

Pulmonary Vein Isolation for Treatment of Atrial Fibrillation



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Executive Summary

Background

Atrial fibrillation (AF) is a common cardiac arrhythmia that is associated with decreased survival, numerous cardiovascular morbidities, and a decrease in quality of life. The current treatment approach for AF is primarily pharmacologic. Pulmonary vein isolation (PVI) is a nonpharmacologic alternative treatment for patients with AF. PVI offers potential benefits compared to current pharmacologic treatments, including the potential to cure AF and to avoid the need for long-term medication management.

Objective

The objective of this Assessment is to determine whether PVI improves health outcomes when used as an alternative to pharmacologic treatment for patients with atrial fibrillation.

Search Strategy

MEDLINE was searched from 1990 to March 2006, using the terms “pulmonary vein isolation,” “PVI,” 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.

Selection Criteria

Controlled trials that were published in the peer-reviewed, English-language literature and compared PVI to alternative treatment(s) were selected for inclusion in this Assessment.*

Main Results

Numerous clinical series of PVI treatment have been published that report primarily on success in maintaining sinus rhythm following PVI. However, these reports provide little evidence on the true efficacy of PVI in maintaining sinus rhythm apart from the natural history of the disorder and/or the impact of ancillary treatment measures. These uncontrolled series also do not provide relevant data on the comparative efficacy of PVI vs. pharmacologic treatment.

Three controlled trials met the inclusion criteria and were reviewed in-depth for this Assessment. One trial was a randomized, controlled trial (RCT) (n=146) that compared PVI plus ancillary treatments (i.e., short-term amiodarone, cardioversion) with ancillary treatments alone for patients with chronic AF. The second trial was a smaller RCT (n=70) that randomized patients with new-onset,

* In addition, 1 trial comparing PVI plus ancillary treatments with ancillary treatments alone was published after this report was presented at the Medical Advisory Panel (Oral et al. 2006); data from this trial are included in this Assessment. The results of this trial did not change the Assessment conclusions.

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paroxysmal AF to PVI or antiarrhythmic drug therapy. The final study was a nonrandomized comparative study (n=1,171) that included patients with symptomatic AF refractory to prior antiarrhythmic drug treatment, and compared outcomes of PVI vs. continued antiarrhythmic drug treatment.

All 3 trials reported improvements in outcomes that favored the PVI group. In the RCT of PVI plus ancillary treatment vs. ancillary treatment alone, maintenance of sinus rhythm was higher in the PVI group, with 74% of patients in the PVI group in sinus rhythm at 1 year, compared to only 4% of patients in the control group who maintained sinus rhythm following ancillary treatment alone.

Two of the 3 trials compared PVI to pharmacologic treatment. The smaller RCT reported a lower incidence of AF recurrence in the PVI group compared to the antiarrhythmic drug group (13% vs. 63%, $p<0.001$). This study also included quality of life outcomes, with a greater improvement on 5 of 8 subscales of the SF-36 reported for the PVI group. The larger nonrandomized trial corroborated the findings of the smaller RCT of lower recurrence of AF following PVI, with an incidence at 1 year of 20% in the PVI group vs. 58% in the medical treatment group ($p<0.001$). This nonrandomized study also reported on mortality and AF-related morbidities. The PVI group had improved survival at 3 years (92% vs. 86%, $p<0.001$) and a reduced likelihood of cardiovascular morbidities (hazard ratio [HR] 0.45; 95% CI: 0.31–0.64).

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 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 PVI technique, mainly with the intention of reducing pulmonary vein stenosis and other complications, and currently there is no standardization of the procedure across medical centers.

Author's Conclusions and Comments

The available controlled trials on PVI are few and the evidence is not currently sufficient to permit conclusions on this treatment. There is only a single, small RCT that compares PVI to pharmacologic management, and this trial does not report on the full range of clinical outcomes. This study is also too small to allow estimation of the complication rates of the procedure. The larger RCT comparing PVI plus ancillary treatment to ancillary treatment alone establishes that PVI is efficacious in maintaining sinus rhythm apart from the effect of natural history and/or ancillary treatment measures. However, this trial does not provide information on the comparative efficacy of PVI vs. alternative treatment modalities. The larger, nonrandomized study is prone to selection bias, since treatment assignment was chosen by the treating physician and/or patient preference. This study does not report systematic evaluation for complications. In addition, these 3 studies treat different patient populations and use different techniques for PVI. Also, the 2 trials with a pharmacologic comparison group compared PVI to a rhythm-control strategy. There are no trials comparing PVI to a rate-control strategy, which is currently the preferred treatment strategy for most patients with AF.

The reported benefits associated with PVI in these trials are of large magnitude, and these preliminary studies suggest that PVI may improve outcomes for patients with AF. However, several questions remain before this treatment can be considered part of standard care. First, the PVI technique needs to be standardized so that results across studies can be compared and so that complication rates can be better estimated. The patient population to be treated needs to be better defined. Many experts suggest that younger patients with no paroxysmal AF and other heart disease should be targeted, but this population is represented only in the smaller RCT. This small trial reported the outcomes of maintenance of sinus rhythm and quality of life, but did not include important morbidity and mortality outcomes related to AF. PVI trials should ideally include both a rhythm-control and a rate-control group for comparison. The available trials use a rhythm-control group only.

Numerous RCTs are currently ongoing or in the planning stages, in both the U.S. and Europe. The results of these trials should become available in the next several years and will substantially expand the evidence available to judge the safety and effectiveness of PVI.

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether PVI 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.

PVI 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 PVI are subject to FDA approval. The FDA has granted approval to numerous catheter ablation systems under the premarket approval process. Indications for use of these catheters include ablation therapy for arrhythmias such as supraventricular tachycardia, atrial flutter, and ventricular tachycardia. Some of the catheter systems also have approval for treatment of refractory atrial fibrillation.

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

The evidence is not sufficient to permit conclusions on the effect of PVI on outcomes of atrial fibrillation. The available evidence includes 3 controlled trials that met the inclusion criteria for this Assessment: 2 RCTs and 1 larger nonrandomized controlled study. One RCT does not compare PVI to pharmacologic management. The second RCT is small and does not report on the full range of clinical outcomes. The third study is a larger, nonrandomized study that is prone to selection bias.

While the results of the available trials are suggestive that PVI may lead to health outcome benefits, larger RCTs are needed that enroll the appropriate population(s) and that include the most relevant comparison groups before conclusions can be made on the efficacy of this treatment.

3. The technology must improve the net health outcome; and

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

The evidence does not permit conclusions as to whether PVI improves health outcomes or is as beneficial as established alternatives.

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

Whether PVI improves the net health outcome has not been established in the investigational settings.

Based on the above, PVI as a treatment for atrial fibrillation does not meet the TEC criteria.

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Assessment Objective

The objective of this Assessment is to determine whether pulmonary vein isolation (PVI) improves health outcomes when used as an alternative to pharmacologic treatment for patients with atrial fibrillation (AF). AF is a common cardiac arrhythmia that is associated with decreased survival, numerous cardiovascular morbidities, and a decrease in quality of life. Recent basic research has revealed that in a large proportion of cases, the origin of AF is at the junction of the pulmonary veins and left atrium. Therefore, ablative therapy designed to interrupt these abnormal electrical impulses by isolating the pulmonary veins from the remainder of the atria has been proposed as a primary treatment for AF.

At present, treatment for AF is primarily pharmacologic. However, pharmacologic treatment is usually not a cure for AF, and is associated with its own risks. Therefore, nonpharmacologic treatments may offer advantages over the current approaches, with the potential of curing AF and avoiding the need for chronic pharmacologic management. This Assessment will compare PVI with currently accepted pharmacologic treatment approaches. The most relevant health outcomes for this Assessment are survival, cardiovascular events, quality of life, and complications of treatment. Recurrence of AF will also be examined as an outcome, although it is less useful as an outcome compared to other measures.

Background

AF is a common cardiac arrhythmia, and is associated with considerable morbidity and a decrease in quality of life. The prevalence of AF increases with age. For individuals younger than 55 years old, 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 AF is increasing for reasons that are not entirely clear. At present, approximately 2.3 million adults in the U.S. have AF. By the year 2050, this number may increase to 5.6 million (Go et al. 2001).

AF 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

conducts electrical impulses to the ventricles. This electrical activity directs the coordinated contractions of the atria and ventricles. AF 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.

AF represents a relatively heterogeneous disorder. There are numerous, different ways that AF may be classified, without a standardized scheme. AF may be paroxysmal or chronic. Paroxysmal AF refers to self-limited episodes that may last for minutes to weeks, with intervening periods of normal sinus rhythm. Chronic AF is defined as continuous AF, with no intervening periods of normal rhythm. AF may or may not be associated with underlying heart disease. A variety of cardiac pathologies can contribute to the initiation and/or maintenance of the disorder. The type of underlying heart disease may be valvular, ischemic, or myopathic. In general, any disorder that involves the atria can lead to AF. “Lone” AF refers to AF in the absence of any demonstrable heart disease. Lone AF is more common in younger patients and is associated with a more favorable prognosis. AF is sometimes the result of another disorder; this is called secondary AF, or acute AF. AF is common following intrathoracic and intracardiac surgery. It may also result from acute medical illness, such as acute lung disease with hypoxia or hyperthyroidism.

The pathophysiology is not well understood, but recent advances in electrophysiology have offered insights into the mechanisms of AF. AF involves both a trigger for initiation and a substrate that promotes maintenance of the abnormal rhythm. The trigger for AF is thought to be an excitable focus within the atrial tissue. There may be one or more foci that initiate AF. The substrate for promoting the maintenance of AF is in general a diseased atrium. Patients with normal atrial function will tend to have paroxysmal AF, with spontaneous restoration of sinus rhythm. Patients with abnormal atria will tend to develop chronic AF, and conversion to normal sinus rhythm is less likely to occur.

Treatment of Atrial Fibrillation

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 are to restore sinus rhythm, thus eliminating the risks of AF. The most commonly used drugs for this purpose are type I antiarrhythmic agents, such as procainamide, flecainide, propafenone, or sotalol; and amiodarone. If pharmacologic treatment fails to restore sinus rhythm, direct-current (DC) cardioversion is usually attempted.

In the rate-control strategy, the goal is not to convert AF to sinus rhythm, but rather to control the ventricular rate, minimize symptoms, and reduce the likelihood of complications of AF. 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.

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 AF, 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 AF 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 AF, often within a very short time.

There are a number of factors that predict the likelihood of a patient maintaining sinus rhythm, and thus may influence the choice of a rhythm- versus a rate-control approach. The length of time that a patient has been in AF is inversely correlated with the likelihood of maintaining sinus rhythm. Patients with underlying heart disease, especially those with atrial dilation, are less likely to maintain sinus rhythm. Some patients, for example, elderly patients with long-standing AF and underlying heart disease, are very unlikely to maintain sinus rhythm. For these types of patients, a rhythm-control strategy is less attractive.

Also, the method used to restore sinus rhythm may itself have risks, in particular, use of antiarrhythmic agents, and 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.

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). These 3 trials enrolled patient populations that were skewed toward more severe disease, as defined by length, chronicity, and prior recurrences of AF. Therefore, they may not be generalizable to patients with new-onset or paroxysmal AF. All 3 studies reported that there were no differences in their main outcome measures between the two strategies.

The explanation for lack of efficacy in the rhythm-control group is likely related to a low rate of success in maintaining sinus rhythm, and to adverse effects of antiarrhythmic agents that may counterbalance the beneficial effects. For example, in the AFFIRM study, only 60% of patients in the rhythm-control group were in sinus rhythm at the 5-year follow-up point. A re-examination of the AFFIRM data revealed favorable outcomes for patients in sinus rhythm but increased risks for patients on 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.

These recent studies have altered the approach to pharmacologic treatment of AF, leading to a greater emphasis on rate-control strategies and a shift away from rhythm-control strategies. With a rate-control strategy, it is likely that similar outcomes will be achieved while avoiding the toxicity of the antiarrhythmic agents. While both approaches remain viable options,

the majority of experts currently recommend a rate-control strategy as the initial pharmacologic approach in most patients with AF.

Catheter-based Ablation Treatment for Atrial Fibrillation. There has been an evolution in percutaneous ablative therapy techniques 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. More recently, researchers have been able to use improved techniques for mapping action potentials of myocardial cells, and can identify abnormal foci that are the triggers for AF in the majority of cases. 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). This began a shift away from treatment of the entire atrium (Maze procedure) to more targeted approaches. The Maze procedure is currently used primarily to treat patients with AF who are undergoing open heart surgery for correction of valvular or ischemic disease.

Catheter-based 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.

Basic science research has now established that a high percentage of patients with paroxysmal AF have excitatory foci in the superior aspect of the left atrium, in the area close to the pulmonary veins. In particular, the small area of cardiac muscle that extends across the ostium of each pulmonary vein is an area that commonly contains excitatory foci. Therefore, some experts have reasoned that this is the area that should be targeted for ablative treatment, with or without prior mapping to precisely locate abnormal foci.

“Pulmonary vein isolation” (PVI) refers to percutaneous, catheter-based ablation technique(s) intended to interrupt conduction of abnormal excitatory foci from the area of the pulmonary veins to other areas of the atria. PVI 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 original technique for PVI involved 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.

By 2002, PVI had become the most common catheter-based treatment for AF, accounting for 80% of all procedures in one recent survey (Cappato et al. 2005). Nonspecific approaches, such as the Maze procedure, are now largely confined to patients who are undergoing open heart surgery for other cardiovascular conditions. The technical complexity and time required to map the entire atrium makes PVI an attractive alternative to complete mapping and focal ablation of all abnormal foci.

There are numerous variations on the technique of PVI, and currently there is no standardization of technique across treatment centers. 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.

Repeat procedures can be performed if AF recurs, especially if there is documented re-establishment of electrical pathways from the pulmonary veins to the left atrium. Most protocols recommend repeat procedures for symptomatic recurrence of AF, without attempting to demonstrate whether or not electrical disconnection between the pulmonary veins and atria had been re-established.

Treatment Guidelines. The most recent guidelines from the American Heart Association/American College of Cardiology/

European Society of Cardiology were published in 2001 (ACC/AHA/ESC Task Force on Practice Guidelines 2001). Treatment recommendations in this document focus on choice of pharmacologic agents, and issues associated with pharmacologic management of AF such as anticoagulation. There are no specific indications for PVI and/or other ablation techniques. The recommendations include the statement that nonpharmacologic treatments “should be considered” in patients with recurrent paroxysmal and persistent AF who have failed antiarrhythmic drug treatment.

The American College of Physicians and American Academy of Family Physicians issued clinical practice guidelines in 2003 for patients with new-onset AF (Snow et al. 2003). These guidelines state that the majority of patients with new-onset AF should be treated with a pharmacologic rate-control strategy and long-term anticoagulation. Similar to the ACC/AHA guidelines, this document does 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,” “PVI,” and “catheter ablation.” These terms were cross-referenced with the terms “atrial fibrillation,” and “a fib.” Search was performed from 1990 through March 2006, 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.

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;
- Compared PVI to alternative treatments. These comparisons can include pharmacologic treatment with either a rhythm-control strategy or a rate-control strategy, or non-pharmacologic approaches;

- Reported on at least one relevant clinical outcome (survival, cardiovascular events, recurrence of atrial fibrillation, quality of life, complications of treatment).

In addition, 1 trial comparing PVI plus ancillary treatments with ancillary treatments alone was published after this report was presented at the Medical Advisory Panel meeting; data from this trial are included in this Assessment.

Medical Advisory Panel Review

This Assessment was reviewed by the Blue Cross and Blue Shield Association’s Medical Advisory Panel (MAP) on February 23, 2006. 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.

Formulation of the Assessment

Patient Indications

PVI is specifically intended to treat patients with AF in whom the arrhythmia originates in the pulmonary vein(s). However, in clinical practice, it is not possible to determine the origin of the arrhythmia without intracardiac mapping, which is invasive and resource intensive, and thus not feasible to perform in all patients. There are several factors that may increase the likelihood that AF originates in the pulmonary vein. These are: paroxysmal AF, younger age, and the absence of other cardiac disease.

Many experts thus believe that PVI is most effective in patients with paroxysmal AF, and/or those patients with recent onset of persistent AF. Younger patients with no other evidence of structural heart disease may be most likely to benefit from PVI, since maintenance of sinus rhythm can avoid the need for long-term pharmacologic treatment.

PVI has also been used in patients who are refractory to pharmacologic management or who have contraindications to pharmacologic treatment. In this sense, PVI may be the final

option in a rhythm-control strategy, or it may be reserved for patients who fail both a rate-control and a rhythm-control strategy. Given results of recent RCTs that a rate-control strategy is as effective as a rhythm-control strategy for most patients, a rate-control strategy is currently preferred prior to nonpharmacologic approaches. Therefore, patients who fail medical management represent a limited patient population that has exhausted all options for pharmacologic treatment, in whom invasive options are considered as a last resort.

Technologies to be Compared

PVI will be compared to alternative treatment options for AF. 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 limited), or other invasive treatments for AF, such as the Maze procedure.

Health Outcomes

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

Adverse events associated with pharmacologic treatment are also important to consider. Bleeding associated with anticoagulant treatment is one important complication. Other complications include the potential proarrhythmic effect of antiarrhythmic medications.

Adverse effects of PVI itself may include bleeding or other vascular complications at the puncture site, MI, 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.

Specific Assessment Question

In patients with atrial fibrillation, does treatment with pulmonary vein isolation improve

outcomes, as compared to standard pharmacologic treatment?

Review of Evidence

Uncontrolled Studies. The literature on PVI consists largely of numerous clinical series that include patients with symptomatic AF 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 PVI. The most common reported outcome is recurrence of AF, and/or freedom from AF. 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. 2003; Nademanee et al. 2004; Kumagai et al. 2005), representing the experience of centers that perform large numbers of PVI procedures.

These uncontrolled series do not provide definitive evidence as to whether PVI improves outcomes compared with medical treatment. There is a large degree of variability in the natural history of AF, especially for the outcome of maintaining sinus rhythm. Patients commonly have intermittent episodes of AF interspersed with periods of sinus rhythm, and these episodes of AF 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. Therefore, it is important to have trials with concurrent control groups to address the question of treatment efficacy apart from the natural history of this disorder.

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 AF, and the presence of underlying heart disease are all important predictors of maintaining sinus rhythm. For clinical outcomes such as stroke and congestive heart failure, there are numerous factors, including blood pressure, cholesterol levels, cigarette smoking, etc., that may impact outcomes. 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).

Pharmacologic treatment is an effective management strategy for patients with AF, and

is currently the standard of practice for the majority of patients with AF. It is important to have control groups who are treated with the current standard of care, in order to determine the comparative efficacy of PVI. Ideally, PVI would be compared to a rate-control strategy, since that is the treatment approach currently recommended for most patients with AF.

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 AF has been prepared by the FDA and reiterates these reasons why randomized, controlled trials (RCTs) are required in order to adequately evaluate the efficacy of new treatments for AF (U.S. Food and Drug Administration 2004).

Controlled Trials. Three controlled trials of pulmonary vein isolation were identified that met the inclusion criteria for this Assessment (Table 1). Two of these trials compared PVI to a rhythm-control strategy consisting primarily of antiarrhythmic drugs, neither of these included a rate-control strategy in the control group. The third trial is an RCT that compares PVI plus ancillary treatments (amiodarone, cardioversion) to ancillary treatments alone. Each of the trials differs in the patient populations enrolled and the specific techniques used for PVI.

Oral et al. (2006) conducted 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 PVI could be attributed solely to PVI, apart from the effect of ancillary treatments (short-term amiodarone therapy, cardioversion as needed) that commonly accompany this procedure. Patients enrolled had chronic AF 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 AF was 4.5 years. This study was rated as “fair” by formal quality assessment (Appendix A). The main methodologic limitations of this trial were the lack of a clinically relevant control group, the high number of crossovers from control to PVI, and the lack of reporting on the full range of clinical outcomes.

The PVI 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 of 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 AF. The control group received ancillary treatments alone, without PVI, but were eligible to cross over to PVI if they did not maintain sinus rhythm after 3 months.

Freedom from recurrent AF was greater in the PVI group than in the control group (Table 2). At 1 year, 74% of patients assigned to PVI were free of AF without the use of antiarrhythmic medications. In the control group, 58% of patients assigned to control were free from AF at 1 year, but most of these were patients who had crossed over to PVI. Only 4% of patients assigned to the control group were free of AF at 1 year following treatment only with ancillary measures without PVI ($p < 0.001$). A number of other beneficial results were reported for the patients receiving PVI, but these were within group comparisons of variables measured pre- and post-procedure. The symptom score significantly improved in patients receiving PVI, 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 PVI, 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.

Wazni et al. (2005) reported on a multicenter, randomized, controlled trial that enrolled 70 patients from two sites in Italy and one site in Germany (Table 1). The trial intended to evaluate PVI as first-line treatment in patients with paroxysmal AF. Patients were eligible for enrollment if they had experienced monthly episodes of symptomatic AF 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 AF 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 A). The main limitations noted were the lack of double-blinding, small

Table 1. Controlled Trials of PVI vs. Medical Management – Study Characteristics

Study/Yr	Study Design	Patient Population	Intervention		Outcome Measures
			PVI	Control	
Oral et al. 2006	RCT Pts. randomized to (PVI + amiodarone for 3 mos. + cardioversion if needed) or (amiodarone for 3 mos. + 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 $\geq 30\%$	Radiofrequency ablation – Circumferential ablation of all four 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 for recurrent AF	Control group – Amiodarone for 3 mos. – Warfarin for at least 3 mos. – Cardioversion as needed for recurrent AF	– Recurrences of AF – Complications – Left atrial diameter – LV ejection fraction – Severity of symptoms
Wazni et al. 2005	RCT Pts. randomized to PVI or antiarrhythmic medications (rhythm-control strategy)	70 pts with AF: – 18–75 years old – Monthly episodes 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 maximum tolerated dose of meds – Anticoagulation with warfarin throughout duration of study	– Recurrences of AF – Hospitalizations – QOL by SF-36 – Adverse events

Table 1. Controlled Trials of PVI vs. Medical Management – Study Characteristics (cont'd)

Study/Yr	Study Design	Patient Population	Intervention		Outcome Measures
			PVI	Control	
Pappone et al. 2003	Nonrandomized controlled trial Choice of treatment at discretion of treating physician and/or pt. preference. Physicians generally recommended PVI for pts. with ≥ 2 previous trials of antiarrhythmic meds, > 2 AF-related hospitalizations in last 2 yrs, ≥ 2 yrs of antiarrhythmic drug treatment	1,171 consecutive patients referred to tertiary care center's electrophysiology unit. Pts. excluded with: – Contraindication to anticoagulation – Previous unsuccessful attempt(s) at cardioversion – Class IV CHF – MI or cardiac surgery within prior 3 mos. – Other atrioventricular conduction disturbances without a pacemaker	Radiofrequency ablation – Circumferential ablation of all four pulmonary veins – Anticoagulation with warfarin for 3 mos., discontinued if no recurrent AF	Antiarrhythmic medications. – Choice of medication per treating physician – DC cardioversion if pharmacologic treatment unsuccessful – Anticoagulation with warfarin, stopped at physician discretion if > 3 mos. in sinus rhythm	– Mortality – Recurrence of AF – QOL (subset of pts, n=211) – Adverse events

Table 2. Controlled Trials of PVI vs. Medical Management – Outcomes

Study/Yr	Group	n	F/U	Mortality	Recurrence	QOL/Symptoms	Adverse Events (% pts)						
							CVA	TIA	TE ¹	CHF	Bleed	Brady	PVsten ²
Oral et al. 2006	PVI	77	12 mos.	NR	26% (20/77) ³	Significant within-group improvement in symptom score following PVI from 17 ± 4 at baseline to 12 ± 4 following PVI (p=0.02)	0	0	0	0	0	0	0
	Med	69	12 mos.	NR	96% (66/69)		0	0	0	0	0	0	0
					p<0.001								
Wazni et al. 2005	PVI	33	12 mos.	NR	13% (4/32)	Greater improvement for PVI group on 5/8 SF-36 subscales (see Table 3)	0	0	0	NR	*	0	3%
	Med	37	12 mos.	NR	63% (22/35)		0	0	0	NR	*	9%	0
					p<0.001								
Pappone et al. 2003	PVI	589	30 mos. (mdn)	6% (38/589)	20% (120/589)	Significant improvement in physical and mental health scores for PVI group; no improvement in medication group (see Table 3)	0.7	1.4	1.4	5.4	NR	NR	NR
	Med	582		14% (83/582)	58% (340/582)		2.6	4.6	1.9	9.8	NR	NR	NR
				<0.001	<0.001								

1 Thromboembolic event, other than CVA

2 Pulmonary vein stenosis

3 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 PVI after 3 mos. (53/69)

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

Table 3. QOL Outcomes in Controlled Trials of PVI 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
Pappone et al. 2003		Aggregate Physical Score		Aggregate mental health score					
	PVI	11		9					
	Control	-1		0					
		*		*					

* Reported significant within-group improvement for PVI, no significant improvement in medical management. No between-group comparisons reported

size of the trial, and the lack of reporting on the full range of relevant clinical outcomes.

The PVI technique in this study involved 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 recurrence of AF up to 12 months post-enrollment. Other endpoints included hospitalizations and quality of life (Tables 2 and 3). Recurrences of AF were less frequent in the PVI group. At 12 months' follow-up, 13% of the patients in the PVI group had symptomatic recurrence, compared to 63% in the medical management group ($p < 0.001$).

There were also significant differences favoring the PVI group in the mean number of recurrences per patient ($p < 0.05$) and the mean time spent in AF (2% vs. 16%; p not reported).

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

Adverse events were reported in this trial, but only a few were recorded given the small numbers in each group. Two patients in the PVI group developed pulmonary vein stenosis, one which was judged to be mild and the other moderate in severity. Bleeding occurred in 2 patients in the PVI group compared to 1 in the medical management group ($p = 0.60$). There were no episodes of thromboembolism reported, and no other serious complications reported from the PVI procedure.

The third controlled trial, Pappone et al. (2003), was a nonrandomized, comparative study of 1,171 consecutive patients referred to a tertiary care center in Italy for treatment of symptomatic AF (Table 1). The choice of treatment was determined by the treating physician and/or patient preference. In general, physicians recommended PVI for patients with 2 or more previous trials of antiarrhythmic drug therapy, 2 or more hospitalizations for AF, or 2 or more years of antiarrhythmic drug treatment. Patients either underwent PVI ($n = 569$) or medical treatment ($n = 582$), primarily a rhythm-control strategy. This trial was rated "poor" on formal quality assessment (Appendix Table A). The major limitation noted was the method of assignment to treatment group. Selection of treatment by physician and patient is likely to result in noncomparability of treatment groups.

In the PVI group, mapping of the left atrium was performed and all 4 pulmonary veins were treated with circumferential radiofrequency ablation. In their technique, a circular area was ablated that surrounded all pulmonary veins, thus "disconnecting" any electrical activity originating in the pulmonary veins. This modification of the PVI approach avoids treatment of the pulmonary vein ostia itself, and is intended to decrease the incidence of pulmonary vein stenosis. Interruption of pulmonary vein potentials was demonstrated following the ablation procedure.

In the medical treatment group, DC cardioversion was attempted if medications failed to convert AF to sinus rhythm. Anticoagulation with warfarin was administered for 3 months, and subsequently could be discontinued by the treating physician if the patient remained in sinus rhythm. Amiodarone was the most common agent used (33%), followed by propafenone (17%), flecainide (15%), sotalol (13%), quinidine (9%), and disopyramide (6%). Seven percent of patients required more than one antiarrhythmic agent.

The patient population for this study had a mean age of 65 and a mean prior duration of AF of over 4 years. Two-thirds of patients had paroxysmal AF while one-third had chronic AF. Approximately two-thirds of patients had evidence of other cardiovascular disease, and slightly less than one-half had hypertension. Comparisons between the PVI and medical treatment group revealed that the groups were comparable on age, gender, prior cardiovascular disease, and echocardiographic parameters. The PVI group had a significantly longer duration of AF (5.5 vs. 3.6 years, $p < 0.001$), and significantly more prior use of antiarrhythmic agents (3.1 vs. 2.3 trials of antiarrhythmics, $p < 0.001$).

This study reported on multiple outcome measures, including mortality, stroke, myocardial infarction, congestive heart failure, hospitalizations, and thromboembolic events. Quality of life was measured in a subset of consecutive patients treated between September 2000 and March 2001 ($n = 211$). Recurrences of AF were also documented and reported.

The PVI group had significantly better outcomes across the range of reported measures (Tables 2 and 3). Estimated survival by life table analysis was 92% in the PVI group vs. 86% in the medical group at 5 years ($p < 0.001$). Morbidities (myocardial infarction, congestive heart failure, transient ischemic attack, stroke, peripheral embolism) were all less frequent in the PVI group, with a combined hazard ratio for these morbidities of 0.45 (95% CI 0.31-0.64). Estimated survival free from any of these morbidities at 5 years was 91% in the PVI group vs. 81% in the medical group. Maintenance of sinus rhythm was more common in the PVI group, estimated by lifetable analysis to be 78% at 5 years in the PVI group vs. 37% in the medical treatment group. There was significant improvement in QOL scores in the PVI group compared with no change in the medical group.

Short-term adverse events from the PVI procedure were reported, but longer-term adverse events were not. Four patients (0.7%) had perforation of the myocardium with bleeding into the pericardium and tamponade requiring pericardiocentesis. There were no periprocedural strokes or thromboembolic events and no patient had early signs of pulmonary vein stenosis.

Discussion

There are 3 controlled studies comparing PVI with alternative treatments. These studies provide limited evidence as to the efficacy of PVI as an alternative to pharmacologic treatment for AF. Each of the studies has limitations, and together they do not constitute definitive evidence on this emerging procedure. Nevertheless, each study reports substantial differences in favor of the PVI group on relevant outcomes.

Oral et al. (2006) was an RCT that did not attempt to compare PVI with pharmacologic management. Rather, this RCT compared PVI plus ancillary treatments vs. ancillary treatments alone. The authors reported that there was a large difference in their main outcome, freedom from AF, associated with PVI. This trial, therefore, establishes that the maintenance of sinus rhythm following PVI can be attributed almost entirely to PVI, and not to the ancillary treatments provided.

Wazni et al. (2005) was a small, randomized, unblinded trial that compared PVI with a rhythm-control strategy. The small numbers of patients in this trial precluded the ability to measure the entire range of relevant health outcomes; as a result, outcomes were limited to recurrences of AF and QOL. On these outcomes, there were large differences in favor of the PVI group. The magnitude of benefit in reducing AF recurrence was large (13% recurrence in PVI vs. 63% recurrence in medical group) at 1 year, and the improvement in quality of life on the SF-36 ranged as high as 20 points for physical functioning, a magnitude of difference that would be considered clinically significant.

Neither of these 2 RCTs provides information on the most important relevant clinical outcomes, including survival, cardiovascular events, and complications of treatment. Recurrence of AF is probably not a reliable surrogate marker for these important health outcomes (U.S. Food and Drug Administration 2004). The differences in QOL are clinically significant for a number of measures, but may be prone to bias due to the subjective nature of these scores and the unblinded study design. Furthermore, this study is inadequate to

evaluate adverse events. In order to accurately determine the rate for uncommon complications, such as pulmonary vein stenosis and cardiac tamponade, trials with much larger numbers of patients are required.

Pappone et al. (2003) is a large, nonrandomized study that reports on a wider range of outcomes, with results showing substantial improvements in survival, quality of life, and maintenance of sinus rhythm for the PVI group. However, the possibility of selection bias is high in this study, given that the treatment group was determined by the treating physician and/or patient preference. Although there are no demonstrable group differences on the majority of demographics and clinical factors measured, it is possible that systematic assignment of patients with a more favorable prognosis was made to the PVI group, thus reducing the validity of the comparison between treatments.

These studies raise the possibility that health outcomes may be improved by PVI, but numerous questions remain unanswered. There is considerable uncertainty regarding technical aspects of the procedure, the patient population that should be targeted, and the rates of adverse events following PVI.

The technique itself is still in evolution, with numerous modifications still being proposed to improve efficacy and reduce risks. The exact location of ablated areas varies by operator, with some treating tissue in closer proximity to the pulmonary veins. Some experts believe that encircling the pulmonary veins outside the ostia of the veins will reduce the incidence of pulmonary stenosis. Transesophageal echo monitor has been used as a means to titrate the amount of radiofrequency energy, thus reducing the risk of perforating the myocardium.

The patient population that should be targeted for PVI is not yet defined. There are many patients with persistent and/or chronic AF who do well with pharmacologic therapy, and who are unlikely to remain in sinus rhythm due to underlying structural heart disease. These patients are unlikely to benefit from PVI. Patients who have failed pharmacologic therapy represent a potential population that may benefit from PVI. However, there are no controlled trials that evaluate PVI in this population. Numerous clinical series and one comparative study (Pappone et al. 2003) selected

patients who had failed antiarrhythmic therapy, but did not require that patients had also failed rate-control therapy. Recent RCTs have established that a rate-control strategy is as least as good as a rhythm-control strategy in patients with longstanding or recurrent AF. Therefore, for most patients with AF, a rate-control strategy would be considered the current standard of care. Controlled trials are needed that enroll patients who have failed all pharmacologic therapy, including a rate-control strategy, and that report on important clinical outcomes such as mortality, morbidity and quality of life.

Some experts believe that patients with paroxysmal AF who have no underlying heart disease, especially those with recent onset of AF, may derive the greatest benefit from PVI. A recent editorial claimed that PVI should be considered standard care for this group of patients (Wood and Ellenbogen 2006). However, this recommendation is based on only one study that targets this population (Wazni et al. 2005). As discussed previously, this is a small, unblinded trial that does not report mortality or morbidity outcomes, and thus is not sufficient to determine that PVI improves health outcomes for this population. The large benefits reported in this trial on the maintenance of sinus rhythm and quality of life underscore the potential for PVI to benefit this population. Larger trials are needed in this population to confirm that PVI does lead to long-term health outcome benefits at an acceptable risk

Serious adverse events can occur following PVI, but accurate rates for these complications cannot be determined. Differences in the technique of PVI may impact the rates of complications. Standardization of technique and long-term follow-up of large numbers of patients are needed in order to estimate the complication rates and the overall benefit/risk ratio for the procedure.

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 PVI 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.

PVI 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 PVI are subject to FDA approval. The FDA has granted approval to numerous catheter ablation systems under the premarket approval process. Indications for use of these catheters include ablation therapy for arrhythmias such as supraventricular tachycardia, atrial flutter, and ventricular tachycardia. Some of the catheter systems also have approval for treatment of refractory atrial fibrillation.

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

The evidence is not sufficient to permit conclusions on the effect of PVI on outcomes of atrial fibrillation. The available evidence includes 3 controlled trials that met the inclusion criteria for this Assessment: 2 RCTs and 1 larger non-randomized controlled study. One RCT does not compare PVI to pharmacologic management. The second RCT is small and does not report on the full range of clinical outcomes. The third study is a larger, nonrandomized study that is prone to selection bias.

While the results of the available trials are suggestive that PVI may lead to health outcome benefits, larger RCTs are needed that enroll the appropriate population(s) and that include the most relevant comparison groups before conclusions can be made on the efficacy of this treatment.

**3. The technology must improve the net health outcome; and
4. The technology must be as beneficial as any established alternatives**

The evidence does not permit conclusions as to whether PVI improves health outcomes or is as beneficial as established alternatives.

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

Whether PVI improves the net health outcome has not been established in the investigational settings.

Based on the above, PVI as a treatment for atrial fibrillation does not meet the TEC criteria.

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Appendix

Table A. Quality Assessment for Controlled Trials of PVI – USPSTF Framework

Study/yr	Initial Assembly of Comparable Groups	Maintenance of Comparable Groups	Comparable intervention(s)	Comparable Measurements	Appropriate Analysis of Outcomes	OVERALL QUALITY LEVEL
Oral et al. 2006	YES	YES/NO Comparability of groups subverted by high number of crossovers in ITT analysis	YES	NO Did not include all relevant clinical outcome measures. Outcomes confined to recurrence of AF and QOL	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	YES	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”
Pappone et al. 2003	NO Choice of treatment per treating physician and patient preference. Baseline imbalances on some clinical measures, including prior duration of AF and prior number of treatment trials	NO	YES	YES	NO PD20 measurements available for only 58/89 (65%) of patients, no intent-to-treat analysis used.	POOR Method of treatment assignment leads to high likelihood of selection bias, represents “fatal flaw”



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