did not make a specific recommendation on the use of cryoablation, they did state that “Cryoballoon ablation is an alternative to point-by-point radiofrequency ablation to achieve pulmonary vein isolation.”

U.S. Preventive Services Task Force Recommendations
Not applicable

Key Words:
Atrial fibrillation, circumferential pulmonary vein ablation (PVA), pulmonary vein isolation, arrhythmogenic, cryoablation, cryoballoon therapy, cryoballoon intervention, cryoballoon technique, cryoballoon isolation, cryoballoon ablation

Approved by Governing Bodies:
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. Food and Drug Administration (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.
**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

**Current Coding:**
**CPT Codes:**

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>93656</td>
<td>Comprehensive electrophysiologic evaluation including transseptal catheterizations, insertion and repositioning of multiple electrode catheters with induction or attempted induction of an arrhythmia including left or right atrial pacing/recording when necessary, right ventricle pacing/recording when necessary, and HIS bundle recording when necessary with intracardiac catheter ablation of atrial fibrillation by pulmonary vein isolation</td>
</tr>
<tr>
<td>93657</td>
<td>; 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</td>
</tr>
<tr>
<td>93799</td>
<td>Unlisted cardiovascular service or procedure</td>
</tr>
</tbody>
</table>

**References:**
19. Calkins H, Kuck KH, Cappato R et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Developed in partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society of Thoracic Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the Heart Rhythm Society. Heart Rhythm 2012; 9(4):632-96 e21.
patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Developed in partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society of Thoracic Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the Heart Rhythm Society. Heart Rhythm. Apr 2012; 9(4):632-696 e621.


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This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.