2.02.19	Catheter Ablation as Treatment for Atrial Fibrillation		
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Policy Statement

I. Transcatheter radiofrequency ablation (RFA), cryoablation or pulsed field ablation to treat atrial fibrillation may be considered **medically necessary** as a treatment for **either** of the following indications, which have failed to respond to adequate trials of antiarrhythmic medications:
   A. Symptomatic paroxysmal or symptomatic persistent atrial fibrillation
   B. As an alternative to atrioventricular nodal ablation and pacemaker insertion in individuals with class II or III congestive heart failure and symptomatic atrial fibrillation

II. Transcatheter RFA, cryoablation or pulsed field ablation to treat atrial fibrillation may be considered **medically necessary** as an initial treatment for individuals with recurrent symptomatic paroxysmal atrial fibrillation (greater than 1 episode, with 4 or fewer episodes in the previous 6 months) in whom a rhythm-control strategy is desired.

III. Repeat RFA, cryoablation or pulsed field ablation may be considered **medically necessary** in individuals with recurrence of atrial fibrillation and/or development of atrial flutter following the initial procedure (see Policy Guidelines section).

IV. Transcatheter RFA, cryoablation and pulsed field ablation to treat atrial fibrillation is considered **investigational** as a treatment for cases of atrial fibrillation that do not meet the criteria outlined above.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Transcatheter treatment of atrial fibrillation (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 individual to individual, even if they are treated by the same physician. Individuals with long-standing persistent AF may need more extensive ablation. Similarly, repeat ablation procedures for recurrent AF generally involve more extensive ablation than initial procedures.

Repeat Procedures

As many as 30% of individuals 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.

It is currently unknown whether there is a feature of the pulsed field ablation approach that alters the conventional 3-month blanking period. Pulsed field ablation is purported to have a desirable safety profile through the avoidance of thermal injury compared to other catheter ablation methods.

Note: For members who undergo an electrophysiology (EP) study on the same day as an ablation, an EP study is considered medically necessary if no prior EP study has been performed within the previous three months.

Contraindications to Antiarrhythmic Drugs:
Contraindications to antiarrhythmic drugs may include, but are not limited to:

- Advanced conduction disease (particularly second or third degree heart block in the absence of a pacemaker)
- Advanced heart failure or markedly depressed cardiac function with the exception of amiodorone and dofetilide
- Prolonged Q-T interval
- Syncope or weakness when taking antiarrhythmic drugs

Coding
See the Codes table for details.

Description

Atrial fibrillation 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 or cryoablation, is a treatment option for various types of AF. Pulsed field ablation is a novel ablation technique for atrial fibrillation.

Summary of Evidence
For individuals who have symptomatic paroxysmal or persistent atrial fibrillation (AF) who have failed antiarrhythmic drugs who receive radiofrequency ablation (RFA) or cryoablation, the evidence includes multiple randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are overall survival (OS), symptoms, morbid events, and quality of life. The 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 to 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 4 to 6 years. Radio frequency ablation 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 an 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 RCTs and systematic reviews. Relevant outcomes are OS, symptoms, morbid events, and quality of life. Findings from the RCTs 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 an 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 OS, symptoms, morbid events, and quality of life. One 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. Quality of life measures reported in this RCT favored catheter ablation. Two other RCTs with low-risk of bias compared RFA for pulmonary vein isolation with antiarrhythmic medications. One RCT demonstrated reduced rates of AF recurrence, while the other reported reduced cumulative overall AF burden. Additionally, 3 RCTs comparing cryoablation to antiarrhythmic drug therapy as first-line therapy demonstrated improved outcomes for atrial arrhythmia recurrence up to 1 year. In a meta-analysis of 6 RCTs, catheter ablation as first-line therapy significantly reduced the risk of recurrence of atrial arrhythmia and the rate of hospitalizations compared to antiarrhythmic drug therapy. In another meta-analysis of the same RCTs, treatment ranking based on the surface under the cumulative ranking curve ranked RFA as most likely to be the best treatment for reducing the overall rates of AF recurrence, symptomatic recurrence, and hospitalizations, whereas cryoablation was most likely to reduce serious adverse events. Together, these results suggest that, when a rhythm-control strategy is desired, catheter ablation using RFA or cryoablation is a reasonable alternative to antiarrhythmic drug therapy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have symptomatic paroxysmal or persistent AF who have failed antiarrhythmic drugs who receive pulsed field ablation, the evidence includes RCTs. Relevant outcomes are overall survival (OS), symptoms, morbid events, and quality of life. One noninferiority RCT compared PFA with thermal ablation techniques in patients with paroxysmal AF. PFA was found to be noninferior for the primary composite outcome of initial procedural failure, documented atrial tachyarrhythmia after a 3-month blanking period, antiarrhythmic drug use, cardioversion, or repeat ablation. The incidence of serious adverse events was similar between groups. The publication provided minimal reporting of thermal ablation technique. One noninferiority RCT compared dual energy PFA and RFA to RFA in patients with persistent AF. Dual energy PFA and RFA was found to be noninferior to RFA for the primary effectiveness and safety outcomes. Both RCTs included primarily White participants. Numerous nonrandomized trials have been conducted and found high success rates with acceptable safety. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information

2025 Input

Clinical input was sought to help determine whether the use of pulsed field ablation for individuals with symptomatic paroxysmal or persistent atrial fibrillation who have failed antiarrhythmic drugs would provide a clinically meaningful improvement in net health outcome and represents generally accepted medical practice in selected patients. In response to requests, clinical input was received from 3 respondents, including 2 specialty society-level responses.

For individuals with symptomatic paroxysmal or persistent atrial fibrillation who have failed antiarrhythmic drugs, clinical input supports this use provides a clinically meaningful improvement in net health outcomes and indicates this use is consistent with generally accepted medical practice. Further details from clinical input are included in the Appendix.

Related Policies

- Open and Thoracoscopic Approaches to Treat Atrial Fibrillation and Atrial Flutter (Maze and Related Procedures)

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

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 the 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.

Pulsed field ablation (non-thermal energy) devices have also been approved by the FDA for catheter ablation of atrial fibrillation (FDA product code: QZI). FARAPULSE™ (Boston Scientific) is approved for paroxysmal AF in drug-resistant patients. PulseSelect™ (Medtronic) is approved for both paroxysmal and persistent AF. Sphere-9™ Catheter and Affera™ Ablation System (Medtronic) is capable of delivering either radiofrequency energy or pulsed field energy is approved for drug refractory, recurrent, symptomatic persistent atrial fibrillation (episode duration less than 1 year).

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

Rationale

Background

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 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.

Atrial fibrillation can be subdivided into 3 types: paroxysmal, persistent, and permanent. Atrial fibrillation 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 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 typically recommended. Atrial fibrillation 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.

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 re-establish and maintain normal sinus rhythm. Rhythm control has long been considered an important treatment goal for the 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 so that drug therapy becomes more effective. Ablative approaches focus on the 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 (see evidence review 2.02.01). The situation is more complex for AF because there may be no single arrhythmogenic focus. Atrial fibrillation 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.

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

Pulsed field ablation (PFA) employs a series of brief electrical pulses to desiccate tissue without significantly heating the tissue and is believed to be more selective for myocardial tissue than other ablative techniques. Two PFA devices were recently approved in the US.

Repeat Procedures

Repeat procedures following initial RFA are commonly performed if AF recurs or if atrial flutter develops post-procedure. 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 associated with the need for a second procedure include the length of AF, permanent AF, left atrial size, and left ventricular ejection fraction.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and 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 technology, 2 domains are examined: the relevance, and 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.

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In patients with paroxysmal or persistent atrial fibrillation (AF), catheter ablation may be considered an alternative to drug therapy.[1,] In patients with permanent AF, catheter ablation may be considered an alternative to drug therapy or atrioventricular (AV) nodal ablation and pacing.[2,] 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 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.[3,4,5,] 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 Individuals with Symptomatic Paroxysmal or Persistent Atrial Fibrillation Who Have Failed Medical Management

Clinical Context and Therapy Purpose

The purpose of catheter ablation using radiofrequency ablation (RFA) or cryoablation is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with symptomatic paroxysmal or persistent AF who have failed medical management.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with symptomatic paroxysmal or persistent AF who have failed medical management. Paroxysmal AF episodes last less than 7 days and are self-

terminating. Persistent AF episodes last for more than 7 days and can be terminated pharmacologically or by electrical cardioversion.

Interventions
The therapy being considered is RFA or cryoablation. In RFA, an electrical current produced by a radio wave is used to destroy an arrythmogenic focus. Cryoablation uses an extreme cold thermoconductive technique to destroy tissue.

Comparators
Comparators of interest include medication management. Medication management can include heart rate or rhythm control medications. Rate control medication therapy includes calcium channel blockers, beta-blockers, and digoxin. Rhythm control medications include dronedarone and amiodarone.

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.

Outcomes
The general outcomes of interest are overall survival (OS), symptoms, morbid events, and quality of life. 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.[6,] 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% confidence interval [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/transient ischemic attack (TIA) (0.6%), and pulmonary vein stenosis (0.5%).

Various outcomes for the treatment of AF may be considered.[7,] 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 is also an important outcome because quality of life measures reflect important manifestations of AF, such as symptoms and reduced exercise tolerance. Atrial fibrillation has been shown to be associated with lower quality of life scores, and maintenance of sinus rhythm has been associated with higher quality of life 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.[7,] 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.[7,] 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 American College of Cardiology, American Heart Association, and European Society of Cardiology (2006) practice guidelines for the treatment of AF.[8,] These guidelines pointed out that the appropriate endpoints 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 endpoint, but this endpoint is less useful in studies of paroxysmal AF. Given all these variables, ideally, controlled clinical trials would report a range of outcomes (including quality of life) and complications in the 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).

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Radiofrequency Ablation

Systematic Reviews

The literature review for this evidence review was informed by a TEC Assessment (2008).[9,]Six RCTs met the Assessment inclusion criteria.[10,11,12,13,14,15,] 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[15,]); (2) patients with symptomatic paroxysmal or persistent AF who had failed treatment with antiarrhythmic drugs (4 trials[10,12,13,14,]); 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[11,]).

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 quality of life outcomes. One of these only reported within-group comparisons, as opposed to between-group comparisons.[12,] The other 3 trials reported improvements in quality of life associated with catheter ablation.[10,11,15,] 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 quality of life 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 quality of life, 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.

Asad et al (2019) reported on the results of a meta-analysis of all-cause mortality using data from 18 RCTs that compared catheter ablation (n=2286) to medical therapy (n=2178) in all types of patients with AF.[16] Although the meta-analysis encompassed a broad range of patient populations, it also reported results of a subgroup analysis based on the presence of heart failure with reduced ejection fraction. Review authors reported that overall, compared to medical therapy, catheter ablation resulted in a significant reduction in all-cause mortality (relative risk [RR], 0.69; 95% CI, 0.54 to 0.88). However, they noted that this finding was largely driven by results from the Catheter Ablation for Atrial Fibrillation With Heart Failure (CASTLE-AF) RCT described below by Marrouche et al (2018),[17] which is comprised of patients with AF and heart failure with reduced ejection fraction.
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.[18] Reviewers selected 3 RCTs (N=261; Forleo et al [2009],[19] Stabile et al [2006],[14] and Mont et al [2014];[20] 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).[18]
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.[18]

Shi et al (2015) reported on the results of a meta-analysis of RCTs comparing catheter ablation with antiarrhythmic drug therapy for AF.[21] The meta-analysis included 11 trials (N=1763), 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 3 RCTs 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 (RR, 0.47; 95% CI, 0.38 to 0.58; p<.001).
A Cochrane review by Chen et al (2012) evaluated catheter ablation for paroxysmal and persistent AF.[22] 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.[23] 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 (N=6167). For a single procedure, the pooled overall success rate at 12 months post-procedure 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 the 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.

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.[24,] In a summary of data from 26 studies enrolling 1821 patients, RFA was associated with improvements in left atrial volume measurements compared with pre-ablation (e.g., for left atrial diameter); the weighted mean difference (WMD) was -1.52 mm (95% CI, -2.57 to -0.47). 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.[25,] 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.[19,] 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. Quality of life 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.[20,] 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=.002). Quality of life 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.[17,] 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=.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=.004) than found in patients treated with medical therapy alone.

Kuck et al (2021) conducted a multicenter RCT comparing RFA with medical therapy in patients with paroxysmal AF to evaluate which strategy is more effective in delaying the progression to persistent AF.[26,] Patients were included if they had paroxysmal AF for at least 2 years and failed treatment with 1 to 2 antiarrhythmic drugs. The trial was terminated early due to slow enrollment after the inclusion of 255 patients (target enrollment was 322); 128 received RFA and 127 received medical therapy. The primary endpoint, rate of persistent AF or atrial tachycardia at 3 years, was significantly lower with

RFA (2.4%; 95% CI, 0.6 to 9.4) than with medical therapy (17.5%; 95% CI, 10.7 to 27.9; one-sided p=.0009). However, only 36% and 41% of patients who received RFA and medical therapy, respectively, completed 3 years of follow-up. The incidence of recurrent AF was consistently lower with RFA than with medical therapy from 6 months through the 3-year follow-up period.

Wu et al (2021) published the results of a multi-center RCT comparing the effects of RFA and antiarrhythmic drug therapy in patients with persistent and long-standing AF.[27,] A total of 648 participants were randomized to either the RFA group (n=327) or the antiarrhythmic drug therapy group (n=321). After a mean follow-up of 54±10.6 months, fewer participants in the RFA versus antiarrhythmic drug therapy group experienced the primary composite outcome of stroke/TIA , systemic embolism, major bleeding, and new-onset congestive heart failure (10.4% vs. 17.4%; HR, 0.59, 95% CI, 0.48 to 0.75). When considering the individual components of the primary outcome, only the difference in the incidence of stroke (both ischemic and hemorrhagic) and new-onset congestive heart failure reached statistical significance in favor of RFA over antiarrhythmic drug therapy.

Longer-Term Outcomes

The available RCTs have mainly reported on short-term outcomes (≤1 year) and, therefore, do not provide data on the rate of recurrences after 3 years. 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).[28,] During the first year after ablation, 23.8% had a recurrence of AF. During the remaining follow-up, recurrences occurred in 8.9% of 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.[29,]

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.[30,] 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 post-procedure, 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<.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 a 5-year follow-up in 100 patients treated with catheter ablation.[31,] 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.[32,] 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.[33,] 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.[34,] 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.[35,] 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.[36,] Atrial fibrillation 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 [15,19,] 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%,[20,] 9%,[13,] 20%,[11,] and 32%[12,] 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 patients in the catheter ablation group.[37,] 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.[14,] 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.[10,]

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 re-ablation increases the success of the procedure when defined as maintenance of sinus rhythm at 1 year.[38,] 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.[38,]

Pokushalov et al (2013) reported on the 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.[39,] After an initial post-ablation 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<.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 intention-to-treat (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=.02).

Cryoablation

Randomized Controlled Trials

Packer et al (2013) reported on the results of the Sustained Treatment of Paroxysmal Atrial Fibrillation trial, an RCT comparing cryoablation with antiarrhythmic medications.[40,] This trial enrolled 245 patients with paroxysmal AF who had failed at least 1 (median, 1.2) membrane-active antiarrhythmic medication. 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 versus 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<.001 for noninferiority). Phrenic nerve injury occurred at a rate of 13.5%, of which 86% resolved at 12 months.

Nonrandomized Controlled Trials

Su et al (2018) performed a multicenter, retrospective study of patients with drug-refractory paroxysmal AF who underwent cryoballoon ablation.[41,] 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.[42,] 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.[43,] 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.[44,] At the 6-, 12-, 24-, and 36-month follow-ups, 88%, 71%, 49%, and 31% had no documented recurrence of AF, respectively. Davies et al (2016) reported on AF recurrence rates (median follow-up, 56 months) for 200 patients with paroxysmal or persistent AF after cryoablation.[45,] 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 Sustained Treatment of Paroxysmal Atrial Fibrillation trial to evaluate the incidence and significance of early recurrence of AF after ablation.[46,] 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<.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.[47,] 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.[48,] Data were collected on 32,569 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 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 Mesh Ablator versus Cryoballoon Pulmonary Vein Ablation of Symptomatic Paroxysmal Atrial Fibrillation investigators evaluated patients pre- and post-catheter 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.[49,] However, these brain lesions were not associated with cognitive dysfunction immediately post-procedure. Longer-term follow-up was reported by Herm et al (2013).[50,] At follow-up MRI 6 months post-procedure, 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.[51,] 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.[52,] 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.[53,] 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 Radiofrequency Ablation 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.[54,] The trial's primary effectiveness endpoint 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=.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.[55,]

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.[56,] 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=.01).

Section Summary: Individuals with Symptomatic Paroxysmal or Persistent Atrial Fibrillation who have Failed Antiarrhythmic Drugs

Radiofrequency Ablation for Atrial Fibrillation

Numerous RCTs of RFA for isolation of the pulmonary veins versus 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. Quality of life 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 number 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. Major adverse events in these studies range 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

Clinical Context and Therapy Purpose

The purpose of RFA or cryoablation is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with symptomatic AF and congestive heart failure who have failed rate control and antiarrhythmic drugs.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with symptomatic AF and congestive heart failure who have failed rate control and antiarrhythmic drugs. Rate control medication therapy includes calcium channel blockers, beta-blockers, and digoxin. Rhythm control medications include dronedarone and amiodarone.

Interventions

The therapy being considered is RFA or cryoablation.

Comparators

Comparators of interest include AV nodal ablation and pacemaker insertion. Atrioventricular node ablation is a cardiac catheterization procedure applying energy to the pathway connecting the upper chambers and lower chamber of the heart through a catheter. 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. It is an invasive procedure indicated when other rate and rhythm control interventions have failed.

Outcomes

The general outcomes of interest are OS, symptoms, morbid events, and quality of life.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
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.[57,] Three trials (N=143; range, 41 to 52) met reviewers' inclusion criteria, all of which used blinded outcome assessment and were considered to have a low risk of bias. For the meta-analysis' primary endpoint, 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 (NYHA) functional class, and quality of life 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.[58,] For the population of patients with chronic heart failure, reviewers identified 17 observational studies, 4 RCTs, and 4 meta-analyses. Among the 4 RCTs, 1 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 the 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.[59,] 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 (WMD= +6.5; 95% CI, 0.6 to 12.5; p=.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<.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=.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.[37,] There was no requirement for patients to have failed antiarrhythmic drug therapy. The trial's primary endpoint was the difference between groups in LVEF at 6 months post-procedure. 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. The LVEF at 6 months post-procedure was 40% in the catheter ablation group compared with 31% (p=.015) in the medical management group. Catheter ablation was also associated with improvements in health-related quality of life.

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.[60,] Fifty-two patients were randomized, 26 each to catheter ablation or medical rate control. At 12 months post-procedure, 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 post-procedure), 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 ; p=.018).

Kuck et al (2019) reported on results from the Atrial Fibrillation Management in Congestive Heart Failure With Ablation (AMICA) RCT that compared catheter ablation in addition to optimal medical treatment with optimal medical treatment alone. The AMICA enrolled patients with a documented episode of symptomatic persistent or longstanding persistent AF and seriously advanced heart failure, defined as NYHA class II or III heart failure, an LVEF of 35% or less, and an indication for an implantable cardioverter defibrillator or cardiac resynchronization therapy defibrillator (CRT-D)

therapy.[61,] A total of 140 patients were randomized, 68 to the ablation group and 72 to the medication alone group. At 1 year, no benefits of the catheter ablation group were revealed and the RCT was terminated early for futility.

Packer et al (2021) reported results on the subgroup of patients with heart failure at baseline in the Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial, which evaluated whether catheter ablation is more effective than conventional medical therapy to prevent major cardiovascular events in AF (main trial results summarized below).[62,] Out of the 2204 patients randomized in the main trial, 35% (n=778) had heart failure at baseline. The CABANA primary endpoint was a composite of death, disabling stroke, serious bleeding, and/or cardiac arrest. For the subgroup with heart failure, RFA resulted in a significant reduction in the primary endpoint (HR, 0.64; 95% CI, 0.41 to 0.99) and all-cause mortality (HR, 0.57; 95% CI, 0.33 to 0.96) compared to drug therapy alone over a median follow-up of 48.5 months.

Parkash et al (2022) reported results from the Randomized Ablation-Based Rhythm-Control Versus Rate-Control Trial in Patients With Heart Failure and Atrial Fibrillation (RAFT-AF) trial.[63,] The trial evaluated whether ablation-based rhythm control would improve clinical outcomes in patients with heart failure and AF compared to rate control (by medication or AV node ablation). The trial enrolled patients (N=411) with high-burden paroxysmal or persistent AF and NYHA class II and III HF; patients were randomized to ablation-based rhythm control (n=214) or rate control (n=197). Antiarrhythmic medications were permitted in the ablation-based rhythm group for 4 to 6 weeks post-ablation, and then could be used as adjunctive therapy if needed. The primary outcome was a composite of HF events and all-cause mortality, and it occurred in 50 (23.4%) patients in the ablation-based rhythm group and 64 (32.5%) patients in the rate-control group (HR, 0.71; 95% CI, 0.49 to 1.03; p=.066). Ablation-based rhythm control was also associated with an increase in LVEF, increase in 6-minute walk distance, and decrease in N-terminal pro brain natriuretic peptide.

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 Atrial Fibrillation and Congestive Heart Failure Who Have Failed Rate Control and Antiarrhythmic Drugs

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. No literature on cryoablation was identified.

Individuals with Recurrent Symptomatic Paroxysmal Atrial Fibrillation

Clinical Context and Therapy Purpose

The purpose of RFA or cryoablation as an initial rhythm-control strategy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with recurrent symptomatic paroxysmal AF.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with recurrent symptomatic paroxysmal AF. Untreated paroxysmal AF recurs with a variable frequency which may be as high as 70% within 5 years. Recurrent paroxysmal AF is a risk factor for progression to persistent or permanent AF with attendant risks for heart failure and stroke.

Interventions

The therapy being considered is RFA or cryoablation as an initial rhythm-control strategy.

Comparators
Comparators of interest include medication management.

Outcomes
The general outcomes of interest are OS, symptoms, morbid events, and quality of life.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Systematic Reviews (Multiple Modalities)
Turagam et al (2021) published a systematic review with a meta-analysis of 6 RCTs to assess the efficacy and safety of catheter ablation versus antiarrhythmic drug therapy as first-line treatment in patients with paroxysmal AF.[64,] Five of the 6 RCTs included in the meta-analysis are summarized in greater detail in the sections below (Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation: A Randomized Prospective Multicentre Study [MANTRA-PAF], First Line Radiofrequency Ablation Versus Antiarrhythmic Drugs for Persistent Atrial Fibrillation Treatment [RAAFT]-2, STOP-AF First: Cryoballoon Catheter Ablation in Antiarrhythmic Drug Naive Paroxysmal Atrial Fibrillation, Early Aggressive Invasive Intervention for Atrial Fibrillation [EARLY-AF], and Cryo-FIRST). Ablation was performed using RFA catheters and cryoballoon catheters in 3 RCTs each. Results demonstrated that catheter ablation significantly reduced the risk of recurrence of any atrial arrhythmia (both symptomatic and asymptomatic) including AF, atrial flutter, or atrial tachycardia (RR, 0.62; 95% CI, 0.51 to 0.74). Furthermore, there was a significant reduction in the rate of hospitalizations with catheter ablation versus antiarrhythmic drug therapy (RR, 0.32; 95% CI, 0.19 to 0.53). The risk of adverse events was similar between treatment groups (RR, 1.52; 95% CI, 0.81 to 2.85).

Elsayed et al (2021) published a systematic review with a meta-analysis of the same 6 RCTs as Turagam et al (2021), but stratified results by the type of catheter ablation technology used.[65,] When compared to antiarrhythmic drug therapy, the overall risk of recurrence of any atrial arrhythmia was significantly reduced with RFA (odds ratio [OR], 0.31; 95% credible interval [CrI], 0.10 to 0.71); the risk reduction with cryoablation was borderline statistically significant (OR, 0.39; 95% CrI, 0.16 to 1.00). Similarly, RFA significantly reduced the risk of hospitalizations compared to antiarrhythmic drug therapy (OR, 0.08; 95% CrI, 0.01 to 0.99), whereas cryoablation did not (OR, 0.77; 95% CrI, 0.44 to 1.39). Freedom from symptomatic AF recurrence was not significantly reduced with either cryoablation or RFA compared to antiarrhythmic drug therapy, but pooled analysis that included both technologies showed a reduced risk of arrhythmia recurrence in favor of catheter ablation (OR, 0.35; 95% CrI, 0.13 to 0.79). The risk of serious adverse events rates did not significantly differ between either ablation technology and antiarrhythmic drug therapy. Treatment ranking based on the surface under the cumulative ranking curve put RFA as most likely to be the best treatment for reducing the overall rates of AF recurrence, symptomatic recurrence, and hospitalizations, whereas cryoablation was most likely to reduce serious adverse events.

Randomized Controlled Trials (Multiple Modalities)
Packer et al (2019) published results from the 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.[66,] A total of 2204 patients were enrolled and randomized 1:1 from November 2009 to April 2016. Follow-up was conducted through December 2017.

Catheter ablation devices used energy sources available at the clinical trial site and with which investigators had the requisite expertise. The primary endpoint (a composite of death, disabling stroke, serious bleeding, and/or cardiac arrest) occurred in 8.0% of patients in the catheter ablation group and in 9.2% of patients in the drug therapy group (HR, 0.86; 95% CI, 0.65 to 1.15; p=.30). 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 quality of life outcomes (median follow-up of 48.5 months) for participants in the CABANA trial.[67,] The Atrial Fibrillation Effect on Quality-of-Life (AFEQT) mean summary score in the catheter ablation group was 86.4 points versus 80.9 points in the drug therapy group (adjusted difference 5.3 points [95% CI, 3.7 to 6.9]: p<.001). The AFEQT scores range from 0 (complete AF-related disability) to 100 (no AF-related disability) and a change in score of at least 5 is considered a clinically meaningful difference (adjusted difference, -1.5 points; 95% CI, -2.0 to 1.1; p<.001). The trial used a modified Mayo AF-Specific Symptom Inventory (MAFSI) questionnaire combining frequency scores ranging from 0 to 4 (never to always) and severity scores ranging from 0 (no AF symptoms) to 40 (most severe AF symptoms). The investigators suggested 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 of the Catheter Ablation compared with Pharmacological Therapy for Atrial Fibrillation trial, an RCT designed to assess the quality of life after catheter ablation compared to medical therapy.[68,]The primary outcome at 12 months was the difference in the General Health subscale score. The quality of life score increases in the catheter ablation group from 61.8 to 73.9 points versus 62.7 to 65.4 points in the medication group (95% CI, 3.1 to 14.7; p=.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.[69,] They selected 3 trials (N=491), including the RAAFT-2 (2014)[70,]and MANTRA-PAF (2012)[71,] trials (described below) and the earlier RAAFT-1 trial. The 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=.02; I^2=38%).

Randomized Controlled Trials

First Line RF Ablation Versus Antiarrhythmic Drugs for Persistent AF Treatment (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.[70,] 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 re-ablation 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 ITT. Patients were followed with biweekly scheduled trans-telephonic 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=.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=.03) or recurrence of symptomatic AF (41% vs. 57%; HR, 0.52; 95% CI, 0.3 to 0.89; p=.02). Quality of life measures did not differ significantly between groups.

Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation: A Randomized Prospective Multicentre Study (MANTRA-PAF)

An earlier RCT (MANTRA-PAF) that evaluated RFA as the initial therapy for paroxysmal AF was reported by Cosedis Nielsen et al (2012).[71,] A total of 294 patients were randomized to initial treatment with catheter ablation or to pharmacologic therapy. Patients were followed for 24 months for the primary outcomes of the 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=.007). The 90th percentile cumulative burden did not differ significantly between groups (13% vs. 19%; p=.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=.004), as was the secondary outcome of freedom from symptomatic AF (93% vs. 84%, p=.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).[72,] 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=.001). Symptomatic AF burden was also significantly lower in the RFA group, although quality of life scores did not differ between groups.

Cryoablation

Randomized Controlled Trials

Andrade et al (2021) evaluated the efficacy of first-line cryoablation in patients with symptomatic, paroxysmal, untreated AF as compared to antiarrhythmic drug therapy for initial rhythm control (EARLY-AF trial).[73,] The primary outcome was the first documented recurrence of any atrial tachycardia between 91 and 365 days after catheter ablation or the initiation of medication. A total of 303 patients were randomized to undergo cryoablation (n=154) or to receive antiarrhythmic drug therapy (n=149) and followed for 12 months. At 12 months, recurrence of atrial tachyarrhythmia occurred in 42.9% of patients receiving cryoablation and 67.8% of patients receiving antiarrhythmic drugs (HR, 0.48; 95% CI, 0.35 to 0.66, p<.001). Symptomatic atrial tachyarrhythmia recurred in 11.0% assigned to cryoablation as compared to 26.2% assigned to receive antiarrhythmic drugs (HR, 0.39; 95% CI, 0.22 to 0.68).

Andrade et al (2023) also reported on 3-year follow-up data of the EARLY-AF trial.[74,] Over a 3-year period, 3 patients (1.9%) in the cryoablation group had a persistent AF episode compared to 11 (7.4%) patients in the antiarrhythmic drug group (HR, 0.25; 95% CI, 0.09 to 0.70). Recurrent atrial tachyarrhythmia was reported in 87 patients (56.5%) in the cryoablation group compared to 115 (77.2%) in the antiarrhythmic drug group (HR, 0.51; 95% CI, 0.38 to 0.67). Hospitalization occurred in 8 patients in the cryoablation group compared to 25 patients in the antiarrhythmic drug group (RR, 0.31; 95% CI, 0.14 to 0.66).

Kuniss et al (2021) evaluated the efficacy of first-line cryoablation in patients with symptomatic, paroxysmal, untreated AF as compared to antiarrhythmic drug therapy for initial rhythm control (Cryo-FIRST trial).[75,] The primary endpoint was at least 1 episode of recurrent atrial arrhythmia (AF, atrial flutter, or atrial tachycardia) more than 30 seconds after a prespecified 90-day blanking period. A total of 218 patients were randomized to cryoablation or antiarrhythmic drug therapy. At month 12, freedom from atrial arrhythmia was achieved in 82.2% of participants in the cryoablation group and 67.6% of participants in the antiarrhythmic drug therapy group (HR, 0.48; p=.01). Pavlovic et al (2021) reported certain quality of life outcomes in the Cryo-FIRST trial that were likewise significantly improved. Symptomatic palpitations were significantly reduced with cryoablation versus antiarrhythmic drug therapy.[76,] At 12 months, the mean adjusted difference in the AFEQT summary score was 9.9 points higher in the cryoablation group (95% CI, 5.5 to 14.2; p<.001). Conversely, while

improvements in the 36-Item Short Form Survey (SF-36) summary score exceeded the clinically important difference (i.e., 2 points) in both groups, the between-group difference did not reach statistical significance. Palpitations were experienced by 28% of patients in the cryoablation group and 44.1% of patients in the antiarrhythmic drug therapy group (p<.001).

Wazni et al (2021) also evaluated the efficacy of first-line cryoablation in patients with symptomatic, paroxysmal, untreated AF as compared to antiarrhythmic drug therapy (STOP-AF trial).[77,] The primary outcome was treatment success (freedom from initial failure of the procedure or atrial arrhythmia recurrence after a 90-day blanking period) at 1 year. A total of 203 patients were randomized to undergo cryoablation (n=104) or to receive antiarrhythmic drug therapy (n=99). In the cryoablation group, 97% of patients achieved initial success with the procedure. At month 12, Kaplan-Meier estimates of the percentage of patients with treatment success were 74.6% (95% CI, 65.0 to 82.0) in the ablation group and 45.0% (95% CI, 34.6 to 54.7) in the drug-therapy group (p<.001). Wazni et al (2021) separately reported that cryoablation significantly improved quality of life outcomes in the STOP-AF trial.[78,] A clinically meaningful improvement (i.e., >5 points) in the AFEQT summary score from baseline to 12 months was observed in 96.0% of patients in the cryoablation group and 72.2% of patients in the antiarrhythmic drug therapy group (p<.001). However, there were no statistically significant between-group differences for the change in the European Quality of Life–5 Dimensions index or visual analog scale scores. After a 90-day blanking period, a higher proportion of patients in the cryoablation versus the antiarrhythmic drug therapy group reported no AF-specific symptom recurrence (54.4% vs. 29.7; p=.0005).

Section Summary: Individuals with Recurrent Symptomatic Paroxysmal Atrial Fibrillation

Numerous systematic reviews and RCTs, including those that evaluated long-term outcomes, have evaluated RFA and cryoablation in patients with recurrent symptomatic paroxysmal AF. The CABANA trial noted that the use of RFA did not show significant improvement over medications. However, 3 RCTs comparing cryoablation to antiarrhythmic drug therapy as first-line therapy demonstrated improved outcomes for atrial arrhythmia recurrence up to 1 year. In a meta-analysis of 6 RCTs, catheter ablation as first-line therapy in patients with paroxysmal AF significantly reduced the risk of recurrence of atrial arrhythmia and the rate of hospitalizations when compared to antiarrhythmic drug therapy. In another meta-analysis of the same RCTs, treatment ranking based on surface under the cumulative ranking curve ranked RFA as most likely to be the best treatment for reducing the overall rates of AF recurrence, symptomatic recurrence, and hospitalizations, whereas cryoablation was most likely to reduce serious adverse events.

Pulsed Field Ablation for Individuals with Symptomatic Paroxysmal or Persistent Atrial Fibrillation Who Have Failed Medical Management

Clinical Context and Therapy Purpose

The purpose of pulsed field ablation (PFA) is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with symptomatic paroxysmal or peristent AF who have failed medical management.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with paroxysmal or persistent AF who have failed medical management. Paroxysmal AF episodes last less than 7 days and are self-terminating. Persistent AF episodes last for more than 7 days and can be terminated pharmacologically or by electrical cardioversion.

Interventions

The therapy being considered is PFA.

Comparators
Comparators of interest include RFA or cryoablation.

Outcomes
The general outcomes of interest are OS, symptoms, morbid events, and quality of life.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Randomized Controlled Trials
Reddy et al (2023) compared PFA to thermal ablation (radiofrequency or cryoballoon) in a randomized, single-blind, noninferiority trial in patients with treatment-refractory paroxysmal AF.[79,] A total of 305 patients were randomized to PFA and 302 to thermal ablation. The primary efficacy endpoint was a composite of initial procedural failure, documented atrial tachyarrhythmia after a 3-month blanking period, antiarrhythmic drug use, cardioversion, or repeat ablation. Tables 2 and 3 summarize the RCT characteristics and results, respectively. PFA was found to be noninferior to thermal ablation with the composite endpoint largely driven by recurrent arrhythmias or antiarrhythmic use after the blanking period (approximately 16% to 17% and 8% to 9% of patients, respectively). In an analysis of pulmonary vein narrowing from the ADVENT study, there was no significant stenosis found with either treatment; however, the change in cross-sectional area was less with PFA than thermal ablation (-0.9% vs -12%).[80,] Limitations are described in Tables 4 and 5.

Anter et al (2024) reported results of the SPHERE Per-AF (NCT05120193) randomized, single-blind, non-inferiority trial comparing a dual-energy (PFA and RFA) platform with a RFA platform in 432 adults ages 18 to 80 with drug-refractory persistent AF.[81,82,] The dual-energy device was a lattice-tip catheter (Sphere-9 catheter, Medtronic) with a compatible proprietary electro-anatomical mapping system (Affera Mapping and Ablation System, Medtronic). The control device was an electro-anatomical mapping system (Carto 3, Biosense Webster), a multi-electrode mapping catheter and a contact force-sensing ablation catheter (THERMOCOOL SMARTTOUCH, Biosense Webster). In the dual-energy arm, operators were instructed to use PFA on the posterior wall, around the left inferior pulmonary vein and near the phrenic nerve but had discretion to use either PFA or RFA in other areas. The trial was conducted from December 2021 to December 2022 in 23 sites in the US (18 sites), Czech Republic (3 sites) and Israel (1 site). The primary composite effectiveness outcome of treatment success was evaluated through 1 year and included freedom from acute procedural failure and repeat ablation at any time, plus arrhythmia recurrence, drug initiation or escalation or cardioversion after a 3-month blanking period. The primary safety outcome was freedom from a composite of serious procedure-related or device-related adverse events. Arrhythmia recurrence was monitored with ECG at follow-up visits, 24-hour Holter monitoring at 6 and 12 months, and both scheduled and symptomatic event monitor recordings. Events were adjudicated by a blinded Clinical Events Committee. The median age of participants was 68 years. Approximately one-third of the participants were female. 94% of participants were White, 2% were Black or African American and 2% were Asian. The median time from first diagnosis of persistent AF was 0.5 years. 69% had a previous electrical cardioversion for AA. 65% had no signs of heart failure. Both the primary effectiveness and primary safety outcomes met the pre-specified criteria for non-inferiority. Study

characteristics, results and limitations are in Tables 2 through 5. The procedure time was shorter in the dual energy group compared to control group (101 min vs 126 min; p<.01).

Table 2. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Reddy et al (2023); ADVENT[79,]	US, other	NR	Mar 2021 to Jun 2022	Patients with paroxysmal AF refractory to ≥1 antiarrhythmic	PFA (n=305)	Thermal ablation (n=302)
Anter et al (2024); SPHERE Per-AF (NCT05120193)[81,82,]	US, other	23	Dec 2021 to Dec 2022	Patients with persistent AF (episode duration < 1 yr) with failure or intolerance of ≥1 Class I or III arrhythmic	Dual PFA and RFA (n=212)	RFA (n=208)

AF: atrial fibrillation; PFA: pulsed field ablation; RCT: randomized controlled trial.

Table 3. Summary of Key RCT Results

Study	Effectiveness Outcome	Safety outcome
	Treatment success at 1 year[a]	**Serious AEs**
Reddy et al (2023); ADVENT	N=607	N=607
PFA, n (%)	204 (73.3%)	6 (2.4%)
Thermal ablation, n (%)	194 (71.3%)	4 (1.5%)
Difference (95% BCI)	2% (-5.2 to 9.2)	0.6% (-1.5 to 2.8)
p for NI	>.999	>.999
p for superiority	.708	NR
Anter et al (2024); SPHERE Per-AF (NCT05120193)	**Treatment success at 1 year[b]**	**Primary safety event[c]**
Dual PFA and RFA, n (%)	155 (73.8%)	3 (1.4%)
RFA, n (%)	133 (65.8%)	2 (1.0%)
Difference (CI)	8.0% (95% CI, -0.9% to 16.8%)	0.5% (90% CI, -2.8% to 3.7%)

AE: adverse event; CI: confidence interval; BCI: Bayesian confidence interval; NI: noninferiority; PFA: pulsed field ablation; RFA: radiofrequency ablation.
[a] Composite of treatment failure included: initial procedural failure, documented atrial tachyarrhythmia after a 3-month blanking period, antiarrhythmic drug use, cardioversion, or repeat ablation
[b] Composite of freedom from acute procedural failure and repeat ablation at any time, plus arrhythmia recurrence, drug initiation or escalation or cardioversion after a 3-month blanking period
[c] Composite of serious procedure-related or device-related adverse events

Table 4. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Reddy et al (2023); ADVENT	4. >90% White; 3. persistent AF patients excluded		1. thermal ablation methods not well-defined	3. phrenic nerve injury not included in AEs	
Anter et al (2024); SPHERE Per-AF (NCT05120193)	4. >90% White				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference

not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 5. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Reddy et al (2023); ADVENT		1. single-blind				
Anter et al (2024); SPHERE Per-AF (NCT05120193)		1. single-blind; however, events were adjudicated by a blinded committee				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Section Summary: Pulsed Field Ablation for Individuals with Symptomatic Paroxysmal or Persistent Atrial Fibrillation Who Have Failed Medical Management

One noninferiority RCT compared PFA with thermal ablation techniques in patients with paroxysmal AF. PFA was found to be noninferior for the primary composite outcome of initial procedural failure, documented atrial tachyarrhythmia after a 3-month blanking period, antiarrhythmic drug use, cardioversion, or repeat ablation. The incidence of serious adverse events was similar between groups. The publication provided minimal reporting of thermal ablation technique. One noninferiority RCT compared dual energy PFA and RFA to RFA in patients with persistent AF. Dual energy PFA and RFA was found to be noninferior to RFA for the primary effectiveness and safety outcomes. Both RCTs included primarily White participants. Numerous nonrandomized trials have been conducted and found high success rates with acceptable safety.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2025 Input

Clinical input was sought to help determine whether the use of pulsed field ablation for individuals with symptomatic paroxysmal or persistent atrial fibrillation who have failed antiarrhythmic drugs would provide a clinically meaningful improvement in net health outcome and represents generally accepted medical practice in selected patients. In response to requests, clinical input was received from 3 respondents, including 2 specialty society-level responses. For individuals with

symptomatic paroxysmal or persistent atrial fibrillation who have failed antiarrhythmic drugs, there was consensus that this use provides a clinically meaningful improvement in net health outcomes and indicates this use is consistent with generally accepted medical practice.

2015 Input

In response to requests, input was received from 3 physician specialty societies (6 reviewers) and 4 academic medical centers while this policy was under review in 2015. Input focused on the use of ablation as an initial procedure for symptomatic paroxysmal and persistent atrial fibrillation (AF) and the use of cryoablation for AF. There was consensus supporting the use of radiofrequency ablation (RFA) as an initial treatment for symptomatic paroxysmal AF, and the use of cryoablation as an alternative to RFA as a treatment for AF. For the use of RFA as initial treatment for symptomatic persistent AF, support from clinical input was more mixed.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Cardiology et al

In 2023, the American College of Cardiology, American Heart Association, American College of Clinical Pharmacy, and Heart Rhythm Society (ACC/AHA/ACCP/HRS) updated guidelines for the management of patients with AF.[83,] The recommendations specific to catheter ablation are summarized in Table 6. In addition, the guidelines recommend, "PVI [pulmonary vein isolation] is recommended as the primary lesion set for all patients unless a different specific trigger is identified." However, no particular ablation method is recommended.

Table 6. Guidelines for Rate and Rhythm in Management of Atrial Fibrillation

Recommendation	COR[a]	LOE[b]
"In patients with symptomatic AF in whom antiarrhythmic drugs have been ineffective, contraindicated, not tolerated or not preferred, and continued rhythm control is desired, catheter ablation is useful to improve symptoms."	1	A
"In selected patients (generally younger with few comorbidities) with symptomatic paroxysmal AF in whom rhythm control is desired, catheter ablation is useful as first-line therapy to improve symptoms and reduce progression to persistent AF."	1	A
"In patients with symptomatic or clinically significant AFL, catheter ablation is useful for improving symptoms."	1	A
"In patients who are undergoing ablation for AF, ablation of additional clinically significant supraventricular arrhythmias can be useful to reduce the likelihood of future arrhythmia."	2a	B-NR
"In patients (other than younger with few comorbidities) with symptomatic paroxysmal or persistent AF who are being managed with a rhythm-control strategy, catheter ablation as first-line therapy can be useful to improve symptoms."	2a	B-R
"In selected patients with asymptomatic or minimally symptomatic AF, catheter ablation may be useful for reducing progression of AF and its associated complications."	2b	B-NR

AF: atrial fibrillation; AFL: atrial flutter; COR: class of recommendation; LOE: level of evidence.
[a] Where 1 is a strong recommendation, 2a is moderate, and 2b is a weak recommendation.
[b] Where Level A is evidence from more than 1 RCT/meta-analyses of RCTs, Level B-R is moderate quality evidence from 1 ore more RCTs, and Level B-NR is moderate quality evidence from 1 ore more well-designed nonrandomized studies.

American Heart Association

In 2021, the American Heart Association published a scientific statement regarding the management of atrial fibrillation in patients with heart failure.[84,] The statement included the following:
"In patients with AF and heart failure with reduced ejection fraction (HFrEF) who already have an indication for a cardiac resynchronization therapy defibrillator (CRT-D) device such as left bundle-

branch block (LBBB) and in whom AF remains poorly controlled despite maximum efforts at restoration and maintenance of sinus rhythm or pharmacological rate control, atrioventricular node (AVN) ablation should be considered for rate control and promotion of adequate biventricular pacing

- In patients with AF and HFrEF who have a narrow QRS but in whom AF remains poorly controlled despite maximum efforts at restoration and maintenance of sinus rhythm or pharmacological rate control, a strategy of AV node ablation with cardiac resynchronization therapy (CRT) implantation is reasonable, and
- In patients with AF and HFrEF, surgical AF ablation is reasonable in those patients undergoing concomitant cardiac surgery"

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 7.

Table 7. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05159492	Ground-Breaking Electroporation-based Intervention for PAROXysmal Atrial Fibrillation Treatment (BEAT PAROX-AF)	292 (Actual)	Feb 2025
NCT05971693	Safety and Effectiveness Evaluation of the OMNYPULSE Catheter With the TRUPULSE Generator for Treatment of Paroxysmal Atrial Fibrillation (PAF)	160	Apr 2025
NCT06039722	Prospective, Multicenter, Single-arm Clinical Trial Evaluating the Safety and Efficacy of the Pulse Field Ablation System in Combination With the Pulse Field Ablation Catheter for the Treatment of Paroxysmal Atrial Fibrillation	166	Aug 2024
NCT05717725	Pulsed-field Ablation Versus Sham Ablation to Treat Atrial Fibrillation	60	Dec 2024
NCT04942171	EMOTIon and COgNitive Function After Atrial FibrillationCatheter Ablation vs. Medical Therapy; Randomized Clinical Trial (EMOTICON Trial)	320	Feb 2026
NCT02150902	Augmented Wide Area Circumferential Catheter Ablation for Reduction of Atrial Fibrillation Recurrence (AWARE)	411	Sep 2025
NCT04037397	First Line Radiofrequency Ablation Versus Antiarrhythmic Drugs for Persistent Atrial Fibrillation Treatment (RAAFT-3)	25 (Actual)	Oct 2024
NCT05534581	Single Shot Pulmonary Vein Isolation: Comparison of Cryoballoon vs. Pulsed Field Ablation in Patients With Symptomatic Paroxysmal Atrial Fibrillation - A Multi-Center Non-Inferiority Design Clinical Trial (The SINGLE SHOT CHAMPION Trial)	210	Jan 2027
Unpublished			
NCT02106663	Evaluating the Efficacy of Circumferential Pulmonary Vein Ablation (CPVA) Versus Segmental Pulmonary Vein Isolation (SPVI) in Paroxysmal Atrial Fibrillation	97	Dec 2021

NCT: national clinical trial.

Appendix 1

2025 Clinical Input

Clinical Input Objective

Clinical input is sought to help determine whether the use of pulsed field ablation for individuals with symptomatic paroxysmal or persistent atrial fibrillation who have failed antiarrhythmic drugs would

provide a clinically meaningful improvement in net health outcome and represents generally accepted medical practice in selected patients. In response to requests, clinical input was received from 3 respondents, including 2 specialty society-level responses.

Clinical Input Respondents

Clinical input was provided by the following specialty societies and physician members identified by a specialty society or clinical health system:

- Society for Cardiovascular Angiography and Interventions (SCAI)
- Heart Rhythm Society (HRS)
- Kamala Tamirisa, MD, Texas Cardiac Arrhythmia, Austin, TX – identified by the American College of Cardiology (ACC)

Clinical Input Ratings

Clinical Indication	Respondent	Identified by	Confidence Level That Clinical Use Expected to Provide Clinically Meaningful Improvement in Net Health Outcome: Yes or No	NO: High 5	4	Intermediate 3	2	Low 1	YES: Low 1	2	Intermediate 3	4	High 5	Confidence Level that Clinical Use is Consistent with Generally Accepted Medical Practice: Yes or No	NO: High 5	4	Intermediate 3	2	Low 1	YES: Low 1	2	Intermediate 3	4	High 5
Use of pulsed field ablation for individuals with symptomatic paroxysmal or persistent atrial fibrillation who have failed antiarrhythmic drugs	SCAI		Yes								■			Yes									■
	HRS		Yes										■	Yes									■
	Dr. Kamala Tamirisi*	ACC	Yes										■	Yes									■

ACC: American College of Cardiology; HRS: Heart Rhythm Society; SCAI: Society for Cardiovascular Angiography and Interventions.
* Indicates that conflicts of interest related to the topic where clinical input is being sought were identified by this respondent (see Appendix).

Respondent Profile

#	Respondent	Clinical Specialty	Board Certification
1	Advocacy Committee and Standards & Guidelines Committee, Society for Cardiovascular Angiography and Interventions (SCAI)	Interventional Cardiology	
2	Health Policy and Regulatory Affairs Committee, Heart Rhythm Society (HRS)	Cardiac Electrophysiology	
3	Kamala Tamirisa, MD, Texas Cardiac Arrhythmia, Austin, TX	Cardiac Electrophysiology	Cardiology and Clinical Cardiac Electrophysiology

Respondent Conflict of Interest Disclosure

#	1) Research support related to the topic where clinical input is being sought		2) Positions, paid or unpaid, related to the topic where clinical input is being sought		3) Reportable, more than $1,000, health care–related assets or sources of income for myself, my spouse, or my dependent children related to the topic where clinical input is being sought		4) Reportable, more than $350, gifts or travel reimbursements for myself, my spouse, or my dependent children related to the topic where clinical input is being sought	
	YES/NO	Explanation	YES/NO	Explanation	YES/NO	Explanation	YES/NO	Explanation
1	NO		NO		NO		NO	
2	NO		NO		NO		NO	
3	YES		NO		NO		NO	

Specialty Society respondents provided aggregate information that may be relevant to the group of clinicians who provided input to the Society-level response.

Clinical Input Responses

Question 1: We are seeking your rationale on whether using the intervention for the above indication provides a clinically meaningful improvement in net health outcome. Please respond based on the

evidence and your clinical experience.
Please address these points in your response:

- Relevant clinical scenarios (e.g., a chain of evidence) where the technology is expected to provide a clinically meaningful improvement in net health outcome.
- Specific outcomes that are clinically meaningful.
- Any relevant patient inclusion/exclusion criteria or clinical context important to consider in identifying individuals for this indication.
- Key supporting evidence from the authoritative scientific literature (please include PMID).

#	Rationale
1	Note that this response is based on a critical review of the evidence rather than clinical experience, as SCAI does not typically represent electrophysiologists who perform this procedure. PFA is expected to be applied to the patient population currently targeted by atrial fibrillation (AF) ablation therapies, including paroxysmal and persistent atrial fibrillation. Conventional techniques currently include thermal ablation (TA) with radiofrequency ablation (RFA) and cryoablation. Clinically relevant outcomes include A) evidence of efficacy: 1) AF recurrence rate 2) timing of AF recurrence, B) procedural complications including but not limited to: 1) stroke, 2) pericardial effusion, 3) pulmonary vein stenosis, 4) tracheesophageal fistula, c) procedural efficiency (time) though this may be less clinically relevant. Inclusion criteria should include: paroxysmal or persistent AF, symptoms of Afib, Exclusion criteria: any current exclusion criterion for Afib ablation, including presence of left atrial thrombus. Notably PFA is FDA approved in Dec 2023 and has had clinical use in Europe since Jan 2021. Key studies include PMID: 37634148, an open label, industry-funded randomized noninferiority study of 607 patients undergoing AF ablation with PFA vs TA. This demonstrated noninferiority in efficacy and safety, with a subsequent substudy of 593 patients PMID: 38864538 from this population suggested a statistically significant if clinically modest increase in the proportion of patients with Afib burden <0.1%. A 300 patient study of the other PFA catheter PMID: 36877118 that was not randomized showed a low rate of safety events and equivalent efficacy to historical comparators. A large registry study PMID: 38977913 of 17642 patients undergoing PFA showed also a low risk of complications. Overall the available evidence is fairly clear that PFA provides effective AF ablation similar to thermal ablation with a similar safety profile. There is not any clear superiority over thermal ablation, but there are theoretical and some clinical suggestion that it may be more safe. In this regard, PFA might be best considered an incremental technological advance, similar to cryoablation over RFA.
2	Pulsed field ablation (PFA) has been shown and is expected to continue to show evidence of clinically meaningful AF ablation safety and efficacy. Specific outcomes from PFA involve acute procedural safety (less risk of thermal damage to cardiac tissue resulting in cardiac perforation and post procedure inflammation), less risk of subacute thermal energy related complications (e.g. phrenic nerve palsy, gastric dysmotility, and atrioesophageal fistula), less risk of pulmonary vein reconnection at time of repeat AF ablation, and long-term AF free survival equivalent or superior to current thermal ablation technologies. PFA is applicable for patients with paroxysmal and persistent atrial fibrillation referred for catheter ablation. Please see HRS/ACC Joint Comment on Coverage for Pulsed Field Ablation for a summary of key supporting evidence.
3	Paroxysmal Atrial Fibrillation (AF) Persistent AF: PFA may improve outcomes with reduced esophageal injury risk, a key complication in traditional thermal ablation methods. Redo Ablation Procedures: PFA may reduce recurrence by more precisely targeting fibrosis and avoiding damage to surrounding tissue, reducing complications. Non-PV Foci Ablation: Emerging evidence supports its utility in ablating other atrial structures without collateral damage. Primary Outcomes: Freedom from atrial arrhythmia recurrence (AF, atrial flutter, atrial tachycardia) at 12 months. Safety Outcomes: Reduced risk of complications such as: Esophageal injury (including atrioesophageal fistula) Phrenic nerve injury Pulmonary vein stenosis Durability of PVI: Improved lesion durability with lower rates of late reconnections. Inclusion Criteria:

#	Rationale
	Symptomatic paroxysmal or persistent AF patients who are refractory to antiarrhythmic drugs (AADs). Patients eligible for catheter ablation as a rhythm-control strategy. Exclusion Criteria: Reduced GFR (Creatinine of 1.9 or over) References 10.1016/j.jacc.2020.07.007. PMID: 32854842. https://article.imrpress.com/journal/RCM/25/4/10.31083/j.rcm2504138/a867c80fd3833f4e7953fe30cb581135.pdf https://doi.org/10.1161/CIRCULATIONAHA.123.063988

Question 2a: Are there any differentiating features of the 2 FDA-approved pulsed field ablation devices as compared to other catheter ablation devices?

#	Rationale
1	Compared with other catheter ablation devices (Cryoballoon and Loop radiofrequency ablation catheters), the PFA devices apply a lower energy / shorter pulse of energy, which would be expected to reduce thermal injury complications.
2	Both approved PFA devices are designed with a form factor for efficient and effective pulmonary vein isolation. They are more like the cryoablation balloon catheter than to current point by point radiofrequency ablation catheters. The form factor is designed to minimize gaps in ablation, which can be proarrhythmic and are a potential risk with point-by-point ablation.
3	PFA used irreversible electroporation. Flower or basket catheter with Farapulse.

Question 2b. Are there any features that differentiate one of the 2 FDA-approved pulsed field ablation devices from the other?

#	Rationale
1	The PulseSelect system uses a circular, lasso-type 9-electrode catheter, while the Farapulse system uses a pulsed-field pentaspline basket/flower ablation catheter. These are fairly similar to each other, and would be considered equivalent clinically.
2	Both approved PFA devices offer a form factor designed for the purpose of pulmonary vein isolation. Both also allow for substrate ablation of cardiac tissue to target specific atrial arrhythmias. Future devices will allow for different form factors (point catheters, and spherical tipped catheters) that will allow for more versatility in treatment of atrial fibrillation and other atrial arrhythmias.
3	Pulse select might have lower risks of hemolysis when compared to Farawave or Farapulse.

Question 2c: Is there any feature of the pulsed field ablation approach that alters the conventional 3-month blanking period immediately after atrial fibrillation (AF) ablation, when early occurrences of AF are thought not to predict long-term AF recurrence?

#	Rationale
1	This is a great question, as the optimal PFA ablation protocols continue to be refined. The concern for PFA would be that lower energy and injury (through PFA's 'irreversible electroporation' mechanism) could lead to less efficacy either in the near-term or long-term period. The optimal evidence that remains to be developed would include comparing the 2-3 year recurrence rates of PFA vs TA.However, specific to the conventional 3-month blanking period, there does not appear to be evidence that would suggest that early recurrence (<3 months) from PFA would suggest long-term AF recurrence any more than early recurrence from TA. The decreased injury to the myocardium might suggest that any inflammation post-procedure is lessened, though, and it might not be unreasonable to shorten the blanking period.Clinically early recurrence is strongly associated with long-term recurrence, and is probably associated with the patient's baseline risk factors along with ablation technique.
2	This is an excellent question that is being actively investigated but cannot yet be definitively answered. PFA may lead to less acute inflammation than thermal ablation, resulting in less post procedure inflammation (pericarditis) and recurrences of atrial fibrillation in the traditional blanking period. This is currently being investigated in multicenter real world evidence registries (e.g., DISRUPT AF). Moreover, there is evidence that early AF recurrences may be associated with later AF recurrence (abstract submitted for HRS 2024 Scientific Sessions, currently under peer review). Additional evidence (also submitted and under peer review for HRS 2024 Scientific Sessions) shows up to 40% pulmonary vein reconnection rate following point by point RF

#	Rationale
	ablation. Durability of pulmonary vein isolation (and freedom from AF) remain an active area of real-world evidence generation.
3	In fact a shorter blinding period might be enough with PFA compared to thermal energy. Maybe around 2 months.

Question 2d: Is there any feature of the pulsed field ablation approach that predicts a difference in the safety profile or adverse event rate compared to other catheter ablation devices?

#	Rationale
1	Yes, as described previously by using lower energy and shorter pulses of energy, the technology is designed to create selective 'irreversible electroporation' of cardiac myocytes rather than thermal injury to both myocardium and surrounding tissues.This would be predicted to improve the safety profile of Afib ablation though events are infrequent enough currently for there to not have been a demonstrated evidence in the randomized clinical trials to date.
2	PFA involves delivery of a cardiac tissue specific high voltage gradient resulting in loss of electrical conductivity with significantly less thermal effect on cardiac and adjacent tissue. Unlike radiofrequency and cryoablation, both of which are based on thermal energy delivery, this reduces the risk of steam pops (vaporization of cardiac tissue and perforation, in the case of RF), and post freeze tissue destruction and perforation (in the case of cryoablation). Each of these types of complications are associated with significant morbidity and mortality at the time of the procedure (requiring pericardiocentesis or cardiac surgery for open repair). Both RF and cryoablation also pose the risk of subacute complications (within 30-45d of procedure, including but not limited to atrioesophageal fistula, phrenic nerve palsy, and gastric dysmotility), which may be less with PFA.
3	Absolutely! PFA technology is MUCH SAFER than thermal energy -no reports of atrioesophageal fistulae (potential serious complication with thermal energy), no phrenic nerve injury, and potentially less risk of stiff left syndrome post ablation. Less discomfort post ablation with PFA.

Question 2e: In the event of AF recurrence, is there any feature of the pulsed field ablation approach that precludes a repeat ablation procedure with the same device?

#	Rationale
1	No
2	Pulsed field ablation, particularly with upcoming catheter designs, will be applicable during redo AF ablation procedures. Current and future catheter form factors will allow for versatile platforms to treat recurrent atrial fibrillation as well as organized or focal atrial arrhythmias that may arise following initial ablation.
3	Not at all. PFA can be used again.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or cardiology consultation reports including:
  - Symptoms and duration of atrial fibrillation
  - Previous treatment plan and response
  - Antiarrhythmic drug trials (medication, dose, duration, response)
  - NYHA classification of congestive heart failure (if applicable)
  - Type of ablation to be performed (e.g., radiofrequency or cryoablation)
- Provider progress notes pertaining to the request

Post Service (in addition to the above, please include the following):

- Cardiology procedure report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	93655	Intracardiac catheter ablation of a discrete mechanism of arrhythmia which is distinct from the primary ablated mechanism, including repeat diagnostic maneuvers, to treat a spontaneous or induced arrhythmia (List separately in addition to code for primary procedure)

Type	Code	Description
	93656	Comprehensive electrophysiologic evaluation with transseptal catheterizations, insertion and repositioning of multiple electrode catheters, induction or attempted induction of an arrhythmia including left or right atrial pacing/recording, and intracardiac catheter ablation of atrial fibrillation by pulmonary vein isolation, including intracardiac electrophysiologic 3-dimensional mapping, intracardiac echocardiography with imaging supervision and interpretation, right ventricular pacing/recording, and his bundle recording, when performed ***(Code revision effective 01/1/2025)***
	93657	Additional linear or focal intracardiac catheter ablation of the left or right atrium for treatment of atrial fibrillation remaining after completion of pulmonary vein isolation (List separately in addition to code for primary procedure)
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
08/01/2006	BCBSA Medical Policy adoption
06/28/2007	BCBSA Medical Policy adoption
07/02/2007	Administrative Review
02/06/2009	Update literature review/MN criteria added/Coding Updated
07/02/2010	Policy Revision
02/22/2013	Coding Update
12/19/2013	Policy revision with position change
06/30/2015	Coding update
08/01/2016	Policy title change from Transcatheter Ablation of Arrhythmogenic Foci in the Pulmonary Veins as Treatment for Atrial Fibrillation Policy revision without position change
07/01/2017	Policy revision without position change
07/01/2018	Policy revision without position change
09/01/2019	Policy revision without position change
09/01/2020	Annual review. No change to policy statement. Literature review updated.
07/01/2021	Annual review. No change to policy statement. Literature review updated.
02/01/2022	Coding update
07/01/2022	Annual review. Policy statement, guidelines and literature review updated.
07/01/2023	Annual review. No change to policy statement. Policy guidelines and literature review updated.
09/01/2024	Annual review. No change to policy statement. Policy guidelines updated.
02/01/2025	Coding update
05/01/2025	Annual review. Policy statement, guidelines and literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished

primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) 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 the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
Catheter Ablation as Treatment for Atrial Fibrillation 2.02.19 **Policy Statement:** I. Transcatheter radiofrequency ablation (RFA) or cryoablation to treat atrial fibrillation may be considered **medically necessary** as a treatment for **either** of the following indications, which have failed to respond to adequate trials of antiarrhythmic medications: A. Symptomatic paroxysmal or symptomatic persistent atrial fibrillation B. As an alternative to atrioventricular nodal ablation and pacemaker insertion in individuals with class II or III congestive heart failure and symptomatic atrial fibrillation II. Transcatheter RFA or cryoablation to treat atrial fibrillation may be considered **medically necessary** as an initial treatment for individuals with recurrent symptomatic paroxysmal atrial fibrillation (greater than 1 episode, with 4 or fewer episodes in the previous 6 months) in whom a rhythm-control strategy is desired. III. Repeat RFA or cryoablation may be considered **medically necessary** in individuals with recurrence of atrial fibrillation and/or development of atrial flutter following the initial procedure (see Policy Guidelines section). IV. Transcatheter RFA or cryoablation to treat atrial fibrillation is considered **investigational** as a treatment for cases of atrial fibrillation that do not meet the criteria outlined above.	**Catheter Ablation as Treatment for Atrial Fibrillation 2.02.19** **Policy Statement:** I. Transcatheter radiofrequency ablation (RFA), cryoablation or pulsed field ablation to treat atrial fibrillation may be considered **medically necessary** as a treatment for **either** of the following indications, which have failed to respond to adequate trials of antiarrhythmic medications: A. Symptomatic paroxysmal or symptomatic persistent atrial fibrillation B. As an alternative to atrioventricular nodal ablation and pacemaker insertion in individuals with class II or III congestive heart failure and symptomatic atrial fibrillation II. Transcatheter RFA, cryoablation or pulsed field ablation to treat atrial fibrillation may be considered **medically necessary** as an initial treatment for individuals with recurrent symptomatic paroxysmal atrial fibrillation (greater than 1 episode, with 4 or fewer episodes in the previous 6 months) in whom a rhythm-control strategy is desired. III. Repeat RFA, cryoablation or pulsed field ablation may be considered **medically necessary** in individuals with recurrence of atrial fibrillation and/or development of atrial flutter following the initial procedure (see Policy Guidelines section). IV. Transcatheter RFA, cryoablation and pulsed field ablation to treat atrial fibrillation is considered **investigational** as a treatment for cases of atrial fibrillation that do not meet the criteria outlined above.