

Radiofrequency Catheter Ablation of the Pulmonary Veins for Treatment of Atrial Fibrillation



Assessment
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Executive Summary

Background

Atrial fibrillation is a common cardiac arrhythmia that is associated with serious cardiovascular morbidities, decreased quality of life, and decreased survival. The current treatment approach for atrial fibrillation is primarily pharmacologic, with invasive interventions reserved for small subsets of patients. Catheter ablation of the pulmonary veins, also known as pulmonary vein isolation (PVI) or circumferential pulmonary vein ablation (CPVA), is a nonpharmacologic alternative treatment for patients with atrial fibrillation. Radiofrequency catheter ablation offers potential benefits compared to current pharmacologic treatments, including the potential to improve a variety of clinical outcomes and to avoid the need for long-term antiarrhythmic medications and anticoagulation.

Objective

The objective of this Assessment is to determine whether radiofrequency catheter ablation improves health outcomes when used as a treatment for patients with atrial fibrillation. Three indications for radiofrequency catheter ablation are addressed: 1) patients with recent onset paroxysmal atrial fibrillation, as first-line treatment; 2) patients with symptomatic paroxysmal or persistent atrial fibrillation, who have failed treatment with antiarrhythmic drugs; 3) patients with class II or III congestive heart failure and symptomatic atrial fibrillation, in whom heart rate is poorly controlled by standard medications, as an alternative to atrioventricular (AV) nodal ablation and pacemaker implantation.

Search Strategy

MEDLINE[®] was searched (via PubMed) from March 2006 to January 2009, using the terms “pulmonary vein isolation,” “PVI,” “CPVA,” “circumferential pulmonary vein ablation,” and “catheter ablation.” These terms were cross-referenced with the terms “atrial fibrillation,” and “a fib.” Search was limited to English language articles on human subjects. This search supplemented a prior search performed over the period of 1990 through March 2006 for the 2006 TEC Assessment.

Selection Criteria

Randomized, controlled trials published in the peer-reviewed, English-language literature that compared catheter ablation of the pulmonary veins with alternative treatment(s).

Main Results

Six randomized, controlled trials met the inclusion criteria and were reviewed in-depth for this Assessment. The trials differed in their patient populations, the specific catheter ablation techniques used, and the comparisons made; all trials used radiofrequency energy for the catheter ablation energy source. The trials addressed three distinct indications for catheter ablation: 1) patients with

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paroxysmal atrial fibrillation, as a first-line treatment option (1 trial); 2) patients with symptomatic paroxysmal or persistent atrial fibrillation, who have failed treatment with antiarrhythmic drugs (4 trials); 3) patients with symptomatic atrial fibrillation and class II or III congestive heart failure, in whom heart rate is poorly controlled by standard medications as an alternative to AV nodal ablation and pacemaker insertion (1 trial).

All 6 trials reported that maintenance of sinus rhythm was improved for the catheter ablation group. Recurrence rates of atrial fibrillation at 1 year ranged from 11–44% for the catheter ablation groups in these trials, compared with 63–96% for the medication groups. Four of the 6 trials reported quality of life (QOL) outcomes. One of these only reported within-group comparisons, as opposed to between-group comparisons. The other 3 trials reported improvements in QOL associated with catheter ablation. These QOL measures were self-reported, and since the trials were unblinded, there is the possibility of reporting bias due to placebo effect.

For the population of patients with recent onset paroxysmal atrial fibrillation, one trial reported improvements in atrial fibrillation recurrences and QOL. For the population of patients with symptomatic atrial fibrillation who have failed antiarrhythmic medications, 4 trials reported improvements in atrial fibrillation recurrence, and one trial reported the outcomes of QOL, symptom scores, and exercise duration. For the population of patients with symptomatic atrial fibrillation and class II or III congestive heart failure, one trial reported improvements for the catheter ablation group on a wider range of outcomes, i.e., recurrence of atrial fibrillation, left ventricular ejection fraction, functional status, and QOL. None of the trials report meaningful data on mortality, thromboembolic complications, or other cardiovascular outcomes.

Adverse events from the procedure can occur, including pulmonary vein stenosis, tamponade, thromboembolism, and perforation of the esophageal wall. The rates of these complications cannot be determined accurately from the available data. The available studies are small in size and do not include sufficient numbers of patients to adequately address uncommon complications. Furthermore, the rates of complications in the available studies reflect the specific procedures performed and may not be generalizable to variations on the procedure. There have been numerous modifications to the original catheter ablation technique, mainly with the intention of reducing pulmonary vein stenosis and other complications, and currently there is little standardization of the procedure across medical centers.

Author's Conclusions and Comments

All 6 trials report substantial differences in favor of the catheter ablation group on some relevant outcomes, particularly recurrence of atrial fibrillation. The consistency of this finding establishes that catheter ablation is more effective than medications in maintaining sinus rhythm across a wide spectrum of patients with atrial fibrillation, and across different variations of catheter ablation. However, the recurrence rate varied widely in these trials from 13–44%, indicating that there may be differences in absolute efficacy for different populations of patients with atrial fibrillation. Also, while the comparison of recurrence rates between treatment groups is valid in these trials, it is not possible to conclude with confidence that the lack of recurrence reported in trials represents the elimination of atrial fibrillation. Atrial fibrillation is often intermittent and of brief duration, thus creating difficulties in assessing recurrence when assessed over short periods of time, as is done in the available trials.

The relevance of maintaining sinus rhythm as a health outcome is variable for different populations of patients with atrial fibrillation. For the broad population of patients with atrial fibrillation who do not have specific reasons to pursue a rhythm control strategy, the value of this outcome is questionable. The goals of therapy in this population are to control ventricular rate, ameliorate symptoms, and prevent complications of atrial fibrillation, such as stroke. These goals can usually be accomplished with medications to control heart rate, with or without anticoagulation. Maintenance of sinus rhythm may not offer any further advantage over rate control in these patients.

For patients in whom symptoms are not adequately controlled with a rate control strategy (Indication 2), maintenance of sinus rhythm becomes a more important goal. In these patients, the alternative to catheter ablation is pharmacologic management with antiarrhythmic medications and anticoagulation. Antiarrhythmic medications are only partially effective in maintaining sinus rhythm and have a variety of adverse effects, including proarrhythmic properties that can lead to serious, life-threatening ventricular arrhythmias. Anticoagulation also has the potential to cause serious hemorrhagic adverse effects. Therefore, maintenance of sinus rhythm by nonpharmacologic methods is a particularly attractive option for this patient group. In addition, it is reasonable to extrapolate that a decrease in the frequency and/or duration of atrial fibrillation episodes will result in a decrease in symptoms. While the available data do not establish the degree of symptom improvement associated with catheter ablation, the large reported difference in the percent of patients maintaining sinus rhythm is likely to translate to a clinically important reduction in symptoms.

For patients with class II or III congestive heart failure and symptomatic atrial fibrillation in whom heart rate is poorly controlled by standard medications (Indication 3), one trial reports benefit on maintenance of sinus rhythm, improved ejection fraction, improved functional status, and improved QOL. While this trial is small, it was judged to be high quality on formal quality assessment and the magnitude of difference on all the outcome measures was relatively large. As a result, it is possible to conclude that radiofrequency catheter ablation of the pulmonary veins is superior to AV nodal ablation and pacemaker insertion for this population.

Data on the most important clinical outcomes is lacking. None of the trials reports on the most relevant clinical outcomes such as mortality, thromboembolic events, and cardiovascular complications. Maintenance of sinus rhythm has the potential to substantially improve important clinical outcomes, but this remains to be determined. This is a major gap in the literature that precludes conclusions on the impact of radiofrequency catheter ablation in the broader population of patients with atrial fibrillation.

Another potential benefit of maintaining sinus rhythm is avoidance of the need for anticoagulation. While anticoagulation is effective in reducing the risk of embolic stroke, it also can lead to serious bleeding complications, such as gastrointestinal or intracranial hemorrhage. Treatment decisions based on the benefits and risks of anticoagulation are challenging for clinicians and patients alike. This is particularly true for elderly patients, in whom both the risks of complications from atrial fibrillation and the risk of complications from anticoagulation are increased. Embolic stroke in elderly patients can lead to severe disability and loss of independence. On the other hand, hemorrhagic complications from anticoagulation, for example, intracranial bleeds in elderly patients at risk for falls, can have devastating consequences. Maintaining sinus rhythm has the potential to reduce the risk for both types of complications.

Larger trials with longer follow-up periods are therefore required to provide useful information on important clinical outcomes and complication rates. The CABANA study (ClinicalTrials.gov Identifier NCT00578617) is an ongoing trial of approximately 4,000 patients that compares radiofrequency catheter ablation with antiarrhythmic medications, and includes the endpoints of mortality, complications of catheter ablation, and other clinical outcomes. This is a 5-year trial that is expected to be completed in 2011. Numerous other smaller randomized, controlled trials are currently underway as well, these should add to the overall evidence base for catheter ablation.

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether radiofrequency catheter ablation as a treatment for atrial fibrillation meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria:

1. The technology must have final approval from the appropriate governmental regulatory bodies.

Radiofrequency catheter ablation is a percutaneous procedure, and as such is not itself subject to U.S. Food and Drug Administration (FDA) approval. However, the devices used for catheter ablation are subject to FDA approval. On February 6, 2009, the FDA granted approval via the premarket application (PMA) approval process for the NaviStar® ThermoCool® saline irrigated radiofrequency ablation catheter and the EZ Steer ThermoCool® Nav Catheter (both from Biosense Webster Inc., Diamond Bar, CA), for the treatment of medication-refractory atrial fibrillation. The FDA has also granted PMA approval to numerous catheter ablation systems for other ablation therapy for arrhythmias such as supraventricular tachycardia, atrial flutter, and ventricular tachycardia.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

The evidence is sufficient to conclude that radiofrequency catheter ablation is superior to pharmacologic treatment for maintaining sinus rhythm in certain patient populations. Four randomized, controlled trials reported decreased recurrence of atrial fibrillation in patients with symptomatic paroxysmal or persistent atrial fibrillation who have failed antiarrhythmic medications, as an alternative to continued medical management. In each case, the magnitude of difference was relatively large, with the absolute risk reduction ranging from 47–70% at 1-year follow-up.

For patients with class II or III congestive heart failure and symptomatic atrial fibrillation in whom heart rate was uncontrolled with standard medications, who would otherwise be candidates for AV nodal ablation and pacemaker insertion, one small randomized, controlled trial reported improvements in QOL, functional status, left ventricular ejection fraction, and recurrences of atrial fibrillation associated with radiofrequency catheter ablation. While small and of short duration, this trial was otherwise a high-quality study, and is sufficient to permit conclusions that outcomes will be improved following catheter ablation for this subgroup of patients.

The evidence is not sufficient to permit conclusions on the impact of radiofrequency catheter ablation on other outcomes in the broader population of patients with paroxysmal atrial fibrillation (e.g., as first-line treatment of recent onset arrhythmia or in patients who are adequately managed with a rate control strategy). While there is some evidence suggesting that catheter ablation may improve QOL, this is not adequately robust to permit conclusions. Only two trials provided comparative data on QOL, with each using a different instrument. In addition, the data on QOL are self reported, and thus prone to bias given that these trials were not double blinded. None of the available trials provided data on clinical outcomes such as cardiovascular morbidity and mortality.

3. The technology must improve the net health outcome.

For patients who have symptomatic paroxysmal or persistent atrial fibrillation uncontrolled by standard medications, radiofrequency catheter ablation will improve outcomes. In this case, reduction or elimination of atrial fibrillation episodes will lead to a corresponding improvement in symptoms. Serious complications of catheter ablation in this group of patients is uncertain, but likely to be low, and is balanced against the risk of long-term, suboptimal medication management, including the adverse effects of antiarrhythmic medications and anticoagulation.

For patients with class II or III congestive heart failure and symptomatic atrial fibrillation in whom heart rate is poorly controlled by standard medications, catheter ablation leads to improvements in left ventricular ejection fraction, QOL, and functional status that are greater than those achieved with AV nodal ablation and pacemaker insertion. Serious complications of both procedures can occur, but are uncommon, and there is no definitive evidence that either procedure is substantially more risky than the other.

For the majority of patients whose condition is adequately controlled with a rate control strategy, maintenance of sinus rhythm is not by itself sufficient to demonstrate improved outcomes. For these patients, it is necessary to demonstrate improvements on other outcomes in order to determine benefit, and therefore, it is not possible to conclude that catheter ablation improves health outcomes for the broader population of patients with atrial fibrillation.

4. The technology must be as beneficial as any established alternatives.

Alternative treatments generally involve pharmacologic management. For patients with symptomatic paroxysmal or persistent atrial fibrillation despite medications, catheter ablation is more beneficial than medications in reducing symptoms. In patients who do not have uncontrolled symptoms (i.e., who are adequately maintained on a rate control strategy) or who have new onset paroxysmal atrial fibrillation, it is not possible to conclude that catheter ablation is more beneficial than medications.

For patients with class II or III congestive heart failure and symptomatic atrial fibrillation in whom heart rate is poorly controlled by standard medications, AV nodal ablation and pacemaker insertion is an alternative treatment. One small, high-quality trial establishes that catheter ablation is more effective than AV nodal ablation in improving QOL, functional status, and left ventricular ejection fraction.

5. The improvement must be attainable outside the investigational settings.

Catheter ablation of the pulmonary veins is a technically complex procedure that requires specialized training and has a substantial learning curve. Currently, expertise to perform these procedures is widely available among interventional cardiologists in the U.S. Therefore, the improvement seen in the clinical trials of patients with symptomatic paroxysmal or persistent atrial fibrillation who have failed antiarrhythmic medications or in patients with class II or III congestive heart failure and symptomatic atrial fibrillation in whom heart rate is poorly controlled by standard medications, is expected to be attainable outside the investigational setting.

Whether radiofrequency catheter ablation improves outcomes for other patients with atrial fibrillation, including patients whose condition is adequately controlled using a rate control strategy or as first-line treatment for patients with paroxysmal atrial fibrillation, has not been established in the investigational setting.

Based on the above, radiofrequency catheter ablation of the pulmonary veins as a treatment for atrial fibrillation meets the TEC criteria for:

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

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

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Assessment Objective

The objective of this Assessment is to determine whether radiofrequency catheter ablation of the pulmonary veins improves health outcomes when used as a treatment for patients with atrial fibrillation. Atrial fibrillation is a common cardiac arrhythmia that is associated with serious cardiovascular morbidities, decreased quality of life, and decreased survival. Basic research has demonstrated that, in a large proportion of cases, the origin of atrial fibrillation is at the junction of the pulmonary veins in the left atrium. Ablative therapy is designed to interrupt these abnormal electrical impulses by isolating the pulmonary veins from the remainder of the atria, and thereby preventing the initiation of atrial fibrillation.

At present, treatment for atrial fibrillation is primarily pharmacologic. For many patients with atrial fibrillation, treatment with medications to control the ventricular rate and to reduce complications of atrial fibrillation is sufficient. However, in some patients with bothersome symptoms or other adverse effects of atrial fibrillation, pharmacologic treatment is not successful and more invasive approaches may be considered. In addition, antiarrhythmic medications currently in use may be only partially effective in preventing atrial fibrillation, and can be associated with serious adverse effects, including proarrhythmic properties that can lead to serious, life-threatening ventricular arrhythmias in some patients. Also, patients are generally on long-term anticoagulation therapy, which poses risks of bleeding. Nonpharmacologic treatments, thus, offer potential advantages over the current approaches, with the potential to improve a variety of clinical outcomes and to avoid the need for long-term antiarrhythmic medications and anticoagulation.

Treatment decisions for patients with atrial fibrillation are often complex, taking into account many factors such as the specific subtype of atrial fibrillation, the presence or absence of structural heart disease, the risks and benefits of rate control versus rhythm control strategy, the need for anticoagulation, and the presence of other comorbidities. Because of these complexities in clinical care, addressing the utility of catheter ablation for a specific indication, or subgroup of patients with atrial fibrillation, is more likely to yield a useful conclusion, rather than attempting to address

the utility of catheter ablation in broader groups of patients or in all patients with atrial fibrillation.

As a result, this Assessment will define and evaluate the evidence for each of three specific indications. These indications were determined primarily from the available clinical trials, with consideration of expert opinion in the field, and existing treatment guidelines. The 3 indications for radiofrequency catheter ablation of atrial fibrillation included in the present Assessment are 1) patients with recent onset paroxysmal atrial fibrillation, as first-line treatment; 2) patients with symptomatic paroxysmal or persistent atrial fibrillation, who have failed treatment with antiarrhythmic drugs; 3) patients with class II or III congestive heart failure and symptomatic atrial fibrillation in whom heart rate is poorly controlled by standard medications, as an alternative to atrioventricular (AV) nodal ablation and pacemaker implantation. For each indication, the Assessment will compare catheter ablation with the current standard treatments for atrial fibrillation, which may vary according the specific indication. All studies evaluated in this Assessment used radiofrequency energy as the energy source for the catheter ablation; therefore, this Assessment only addresses radiofrequency catheter ablation techniques for treatment of atrial fibrillation. No other energy sources (e.g., cryoablation) will be addressed in this Assessment.

The most relevant health outcomes for this Assessment are survival, cardiovascular events, quality of life, and complications of treatment. The most common outcome reported in the available literature, however, is the recurrence rate for atrial fibrillation. Recurrence of atrial fibrillation is a potentially useful outcome, but cannot substitute for clinical outcomes such as cardiovascular morbidity and mortality. Recurrence of atrial fibrillation will, therefore, be evaluated as a potentially relevant outcome measure, but its utility may be interpreted differently, depending on the specific clinical indication.

Background

Atrial fibrillation is the most common cardiac arrhythmia, with a prevalence that increases with age. For individuals younger than 55 years of age, the prevalence has been estimated at approximately 1% (Go et al. 2001), increasing

to 9% for patients aged 80 years or older. The prevalence of atrial fibrillation is increasing in the U.S., partly due to the aging population, but also as a result of other factors that are not entirely clear. At present, approximately 2.5 million adults in the U.S. have atrial fibrillation. By the year 2050, this number may increase to 5.6 million (Go et al. 2001).

Atrial fibrillation is primarily a disorder of the atrial pacemaker, which initiates the electrical activity leading to contractions of the atria and ventricles. The normal atrial pacemaker delivers regular impulses to the AV node, which then conducts electrical impulses to the ventricles. This electrical activity directs the coordinated contractions of the atria and ventricles. Atrial fibrillation is initiated by ectopic atrial pacemakers, and/or re-entry circuits that result in disorganized electrical activity of the atria. Rather than contract in an orderly manner, the atria “fibrillate” or oscillate, with ineffective pumping function. Electrical impulses are transmitted chaotically to the ventricles, resulting in ventricular contractions that are rapid and irregular.

Atrial fibrillation represents a complex and heterogeneous disorder. A variety of cardiac and noncardiac conditions can contribute to the initiation and/or maintenance of the disorder (Table 1). Atrial fibrillation may or may not be associated with underlying heart disease. The type of underlying heart disease may be valvular, ischemic, or myopathic. In general, any disorder that involves the atria can lead to atrial fibrillation. Atrial fibrillation is sometimes the result of another disorder; this is called “secondary,” or “acute” atrial fibrillation. Atrial fibrillation is common following intrathoracic and intracardiac surgery. It may also result from acute medical illness, such as acute lung disease with hypoxia or hyperthyroidism. “Lone” atrial fibrillation refers to atrial fibrillation in the absence of any demonstrable heart disease or secondary cause. Lone atrial fibrillation is more common in younger patients and is associated with a more favorable prognosis.

The most common classification scheme characterizes atrial fibrillation into three subtypes: paroxysmal, persistent, or permanent. Paroxysmal atrial fibrillation refers to recurrent episodes that are self-terminating, with intervening periods of normal sinus rhythm. These episodes may last for minutes, or up to 7 days.

Persistent atrial fibrillation refers to episodes that last for more than 7 days, but which are self-terminating or can be terminated pharmacologically or by cardioversion. Permanent atrial fibrillation is defined as continuous atrial fibrillation, with no intervening periods of normal rhythm.

Recent advances in electrophysiology have offered insights into the pathophysiologic mechanisms of atrial fibrillation. Atrial fibrillation involves both a trigger for initiation and a substrate that promotes maintenance of the abnormal rhythm. The trigger for atrial fibrillation is thought to be an excitable focus within the atrial tissue. There may be one or more foci that initiate atrial fibrillation. The substrate for promoting the maintenance of atrial fibrillation is, in general, a diseased atrium. Patients with normal atrial function will tend to have paroxysmal atrial fibrillation, with spontaneous restoration of sinus rhythm. Patients with abnormal atria will tend to develop chronic atrial fibrillation, and conversion to normal sinus rhythm is less likely to occur.

Atrial fibrillation is associated with increased mortality, considerable cardiovascular morbidity, and a decrease in quality of life. The increased mortality associated with atrial fibrillation may be a result of atrial fibrillation itself, or may be secondary to other cardiovascular morbidities. Long-standing atrial fibrillation may lead to structural and electrical remodeling of the heart, which may in turn lead to adverse long-term changes such as cardiac fibrosis, decreased ejection fraction, and clinical congestive heart failure. Decreased quality of life can be due to symptoms associated with atrial fibrillation, which can vary from very mild to disabling. Atrial fibrillation also often results in decreased exercise tolerance.

Treatment of Atrial Fibrillation

Analytic frameworks for the treatment of different subgroups of patients with atrial fibrillation are shown in Figures 1–3. The most common approach to treatment is pharmacologic. Pharmacologic treatment may entail one of two different approaches, a rhythm control strategy or a rate control strategy. In the rhythm control strategy, the goals of treatment include restoration and maintenance of sinus rhythm. The most commonly used drugs for this purpose are type I antiarrhythmic agents, such as procainamide, flecainide, propafenone, sotalol, and

Table 1. Contributing factors to the development of atrial fibrillation (adapted from Fuster et al. 2006)

Cardiac Factors	Noncardiac Factors
<p>Electrophysiologic abnormalities</p> <ul style="list-style-type: none"> enhanced automaticity (focal AF) conduction abnormality (reentry) <p>Atrial pressure elevation</p> <ul style="list-style-type: none"> mitral and/or tricuspid disease myocardial disease leading to systolic or diastolic dysfunction semilunar valvular abnormalities causing left-ventricular hypertrophy systemic or pulmonary hypertension intracardiac tumors or thrombi <p>Atrial ischemia</p> <ul style="list-style-type: none"> coronary artery disease <p>Inflammatory or infiltrative disease</p> <ul style="list-style-type: none"> pericarditis amyloidosis myocarditis <p>Congenital heart disease</p> <p>Primary or metastatic disease in or adjacent to the atrial wall</p>	<p>Changes in autonomic tone</p> <ul style="list-style-type: none"> increased parasympathetic activity increased sympathetic activity <p>Endocrine disorders</p> <ul style="list-style-type: none"> hyperthyroidism pheochromocytoma <p>Drugs</p> <ul style="list-style-type: none"> alcohol caffeine <p>Neurogenic</p> <ul style="list-style-type: none"> subarachnoid hemorrhage nonhemorrhagic, major stroke <p>Postoperative state</p> <ul style="list-style-type: none"> cardiac, pulmonary or esophageal surgery <p>Idiopathic ("Lone AF)</p> <p>Familial AF</p>

AF: atrial fibrillation

Figure 1. Analytic Framework for Catheter Ablation in Patients with Recent Onset Paroxysmal Atrial Fibrillation

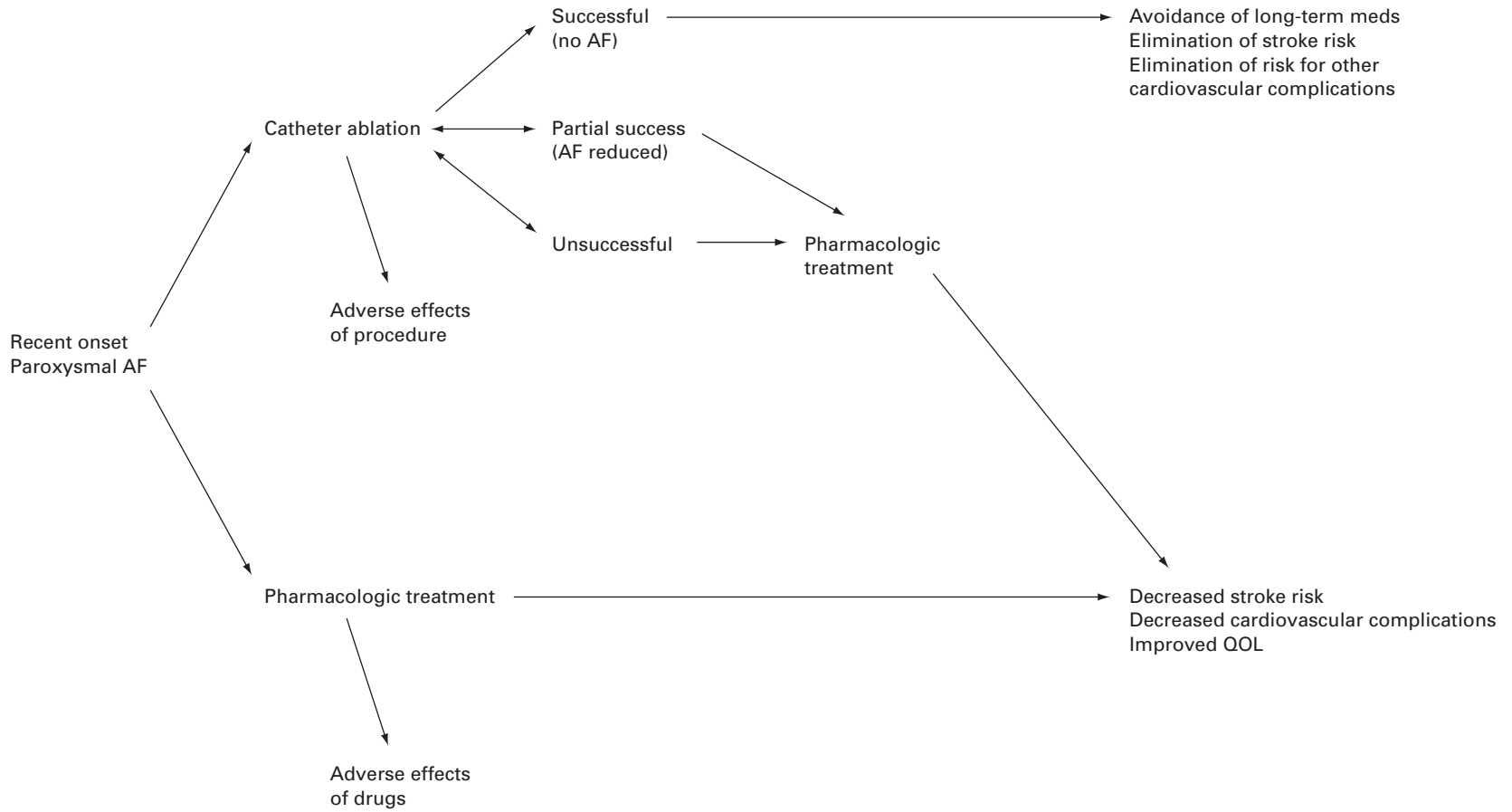


Figure 2. Analytic Framework for Catheter Ablation in Symptomatic Patients with Paroxysmal or Persistent Atrial Fibrillation Who Have Failed Standard Medications

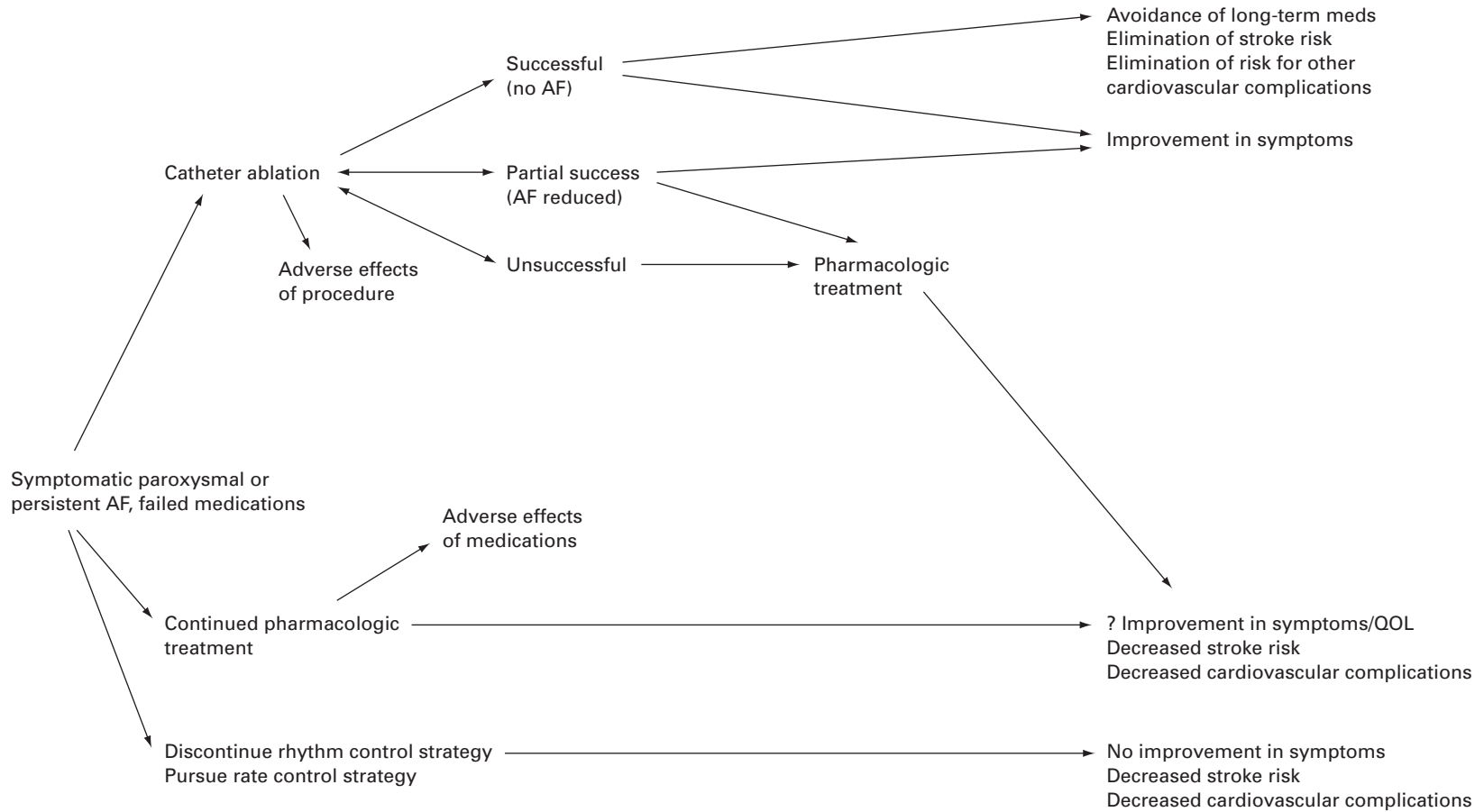
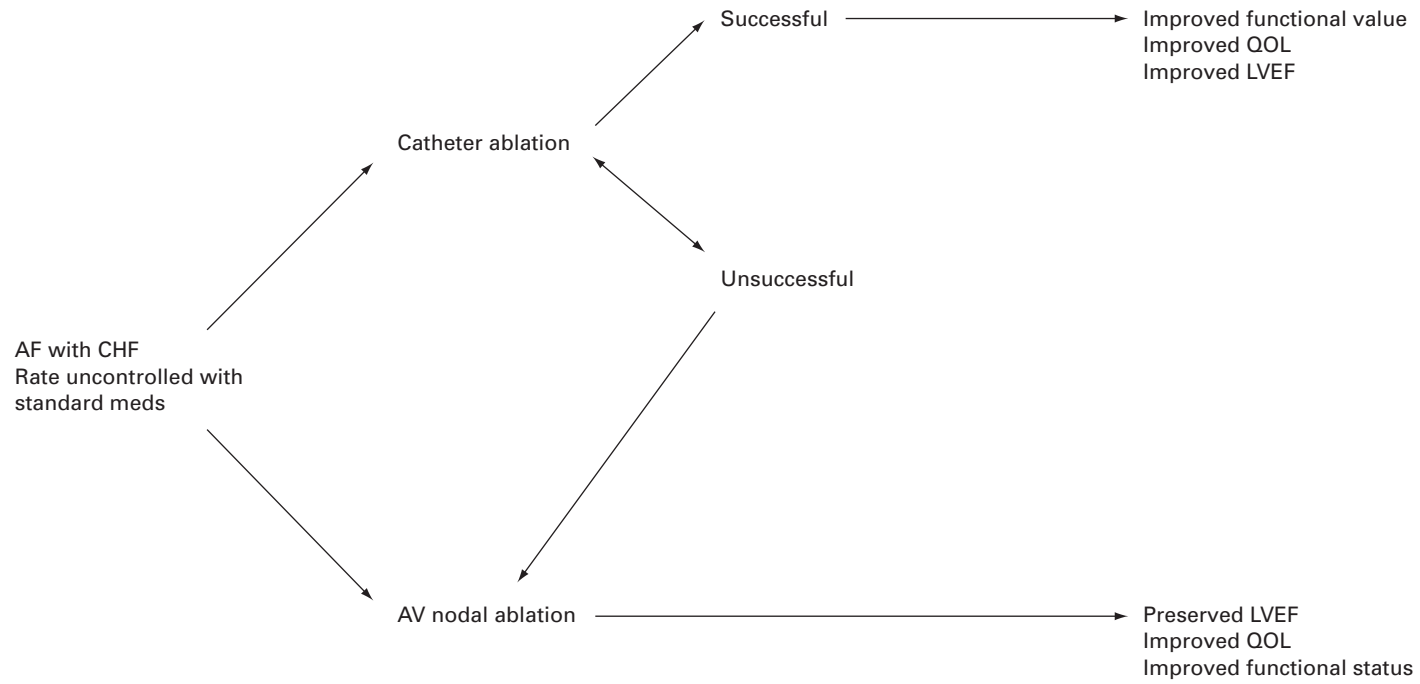


Figure 3. Analytic Framework for Catheter Ablation in Patients with Congestive Heart Failure and Atrial Fibrillation Who Have Failed Standard Medications



amiodarone. If pharmacologic treatment fails to restore sinus rhythm, direct-current (DC) cardioversion can be attempted.

In the rate control strategy, the goals of therapy are to control the ventricular rate, minimize symptoms, and reduce the likelihood of complications of atrial fibrillation. In this approach, attempts are not made to convert atrial fibrillation to sinus rhythm. Drugs used in this strategy include agents that inhibit conduction of atrial impulses through the AV node, such as digoxin, beta blockers, or calcium-channel blockers. Anticoagulation, usually with warfarin, is used to reduce the possibility of thromboembolism.

Anticoagulation to prevent thromboembolic complications is effective, but is associated with its own risks of hemorrhagic complications. Bleeding complications such as gastrointestinal or intracranial hemorrhage can have serious consequences, including death. As a result, the decision to use anticoagulation is often a difficult one based on the benefits and risks of treatment. Patients at increased risk of complications, such as elderly patients at risk for falls and head injuries, are sometimes deemed not to be candidates for anticoagulation. In this situation, the increased risk of thromboembolic complications remains.

Neither pharmacologic strategy is clearly superior to the other. There are theoretical advantages to a rhythm control strategy, including improved ejection fraction, elimination of symptoms associated with atrial fibrillation, reduced risk of thromboembolic events, and no need for chronic anticoagulation. However, it may be difficult or impossible to maintain normal sinus rhythm in many patients. While conversion from atrial fibrillation to normal sinus rhythm can be achieved in the majority of patients through medications or DC cardioversion, a high percentage of patients will revert back to atrial fibrillation, often within a very short time.

The method used to restore sinus rhythm may itself have risks, in particular, use of antiarrhythmic agents. These risks must be taken into account when deciding on the treatment strategy. Class I antiarrhythmic drugs may have a proarrhythmic effect in a minority of patients, and have been associated with increased mortality when used for some ventricular arrhythmias. Amiodarone can be toxic to a number

of organ systems, including the lung, liver, and thyroid. Patients need to be monitored closely while taking amiodarone, and the drug is discontinued if signs of toxicity are present. Patients receiving chronic anticoagulation (e.g., warfarin), must have their bleeding times monitored; patients are also at increased risk for bleeding.

At least 3 recent clinical trials have compared a rate control strategy with a rhythm control strategy (Van Gelder et al. 2002; AFFIRM Investigators 2002; Hohnloser et al. 2000). All 3 studies reported that there were no differences in their main outcome measures between the two strategies. These 3 trials enrolled patients who did not have compelling reasons or strong desires to pursue a rhythm control strategy. As a result of this selection process, the patient populations were skewed toward more severe disease, as defined by length, chronicity, and prior recurrences of atrial fibrillation. Therefore, they may not be generalizable to patients with new onset or paroxysmal atrial fibrillation.

The explanation for lack of benefit in the rhythm control group may be related to a relatively low rate of success in maintaining sinus rhythm. For example, in the AFFIRM study (AFFIRM Investigators 2002), only 60% of patients in the rhythm control group were in sinus rhythm at the 5-year follow-up point. The medications used to maintain sinus rhythm have known serious adverse effects, including a proarrhythmic effect in some patients. The lack of benefit may also be related to adverse effects of antiarrhythmic agents, which may counterbalance the beneficial effects of maintaining sinus rhythm.

A re-examination of the AFFIRM data revealed favorable outcomes for patients who maintained sinus rhythm but increased risks for patients treated with antiarrhythmic drugs. Patients who were in sinus rhythm, regardless of treatment group, had a lower risk of mortality (hazard ratio [HR] 0.53; 95% CI: 0.39–0.72; $p < 0.0001$). On the other hand, patients treated with antiarrhythmic agents had an increased mortality (HR 1.49, 95% CI: 1.11–2.01; $p = 0.0005$). This analysis suggests that the adverse effects of the antiarrhythmic agents may negate the beneficial effects of maintaining sinus rhythm, resulting in no net benefit for this treatment strategy.

Catheter-based Ablation Treatment for Atrial Fibrillation. By definition, catheter ablation techniques represent one option for a rhythm control treatment strategy. Catheter ablation of the pulmonary veins refers to percutaneous, catheter-based ablation technique(s) intended to interrupt conduction of abnormal excitatory foci from the pulmonary veins. Catheter ablation involves ablating tissue in the area of the pulmonary veins, thus blocking the transmission of electrical impulses that originate in the area around the pulmonary veins.

The rationale for catheter-based ablation of atrial fibrillation arises from success of catheter ablation for other cardiac arrhythmias. Ablation techniques have been used successfully for other arrhythmias that originate in the atria of the heart, including supraventricular tachycardia and atrial flutter. In these disorders, an abnormal focus of excitation, with or without an abnormal re-entry loop, originates from the atria and can be identified by electrophysiologic studies. Ablation of these abnormal foci has been successful in controlling supraventricular arrhythmias that arise in this manner.

Ablation techniques for atrial fibrillation have evolved over the last two decades. Earlier techniques, such as the Maze procedure and its variants, represented a nontargeted approach creating multiple, nonspecific ablation tracts throughout the atria. This procedure requires open surgery or mediastinoscopy. While the technique has been successful in maintaining sinus rhythm, it has not achieved widespread acceptance due to its invasive nature. Currently, it is used primarily for patients undergoing open heart surgery for other reasons, who have or are at high risk for atrial fibrillation. A second ablation technique for atrial fibrillation is AV nodal ablation and pacemaker insertion. Ablation of the AV node eliminates transmission of any atrial impulses to the ventricle, thus necessitating pacemaker insertion. This procedure is reserved as the last-resort therapy for patients in whom rate control is unsuccessful. It is thought to be especially useful in patients with congestive heart failure, in whom adequate rate control and restoration of atrial pump function can help to optimize cardiac parameters.

More recently, researchers have moved away from a nontargeted approach to ablation toward an approach that targets potential abnormal

foci that initiate atrial fibrillation. Improved techniques for mapping action potentials of myocardial cells have led to the ability to identify abnormal foci that are the triggers for atrial fibrillation in the majority of patients. In the mid-to-late 1990s, electrophysiologists began to identify abnormal atrial foci by mapping and targeting ablative treatment to the specific abnormal area (Cappato et al. 2005). By this time, researchers had learned that the majority of abnormal foci for atrial fibrillation are at or near the junction of the pulmonary veins in the left atrium. As a result, the majority of attention in this area shifted toward development of techniques to ablate the areas around the pulmonary veins.

There are numerous variations on the technique of catheter ablation of the pulmonary veins, and currently there is no standardization of technique across treatment centers. Pulmonary vein isolation (PVI) was the first catheter ablation technique that achieved widespread clinical use. PVI involves circumferential ablation of cardiac tissue at the origin of the pulmonary vein (ostia). However, due to concern over the development of pulmonary vein stenoses, modified approaches have been proposed that ablate tissue in a larger circular area that encompasses all 4 pulmonary veins. Circumferential pulmonary vein ablation (CPVA) is currently the procedure that is most commonly used in the U.S. In this technique, ablation lines are made in the left atrium encircling the pulmonary veins, and thus isolating any electrical impulses originating in the pulmonary veins. Additional ablation lines are sometimes used, such as linear ablation of the mitral isthmus or cavotricuspid isthmus.

Different sources of energy have been used. Most commonly, radiofrequency energy source is employed; however, alternate sources such as ultrasound, laser, and cryotherapy have also been used. The majority of experts treat all 4 pulmonary veins, but others will treat only 2 or 3 of the 4 veins. Some experts recommend mapping pulmonary vein potentials prior to treatment, and treatment of only those areas that show excitatory foci. Other experts employ mapping to document that transmission of pulmonary vein potentials are blocked following ablation. Another variation on the technique is the addition of linear ablation lines in the left atrium to enhance isolation of the pulmonary vein potentials.

The early literature on catheter ablation consists largely of numerous clinical series that include patients with symptomatic atrial fibrillation that is refractory to pharmacologic management. The majority of these are small, single-center series, in which patients who have failed antiarrhythmic drug therapy are treated with catheter ablation. The most common reported outcome is recurrence of atrial fibrillation, and/or freedom from atrial fibrillation. Some of the larger clinical series have included more than 100 patients (Kluge et al. 2004; Kottkamp et al. 2004; Jais et al. 2004; Oral et al. 2004; Saad et al. 2005; Nademanee et al. 2004; Kumagai et al. 2005), representing the experience of centers that perform large numbers of catheter ablation procedures. These clinical series generally reported that catheter ablation techniques can be performed with high rates of success and relatively low rates of complications, and that a substantial percentage of patients undergoing these procedures remained free from atrial fibrillation for up to 1 year.

These uncontrolled series do not provide definitive evidence as to whether catheter ablation improves outcomes compared with medical treatment. As a result of these factors, randomized, controlled trials with clinically relevant control groups are especially important in this area. A guidance document for industry trials in atrial fibrillation has been prepared by the U.S. Food and Drug Administration (FDA) and reiterates these reasons why randomized, controlled trials are required in order to adequately evaluate the efficacy of new treatments for atrial fibrillation (U.S. Food and Drug Administration 2004).

FDA Status. Radiofrequency catheter ablation is a percutaneous procedure, and as such is not itself subject to FDA approval. However, the devices used for catheter ablation are subject to FDA approval. On February 6, 2009, the FDA granted approval via the premarket application (PMA) approval process for the NaviStar® ThermoCool® saline irrigated radiofrequency ablation catheter and the EZ Steer ThermoCool® Nav Catheter (both from Biosense Webster Inc., Diamond Bar, CA), for the treatment of medication-refractory atrial fibrillation. The FDA has also granted PMA approval to numerous catheter ablation systems for other ablation therapy for arrhythmias such as supraventricular tachycardia, atrial flutter, and ventricular tachycardia.

Outcome Assessment in Atrial Fibrillation Research

A variety of outcomes can be used in research on atrial fibrillation. The main classes of outcomes are cardiovascular morbidity and mortality, symptoms and quality of life (QOL), and maintenance of sinus rhythm. The utility of each these outcomes is discussed below.

Cardiovascular Morbidity and Mortality.

This category includes cardiovascular mortality, stroke, other thromboembolic events, congestive heart failure, myocardial infarction, and progressive cardiomyopathy. These are the most important clinical outcomes associated with atrial fibrillation. They are also the least frequent outcomes, thereby requiring larger, longer-term trials in order to adequately assess any differences between treatment groups.

Symptoms and QOL. Symptoms and QOL are also important outcome measures in atrial fibrillation. Symptoms in atrial fibrillation are variable, and may include palpitations, chest pain, lightheadedness, shortness of breath, decreased exercise tolerance, anxiety, and/or malaise. There is evidence that QOL is decreased in atrial fibrillation, and that maintenance of sinus rhythm may be associated with improvements in QOL.

The clinical importance of symptoms and QOL may vary in different populations. Many patients with atrial fibrillation are asymptomatic, so that measurement of symptoms has less meaning. Similarly, the impact of atrial fibrillation on QOL can be quite variable. For example, patients who are elderly and sedentary may not perceive any decreased QOL with atrial fibrillation, while younger, active patients may experience a large decrease in QOL as a result of symptoms and decreased exercise tolerance.

Symptoms and QOL are self-reported measures, and may be more prone to bias than other potential atrial fibrillation outcomes. Since it is difficult, if not impossible, to perform double-blind trials of an invasive versus a pharmacologic strategy, this outcome measure is prone to reporting bias due to the placebo effect. This may result in an overestimation of the treatment effect for catheter ablation when compared to a noninvasive strategy.

Maintenance of Sinus Rhythm. The utility of this outcome is less certain. First, mainte-

nance of sinus rhythm is a difficult outcome to measure accurately due to the large degree of variability in the natural history of atrial fibrillation episodes. Patients with paroxysmal or persistent atrial fibrillation have intermittent episodes of atrial fibrillation interspersed with periods of sinus rhythm, and these episodes of atrial fibrillation may be asymptomatic and not recognized by the patient. Measurement of maintenance of sinus rhythm at one point in time will not reflect this variability in the disorder. Continuous ECG monitoring is required to capture all episodes of atrial fibrillation with certainty, but is rarely feasible due to the resource intensity, cost, and inconvenience. Therefore, measurement of atrial fibrillation recurrences may be inaccurate and may underestimate the true recurrence rate. This is especially problematic when trying to decide whether an individual patient is free of any episodes of atrial fibrillation.

In addition, there are numerous confounding factors that may have an impact on the outcomes examined. For maintenance of sinus rhythm, clinical factors such as age, duration of atrial fibrillation, and the presence of underlying heart disease are all important predictors of maintaining sinus rhythm. Thus, randomization of patients to treatment groups is crucial in maximizing the likelihood that these confounders will be equally distributed among groups (U.S. Food and Drug Administration 2004).

The value of maintaining sinus rhythm is greatest when particular symptoms or other adverse events occur predictably with the occurrence of atrial fibrillation. In this case, reduction of episodes of atrial fibrillation will undoubtedly lead to a corresponding reduction in symptoms. For other outcomes, especially cardiovascular morbidity and mortality, it is not possible to be confident that a reduction in atrial fibrillation episodes will lead to an improvement in those clinical outcomes.

Existing Treatment Guidelines. The most recent guidelines from the American Heart Association/American College of Cardiology/European Society of Cardiology were published in 2006 (Fuster et al. 2006). Treatment recommendations in this document focus on choice of pharmacologic agents and issues associated with pharmacologic management of atrial fibrillation such as anticoagulation. They emphasize individualizing the decision on rate versus rhythm control, and do not provide

explicit recommendations on which approach is preferred (Fuster et al. 2006). Rather, they provide guidance on the types of factors that should be considered in making this decision. First, they state that the short- and long-term goals for each patient should be determined. For example, for a patient who is symptomatic, one important goal is control of symptoms. If symptoms are not adequately controlled with a rate control strategy, then attempts to maintain sinus rhythm may be an important long-term goal (Fuster et al. 2006).

These guidelines state the following:

Depending upon symptoms, rate control may be reasonable initial therapy in older patients with persistent [atrial fibrillation] who have hypertension or heart disease. For younger individuals, especially those with paroxysmal lone [atrial fibrillation], rhythm control may be a better initial approach.

These guidelines recommend catheter ablation of the pulmonary veins for a subset of patients in whom a rhythm control strategy is pursued. These are patients with paroxysmal or persistent atrial fibrillation being treated with a rhythm control strategy and who have failed multiple antiarrhythmic drugs (Figures 4 and 5). The guidelines state that

Catheter ablation should be considered to maintain sinus rhythm in selected patients who failed to respond to antiarrhythmic drug therapy.

The formal recommendations from this document include the following Class IIa recommendation:

Catheter ablation is a reasonable alternative to pharmacological therapy to prevent recurrent [atrial fibrillation] in symptomatic patients with little or no [left atrial] enlargement. (*Level of Evidence: C*)

The American College of Physicians and American Academy of Family Physicians issued clinical practice guidelines in 2003 for patients with recent onset atrial fibrillation (Snow et al. 2003). These guidelines state that the majority of patients with recent onset atrial fibrillation should be treated with a pharmacologic rate control strategy and long-term anticoagulation. These guidelines state that rhythm control is appropriate when based on considerations

Figure 4. AHA/ACC Guidelines – Paroxysmal Atrial Fibrillation (Adapted from Fuster et al. 2006)

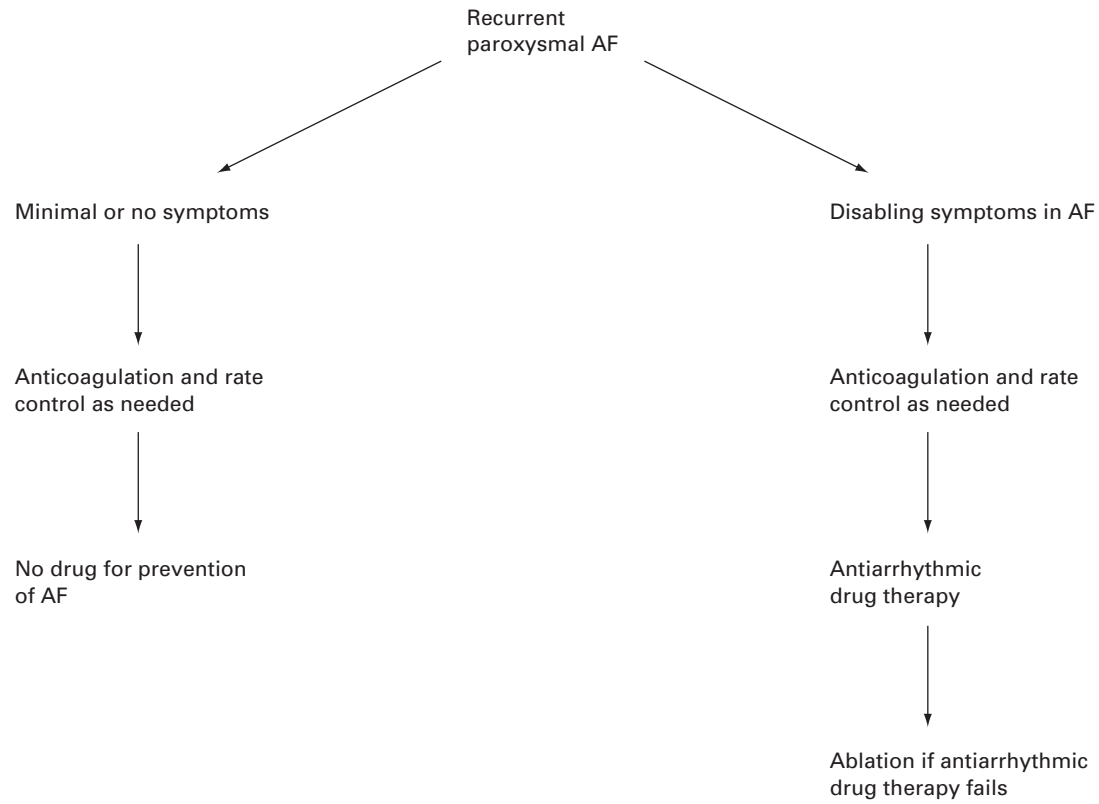
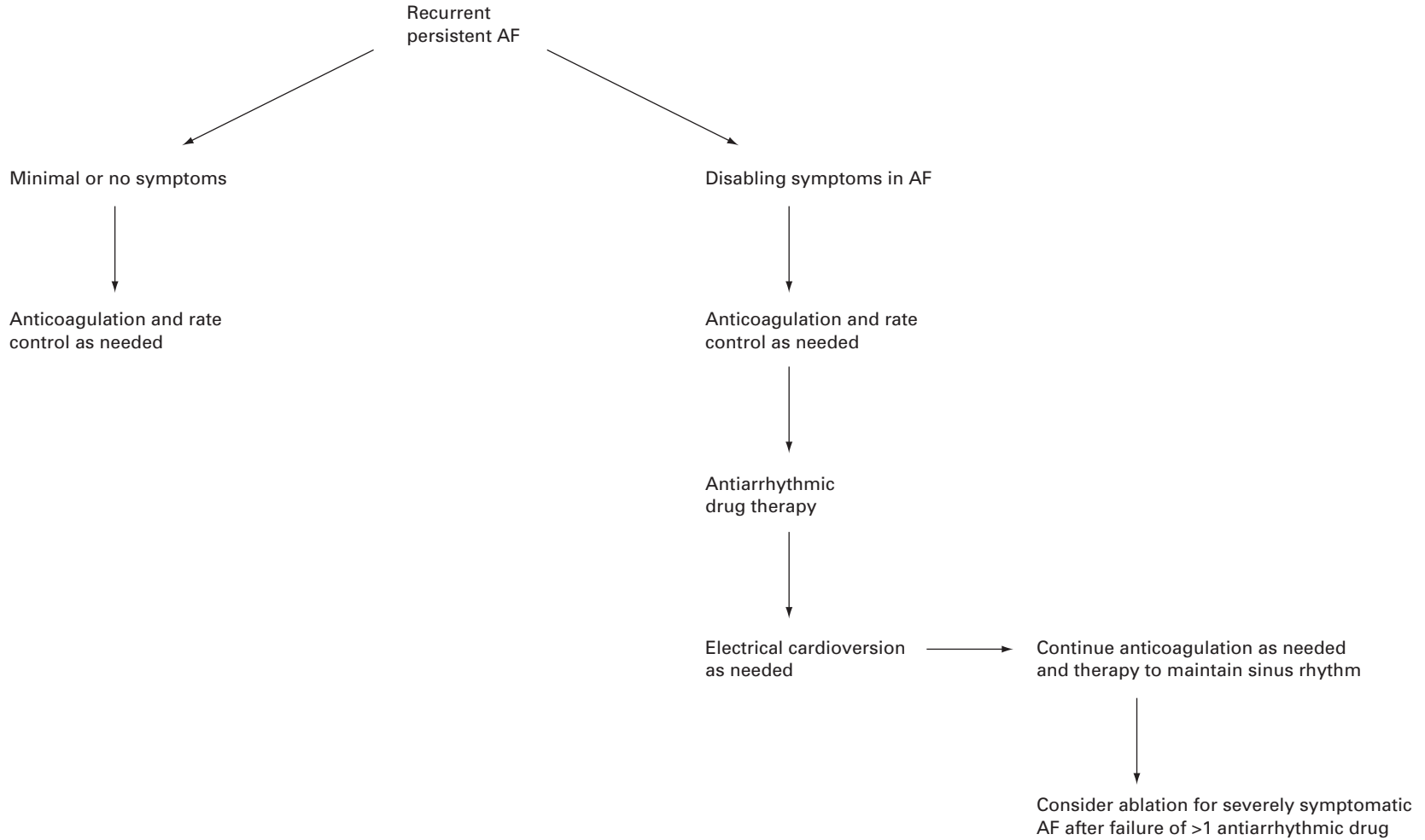


Figure 5. AHA/ACC Guidelines – Persistent Atrial Fibrillation (Adapted from Fuster et al. 2006)



such as symptoms, exercise tolerance, and/or patient preference. They do not include specific recommendations for catheter-based ablation techniques in their treatment algorithms.

Methods

Search Methods

MEDLINE[®] was searched (via PubMed) using the terms “pulmonary vein isolation,” “circumferential pulmonary vein ablation,” “CPVA,” “PVI,” and “catheter ablation.” These terms were cross-referenced with the terms “atrial fibrillation,” and “a fib.” Search was performed from March 2006 through January 2009, limited to English-language articles on human subjects. Electronic search was supplemented with the “related articles” function on PubMed for key studies, and with a hand-search of bibliographies from recent review articles and clinical studies. This search supplemented the original MEDLINE[®] search performed for the 2006 TEC Assessment for the period of 1990 through March 2006.

Study Selection

Studies were selected for inclusion in the current Assessment by the following criteria:

- Full-length, peer-reviewed articles published in an English-language journal;
- Treated patients with atrial fibrillation with percutaneous, catheter-based ablation of the pulmonary vein, or a related procedure;
- Randomized patients to catheter ablation or alternative treatments. Alternative treatments may include pharmacologic treatment with either a rhythm or a rate control strategy, or nonpharmacologic approaches;
- Enrolled at least 25 patients per treatment group.
- Reported on at least one relevant clinical outcome (survival, cardiovascular events, recurrence of atrial fibrillation, quality of life, exercise tolerance, complications of treatment).

Medical Advisory Panel Review

Current Assessment. This Assessment was reviewed by the Blue Cross and Blue Shield Association’s Medical Advisory Panel (MAP) on December 16, 2008. To maintain the timeliness of the scientific information in this Assessment, literature search updates were performed subsequent to the Panel’s review (see “Search Methods”). If the search updates identified

any additional studies that met the criteria for detailed review, the results of these studies were included in the text where appropriate. There were no studies that would change the conclusions of the Assessment.

Previous Assessment. A prior TEC Assessment was completed in 2006. At that time, there were 3 controlled trials comparing catheter ablation techniques with alternative treatments. The MAP concluded that the evidence did not permit conclusions on whether catheter ablation improved outcomes in patients with atrial fibrillation.

Formulation of the Assessment

Patient Indications

Catheter ablation is specifically intended to treat patients with atrial fibrillation in whom the arrhythmia originates in the pulmonary vein(s). Within this overall population of patients with atrial fibrillation, there are specific indications for which catheter ablation has been targeted. These indications form the basis of the patient indications for this Assessment. Three separate indications will be addressed.

1. Patients with recent onset paroxysmal atrial fibrillation, as first-line therapy. Many experts believe that catheter ablation is most effective in patients with paroxysmal atrial fibrillation, and/or those patients with recent onset of persistent atrial fibrillation. Younger patients with no other evidence of structural heart disease may be most likely to benefit from catheter ablation, since the success rate in maintaining sinus rhythm is highest in this population. In addition, maintenance of sinus rhythm can avoid the need for long-term pharmacologic treatment with antiarrhythmic medications and/or anticoagulants, both of which may be associated with serious adverse effects.

2. Patients with symptomatic paroxysmal or persistent atrial fibrillation who have failed antiarrhythmic drugs. Catheter ablation has also been used in patients with symptomatic paroxysmal or persistent atrial fibrillation who are refractory to pharmacologic management or who have contraindications to pharmacologic treatment. For these patients, a rhythm control strategy is often used in order to eliminate or reduce these symptoms associated with episodes of atrial fibrillation. In the subset of these patients who have highly symptom-

atic atrial fibrillation, catheter ablation is a particularly attractive option as reduction or elimination of episodes of atrial fibrillation will correspondingly decrease or eliminate symptoms. In this sense, catheter ablation may be considered the final option in a rhythm control strategy.

3. Patients with congestive heart failure and symptomatic atrial fibrillation who have failed standard medications for rate control, as an alternative to AV nodal ablation and pacemaker implantation. In patients with congestive heart failure, maintenance of sinus rhythm has the potential advantage of optimizing cardiac output by maintaining coordinated atrial contractions. In addition, medications used for rate control may be poorly tolerated in patients with congestive heart failure due to hypotension or bradycardia. AV nodal ablation and pacemaker insertion has been used in patients with congestive heart failure when standard medications for rate control are not successful.

Technologies to be Compared

Catheter ablation will be compared to alternative treatment options for atrial fibrillation. For the majority of patients, this will consist primarily of pharmacologic management. Pharmacologic treatment may follow a rhythm control strategy or a rate control strategy, since there is not clear superiority of one approach over the other.

For patients who are refractory or intolerant to pharmacologic management, the alternative treatment is continued medical management (albeit of limited effectiveness), or other invasive treatments for atrial fibrillation, such as the Maze procedure or AV nodal ablation with pacemaker insertion.

Health Outcomes

Health outcomes include the excess morbidity and mortality associated with atrial fibrillation. This includes survival, symptoms relating to atrial fibrillation such as worrisome palpitations and decrease in exercise tolerance. Complications of atrial fibrillation include thromboembolism, particularly embolic stroke, and development of cardiomyopathy as a result of long-standing atrial fibrillation.

Adverse events associated with pharmacologic treatment are also important to consider. Bleeding associated with anticoagulant treat-

ment is one important complication. Other complications include the potential proarrhythmic effect of antiarrhythmic medications.

Adverse effects of catheter ablation itself may include bleeding or other vascular complications at the puncture site, myocardial infarction, or cardiac tamponade due to myocardial perforation and bleeding into the pericardium. The most common late complication of the procedure is pulmonary vein stenosis, which can result from inflammation and scarring at the treatment site.

Maintenance of sinus rhythm is the most common outcome measure reported in available studies. This outcome is not by itself sufficient to establish benefit, since rhythm control has not been proven superior to rate control for the majority of patients with atrial fibrillation. However, maintenance of sinus rhythm may be beneficial in patients for whom a rate control strategy fails to control symptoms. Therefore, the utility of maintaining sinus rhythm is variable depending on clinical characteristics of the patients being treated.

Specific Assessment Questions

1. In patients with recent onset paroxysmal atrial fibrillation, does catheter ablation of the pulmonary veins as first-line treatment improve outcomes, as compared to standard pharmacologic treatment?
2. In patients with symptomatic paroxysmal or persistent atrial fibrillation who have failed treatment with antiarrhythmic medications, does catheter ablation of the pulmonary veins improve outcomes, as compared to continued pharmacologic treatment?
3. In patients with congestive heart failure and symptomatic atrial fibrillation who have failed rate control with standard medications, does catheter ablation of the pulmonary veins improve outcomes, as compared to AV nodal ablation and pacemaker therapy?

Review of Evidence

Prior TEC Assessment. A prior TEC Assessment was completed in 2006. At that time, there were 3 controlled trials comparing catheter ablation techniques with alternative treatments. Two of these were randomized, controlled trials and the third was a nonran-

domized comparative trial. Conclusions of the TEC Assessment were that the evidence did not permit conclusions on whether catheter ablation improves health outcomes. One small randomized, controlled trial (Wazni et al. 2005) treated patients with recent onset paroxysmal atrial fibrillation and reported a decreased recurrence of atrial fibrillation at 1 year. This trial did not report on the full range of clinical outcomes and was too small to estimate complication rates of the procedure. A second randomized, controlled trial (Oral et al. 2006) compared catheter ablation plus antiarrhythmic drug treatment with antiarrhythmic drug treatment alone. This trial did not directly compare catheter ablation alone with antiarrhythmic drug therapy alone, and as a result it is difficult to form conclusions on the comparative efficacy of catheter ablation from this trial. The third trial (Pappone et al. 2005) was nonrandomized and had a high likelihood of selection bias, since the choice of treatment was made by the patient's primary physician.

Since the prior TEC Assessment, 4 additional randomized, controlled trials have been published (Pappone et al. 2006; Stabile et al. 2006; Khan et al. 2008; Jais et al. 2008). For the current Assessment, review of evidence will be confined to the 6 available randomized, controlled trials of catheter ablation versus alternative treatments (Tables 2 and 3); nonrandomized comparative trials will not be included. One additional randomized, controlled trial was excluded from the analysis due to enrollment of less than 25 patients per treatment group (Krittayaphong et al. 2003). These 6 trials will be classified according to each of the three patient indications previously defined. All 6 trials used radiofrequency energy as the catheter ablation energy source; therefore, the scope of this Assessment is limited to radiofrequency catheter ablation techniques.

1. In patients with recent onset paroxysmal atrial fibrillation, does catheter ablation of the pulmonary veins as first-line treatment improve outcomes, as compared to standard pharmacologic treatment?

One randomized, controlled trial (Wazni et al. 2005) addressed this indication. This study was a multicenter, randomized, controlled trial that enrolled 70 patients with recent onset paroxysmal atrial fibrillation from two sites in Italy and one site in Germany (Tables 2 and 3). The trial intended to evaluate radiofrequen-

catheter ablation as first-line treatment in this patient population. Patients were eligible for enrollment if they had experienced one or more episodes of symptomatic atrial fibrillation per month for at least 3 months and had not been previously treated with antiarrhythmic drugs. The population enrolled was relatively young, with a mean age of 53 years. The mean duration of atrial fibrillation was 5 months, and approximately three-quarters of the patients did not have any evidence of structural heart disease or hypertension. This study was rated as "fair" on formal quality assessment (Appendix Table). The main limitations noted were the lack of double-blinding, small size of the trial, and the lack of reporting on the full range of relevant clinical outcomes.

The catheter ablation technique in this study included mapping of pulmonary vein potentials around the area of the pulmonary vein antra. Radiofrequency ablation was done in areas where mapping identified pulmonary vein potentials. Intracardiac echocardiography was utilized to position the mapping catheter and to titrate the radiofrequency energy used for ablation. Ablation was complete when no further pulmonary vein potentials were present, or when complete electrical dissociation was demonstrated between the pulmonary vein antra and the left atrium. Anticoagulation with warfarin was given to all patients for 3 months following the procedure, and then discontinued in patients who remained in sinus rhythm.

In the medical treatment group, choice of antiarrhythmic agents was at the discretion of the treating physician. Treating physicians were advised to use the maximal tolerated dose of medication, and to reserve use of amiodarone for patients who failed at least two other antiarrhythmic medications. Anticoagulation with warfarin was given to all patients in the medical treatment group for the duration of the trial.

The primary endpoint of this trial was self-reported, symptomatic recurrence of atrial fibrillation up to 12 months post-enrollment. Other endpoints included hospitalizations and quality of life (Tables 3 and 4). Recurrences of atrial fibrillation were less frequent in the catheter ablation group. At 12 months' follow-up, 13% of the patients in the catheter ablation group had symptomatic recurrence, compared to 63% in the medical management group ($p < 0.001$). There were also significant differences favoring the catheter ablation group in

Table 2. Randomized, Controlled Trials of Radiofrequency Catheter Ablation vs. Alternative Treatments: Study Characteristics

Study/Yr	Study Design	Patient Population	Intervention		Outcome Measures
			Catheter Ablation	Control	
First-line treatment of patients with recent-onset paroxysmal AF					
Wazni et al. 2005	Single center RCT Pts. randomized to PVI or antiarrhythmic medications (rhythm control strategy)	70 pts with AF: – 18–75 years old – ≥1 episode/month of symptomatic AF for at least 3 mos. – No previous ablative therapy, a flutter, open heart surgery or treatment with antiarrhythmic drugs – No contraindication to anticoagulation	Radiofrequency ablation – Ablation of pulmonary vein antra in locations where pulmonary vein potentials were recorded by intracardiac mapping – Anticoagulation with warfarin for 3 mos., discontinued if no recurrent AF	Antiarrhythmic medications. – Choice of medication per treating physician – Centers advised to use max tolerated dose of meds – Anticoagulation with warfarin throughout duration of study	– Recurrences of AF – Hospitalizations – QOL by SF-36 – Adverse events
Treatment of symptomatic patients with paroxysmal or persistent AF who have failed antiarrhythmic drugs					
Jais et al. 2008	Multicenter RCT Patients randomized to circumferential ablation or medical therapy Crossover to alternative treatment allowed if recurrent AF at 3 mos. or longer follow-up	112 patients with paroxysmal AF – >18 years old – Symptomatic AF for >6 mos., ≥2 episodes/month – Failed ≥1 prior AAD drug trial	Radiofrequency ablation – Circumferential ablation of all 4 pulmonary veins – Ablation of cavotricuspid isthmus – Additional ablation lines per treating physician(s) – Post-procedure anticoagulation per treating physician(s)	Antiarrhythmic medications – Trial of “new” AAD or combination, not previously used, at discretion of treating physician – Anticoagulation at discretion of treating physician	– Recurrence of AF – AF burden – QOL – Exercise capacity – Left heart dimensions and LVEF – Complications/adverse effects – Efficacy of amiodarone

Table 2. Randomized, Controlled Trials of Radiofrequency Catheter Ablation vs. Alternative Treatments: Study Characteristics (cont'd)

Study/Yr	Study Design	Patient Population	Intervention		Outcome Measures
			Catheter Ablation	Control	
Treatment of symptomatic patients with paroxysmal or persistent AF who have failed antiarrhythmic drugs (cont'd)					
Oral et al. 2006	Multicenter RCT Pts. randomized to: PVI plus amiodarone for 3 mos. plus cardioversion, if needed OR amiodarone for 3 mos. plus cardioversion, if needed Pts. in control group offered PVI after 3 mos. if still in AF	146 pts with AF: – 18–70 years old – Chronic AF for at least 6 mos., without intervening episodes of sinus rhythm – Left atrial diameter ≤55 mm – LV ejection fraction ≥30%	Radiofrequency ablation – Circumferential ablation of all 4 pulmonary veins, 1–2 cm from the ostia – Additional ablation lines created, as per results of electro-anatomic mapping – Amiodarone for 3 mos. – Warfarin for at least 3 mos. – Cardioversion as needed	Control group – Amiodarone for 3 mos. – Warfarin for at least 3 mos. – Cardioversion as needed	– Recurrences of AF – Complications – Left atrial diameter – LV ejection fraction – Severity of symptoms
Pappone et al. 2006	Single center RCT Pts. randomized to CPVA or antiarrhythmic drug therapy	198 patients with paroxysmal AF – 18–70 years old – AF for >6 mos.; >2 episodes per month – Failed previous AAD – Left atrial diameter ≤65 mm – LV ejection fraction ≥35%	Radiofrequency CPVA Ablation of cavotricuspid isthmus in all pts. AAD for 6 weeks following procedure Warfarin for 6 weeks in all pts.; discontinued if no evidence of AF for 6-week period	– Amiodarone, flecainide, or sotalol administered at discretion of investigator – Warfarin for 6 weeks in all pts; discontinued if no evidence of AF for 6-week period – Eligible for crossover to ablation after two unsuccessful drug trials	– Recurrences of AF – Complications

Table 2. Randomized, Controlled Trials of Radiofrequency Catheter Ablation vs. Alternative Treatments: Study Characteristics (cont'd)

Study/Yr	Study Design	Patient Population	Intervention		Outcome Measures
			Catheter Ablation	Control	
Treatment of symptomatic patients with paroxysmal or persistent AF who have failed antiarrhythmic drugs (cont'd)					
Stabile et al. 2006	Multicenter RCT Pts. randomized to CPVA plus antiarrhythmic drug therapy or antiarrhythmic drug therapy alone	137 patients with paroxysmal or persistent AF – 18–80 years old – AF for >6 mos., ≥1 episode per month – Failed at least 2 previous AAD – Left atrial diameter ≤60 mm – LV ejection fraction 35%	Radiofrequency CPVA – Ablation of mitral isthmus in all pts. – Ablation of cavotricuspid isthmus in pts with abnormal conduction – Warfarin for 4 weeks in all pts.; discontinued if no evidence of AF after 4 weeks	– AAD at discretion of treating physician; amiodarone preferred agent – Anticoagulation at discretion of treating physician	– Recurrences of AF – Complications
Treatment of patients with AF and CHF who have failed standard medication regimens					
Khan et al. 2008	Multicenter RCT Pts. randomized to PVI or AV nodal ablation and biventricular pacing Repeat PVI procedure performed at 3 months, if necessary Six-month follow-up	146 pts with symptomatic AF and: – Class II-III CHF – Failed AAD – 18 years or older – LVEF ≤40%	Radiofrequency ablation – Circumferential ablation of all 4 pulmonary veins. – Additional ablation lines per preference of treating center – Antiarrhythmic meds for 2 mos. – Warfarin for at least 3 mos. – Cardioversion as needed	AV nodal ablation: – Catheter-based AV nodal ablation and ablation of bundle of His – Insertion of biventricular pacemaker/ICD – Warfarin for at least 3 mos.	Primary outcome composite of: – LVEF – 6-minute walk test – QOL by MLWHF* score Secondary outcomes: – Recurrence of AF – LA diameter

*MLWHF – Minnesota living with heart failure questionnaire; 21 questions with score from 0-105, higher score indicates worse QOL

AAD: antiarrhythmic drug; AF: atrial fibrillation; AV: atrioventricular; CHF: congestive heart failure; CPVA: circumferential pulmonary vein ablation; ICD: implantable cardioverter-defibrillator; LVEF: left-ventricular ejection fraction; PVI: pulmonary vein isolation; QOL: quality of life; RCT: randomized, controlled trial

Table 3. Randomized, Controlled Trials of Radiofrequency Catheter Ablation Versus Alternative Treatments: Outcomes

Study/Yr	Group	n	F/U	Mortality	Recurrence	QOL/Symptoms	Ejection fraction		Exercise capacity		
First-line treatment of patients with recent onset paroxysmal AF											
Wazni et al. 2005	PVI	33	12 mos.	NR	13% (4/32)	Greater improvement for PVI group on 5/8 SF-36 subscales					
	Med	37	12 mos.	NR	63% (22/35) p<0.001						
Treatment of symptomatic patients with paroxysmal or persistent AF who have failed antiarrhythmic drugs											
Jais et al. 2008	CPVA	53	12 mos.		11% (7/53)	Greater improvement for PVI group on 6/8 SF-36 subscales	Pre-	Post-	Treadmill exercise time		
	Med	59			77% (42/55) p<0.0001		63.1±11.0	65.4±8.9	Pre-	Post-	
							65.6±7.2	65.4±5.9	9.5±4.0	12.4±5.3	
							p=0.99		9.1±4.1	10.3±4.6	
									p=0.17		
Oral et al. 2006	CPVA	77	12 mos.	NR	26% (20/77)*	Significant within-group improvement in symptom score following PVI from 17±4 at baseline to 12±4 following PVI (p=0.02)	NR		NR		
	Med	69	12 mos.	NR	96% (66/69) p<0.001		NR		NR		
Stabile et al. 2006	PVI	68	12 mos.	1.5% (1/68)	44% (30/68)	NR	NR		NR		
	Med	69		2.9% (2/69) NS	91% (63/69) p<0.001						
Pappone et al. 2006	CPVA	99	12 mos.	6% (38/589)	14%**	NR	NR		NR		
	Med	99	(md)	14% (83/582) p<0.001	78% p<0.001						
Treatment of patients with AF and CHF who have failed standard medication regimens											
Khan et al. 2008						MLWHF scale				Six-minute walk	
						Pre-	Post-	Pre-	Post-	Pre-	Post
	PVI	41	6 mos.	0%	26% (20/77)*	89±12	60±8	27±8%	35±9%	269±54m	340±49m
AVN ablation	40	6 mos.	0%	96% (66/69) p<0.001	89±11	82±14	29±7%	28±6%	281±44m	297±36m	
						p<0.001		p<0.001		p<0.001	

* Outcome defined as "Freedom from AF at 12 mos. without use of antiarrhythmic medications." Reported numbers in table are percent who did not meet this endpoint. Does not include results of crossovers from control to catheter ablation after 3 mos. (53/69)

** Recurrence of AF at 1-year by Kaplan Meier analysis

AVN: atrioventricular node; CPVA: circumferential pulmonary vein ablation; md: median; NR: note reported; NS: not significant; PVI: pulmonary vein isolation

Table 4. QOL Outcomes in Trials of Radiofrequency Catheter Ablation vs. Medical Management

Study/Yr	Group	Δ SF-36 Measure							
		General Health	Phys Functional	Role Physical	Mental Health	Role Emotional	Social	Pain	Vitality
Wazni et al. 2005	PVI	22	26	18	0	6	15	26	13
	Control	11	6	2	4	5	6	20	9
		<0.001	0.001	0.05	0.62	0.90	0.004	0.004	0.21
Jais et al. 2008		Δ SF-36 Measure				Δ Symptom Frequency		Δ Symptom Severity	
		Physical Component		Mental Component					
	PVI	7.2		9.7		14.0		11.5	
	Control	6.0		9.1		12.2		8.8	
		p<0.02		p<0.09		p<0.10		p<0.001	

the mean number of recurrences per patient ($p < 0.05$) and the mean time spent in atrial fibrillation (2% vs. 16%; p not reported).

Quality of life (QOL) was measured at 6 months with the SF-36 instrument (Table 4). Improvement in QOL was significantly better for the catheter ablation group on 5 of the 8 subscales, with a mean corrected difference ranging from 6 points (pain) to 20 points (physical functioning). Hospitalizations during follow-up were also less frequent in the catheter ablation group, with 9% of the catheter ablation patients hospitalized at least once, compared with 54% of patients in the medical management group ($p < 0.001$).

2. In patients with symptomatic paroxysmal or persistent atrial fibrillation who have failed treatment with antiarrhythmic medications, does catheter ablation of the pulmonary veins improve outcomes, as compared to continued pharmacologic treatment?

There were 4 trials that enrolled patients with long-standing atrial fibrillation who had failed previous antiarrhythmic drug treatment (Oral et al. 2006; Pappone et al. 2006; Stabile et al. 2006) (Table 1). The largest of these trials was Pappone et al. (2006), which compared radiofrequency catheter ablation to antiarrhythmic medications in patients with recurrent paroxysmal atrial fibrillation who had failed antiarrhythmic drug treatment (Pappone et al. 2006). This trial randomized 198 consecutive patients to either catheter ablation alone or a different antiarrhythmic medication. The average age of the population was 56 years, and the duration of prior atrial fibrillation was approximately 6.5 years. This study was rated as “fair” by formal quality assessment (Appendix Table). The main methodologic limitations of this trial were the lack of double-blinding and the lack of a full range of clinically relevant outcomes.

The ablation technique used by these authors consisted of circumferential pulmonary vein isolation, in combination with linear ablation of the tricuspid isthmus. All patients were treated with amiodarone and warfarin for at least 6 weeks following the procedure. In patients receiving ablation, antiarrhythmic drugs and warfarin were discontinued if there was no evidence of atrial fibrillation recurrence. Patients were followed for 12 months and the main outcome measure reported was

freedom from atrial fibrillation. Antiarrhythmic drug therapy was prescribed at the discretion of the treating physician, with amiodarone as the preferred agent.

At 12 months’ follow-up, estimates of atrial fibrillation recurrence by Kaplan-Meier analysis was 7% for the ablation group compared with 35% for the medication group ($p < 0.001$). There were two serious complications in the ablation group for a rate of 2.0%; one transient ischemic attack (TIA) and one pericardial effusion that did not require pericardiocentesis.

Two additional randomized, controlled trials enrolled a similar population of patients with long-standing atrial fibrillation who had failed previous antiarrhythmic drug treatment (Oral et al. 2006; Stabile et al. 2006). These trials differed from Pappone et al. (2006) in that they compared radiofrequency catheter ablation plus antiarrhythmic medications with antiarrhythmic medications alone. The primary outcome in both trials was freedom from atrial fibrillation at 1 year.

Oral et al. (2006) was a randomized, controlled trial performed at two clinical centers, one in the U.S. and one in Italy. This trial intended to evaluate whether maintenance of sinus rhythm following catheter ablation could be attributed solely to catheter ablation, apart from the effect of ancillary treatments (short-term amiodarone therapy, cardioversion as needed) that commonly accompany this procedure. Patients enrolled had chronic atrial fibrillation for at least the preceding 6 months, without intervening episodes of sinus rhythm. The average age of the population was 56.4 years, and the duration of prior atrial fibrillation was 4.5 years. This study was rated as “fair” by formal quality assessment (Appendix Table). The main methodologic limitations of this trial were the lack of the most clinically relevant comparisons (ablation alone versus antiarrhythmic drugs alone), the high number of crossovers from control to catheter ablation, and the lack of reporting on the full range of clinical outcomes.

The catheter ablation technique used by these authors involved two circumferential ablation lines approximately 1–2 cm from the ostia of the pulmonary veins. One of these ablation lines encircled the two superior pulmonary veins and the other ablation line encircled the two inferior pulmonary veins. Additional ablation lines were created depending on the

results of electroanatomic mapping performed for each patient. Ancillary treatments included amiodarone for 3 months and cardioversion as needed if there was recurrence of atrial fibrillation. The control group received ancillary treatments alone, without catheter ablation, but were eligible to cross over to catheter ablation if they did not maintain sinus rhythm after 3 months.

Freedom from recurrent atrial fibrillation was greater in the catheter ablation group than in the control group (Table 3). At 1 year, 74% of patients assigned to catheter ablation were free of atrial fibrillation without the use of antiarrhythmic medications. In the control group, 58% of patients assigned to control were free from atrial fibrillation at 1 year, but most of these were patients who had crossed over to catheter ablation. Only 4% of patients assigned to the control group were free of atrial fibrillation at 1 year following treatment only with ancillary measures without catheter ablation ($p < 0.001$). A number of other beneficial results were reported for the patients receiving catheter ablation, but these were within group comparisons of variables measured pre- and post-procedure. The symptom score significantly improved in patients receiving catheter ablation, from 17 ± 4 pretreatment to 12 ± 4 post-treatment ($p = 0.02$). Left atrial size also improved, with a decrease from 45 ± 6 to 40 ± 6 following treatment ($p < 0.001$). Left ventricular ejection fraction likewise improved in patients receiving catheter ablation, from $55\% \pm 6$ to $62\% \pm 8$ ($p < 0.001$). The authors reported that there were no complications in either group, but did not elaborate further on adverse events.

Stabile et al. (2006) enrolled patients with either paroxysmal or persistent atrial fibrillation who had failed or were intolerant of at least two different antiarrhythmic medications. The average age of the population was 62 years, and the duration of prior atrial fibrillation was approximately 6 years. This study was rated as “fair” by formal quality assessment (Appendix Table). The main methodologic limitations of this trial were the lack of the most clinically relevant comparison (ablation alone versus pharmacologic treatment alone), and the lack of a full range of clinically relevant outcome measures.

The ablation technique used by these authors consisted of circumferential radiofrequency pulmonary vein ablation, plus ablation of the mitral isthmus for all patients. Additional

ablation of the cavotricuspid isthmus was performed in patients who had evidence of abnormal p-wave conduction at this site. Patients were followed for 12 months and the main outcome measure was freedom from atrial fibrillation. In the medication group, antiarrhythmic drug therapy was prescribed at the discretion of the treating physician, with amiodarone as the preferred agent.

At 12 months' follow-up, the majority of patients in the medication group (91%, 63/69) had experienced at least one recurrence of atrial fibrillation, compared to less than half of patients in the ablation group (44%, 30/68; $p < 0.001$). Cox proportional hazards analysis revealed that treatment group was the only significant predictor of atrial fibrillation recurrence, with an increased hazard ratio for recurrence of atrial fibrillation in the medication group of 3.2 (95% CI: 2.0–5.1). There were 3 major complications associated with ablation (Table 5), for a serious complication rate of 4.4%.

The most recent trial for this indication was a multicenter randomized, controlled trial published by Jais et al. (2008). This study enrolled 112 patients with symptomatic, paroxysmal atrial fibrillation of at least 6 months' duration and who had failed at least one previous trial of antiarrhythmic medications. Patients were randomized to circumferential radiofrequency ablation of all four pulmonary veins or continued medication management. This trial was notable in that it reported a number of clinically relevant outcome measures in addition to recurrence of atrial fibrillation. These included QOL, as measured by the SF-36 instrument, symptom frequency and severity, exercise capacity, and left heart dimensions measured by echocardiography.

On formal quality assessment, this trial did not meet all quality indicators but did not contain any “fatal flaws” and was therefore assigned a rating of “fair” (Appendix Table). The main methodologic limitations identified included lack of blinding, unequal intensity of treatment modalities, and a high number of early cross-overs, particularly from the medication management to the catheter ablation group.

Outcomes were reported at 3-month intervals, up to 1 year total duration. The recurrence of atrial fibrillation was markedly higher in the medication management group (Table 3), with 42/55 (77%) patients treated with medications

experiencing at least one recurrence compared with 7/53 (11%) patients treated with catheter ablation ($p < 0.0001$). QOL was improved to a greater extent in the catheter ablation group, with greater QOL scores reported for 6 of 8 SF-36 subscales over the course of the trial. The greatest differences in QOL were seen at 3 months post-treatment, with smaller differences reported at 1 year (Table 4). A similar pattern was seen for symptom frequency and severity, with larger differences reported at 3 and 6 months. At 1-year follow-up, significant differences on symptom severity remained, while there was a nonsignificant trend toward differences on symptom frequency. Exercise duration measured by exercise treadmill time also showed a nonsignificant trend in favor of the catheter ablation group at 1 year. Other measures of exercise capacity, including maximum workload and total metabolic equivalents (METs) were significantly better for the catheter ablation group.

The attenuation in differences between groups on QOL, symptom severity, and exercise duration at the 1-year follow-up may have been largely due to the large number of crossovers from medication management to catheter ablation. Crossover was allowed if the primary endpoint, recurrence of atrial fibrillation, was reached. A total of 37 patients (63%) in the medical management group crossed over to catheter ablation at a mean of 192 ± 80 days. In the catheter ablation group, 5 patients (9%) with atrial fibrillation recurrence crossed over to the medical management group. All comparisons of outcomes were reported on an intention-to-treat basis.

3. In patients with congestive heart failure and symptomatic atrial fibrillation who have failed rate control with standard medications, does catheter ablation of the pulmonary veins improve outcomes, as compared to AV nodal ablation and pacemaker therapy?

One study addressed this indication (Khan et al. 2008). This study was a multicenter, unblinded randomized, controlled trial of 81 patients enrolled from centers in Europe and the U.S. Eligibility criteria included patients with class II or III congestive heart failure and symptomatic drug-resistant atrial fibrillation. Patients were randomized to catheter ablation or AV nodal ablation and pacemaker implantation and followed for 6 months. The authors defined

their primary outcome as a composite of distance on 6-minute walk test, ejection fraction, and QOL as measured by the Minnesota Living with Heart Failure (MLWHF) questionnaire. Secondary outcome measures included recurrence of atrial fibrillation and morphologic measures of the heart on echocardiogram.

This study met all the quality indicators on formal quality assessment and was assigned an overall quality rating of "good." The main methodologic limitations included the small size of the trial, the lack of blinding to treatment assignment, and the short duration of follow-up (i.e., 6 months).

The ablation technique used in this trial was the same as used for the Wazni et al. (2005) trial. This included mapping of pulmonary vein potentials around the area of the pulmonary vein antra. Radiofrequency ablation was done in areas where mapping identified pulmonary vein potentials. Intracardiac echocardiography was utilized to position the mapping catheter and to titrate the radiofrequency energy used for ablation. Ablation was complete when no further pulmonary vein potentials were present, or when complete electrical dissociation was demonstrated between the pulmonary vein antra and the left atrium. Anticoagulation with warfarin was given to all patients for 3 months following the procedure, and then discontinued in patients who remained in sinus rhythm.

Outcomes on all of the primary and secondary outcomes favored the catheter ablation group. For the three components of the primary outcome, the catheter ablation group had significantly better outcomes on each of the measures (Table 3). The magnitude of differences on these outcomes were relatively large with a very small p value for each (< 0.001). Similarly, the difference on the secondary outcome of atrial fibrillation recurrence showed a large difference in favor of the catheter ablation group (26% vs. 96%, $p < 0.001$). The authors also reported the rate of atrial fibrillation progression, i.e., transition to a more advanced form of disease such as from paroxysmal to persistent atrial fibrillation. In the catheter ablation group, there were no patients who progressed to a more advanced stage, while in the AV nodal ablation group, 30% of patients progressed ($p < 0.001$).

Adverse events were uncommon in both groups (Table 5), with no significant differences in complication rates between groups.

Table 5. Adverse Effects of Catheter Ablation for Atrial Fibrillation

Study/Yr	Group	n	F/U	Adverse Events (% pts)								
				CVA	TIA	TE*	CHF	Bleed	Brad	PVsten	Per Eff	
Wazni et al. 2005	PVI	33	12 mos.	0	0	0	NR	**	0	3%		
	Med	37		0	0	0	NR	**	9%	0		
Jais et al. 2008	CPVA	68	12 mos.	0	0	0	0	0	0	0	1.9	3.8
	Med	69		0	NR	NR	NR	NR	NR	NR	NR	NR
Oral et al. 2006	PVI	77	12 mos.	0	0	0	0	0	0	0	0	
	Med	69		0	0	0	0	0	0	0	0	
Stabile et al. 2006	CPVA	68	12 mos.	1.5	0	NR	NR	0	NR	0	0	1.5
	Med	69		0	1.4	NR	NR	0	NR	0	0	0
Pappone et al. 2006	CPVA	99	12 mos.	0	1.0	NR	NR	0	NR	NR	NR	1.0***
	Med	99		0	0	NR	NR	0	NR	NR	NR	
Khan et al. 2008	PVI	41	6 mos.	0	0	0	0	7.3%	0	4.9%	2.4%	
	AVN ablation	40		0	0	0	2.5%	5.0%	0	0	0	

* Thromboembolic event other than CVA

** reported "bleeding rates were similar in both groups" without further quantification

*** Pericardial effusion requiring pericardiocentesis

Brad: bradycardia; CVA: cerebrovascular accident; NR: not reported; Per Eff: pericardial effusion/tamponade; PVI: pulmonary vein isolation; PVsten: pulmonary vein stenosis; TE: thromboembolic; TIA: transient ischemic attack;

In the catheter ablation group, there were 3 patients with groin bleeding, one patient with postoperative pulmonary edema, one patient with a pericardial effusion, and two patients with asymptomatic pulmonary vein stenosis. In the AV nodal ablation group, two patients had bleeding at the pacemaker site and one patient had pneumothorax. Four additional patients had dislodgement or dysfunction of the left ventricular pacemaker lead.

Discussion

There are 6 randomized, controlled trials comparing radiofrequency catheter ablation with alternative treatments for atrial fibrillation. Each of these 6 trials reports differences in favor of the catheter ablation group on at least one relevant outcome. The most consistently reported outcome in these trials is recurrence of atrial fibrillation, which was a primary outcome measure in 5 trials and a secondary outcome measure in the sixth. Therefore, it is possible to conclude that catheter ablation is more effective than alternative treatments in maintaining sinus rhythm for the three patient populations evaluated.

However, the utility of this outcome varies according to the indication being treated and the goals of treatment. For patients in whom symptoms are adequately controlled by rate control, maintenance of sinus rhythm by itself may not be the most important health outcome. In this case, continued control of symptoms, prevention of thromboembolic complications, and prevention of cardiovascular complications such as congestive heart failure are the goals.

In contrast, for patients with paroxysmal or persistent atrial fibrillation in whom symptoms are not adequately controlled, rhythm control becomes a more important option. For these patients, maintenance of sinus rhythm can be more firmly linked to the reduction of symptoms and improvement in QOL. Moreover, a rhythm control strategy with antiarrhythmic medications is an imperfect option. Antiarrhythmic medications are only partially effective in maintaining sinus rhythm, and are associated with serious adverse effects, including potentially lethal proarrhythmic effects in some patients. For these reasons, a nonpharmacologic approach to rhythm control is particularly attractive in this patient group.

There is some evidence on the outcome of QOL, but it is less robust than that for recurrence of atrial fibrillation. Only 4 trials report any results on QOL, one of which reported only within-group differences and not between-group differences. The three remaining trials treat distinct patient groups, i.e., recent onset paroxysmal atrial fibrillation, drug-resistant atrial fibrillation, and class II or III congestive heart failure with symptomatic atrial fibrillation; QOL is likely to differ markedly among these groups. Two of the studies (Wazni et al. 2005; Jais et al. 2008) used the SF-36 instrument, a general QOL measure. The third study (Kahn et al. 2008) used the Minnesota Living with Heart Failure questionnaire, a disease-specific QOL measure.

None of the randomized, controlled trials provide meaningful information on the most important relevant clinical outcomes, including survival, cardiovascular events, and complications of treatment. Recurrence of atrial fibrillation is probably not a reliable surrogate marker for these important health outcomes (U.S. Food and Drug Administration 2004). This is a major gap in the literature that precludes conclusions on the impact of radiofrequency catheter ablation in the broader population of patients with atrial fibrillation.

Another potential benefit of maintaining sinus rhythm is avoidance of the need for anticoagulation. While anticoagulation is effective in reducing the risk of embolic stroke, it also can lead to serious bleeding complications, such as gastrointestinal or intracranial hemorrhage. Treatment decisions based on the benefits and risks of anticoagulation are challenging for clinicians and patients alike. This is particularly true for elderly patients, in whom both the risks of complications from atrial fibrillation and the risk of complications from anticoagulation are increased. Embolic stroke in elderly patients can lead to severe disability and loss of independence. On the other hand, hemorrhagic complications from anticoagulation, for example, intracranial bleeds in elderly patients at risk for falls, can have devastating consequences. Maintaining sinus rhythm has the potential to reduce the risk for both types of complications.

The interpretation of these reported outcomes for each specific indication is discussed more thoroughly below.

First-line Treatment for Paroxysmal Atrial Fibrillation. One small trial addressed this indication (Wazni et al. 2005) and reported on the outcomes of atrial fibrillation recurrence and QOL.

For this indication, the utility of atrial fibrillation recurrence as a relevant outcome is questionable. A large percentage, if not most, patients who present with paroxysmal atrial fibrillation can be successfully managed with a rate control strategy, with or without anticoagulation. Data from prior clinical trials such as the AFFIRM and PIAF studies suggest that outcomes for these patients treated with a rate control strategy will be as good or better than if treated with a rhythm control strategy.

In addition, because of the difficulty in measuring recurrence of atrial fibrillation, it is difficult to distinguish between patients who have a reduction in episodes of atrial fibrillation and those who have no recurrence. This is important because patients who have no recurrence of atrial fibrillation can safely discontinue anticoagulation and/or other medications, while those who still have recurrences, even at decreased frequency, are likely to benefit from continued medications. As a result, there is a potential for harm if this outcome measure is not recorded accurately. For example, patients treated with ablation who have undetected recurrences of atrial fibrillation may be labeled incorrectly as having no recurrences. Anticoagulation and/or other medications may then be stopped inappropriately, leading to an increased risk for stroke and other complications.

The Wazni trial (Wazni et al. 2005) also provides data on QOL, which is an important outcome measure for this group of patients. Prior research has demonstrated that patients with atrial fibrillation have reduced QOL and that maintenance of sinus rhythm may be associated with improved QOL. This trial does in fact report relatively large improvements in some SF-36 measures, suggesting that QOL may be improved as a result of decreased recurrences of atrial fibrillation. However, the trial is small in numbers and unblinded, leaving the possibility of a placebo effect for these self-reported measures. Therefore, this evidence is not sufficient to conclude that health outcomes are improved following catheter ablation.

Treatment of Symptomatic Patients with Paroxysmal or Persistent Atrial Fibrillation Who Have Failed Antiarrhythmic Medications.

There were 4 trials that addressed this indication and reported on the outcome of atrial fibrillation recurrence (Oral et al. 2006; Pappone et al. 2006; Stabile et al. 2006; Jais et al. 2008). Only one of the four trials (Jais et al. 2008) provided meaningful data on any of the other relevant outcomes. All 4 trials reported a large decrease in atrial fibrillation recurrence associated with catheter ablation. The absolute risk reduction for atrial fibrillation recurrence at 1 year ranged from 47–70%, indicating that a large percentage of patients benefited in terms of avoiding recurrence of atrial fibrillation.

For this indication, the utility of atrial fibrillation recurrence as a health outcome is most compelling. This patient group is selected for patients who have intolerable symptoms associated with episodes of atrial fibrillation, and who are asymptomatic between episodes. Symptom control is one of the main goals of treatment for this patient group. A reduction in atrial fibrillation episodes will undoubtedly lead to a corresponding decrease in atrial-fibrillation-related symptoms. Therefore, it is reasonable to extrapolate that the decreased recurrence rate of atrial fibrillation translates to a decrease in symptoms for this patient group.

Jais et al. (2008) also reported improvements on QOL, symptom severity, and exercise tolerance. The differences on these outcome measures were greatest at 3 months, with smaller differences reported at 1 year. However, the 1-year outcomes on these measures may have been attenuated by a large number of crossovers from medication management to catheter ablation (63%), since the comparisons were reported on an intention-to-treat basis. Therefore, these data do not establish the degree of improvement in QOL, symptoms, or exercise capacity associated with catheter ablation. The reported difference in maintenance of sinus rhythm was relatively large, however, so it is likely that there is a clinically important reduction in symptoms associated with catheter ablation.

Patients with Class II or III Congestive Heart Failure and Symptomatic Atrial Fibrillation in whom Heart Rate Is Poorly Controlled by Standard Medications. There is one trial that addressed this indication (Khan et al. 2008),

and which enrolled a very specific subgroup of patients with class II or III congestive heart failure and symptomatic atrial fibrillation in whom heart rate was uncontrolled by standard medications. While relatively small and of short duration, this was a multicenter randomized, controlled trial that met all of the formal quality indicators and received a quality rating of “good.” Notably, this trial did not rely on atrial fibrillation recurrence as the primary outcome, but rather used a rigorous composite outcome of QOL, ejection fraction, and functional status. The trial reported significant improvements on all of the individual outcome measures, and their results met their prespecified threshold for the composite outcome. In addition, recurrence of atrial fibrillation was measured as a secondary outcome and was also significantly reduced for the catheter ablation group.

The individual components of the primary outcome measure are all important clinical outcomes. The differences reported in the trial are relatively large, indicating both statistical and clinical significance.

Future Research. Larger trials with longer follow-up periods are required to provide useful information on important clinical outcomes and complication rates. The CABANA trial (ClinicalTrials.gov Identifier NCT00578617) is an ongoing trial of approximately 4,000 patients that compares catheter ablation with antiarrhythmic medications, and includes the endpoints of mortality, complications of catheter ablation, and other clinical outcomes. This trial is expected to be completed in 2011 and will provide the best evidence to date on the effect of catheter ablation on clinical outcomes.

Numerous other small- to moderate-sized randomized, controlled trials comparing catheter ablation to medical therapy are currently underway. Two examples of these types of trials are the RAAFT trial and the MANTRA-PAF. RAAFT compares medical therapy with catheter ablation in 400 patients with atrial fibrillation, and is expected to be completed in 2009. The MANTRA-PAF trial is also expected to be completed in 2009, and compares medical therapy versus catheter ablation in 300 patients with paroxysmal atrial fibrillation. These trials will add to the evidence base on the efficacy of catheter ablation in maintaining sinus rhythm, and may also contribute useful information on the impact of catheter ablation on symptoms and QOL.

Further research on the technical aspects of catheter ablation is also needed. There is considerable uncertainty regarding technical aspects of the procedure. The technique continues to evolve, with numerous modifications still being proposed to improve efficacy and reduce risks. The exact extent and location of ablated areas varies by operator. Some operators currently recommend a more extensive ablation, which may include linear ablation lines in the atria and/or treatment of “complex atrial electrograms” identified by mapping. Complication rates may vary according to the specific technical aspects of the procedure; as a result it is difficult to determine complication rates given the wide variety of technical variations among the available literature. The type of energy used also varies by treatment center. Radiofrequency ablation is most commonly used; however other energy sources such as cryotherapy, ultrasound, or laser may also be employed.

Summary and Conclusions

In summary, the current evidence base on radiofrequency catheter ablation for atrial fibrillation establishes that ablation is superior to medications for maintaining sinus rhythm. Patients who require a rhythm control strategy to control symptoms and who have failed antiarrhythmic medications will benefit from catheter ablation since reduction or elimination of atrial fibrillation episodes will lead to a corresponding improvement in symptoms. The evidence also is sufficient to determine that patients with class II or III congestive heart failure and symptomatic atrial fibrillation in whom heart rate is uncontrolled have better outcomes following catheter ablation of the pulmonary veins than with AV nodal ablation and pacemaker insertion.

However, important gaps in the evidence are present. In particular, evidence on the most important clinical outcomes associated with atrial fibrillation is lacking. Therefore it is not possible to conclude whether the majority of patients with atrial fibrillation, who do not require maintenance of sinus rhythm for symptom control, benefit from catheter ablation.

This evidence is also inadequate to evaluate adverse events. In order to accurately determine the rate for uncommon complications, such as pulmonary vein stenosis and cardiac

tamponade, larger numbers of patients are required. Furthermore, there is continued evolution of the technique and precise estimates of complication rates according to variations in the procedure are not available.

Summary of Application of the Technology Evaluation Criteria

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether radiofrequency catheter ablation as a treatment for atrial fibrillation meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria:

1. The technology must have final approval from the appropriate governmental regulatory bodies.

Radiofrequency catheter ablation is a percutaneous procedure, and as such is not itself subject to U.S. Food and Drug Administration (FDA) approval. However, the devices used for catheter ablation are subject to FDA approval. On February 6, 2009, the FDA granted approval via the premarket application (PMA) approval process for the NaviStar® ThermoCool® saline irrigated radiofrequency ablation catheter and the EZ Steer ThermoCool® Nav Catheter (both from Biosense Webster Inc., Diamond Bar, CA), for the treatment of medication-refractory atrial fibrillation. The FDA has also granted PMA approval to numerous catheter ablation systems for other ablation therapy for arrhythmias such as supraventricular tachycardia, atrial flutter, and ventricular tachycardia.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

The evidence is sufficient to conclude that radiofrequency catheter ablation is superior to pharmacologic treatment for maintaining sinus rhythm in certain patient populations. Four randomized, controlled trials reported decreased recurrence of atrial fibrillation in patients with patients with symptomatic paroxysmal or persistent atrial fibrillation who have failed antiarrhythmic medications, as an alternative to continued medical management. In each case, the magnitude of difference was relatively large, with the absolute risk reduction ranging from 47–70% at 1-year follow-up.

For patients with class II or III congestive heart failure and atrial fibrillation in whom heart rate was uncontrolled with standard medications, who would otherwise be candidates for AV nodal ablation and pacemaker insertion, one small randomized, controlled trial reported improvements in QOL, functional status, left ventricular ejection fraction, and recurrences of atrial fibrillation associated with radiofrequency catheter ablation. While small and of short duration, this trial was otherwise a high-quality study, and is sufficient to permit conclusions that outcomes will be improved following catheter ablation for this subgroup of patients.

The evidence is not sufficient to permit conclusions on the impact of radiofrequency catheter ablation on other outcomes in the broader population of patients with paroxysmal atrial fibrillation (e.g., as first-line treatment of recent-onset arrhythmia or in patients who are adequately managed with a rate control strategy). While there is some evidence suggesting that catheter ablation may improve QOL, this is not adequately robust to permit conclusions. Only two trials provided comparative data on QOL, with each using a different instrument. In addition, the data on QOL is self-reported, and thus prone to bias given that these trials were not double-blinded. None of the available trials provided data on clinical outcomes such as cardiovascular morbidity and mortality.

3. The technology must improve the net health outcome.

For patients who have symptomatic paroxysmal or persistent atrial fibrillation uncontrolled by standard medications, radiofrequency catheter ablation will improve outcomes. In this case, reduction or elimination of atrial fibrillation episodes will lead to a corresponding improvement in symptoms. Serious complications of catheter ablation in this group of patients is uncertain, but likely to be low, and is balanced against the risk of long-term, suboptimal medication management, including the adverse effects of antiarrhythmic medications and anticoagulation.

For patients with class II or III congestive heart failure and symptomatic atrial fibrillation in whom heart rate is poorly controlled by standard medications, catheter ablation leads to improvements in left-ventricular ejection fraction, QOL and functional status that are greater than those achieved with AV nodal ablation and pacemaker insertion. Serious complications of both proce-

dures can occur, but are uncommon, and there is no definitive evidence that either procedure is substantially more risky than the other.

For the majority of patients whose condition is controlled with a rate control strategy, maintenance of sinus rhythm is not by itself sufficient to demonstrate improved outcomes. For these patients, it is necessary to demonstrate improvements on other outcomes in order to determine benefit, and therefore, it is not possible to conclude that catheter ablation improves health outcomes for the broader population of patients with atrial fibrillation.

4. The technology must be as beneficial as any established alternatives.

Alternative treatments generally involve pharmacologic management. For patients with symptomatic paroxysmal or persistent atrial fibrillation, catheter ablation is more beneficial than medications in reducing symptoms. In patients who do not have uncontrolled symptoms (i.e., who are adequately maintained on a rate control strategy) or who have recent-onset paroxysmal atrial fibrillation, it is not possible to conclude that catheter ablation is more beneficial than medications.

For patients with class II or III congestive heart failure and symptomatic atrial fibrillation in whom heart rate is poorly controlled by standard medications, AV nodal ablation and pacemaker insertion is an alternative treatment. One small, high-quality trial establishes that catheter ablation is more effective than AV nodal ablation in improving QOL, functional status, and left ventricular ejection fraction.

5. The improvement must be attainable outside the investigational settings.

Catheter ablation of the pulmonary veins is a technically complex procedure that requires specialized training and has a substantial

learning curve. Currently, expertise to perform these procedures is widely available among interventional cardiologists in the U.S. Therefore, the improvement seen in the clinical trials of patients with symptomatic paroxysmal or persistent atrial fibrillation who have failed antiarrhythmic medications or in patients with class II or III congestive heart failure and symptomatic atrial fibrillation in whom heart rate is poorly controlled by standard medications, is expected to be attainable outside the investigational setting.

Whether radiofrequency catheter ablation improves outcomes for other patients with atrial fibrillation, including patients whose condition is adequately controlled using a rate control strategy or as first-line treatment for patients with paroxysmal atrial fibrillation, has not been established in the investigational setting.

Based on the above, radiofrequency catheter ablation of the pulmonary veins as a treatment for atrial fibrillation meets the TEC criteria for:

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

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

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Appendix

Table. Quality Assessment for Controlled Trials of Catheter Ablation – U.S. Preventive Services Task Force Framework (Harris et al. 2001)

Study/year	Initial Assembly of Comparable Groups	Maintenance of Comparable Groups	Comparable Intervention(s)	Comparable Measurements	Appropriate Analysis of Outcomes	OVERALL QUALITY LEVEL
Khan et al. 2008	YES	YES	YES Differences in procedures performed in groups, but roughly of same intensity	YES/NO Patients not blinded to treatment assignment, outcome assessors blinded	YES	GOOD Meets all quality indicators
Jais et al. 2008	YES	YES/NO Comparability of groups compromised by high number of early crossovers	NO Unequal intensity of treatments; invasive procedure vs. medication management; no sham procedure	YES/NO Patients not blinded to treatment assignment,	yes	FAIR Does not meet all quality criteria, but no fatal flaws
Oral et al. 2006	YES	YES/NO Comparability of groups subverted by high number of crossovers in intention-to-treat analysis	NO Compared ablation + meds with meds alone. No direct comparison of ablation vs. meds. Unequal intensity of treatments;	NO Did not include all relevant clinical outcome measures. Outcomes confined to recurrence of AF	YES ITT analysis included crossovers to PVI. Treatment received analysis also performed	FAIR Does not meet all quality criteria, but no fatal flaws
Wazni et al. 2005	YES	YES	NO Unequal intensity of treatments; invasive procedure vs. medication management; no sham procedure	NO Did not include all relevant clinical outcome measures. Outcomes confined to recurrence of AF and QOL	YES	FAIR Does not meet all quality criteria, but no fatal flaws

Table. Quality Assessment for Controlled Trials of Catheter Ablation – U.S. Preventive Services Task Force Framework (Harris et al. 2001) (cont'd)

Study/year	Initial Assembly of Comparable Groups	Maintenance of Comparable Groups	Comparable Intervention(s)	Comparable Measurements	Appropriate Analysis of Outcomes	OVERALL QUALITY LEVEL
Stabile et al. 2006	YES	YES	NO Compared ablation + meds with meds alone. No direct comparison of ablation vs. meds. Unequal intensity of treatments;	NO Did not include all relevant clinical outcome measures. Outcomes confined to recurrence of AF	YES	FAIR Does not meet all quality criteria, but no fatal flaws
Pappone et al. 2006	YES	YES	NO Unequal intensity of treatments; invasive procedure vs. medication management; no sham procedure	NO Did not include all relevant clinical outcome measures. Outcomes confined to recurrence of AF	NO	FAIR Does not meet all quality criteria, but no fatal flaws



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